Renal Palliative Care - A Reader

Selected articles in Renal - Palliative Medicine with a recommended reading list and detailed Bibliography by subject.

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Introduction

The interface of two disciplines – Renal Medicine and Palliative Medicine - continues to expand. Every year the numbers of patients being diagnosed with end-stage renal disease (ESRD) around the world is increasing. Whether or not they are commenced on Renal Replacement Therapy or managed conservatively, the needs of these patients and their families and carers are complex and challenging. Co-ordinating care that includes physical, emotional, psychosocial and financial needs is difficult. Knowledge of these areas is spread across multiple disciplines.

This Reader is an attempt to draw together in the one collection a selection of the most comprehensive, seminal and authoritative articles in the area of Renal-Palliative Medicine. An attempt has been made to make the collection as useful as possible for the clinician or student. With that in mind the Reader includes a list of the most highly recommended textbooks and articles in this area. Given that there is an inevitable subjectivity in making this selection, each subject area should be consulted together with the detailed bibliography that concludes the Reader.

It is important to note that the subject matter of the bibliography is broader than the reproduced articles and pertains to all aspects of this area. The bibliography was drawn from many sources including a search of literature in the English language on each subject from MEDLINE, PUBMED, the Cochrane Library Database and detailed hand searches. Given the rapidity in knowledge in many of the areas listed, I have concentrated, although not exclusively, on literature published in recent years. I have also included foundation and seminal articles in each area, irrespective of the date of the publication.

Inevitably an individual article may be relevant to multiple subject matters. An example would be an article on quality of life and symptom management of elderly patients with ESRD. I have included that article within the bibliographies of each subject matter. Both the articles reproduced and the accompanying bibliography should be seen by the clinician and student as a beginning and not an end to their reading and enquiry. The purpose of this collection is to open up this area for the reader, guide the reader and, hopefully, initiate ideas, stimulate clinical innovation and improve patient care.

Obviously, literature in this area continues to expand rapidly. This Reader and the accompanying Bibliography represent the literature available at the time of publication. Express permission for reproduction of all articles contained within has has been granted by the publishers.

This collection would not have been possible without the extraordinary support of the staff of the Medical Library at St George Hospital, Kogarah, Sydney.

I would also like to acknowledge the leadership of Professor Mark Brown, head of the Department of Nephrology and the support of Dr Jan Maree Davis, head of the Department of Palliative Care at St George Hospital Sydney.

Much work has been done in this area. Much work continues to be done. Inevitably new streams of enquiry, thought and research will flow. This Reader attempts to reflect the work done to date and looks forward to future developments.

Frank Brennan, St George Hospital, Sydney 2012

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Renal supportive care: why now?

It is impossible that anything so natural, so necessary, and so universal as death, should ever have been designed by Providence as an evil to mankind.

Jonathan Swift (1667–1745)

Nephrology is still a relatively new area of medicine. It was only 40 years ago that the first patients were kept alive with dialysis for longer than a few months. In its infancy, nephrology focused on the new technology of dialysis and on keeping patients alive at all costs. It did not matter how much time, money and suffering were expended on this goal. The first dialysis patients were predominantly young, male, employed, and otherwise healthy; once chosen, they were expected to endure all the pain and rigors of treatment with gratitude. In its adolescence, nephrology expanded the focus of dialysis to include older and sicker people with significant co-morbidities. However, the same ethos of keeping a patient alive at any cost informed this approach.

Although some nephrologists persist in this stance, there are indications that change is occurring. In a recent (2007) survey[1] that compared the beliefs of nephrologists from the US and Canada in 1990 with those from 2005, considerably more nephrologists had come to affirm that it was correct to withhold or withdraw dialysis in severely demented or permanently unconscious patients, and that ethical physicians were bound to honour patients' 'do not resuscitate' (DNR) directives. The survey also found that more dialysis units had instituted written policies affirming these decisions, whereas in the past many dialysis facilities would not allow DNR orders to be carried out. The rationale was that such an order was inconsistent with the patient having chosen a life-maintaining treatment.[1] Presently, while most nephrologists are still not sufficiently knowledgeable or educated in the nuances of end-of life discussions, there is increasing pressure in the field for more training and attention to these issues.[2]

As the treatment of end-stage renal disease (ESRD) approaches maturity, nephrologists are caring for an increasing sick and elderly population. The 2008 United States Renal Data System (USRDS) data (<www.usrds.org>), demonstrate that the elderly (> 75 years of age) represent the fasting growing incident population, and that they often have multiple co-morbidities. As discussed by Panzetta and colleagues in this issue of the journal, the degree of frailty and its implications in the management of the elderly is often overlooked. In the prevalent dialysis population from 1993 to 2005, there has been a modest, but steady, decline in mortality, but there has been an increase in the mortality rates of the incident population in the first 3 months after starting dialysis. In the first month, it has increased from 182 per 1000 patient-years to 262 per 1000 patient-years; the mortality rate for incident ESRD patients over 75 years of age is > 400 per 1000 patient-years at 2 months after initiation of dialysis. Overall, the mortality rate for dialysis patients is > 25% a year, and this population has a dramatically diminished life expectancy that is worse than HIV and most cancers. It seems clear from these statistics that many of the patients who presently are beginning dialysis are unlikely to benefit either in terms of increased survival or quality of life.

In order to provide our patient with better quality care at end-of-life, nephrologists need to improve in a number of areas:

1. It is time to begin identifying patient who have less that a 6-month prognosis, so appropriate palliative care can be provided. In this issue of the journal, Wittenberg and Cohen provide an excellent review of how knowledge is improving. One means is by clinician predictions, such as the Surprise Question ('Would you be surprised if the patient dies in the next 6 months [or 1 year]?') This appears to be a powerful predictor of mortality, but one that needs to be supplemented by the use of actuarial predictors, such as serum albumin and age. Progress in this area is likely to lead to clinical applications in the near future.
2. Communicating poor prognosis and discussing supportive care treatment options with patients and family is critical to ensuring the provision of appropriate supportive care. Davison provides a

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state of the art review of the current literature on advanced care planning and communication.

3. Withholding and withdrawal from dialysis need to be more freely discussed. As reviewed by Murtagh and colleagues, our knowledge concerning the management and outcomes of patients under these circumstances has greatly increased. Patients can be assured of peaceful and dignified deaths when appropriate palliative care is provided.
4. Finally, dialysis patients have an extremely high symptom burden that is not very different from cancer patients.[3–5] It is important that nephrologists pay as much attention to these symptoms as they do to the laboratory values that are more routinely monitored. Symptom treatment protocols that are evidence-based should improve quality of life for patients. In particular, pain is one of the most prevalent and troublesome symptoms, and Davison lucidly describes how our knowledge and management of pain in dialysis patients is greatly expanding.

The 500,000 plus ESRD patients are only the tip of the iceberg of chronic kidney disease. Recent demographic data suggest that there are up to 26 million patients with chronic kidney disease in the US (<usrd.org>). The complications, symptoms and poor prognosis of these patients mirror the ESRD population – only the magnitude changes. As the stages of chronic kidney disease advances, the incidence of these factors increases exponentially.

For this reason, it is important to intervene in these four ways as early as possible in the stage of chronic kidney disease. Early, frank discussions and planning prior to the need for dialysis is most likely to provide these patient with the quality of life and end-of –life care they desire and deserve.

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Review Article

Palliative care in end-stage kidney disease

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SUMMARY AT A GLANCE

Palliative care and conservative care pathways have become very important components of the care of our patients in Nephrology and this article reviews many aspects of this.

ABSTRACT:

Patients with end-stage kidney disease have significantly increased morbidity and mortality. While greater attention has been focused on advanced care planning, end-of-life decisions, conservative therapy and withdrawal from dialysis these must be supported by adequate palliative care incorporating symptom control. With the increase in the elderly, with their inherent comorbidities, accepted onto dialysis, patients, their nephrologists, families and multidisciplinary teams, are often faced with end-of-life decisions and the provision of palliative care. While dialysis may offer a better quality and quantity of life compared with conservative management, this may not always be the case; hence the patient is entitled to be well-informed of all options and potential outcomes before embarking on such therapy. They should be assured of adequate symptom control and palliative care whichever option is selected. No randomized controlled trials have been conducted in this area and only a small number of observational studies provide guidance; thus predicting which patients will have poor outcomes is problematic. Those undertaking dialysis may benefit from being fully aware of their choices between active and conservative treatment should their functional status seriously deteriorate and this should be shared with caregivers. This clarifies treatment pathways and reduces the ambiguity surrounding decision making. If conservative therapy or withdrawal from dialysis is chosen, each should be supported by palliative care. The objective of this review is to summarize published studies and evidence-based guidelines, core curricula, position statements, standards and tools in palliative care in end-stage kidney disease.

The role of palliative care in end-stage kidney disease (ESKD) is well developed in the UK, USA, Italy and Canada.[1–9] Palliative care in ESKD is important in the contexts of conservative therapy (choosing a non-dialysis pathway), withdrawal of therapy and in symptom control. Advanced care directives and end-of-life decisions overarch these pathways. There is a recognized need for education regarding provision of palliative care in dialysis patients.[10] However, there is no clear pathway to palliative care,[11] considerable variation in the provision of palliative care services for ESKD patients[12] and little evidence upon which to develop standards of renal palliative care in ESKD.[13] There has been an increase in the elderly accepted onto dialysis in Australia. In 2004, 244 (445 per million population) new patients were accepted on dialysis in the 75–79 year age group. This increased to 277 (504 per million) in 2008. In the 80–84 year age group 103 (267 per million) started dialysis in 2004, which increased to 187 (442 per million) in 2008 and in the >85 year group 32 (107 per million) started dialysis in 2004, which increased to 58 (159 per million) in 2008.[14] Despite this, the Caring for Australasians with Renal Impairment (CARI) Guidelines do not address palliative care.[15] In addition, many elderly assessed for dialysis either do not progress[16] or die before they would have required dialysis therapy.[17]

We will review the existing literature on palliative care provision in ESKD in the contexts of conservative therapy and withdrawal from dialysis. The available observational,

retrospective and case studies are summarized in Table 1. There are no reported randomized controlled trials.

PALLIATIVE CARE SUPPORTING CONSERVATIVE CARE IN ESKD

The literature reporting on withdrawal of dialysis extends back many years and has been the focus of palliative care in ESKD until recently.[34] However, the emphasis on making a choice between conservative (non-dialysis therapy) as an alternative to active (dialysis) treatment pathway before the need to start dialysis is gaining importance with some recent studies reporting comparable outcomes between these pathways in the elderly with multiple comorbidities.[18,30] These studies may enable renal multidisciplinary teams to provide evidence-based advice to patients before committing to ESKD therapies.[22,30] There is increased recognition in critical care medicine that a holistic approach is required to support end-of-life decisions,[35] and in renal medicine the role of palliative care is also gaining importance.[11,13] The interrelationships of these issues are summarized in Figure 1.

Pre-dialysis education is considered an essential part of the preparation for ESKD management[36–39] as it acts to inform the choices made by patients and their carers and enhances shared care planning with multidisciplinary teams.[5] Patients and their families may be unwilling or unable to choose not to commence treatment or to withdraw from it[40] and therefore information about palliative care options is an important inclusion in pre-dialysis education. Hence, in addition to discussing dialysis modality options and transplantation, discussion of a conservative approach supported by palliative care should be offered to those particularly of advanced age and/or with multiple comorbidities. Although some observational and retrospective studies have been published[18,19] and are summarized in Table 1, there are limited studies available upon which to base such discussions.

The issue of conservative therapy was addressed in an observational cohort study where patients approaching dialysis who had undertaken a multidisciplinary assessment were recruited over 54 months.[18] Investigators looked for features that influenced clinicians to advise a conservative approach rather than starting dialysis. The patients were followed for 3–57 months on the basis of the therapy option selected, dialysis or palliative care. Of 321 patients recruited, 258 were recommended for renal replacement therapy and 63 for palliative care. The patients that were recommended to take a palliative care pathway had greater functional impairment, were older and more often diabetic. Of the 63 patients, 34 recommended for palliative care died, 26 of these from kidney failure. Ten patients recommended for palliative care actually chose dialysis but had a median survival of only 8.3 months. This was not significantly longer than those that actually chose the palliative care pathway. In this group of patients the decision to accept either dialysis or palliative care had no significant effect on survival.

A retrospective study of 129 stage 5 CKD patients over 75 years of age who attended pre-dialysis multidisciplinary clinics assessed patient survival defined as time from reaching an eGFR of <15 mL/min until death or the end time point of the study.[19] There were 52 patients in the dialysis group and 77 in the conservative treatment group. The survival of the dialysis group was significantly greater than that of the conservative treatment group both at 1 and 2 years. However, when adjusted for comorbidities, particularly ischaemic heart disease, there was no such advantage seen.

Survival, scored using the validated Stoke comorbidity grade, was assessed in a prospective observational study of patients, managed through a multidisciplinary team, who chose not to undertake dialysis.[20] Seventy-three patients were recruited with a median age of 79 years. The median survival was 1.95 years and 1 year survival was 65%. The Stoke comorbidity grade independently predicted survival. Based on these results the authors advocated pre-dialysis multidisciplinary care supporting conservative therapy particularly for elderly patients with comorbidities. The Stoke comorbidity grade may provide prognostic information for predicting survival that will help multidisciplinary teams counsel ESKD patients approaching dialysis.

Nursing home patients

To be able to offer accurate advice to nursing home patients of advanced age and/or multiple comorbidities, it is necessary to know how outcomes compare between conservative therapy and dialysis treatment. A recent study attempted to address this issue. The US Renal Data System, and was used to identify residents of nursing homes that started dialysis over a 2 year 4 month period. The outcomes for residents of nursing homes in the USA were poor with a mortality rate of 58% in the first year and 29% having decreased functional status. Pre-dialysis functional status was only maintained in 13%.[30] This highlights the importance of offering palliative care with its associated focus on symptom control.[41] In an associated editorial the paucity of data in this area was noted. Increased comorbidity can predict death in dialysis patients.[42] However, unless there are data comparing quality and quantity of life in ESKD therapy compared with conservative management we struggle to identify those that would most likely benefit from such therapy. More studies are required to particularly enable us to define which patients will benefit from conservative rather than dialysis therapy.[41] In addition, it is important to adequately inform patients of potential outcomes to assist them with their decisions.

The elderly

The increasing acceptance of the elderly onto dialysis programmes has heightened the interest in and study of the process of end-of-life decision making, supported by palliative care, in ESKD.[43] This is particularly relevant as the mor-

Table 1 Studies investigating palliative care in kidney disease

Study	Study population (*n* = subject numbers)	Stage	Study design	Duration of follow-up	Outcome
Smith *et al.*[18]	Renal district general hospital Stephenage UK (*n* = 321)	Pre-dialysis	Observational cohort study	3–57 months	The decision whether to dialyse high-risk, dependent patients has no impact on survival
Berzoff *et al.*[10]	Medical health professionals, dialysis patients, family and bereaved family (*n* = 36 participants in 6 groups)	Dialysis	Qualitative focus groups	3 years	Greater education of both patients and families required
Murtagh *et al.*[19]	South Thames Region UK (*n* = 129)	Stage 5 CKD (pre-dialysis)	Retrospective review	12 months	Dialysis survival advantage substantially reduced by comorbidities
Wong *et al.*[20]	Renal Unit Royal Liverpool University Hospital (*n* = 73)	Pre-dialysis (dialysis not selected)	Prospective observational study	N/A	Stroke comorbidity grade was an independent prognostic factor for survival
Siegler *et al.*[21]	Community teaching hospital Cornell New York (*n* = 5)	Dialysis	Case discussions and chart review	N/A	End-of-life discussions occurred late and should encompass the full range of palliative care services
Yong *et al.*[22]	Caritis Medical Centre Kowloon (*n* = 179)	Pre-dialysis compared with Dialysis	Prospective cross-sectional study	14 months	Palliative care dialysis patients had significant symptom burden and impaired quality of life
Chater *et al.*[23]	Otaawa Teaching Hospital (*n* = 35)	Dialysis	Retrospective chart review	7 years	Palliative medicine has the potential to improve care for patients withdrawing from dialysis
Gunda *et al.*[12]	United Kingdom (*n* = 69 Directors of Renal Units)	Dialysis	National survey	N/A	Palliative care service provision varied through UK with ESRD patients excluded in some areas
Hackett and Watnick[24]	Oregon USA (*n* = 1)	Dialysis	Case report	N/A	Better education required to provide best care
Moss *et al.*[25]	North Central West Virginia (*n* = 147)	Dialysis	Prospective cohort study	1 year	The surprise question was effective in identifying patients at high risk of early mortality These patients should be prioritized for palliative care intervention
Murphy *et al.*[26]	United Kingdom 2 renal units (*n* = 55)	CKD stages 4–5 not receiving dialysis	Retrospective chart review	10 months	Demonstrated extent and severity of symptoms in conservatively managed patients with CKD stages 4–5 using an assessment tool
Murtagh *et al.*[13]	Kings College London UK (*n* = 78)	CKD stages 4–5 not receiving dialysis	Retrospective service review	1 year	The review highlighted the absence of research into models of care
Noble and Rees[27]	Barts and London NHS Trust UK (*n* = 45)	Renal patient deaths Dialysis, Transplant and CKD pre-dialysis	Retrospective chart audit	2 years	27% of patients were referred to palliative care. Significant residual symptoms were identified
Fried D[28]	Alice Springs Australia (*n* = 27)	Dialysis	Retrospective chart audit and case report	5 years	Palliation for ESKD patients should be based on standard principles, but modified in accordance with local practical requirements and community needs
Saini *et al.*[29]	Hillingdon Hospital NHS Trust, UK ESKD (*n* = 11) Cancer (*n* = 11)	Comparison ESKD and cancer patients	Cross sectional study	6 months	Patients with advanced renal failure experience a symptom burden and impairment of quality of life similar to that of patients with terminal malignancy
Kurella Tamura *et al.*[30]	Nursing home ESKD residents (*n* = 3 702)	Dialysis	U.S. Renal Data System (USRDS)	2 years 4 months	58% of patients died within 12 months of starting dialysis Functional status was maintained in only 13%
Ashby *et al.*[11]	Two dialysis units Melbourne Australia (*n* = 16) patients and/or caregivers	Dialysis	Qualitative, semistructured interviews	18 months	There would be benefit from a more proactive open approach to palliative care The study was limited by a high exclusion rate
Lamble *et al.*[31]	DOPPS (*n* = 242) dialysis units from six countries	Dialysis	Observational data questionnaires	N/A	Nephrologists opinions varied between countries on the issue of haemodialysis withdrawal
Murray *et al.*[32]	USA (*n* = 115 239)	Dialysis	USRDS observational study	2 years	Hospice care was underutilized in the USA ESKD population ESKD patient hospice use may result in reduced costs
Cohen *et al.*[33]	USA and Canada Eight dialysis clinics (*n* = 131)	Dialysis	Prospective observational	N/A	End-of-life planning should be an expected part of care supported by provision of palliative care

DOPPS, Dialysis Outcomes and Practice Patterns Study; N/A, not available; NHS, National Health Service.

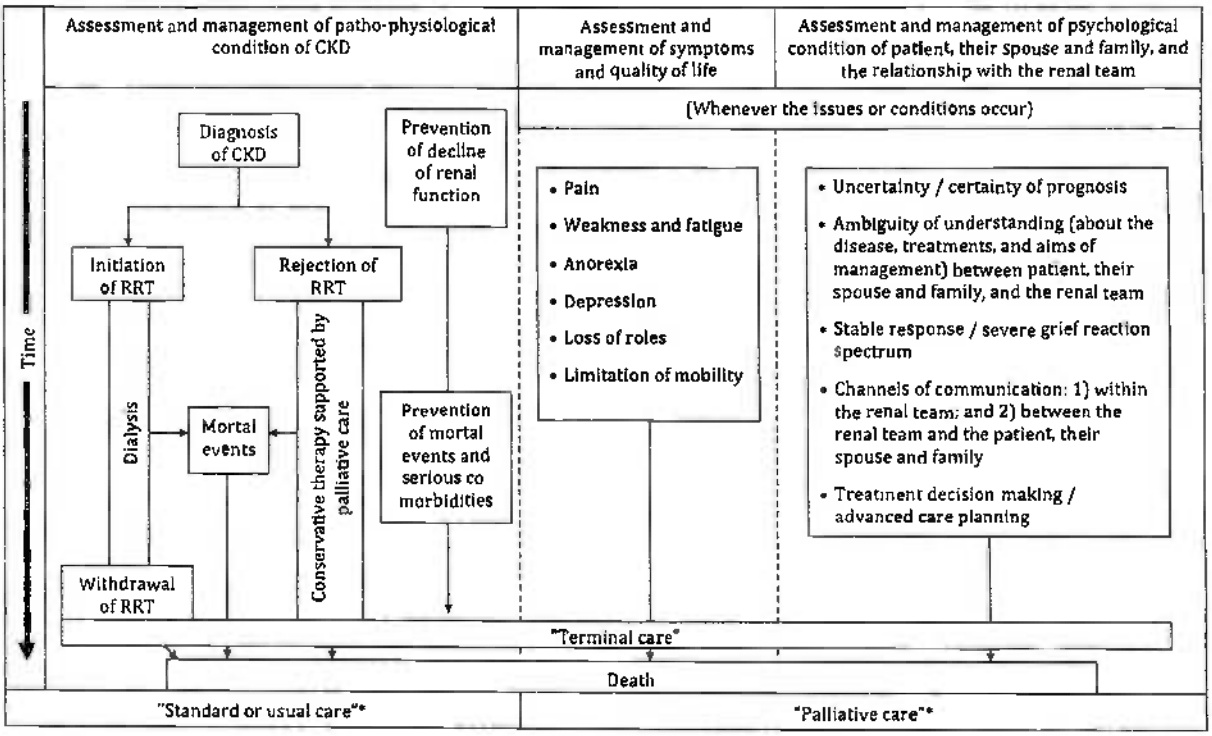

Fig. 1 Figurative description of the different functions of an idealized model of care of patients with chronic kidney disease. Our outline understanding of management of CKD over time is described in Figure 1. This arbitrarily divides the overall management of the patient into: (i) the technical issues related to the renal disease itself (and comorbidities) and its treatment; (ii) the immediate symptoms and quality-of-life issues suffered by the particular patient; and (iii) psychological impact of the disease and its prognosis on the patient, their spouse and family, and how this affects communication and decision making between them and the renal team. Optimal patient care through the course of the disease will involve combining technically proficient disease assessment and management, attention to the immediate condition as perceived by the patient, and guidance of the emotional condition of the patient, their knowledge and understanding of their disease and its prognosis, in order to allow decision making that maximally satisfies the patient. While we believe that this is implied in the publications on renal palliative care cited in this review, the relationships between the components of care have not been made explicit, and the effects of symptomatic and psychological management, and quality of communication, on patient satisfaction have not been measured to any useful extent. We might speculate that a patient who is uncertain about their prognosis, or whose understanding differs significantly from their professional advisors, suffering from denial or depression as a reaction to realizing their mortally threatening and severely restrictive disease, whose communication with the renal team seems to be at cross-purposes, might have difficulty in being brought into an effective partnership with their physicians in deciding on the nature and timing of transitions in their renal replacement therapy. However, evidence would be more helpful than speculation. *The 'standard or usual' and 'palliative' designations do not imply separate functions, but might be regarded as integrated components of overall patient care. Current good practice will be intuitively performing these functions, but are stated explicitly here to assist service planning, and information recording and communication between the patient's health carers. The list of activities is not intended to be exhaustive, but only illustrative of types of activity. Also, health-funding models, notably item-of-service payment, may need to be modified to facilitate this integrated model of care.

bidity and mortality seen in ESKD in its latter stages is very high.[44] Mortality in ESKD is mainly a consequence of cardiovascular disease, which may be 10- to 100-fold greater than age- and gender-matched controls in the general population,[45,46] or may be due to a higher prevalence of other causes such as pneumonia.[47,48] However, one study in dialysis patients found older dialysis patients had a lower excess mortality in the first 3 years of therapy than younger patients.[49] This can make individual survival and quality-of-life predictions difficult in the elderly. Despite this, the overall mortality is high and the assessment of the benefit of dialysis in the elderly is difficult. Available studies do suggest dialysis is still life extending in the elderly.[19,50] However, in the retrospective study by Murtagh *et al.* the survival advantage conferred by dialysis was abrogated by comorbidities such as ischaemic heart disease.[19] In a small prospective randomized controlled trial in those over 70 years a low protein diet delayed dialysis and was associated with an equivalent mortality when compared with those who started dialysis.[51,52] Factors identified as indicators associated with not opting for dialysis among octogenarians included social isolation comorbidities such as diabetes, late referral and Karnofsky score.[50] In those selecting dialysis therapy, dependent predictors of death included poor nutritional status, late

referral and functional dependence.[50] Octogenarians also have been shown to lose independence after dialysis initiation.[53] The quality-of-life benefits of dialysis therapy in the elderly remain unclear.[18] In a small observational study in ESKD patients over 75 years of age conservative therapy was associated with a quality of life similar to haemodialysis.[8]

PALLIATIVE CARE AFTER DIALYSIS WITHDRAWAL

Withdrawal from dialysis is one of the commonest causes of death and represents 35% of dialysis deaths in Australia.[54] The Dialysis Outcomes and Practice Patterns Study, reported differences in withdrawal from dialysis between and within countries and that this was correlated with nephrologists' opinions on these issues.[31] The mortality rate among dialysis patients is very high and may be greater than in HIV and some cancers. In addition, their symptom burden and rate of hospitalization are very high.[55] As more elderly patients are being accepted onto dialysis the focus of care needs to shift from the life extension aspects of dialysis care to relief of symptom burden and palliative care. Withdrawal from dialysis is a generally accepted process[56] and provided it is supported by adequate palliative care, the subsequent death can be good.[56] In the USA, end-of-life support for renal patients is well developed with a specific website that includes pain management guidelines.[3] In a study of 131 patients who withdrew from dialysis, 79 were followed prospectively until they died.[13] These patients had multiple comorbidities and their main symptoms in the last day of their life were agitation and pain. This study recommended mandatory end-of-life planning in ESKD management incorporating palliative care provision.

There is a documented underutilization of hospice facilities in ESKD patients in the USA where only 14% of all ESKD deaths occurred in patients using these facilities.[32] Only 40% of ESKD deaths from withdrawal of dialysis entered a hospice for care. This study also demonstrated a cost saving associated with dialysis patients dying in a hospice after withdrawal from therapy. ESKD patients use a hospice at a rate of 25% compared with that seen in cancer patients.[55]

A pilot study reviewed the charts of 35 dialysis patients that withdrew from therapy and were followed by a palliative care team.[23] The mean survival time from dialysis withdrawal to death was 10 days. Symptoms were reduced in the last day with palliative care input. The study suggested improved education of multidisciplinary nephrology staff was required.

A small Australian study assessed the abatement of medical treatment in ESKD that encompassed both withdrawal and non-initiation of dialysis treatment.[11] This study included four patients that withdrew from dialysis, seven that did not initiate dialysis and five spouses of these patients. The participants undertook semistructured interviews from which the investigators gleaned there would be benefits from a greater discussion of end-of-life issues with acceptance of this as part of standard practice. These findings are supported by a study into the experience of patients after cessation of dialysis that found early palliative care referral could assist the patient and multidisciplinary team to manage areas such as pain and create opportunities to discuss palliative care options.[23]

Factors identified as indicators associated with dialysis withdrawal include poor functional status, functional dependency, gender, ethnicity, social isolation and comorbidities.[28,36,57] Recently, Kurella Tamura *et al.* explored dialysis withdrawal preferences and found these varied with race, with blacks less likely to withdraw from dialysis than whites.[58] Also they found the elderly did not have an increased preference for dialysis withdrawal whereas younger patients were less likely to record their preferences and be open to end-of-life discussion.[58]

SYMPTOM ASSESSMENT AND TREATMENT IN PALLIATIVE CARE IN ESKD

Symptom control is of paramount importance in ESKD patients on dialysis with pain being the most common.[59] The use of the World Health Organization three-step analgesic ladder is effective in pain management in haemodialysis patients.[59] A prospective cross-sectional pilot study compared symptom burden and quality of life between patients with advanced ESKD with an eGFR <17 mL/min and a contemporary cohort with terminal malignancy.[29] Those patients with ESKD had similar symptom burden and reduced quality of life as the terminal malignancy group. This highlights that the palliative care needs of patients with ESKD are just as important as those with terminal cancer.

In a retrospective chart review of conservatively managed stage 4–5 CKD patients Murphy *et al.* assessed symptom burden using a short patient-completed assessment tool.[26] Patients all attended a renal palliative care service over a 10 month period. Comorbidity data were collected and a modified patient symptom module was completed. Fifty-five patients who were managed without dialysis were reviewed and the symptom burden recorded was high. Using a tool that may lead to assessing more effective symptom treatments, revealed the extent of symptom burden in conservatively managed ESKD. It is also important to emphasize that a conservative, non-dialysis approach to ESKD management should not be a vacuum, but in fact can provide an intensive programme of multidisciplinary care and support. It also provides the patient and their family with the confidence that there will be no reduction in medical and nursing care.[60]

A study from Hong Kong assessed and compared the quality of life and symptom burden between patients on haemodialysis and peritoneal dialysis with palliative care ESKD patients with an eGFR <15 mL/min.[22] This prospective observational study included 179 patients, 134 who had dialysis and 45 who undertook palliative care. Those that received palliative care had greater comorbidity and were older. There was no significant difference in symptom

burden between groups and the quality of life was significantly reduced in both groups. In this setting there was little difference in symptoms and quality of life whether they had dialysis or palliative care.

EMOTIONAL FACTORS IN PALLIATIVE CARE

The palliative care process needs to consider acknowledging and dealing with this grieving both in the patient, their family and health-care providers. A study conducted by Badger exploring factors impacting on end-of-life transitions in critical care found two key areas of concern for nurses.[61] These were the 'complex emotions and frank indecisiveness expressed by patients' families. Grief and loss are issues intertwined throughout the course of CKD and ESKD management.[62] Although grief is clearly associated with death, it is also evident and experienced much earlier in the trajectory of an illness and is even felt immediately a new high impact diagnosis is realized. Clinicians may avoid discussing end-of-life decisions with patients for fear of causing undue anxiety.[63] This is despite the patients desire to address the issues.

CULTURAL DIFFERENCES IN PALLIATIVE CARE

Cultural differences in the approach to end-of-life decisions, advanced care planning and withdrawal from dialysis have been addressed by Davison and Holley.[43] Non-Western cultures, significantly represented in the Australian population, may have very different understandings of the medical system, health and disease. These cultural sensitivities need to be taken into account when discussing palliative care and end-of-life decisions.

DIALYSIS STAFF INVOLVEMENT IN PALLIATIVE CARE

Several studies have indicated that the beliefs and values of health professionals have a clear impact on the integration of palliative care into the management of ESKD patients. Twohig and Byock[64] found that the focus of care remained on cure and prolongation of life and that ethical cultural and legal issues impact on the clinical decision to withdraw or withhold dialysis. In their study on physicians' decisions to withhold or withdraw life-sustaining treatment, Farber *et al.* reported that internists found it emotionally harder to withdraw rather than withhold treatment.[65]

In 2002, Siegler *et al.* reported inadequate communication and planning for patients with ESKD around palliative care transition, increased patient suffering.[21] This was later supported by a survey conducted of staff directly involved in dialysis care including nurses and social workers and found there was a deficiency in end-of-life discussion with patients and poor communication of the discussions that had occurred with staff actually caring for the patients.[66] Not only should dialysis patients selecting conservative management be clearly identified, those directly caring for the patient also need to be aware of the outcome of end-of-life discussions.

REVIEWS ON PALLIATIVE CARE IN ESKD

There have been previous reviews of palliative care in ESKD. Brown *et al.* reviewed palliative care in nephrology and issues covered under the palliative care umbrella.[67,68] Germain and Cohen noted the increasing mortality of incident dialysis patients associated with more elderly accepted for dialysis.[35] Haras highlighted the lack of advanced directives and palliative care among patients with ESKD and how senior nurses are well placed to initiate such care and discussion.[69] Jablonski, reviewed misconceptions that may be barriers to incorporating palliative care into the routine management of ESKD.[70] Holley reviewed palliative care management in ESKD with a focus on advanced care planning, referrals to hospices and bereavement.[71,72] Lichodziejewska-Niemierko and Rutkoski focused on the provision of palliative care support from the time of diagnosis through to family bereavement and on symptom relief.[73] Poppel *et al.* reviewed the Renal Palliative Care Initiative at a tertiary hospital and described the benefits to their patients.[44] They also described the evolution of renal supportive care from an initial focus on dialysis withdrawal through its expansion to incorporate the full continuum of CKD.[74] They highlighted the need to provide guidelines and tool kits to enable clinicians to achieve their goals in this population. Dialysis withdrawal has been reviewed by Murtagh *et al.*[56] along with White and Fitzpatrick who highlighted the paucity of available data.[75] These authors provide practical ways of handling the palliative care patient withdrawing from dialysis and emphasize the importance of advanced directives and thorough assessment before stopping treatment. The role and benefits of a comprehensive conservative management approach were reviewed by Burns and Carson.[76] Price reviewed the role of the nephrology nurse in palliative care for patients highlighting the importance of early referral and shared care.[77]

EVIDENCE-BASED GUIDELINES, CORE CURRICULUM, POSITION STATEMENTS, STANDARDS AND TOOLS IN PALLIATIVE CARE

There are many resources available, developed predominantly in the USA and the UK, to support those enquiring about palliative care in ESKD. A selection of these is summarized below to illustrate the breadth of resources available.

Evidence-based guidelines

The UK Expert Consensus Group have developed evidence-based guidelines for symptom management in adults who are dying from ESKD.[4] These guidelines developed from the

Liverpool Care Pathway for the Dying Patient, which was used initially for terminal cancer but subsequently for stroke and heart failure patients. An Expert Consensus Group for patients dying with renal failure found those dying with renal failure had similar symptoms to those dying with terminal cancer hence the Renal Liverpool Care Pathway prescribing guidelines were developed with the aim of controlling these symptoms.[78] The NKF KDOQI guidelines state Nephrologists should be familiar with the principles of palliative care and should not neglect hospice referral for patients with advanced kidney failure.[2,3] The CARI guidelines do not address palliative care[1,3] and formulating guidelines in the Australian context should be a high priority. However, the Kidney Health Australia website provides information for patients on conservative approaches both pre-dialysis and withdrawing from dialysis.[79]

Core curriculum

National Kidney Foundation core curriculum in nephrology summarized the relevance of palliative care and its incorporation into dialysis units.[5] It highlights the usefulness of advanced care planning in patients with ESKD and strategies to increase its use.

Position statement

The American Society of Nephrology and the Renal Physicians Association produced a position statement on End of Life Care in 2002.[1] This is a comprehensive document that addresses advanced care planning and directives, hospice care and palliative care. It also makes recommendations, which includes ensuring education of multidisciplinary renal team members in palliative care principles including advanced care planning, supporting the patient requesting dialysis withdrawal with palliative care referral and the development of renal unit policies and protocols to ensure advanced care planning occurs.

Clinical practice guidelines

The Renal Physicians Association and the American Society of Nephrology also provide a clinical practice guideline on dialysis initiation and withdrawal.[80]

Standards

Standards for providing Quality Palliative Care for all Australians were published in 2005.[81] Although there is no specific reference to patients with kidney disease the standards provide guidelines that can be applied to all diseases. The standards do emphasize the need to encompass the patient and their family's wishes and needs in the decision-making process of care planning. In addition, access to palliative care services should be available independent of diagnosis and should be based on clinical need.

Tools

The only tool in the public domain that we could find was in the National Health Service National End of Life Care Program to enhance end-of-life care in those without cancer. It introduced the tool to support patients with kidney failure.[6,82]

DISCUSSION AND CONCLUSIONS

Palliative care support should be offered to patients selecting ESKD management options including a conservative treatment pathway or withdrawal from dialysis. The increased acceptance of the elderly with comorbidities, nursing home patients with their inherent poor outcomes emphasizes the importance of supporting end-of-life decisions with palliative care. There should be an associated focus on adequate symptom control, which has been poorly attended to in ESKD as evidenced from some studies. The strong emotional influence, including grief and loss, apparent in the literature for patients, family and health professionals, suggests that there is a real need for education and support in relation to palliative care planning for each of these groups. To do this effectively further rigorous studies are needed to provide a stronger evidence base upon which to advise patients and their families when faced with impending dialysis. Some countries such as the UK, USA, Italy and Canada are well advanced in providing treatment guidelines and resources once dialysis withdrawal is planned but a greater focus on the pre-dialysis phase is required. Multidisciplinary nephrology teams must ensure that patients and their families are accurately informed so they can choose between dialysis and conservative treatment supported by palliative care. The inclusion of palliative care guidelines for Australian nephrology through the CARI guidelines should be considered.

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Editorial

Renal palliative care in Australia: Time to engage

The number of patients with end-stage kidney disease (ESKD) is growing, with a disproportionate increase among those who are elderly, dependant and with multiple comorbidities. The annual acceptance rate for renal replacement therapy in Australia is rising with the highest prevalence dialysis groups being the 65–74 year age cohort (24%) and those over 75 years (24%).[1] In the past 5 years the greatest percentage increase in acceptance onto dialysis has been in the over 85 age group. Dialysis technology and nursing skills have improved to such a degree that there are few limitations to the ability to commence dialysis irrespective of age or comorbidities. However, in conjunction with this change in practice, there is increasing recognition among nephrologists and renal service providers that dialysing those with increasing dependency and multiple comorbidities may not improve their survival and may in fact adversely affect their quality of life. Indeed, 37% of deaths on dialysis are now due to 'social' causes, predominantly following withdrawal from dialysis.[1]

The timely review by Fassett and colleagues in this issue of the Journal[2] provides an excellent review of available literature and emphasizes the potential benefits of palliative care within renal medicine. The authors state that 'patients and their families may be unwilling or unable to choose not to commence (dialysis) treatment or to withdraw from it and therefore information about palliative care options is an important inclusion in pre-dialysis education; and ..... discussion of a conservative approach supported by palliative care should be offered to those particularly of advanced age and/or with multiple co-morbidities'. In an interesting USA editorial entitled 'Geriatric renal palliative care is coming of age', Swidler points out that 'although dialysis is life-sustaining therapy and extends life, it may also create, increase or prolong suffering while not restoring or maintaining well-being, function or cognition'.[3]

Australian nephrology services need to first acknowledge the shortcomings of dialysis with respect to supporting quality of life and second amend our service to better meet the needs of those who are dying with or without dialysis. This means the development of integrated renal palliative care support services but in Australia we lag behind similar services established in other Western countries. The reasons for this are likely to be multifactorial. First, dialysis is a therapy that generally prolongs life, thus making it difficult for nephrologists to recommend against such a treatment. Patients also assume that if a physician is willing to offer a treatment it must be beneficial. This is, however, a large assumption as few studies have been specifically devoted to addressing outcomes in elderly patients on dialysis. Of the studies that have been published, many suffer an important selection bias in that they describe only the outcomes of those who were actually treated by dialysis, with little being known about the prevalence and outcome of other elderly people for whom dialysis was withheld. Moreover, data are lacking on specific predictive factors that could help in deciding whether or not dialysis would offer pre-ESKD octogenarians, or indeed those with significant comorbidities at any age, a substantial prolongation of life expectancy with an acceptable quality. Fassett *et al.*[2] discuss some recent observational studies that have, within the limitations of their retrospective nature, attempted to identify these factors. These studies suggest that survival advantage on dialysis in the very elderly is lost when there is a high comorbidity score, particularly coronary disease,[4] poor functional ability and high social dependency.[5] One observational study from the UK found that although dialysis prolonged survival in patients over 70 years of age, this was at the expense of increased hospitalization and interventions and a reduced likelihood of dying at home or in a hospice setting.[6]

While the numbers of patients with stage 5 CKD are increasing, the prevalence and severity of symptoms are only just beginning to be recognized for both those who choose to dialyse and those who are managed conservatively. The poor quality of life in advanced CKD and need for symptom control is similar to that found in advanced cancer populations.[7] Unfortunately, in the absence of an integrated renal palliative care service, the current reality in Australia is that many patients' symptoms are both under recognized and poorly addressed.

A significant barrier to combining renal and palliative care in Australia is that the vast majority of nephrologists have never received palliative care training or indeed had much exposure to this area of medicine; for some it is likely to be a taboo subject. This is in contrast to some other Western countries where palliative care services expanded earlier to encompass the management of chronic illnesses other than cancer, being introduced earlier in the trajectory of an illness rather than reserved for when the patient is on death's door. In Australia, there remains a poor medical and community understanding of what constitutes palliative care, the key perception being that it is only about death and dying. The WHO definition of palliative care medicine needs to be embraced as 'an approach which improves the quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.'[8]

With the anticipated increase in the number of elderly people with multiple comorbidities presenting with advanced chronic kidney disease, there is urgency about

developing formalized renal conservative care pathways that encompass patient and family education, symptom management protocols, advance care planning and ultimately bereavement support. The current CARI guidelines state that 'an expectation of survival with an acceptable quality of life is a useful starting point for recommending dialysis':[9] while these guidelines recognize that supportive care is another option for patients with ESKD, using palliative care services at this early stage is not yet recommended, although analogous studies in lung cancer suggest that it should be.[10]

If embraced early palliative care medicine may improve the huge symptom burden of patients pursuing an active dialysis pathway. Patients and families often labour under the impression that dialysis is curative whereas in reality many endure significant symptoms that adversely impact on their quality of life. While nephrologists pay great attention to the mechanics and measurable markers of dialysis, we need to teach ourselves to better recognize the high symptom load of these patients and consider an integrated palliative care approach even while they are actively dialysing.

A renal palliative care service can, as Fassett *et al.*[2] address, provide excellent care and support of the patient and their family during the difficult phase of withdrawal from dialysis.

If we are to make serious progress in this field we first need data that allow us to discuss not only quantity but also likely quality of life for dialysis patients of various age and comorbidities. Importantly, nephrologists need to take the lead. Research in the area of advance care planning shows that patients expect this from us; we need to work as a team that directs patients and their families towards the best mode of care, be it to dialysis or a conservative non-dialysis pathway.

Finally, resources and education are paramount. It will be another generation before there are anywhere near sufficient palliative care doctors to provide these services. In fact, with the increasing recognition of palliative care as a specialty involved in the expert management of patients' symptoms, there will be a calling for such doctors in many fields of medicine, no longer just in cancer care, nor just nephrology. Therefore, nephrologists will need to become expert themselves in palliative care medicine as it applies to renal medicine. This will require training for many of us who have had limited, if any, exposure to this field. We need to focus on ensuring that the next generation of nephrologists in Australia and New Zealand are all trained in this field. Sadly, the current curriculum does not provide for this but at least it's not yet set in concrete!

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ORIENTEERING

Integrating Palliative Care for Patients with Advanced Chronic Kidney Disease:

Recent advances, remaining challenges

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INTRODUCTION

More than 87,000 patients with end-stage renal disease (ESRD) die each year in the United States (1). This reflects an elderly patient population with substantial comorbidity. The median age of incident dialysis patients is 65. The population aged 75 and older is the largest group, having nearly doubled since 1997 (1). While dialysis prolongs life for most patients, life expectancy remains poor, with overall one- and five-year mortality rates of 25 percent and 60 percent, respectively. Dialysis patients often experience existential distress (2, 3), and the burden of physical and psychosocial symptoms is high (4-8). The number and the severity of their symptoms — such as pain, nausea, anorexia, shortness of breath, insomnia, anxiety, and depression — rival those of many cancer patients (9). It is therefore not surprising that an increasing number of patients are dying after withdrawal of dialysis (10 to 15 percent in 1990, and 20 to 25 percent in 2005) (1). Unfortunately, most patients are not involved in these decisions, as they lack decision-making capacity at the time the decision to withdraw dialysis is made (10). The vast majority of patients die in acute care facilities without accessing palliative care services (11), and current end-of-life practices are not consistent with patient preferences (12). It is now widely recognized that palliative care principles must be integrated into the routine care of these patients (13). Unfortunately, there remains a lack of evidence to help us determine how best to deliver that care. This review highlights recent advances in renal palliative care and suggests how new knowledge can be integrated into routine care for chronic kidney disease (CKD) patients. Remaining challenges that should be prioritized in future research will also be discussed.

THE DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES AND A FRAMEWORK FOR RENAL PALLIATIVE CARE

As research and evidence on end-of-life issues in ESRD accumulated, the clinical practice guideline Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis was developed to assist nephrologists, patients, and families in reaching decisions on whether to initiate or stop dialysis (14). The guideline includes recommendations for estimating and communicating prognosis, advance care planning (ACP) with clarification of goals of care, and renal palliative care. It has created greater awareness in the North American renal community of the need to incorporate palliative care principles into routine CKD care, and nephrologists who are knowledgeable about the guideline report greater preparedness to make end-of-life decisions (15). In the United Kingdom, a framework has recently been published that is aimed at achieving high-quality end-of-life care for patients with advanced CKD (16). It builds on national work to develop and implement end-of-life clinical pathways for all patients and to initiate timely ACP and link renal care with primary and palliative care services.

However, considerable variation in end-of-life care practices remains, and most nephrologists still feel inadequately prepared to deal with the numerous end-of-life challenges inherent in the care of their patients (15, 17). With the increasing awareness of the need for a more systematic approach to renal palliative care, a framework (Figure 1) is emerging to guide and support health professionals, patients, and families as ESRD patients approach the end of life. This framework encompasses care beginning early in the illness trajectory, often at the time of CKD diagnosis, and

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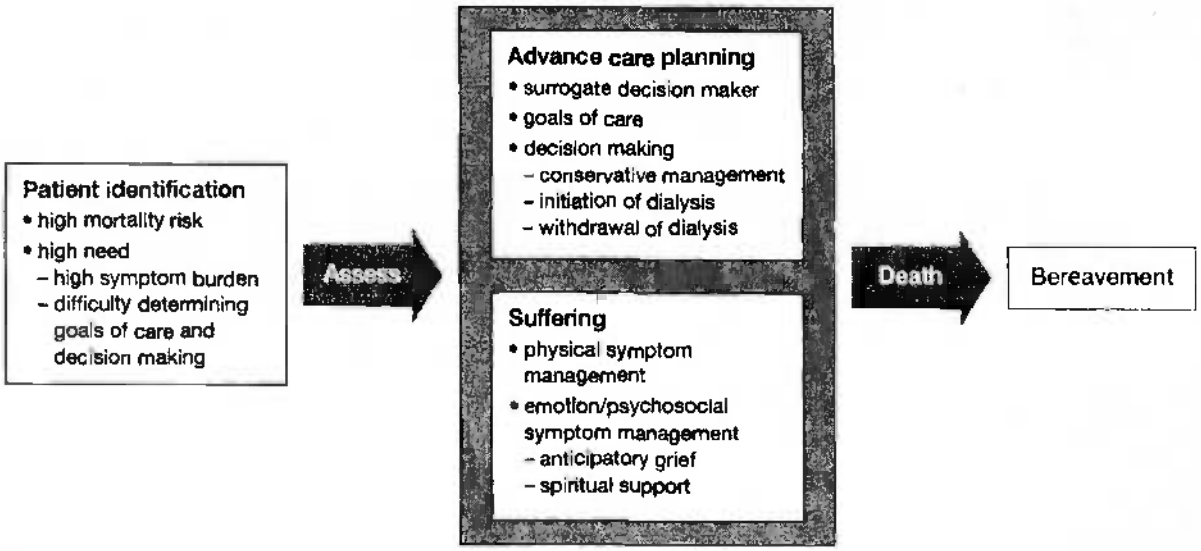
Figure 1 / **End-of-Life Care Framework for Patients with Advanced Chronic Kidney Disease**



it continues throughout its course to include terminal care and bereavement. It highlights the need to: identify those patients most likely to benefit from palliative care interventions, engage in ACP, clarify goals of care, consider treatment options such as conservative management (withholding dialysis), engage in shared decision making about appropriate and timely withdrawal of dialysis, relieve suffering (physical, psychosocial, and spiritual), and, where appropriate, refer to hospice.

IDENTIFYING CKD PATIENTS WITH HIGH PALLIATIVE CARE NEEDS

The success of a renal palliative care program will depend, to a large extent, on its ability to prospectively identify patients who need supportive and palliative care. Not all ESRD patients require palliative care: some have minimal comorbidity and/or are eligible for kidney a transplant, which, if they obtain it, would substantially change their health-related quality of life (HRQL) and mortality risk. However, at some point, most patients will move onto a trajectory of progressive functional decline associated with complex clusters of physical and psychological symptoms. Unfortunately, the illness trajectories of ESRD patients appear particularly heterogeneous (18, 19). The physical, psychosocial, and spiritual needs of patients and their carers will likely vary according to the illness trajectory. Predicting and understanding the function and symptom trajectories of an illness may contribute to the timely and effective planning of palliative services; it will assist health care professionals to provide care aligned with patient preferences and to prevent crises as patients approach the end of life. The UK Gold Standards Framework includes a prognostic indicator guide to enable better identification of patients who need supportive and palliative care (20). Within the renal palliative care framework, this would include, at minimum, patients at high risk of death within the next year and those experiencing significant suffering, whether physical, psychosocial, or spiritual.

Prognostication

Prognostication is inherently difficult. Even for patients close to death, it has historically been poor. While traditional risk factors for mortality in ESRD — such as increased age, low serum albumin, poor functional status, and comorbidity — have been identified, they have not proven clinically useful in prospectively identifying individual patients at high risk of mortality within the next year. Simple and more accurate instruments for prognostication are required.

A modified Charlson Comorbidity Index (CCI) that takes into account age (Table 1) has been applied to dialysis patients. CCI scores of ≥8 have been used to identify a subpopulation of patients with approximately a 50 percent one-year mortality rate (21, 22); scores of ≥8 have been used to identify patients who may be appropriate for palliative care assessment (23).

One of the most simple and useful clinical tools proposed recently to identify dialysis patients at a high risk for early mortality is the "surprise question" (SQ): "Would you be surprised if this patient were to die in the next 12 months?" The intent of the SQ is to counter the tendency of physicians to overestimate prognosis. Instead of asking clinicians whether a patient will be dead in one year, it

asks them whether they think that the patient dying within one year is within the realm of possibility. The SQ has been asked by both nephrologists and nurses, and it has been found effective in identifying dialysis patients who have higher comorbidity scores, who have lower performance status scores, and who are 3.5 times more likely to die within one year (24).

Unfortunately, neither the CCI nor the SQ alone is sufficiently sensitive or specific to identify individuals at high risk of early mortality. A recently developed integrated prognostic model for prevalent hemodialysis patients has taken prognostication a step further by combining the presence of two comorbidities, peripheral vascular disease, and dementia with the SQ and the more traditional risk factors of age and serum albumin (25). Although age, peripheral vascular disease, and dementia are components of the CCI, the full CCI was not statistically significant after controlling for age, serum albumin, and other comorbidities. The area under the curve for this prognostic model's prediction of six-month mortality was 0.87 (95 percent CI 0.82 to 0.92) in a derivation cohort of 512 prevalent hemodialysis patients and 0.80 (95 percent CI 0.73 to 0.88) in a validation cohort of 514 prevalent hemodialysis patients. The model also predicts 12- and 18-month mortality, although the accuracy of these predictions has yet to be described. This tool is available online (http://touchcalc.com/calculators/sq) and as an application for hand-held devices (www.qxmd.com). Whether it can be extended to peritoneal dialysis patients is not yet known.

These prognostic approaches have not been applied to incident dialysis patients who may be at risk for early mortality. Data from the French Renal Epidemiology and Information Network (REIN) registry was used to develop a scoring system, similar to the CCI, which uses comorbidity to predict six-month survival in patients 75 and older starting chronic dialysis (26) (Table 2). I will discuss this further when I address conservative management.

The vast majority of ESRD patients appear to have high levels of disability during the last year of life, and functional decline often signals shortened survival; it acts as a sentinel event that can be readily observed and measured (19). Making an assessment with a modified Karnofsky activity scale or screening activities of daily living have been shown to be simple and reliable ways to independently identify ESRD patients at risk for early death (27, 28). Performing these actions may enhance the approaches to prognostication mentioned earlier.

Table 1 / Scoring for the Modified Charlson Comorbidity Index

Points				
1 point each for coronary artery disease, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes				
1 point for every decade over 40 (for example, a 64-year-old would receive 3 points)				
2 points each for hemiplegia, moderate-severe renal disease (including being on dialysis), diabetes with end-organ damage, cancer (including leukemia or lymphoma)				
3 points for moderate-severe liver disease				
6 points each for metastatic solid tumour, AIDS				
Score totals	**low**	**moderate**	**high**	**very high**
	(≤3)	(4-5)	(6-7)	(≥8)
Annual mortality rate	**3%**	**13%**	**27%**	**49%**

Table 2 / Scoring for the Renal Epidemiology and Information Network (REIN) Prognostic Model

Comorbidity points							
1 point each for diabetes, dysrhythmia, active malignancy							
2 points each for body mass index <18.5 kg/m², congestive heart failure stages III to IV, peripheral vascular disease stages III to IV, severe behavioural disorder, unplanned dialysis start							
3 points for total dependency for transfers							
Score totals	**0**	**1**	**2**	**3-4**	**5-6**	**7-8**	**≥9**
6-month mortality rate	**8%**	**10%**	**17%**	**21%**	**33%**	**50%**	**70%**

Screening of Patients with Physical, Psychosocial, and Spiritual Distress

Clearly, patients who suffer from physical, psychosocial, and spiritual distress can also benefit from supportive care interventions, regardless of their predicted survival time. Identifying these patients is a priority within the renal supportive and palliative care framework. A growing body of literature demonstrates that approximately 50 percent of ESRD patients, regardless of their age, experience chronic pain; as many as 82 percent report this pain as moderate to severe (5, 7, 29, 30). In fact, the number and severity of symptoms, including pain, reported by patients, whether treated with dialysis or managed conservatively, is similar to that reported by many cancer patients in palliative care settings (6, 9, 29). Unfortunately, pain in ESRD is both under-recognized (31) and under-treated (5, 32). Research suggests that symptom burden is more important than objective clinical parameters in determining HRQL in ESRD patients (33, 34). Dialysis patients with chronic pain are two to three times more likely to suffer

from depression and insomnia than patients without chronic pain (35). Symptom burden accounts for 29 percent of the impairment in their physical HRQL and 39 percent of the impairment in their mental HRQL (6). Similarly, changes in symptom burden have been shown to account for 34 percent and 46 percent of the changes in physical and mental HRQL, respectively (36). ESRD patients typically experience chronic pain in the context of multiple other debilitating symptoms, such as anorexia, fatigue, nausea, insomnia, pruritus, anxiety, and depression, as well as end-of-life issues, all of which may interfere markedly with psychosocial and physical coping strategies. These findings reinforce the importance of integrating effective clinical approaches to symptom assessment and management.

The modified Edmonton Symptom Assessment System (mESAS) is a reliable, simple, useful, and valid method for regular physical and psychological symptom screening in CKD (6, 36). This tool was adapted from the Edmonton Symptom Assessment System (ESAS), which is a widely used tool for measuring symptom distress in cancer patients (37). The ESAS consists of nine visual analog scales with a superimposed 0-to-10 scale for pain, activity, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. To address the symptom burden experienced by CKD patients, the ESAS was modified by adding pruritus and insomnia. While the intervention goal is to improve HRQL, symptoms such as anorexia, pruritus, and depression (38, 39) have been associated with the risk of early mortality. Whether interventions aimed at reducing symptom burden will reduce mortality is unknown and is an area for future research.

Spiritual distress in ESRD has not been as well researched, but single screening questions such as "Are there any spiritual concerns you would like to address or discuss with a member of the health care team?" can serve as a gateway to larger discussions and a more profound spiritual assessment of those who indicate distress (2, 3).

Implementation of Strategies for Prospectively Identifying CKD Patients with High Palliative Care Needs

Given the large number of patients most renal programs care for and the complex nature of their illness, identification strategies need to be simple and systematically integrated so assessments can be completed quickly and easily. The assessment will also have to be appropriate for the patient's degree of comorbidity, frailty, and cognitive impairment. The SQ, mESAS, modified Karnofsky, and single spiritual distress question are all simple assessments that can be easily integrated into routine clinical practice with limited staff and patient burden. When combined with routinely available information such as comorbid conditions, age, and serum albumin, these assessments should provide nephrology programs with an effective way to identify those patients more likely to require supportive and palliative care. Predicted survival probabilities for a given patient do not need to be recorded on the medical chart or communicated in detail to the patient and health care team if this would be inappropriate. Rather, this information can be used solely as a tool to identify patients with predefined mortality risks, such as a predicted 6- or 12-month mortality rate of 50 percent or greater.

Such an approach to identifying high-needs patients has yet to be evaluated at a program level. The indicators must be interpreted with clinical judgment for each individual. The approach can, however, help alert the health care team to shifts in illness trajectory and to the presence of supportive and palliative care needs. The more accurate health care teams become in their prognostication, the better their chances of meeting the needs of patients and their families during the patients' final months of life.

CONSERVATIVE MANAGEMENT

Conservative management entails choosing active disease management (such as treatment of anemia, metabolic bone disease, or electrolyte abnormalities) and aggressive palliative care while opting not to start chronic dialysis. There is a growing understanding that initiating conservative management does not signal imminent death, and that conservatively managed patients can remain stable for long periods. However, during the period shortly before and after the initiation of dialysis, there is a high risk of accelerated rates of functional and cognitive decline and/or death (1, 40). Therefore, for some patients, the initiation of dialysis confers neither an HRQL nor a survival advantage.

The challenge has been to identify those patients for whom conservative management is the most effective option for promoting their goals. This is one of the most important areas in renal palliative care that requires further research. Almost all available data on conservative management come from Europe — in particular, the UK. It was recently shown that the survival advantage of dialysis for patients 75 and older was lost among those with high comorbidity scores, especially ischemic heart disease (41). These conservatively managed patients had one- and two-year survival rates of 68 percent and 47 percent, respec-

tively, once glomerular filtration rates (GFR) dropped below 15 ml/min. Another study of 29 conservatively managed patients with a mean age of 81.6 showed a mean survival rate of 13.9 months after a putative dialysis start date (GFR of 10.8 l/min) (42). Unfortunately, comparative data for conservative management and chronic dialysis are lacking. However, if predicted survival time after initiating dialysis (using prognostic models such as the REIN) is less than six months, there is less likely to be a significant survival advantage of chronic dialysis over conservative management, and HRQL factors will likely take precedence.

How initiation of dialysis affects functional status and HRQL is a highly relevant issue to consider in determining the benefits of dialysis versus conservative management. Dialysis patients have one of the highest prevalence rates for frailty of any single population; 67.7 percent of all dialysis patients meet criteria for frailty, with the maximal prevalence of 78.8 percent among patients older than 80 years (43). Frailty is strongly associated with increased morbidity, hospitalization, and early mortality (43). Patients with significant functional impairment, poor HRQL, and/or multiple comorbidities might have little to gain and potentially something to lose from dialysis. For some of these patients, conservative management may be more appropriate. A recent retrospective analysis of a national registry of nursing home residents in the United States showed that the initiation of dialysis was associated with a substantial and sustained decline in functional status (40). Mortality rates were 24 percent in the first three months after dialysis initiation, and 58 percent at 12 months. Among the survivors, there was a substantial decline in functional status, particularly within the first three months. By 12 months, 87 percent of patients had either died or had experienced functional decline; only one in eight had maintained functional status. A Canadian study reported that 30 percent of patients over 80 years of age experienced functional loss and required assistance or transfer to long-term care facilities within the first six months of starting dialysis (44). The true extent of functional decline was likely underestimated, as there was no formal assessment of functional status. This is a considerably higher rate than that reported in the literature, where it is indicated that less than 20 percent of frail-elderly (non-dialysis) patients require nursing home care within 18 months of hospital discharge (45). Similarly, maintenance dialysis was not able to return inner-city patients 65 years and older to their pre-dialysis level of functioning (46). Because there were no controls in these studies, these data cannot tell us whether dialysis was the cause of functional decline or whether it conferred a survival advantage. At minimum, however, these data suggest that for most elderly and nursing home patients, the initiation of dialysis does not restore or even maintain functional status. The current clinical practice guideline suggests that appropriate criteria for conservative therapy include patient or surrogate wishes, profound neurologic impairment, the presence of a non-renal terminal condition with an estimated prognosis of less than six months, or a medical condition that precludes the technical process of dialysis (47). While age, comorbidity, and functional status are not listed as criteria for withholding dialysis, they clearly impact patient survival and HRQL, and, therefore, they are factors to be considered in discussions with patients and their families prior to initiating dialysis (48).

ADVANCE CARE PLANNING

ACP has not been routinely integrated into the care of CKD patients. Most nephrologists do not convey prognosis or have end-of-life discussions with their patients, even though most patients want them to do so (12, 49). Most dialysis patients are unaware of their poor likelihood of survival following cardiopulmonary resuscitation (CPR) (50), and relatively few issue a do-not-resuscitate order (51). In fact, most dialysis patients do not issue advance directives. Those who do tend to address only limited treatment options and typically do not indicate health states in which they would no longer wish to continue dialysis (52, 53). Despite this, 20 to 25 percent of North American patients withdraw from dialysis prior to death (1). The majority of patients lack decision-making capacity at the time the decision to withdraw dialysis is made, so such decisions usually fall to staff or family (10). Unfortunately, neither family members nor physicians can accurately predict patients' desires for life-sustaining treatments, including dialysis (54-56). In a Japanese study of 398 paired subjects — a dialysis patient and a family member — only 50 percent of the family members correctly predicted the patients' preference for CPR; 44 percent predicted the preference for dialysis in a severely demented state, and 47 percent predicted the preference for dialysis in the event of terminal cancer. The corresponding figures for physicians were 44 percent, 47 percent, and 43 percent (57).

With informed consent and shared decision making that balances beneficence, non-maleficence, and justice, withdrawal from dialysis is ethically and clinically acceptable (13). ACP should include discussions about health states in which patients would no longer wish to continue dialy-

sis. Advanced age, comorbid conditions, poor functional status, gender, ethnicity, and compromised HRQL all influence the decision to stop dialysis (58). It is incumbent upon all those caring for a patient contemplating withdrawal to address remedial factors contributing to the decision to stop dialysis.

There are no standards governing when to initiate or how to facilitate ACP for patients with advanced CKD. Major barriers to initiating end-of-life discussions include the concern that these conversations will diminish hope, a lack of accurate prognostic tools, inadequate training in how to conduct discussions, and a lack of evidence that clearly demonstrates the impact of ACP on end-of-life care.

Patients are often less concerned than physicians that end-of-life care discussions will damage hope. Many dialysis patients will have already considered end-of-life options (59-61) and would welcome the opportunity to engage in these discussions with their nephrologists (49, 59, 60, 62). Their hope appears as much related to how medical interventions can assist them in sustaining valued roles and relationships in their daily lives as it is to survival statistics (59). Regardless, one study reported that 97 percent of CKD patients wanted their nephrologists to give them life-expectancy information and to do so without having to be prompted (49). Research has shown that open, honest discussion with dialysis patients about prognosis and end-of-life care promotes self-reliance, alleviates fear and uncertainty, and reinforces trust and hope (59). Varying amounts of time are required for this process to be effective. Research is underway to determine whether communicating prognosis using the integrated prognostic model described earlier will positively impact ACP and ultimately end-of-life care.

Teaching staff the skills to facilitate ACP will be critical to the success of any ACP initiative. A 2003 survey of second-year nephrology fellows revealed that only 22 percent had been taught how to tell a patient that he or she is dying; 32 percent had conducted two or fewer family meetings, and 26 percent of all family meetings occurred without an attending nephrologist (63). Dialysis patients' preferences regarding how the health care team facilitates ACP have recently been explored (64). This has lead to the development of new tools to guide facilitated ACP in ESRD (65). Some health regions are beginning to systematically integrate ACP into their nephrology programs, and online resources are available to help staff, patients, and family members (66). Skill-based training programs, such Respecting Choices, are also available (67).

The timing of end-of-life discussions is important. Cognitive impairment affects patients' ability to meaningfully participate in shared decision making. Murray and colleagues showed that 73 percent of 338 dialysis patients had either moderate or severe cognitive impairment on formal testing (68). Only 2.9 percent of these patients had a documented history of cognitive impairment. Unpredictable illness trajectories and progressive cognitive decline highlight the importance of initiating early ACP with ongoing communication and re-evaluation throughout the illness trajectory to ensure that end-of-life crises are avoided and decisions are consistent with patients' wishes (69). Ideally, these discussions will be included in the education process that occurs when patients are presented with dialysis options. Research suggests that dialysis patients would support this approach (49, 59). Sentinel events (hospitalization, acute illness, and decline in functional status) present additional opportunities to engage in ACP.

Policy may aid in successfully implementing ACP. Failure to accompany patients across sites of care limits the effectiveness of advance directives. The Physician Orders for Life-Sustaining Treatment (POLST) Paradigm program (70) was developed in Oregon to ensure that patient treatment preferences are honoured. It does so by converting patients' treatment preferences into medical orders that are transferable throughout the health care system. POLST orders regarding CPR were universally accepted in a study of 180 nursing home residents. These patients had remarkably high levels of comfort care and low rates (15 percent) of transfer for aggressive life-extending treatments (71). When POLST forms were used in the hospice setting, preferences for treatment limitations were respected in 98 percent of cases, and no one received unwanted CPR, intubation, intensive care, or feeding tubes (70). The POLST program is being advocated for ESRD patients, although it has yet to be evaluated in this context (13).

How effective ACP can be in improving the quality of end-of-life care for ESRD patients remains to be established. However, a recent randomized controlled trial of facilitated ACP using the Respecting Choices program demonstrated that the end-of-life wishes of trial participants were much more likely to be known and followed than those of a control group (86 percent versus 30 percent, $p<0.001$) of medical in-patients aged 80 or more (72). There is also evidence that using disease-specific ACP for patients with ESRD can increase surrogate understanding of patient goals (73).

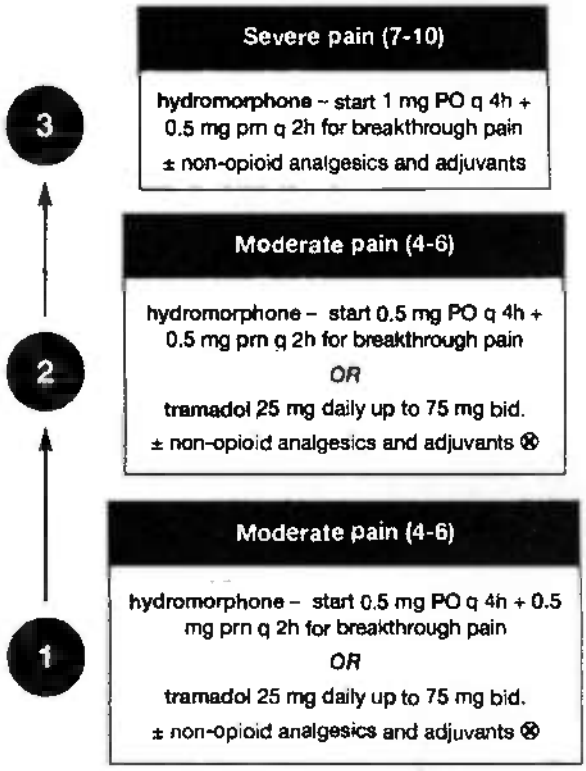
PAIN MANAGEMENT

With the development of symptom assessment tools and research into the prevalence and impact of chronic pain in CKD, there has been greater focus on pain management. Effectively treating pain is an integral component of chronic disease management as well as palliative care; and screening all ESRD patients is important, given the high prevalence of chronic pain, regardless of age, comorbidity, or predicted survival time. The Centers for Medicare and Medicaid Services partially funded the Mid-Atlantic Renal Coalition to convene an expert panel consisting of researchers and clinicians from across North America and the United Kingdom with the goal of developing a clinical algorithm for the treatment of chronic pain in CKD (74). This algorithm is increasingly being adapted and utilized by nephrology programs across North America. It includes a pain assessment tool, an overview of the essentials of pain management, an adapted World Health Organization analgesic ladder, specific recommendations for the appropriate use of several opioids and adjuvant analgesics, and a brief review of the management of common opioid adverse effects. These are tools that can be implemented in predialysis and dialysis clinics.

The UK has also established renal-specific terminal symptom algorithms as part of the Liverpool Care Pathway (75, 76), an integrated tool, implemented across the UK, that was designed to be used by those caring for patients in their last days of life. These algorithms can be used across health care settings to better manage terminal symptoms for patients in hospitals, long-term care facilities, hospices, or nursing homes.

While advances have clearly been made over the past few years with respect to pain management in CKD, research is still required on the impact of these algorithms on functional status and overall HRQL, as well as on the management of the numerous other symptoms experienced by CKD patients. Alternative analgesic approaches are required for patients who are unable to tolerate opioids (the adverse effects of opioids are more likely to occur in people with kidney failure). Research is underway to assess the effectiveness of cannabinoids in controlling pain while simultaneously addressing other symptoms, such as nausea, vomiting, anorexia, insomnia, and pruritus.

Figure 2 / Adapted World Health Organization Three-Step Analgesic Ladder for Patients with Advanced Chronic Kidney Disease



PRN dosing for breakthrough pain: titrate to ~10% of the 24-hour dose of opioid prescribed every 1 to 2 hours as needed.

*Do not exceed 3.2 g/day of acetaminophen to avoid hepatotoxicity as per FDA recommendations. In high-risk patients (malnourished, alcoholic), limit to 2.6 g/day.

** Adjuvants include medications such as anticonvulsants for neuropathic pain. They can also be agents administered to manage adverse effects of an opioid. This includes anti-emetics or laxatives.

HOSPICE CARE

Hospices are recognized for providing excellent end-of-life care, but few dying ESRD patients receive it, even following withdrawal from dialysis (11). Based on the United States Renal Data System, it was determined that only 13.5 percent of 115,239 dialysis patients in the US who died between January 1, 2001 and December 31, 2002 used a hospice. Of these patients, 21.8 percent withdrew from dialysis; in this subset, 41.9 percent used a hospice. Only 22.9 percent of dialysis hospice patients died in hospital, compared with 69.0 percent of non-hospice patients ($p < 0.001$). In the US, a poor understanding of Medicare ESRD benefits and Medicare hospice benefits contributes to the low referral rate of dialysis patients to hospice (77). If the terminal diagnosis that results in referral to hospice care is unrelated to the ESRD diagnosis, then both Medicare benefits can be paid while the patient continues with chronic dialysis. Of those patients who withdraw from dialysis, approximately 96 percent will die within one month. Enhanced knowledge about the eligibility of dialysis patients to use hospice services and further research on the benefits and cost-effectiveness of hospice care for dialysis patients are needed to increase hospice utilization (77).

SUMMARY

Patients with ESRD have extensive and unique end-of-life care considerations and needs. Despite substantial advancements in renal palliative care over the past decade, much research is still required. Identifying CKD patients whose illness trajectory has shifted and would likely benefit from a palliative approach to care should be a priority of all nephrology programs. Further research on symptom management, the effectiveness of ACP, the life expectancy of conservatively managed and incident dialysis patients, anticipated changes in functional status and HRQL with the initiation of dialysis (especially among the frail elderly), and the best way to deliver renal palliative care is required to maximize the integration and effectiveness of renal palliative care services.

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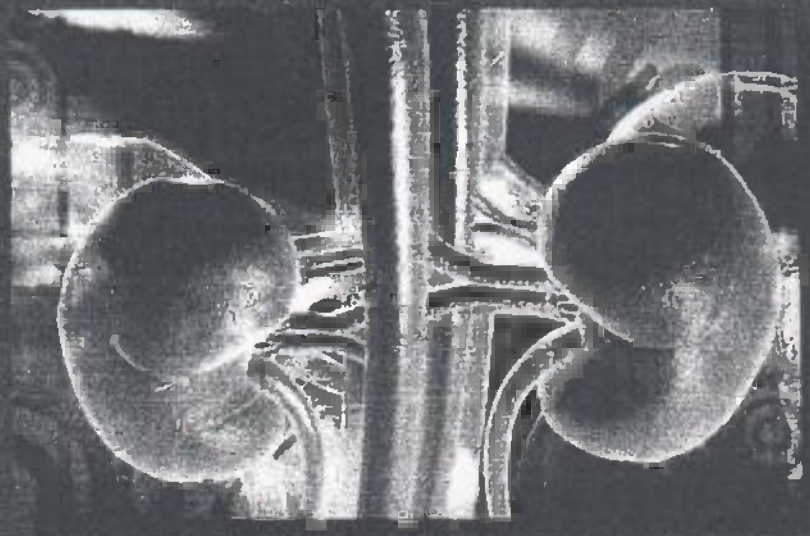
Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis

Clinical Practice Guideline

Second Edition



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Renal Physicians Association

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RECOMMENDATION SUMMARY

These recommendations are based on the expert consensus opinion of the RPA Working Group. They used a priori analytic frameworks regarding decisions to withhold or withdraw dialysis in adult and pediatric patients with AKI, CKD, and ESRD. Systematic literature reviews were conducted to address pre-specified questions derived from the frameworks. The research evidence, case and statutory law, and ethical principles were used by the Working Group in the formulation of their recommendations.

Adult Patients

Establishing a Shared Decision-Making Relationship

Recommendation No. 1

We recommend a shared decision-making physician-patient relationship.

Because of the number and complexity of decisions involved in treatment of kidney failure, such a relationship is important for patients with acute kidney injury (AKI), stage 4 and 5 chronic kidney disease (CKD), and stage 5 CKD requiring dialysis, referred to in this guideline as end-stage renal disease (ESRD). Participants in shared decision-making should involve at a minimum the patient and the physician. If a patient lacks decision-making capacity, decisions should involve the person legally authorized to make health care decisions on behalf of the incapacitated patient. This person is often (though not always) a family member and will be called "the legal agent" in the remainder of this document (see the glossary for a full description). With the patient's consent, shared decision-making may include family members or friends and other members of the renal care team.

Informing Patients

Recommendation No. 2

We recommend that physicians should fully inform AKI, stage 4 and 5 chronic kidney disease (CKD) and ESRD patients about their diagnosis, prognosis, and all treatment options.

These options include: 1) available dialysis modalities and kidney transplantation if applicable, 2) not starting dialysis and continuing medical management, 3) a time-limited trial of dialysis, and 4) stopping dialysis and receiving end-of-life care. Choices among options should be made by patients or, if patients lack decision-making capacity, their designated legal agents. Their decisions should be informed and voluntary. The renal care team, in conjunction with the primary care physician, should insure that the patient or legal agent understands the benefits and burdens of dialysis and the consequences of not starting or stopping dialysis. Research studies have identified a population of chronic

kidney disease patients for whom the prognosis is particularly poor. This population has been found to include patients with two or more of the following characteristics: 1) elderly (defined by research studies identifying poor outcomes in patients equal to or greater than 75 years); 2) patients with high comorbidity scores (e.g., modified Charlson Comorbidity score equal to or greater than 8); 3) marked functional impairment (e.g., Karnofsky performance status score < 40); and 4) severe chronic malnutrition (e.g., serum albumin level < 2.5 g/dL using the bromcresol green method). Patients in this population should be informed that dialysis may not confer a survival advantage or improve functional status over medical management without dialysis and that dialysis entails significant burdens which may detract from their quality of life.

Recommendation No. 3

We recommend that all patients with AKI, stage 5 CKD or ESRD receive patient-specific estimates of prognosis.

To facilitate informed decisions about starting dialysis for AKI, stage 5 CKD, or ESRD, all patients should have their prognosis estimated, with the realization that the ability to predict survival in the individual patient is limited. Depending on the setting, a primary care physician, intensivist, or nephrologist who is familiar with estimating and communicating prognosis should conduct these discussions (See recommendation #10 for communication strategies). For patients with ESRD, the "surprise" question "Would I be surprised if this patient died in the next year?" can be used together with known risk factors for poor prognosis: age, comorbidities, severe malnutrition, and poor functional status. For patients with stage 5 CKD pre-dialysis, the estimate of prognosis should be discussed with the patient or legal agent, patient's family, and among the medical team members to develop a consensus on the goals of care and whether dialysis or active medical management without dialysis should be used to best achieve these goals. These discussions should occur as early as possible in the course of the patient's kidney disease and continue as the kidney disease progresses. For ESRD patients on dialysis who experience major complications that may substantially reduce survival or quality of life, it is appropriate to reassess treatment goals, including consideration of withdrawal from dialysis.

Facilitating Advance Care Planning

Recommendation No. 4

We recommend advance care planning.

The purpose of advance care planning is to help the patient understand his/her condition, identify his/her goals for care, and prepare for the decisions that may have to be made as the condition progresses over time. For chronic dialysis patients, the interdisciplinary renal care team (see glossary for definition of renal care team) should encourage patient-family discussion and advance care planning and include advance care planning in the overall plan of care for each individual patient. The renal care team should designate a

person to be primarily responsible for ensuring that advance care planning is offered to each patient. Patients with decision-making capacity should be *strongly* encouraged to talk to their legal agents to ensure that the legal agent knows the patient's wishes and agrees to make decisions according to these wishes.

The renal care team should attempt to obtain written advance directives from all dialysis patients and where legally accepted Physician Orders for Life-Sustaining Treatment (POLST), or similar state-specific forms, should be completed as part of the advance care planning process. At a minimum, each dialysis patient should be asked to designate a legal agent in a state-specific advance directive. Advance directives should be honored by dialysis centers, nephrologists, and other nephrology clinicians except possibly in situations in which the advance directive requests treatment contrary to the standard of care (see the recommendation on conflict resolution).

Making a Decision to Initiate or Discontinue Dialysis

Recommendation No. 5*

It is appropriate to forgo (withhold initiation or withdraw ongoing) dialysis for patients with AKI, CKD, or ESRD in certain, well-defined situations.

These situations include the following:

Patients with decision-making capacity, who being fully informed and making voluntary choices, refuse dialysis or request that dialysis be discontinued

Patients who no longer possess decision-making capacity who have previously indicated refusal of dialysis in an oral or written advance directive

Patients who no longer possess decision-making capacity and whose properly appointed legal agents/surrogates refuse dialysis or request that it be discontinued

Patients with irreversible, profound neurological impairment such that they lack signs of thought, sensation, purposeful behavior, and awareness of self and environment

*Medical management incorporating palliative care is an integral part of the decision to forgo dialysis in AKI, CKD, or ESRD, and attention to patient comfort and quality of life while dying should be addressed directly or managed by palliative care consultation and referral to a hospice program (see recommendation #9).

Recommendation No. 6

It is reasonable to consider forgoing dialysis for AKI, CKD, or ESRD patients who have a very poor prognosis or for whom dialysis cannot be provided safely.

Included in these categories of patients are the following:

- Those whose medical condition precludes the technical process of dialysis because the patient is unable to cooperate (e.g., advanced dementia patient who pulls out dialysis needles) or because the patient's condition is too unstable (e.g., profound hypotension)
- Those who have a terminal illness from non-renal causes (acknowledging that some in this condition may perceive benefit from and choose to undergo dialysis)
- Those with stage 5 CKD over the age of 75 who meet two or more of the following statistically significant very poor prognosis criteria (see recommendations no. 2 and 3): 1) clinicians' response of "No, I would not be surprised" to the surprise question; 2) high comorbidity score; 3) significantly impaired functional status such as Karnofsky Performance Status score less than 40, and 4) severe chronic malnutrition (serum albumin <2.5 g/dL using the bromcresol green method).

Resolving Conflicts about What Dialysis Decisions to Make

Recommendation No. 7

For patients requiring dialysis, but who have an uncertain prognosis, or for whom a consensus cannot be reached about providing dialysis, we recommend the consideration of a time-limited trial of dialysis.

If a time-limited trial of dialysis is conducted, the nephrologist, the patient, the patient's legal agent, and the patient's family (with the patient's permission to participate in decision-making) should agree in advance on the length of the trial and parameters to be assessed during and at the completion of the time-limited trial to determine if dialysis has benefited the patient and if dialysis should be continued.

Recommendation No. 8

We recommend a systematic due process approach for conflict resolution if there is disagreement about what decision should be made with regard to dialysis.

Conflicts may occur between the patient/ legal agent and the renal care team about whether dialysis will benefit the patient. Conflicts may also occur within the renal care team or between the renal care team and other health care providers. In sitting down and talking with the patient/legal agent, the nephrologist should try to understand their views, provide data to support his/her recommendation, and correct misunderstandings. In the process of shared decision-making, the following potential sources of conflict have been recognized: 1) miscommunication or misunderstanding about prognosis, 2) intrapersonal or interpersonal issues, or 3) special values. If dialysis is indicated emergently, it should be provided while pursuing conflict resolution, provided the patient or legal agent requests it.

Providing Effective Palliative Care

Recommendation No. 9

Palliative care services and interventions should be offered to all AKI, CKD, and ESRD patients who suffer from burdens of their disease in an effort to improve patient-centered outcomes.

These services are appropriate for people who chose to undergo or remain on dialysis and for those who choose not to start or continue dialysis. With the patient's consent, a multi-professional team with expertise in renal palliative care--including nephrology professionals, family or community-based professionals, and specialist hospice or palliative care providers--should be involved in managing the physical, psychological, social, and spiritual aspects of treatment for these patients, including end-of-life care. Physical and psychological symptoms should be routinely and regularly assessed and actively managed. The professionals providing treatment should receive training in assessment and management of symptoms and in advanced communication skills. Patients should be offered the option of dying where they prefer, including at home with hospice care, provided there is sufficient and appropriate support to enable this option. Support should also be offered to patients' families, including bereavement support where appropriate. Dialysis patients for whom the goals of care are primarily comfort should have quality measures distinct from patients for whom the goals are aggressive therapy with optimization of functional capacity.

Recommendation No. 10

We recommend a systematic approach for communication about diagnosis, prognosis, treatment options, and goals of care.

Good communication improves patients' adjustment to illness, increases adherence to treatment, and results in higher patient and family satisfaction with care. Patients appreciate sensitive delivery of information about their prognosis and the ability to balance reality while maintaining hope. In communicating with patients, the critical task for clinicians is to integrate complicated biomedical facts and conditions with emotional, social, and spiritual realities that are equally complex but not well described in the language of medicine. This information must be communicated in a way that patients, legal agents, and families can understand and use to reach informed decisions about dialysis and transplantation options. Patients' decisions should be based on an accurate understanding of their condition and the pros and cons of treatment options. Shared decision-making depends upon this effective, empathic communication, but research shows that nephrologists are not prepared to communicate in this manner in their fellowship training.

Section 4. Guideline Recommendations and Their Rationales for the Treatment of Adult Patients

Establishing a Shared Decision-Making Relationship

Recommendation No. 1

We recommend a shared decision-making physician-patient relationship.

Because of the number and complexity of decisions involved in treatment of kidney failure, such a relationship is important for patients with acute kidney injury (AKI), stage 4 and 5 chronic kidney disease (CKD), and stage 5 CKD requiring dialysis, referred to in this guideline as end-stage renal disease (ESRD). Participants in shared decision-making should involve at a minimum the patient and the physician. If a patient lacks decision-making capacity, decisions should involve the person legally authorized to make health care decisions on behalf of the incapacitated patient. This person is often (though not always) a family member and will be called "the legal agent" in the remainder of this document (see the glossary for a full description). With the patient's consent, shared decision-making may include family members or friends and other members of the renal care team.

Rationale

The recommended process by which health care professionals and patients come to agreement on a specific course of action is shared decision-making. It is based on a common understanding of the goals of treatment and the risks and benefits of the chosen course compared with any reasonable alternative.[1] Ethical principles supporting this process include respect for patient autonomy, beneficence, and nonmaleficence. Observational evidence indicates that shared decision-making, especially the legal requirements for full disclosure and informed decisions, is often not achieved in the dialysis setting.[2-6] (Level B Observational Evidence) Many patients initiating dialysis receive or perceive inadequate information and may not understand the information they do receive, despite the fact that most dialysis occurs in the setting of progressive CKD where the prognosis is known well before the actual need for dialysis arises.[2,6-11] (Level B Observational Evidence)

A factor that could limit patients' understanding of information presented to them and their participation in shared decision-making is cognitive impairment which is severe enough to cause dialysis patients to lose decision-making capacity. Studies have found a high prevalence of cognitive impairment in certain populations of dialysis patients. In two studies in which the dialysis patients were randomly selected, cognitive impairment was found in 30 and 35 percent respectively.[12,13] In a study of dialysis patients aged 55 years and older, cognitive impairment was found in 87 percent. It was mild in 14 percent, moderate in 36 percent, and severe in 37 percent.[14] The authors of these studies recommend cognitive testing before dialysis initiation and periodically thereafter. The tool kit in this guideline contains three instruments for assessing dialysis patients for cognitive impairment: the Montreal Cognitive Assessment Test, the Trail Making Part B test and the Short Memory Questionnaire (does not require manual skills on the part of the patient and uses reliable informant to assess cognitive ability).

It is important for physicians treating patients with chronic kidney disease to identify cognitive impairment because patients with moderate to severe impairment are likely to lack decision-making capacity and be unable to meaningfully participate in shared decision-making. For those patients without decision-making capacity, the physician should identify the patient's legal agent and involve him or her in decision-making, including advance care planning. Because of the progression of cognitive impairment over time, earlier and more frequent advance care planning is recommended for the dialysis population.[15] See recommendation #4 for additional discussion of the process of ensuring that each patient has a legal agent who can make health care decisions if the patient is unable to do so.

Informing Patients

Recommendation No. 2

We recommend that physicians should fully inform AKI, stage 4 and 5 chronic kidney disease (CKD) and ESRD patients about their diagnosis, prognosis, and all treatment options.

These options include: 1) available dialysis modalities and kidney transplantation if applicable, 2) not starting dialysis and continuing medical management, 3) a time-limited trial of dialysis, and 4) stopping dialysis and receiving end-of-life care. Choices among options should be made by patients or, if patients lack decision-making capacity, their designated legal agents. Their decisions should be informed and voluntary. The renal care team, in conjunction with the primary care physician, should insure that the patient or legal agent understands the benefits and burdens of dialysis and the consequences of not starting or stopping dialysis. Research studies have identified a population of chronic kidney disease patients for whom the prognosis is particularly poor. This population has been found to include patients with two or more of the following characteristics: 1) elderly (defined by research studies identifying poor outcomes in patients equal to or greater than 75 years); 2) patients with high comorbidity scores (e.g., modified Charlson comorbidity score equal to or greater than 8); 3) marked functional impairment (e.g., Karnofsky performance status score < 40); and 4) severe chronic malnutrition (e.g., serum albumin level < 2.5 g/dL using the bromcresol green method). Patients in this population should be informed that dialysis may not confer a survival advantage or improve functional status over medical management without dialysis and that dialysis entails significant burdens which may detract from their quality of life.

Rationale

There is widespread consensus that patients with decision-making capacity should participate in medical decisions if they so choose.[16-23] Competent patients have an absolute right to accept or refuse medically indicated treatment. This recommendation is supported by the ethical principle of respect for patient autonomy. Case law requires informed consent or refusal, and state and federal statutes provide for advance directives as written legal documents to be used to make decisions for patients when they lose decision-making capacity. Most states have health care surrogate acts that provide for the selection and authority of a surrogate decision maker when the patient lacks decision-making capacity and has not completed a written advance directive. Treating physicians are ethically and legally obligated to insure that these decisions are well-informed and documented. Observational studies show that patients infrequently think about

end-of-life issues, discuss them with family, friends, or the renal care team, or complete advance directives.[3-5,7,24-29] (Level B Observational Evidence) Dialysis patients may discuss advance directives more with their families than physicians, but 50 to 90% report no or inadequate discussions with health care professionals about therapeutic options including forgoing dialysis.[2-11,20,30,31] (Level B Observational Evidence) Observational studies show most patients want information about their medical conditions and many (75-90%), though not all, desire to participate in care decisions.[2,5,7,8,20,25,32-37] (Level B Observational Evidence) A review of shared decision-making in non-dialysis patient populations suggests that increased patient involvement in decision-making can lead to more fully informed consent, shared responsibility for treatment decisions, improved patient compliance, increased patient satisfaction, improved outcomes, and an overall increase in the quality of care.[38]

Elderly (equal to or greater than 75 years) patients with stage 4 or 5 CKD constitute a special group for whom the informed consent process regarding initiation of dialysis requires special consideration of the risk:benefit ratio. Because of the severe comorbidities, functional impairment, and malnutrition of some elderly CKD patients, research shows that nephrologists should not take an "age neutral" approach to the management of CKD patients.[39] On the other hand, age alone should not constitute a contraindication to starting dialysis since comorbidity is the single most important determinant of outcome in dialysis patients.[40-43] Age and comorbidity are additive in predicting dialysis patient survival. Thus, prior to placement of an arteriovenous access or peritoneal dialysis catheter, elderly patients with stage 4 or 5 CKD and severe comorbidities should be specifically informed that

1) dialysis may not confer a survival advantage;

2) patients with their level of illness are more likely to die than live long enough to progress to ESRD;

3) life on dialysis entails significant burdens which may detract from their quality of life;

4) it is likely that they may not experience any functional improvement with dialysis and that they may undergo significant functional decline during the first year after dialysis initiation;[44-46]

5) the burdens of dialysis include surgery for vascular or peritoneal access placement and complications from the vascular access or peritoneal dialysis catheter; and

6) they may experience adverse physical symptoms on dialysis such as dizziness, fatigue, and cramping, and a feeling of "unwellness" after dialysis.

Further, patients need to be informed that there will be travel time and expense to and from dialysis, long hours spent on dialysis, and a reduction in the time available for physical activity.[46,47] Dialysis may entail an "unnecessary medicalization of death" resulting in invasive tests, procedures, and hospitalizations.[48]

In one study, elderly patients with significant comorbidity treated with dialysis as opposed to medical management without dialysis were more than four times as likely to die in the hospital as at home and spent 47.5 percent of the days they survived either in the hospital or at the dialysis clinic.[49] Such patients should be informed that medical management without dialysis is an acceptable alternative that may better achieve patients' goals of care. It is active treatment which entails advance care planning, implementation of patients' goals, and management of

anemia, bone disease, fluid balance, acidosis, and blood pressure. Multiple studies report a median survival ranging from 6.3 to 23.4 months for patients managed medically without dialysis.[49-52]

Box 1. Suggested Steps for Implementing Recommendation Nos. 1 and 2.

- Identify provider(s) who will coordinate communication with the patient or legal agent and family (e.g., nephrologist in conjunction with the primary care provider for ESRD patients or intensivists for AKI).
- Assess patient decision-making capacity and whether it is diminished by major depression, encephalopathy, or other disorder (see tool kit section for helpful instruments). Obtain psychiatric and/or neurological consultation as appropriate, and institute treatment for conditions impairing decision-making capacity.
- Communicate diagnosis to patient (or legal agent) and family (if the patient agrees).
- Discuss prognosis based upon patient's medical condition, comorbidities, functional status, and age (see tool kit section for information about assessing functional status and quality of life, and estimating prognosis).
- Identify the patient's wishes.
- Communicate options, taking advantage of educational resources, such as other patients or videotapes and brochures.
- If the patient wants to forgo dialysis, determine why.
  - Are the patient's perceptions about dialysis accurate? Does the patient know what to expect if dialysis is not started or discontinued?
  - Does the patient really mean what he/she says or is the decision to refuse or stop dialysis made to get attention, help, or control?
  - Are there changes that might improve quality of life and would the patient be willing to start or continue dialysis while the factors responsible for the patient's request are addressed?
  - Are there persons (e.g., social worker, chaplain) with whom the patient would be willing to discuss the decision?

  (Also, see tool kit for NKF checklist on withdrawing dialysis.)
- Reach decision based on medical indications and patient's preferences.
- Encourage patient to discuss end-of-life issues with others such as family, friends, or spiritual advisors (see tool kit section for helpful questions to use).
- Refer for palliative care and hospice as appropriate.

Recommendation No. 3 (See Appendix for Tables and Figures)

We recommend that all patients with AKI, stage 5 CKD or ESRD receive patient-specific estimates of prognosis.

To facilitate informed decisions about starting dialysis for AKI, stage 5 CKD, or ESRD, all patients should have their prognosis estimated, with the realization that the ability to predict survival in the individual patient is limited. Depending on the setting, a primary care physician, intensivist, or nephrologist who is familiar with estimating and communicating prognosis should conduct these discussions (See recommendation #10 for communication strategies). For patients with ESRD, the "surprise" question "Would I be surprised if this patient died in the next year?" can be used together with known risk factors for poor prognosis: age, comorbidities, severe malnutrition, and poor functional status. For patients with stage 5 CKD pre-dialysis, the estimate of prognosis should be discussed with the patient or legal agent, patient's family, and among the medical team members to develop a consensus on the goals of care and whether dialysis or active medical management without dialysis should be used to best achieve these goals. These discussions should occur as early as possible in the course of the patient's kidney disease and continue as the kidney disease progresses. For ESRD patients on dialysis who experience major complications that may substantially reduce survival or quality of life, it is appropriate to reassess treatment goals, including consideration of withdrawal from dialysis.

Rationale

Acute Kidney Injury (AKI)
Effect of AKI on Prognosis and Decision-making

The nephrologist can play a critical role in determining the aggressiveness of care for patients with AKI. AKI requiring renal replacement therapy provides a natural break point in the escalation of care. Discussions regarding the patient's ability to withstand dialytic therapy can give family members a feeling that "everything" reasonable has been done to provide for the recovery of the patient. Multiple prospective and retrospective studies have documented intensive care unit (ICU) and in-hospital mortality rates of approximately 50 to 75% for patients with AKI receiving dialysis.[53-102] (Level A Prognostic Evidence) Medical and surgical patients had roughly similar mortality rates in these studies. A recent meta-analysis demonstrated the long-term morbidity and mortality after AKI.[103] The one retrospective study in bone marrow transplant patients showed a mortality rate of 85% with AKI-requiring dialysis and variable mortality risks depending on the type of bone marrow transplant.[104] In a prospective study of acute kidney injury cases requiring dialysis in an intensive care unit, life support withdrawal occurred in many more AKI deaths (72%) than in intensive care unit patients who did not have AKI (40-50%).[105] In one large intensive care unit study, AKI requiring dialysis was found often to reflect the severity of underlying illness, impact overall survival negatively, and be associated with more frequent withdrawal from life support.[106] Recovery from AKI is low in patients discharged to a long-term care hospital while still requiring dialysis. In a study of 110 patients with AKI requiring dialysis who were admitted to a long-term care hospital, only 30 percent regained kidney function and were able to stop dialysis. Patients who did not recover renal function were significantly older and had higher baseline creatinine levels.[107]

Prognosis Tools for Patients with AKI

Mortality prognosis can be quantified using routinely available measurement tools and scoring systems.[60,98,100,101,108-131] Development of such measurement tools and prognostic scores has involved various multivariate modeling techniques and testing of over 75 potential prognostic variables. Variables most often independently associated with increased mortality have been

liver failure, mechanical ventilation, and multiorgan failure.[53,54,56-58,61,101,132] Two retrospective and three prospective studies, with sample sizes ranging from 100 to 500, have shown prognostic models do not have better than 80 to 85% discriminating ability in identifying individual patients with poor prognosis.[54-57,60]

In dialysis-dependent patients with AKI, general scoring systems may underestimate mortality risk.[133-135] Recognizing the inability to precisely predict individual prognosis, the Working Group supported provision of gross estimates of prognosis based on the belief that this information facilitates realistic patient and family expectations and promotes informed decision-making. Time-limited trials of dialysis for AKI with goals and parameters to be assessed agreed upon in advance allow the physicians and family to determine if dialysis has benefited the patient and if dialysis should be continued.

Recovery Rate from AKI

Collective studies are inconclusive regarding the rate of recovery from AKI. Several studies report dialysis-free rates of approximately 70% to 90% among survivors of AKI that required renal replacement therapy.[53,57,58,61,62,67,71,78-81,85,86,99,136,137] (Level B Prognostic and Observational Evidence) Most of these studies were small, retrospective, and only followed patients to hospital discharge. Two more recent clinical trials have shown widely disparate rates of recovery of kidney function ranging from 75% to 95% at 2-3 months of follow up.[137,138] Complete recovery of kidney function to within 0.5 mg/dL of baseline serum creatinine concentration at 28 days after the initiation of renal replacement therapy was observed in fewer than 30% of patients surviving an episode of severe AKI in one clinical trial.[104] Adequate evidence regarding how many patients recover normal function and how long it takes for them to recover function was not found. In a study by Wald, the risk of developing ESRD after an episode of AKI requiring dialysis was 2.63/100 person years, nearly triple that of the control group (0.91/100 person years) who did not have AKI.[139] (Figure 1 & Table 1). The Working Group recommended that patients with AKI who no longer require dialysis but who still have significant kidney dysfunction continue to be followed by a renal care team. The follow-up care should be individualized to the patient's needs and community resources. It may be provided by the patient's primary care physician in conjunction with a renal care team. The Working Group agreed that patients with AKI of duration greater than two months have a strong likelihood of ESRD. They should be told that they have ESRD and counseled accordingly within six months and asked to repeat back this information to ensure their understanding.

When Discussions of Prognosis Should Occur in Chronic Kidney Disease Patients

Although with some patients it is difficult to predict if their CKD will progress to ESRD, the majority of patients have relatively slow disease progression allowing sufficient time for counseling about treatment options. These counseling sessions should occur prior to the time that dialysis is absolutely necessary. Furthermore, late referral to nephrology may prevent the nephrologist from developing the therapeutic relationship needed to achieve a consensus regarding the goals of care until *after* the patient starts dialysis. Several studies suggest that 40-70% of patients with ESRD are either not referred to nephrologists prior to commencing dialysis or have emergent first dialysis sessions (rather than electively planned first sessions) and/or are using a venous catheter for dialysis access.[37,140-144] Data from USRDS patients beginning dialysis in 1996 showed 33% and 21% of patients were first seen by a nephrologist < 3 months and < 1 month, respectively of beginning dialysis.[145] Recent Dialysis Outcomes and Practice Patterns

Study (DOPPS) data demonstrated a mortality hazard ratio of 0.65 for patients seen by a nephrologist > 1 month prior to starting dialysis.[144] The French Renal Epidemiology and Information Network study[143] and others found negative consequences of an unplanned start for dialysis.[146-148] (Level B Prognostic Evidence) If the patient has already begun dialysis, a discussion about prognosis during the Comprehensive Assessment Process and development of the Plan of Care should begin as soon as the nephrologist and the other members of the renal care team determine the patient and/or legal agent can engage in meaningful conversation. With the patient's consent, the family should be encouraged to participate in the Plan of Care discussion. The occurrence of sentinel events (see below) should also prompt further discussion of prognosis, values, preferences, and treatment goals.

Special Prognostic Considerations for Stage 4 and 5 CKD

Recent studies have shed light on the poor prognosis of many CKD patients. Studies have demonstrated that CKD patients are more likely to die than to reach dialysis, due to increasing cardiovascular mortality with higher stages of CKD.[39,149,150] In one study, patients greater than 85 years of age had no baseline glomerular filtration rate at which they were more likely to progress to dialysis than die.[39] Studies of selected sicker CKD patients have usually demonstrated a small survival benefit to dialysis versus active medical management without dialysis but not uniformly so.[41,48,49,51,52,151,152] (Table 2) In a study by Murtagh, patients greater than 75 years of age with ischemic heart disease or greater than 1 comorbidity had no survival benefit from dialysis.[52] (Figure 2) Likewise, in a study of patients with more comorbidities and lower functional status who had been recommended a non-dialytic approach to management but chose dialysis instead, no significant survival advantage was shown.[48] (Level B Observational Evidence)

ESRD

Estimating Prognosis for Survival

Many studies report the effect of prognostic factors on survival for patients with ESRD on dialysis, but most of these studies in large databases (United States Renal Data System, Dialysis Outcomes and Practice Patterns Study) are investigating variables that may point to potentially treatable causes of increased mortality. Furthermore the survival time frame is often >1 year. The working group was interested in identifying patients with an estimated prognosis of less than or equal to 12 months for the purpose of distinguishing patients who want to continue dialysis but have a poor prognosis and who are more likely to benefit from a predominantly comfort and symptom management approach to care as opposed to patients who want an aggressive treatment approach that focuses on prolonging life and optimizing function. This is not to say that pain and symptom management and advance care planning are not important to patients receiving an aggressive approach to treatment, but the point of the distinction is to identify patients for whom the goals of care are focused on reducing suffering more than on prolonging life. Eventual referral to hospice would be an appropriate near-term consideration for dialysis patients with a poor prognosis. It is assumed that all potentially treatable conditions have been addressed in these patients, and that the factors causing the poor prognosis are not reversible.

Magnitude of risk conferred by individual risk factors can be estimated from existing data with increasing numbers of risk factors conferring increasing risk. Comparison of relative risks or hazards between studies in this literature poses a challenge. Diversity in studies includes both retrospective and prospective data collection, wide variation in number of patients observed

(anywhere from less than 20 to 150,000), and wide variation in data sources (single dialysis facilities, multicenter studies, commercial dialysis chains, and regional and national registries).

Other sources of variation include the type of population enrolled in each study, length of follow-up, and how deaths are designated. In the U.S. most, but not all, studies exclude the first 90 days of dialysis and so exclude deaths and withdrawals within this same time frame. Some studies enroll incident patients (patients who start dialysis in a defined time period) only while most enroll both prevalent (patients who are already being treated with dialysis for a variable amount of time prior to the start of the study) and incident patients. Length of follow-up can be as short as six months and as long as 20 or more years. Results from the studies may be reported annualized or within the time frame of the observations. Withdrawal is not always reported as a cause of death. On the CMS 2746 Death Notification form (revised in 2004), "withdrawal yes/no" is a separate item from cause of death. In addition uremia/withdrawal is listed as a cause of death. In the United States annually about 25% of patients withdraw from dialysis before death, and this number has been increasing over the past 10 years.[153] The rate of withdrawal varies by age (higher in the elderly), ethnicity (lower in blacks) and geographic region.[145,153,154] In a recent Dialysis Outcomes and Practice Patterns Study in which withdrawal from dialysis was assessed in the first 120 days of starting dialysis (when the majority of withdrawals occur), the predictors of early mortality were no longer valid after dialysis withdrawal deaths were censored.[144] This suggests that the very high early mortality in incident dialysis patients is not "caused" by withdrawal, and that it is likely that many patients who die in the first few months of dialysis had limited prospects for survival or quality of life benefit from dialysis.

Age is a powerful and consistent risk factor for death. For 1-year increments in age beginning at age 18, there is a remarkable consistency of risk ratios (RR) between 1.03 and 1.04 or a 3 to 4% increase in death rate per additional year of age.[153-168](Level A Prognostic Evidence) The effect of age is illustrated in Tables 3 and 4.[169] In comparison to the U.S. population as a whole, dialysis patients have remaining lifetimes that are on average only one-fourth as long as non-dialysis patients of the same age and gender. Survival is significantly better in ESRD patients of all age groups after renal transplantation.

Although there has been a small but consistent decrease in mortality (in particular from cardiovascular causes) in prevalent hemodialysis patients over the past 20 years (Figure 4 & Figure 5) there has been little improvement in survival of incident patients in the first 6-12 months of dialysis.[169] The 30-120 day mortality rates remain extraordinarily high particularly in the elderly.[169] (Figure 5) In the first 3 months after starting dialysis mortality rates have risen from 1993 to 2005.

Serum albumin level, both at baseline and during the course of dialysis treatment, is a consistent and strong predictor of death with multiple studies showing a statistically significant relationship.[153,155-158,160,161,168,170-181] (Level A Prognostic Evidence) The lower the serum albumin level, the higher the risk of death.[182] (Figure 7) For example, an albumin of <3.0 grams per deciliter (g/dL) versus >4.0 g/dL confers a 4.4 times greater risk of early death.[170] An albumin level <3.5 g/dL is associated with one year mortality of approximately 50%.[156,170,172,176,183,184] (Level A Prognostic Evidence) A more recent large study from 2008 in incident dialysis patients from 1995 to 2004 with CMS 2728 forms completed supports the prognostic value of serum albumin. It demonstrates that serum albumin levels have declined over time in the incident US ESRD population and confirms the previously reported strong

association with the first value after starting dialysis and mortality. With case-mix adjustment, incident dialysis patients with an initial serum albumin less than 2.5 g/dL have an odds ratio of dying in 1 year more than 3 times greater than patients with a serum albumin equal to or greater than 4 g/dL.[185]

Apart from the serum albumin, other nutritional status markers are also powerful predictors of survival. Numerous markers of nutritional status have been studied: "cachexia"(provider assessment, not further defined), "undernourished"(documentation in the medical records of these words), obesity (based on information in the medical record from between one month prior to the onset of ESRD to six weeks after the first treatment), body mass index, subjective global assessment of nutritional status (per the method of Baker and Detsky),[186,187] protein catabolic rate, skin fold thickness, and creatinine level. Cachexia, poor subjective global assessment of nutritional status, and "undernourished" all convey a significantly elevated risk of death.[160,164,165,168,181,188] (Level B Prognostic Evidence)

Recently the malnutrition inflammatory complex syndrome (MICS) has been shown to predict short-term mortality.[189] (Tables 5 & 6) In one study, the MIS (malnutrition inflammation score), Charlson Comorbidity Index, and C-reactive protein (CRP) level were superior to the serum albumin in predicting 12 month mortality.[189] The MIS takes into account dry weight change in the past 3-6 months, gastrointestinal symptoms/appetite, functional capacity, years on dialysis and severe comorbidities (congestive heart failure, AIDS, severe coronary artery disease, moderate to severe chronic obstructive pulmonary disease, metastatic cancer, and major neurologic conditions), muscle wasting, loss of fat stores, body mass index, serum albumin, and total iron binding capacity. Interleukin 6 and tumor necrosis factor were also measured, and although correlated with mortality, in the multivariate analysis they did not add prognostic value to the above factors.[189]

Other laboratory values that correlate with malnutrition-inflammation and are predictors of short-term mortality are low serum cholesterol and low serum low phosphorus.[144,189] Vitamin D levels and use of Vitamin D also have shown an association with mortality.[190]

High serum troponin,[191,192] beta-natriuretic peptide (BNP),[193-195] low blood pressure, use of a venous catheter for dialysis access,[196] and unplanned start of dialysis[144] are also short-term mortality predictors.

Poor functional status is highly predictive of early death (relative risk ranges of 1.5 to 3).[153,158,160,170,171,174,177,179,180,197-203] (Level A Prognostic Evidence) Fifteen of 16 studies reporting functional status show worse functional status is associated with early death. In studies where functional status and comorbidity are both measured, functional status sometimes displaces comorbidity in the multivariate analyses. A potential explanation of this finding may be that comorbidity measures are highly variable with regard to the manner in which they are defined and may not always capture severity. Functional status captures the severity of disability the patient is experiencing from whatever comorbid illness she or he may have. Measures of functional status used in these studies include ability to ambulate (yes/no)[160,165,171,204] mild-severe mobility impairment,[170] Karnofsky or modified Karnofsky scale,[153,174,177,180,198-200,205,206] Gutman functional status,[198] Activities of Daily Living,[297,201] and the Medical Outcomes Study 36-item Short Form (SF-36).[203] Frailty scores also correlate with increased mortality.[207] In most studies, functional status was assessed by the health care providers rather than the patients, who may rate their quality of life higher. The Karnofsky Performance Status scale is included in the Appendix.

In particular the inability to transfer and falls are indicators of a poor prognosis.[208] Dialysis in nursing home residents is associated with a marked decline in functional status at 1 year (only 13 percent maintained baseline function) and a 58 percent mortality.[46] In another study of dialysis patients age 80 years or older, the initiation of dialysis was found to be marked by functional loss requiring community or private caregiver support or transfer to a nursing home in 30 percent of patients by 6 months. At the end of a year, 22 percent of patients remained independent, 31 percent were supported, and 44 percent were dead.[45]

Comorbidity is the single most important determinant of outcome in ESRD patients on dialysis.[40] Multiple comorbid illnesses are related to risk of death on dialysis. These have been studied individually and aggregated into overall comorbidity scores. Unfortunately, definitions of congestive heart failure, ischemic heart disease, cardiovascular disease, etc. vary significantly from one study to the next. Despite these methodological shortcomings, comorbid illness must be taken into account in counseling patients about their prognosis. Scoring systems run the gamut from simply noting the presence of at least one comorbid illness,[163,209,210] to grading the comorbidity burden,[154] to using aggregations of ICD-9 codes from hospitalizations.[211] One study specifically developed a severity of illness index for patients with ESRD.[211] In all of these studies, having comorbid illness conferred higher risk although the magnitude of relative risk varied widely 1.11 to 12.8.(Level A Prognostic Evidence). The Charlson Comorbidity Index and modification of the Charlson Comorbidity Index for ESRD have good predictive value (Level A Prognostic Evidence).[212-214] In chronic dialysis patients, a Charlson Comorbidity Index score of equal to or greater than 8 has been shown to be associated with about a 50 percent one-year mortality.[215]

Numerous comorbid conditions have been studied for their effect on survival: diabetes, congestive heart failure (CHF), coronary artery disease (CAD), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), and cancer. Diabetes conferred a higher mortality risk in the majority of cohorts in which it was studied.[153,155,160,162,164,167,173,176,178,188,198,199,202,216-221] (Level A Prognostic Evidence) Some studies find diabetes' significance diminishes when laboratory abnormalities are included in multivariate models.[161,176] A few studies have explored whether having Type 1 or Type 2 diabetes confers more risk. After controlling for age, at least two studies suggest that Type 1 DM confers a significantly higher risk of death.[165,166,222] Most studies found CHF to be predictive of poorer survival, with a relative risk anywhere from 14% to 84% higher than those without CHF.[153,155,167,168,170,223] (Level A Prognostic Evidence) Numerous different names and definitions are used to describe the category of CAD (cardiovascular illness, angina, ischemic heart disease, CAD, cardiovascular comorbidity, heart disease, and vascular disease). These syndromes are inconsistently associated with increased mortality: seven studies showed no significant impact[153,155,165,168,171,202,217,219] and 14 studies showed an increased risk of anywhere from 26% up to 780%.[160,162,164-166,168,170,171,179,181,183,188,198,220,224] (Level A Prognostic Evidence) In 6 of 7 studies, PVD conveyed an increased risk of death between 11 and 862%.[153,155,160,168,171,181,223] (Level A Prognostic Evidence) Cancer confers anywhere from 30 to 250% increased risk of death.[153,162,164,170,171,202,203] (Level A Prognostic Evidence) The variability probably relates to the type of cancer that is lumped together within this variable. COPD confers an increased risk of 14 to 44%.[153,155,161,167-171,173,223] (Level A Prognostic Evidence)

The most consistent comorbid factors that predict less than 12 month survival are New York Heart Association class 4 heart failure, moderate to severe COPD, severe PVD, dementia, severe

behavioral conditions, acquired immunodeficiency syndrome, and metastatic cancer. Quality of life scores, depression, pruritus, and restless leg syndrome also correlate with poor outcomes.[225-234]

Predicting Who Will Die Within the First Year on Dialysis: Eleven articles[41,42,144,170,235-240] specifically address issues in predicting early mortality and a number of other articles give data covering the first 90 to 180 days. In a prospective incident cohort, Barrett[239] found that although a scoring system using age and comorbidity did predict prognosis, no score cutoff point combined high true-positive and low false-positive rates for predicting early death. Barrett and Chandna[42] concluded that trials of therapy may be a better idea than denying dialysis based on these results. (Level A Prognostic Evidence)

Effect of Sentinel Events on Prognosis: A few studies have addressed the specific issue of risk of death after intercurrent medical events while on dialysis. Two striking examples of events that have very high post-event mortality in ESRD patients on dialysis are acute myocardial infarction (AMI)[223] and above the knee amputation (AKA)[184,241,242] (Level A Prognostic Evidence). For both of these events survival at one year is less than 50% (38 to 44% for AMI and 27% for AKA). These events might be considered as reminders for discussions about end-of-life care and the benefits and burdens of ongoing dialysis with patients and their families. A 2009 study demonstrates the poor prognosis after strokes and pneumonia.[243,244] Survival after coronary artery bypass surgery in ESRD is much worse than an aged-matched cohort, especially when associated with PVD and CVA.[245,246] Falls (and the number of falls) in the elderly is associated with increased mortality.[208] Table 10 displays the ranges of risk estimates from these studies.

In the Dialysis Outcomes and Practice Patterns study database a number of sentinel events were associated with withdrawal from dialysis: failure to thrive, gangrene, cancer, dementia, stroke, amputation, pneumonia, CHF, myocardial infarction, and gastrointestinal bleed.[247]

Summary risks and mathematical models: Recently there have been attempts to develop and test mathematical models for identifying ESRD patients with a poor short-term prognosis.[235] An integrated prognostic model takes into account the clinician's estimate of prognosis, laboratory values, comorbidities,[41,143,212,236,248-250] changes in comorbidity score over time,[236] functional status/fragility, quality of life,[225-229] and possibly the patient's prediction of prognosis.[251] Two recent studies have supported the value of this approach. The simple "surprise question" is a strong indicator of 6-12 month mortality[251] (Figure 3). Cohen and colleagues developed and validated a mathematical model for estimating patient survival at 6 months which used the surprise question, serum albumin, age, and presence or absence of two comorbidities: dementia and peripheral vascular disease. This model had a receiver operating curve (ROC) of .82.[252] Use of large databases[253] and results from multivariate analyses of various prognostic studies allow comparison of the magnitude of effect between risk factors. Newer statistical methods such as time-variate and additive damage models[254-256] have the potential to improve mortality risk prediction. Couchoud and colleagues developed and validated a model and scoring system from the French database in incident dialysis patients to predict 6 month mortality.[41] Independent risk factors were BMI<18.5, diabetes, CHF (stage 3,4), PVD (stage 3,4), unplanned dialysis, inability to transfer, active malignancy, and severe behavioral disorder. A point score was developed that predicted 6 month mortality with the intention to provide guidance for recommending a palliative approach to care.[41] (Tables 7 & 8)

Using the Catalonian data base Mauri and colleagues developed and validated a 12-month mortality model in incident patients based on age, sex, cause of kidney disease, physical function, COPD, liver disease, cardiovascular disease , dialysis vascular access, malnutrition, and malignancy.[152] (Table 9)

Additional approaches to improving prognostic modeling include changes to comorbidities and severity of comorbidities over time,[236] and a self-learning rules based model.[237]

These data and other studies suggest that it may be possible with further research to identify a subset of elderly patients who will not benefit from starting dialysis. Dialysis in these patients may be associated with significant morbidity, deterioration in functional capacity and quality of life, and the shortest survival. A prognosis prediction tool that incorporates the surprise question, age, comorbidities, and functional status is likely to be able to help identify these patients. Once identified, the kidney care team should engage these patients and family/legal agents in discussions of goals of care and end-of-life treatment preferences.

Box 2. Suggested Steps for Implementing Recommendation No. 3.

- Estimate prognosis based upon patient's age, functional status, medical condition, including comorbidity and recent sentinel events, and the "surprise" question. The website http://nephron.com provides a calculator for use of the surprise question response and other variables to estimate prognosis in dialysis patients. There is not the same degree of precision of tools to estimate prognosis for patients with AKI.
- Present the prognosis in a manner that is considerate of the patient's emotional condition, balance the patient's desire for quality and quantity of life, and provide reassurance that the physician has kept the patient's best interest in mind. With the patient's permission, strongly encourage the patient's legal agent/family to participate in the discussion of prognosis and treatment options. See recommendation #10 for suggested approaches to discussing prognosis, treatment options, and goals of care with AKI, CKD, and ESRD patients.
- Identify patient's wishes and goals for treatment at onset of dialysis and again after any irreversible change in medical condition.
- Reassess and communicate prognosis on at least an annual basis, and more often as indicated by any major change in status.
- For CKD and ESRD patients, during each annual Comprehensive Assessment and Plan of Care discussion, communicate appropriate options based on the patient's condition, prognosis, and goals for care. Regardless of choice, palliative care should be offered for pain and symptom management and advance care planning. Hospice referral is appropriate for ESRD patients stopping dialysis.
- Provide recommendation to withhold/stop dialysis in patients who are not likely to benefit
- If conflicts arise in shared decision-making, consider palliative care or ethics consultation (see recommendation #8).

Facilitating Advance Care Planning

Recommendation No. 4

We recommend advance care planning.

The purpose of advance care planning is to help the patient understand his/her condition, identify his/her goals for care, and prepare for the decisions that may have to be made as the condition progresses over time. For chronic dialysis patients, the interdisciplinary renal care team (see glossary for definition of renal care team) should encourage patient-family discussion and advance care planning and include advance care planning in the overall plan of care for each individual patient. The renal care team should designate a person to be primarily responsible for ensuring that advance care planning is offered to each patient. Patients with decision-making capacity should be *strongly* encouraged to talk to their legal agents to ensure that the legal agent knows the patient's wishes and agrees to make decisions according to these wishes.

The renal care team should attempt to obtain written advance directives from all dialysis patients and where legally accepted Physician Orders for Life-Sustaining Treatment (POLST), or similar state-specific forms, should be completed as part of the advance care planning process. At a minimum, each dialysis patient should be asked to designate a legal agent in a state-specific advance directive. Advance directives should be honored by dialysis centers, nephrologists, and other nephrology clinicians except possibly in situations in which the advance directive requests treatment contrary to the standard of care (see the recommendation on conflict resolution).

Rationale

Goals of care discussions are an inherent part of advance care planning and necessary prior to completion of advance directives. Goals of care discussions for the AKI, CKD, and ESRD patient, broadly defined, should be explicit about: 1) whether cure is feasible (where the main aim will be achieving that cure), 2) whether life can realistically be extended with acceptable functional capacity, 3) whether the principal goals of care in a patient who wants to start or continue dialysis are life prolongation and comfort, and 4) whether the patient prefers a natural death without life-sustaining treatment (active medical management without dialysis-see the glossary for an expanded explanation). The key times of transition are likely to include: 1) when active medical management without dialysis is being considered in stage 5 CKD; 2) preparation for and transition onto dialysis; 3) clinical physical and/or cognitive deterioration despite dialysis, associated with increasing dependency; and 4) consideration of withdrawal from dialysis and likely referral to hospice.

Advance care planning is a patient-centered, comprehensive, ongoing discussion among care providers and their patients and families (or the patient's designated legal agent) about values, treatment preferences, decision-makers in the event of the patient's incapacity, and goals of care[257-260] The advance care planning process includes communicating information to the patient and family about the current clinical condition, prognosis, and treatment options within the context of the patient's values and goals which will ultimately guide medical decision-making. Because one's medical condition is a primary factor influencing treatment choices[7,261] advance

care planning interactive discussions must be re-visited at critical points in a patient's care or whenever a patient or a legal agent wishes to revisit these issues.

Advance care planning is grounded in the ethical principle of respect for patient autonomy. Multiple observational studies demonstrate many, though not all, patients want to communicate about their future medical care and to discuss their preferences for care in the event they lose decision-making capacity.[5,7,8,23,25,32-37,262,263] (Level A Observational Evidence) In observational studies and opinion surveys, nephrologists report that patients' and families' preferences are very important to them in decision-making, but physicians may not know their patients' preferences or may incorrectly presume them.[21-23,91,264,265] (Level B Observational Evidence) Few physicians, nurses, and social workers on renal care teams discuss advance directives electively with patients; most discussion appears prompted by a deterioration in the patient's health status.[266,267] (Level C Observational Evidence). Patients and families generally assume physicians will introduce advance care planning discussions and usually want these discussion to occur earlier in the course of CKD than they typically do.[5,268-270] Advance care planning can facilitate the completion of written advance directives, but the advance care planning process itself can increase congruence between patient, family, and physician understanding and therefore improve satisfaction and compliance with patient preferences.[271] Key components of advance care planning (See Boxes 4 and 5) can provide a structure for the process.[268,272]

Advance directives are a legal and ethical means for communicating patients' preferences for end-of-life care to legal agents, families, renal care teams, and others. They are a mechanism for facilitating adherence to patients' end-of-life wishes by legal agents and health care providers. Advance directives flow from advance care planning and are an integral part of the process. Proxy directives (formally naming a person to make decisions in the event the patient is unable to make his or her own decisions) and instruction directives (e.g., living wills or do not resuscitate documents) are examples of advance directives. Written advance directives are always preferable to oral directives because they provide better legal protection. Some patients may not prefer or refuse written directives. In such instances, it is acceptable to obtain an oral statement with two witnesses present and to document the oral advance directive in the chart. Patients who decide to forgo dialysis should be questioned to be sure their reasons are understood and informed of the implications of their decision. Since death from cardiac arrest as a late complication of uremia is likely, patient agreement to a do-not-resuscitate/do-not-intubate order should be obtained in advance, and the patient's legal agent should be part of the discussion. Such directives and discussions will help to avoid situations in which patients lacking written advance directives have their wishes overridden by a legal agent later in their disease course.

Studies show variability in how well patients understand and trust advance care documents.[273,274] (Level C Observational Evidence) Several observational studies show that while most patients support the concept of advance directives, a minority actually complete them[3,5,26-29,261,266,275,276] (Level A Observational Evidence) and certain groups of patients and families (e.g., ethnic minorities) are less likely than others to complete advance directives.[277]

Several attempts have been made to increase the use of advance directives. The Patient Self-Determination Act (PSDA),[257] effective in 1991, mandated that health care providers advise patients of their rights to make health care decisions and to complete advance directives. The PSDA was mandated for facilities such as hospitals and nursing homes, and not specifically for

free-standing dialysis units. In 2008, in the updated Conditions for Coverage for End-Stage Renal Disease Facilities, dialysis units are required to inform dialysis patients about their right to complete advance directives and the facility's policy with regard to advance directives. Since the PSDA, one study has shown the proportion of inpatients with advance directives has not increased though documentation of their existence in the medical chart has increased from 6 to 35%.[258] (Level C Observational Evidence) Having advance directives has been correlated with having discussions with health care providers about life-sustaining therapies.[5,258] (Level C Observational Evidence) Providing patients educational material about advance directives has had variable impact on completion rates.[262,263,273,274] (Level C Observational Evidence) Physician counseling has been shown to increase frequency of specification of a health care proxy in a geriatrics clinic, and an uncontrolled multidisciplinary intervention involving social workers and volunteers stimulated 71% of frail elders to complete an advance directive, among whom 96% specified a proxy.[278] (Level C Observational Evidence). Efforts to increase the completion of advance directives have generally failed, making encouragement of advance care planning discussions among patients and families even more important. Patient-centered advance care planning can be effective in promoting shared decision-making between patients and their surrogates.[271]

Surveys show physicians in general are willing to honor advance directives,[9,21,22] but that approximately a quarter express difficulty honoring directives when the directives conflict with what they personally think is best for patients.[265] (Level C Observational Evidence) A scenario-based study of physicians at one academic center found that more specific preferences listed in advance directives were more likely to be followed.[279] (Level C Observational Evidence) Seventy-three percent of the physicians said they would be willing to withhold resuscitation based on a general advance directive, 84% based on a specific statement, and 100% if the specific statement was supported by a prior discussion and a surrogate decision maker. Unfortunately, a cohort study of advance directives showed advance directive documents rarely contained specific information to guide care.[280] (Level C Observational Evidence). Use of the Physician Orders for Life-Sustaining Treatment (POLST) has been adopted by multiple states and regions (www.POLST.org) in response to inadequacies in general written advance directives.[281] Unlike living wills (instruction directives) or documents naming legal agents (proxy directives), POLST forms are signed physician (in some states nurse practitioners are authorized to sign) orders directing treatments based on patient choice. POLST forms are especially appropriate for patients for whom the nephrologist would not be surprised if the patient died in the next year. They have shown to be effective in honoring patients' end-of-life treatment preferences in part because they ensure continuity of orders for the patient across treatment settings.[282] Where available, such documents are particularly applicable to many, if not most, CKD and dialysis patients and should be offered, completed, and honored.

Few studies have examined effects of advance care directives on clinical outcomes. A retrospective study of 182 chronic hemodialysis patients who died found those who completed advance directives were more likely to die in a planned, non-emergent fashion and to have a greater sense of control.[278] (Level C Observational Evidence) Two randomized trials and a prospective uncontrolled study have failed to demonstrate that advance care planning affects clinical outcomes, while one observational study demonstrated advance directives can be widely promulgated, successfully communicated to physicians, maintained in continuity across health care venues, and guide care at end of life. Nearly all specified preferences were followed in this

latter small homogenous community study.[283] (Level C Observational Evidence) One of the randomized trials that involved 204 sick outpatients found no differences in health outcomes, perceived well-being, patient satisfaction or health care costs between patients randomized to receive advance directive instruction versus those randomized to usual care.[284] (Level B Therapy/Prevention Evidence) A large multisite trial of 9,105 medically ill hospitalized patients (including 204 in whom decisions to withhold dialysis were sometimes made) studied interventions aimed at improving end-of-life decision-making and reducing the frequency of a mechanically supported, painful, and prolonged process of dying.[385] (Level A Therapy/Prevention Evidence) Interventions were designed to provide physicians with serial prognostic information for their patients, provide physicians with patient and surrogate responses to questions about preferences, and have specially trained nurses attempt to conduct advance care planning. The study found the following: half of the physicians misunderstood patient's preferences to forgo CPR; nearly half of DNR orders were written within two days of death; approximately a third of patients who died spent at least ten days in an ICU; and half of conscious patients who died reported moderate to severe pain at least half of the time prior to death. The intervention failed to affect any of these factors. Retrospective analysis suggested the designed intervention failed to stimulate physician-patient communication about end-of-life care.[286] A prospective uncontrolled study of written advance directives for nursing home patients found that while most life-sustaining therapy was provided in a manner consistent with patient's or surrogate decision maker's expressed preferences, there was no relationship between the written advance directive and the care provided.[287] (Level C Observational Evidence) The study also found that care in the nursing home was more likely to be in conflict with patients' wishes than care in the hospital, emphasizing the importance of transferring advance care planning between health care venues. A retrospective study of advance care planning in peritoneal dialysis patients in long-term care found that age and functional status strongly influenced plans not to hospitalize and not to attempt resuscitation but such plans did not affect patient survival.[288] Plans were established for nearly all the 109 patients in this study, and no patient with a do not attempt resuscitation order underwent unwanted cardiopulmonary resuscitation.[288] Taken together these studies show many aspects of end-of-life care, especially advance care planning, need to be improved.

Several studies suggest that nephrologists may be able to enhance communication of patients' preferences for end-of-life care by facilitating patient-family discussions of patients' specific treatment preferences and values regarding suffering.[259,273,289] The five key components in advance care planning with ESRD patients include: facilitated ACP,[272] documentation of the process and the patient's preferences, timing of the discussion, involving the optimal systems and processes for success, and assessing the process through quality improvement.[272] Patient participation is essential, as is the involvement of individuals identified by the patient as central to the process. Although patients and families expect physicians to raise the issues involved in advance care planning,[5,268,270,272] other dialysis unit personnel such as social workers, nurses, or peer counselors, may be integral to the process.

Box 3. Suggested Steps for Implementing Recommendation No. 4.

- Assess decision-making capacity (see Tool Kit).
- Include advance care planning in the Comprehensive Assessment and Plan of Care for each individual

patient

- Inform dialysis patient of his/her right to complete an advance directive and of the dialysis facility's policy with regard to advance directives as required by the 2008 Conditions for Coverage
- Encourage patient-centered advance care planning among patients and families; raise the issue of advance care planning with each patient at the initiation of dialysis (earlier is preferred) and on at least a yearly basis. Hospitalizations and/or significant changes in medical, physical, or functional status should prompt reconsideration of advance care planning
- Discuss advance care planning by asking:
  - If you become unable to make decisions for yourself, whom do you want to make decisions for you?
  - If you had to choose between being kept alive as long as possible regardless of personal suffering or living a shorter time to avoid suffering which would you choose?
  - Under what circumstances, if any, would you want to stop dialysis?
  - If your heart stops beating or you stop breathing, would you want to allow a natural death?
  - Under what circumstances, if any, would you not want to be kept alive with medical means such as cardiopulmonary resuscitation, a feeding tube, or mechanical ventilation?
- —Where do you prefer to die and who do you wish to be with you when you die?
- Determine whether the patient has an appointed legal agent through a written advance directive.
- If the patient lacks decision-making capacity and has not completed an advance directive, arrange for or initiate the process for appointment of a surrogate according to state law.
- Encourage patients to be specific about their preferences with legal agent, family, friends, and providers.
- Document provider's discussion and understanding of patient's preferences, show the patient the documentation, and offer to assist the patient in documenting the patient's agreement or modification of the documentation. Where available, complete a Physician Orders for Life-Sustaining Treatment (POLST) or similar form to translate patients' wishes into medical orders (see www.polst.org)
- Place a copy of advance directives, do not resuscitate order card, and/or POLST form in multiple medical records as appropriate, including dialysis facility, commonly attended clinics, hospital, and nursing home.
- Encourage the patient, family and/or legal agent to carry a current copy of the patient's advance directive, do not resuscitate order card, and/or POLST form whenever traveling or being admitted for overnight medical care.

Box 4. Desired Outcomes for Advance Care Planning for CKD and ESRD Patients[259,260,270,272,282]

Enhance patient and family understanding about their illness and end-of-life issues, including prognosis and likely outcomes of alternative plans of care

Define the particular patient's key priorities in end-of-life care and develop a care plan that addresses these issues and identifies the patient's overall goals of care

Enhance patient autonomy by shaping future clinical care to fit the patient's preferences and values

Improve the process of health care decision-making generally, including 1) patient and family satisfaction with the advance care planning process, 2) health care provider understanding of advance care planning and advance directives, and 3) provider comfort in participating in advance care planning

Help patients find hope and meaning in life and achieve a sense of spiritual peace

Explore ways to ease the emotional and financial burdens borne by patients and families

Strengthen relationships with loved ones

Making a Decision to Initiate or Discontinue Dialysis

Recommendation No. 5*

It is appropriate to forgo (withhold initiation or withdraw ongoing) dialysis for patients with AKI, CKD, or ESRD in certain, well-defined situations.

These situations include the following:

Patients with decision-making capacity, who being fully informed and making voluntary choices, refuse dialysis or request that dialysis be discontinued

Patients who no longer possess decision-making capacity who have previously indicated refusal of dialysis in an oral or written advance directive

Patients who no longer possess decision-making capacity and whose properly appointed legal agents/surrogates refuse dialysis or request that it be discontinued

Patients with irreversible, profound neurological impairment such that they lack signs of thought, sensation, purposeful behavior, and awareness of self and environment

*Medical management incorporating palliative care is an integral part of the decision to forgo dialysis in AKI, CKD, or ESRD, and attention to patient comfort and quality of life while dying

should be addressed directly or managed by palliative care consultation and referral to a hospice program (see recommendation #9).

Rationale

The legal and ethical principles supporting this recommendation include informed refusal, respect for patient autonomy, beneficence, non-maleficence, justice, and professional integrity. In both state and federal case law and by federal statute (PSDA), competent patients have an absolute right to accept or refuse medically indicated treatment. Authoritative psychiatry and nephrology opinion supports the notion that patients in the general nephrology setting who choose to forgo dialysis are neither psychopathological nor suicidal even though depression may be present.[290] Relevant observational evidence is limited but suggests that withdrawal is common, with rates ranging from 17% to 50% of deaths in different dialysis populations.[291-294] (Level C Observational Evidence) However, often patients have neither discussed their preferences with family or renal care team members nor completed written advance directives.[3-5,7,25-29] (Level B Observational Evidence) A few studies suggest that patients with decision-making capacity most often initiate the discussion of withdrawal of dialysis themselves and that physicians most often raise the issue for patients without decision-making capacity.[291-293,295] (Level C Observational Evidence) There is also evidence that patients often expect medical staff to initiate these discussions and that staff are reluctant often because of a lack of experience, either professional or personal, with end-of-life discussion.[26,29,276,296]

The evidence regarding patients' preferences for continuing or discontinuing dialysis in the event of certain health states is based on studies using hypothetical vignettes. This evidence demonstrates some variability in hypothetical preferences among patients, with approximately 50 to 85% saying they would want to stop dialysis in conditions of severe permanent neurologic impairment such as severe dementia or permanent coma.[7,261,297,298] (Level C Observational Evidence) Evidence is lacking regarding agreement between what patients say they would prefer hypothetically and what they actually do. Surveys and observational studies show nephrologists may be inconsistent and variable in their withdrawal practices. Prominent factors that they have reported affect their withdrawal decisions include patient's neurological and physical functional status, comorbidities, family wishes, and age.[21-23,263,265,295,299] (Level C Observational Evidence) More recent evidence suggests that depression, as measured using survey and questionnaire methods, is associated with forgoing dialysis, although it is uncertain whether this depression is causative or a concomitant phenomenon.[300,301] Previous studies have found that diabetes, severe pain, lack of a significant partner, Caucasian race, female gender, nursing home residence, and terminal illness are associated with withdrawal from dialysis.[22,265,276,291-293,295,297,299,302,303] (Level C Observational Evidence) More recent evidence suggests that inadequately treated pain may be an important concomitant of depression and independently predict withdrawal decisions.[300] (Level C Observational Evidence) Data on withholding of dialysis is limited. Information on withholding can be inferred from studies of referral practices. Of six relevant studies on dialysis referral, one large prospective cohort study indicates that the withholding rate for AKI is substantial (29%) and that increasing age and dementia were independent predictors of withholding in multivariate analyses adjusting for confounders.[91] (Level B Observational Evidence) Two retrospective cohort studies and two studies using cross-sectional surveys suggest that withholding in ESRD increases with age (15% to 83% over age strata from 16 to >70 years old), and may be higher in women.[264,275,304,305] (Level C Observational and Prognostic Evidence) These studies also suggest that cultural or financial contexts may influence

physicians' rates of initiating dialysis. A large Canadian survey study suggests that family practitioners and internists consider the following in their decisions on whom to refer for dialysis: age, serum creatinine level, mental and psychiatric status, distance from dialysis center, overcrowding of dialysis centers, and comorbid illnesses.[306] (Level C Observational Evidence) Over half of the Canadian physicians felt rationing should be based on patient wishes, cognitive status, life expectancy, quality of life, age, and long-term institutionalization.

The ethical principles of beneficence and nonmaleficence allow and support a judgment that, in certain conditions, dialysis does not offer a reasonable expectation of benefit.[307,308] The request of patients with a poor prognosis or their legal agents for dialysis should be considered within the framework of goals for care. Dialysis might allow additional time deemed of acceptable quality by the patient while at the same time there is agreement that aggressive end-of-life therapy will not be pursued; however this consideration must be balanced against continuing treatment that violates the ethical principle of professional integrity when the burdens of dialysis substantially outweigh the benefits.[307-311] The renal team should be sensitive to patient goals and individual circumstances. For example, a person with a terminal illness may desire to have dialysis to help them live long enough for a special family event (e.g., the pending birth of a grandchild) or to participate in the ongoing family life in a way which is personally meaningful and in which the family participates directly in the care of the patient (e.g. home peritoneal dialysis). There are some anecdotal examples in which dialysis enables unexpected survival with subjectively acceptable quality of life for some functionally dependent elderly patients, patients with chronic cardiac or liver disease, or patients with terminal illness. An innovative alternative, a "No Dialysis Clinic" has been described in Great Britain in which patients with CKD who so chose are managed for the duration of their survival – even in this setting there are still some patients who ultimately opt for a short course of dialysis before they die.[50] In the acute hospital setting, review of hospital death experience suggests that advance directives often do not focus sufficiently on palliative measures when treatment is withdrawn.[312] Nonetheless, family satisfaction can be favorably influenced by more discussion concerning general prognosis and comfort measures, even if these discussions prolong the process and even when terminal extubation is ultimately chosen.[107,313]

Generally, "terminal illness" for the purposes of hospice referral is defined as a life expectancy of less than or equal to 6 months if the disease process takes its normal course. AKI, CKD, or ESRD patients with non-kidney terminal illness include those with end-stage liver, heart, or lung disease who are deemed inappropriate organ transplantation candidates. Non-kidney terminal illnesses which AKI, CKD, or ESRD patients may have include end-stage cirrhosis with hepatorenal syndrome, severe congestive heart failure, widely metastatic cancer unresponsive to chemotherapy, end-stage pulmonary disease, end-stage acquired immunodeficiency syndrome, bone marrow transplant recipients with multiorgan failure, and advanced neurodegenerative diseases. Such conditions affect the survival of patients requiring renal replacement therapy.[64,65,67-71,123] (Level A Prognostic Evidence) The survival for patients with intact kidney function and such selected terminal comorbid conditions may be estimated. When the expected survival for patients with a specific terminal illness but intact kidney function is estimated to be less than six months, it is logical to conclude that dialysis for patients with AKI, CKD, or ESRD and one or more of the above conditions is unlikely to extend survival beyond six months.

Another situation where dialysis may be considered medically inappropriate is a patient with permanent inability to purposefully relate to others. This is defined as being unable to recognize

familiar persons, lacking orientation to self, place, and time, and the absence of higher cognitive functioning. All forms of severe irreversible dementia and permanent vegetative states fulfill this definition.

Recommendation No. 6

It is reasonable to consider forgoing dialysis for AKI, CKD, or ESRD patients who have a very poor prognosis or for whom dialysis cannot be provided safely.

Included in these categories of patients are the following:

Those whose medical condition precludes the technical process of dialysis because the patient is unable to cooperate (e.g., advanced dementia patient who pulls out dialysis needles) or because the patient's condition is too unstable (e.g., profound hypotension)

Those who have a terminal illness from non-renal causes (acknowledging that some in this condition may perceive benefit from and choose dialysis)

Those with stage 5 CKD over the age of 75 who meet two or more of the following statistically significant very poor prognosis criteria (see recommendations no. 2 and 3): 1) clinicians' response of "No, I would not be surprised" to the surprise question; 2) high comorbidity score; 3) significantly impaired functional status such as Karnofsky Performance Status score less than 40, and 4) severe chronic malnutrition (serum albumin <2.5 g/dL using the bromcresol green method).

Rationale

The ethical principles of beneficence and nonmaleficence allow and support a judgment that, in certain conditions, dialysis does not offer a reasonable expectation of benefit.[307,308] Patients with advanced cognitive impairment who are unable to cooperate with the dialysis process may be harmful to themselves, other patients, and personnel in the dialysis unit and may create an unsafe working environment.[214] Examples of patients who might be in this category include those who are unsafe despite physical or chemical restraints or a sitter during dialysis. The Working Group, however, felt that the renal team should be sensitive to patient goals and individual circumstances. For example, a person with a terminal illness may desire to have dialysis to help them live long enough for a special family event (e.g., the pending birth of a grandchild). If there is conflict with regard to the appropriateness of dialysis of a patient described by recommendation no. 7, then conflict resolution is recommended (see recommendation no. 9).

There is increasing evidence that elderly patients with stage 5 CKD and high comorbidity scores, significant functional impairment, and severe malnutrition may not benefit from dialysis in terms of increased survival or improved quality of life. See "Special Considerations for Stage 4 and 5 CKD" in the rationale for recommendation #3 for a discussion of these studies and findings. Palliative care consultation for such patients may assist with comprehensive goals of care discussions and explicit expressions of the patients' treatment preferences for their present condition and in the future when there are changes in their condition.

Resolving Conflicts about What Dialysis Decisions to Make

Recommendation No. 7

For patients requiring dialysis, but who have an uncertain prognosis, or for whom a consensus cannot be reached about providing dialysis, we recommend the consideration of a time-limited trial of dialysis.

If a time-limited trial of dialysis is conducted, the nephrologist, the patient, the patient's legal agent, and the patient's family (with the patient's permission to participate in decision-making) should agree in advance on the length of the trial and parameters to be assessed during and at the completion of the time-limited trial to determine if dialysis has benefited the patient and if dialysis should be continued.

Rationale

Experts recommend time-limited trials of life-sustaining treatment such as dialysis in situations when the benefit to the patient is uncertain. The patient's clinical course during the period of time-limited dialysis may provide patients and families with a better understanding of dialysis and its benefits and burdens and may provide the renal care team with a more informed assessment of the likelihood of the benefits of dialysis outweighing its burdens. In this way, time-limited trials may promote informed shared decision-making.[16,314-316] For example, a patient who is uncertain about his/her quality of life on dialysis may benefit from a time-limited trial. No research data regarding outcomes of time-limited trials of dialysis was found. The exact time period for the trial may be made on a case-by-case basis. For patients with AKI, time periods of several days to two weeks may be reasonable; for patients with ESRD, time periods of one to three months are reasonable. If there is uncertainty about the ability of a patient to cooperate with dialysis, the patient should be considered for a time-limited trial of dialysis before it is withheld. In one study, nephrologists who reported they were very well prepared to participate in end-of-life decision-making with dialysis patients were more likely to use time-limited trials than those who reported a lower level of preparedness.[317] In addition, nephrologists who reported they were very well prepared to participate in end-of-life dialysis decision-making were more likely to be aware of the first edition of this clinical practice guideline.

Recommendation No. 8

We recommend a systematic due process approach for conflict resolution if there is disagreement about what decision should be made with regard to dialysis (Figure 8).

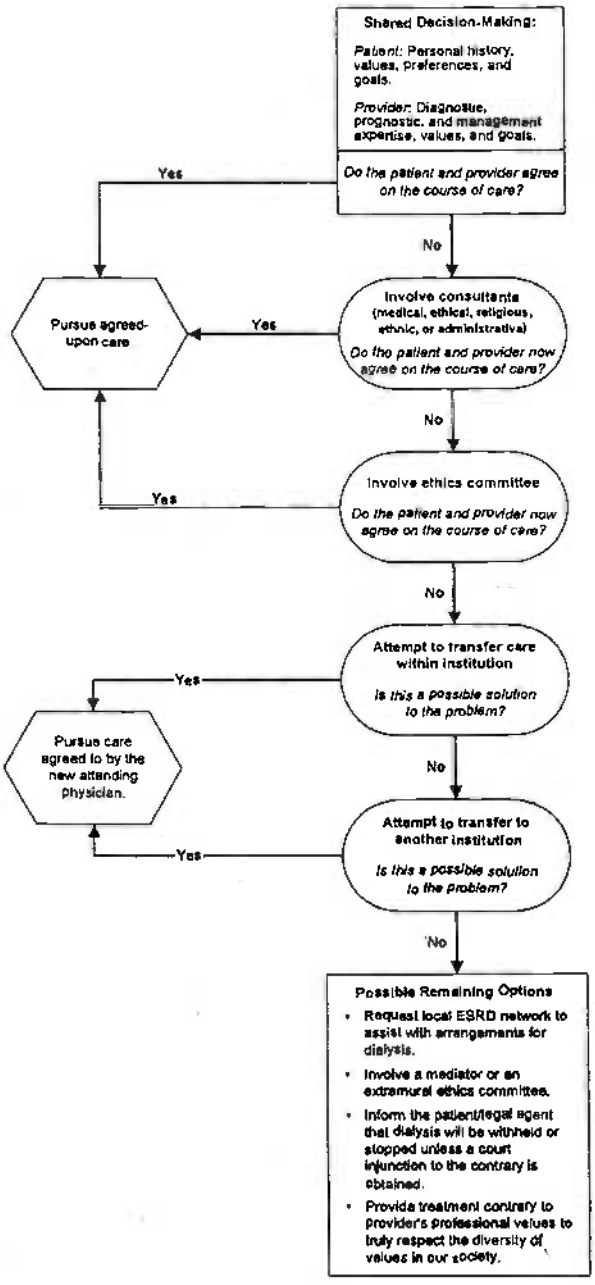
Conflicts may occur between the patient/ legal agent and the renal care team about whether dialysis will benefit the patient. Conflicts may also occur within the renal care team or between the renal care team and other health care providers. In sitting down and talking with the patient/legal agent, the nephrologist should try to understand their views, provide data to support his/her recommendation, and correct misunderstandings. In the process of shared decision-making, the following potential sources of conflict have been recognized: 1) miscommunication or misunderstanding about prognosis, 2) intrapersonal or interpersonal issues, or 3) special values. If dialysis is indicated emergently, it should be provided while pursuing conflict resolution, provided the patient or legal agent requests it.

Rationale

The ethical principles of beneficence, justice, nonmaleficence, and respect for patient autonomy support this recommendation. Disagreement regarding initiating or continuing dialysis may occur among the patient or legal agent, family members, renal care team, and/or other health care providers (e.g., intensivists and primary care physicians). Observational evidence about disagreements suggests that patients' or legal agents' wishes are usually, but not always, honored.[21-33,275,318] (Level C Observational Evidence) When the clinician determines that, based on the medical evidence, the burdens of dialysis substantially outweigh the benefits, he/she should meet with patient/legal agent and present the factors that indicate a poor outcome with dialysis. The aim is to reach agreement about the goals of care. If agreement is not reached on the course of care, then conflict resolution using the due process approach in Figure 8 should be initiated, and an ethics consultation should be considered.[319] A single study indicates that nephrology nurses sometimes disagree with nephrologists' decisions to continue dialysis. In this study, nurses perceived such disagreements as ethical conflicts, had no formal structure for raising and resolving the issue, and felt unable to resolve their dilemma.[320] (Level C Observational Evidence) If it is felt by the renal care team or the patient that an extramural ethics committee or consultant has more expertise, the renal care team or patient should feel free to consult them. There are no controlled studies of the outcomes of ethics consultation for dialysis patients, but the medical literature documents the benefits of ethics consultation in situations similar to dialysis in which the use of a life-sustaining treatment is at issue. Ethics consultants and committees possess knowledge and skills in ethics, law, interpersonal communication, and conflict resolution. Ethics consultations have been found to be helpful by physicians in clarifying ethical issues in patient care and assisting in patient management.[320-326] (Level B Observational Evidence) In contrast to 1990, a survey of nephrologists in 2005 indicated that a majority of nephrologists use ethics committees to assist with decision-making in challenging situations.[327]

Conflict may also occur when a patient with decision-making capacity refuses to start or continue dialysis that the physician believes is or will be beneficial. In such circumstances it is important to ensure that the decision to refuse recommended dialysis is based on good information and consistent with the patient's values and goals. Nephrologists are required by ethics and the law to respect the informed decision of a patient with decision-making capacity who chooses to refuse dialysis. See recommendation no. 5 for further discussion of this issue. If there are nephrologists who are unwilling to respect such a decision, then the nephrologist should transfer the patient's care to another physician.

Figure 8: Systematic Approach to Resolving Conflict between Patient and Kidney Care Team.


Shared Decision-Making:
Patient: Personal history, values, preferences, and goals.
Provider: Diagnostic, prognostic, and management expertise, values, and goals.
Do the patient and provider agree on the course of care?
Yes
No
Involve consultants (medical, ethical, religious, ethnic, or administrative)
Do the patient and provider now agree on the course of care?
Yes
Pursue agreed-upon care
No
Involve ethics committee
Do the patient and provider now agree on the course of care?
Yes
No
Attempt to transfer care within institution
Is this a possible solution to the problem?
Yes
Pursue care agreed to by the new attending physician.
No
Attempt to transfer to another institution
Is this a possible solution to the problem?
Yes
No
Possible Remaining Options
Request local ESRD network to assist with arrangements for dialysis.
Involve a mediator or an extramural ethics committee.
Inform the patient/legal agent that dialysis will be withheld or stopped unless a court injunction to the contrary is obtained.
Provide treatment contrary to provider's professional values to truly respect the diversity of values in our society.

Box 5. Suggested Steps for Implementing Recommendation No. 8.

- Extended conversation for either request for dialysis when not recommended or refusal of dialysis when recommended
  - Why does the patient or legal agent desire dialysis when it is not recommended by the renal care team?
  - Does the nephrologist misunderstand the patient's or legal agent's reasons for requesting dialysis?
  - Does the patient or legal agent misunderstand the diagnosis, prognosis, and treatment alternatives and why dialysis is not recommended?
  - Why does the patient or legal agent refuse dialysis when it is recommended by the renal care team?
  - Is the patient's refusal of recommended dialysis based on an accurate understanding of the likely benefits of dialysis?
  - Is the patient's refusal of recommended dialysis consistent with the patient's values and goals?
  - Does the nephrologist understand the psychosocial, cultural, or spiritual concerns and values the patient or legal agent has?
  - Has the nephrologist consulted a psychologist, social worker, or chaplain for assistance in fully understanding the concerns of the patient or legal agent/family? Have strategies in the Decreasing Provider Patient Conflict project been used as appropriate?

    (http://esrd.aclark.net/special-projects/copy_of_DPPCProviderManual.pdf)

For circumstances in which the patient/legal agent requests dialysis when it is not recommended, the following process may be helpful to resolve the conflict:

- Consultation with other physicians
  - Do other physicians agree or disagree with the attending physician's recommendation to withhold or withdraw dialysis?
  - Is the request for dialysis by the patient or legal agent medically appropriate?
- Consultation with an ethics committee or ethics consultants.
  - Has the patient or legal agent been informed that the purpose of the ethics consult is to clarify issues of disagreement, and ideally, to enable resolution?
  - Has the patient or legal agent met with the ethics committee or ethics consultants to explain their perspective and reasoning behind their request for dialysis?
  - Can the ethics committee identify the reasons why the patient or legal agent is resistant to the physician's recommendation to forgo dialysis?
  - Can the ethics committee identify the reasons why the health care provider is resistant to the patient's or legal agent's desire to begin or continue dialysis?
  - Has the ethics committee explained in understandable terms to the patient or legal agent its conclusions and the reasoning behind them?
  - Can the impasse be resolved with accommodation, negotiation, mediation, or a time-limited trial of dialysis?

- Documentation
  - The physician must document the medical facts and his/her reasons for the recommendation to forgo dialysis and the decision not to agree to the request by the patient or legal agent.
  - The consultants should also document their assessment of the patient's diagnosis, prognosis, and their recommendations in the chart.
- Attempt to transfer the patient's care
  - If reconciliation is not achieved through the above procedure and the physician in good conscience cannot agree to the patient or legal agent's request, the physician may ethically and legally attempt to transfer the care of the patient to another physician.
  - Another physician and/or institution may not be found who is willing to accept the patient under the terms of the family's request. Physicians and institutions that refuse to accept the patient in transfer and their reasons should also be documented in the medical record.
- Consider consultation with a mediator, extramural ethics committee, or the ESRD Network in the region.
- Request regional ESRD network to assist with arranging dialysis.
- Notification of the patient, legal agent, and/or family
  - If no other physician or institution can be found in the community or region by the treating nephrologist to provide dialysis as requested, the physician may inform the patient or legal agent that the nephrologist will cancel the patient's dialysis orders and the dialysis center will no longer provide dialysis to the patient. The nephrologist is obligated to give the patient sufficient advance notice and the names and addresses of other nephrologists and other dialysis facilities in the area.
- The options of filing a grievance with the ESRD network (chronic patients only) or seeking legal or regulatory recourse by the patient or legal agent should be communicated.

Providing Effective Palliative Care

Recommendation No. 9

Palliative care services and interventions should be offered to all AKI, CKD, and ESRD patients who suffer from burdens of their disease in an effort to improve patient-centered outcomes.

These services are appropriate for people who chose to undergo or remain on dialysis and for those who choose not to start or continue dialysis. With the patient's consent, a multi-professional team with expertise in renal palliative care--including nephrology professionals, family or community-based professionals, and specialist hospice or palliative care providers--should be involved in managing the physical, psychological, social, and spiritual aspects of treatment for these patients, including end-of-life care. Physical and psychological symptoms should be routinely and regularly assessed and actively managed. The professionals providing treatment should receive training in assessment and management of symptoms and in advanced communication skills. Patients should be offered the option of dying where they prefer, including at home with hospice care, provided there is sufficient and appropriate support to enable this option. Support should also be offered to patients' families, including bereavement support where appropriate. Dialysis patients for whom the goals of care are primarily comfort should have quality measures distinct from patients for whom the goals of therapy are aggressive life prolongation with optimization of functional capacity.

Rationale

The evidence shows that although patients and families place a high priority on good symptom control and preparation for death, both patients and professionals find it difficult to address these concerns, including end-of-life issues. Nephrologists' identification, assessment and management of symptoms is poor,[328] and many symptoms (such as pain) are under-recognised and under-treated.[329,330] Nephrology professionals also find it challenging to help patients engage with end-of-life issues.[331] In addition, patients doing less well on dialysis often find it difficult to make sense of what they perceive as 'not quite living' while on dialysis and struggle with issues raised by the use of dialysis and the prolongation of poorer quality life.[331] To some extent, nephrology staff recognize the need for symptom control and the importance of psychosocial aspects of care, but implementation of these aspects of care are perceived to be difficult.[332]

Kidney patients have considerable and complex healthcare needs towards the end of life. There is growing evidence of a high physical and psychological symptom burden among dialysis patients,[329,333-337] especially among those with multiple co-morbidities.[328] Those who opt for active medical management without dialysis[338] or dialysis withdrawal[339] have similarly high symptom burden, and need pro-active management.[340] While dying is peaceful and symptom-free for some, others experience considerable uncontrolled symptoms.[341]

There is some early evidence as to how these needs are best addressed. In general, the complex needs of those dialysis patients with palliative goals of care are best addressed through the collaboration of nephrology professionals with family/community-based professionals and hospice or palliative care providers.[342,343] Who actually provides care may be determined by the strengths of local service programs, but the approach is characterized by:

1) holistic and patient-centered care;
2) multi-disciplinary professional collaboration to provide this care;
3) high quality, skilled communication, and sensitive advance care planning;
4) addressing needs across the physical, psychological, social and spiritual domains of care; and
5) consideration of family needs, including bereavement support

There is evidence that hospice is underutilized for dialysis patients, especially for those who withdraw from dialysis and that those dialysis patients who use hospice are more likely to die at home and spend less time in an acute hospital care.[344] At home, symptoms may be more easily recognized and communicated.[339]

There are specific interventions that can be used for CKD and ESRD patients. Tools have been developed which can effectively measure symptoms[345-348] and quality of life[349] toward the end of life, although there is limited validation as yet in populations with ESRD. Pharmacological interventions for pain[334,350] and depression[336] have been identified as useful.[351] In particular, using the WHO analgesic ladder to treat pain has been shown to be effective for kidney patients.[334,352,353]

Although there is growing evidence relating to those on dialysis, there is an urgent need for further research to clarify which stage 5 CKD patients will do best with active medical

management without dialysis. In the United Kingdom, older age, higher co-morbidity, and poorer functional status are associated with the recommendation for active medical management without dialysis.[48]

There is a need to define appropriate quality measures for patients whose main goal for dialysis is comfort as opposed to rehabilitation and optimization of function. Care delivered to dialysis patients whose goals of care are focused on minimizing the burdens of treatment should be evaluated by quality measures such as documented discussion of patient's prognosis, designation of a legal agent, pain and symptom assessment and management, documentation of an end-of-life care plan including patients' preferences regarding life-sustaining treatments and preferred site of death, and timely referral to hospice. Quality care measures used for dialysis patients in whom the goals of care are aggressive therapy with optimization of function such as dialysis adequacy, anemia and bone disease management, patient survival, and vascular access type and function (for hemodialysis patients only) are inappropriate for dialysis patients for whom the goals are maximizing comfort and minimizing procedures and hospitalizations. Furthermore, dialysis patients with a poor prognosis who have chosen dialysis with a goal of maximizing comfort should not be included in the calculations of dialysis unit-specific standardized mortality ratios and quality measures for dialysis patients seeking aggressive therapy and rehabilitation to avoid misrepresentations of the quality of dialysis unit care on public reporting sites. Current practices of aggregating all dialysis patients regardless of their goals of care in quality measures discourages the appropriate setting and honoring of different expectations and goals of dialysis patients.

Box 6: Recommendations for end-of-life care practices in chronic kidney disease*[354]

1. Identify patients who would benefit from palliative care interventions

a. Those who are being managed medically, i.e., a GFR ≤ 15ml/min/1.73m2 with no dialysis.

b. High risk of death within the next year. Consider using an integrated prognostic model and/or the surprise question, "Would I be surprised if this patient died in the next year?"

2. Screen for and manage pain and other physical symptoms routinely.

a. A simple tool such as the Edmonton Symptom Assessment Scale (ESAS) is appropriate and has been validated in CKD.

3. Screen for and manage emotional, psychosocial and spiritual distress; refer to allied health professionals as appropriate.

a. The ESAS is also appropriate for screening for anxiety and depression.

b. A simple question such as "Do you have any spiritual needs or concerns that your health care providers may help address?" may be appropriate for screening for spiritual distress

4. Assess patients' desire for prognostic information

5. Enhance pre-dialysis education

a. Educate regarding active medical management without dialysis option as appropriate

b. Education should include available palliative care and hospice services

6. Provide routine advance care planning (ACP) as described in recommendation no. 5

a. Ensure patients and families are aware of the relevance of these discussions (i.e., have an understanding of their overall health state and prognosis)

b. Consider initiating ACP at the time that patients are being educated with respect to renal replacement options.

c. Include discussions of patients' goals of care, health states that the patient would no longer want dialysis, and preferred location of death.

d. Establish a surrogate decision-maker

e. Ensure that family and other important people (as identified by the patient) are present for these discussions, especially the surrogate decision-maker.

Recommendation No. 10

We recommend a systematic approach for communication about diagnosis, prognosis, treatment options, and goals of care.

Good communication improves patients' adjustment to illness, increases adherence to treatment, and results in higher patient and family satisfaction with care. Patients appreciate sensitive delivery of information about their prognosis and the ability to balance reality while maintaining hope. In communicating with patients, the critical task for clinicians is to integrate complicated biomedical facts and conditions with emotional, social, and spiritual realities that are equally complex but not well described in the language of medicine. This information must be communicated in a way that patients, legal agents, and families can understand and use to reach informed decisions about dialysis and transplantation options. Patients' decisions should be based on an accurate understanding of their condition and the pros and cons of treatment options. Shared decision-making depends upon this effective, empathic communication, but research shows that nephrologists are not prepared to communicate in this manner in their fellowship training.

Rationale

Nephrologists care for a patient population with significant comorbidities and a yearly mortality rate that surpasses most cancers. Patients with chronic disease, such as advanced CKD, face a number of challenges. They deal with the emotional aspect of having a life-limiting illness and, concurrently, must participate in difficult decisions regarding the management of their disease. The quality of physician communication impacts how patients respond to these challenges and plan for the future. Although limited data exists describing how nephrologists communicate serious news such as prognosis, the nephrology literature has shown effective communication results in increased patient satisfaction, understanding, and hope.[269,355] Research also shows that empathic communication decreases patient anxiety and improves patient trust at end of life.[249]

Despite these data, discussions about prognosis are difficult, and physicians frequently feel stressed approaching these conversations. This anxiety is understandable and not surprising as communication skills are often not specifically taught or reinforced. Barriers to these conversations include time constraints and concern that discussing such topics may take away patient hope.[356-358] These concerns are shared by all specialists and nephrologists appear to be no exception.[359] The lack of conversations between nephrologists and patients impacts their disease and treatment decisions. Data suggests patients report lacking knowledge regarding specific treatment options, such as hemodialysis, peritoneal dialysis and transplantation.[360] They also tend to have increased anxiety regarding their treatment and prognosis.[361] Most importantly, patients want to hear information about their disease and its prognosis. A survey of CKD and ESRD patients found almost all respondents felt information regarding their diagnosis, including prognosis, was important. Yet only 10% reported having had a discussion about of end-of-life care with their nephrologists.[354] As patients' comorbidities and care become more complex, the role of effective communication becomes essential in patient care and decision-making. A focus group of patients with life-limiting illness and their caregivers identified communication components most important to them including talking in an honest and straightforward way with understandable language. Patients appreciated sensitive delivery of the news and the ability to balance reality while maintaining hope. Patients also expressed better understanding and comfort when physicians encourage and are open to conversations.[362]

Core communication skills

There is a growing body of literature with regard to good communication techniques with seriously ill patients. Good communication involves the ability to recognize and respond to patients' informational and emotional concerns regarding their disease. There are a core set of communication skills that are described briefly below and examples of this communication strategy are described in the tool kit with helpful questions to.[363]

Identifying concerns: eliciting and recognizing concerns
The ability to respond to patients' concerns and needs begins with the ability to effectively elicit and recognize these concerns. Open-ended questions elicit patient concerns and allow patients time to speak. Continuing to probe until the patient has nothing else to add is important as the patient may not bring up concerns the first time you ask.[364,365]

Responding to informational concerns: Ask-Tell-Ask
As physicians approach discussions, such as prognosis or treatment options, it is helpful to learn how patients want to hear this information. This is includes both the timing and content of the information disclosed. For example, while studies show that most patients want prognostic information, a significant minority do not. There is no way to predict this, and data from focus groups suggest that patients want the doctor to negotiate about if and when to discuss prognostic information. By eliciting these patients' needs, physicians can ensure that patients get the information they need but are not forced to talk about things which they are not ready to hear. This can best be accomplished with the Ask-Tell Ask communication skill.

The first "**Ask**" involves eliciting what the patient understands about their disease. This helps the physician understand what the patient knows and allows misperceptions to be identified and correct. Asking before giving prognostic information also means ensuring that the patient wants to know about prognosis ("*Are you the kind of person who wants to know what might happen next or would you rather that be something I talk with your wife about*?). It also ensures that it is an appropriate time to have the conversation ("*Is it ok that we talk about your prognosis now? Is there anyone else you want there?* ").

Having established the patient's interest in talking about prognosis, the physician can then "**Tell**" the news in a way that addresses the patient's concerns. Given that people can only retain three to seven pieces of information at a time, it is important to focus on the key information. Giving all the medical details is likely to overwhelm the patient and may lead them to focus on details that are not critical. Experts thus recommend that information be given in small chunks and frequently checking in to ensure that the information was understood (*"Any questions about what I said?")* In addition, it is important, particularly in the beginning to start at a literacy level that most patients will understand, typically fifth or sixth grade.

The second "**Ask**" provides an opportunity to ensure that the patient understands what has been said. The only way to ensure adequate understanding is to ask the patient. An indirect way to do this is to ask about the questions or concerns they have about the information you provided. Another way is to ask what they will tell their loved one about the conversation when they go home ("*To make sure I have done a good job explaining*

what is going on, can you tell me what you will tell your husband about our conversation? ").

Responding to emotional concerns: Empathy
Patients respond to discussions of prognosis with emotions such as sadness, anger, or disbelief. When their physicians identify these emotions, patients feel more supported. Emotional support includes listening and using specific language that expresses empathy. By responding to these emotions, physicians improve the likelihood the patient will be receptive to the information. For example, in one study, patients with breast cancer were more likely to believe their physician cared about then and were less anxious when the physician expressed empathy.[366]

Physicians can respond to patients' emotions both verbally and nonverbally. Use of the N-U-R-S-E acronym (see the tool kit) and "wish" statements assists physicians to express verbal empathy.[367] The former includes naming the patient's emotion and attending to it in an empathic manner. The latter tool allows physicians to walk in the shoes of the patient and respond as human beings faced with overwhelming circumstances that are not of their choosing.[367] The acronym S-O-L-E-R employs nonverbal expressions such as body posture and facial expressions to convey empathy (See tool kit).

A Six-Step Approach for Talking about Serious Illness
Patients report the manner in which news is delivered is more important that the actual content of the discussion.[368] A frequently used model for delivering serious news includes six steps, originally called "SPIKES" (Setup, Perception, Invitation, Knowledge, Emotion, Summarize). These steps are presented in Box 7 and facilitate the development of a treatment plan which includes input and cooperation of the patient.[369]

Box 7. A Six-Step Approach to Talking about Serious Illness

1) *Prepare for the conversation: **setup***. This includes making the environment private and quiet. Also having a nurse or social worker available for further discussion after you leave.
2) *Assess the patient's **perception***. Asking what the patient understands or expects can be helpful in determining how you approach and plan the conversation.
3) *Ask for an **invitation** to talk about the news*. By asking the patient if you can discuss the news gives them some control and emphasizes you goal to work cooperatively.
4) *Disclose the news straightforwardly: **knowledge***. It is best to start with a warning statement to let the patient brace themselves for bad news. The news should be straightforward with comprehensible language.
5) *Respond to the patient's **emotions***. The physician must be aware of the patient's emotion and be able to respond to it in an empathic way.
6) *Summarize the plan*. At the close of the visit, you should summarize what has been discussed and describe the next steps which the patient will need to take.

Communicating with Patients Whose Health Is Declining

For many patients who decide to undergo dialysis, the disease trajectory is often marked by decline from new illnesses (e.g., heart attack or stroke) or loss of function resulting from hospitalizations. The events triggering these setbacks serve as a prompt to discuss if the present treatment plan remains consistent with the patient's goals *("I wanted to check in with you to see how our treatment plan was going. You had said that dialysis was worth it, because it allowed you to stay at home and have more time with your grandchildren. How has that been going for you?")* For a patient on dialysis, the transition may occur when the burdens of dialysis outweigh the benefits of life prolongation. (*"Is being on dialysis still worth it for you? I worry that for some people, dialysis may no longer be a benefit to them as they may be unable to do what they like to do. Can we talk about this?").*

These deteriorations can be challenging for physicians as they involve giving bad news, or directly confronting the dying process. However, patients and caregivers report these are important conversations that they want to have and that they want the doctor to raise the topic. By avoiding conversations about whether continued dialysis is meeting the patient's goals, physicians risk missing opportunities to address concerns and fears, focus the treatment plan in a way that meets the patient's goals, and explore issues related to life closure.

This approach of balancing discussions of hope with preparation for future outcomes respects the patient's hopes and fears while still allowing for opportunities to reassess and redefine the patient's goals of care over time. The treatment plan can be modified to focus on what can be achieved given the patient's values, and treatments that are no longer beneficial can be discontinued. After such discussions, patients may decide to switch from a more aggressive approach to dialysis to one in which the focus on dialysis is on a reduction in suffering with concerted attention to pain and symptom management and advance care planning. Thus, these conversations may allow for timely involvement of palliative care services and hospice referral.[370]

Nephrologists are faced with the challenge of caring for a complex patient population with multiple comorbidities. How physicians communicate with patients impacts their experience with their disease and their treatment decisions. This recommendation provides tools to gather and effectively deliver information and to respond to patient's emotional concerns. Through practice and close attention to how communication is delivered, physicians can effectively communicate and negotiate a plan of care consistent with the patient's own values and needs.

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Chapter 7

Symptoms in renal disease; their epidemiology, assessment, and management

Fliss Murtagh and Steven D Weisbord

7.1 Introduction

Patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD) are among the most symptomatic of any chronic disease group.[1] Identifying and controlling symptoms is a high priority for patients and families,[2] and notably improves their quality of life.[3] For those with ESRD, excellent symptom management becomes an increasingly high priority as the duration of time they remain dependent on chronic renal replacement therapy (RRT) increases.[2,4] It is also important to recognize that, while RRT provides major benefit, including symptom relief, it will not always ameliorate or abolish symptoms and may sometimes contribute to them.

7.2 Causes for symptoms in end-stage renal disease

Symptoms arise in advanced renal disease for a number of reasons; they may be a direct consequence of the renal disease, a consequence of dialysis, or due to co-morbid conditions. Co-morbidity is increasingly important as the ESRD population becomes older and is more likely to have multiple and often chronic medical conditions.

7.2.1 Symptoms directly related to renal disease

Prior to dialysis (or if dialysis is subsequently withheld or withdrawn), uraemia can affect all organ systems, leading to symptoms such as pruritus, fatigue, gastrointestinal symptoms, sexual dysfunction,[5] uropathy, and arthropathy.[6] Experience with daily or nocturnal dialysis has demonstrated a significant reduction in uraemic symptoms, although distressing symptoms may remain or develop.[7]

Few symptoms can be easily attributable to one cause alone, however. For example, itch or pruritus is commonly attributed to uraemia (although 'CKD-associated pruritus' may be a more accurate term[8] because the pathogenesis remains uncertain and it is not clearly a direct consequence of uraemia). There is evidence, however, that about a third of patients with pruritus report intensification of the symptom during or immediately following dialysis.[9] Similarly, symptoms arising directly from the renal disease may interact with a co-morbid condition to give rise to a worsening and more complex symptom picture. Examples are fluid overload because of renal failure exacerbated by cardiac failure, or uraemic neuropathy complicated by co-existing diabetic neuropathy.

7.2.2 Symptoms related to dialysis

Intradialytic symptoms are those relating directly to the dialysis procedure. Approximately 40% of haemodialysis sessions are associated with symptomatic hypotension, cramps, nausea and vomiting, and pruritus. In addition, post-dialysis hypotension and a 'washed-out' feeling lasting up to 24 h are common. Other symptoms, such as headache, may be very common (affecting up to 70% of haemodialysis patients), but are often difficult to classify and attribute to specific causes.[10]

Those symptoms occurring early in the dialysis are commonly related to a lack of appropriate vasoconstriction, whilst those occurring later may be related to or caused by the target dry weight being too low. Many of these symptoms are reduced or eliminated by peritoneal dialysis, or by frequent, slow haemodialysis – such as nocturnal or daily. Shorter dialysis treatments, high-flux dialysis, elderly patients, and high co-morbid burden correlate with increased symptoms on dialysis. Recent studies have supported the value of changes in the dialysis prescription in decreasing intradialytic symptoms. Monitoring blood volume, decreasing the dialysis temperature, and modelling of dialysate sodium and ultrafiltration rates are effective and inexpensive.[11,12]

Some specific symptoms may occur in relation to dialysis. Symptomatic hypotension can occur early in dialysis, often in association with rapid or large intravascular volume changes. Loss of autonomic nervous system control can sometimes play a part. Hypotensive symptoms later in dialysis are more usually related to the target dry weight being too low. Pruritus may worsen during or just after dialysis, and has been associated with inadequate dialysis. Anorexia is also common in dialysis patients, and it may indicate uraemia and inadequate dialysis, although it is more often multi-factorial, with other factors (such as anaemia, depression, taste disturbance, dry mouth, gastrointestinal symptoms, or gastroparesis) likely to play a part. Constipation is common for dialysis patients, and immobility, fluid restriction, dietary restrictions, and/or medication (such as aluminium and calcium phosphate binders, iron supplements, and opioids) may all contribute.

7.2.3 Symptoms due to co-morbid conditions

Because of limited symptom research, 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 does, in reality, together contribute to their overall symptom burden. Co-morbid conditions do, however, 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 ESRD 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 go on to cause gastric reflux and dyspepsia. Diabetic patients also suffer from other neuropathies. Autonomic neuropathy can also affect the mid- and lower gut, leading to an enteropathy characterized by alternating diarrhoea and constipation, and sometimes faecal incontinence. Non-autonomic diabetic neuropathies that affect the peripheral nerves may take a number of different forms, including polyneuropathies, radiculopathies, or mononeuropathies. Paraesthesia – with sensory disturbance or loss, and sometimes associated pain – is a typical

presentation of these non-autonomic neurological complications, whilst motor impairment occurs late in the course of the condition. 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 too are difficult to control.

Cardiovascular disease encompasses a wide range of clinical problems, including coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, and left ventricular hypertrophy. All forms of cardiovascular disease are notably more common in those with CKD, and the risk of cardiac events in patients with ESRD is estimated to be about 3–5 times higher than in the general population.[13] Cardiovascular causes account for about 45% of deaths in those on dialysis, and the proportion is similar or even higher for those managed conservatively, without dialysis. The main symptoms associated with cardiovascular disease are pain, breathlessness, and hypotension, although this depends very much on the particular presentation and problems of the individual patient. Peripheral vascular disease, if present, is a particular challenge because it is often far advanced before symptoms develop. Pain (ranging from intermittent claudication to rest pain), ischaemic ulceration, and gangrene are easier to prevent rather than relieve. Smoking cessation and regular exercise are important even in advanced peripheral vascular disease, and preventative foot care is of paramount importance (as for the diabetic patient).

Calciphylaxis is a problem seen most often either in dialysis patients or immediately following transplantation. It is infrequent but when it does occur, it can be extremely painful. Small vessels are calcified and become occluded, with ischaemic necrosis of the surrounding tissue. Skin changes occur, with livedo reticularis and palpable tender subcutaneous nodules, which most often affect the lower trunk and lower extremities.[14] (See also Chapter 8.)

Hypotension from a variety of causes may be a common contributory factor in falls, especially for older patients. Hypotension occurs most often in relation to dialysis, but may also occur in diabetes (the postural hypotension caused by diabetic autonomic neuropathy), and be precipitated by medications such as beta-blockers, calcium-channel blockers, and nitrates.

7.3 Symptom prevalence

How common symptoms are depends to some extent on which CKD population is being considered. Although little comparative study has been made of symptoms across the different stages of CKD, those with more advanced disease are likely to be most symptomatic. Fig. 7.1 illustrates the prevalence of common symptoms in three populations with advanced CKD: those on dialysis,[15] those with Stage 5 CKD managed conservatively (without dialysis),[16] and those withdrawing from dialysis in the last 24 h of life.[17]

7.3.1 Prevalence of anxiety and depression

Although anxiety and depression (particularly depression) have been widely studied in ESRD, their exact prevalence remains contentious, and this is reflected in the wide range of reported prevalence for these conditions.

Most evidence comes from dialysis populations. Anxiety is reported as occurring in 12–52%[3,18–24] and depression in 5–71%[3,20–39] of dialysis patients. Much of this variation reflects differences in the populations assessed, the definitions of anxiety and depression used, and the instruments used to detect them. For instance, studies using formal diagnostic criteria (as defined in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV))

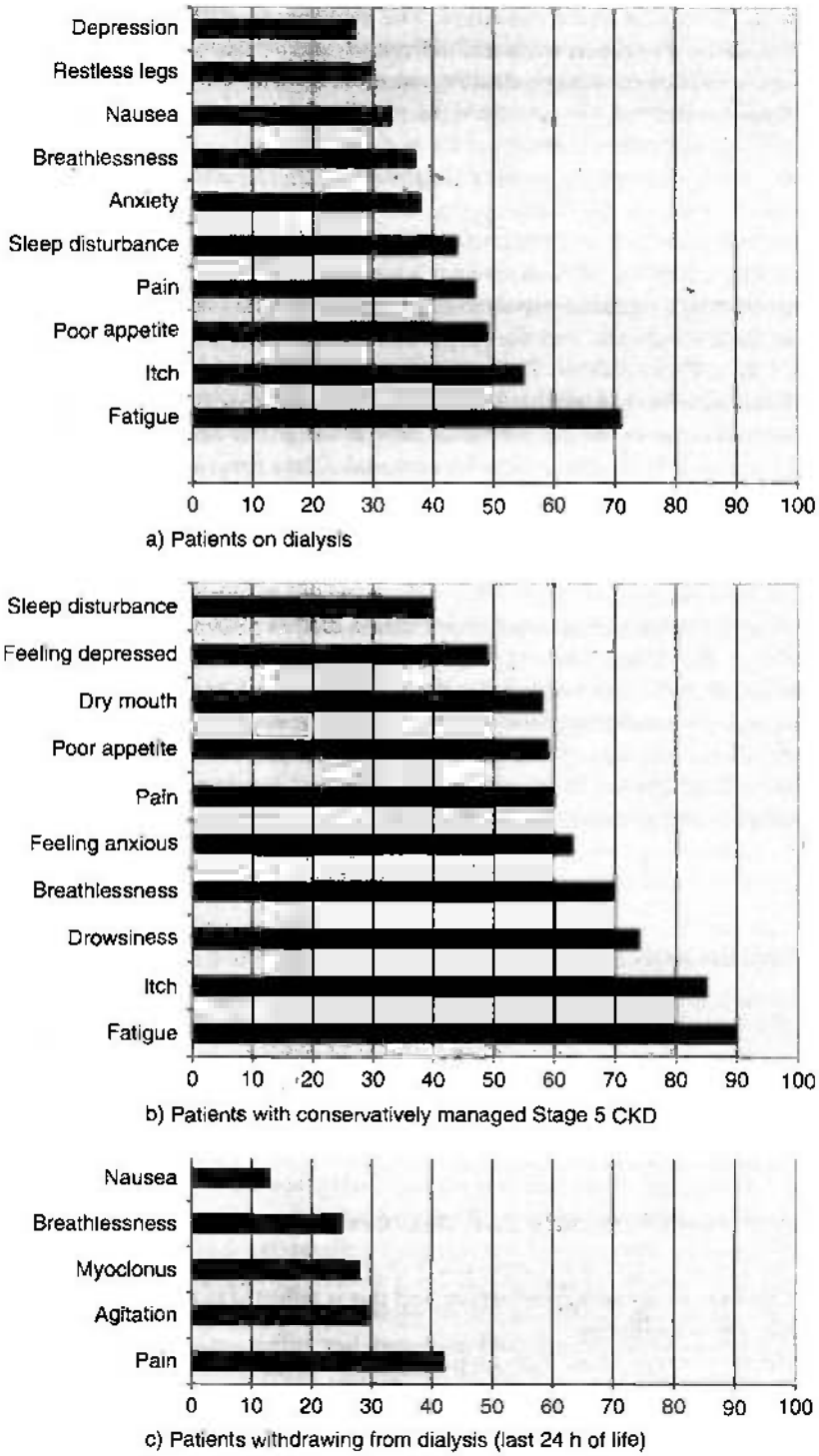

Fig. 7.1 Proportion (%) of patients with common symptoms in renal disease.

suggest that 27–46% of haemodialysis patients have an anxiety disorder,[18,19] and 26–30% have a depressive disorder.[39] 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 in the screening tool.[26,38] It is important to distinguish between the formal diagnosis of anxiety or depressive disorder (less common), and more non-specific symptoms of feeling anxious or depressed (which are inevitably more common). Both need to be determined; the former because formal anxiety or depressive disorders need defined interventions, proactive management, and detailed, skilled follow-up, the latter because it is important to know from the patients themselves what is troubling to them. While feelings of anxiety and sadness may not necessarily reflect full-blown anxiety or depression, these symptoms will still need to be addressed, such as through information, communication, and preparation, or through psychological and social support. However for clinical and research purposes, they should be carefully distinguished.

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.[15] 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.[15]

7.3.2 Prevalence of pain

In the past, data on pain prevalence has sometimes been collected within studies of quality of life, where pain is just one of the many domains influencing quality of life. However, pain prevalence is more accurately determined with a specific, validated pain- or symptom-assessment measure. When used both in dialysis populations and the general population, quality of life measures do, however, indicate that (after adjustment for age and gender) dialysis patients experience notably more pain than their counterparts in the general population.[40–42]

Now that specific validated pain measures are beginning to be more widely adopted, it is becoming clear that pain is a common problem for patients with advanced renal disease. Studies from Canada,[43] Italy,[44] and the US[45] have reported 48–50% of all haemodialysis patients reporting pain using, respectively, the McGill Pain Questionnaire, a numerical pain score, and the Dialysis Symptom Index; each convincingly demonstrate that pain is more common in dialysis patients than previously recognized. Pain prevalence has also been identified in this more rigorous way in patients with Stage 5 CKD managed without dialysis, revealing a similar baseline pain prevalence of 53%,[46] although pain prevalence was demonstrated to increase markedly over time, increasing to affect 73% of all conservatively managed Stage 5 CKD patients by the month before death, with over half of these reporting severe pain.[15] Studies of patients withdrawing from dialysis suggest pain affects about 50% of patients,[47,48] allowing for the reduced accuracy of proxy measures.[49]

It is important to understand, not only the overall prevalence, but also the nature and patterns of pain experienced by patients. Pain which is recurrent or persistent is more likely to be intrusive and will impair quality of life of patients more substantially.[50] For this reason, longitudinal study of pain (as well as other symptoms) is particularly important. The majority of studies to date is cross-sectional, and provides only a 'snapshot' of pain at any one time point. The few longitudinal studies of pain indicate that worsening or fluctuating pain over time contributes substantially to deterioration in both physical and mental components of quality of life.[15,45] This is discussed more fully in Chapter 8.

7.3.3 Prevalence of pruritus

Numerous cross-sectional studies provide evidence on the prevalence of itch.[3,9,23,52–68] Together, these studies (most of which are small, mostly involving <300 participants) suggest that pruritus affects between 28% and 60% of patients on haemodialysis, and between 50% and 68% of those on peritoneal dialysis. Four studies report higher prevalence (between 70% and 74%) among haemodialysis patients,[24,69–71] but this may reflect the longer periods of prevalence used in these studies. Pruritus prevalence in those with Stage 5 CKD managed without dialysis was also shown to be high (74%) in a study using a shorter period of prevalence (pruritus occurring in the previous week), suggesting it is more prevalent in this population.[46]

There has also been some suggestion that the prevalence of pruritus has been decreasing over time, parallel with advances in techniques and efficiency of dialysis. A recent epidemiological study of >18 000 patients refutes this, however, indicating that between 36% and 50% of all haemodialysis patients report moderate to extreme pruritus, despite the continuing advances in dialysis techniques.[72] Given the size of this study, it provides the most reliable evidence as to pruritus prevalence in haemodialysis patients, and confirms that the mid-range from the smaller studies provides the most accurate prevalence data. More importantly, it demonstrates that pruritus is associated with worse physical and mental quality of life domains, and a 17% higher mortality risk, mediated in part through disturbances in sleep quality.[72] This finding is supported elsewhere, with clear indication that severe pruritus is associated with worse prognosis.[73] Pruritus is, therefore, not only a common symptom, often distressing to patients, but it has implications beyond impairment of quality of life, of worse prognosis and survival.[74]

7.3.4 Prevalence of restless legs

The reported prevalence of the symptom of restless legs among dialysis patients varies considerably, from 12% to 58%.[24,58,59,65,75–83] This compares with prevalence of at least 10–15% in the general population.[84] 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).[85] These latter studies indicate a somewhat lower prevalence of the syndrome of restless legs amongst patients receiving dialysis, between 12% and 22%.[74] Amongst transplanted patients, the incidence of RLS is lower, at about 5%.[85] Of those with Stage 5 disease and not receiving dialysis, 48% report the symptom of restless legs,[46] although this reflects the less defined symptom as reported by patients, rather than 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.[79]

7.3.5 Prevalence of sleep disturbance

Sleep disturbance is a common problem in patients with ESRD 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,[86] but the prevalence of sleep disturbance in renal patients is notably higher. Several studies have described prevalence,[23,52,53,59,62,65,82,86–97] and findings range from 20% to 83% of dialysis patients affected by sleep problems. This wide range reflects variable periods of prevalence – from point prevalence (symptom currently present) up to sleep disturbance at some time in the preceding 3 months. Definitions range from simple patient report of a 'sleep problem' to more specific definitions such as 'at least one of the following: problems initiating or maintaining sleep, early or difficulty waking, tiredness on waking, daytime sleepiness'.

Whatever definition is used, however, it is clear that this is a symptom which troubles many dialysis patients. Given the concerns regarding the relationship between poor quality of sleep and worse prognosis,[73] it is important that sleep problems are assessed and addressed carefully, together with the other symptoms which tend to cluster with sleep disturbance (pruritus and RLS in particular). All probably interact to adversely impact quality of life for individual 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.[46] Over time, the prevalence of sleep problems seems to remain constant in this conservatively managed population, with similar proportions affected in the month before death as earlier in Stage 5 disease.[15]

Poor sleep has been shown to be associated with depression in renal patients,[86] and polysomnographic studies suggest that obstructive sleep apnoea is disproportionately common in dialysis patients.[98] Other studies of selected ESRD populations show prevalence of sleep apnoea up to 50%,[99] and this may contribute to daytime fatigue and sleepiness, as well exacerbating the cardiovascular complications of ESRD. The reasons for this high prevalence of sleep apnoea are unclear – it may be directly linked to the renal disease, with both destabilization of central ventilatory control and a degree of upper airway occlusion. There is also some suggestion that sleep patterns change early in CKD, so that sleep disturbance is common in the early stages, as well as advanced CKD, although the reasons for this are poorly understood.[100]

7.3.6 Prevalence of tiredness or 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.[13,22,101,102] 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.[15] Qualitative studies also suggest it is one of the most difficult symptoms for patients to cope with.[15,102]

Renal professionals may often be unaware of the presence and severity of fatigue in their patients,[103] especially since it may be less apparent than other, more tangible, symptoms. However, careful identification and assessment is important because of the high prevalence of this symptom, its major impact, and because it may be potentially treatable.

7.3.7 The prevalence of other symptoms

There are a number of other key symptoms which have been shown to be important for patients with advanced renal disease. Because the majority of studies of symptom prevalence focus on one or two symptoms of interest, rather than the whole range of symptoms experienced by the patients, there is much less evidence on the epidemiology of these remaining symptoms. Some studies have evaluated the whole range of symptoms, and provide data on how common these other symptoms are.[3,13,24,46,53,62] These symptoms include nausea and vomiting, drowsiness, breathlessness, leg oedema, dry mouth, lack of appetite and altered taste, poor concentration, dry skin, and constipation. Sexual dysfunction is also common (more fully described in the first edition of this book). Some symptoms, e.g. breathlessness, are frequently linked to co-morbidity, such as co-existing cardiac or respiratory disease, and their prevalence very much reflects the demographics of the population, with older populations and those conservatively managed (without dialysis) displaying a notably higher prevalence of these symptoms.[15]

7.4 Assessment of symptoms

There is growing evidence that symptoms in renal disease are under-recognized. A recently published study indicates that renal professionals substantially underestimate both the presence and the severity of the symptoms that their patients experience.[104] Appropriate, clinically relevant and valid instruments are essential to measure symptoms, both in clinical practice and the research setting.

7.4.1 Symptom measurement tools

A variety of tools have been used to evaluate symptoms in renal disease. Over two decades ago, Parfrey and colleagues developed a tool to capture the overall health status of patients with ESRD, including symptoms.[52–54,105] This questionnaire assessed the presence and severity of key symptoms, and also included emotional and psychological dimensions, the patient's life satisfaction, and a simple 0–100 visual quality-of-life scale.[54] However, it did not include certain symptoms important in renal disease (such as restless legs or poor appetite), and it used terms which were rather medical for a patient-completed measure, such as 'dyspnoea' and 'angina'. Perhaps for these reasons, it was not widely adopted, and other, more patient-centred instruments have been used instead. These include instruments which have been widely used in other advanced diseases, such as the Edmonton Symptom Assessment System[51,54,106] and the Memorial Symptom Assessment Scale short form.[3,46]

Other measures have been adapted and validated specifically for use in those with renal disease. These include the Dialysis Symptom Index, developed from the Memorial Symptom Assessment Scale by Weisbord,[107] and the renal version of the Patient Outcome Scale (symptom module), derived from the generic version of the Patient (or Palliative) Outcome Scale which is used across a wide number of conditions and countries.[108] Both are patient-completed tools, and each of these symptom measures validated in renal populations will be briefly discussed here (see Appendix for both tools).

7.4.1.1 The Edmonton Symptom Assessment System

The Edmonton Symptom Assessment System (ESAS) measures nine physical and emotional symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath).[109] Each symptom is scored on a visual analogue scale from 0 (absence of the symptom) to 10 (worse possible level of the symptom). It was originally developed and validated for cancer patients, but has been modified and validated for renal patients by Davison and colleagues.[106] The modification includes the addition of a 10th item, itching (scored in the same way), and their original work also included a further unlabelled item for the patient to define themselves, to ensure key symptoms were not being missed.

This tool has the advantage of brevity and simplicity, although some patients (depending on the population) may find visual analogue scales less easy to use.[110] It has been validated in the dialysis population, and the wide use of this tool in other populations facilitates comparison across different conditions.

7.4.1.2 The Memorial Symptom Assessment Scale and the Dialysis Symptom Index

The Memorial Symptom Assessment Scale was also originally developed for cancer patients, and measures the frequency, severity, and distress of 32 common physical and psychological symptoms.[111] Chang et al. developed a short form (MSAS-SF), with the same number of items but focussing predominantly on severity and distress of symptoms, rather than frequency.[112] Weisbord and colleagues undertook a detailed development process to modify the MSAS-SF for

use in the dialysis population. This revised instrument is called the Dialysis Symptom Index (DSI).[107] The DSI is a 30-item index that assesses the presence and severity of 30 individual physical and emotional symptoms. It provides an estimate of the prevalence and severity of these individual symptoms as well as an overall symptom burden and symptom severity score. The DSI has been shown to be a reliable and valid tool to assess symptoms in the haemodialysis population.

Both MSAS-SF and DSI are longer than the ESAS, although each individual item within them is perhaps simpler to complete than a visual analogue scale (it requires the patient simply to indicate (by tick or check) the presence of a symptom, and if present the amount of distress the symptom caused in the last week; either 'no' distress, 'a little bit', 'somewhat', 'quite a bit', or 'very much' distress. The MSAS-SF offers considerable scope for comparison with other populations, since it is used widely across other advanced diseases.

7.4.1.3 The Patient Outcome Scale

The Patient Outcome Scale (POS) was developed as a brief measure for use in those with far advanced disease, for whom completion of questionnaires may be most burdensome and difficult. The original instrument extends beyond physical and psychological symptoms, to include information needs, family communication, and practical matters.[113] More recently, a symptom module (Patient Outcome Scale symptom (POSs)) has been developed [114] which scores 10 symptoms (pain, shortness of breath, weakness or lack of energy, nausea, vomiting, poor appetite, constipation, mouth problems, drowsiness, and immobility) as having 'no' effect, 'slight', 'moderate', 'severe', or 'overwhelming' effect. Patients can also specify additional symptoms if needed, and indicate what symptom is affecting them the most and which has improved the most. This provides additional useful information, especially in the clinical setting where a brief tool is needed, and scarce clinical time addressing symptoms may need to be prioritized to quickly focus on the most severe symptoms. POSs has been validated across a number of conditions, including renal disease.[15] The renal version includes seven additional symptoms; itch, difficulty sleeping, restless legs, feeling anxious, feeling depressed, skin changes, and diarrhoea.[108]

POSs is intermediate in length between ESAS and DSI, and is effective as a brief symptom assessment tool, even in an elderly renal population.[108] It also enables the most severe symptom to be highlighted and responded to rapidly.

7.4.1.4 Symptom-specific measures

Although there is considerable need for the whole range of symptoms which patients experience to be captured, there is a wider range of instruments which have been used to assess individual symptoms, such as pain, pruritus, or depression. It is important to recognize that 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,[115,116] depression,[20,22,117] pruritus,[118] or RLS.[119] The Cambridge–Hopkins restless legs questionnaire is patient-completed and is based on the IRLSSG criteria, but also distinguishes RLS from other conditions, with good sensitivity and specificity.[119] 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.

7.5 The management of symptoms

Once symptoms have been identified and carefully assessed, they need to be actively managed. Evidence shows that management of symptoms is less than optimal for renal patients.[120,121]

Symptom assessment and management is an area which has received only limited clinical or research attention in the past, although this is changing, and research evidence, plus related symptom guidelines are now beginning to emerge for pain and end-of-life care.[122–124] There is some evidence on management derived from the renal population, while other evidence can be extrapolated (to a limited extent) from other populations with chronic disease. However, the renal impairment itself places a major constraint on use of medication, since many medicines are renally excreted, and may therefore accumulate substantially in renal impairment. Careful consideration needs to be given to the effect of dialysis on clearance for those on dialysis.

This section addresses the management of some of the more common symptoms which occur in patients with CKD. Management of pain is addressed in Chapter 8, that of anxiety and depression in Chapter 9, and symptom management in the last days of life – including controlling agitation and myoclonus – are discussed in Chapter 15.

7.5.1 Management of anorexia and dry mouth

Anorexia (loss of appetite) is a distressing symptom for patient and family. The pathogenesis of anorexia is complex and poorly understood,[125] but it is thought that uraemic toxins, altered amino acid patterns, leptin, ghrelin, and neuropeptide Y are involved.[126] There is some debate about the significance of anorexia as a prognostic factor: some evidence indicates that anorexia in dialysis patients is associated with increased risk of death,[127] but a large study of >1800 haemodialysis patients (the HEMO study) suggests this association is lost when co-morbidity is also considered.[128]

In practice, many factors can contribute, and good management requires a thorough and detailed assessment to identify reversible causes. Contributing (and potentially reversible) factors can include nausea or vomiting, constipation, uncontrolled pain, oesophagitis, dyspepsia, dry mouth, and oral candidiasis (common in far advanced disease). In older patients, poor condition or fit of dentures may also need addressing. Dry mouth needs to be actively managed; by ensuring the patient is not dehydrated, using an artificial saliva preparation 1–2 hourly, stopping medications which exacerbate dry mouth (such as cyclizine) whenever possible, and using ice chips to moisten the mouth (particularly useful if fluid restriction remains clinically important). If oral candidiasis is present, nystatin or fluconazole can be used to treat it, in accordance with local sensitivities to these drugs. Fluconazole should be given at a reduced dose of 50–100 mg daily (based on 50% of normal dose if glomerular filtration rate (GFR) is <10 or if the patient is on dialysis) short term (longer term is more likely to select out resistant strains and will cause more adverse effects). If there is taste disturbance, herbs or spices can help in seasoning. Plastic utensils may remove the unpleasant metallic taste sometimes experienced from metal cutlery. Psychological factors are also important, and anorexia may be a feature of underlying depression (which can be particularly difficult to diagnose in debilitated patients); this needs to be assessed fully.

Food is an integral part of social interaction and care. Family carers may need to understand that food intake will reduce as disease advances (especially near end-stage), and offering food too frequently or in the usual portion size can be counter productive. Smaller, attractively presented meals, offered more frequently, may be more palatable, with high-calorie foods in the small amounts that are managed (if diabetic control permits). Dietetic help is very useful in advising and supporting this approach, as well as providing the more usual renal dietary advice. Detailed dietetic assessment and support of CKD patients with anorexia has been shown to improve their biochemical outcomes.[129] Other advice includes trial of metoclopramide to improve gastric emptying, avoiding early satiety by not drinking with meals, and avoiding regular weighing, which can be demoralizing (unless it is important for fluid balance).

The next step to relieve anorexia is to ensure the patient is well-dialysed (a *Kt/V* of at least 1.2). An increase in the number of dialysis sessions to daily haemodialysis has also been shown to improve appetite and food intake.[130] There is some evidence, recently reviewed by Bossola et al.[126] that megestrol acetate (which improves appetite, and possibly nutritional status, in cancer patients) is effective in improving appetite in CKD patients, but the high rate of adverse effects in the renal population means it cannot be recommended for clinical use at present. Dietary supplementation, including with branched-chain amino acids, may offer future avenues for management.

7.5.2 Management of breathlessness

The most common causes of breathlessness or dyspnoea in the renal patient are anaemia, pulmonary oedema (related to fluid overload or to co-existing 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 the situation may arise (particularly in far advanced disease or close to the end of life) where 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,[131] inhaled oxygen if hypoxia is confirmed or suspected,[132] 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 is therefore critical. Detailed explanation of how to cope with and respond to breathlessness should be integral to this. Regular use of relaxation techniques and complimentary therapies can be useful, according to patient preference.

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. This is usually only when treatment of the underlying cause of breathlessness has been exhausted. Note that 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. It is also important to remember that breathlessness is an increasingly important and dominant symptom in renal patients towards the end of life,[15] so it is important to plan with the patient who has had one or more episode of acute breathlessness (or steadily increasing breathlessness over time) how they would like to be treated if they become more symptomatic in the future. 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,[133,134] and clinical experience suggests that this is true for renal patients too. However, there are considerable constraints on the use of opioids in renal patients; the guidance as for pain management should be followed (see Chapter 8), 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 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. These issues are discussed more fully in Chapter 15.

Benzodiazepines are useful when there is co-existing 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 q.d.s. (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 < 10) can be given subcutaneously and titrated according to effect. Midazolam can be given every 2–4 h, although CKD patients are sensitive to its effects and do not usually need frequent or large doses. A starting dose of 2.5 mg is common. If more than one or two doses are required, a subcutaneous infusion over 24 h is most practical.

7.5.3 Management of constipation

Constipation is common among CKD patients. The causes can be multi-factorial – fluid restriction, reduced mobility, medication (such as aluminium or calcium phosphate binders, iron supplements, and opioids), poor dietary intake, depression, and reduced muscle tone, through debility, can all contribute. The dietary restriction of high-potassium fruits and vegetables decreases the fibre content of food ingested. Management requires detailed assessment, treatment of reversible causes where appropriate/possible, acute management to overcome current constipation (including rectal measures), and then action to prevent further recurrence. Mobility and adequate dietary intake – including sufficient fibre and fluid (within the constraints of reduced fluid intake) – need to be encouraged. Table 7.1 shows which laxatives are useful. All are safe in dialysis, although other common laxatives which contain magnesium, citrate, or phosphate (not included in Table 7.1) should be avoided in ESRD. Often, a combination of softener or

Table 7.1 Laxatives for use in renal patients

Drug	Mode of action	Dose	Notes
Lactulose	Osmotic	10–20 ml bd	Ensure adequate oral intake for efficacy
Senna	Stimulant	1–2 tablets nocte or bd	Can cause colic
Bisacodyl	Stimulant	5–10 mg nocte or bd	Can cause colic
Docusate sodium	Softener	100–200 mg bd	
Polyethylene glycol	Osmotic	1–2 sachets	Short-term use only for resistant constipation or impaction (requires high fluid intake which may preclude use)

osmotic laxative with a stimulant is required. Polyethelene glycol (Movicol) is not ideal for renal patients because it requires high concurrent fluid intake, and also contains potassium. However, it may be useful in the short term for constipation which does not respond to other measures, or (in higher doses) for faecal impaction.

7.5.4 Management of fatigue

Fatigue is multi-dimensional,[135] with physical, cognitive, and emotional elements,[136] There is a complex relationship between fatigue, sleep disturbance, physical functioning, and depression in those with renal disease.[23,137] but it is poorly understood. 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;[138] as haematocrit increases, so energy levels increase and fatigue reduces. When anaemia is due to CKD, which is likely if GFR < 30 ml/min/1.73 m^2 (<45 in diabetics) and no other cause, such as blood loss and folic acid or B12 deficiency, is identified, then active treatment with erythropoietin-stimulating agents is likely to improve fatigue. Haemoglobin should be maintained between 10.5 and 12.5 g/dl (per UK Renal Association guidelines). It is not clear, however, how long treatment should be maintained in those who are nearing end of life; most clinicians continue treatment while the patient still continues to gain symptomatic benefit.

7.5.5 Management of nausea and vomiting

Nausea and vomiting are extremely unpleasant symptoms. They may frequently be multi-factorial. Assessment requires a thorough history including establishing the history and pattern of both nausea and vomiting separately. The relationship between the two should also be established, as well as the frequency and volume of vomits, whether there is associated constipation, and a detailed medication history. 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. If medication or toxins are causing nausea, then nausea is usually persistent and unremitting, and sometimes unaccompanied by vomiting. Uraemia, and a variety of drugs (including opioids, anti-convulsants, antibiotics, and anti-depressants) can cause this kind of persistent nausea. Gastroparesis or delayed gastric emptying (which may be caused by drugs such as opioids, as well as occurring secondary to diabetes mellitus,

Table 7.2 Anti-emetics used for CKD patients*

Suspected cause	Drug of choice	Oral dose	Notes
Gastroparesis, delayed gastric emptying	Metoclopramide	5–10 mg tds	Do not use in bowel obstruction with colic. Do not use with cyclizine. Increased risk of dystonia in CKD patients
	Domperidone	20 mg tds	Domperidone can also be used rectally (30–60 mg bd or tds)
Uraemia	Haloperidol Levomepromazine	0.5–2 mg od or bd 6 mg od	Increased cerebral sensitivity in renal failure Sedative at higher doses
	5HT3 antagonists: Ondansetron Granisetron	 8 mg bd 1 mg bd	Side effects of constipation and headaches may limit use
Drug induced	Haloperidol Cyclizine	0.5–3 mg od or bd 25–50 mg tds (caution – adverse cardiac effects may need consideration given the high proportion of CKD patients with cardiac co-morbidity)	First step is to stop medication causing drug-induced nausea if possible. Note: opioid-induced nausea usually settles spontaneously after about 7–10 days on the opioid
Gastritis (low threshold for treatment)	Omeprazole or other proton-pump inhibitor	20 mg od	

*Also see Chapters 8 and 15

for instance) 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.

7.5.6 Management of pruritus

Although there are a number of studies into the pathogenesis and treatment of pruritus in CKD patients, its aetiology and pathogenesis remains unclear, and treatment options remain somewhat limited in their effectiveness.

Pruritus is thought to arise in C-fibres located in the skin and distinct from those which mediate pain; a subgroup of C-fibres has been identified which discharge in a pattern matching that induced by itch.[139] These C-fibres transmit via the contralateral spinothalamic tract to the brain (thalamus and hypothalamus) via the reticular formation.[140] 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 within this convoluted 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 CKD-related itch, it appears that complex interacting factors operate at more than one place in the pathway,[140] 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.

Firstly, it is known that CKD leads to an immune system derangement, and it has been suggested that this results in a pro-inflammatory or inflammatory state that precipitates itch;[8] for this reason, 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. This inflammatory hypothesis resonates with evidence that a high white blood cell count is predictive of itch in haemodialysis patients,[72] and dialysis patients on statins (which reduce serum pro-inflammatory cytokines) have lower levels of itch.[141] Others have shown that pro-inflammatory and inflammatory cytokines are associated with pruritus,[142] and that increasing levels of C-reactive protein correlate with severity of itch in dialysis patients.[55]

Secondly, a number of authors have proposed disturbance in the endogenous opioids system as a cause of itch.[8,143] It is well established that μ-opioids can induce itch, particularly spinally administered μ-opioid receptor agonists, and μ-opioid receptor antagonists can reduce itch.[144] In contrast, κ-opioid receptor agonists have been shown to have anti-pruritic effects in animals, and κ-opioid receptor antagonists enhance itch in animal studies.[144] It is for this reason that opioids such as butorphanol (which has μ-opioid antagonist and κ-opioid agonist action),[145] and opioids antagonists such as naloxone and naltrexone, have been proposed to treat itch. There is also some evidence that a new κ-opioid agonist (nalfurafine) may be useful.[146]

Thirdly, there is some evidence 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.[9] Other studies have explored the use of neuropathic agents (lidocaine, gabapentin, and capsaicin) to treat itch, with some success. However, the neuropathic component could be a secondary, rather than primary, cause of CKD-related pruritus.

Lastly, 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 CKD-related pruritus. Nevertheless, anti-histamines are widely used in the management of CKD-related pruritus, with varying results.

A further important factor in CKD-related itch is xerosis, or dry skin. There is conflicting evidence about the relationship between xerosis and itch in CKD patients,[9,64,66] but it may be an important factor in older people with CKD.[147] In addition, although uraemia is the most likely cause of pruritus, other common causes of pruritus, such as skin disorders, skin infections such as scabies, and liver impairment, need to be considered if the symptom is not resolving.

Given the confusion and complexity in understanding the causes of pruritus in CKD, it is not surprising that it can be a difficult symptom to manage, with a variety of different treatments proposed, each of limited effectiveness. The first step in management is to optimize renal management; high phosphate may contribute to pruritus,[140] so attention to reducing phosphate levels may be important – consider dietary advice and the use of phosphate-binders. 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), keeping cool (light clothing, and tepid baths or showers) are useful concurrent measures.

The evidence as to which medications are effective is limited, often conflicting, and no single preparation can be recommended above others. Choice of treatment for should be influenced by the stage of disease – for instance, UV light may be practical for those who remain relatively well, while anti-histamines may be more appropriate nearer end of life. Table 7.3 provides details of possible drug treatments and the evidence to support each. Whatever the evidence, individual patients do report significant benefit with some of these options. Time should be taken to discuss with the patient the need to persist with any one medication, and to explaining and minimizing 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 symptoms can sometimes cause. The psychological and social dimensions of severe itch are considerable,[15] and psychological, family, and social support is an important component of management.

7.5.7 Management of restless legs

Restless legs syndrome is characterized by 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 (1) urge to move the legs, usually with unpleasant sensations in the legs, (2) worse during periods of rest or inactivity like resting or sitting, (3) partial or total relief by physical activity, and (4) worse symptoms in the evening or night rather than the day.[84] The exact cause for restless legs is not understood as yet; it is widely accepted, however, that the dopaminergic system in the central nervous system is somehow disrupted.[74] There may also be a relationship between brain iron metabolism and RLS.[172] There is limited evidence in uraemic RLS that iron deficiency,[173] low parathyroid hormone,[76] hyperphosphataemia, and psychological factors[174] may all 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 anti-histamines, metoclopramide, tricyclic antidepressants, selective serotonin uptake inhibitors, lithium and dopamine antagonists).[74] Calcium antagonists may also exacerbate RLS.[175]

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.[176]

7.5.8 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; each of these 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 day-time 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 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 CKD patients may be more sensitive to benzodiazepines in general, and lower doses are often required than in the general population.

Table 7.3 Proposed treatments for pruritus in CKD patients

Drug	Dose	Evidence of effectiveness	Notes
Topical and external treatments			
Emollients (aqueous cream, Diprobase, Balneum, etc.)	Topical, applied liberally 2–4 times daily	In an uncontrolled study, 9 out of 21 dialysis patients with dry skin had marked reduction in itch following regular use of twice daily aqueous cream for 1 week[148] In a small controlled study, 10 haemodialysis patients with mild pruritus showed benefit from an aqueous gel applied twice daily for two weeks, compared with 10 control patients[149] In an uncontrolled study, 26 out of 30 dialysis patients had resolution of pruritus following baths using Balneum bath oil every 1–2 days for 4 weeks[150] In an uncontrolled study, eight out of 21 haemodialysis patients with dry skin and pruritus had resolution of pruritus following twice daily use of a lipid-based cream containing endocannabinoids for 3 weeks[151]	**RECOMMENDED FIRST LINE** especially if xerosis (dry skin) Use spray preparations for ease of application where appropriate (e.g. older patients living alone)
Capsaicin cream	0.025% cream applied qds	In a double-blind RCT with cross-over design, 19 haemodialysis patients with moderate-to-severe pruritus received 0.025% cream qds; 14 out of 17 showed marked improvement, although burning on application of the cream was problematic and caused two patients to drop out[152] Eight of nine haemodialysis patients in an uncontrolled study, and two out of 5 in a double-blind RCT reported complete resolution of pruritus following 0.025% cream qds[153]	**CONSIDER IF LOCALIZED RATHER THAN GENERALIZED ITCH** Capsaicin cream is best used when pruritus is localized, as it is not practical to apply it widely. It works by depleting Substance P, and some persistence is needed to continue use with local burning discomfort until it can take effect. Cost may be a limiting factor in its use.
Tacrolimus ointment	0.03% or 0.1% ointment bd	In an controlled study, three dialysis patients reported benefit following use of 0.03% ointment bd[154] In an uncontrolled study, 25 haemodialysis patients showed small reduction in pruritus scores following use of 0.1% then 0.03% ointment bd, although five out of 25 patients reported troublesome side effects (rash, tingling/burning)[155] In a double-blind RCT of 22 haemodialysis patients, the 0.1% ointment bd for 4 weeks showed no benefit over control[156]	**NOT RECOMMENDED** Little evidence to support use, and safety in longer term use is uncertain.

(Continued)

Table 7.3 (continued) Proposed treatments for pruritus in CKD patients

Drug	Dose	Evidence of effectiveness	Notes
UVB light		In an uncontrolled study, 32 out of 38 dialysis patients improved after UVB treatment twice weekly for 4 weeks[157,158] In an uncontrolled study, 17 dialysis patients given UVA or UVB light 3 times weekly for 2–3 min all had resolution of their pruritus[159]	**RECOMMENDED IF LOCALLY AVAILABLE** Some uncertainty regarding long-term effects
Systemic therapy			
Anti-histamines, such as:		Evidence in respect of anti-histamines for pruritus is scanty, and much of the rationale for their use is extrapolated from other disease populations.	**IT IS CURRENT CLINCAL PRACTICE TO USE ANTI-HISTAMINES ALTHOUGH EVIDENCE DOES NOT SUPPORT THIS** May be useful mostly for their sedative effects, especially at night.
Cetirizine	10 mg od (5 mg if eGFR < 10)	In a double-blind RCT, cross-over design, 18 out of 27 patients showed remission of pruritus following treatment with terfenadine[160]	
Chlorpheniramine	4 mg qds (tds if eGFR < 10)	In an uncontrolled study, all five haemodialysis patients had reduction in pruritus following treatment with ketotifen over 6 weeks[161]	
Gabapentin	100–400 mg after dialysis sessions	In a double-blind RCT of 25 haemodialysis patients with itch, there was statistically significant reduction in itch scores in those treated with gabapentin thrice weekly following dialysis for 4 weeks[162] In a double-blind RCT of 34 haemodialysis patients with itch unresponsive to anti-histamines, there was statistically significant reduction in itch scores in those treated with gabapentin 400 mg twice weekly after dialysis for 4 weeks[163] Both studies reported no adverse effects	**RECOMMENDED FOR DIALYSIS PATIENTS** Needs substantial dose reduction in those on dialysis, and should be given only after dialysis. Accumulates rapidly in those not dialysed who have Stage 4 and 5 CKD; use with caution and in very low doses. In Stage 5 CKD without dialysis, it is preferable not to use it at all.

5-HT3 receptor antagonists, such as: Ondansetron Granisetron	 2–8 mg bd 1 mg bd	In a double-blind RCT with cross-over design, 17 haemodialysis patients with pruritus of all levels of severity were given ondansetron 8 mg tds, and both placebo and treatment groups showed benefit with no statistically significant difference[164] In an uncontrolled study, 11 dialysis patients with moderate to severe pruritus were given ondansetron 4 mg bd and all responded within 2 weeks[63] In a double-blind RCT with cross-over design, 16 haemodialysis patients with persistent pruritus were given ondansetron 8 mg tds for 2 weeks, and pruritus scores did not change during treatment in either control or treatment groups[165] In an uncontrolled study of 14 haemodialysis patients with pruritus, granisteron 1 mg bd was given for 4 weeks, with significant reduction in itch from the first week of treatment[166]	**NOT RECOMMENDED** A few very small trials undertaken with conflicting results, and the RCTs in particular suggest no benefit. It could be considered in those with co-existing nausea since it is an effective anti-emetic. It is highly constipating (laxative should be co-prescribed).
Naltrexone	50 mg daily	In a double-blind RCT with cross-over design, 15 haemodialysis patients with severe pruritus were given naltrexone 50 mg daily for 1 week. Pruritus improved following naltrexone, within the first 48 h of treatment[167] In a double-blind RCT with cross-over design, 23 dialysis pts with moderate to severe pruritus were given naltrexone 50 mg daily for 1 week. Pruritus reduced in both treatment and control phases with no statistically significant difference. The level of adverse effects was high, with gastrointestinal side effects occurring in 10 out of 23 patients[168] Naloxone has also been proposed, but only case study evidence exists[169]	**NOT RECOMMENDED** Evidence is conflicting and based on small studies, with concern about adverse effects. Opioid antagonists also cannot be given if opioids are to be used for pain management. Opioid receptor imbalance may become more relevant only in severe pruritus[170] and this may be one of the reasons for conflicting evidence.

(Continued)

Table 7.3 (continued) Proposed treatments for pruritus in CKD patients

Drug	Dose	Evidence of effectiveness	Notes
Thalidomide	100 mg at night	In a double-blind RCT with cross-over design, 29 haemodialysis patients received thalidomide daily for 1 week, and over half showed significant response in the thalidomide phase of the study[171]	**CONSIDER IF RESISTANT TO OTHER TREATMENTS** The evidence is very limited, and the risks and adverse effects of thalidomide should be considered carefully. Thalidomide has a risk of (reversible) peripheral neuropathy, and there is risk of teratogenic effects to those who are pregnant, even from handling tablets.
Nalfurafine	5 μg 3 times weekly by infusion	In one double-blind placebo controlled RCT, 79 haemodialysis patients received nalfurafine thrice weekly after dialysis, over 4 weeks. In a second placebo controlled cross-over study, 34 haemodialysis patients received nalfurafine or placebo for 2 weeks before crossing over for a further 2 weeks.[146] In both studies, nalfurafine produced a statistically significant improvement in 'worst itching'	These findings are promising although nalfurafine is not widely available at the time of publication.

Table 7.4 Proposed treatments for restless legs in CKD patients

Drug	Starting dose	Evidence of effectiveness	Notes
Co-careldopa (levodopa with carbidopa)	12.5 mg/50 mg od	In a double-blind RCT cross-over study, 11 uraemic patients had improved sleep, quality of life, and reduced movements on levodopa 100–200 mg od with no adverse effects[177] In an RCT with just five haemodialysis patients, there were reduced movements and improved sleep on levodopa/carbidopa (25/100 mg)[178] In an uncontrolled study, eight haemodialysis patients on 25/100–25/250 mg of levodopa and carbidopa had reduced perception of RLS[179]	**RECOMMENDED** RLS may become, over time, worse in 80% of cases (augmentation). This correlates with greater accumulated dose of L-dopa, so treat with lowest dose for shortest duration.
Dopamine agonists: Pergolide Pramipexole Ropinirole	 25 µg od 88 µ tds 250 µg tds	In an RCT, cross-over design, with 11 haemodialysis patients, ropinirole was better than levodopa in controlling the symptoms of RLS[180] In a uncontrolled study, the RLS symptoms of 10 haemodialysis patients improved with pramipexole[181] In a double-blind RCT, 16 haemodialysis patients with RLS had benefit from pergolide, nausea and nightmares were noted adverse effects[182]	**RECOMMENDED** Nausea common with pergolide, but in general augmentation is less likely to occur with the dopamine agonists than with levodopa, and the side effects may also be less Long-term use may be precluded by restrictive cardiac valve disease and pulmonary fibrosis[74]
Clonazepam	250–500 µg od	In an uncontrolled study, 14 out of 15 patients with end-stage renal disease benefited from clonazepam 1–2 mg daily[183]	**CONSIDER IF OTHER TREATMENT INEFFECTIVE OR CONTRAINDICATED** Can cause day-time sleepiness and cognitive impairment
Gabapentin	100–400 mg (post dialysis)	In a controlled study comparing levodopa and gabapentin, with 15 haemodialysis patients, gabapentin was more effective[184] In a double-blind RCT with cross-over, comparing placebo and gabapentin, in 16 haemodialysis patients, gabapentin was more effective[185]	**RECOMMENDED IN DIALYSIS PATIENTS** Needs substantial dose reduction in those on dialysis, and should be given only following dialysis. Accumulates rapidly in those not dialysed who have Stage 4 and 5 CKD, use with caution and in very low doses. In Stage 5 CKD without dialysis, it is preferable not to use it at all.

7.6 Conclusions

For people with CKD, symptoms can arise directly from the renal disease itself, as a consequence of dialysis, or from co-morbid conditions (particularly in older patients). For any single individual, it is often a combination of causes which contributes to their overall symptom burden. Fatigue, itch, pain, and breathlessness are highly prevalent, and other physical symptoms (such as restless legs, muscle cramps, headaches, and dizziness) are particularly characteristic of renal disease. Mild psychological symptoms are also frequent in this population, and formal depressive illness – although seen less often – is notably more frequent than in the age-matched general population.

This chapter highlights the importance of regular and routine symptom assessment as an integral part of clinical practice. Symptom measures have been briefly reviewed, and the importance of assessing the whole range of symptoms underlined. Two symptom measures, the DSI and the renal version of the POSs module, are presented. Pharmacological management of symptoms is discussed in detail, since this is one of the most challenging aspects of the care of those on dialysis, withdrawing from dialysis, or managed conservatively, without dialysis. Although the emphasis 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 these reasons that care of renal patients is best managed with multi-professional teams, including counsellors and psychologists, occupational and physiotherapists, dieticians, and chaplains, and most importantly, professionals with both nephrology and palliative care skills.

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Management of pain in chronic kidney disease

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Pain is a significant problem for a substantial number of chronic kidney disease (CKD) patients which often goes unrecognized. The World Health Organization analgesic ladder and basic pharmacological principles can be used as a template for the assessment and treatment of pain in CKD patients. This review examines pain management principles for patients with CKD.

Keywords: pain, opioids, end-of-life care, end-stage renal disease, palliative care

A growing body of literature demonstrates that approximately 50% of chronic kidney disease (CKD) patients experience chronic pain, with as many as 82% reporting this pain as moderate to severe in intensity.[1–3] In fact, the number and severity of pain and other symptoms reported by end-stage renal disease (ESRD) patients, whether they be treated with dialysis or managed conservatively (without dialysis), is similar to that reported by many cancer patients in palliative care settings.[3–5] Unfortunately, pain in CKD is both under-recognized[6] and under-treated.[7] This review will examine pain management principles for patients with CKD.

Impact of pain on health-related quality of life

Chronic pain is associated with psychological distress, depressive disorders, substantial limitations in work, family, and social life, and excessive use of the healthcare system. Recent research has confirmed the tremendous psychosocial burden of pain in CKD patients.[8–11] Dialysis patients with chronic pain are 2–3 times more likely to suffer from insomnia and depression than patients without chronic pain.[12] Symptom burden accounts for 29% of the impairment in their physical health-related quality of life (HRQL) and 39% of the impairment in mental HRQL.[4] Similarly, changes in symptom burden have been shown to account for 34% of the change in physical HRQL and 46% of the change in mental HRQL in haemodialysis patients.[13] These findings reinforce the importance of integrating effective clinical approaches to pain management in the care of CKD patients.

In CKD, pain is often experienced in the context of multiple, debilitating symptoms such as anorexia, fatigue, nausea, insomnia, pruritus, anxiety, and depression as well as end-of-life issues, all of which may interfere markedly with psychosocial and physical coping strategies. Pain management is unlikely to be successful unless these other issues are also addressed.[14]

Causes and categorization of pain

Pain in patients with CKD may be due to the primary renal disease (*e.g.* polycystic kidney disease), concurrent co-morbidity (*e.g.* diabetic neuropathy or peripheral vascular disease), or disease consequent upon renal failure (*e.g.* calcific uremic arteriolopathy [CUA] or renal bone disease). Pain may also result from the treatment of ESRD (*e.g.* osteomyelitis from central lines and ischaemic neuropathies from arteriovenous fistulae). Patients on peritoneal dialysis often contend with lower back strain from abdominal distension and haemodialysis patients may experience

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Table 1 Barriers to adequate pain management in CKD

Lack of recognition of the problem	Patients under-report pain. Nephrology staff under-recognize the prevalence, severity and impact of pain in CKD
Lack of research/knowledge	Studies of the pattern and types of pain seen in CKD are needed in addition to those evaluating the efficacy of analgesia with particular reference to the toxicity in this group of patients
Altered pharmacokinetics and pharmacodynamics of analgesics	CKD patients are much more likely to experience adverse effects to analgesics. The pharmacokinetics and pharmacodynamics of most analgesics in CKD are unknown
Adverse effects of analgesics	Adverse effects of analgesics are mimicked by uremic symptoms and may result in the inappropriate withdrawal of analgesics
Co-morbid disease	CKD patients are frequently on multiple drugs with the consequent increase in risk of adverse drug interactions
Lack of training in pain management	Pain evaluation and management have not been a focus of training in renal medicine
Limb preservation	Efforts to preserve a limb or defer high-risk surgery results in on-going ischaemic pain

recurrent cramps or headaches while on dialysis.[1,15,16] Patients frequently have more than one cause of pain.[1]

Categorizing pain helps the physician choose appropriate drug and non-drug therapies. Nociceptive pain results from tissue damage that stimulates sensory receptors. Pain is characteristically felt at the site of damage and may be described using terms such as sharp or like a knife (*e.g.* joint pain in dialysis-related amyloid arthropathy, flank pain from capsule distension in polycystic kidney disease) or dull, poorly localized pain (*e.g.* gut ischaemia). Generally, nociceptive pain responds well to opioids.

Neuropathic pain results from damage to the nervous system, either at the site of damage or at the level of the dorsal horn. Common descriptors include burning, shooting, and stabbing. It characteristically occurs in an area of abnormal sensation, and may be felt at a site distant from its cause. It may be associated with episodes of spontaneous pain, hyperalgesia, and allodynia. The pain of peripheral neuropathy and phantom limb pain belongs in this category. Neuropathic pain may be poorly responsive to opioids or require doses for analgesia that are associated with unacceptable toxicity. Adjuvant analgesics such as antidepressants and anticonvulsants are often required. Many causes of pain are of mixed type (*e.g.* ischaemia, CUA).

Barriers to adequate pain relief

Despite what appears to be an increasing prevalence of chronic pain, analgesic use in ESRD has decreased over the last few years. The Dialysis Outcomes and Practice Patterns Study (DOPPS) compared analgesic use in 1997 to 2000 for 3749 dialysis patients in 142 US facilities.[7] The percentage of patients using any analgesic decreased from 30% to 24%. Opioid use decreased from 18% to less than 15% and acetaminophen use decreased from 11% to 6%. Of patients with pain that interfered with work, 74% had no analgesic prescribed. These findings are consistent with other reports where 35% of haemodialysis patients with chronic pain were not prescribed analgesics despite the vast majority experiencing moderate or severe pain and less than 10% were prescribed strong opioids.[1]

The high prevalence of unrelieved pain is not unique to CKD. Inadequate pain assessment, reluctance of the patient to report pain, fear of addiction, and lack of staff time and training in the basic principles of pain management have been identified as barriers to adequate pain management in cancer patients.[17] These also apply to CKD; however, there are additional challenges in pain management in CKD (Table 1).

Evaluation of pain

Evaluation starts with a pain history that includes documentation of sites, severity, and postulated causes, previous measures of pain relief, their effectiveness, and toxicity, and the effects on psychosocial and spiritual issues. Pain can be recorded using simple, unidimensional pain measurement tools such as visual analogue scales and verbal/numerical rating scales. More sophisticated multidimensional tools, such as the McGill Pain Questionnaire (MPQ)[18] or the Brief Pain Inventory (BPI),[19] incorporate quality-of-life questions. Recently, global symptom assessment tools, developed for advanced cancer

hyperkalaemia. The major limitation of NSAIDs is gastrointestinal toxicity and there may be an increased risk of bleeding in patients with CKD. Selectivity for cyclooxygenase-2 (COX-2) reduces the risk for peptic ulceration but does not lessen the risk of other adverse effects and studies have suggested that there might be an increased risk of myocardial infarction.[35,36] NSAIDs can be used in conjunction with acetaminophen but their use in CKD is best reserved for specific indications of acute pain such as gout or renal colic.[41,42]

WHO analgesic ladder: Step 2

Codeine is metabolized in the liver to form morphine and norcodeine.[37] The active metabolites are renally excreted and accumulate in patients with renal impairment.[38–40] There have been several case reports of prolonged narcosis and respiratory depression in patients with renal impairment following ingestion of codeine, even at trivial doses.[40,41] This appears to be an idiosyncratic phenomenon with some patients able to tolerate regular doses of codeine for prolonged periods without experiencing toxicity. We advise caution with chronic use of codeine in CKD patients and suggest limiting doses to ≤ 120 mg/day.

Oxycodone is a semisynthetic opioid[42] with a similar analgesic and side-effect profile to morphine.[43,44] It is metabolized in the liver to noroxycodone and oxymorphone (analgesic but of unknown importance clinically), both of which accumulate in dialysis patients.[45] Less than 10% is excreted unchanged in the urine.[46] In a single case study, oxycodone and its metabolites were reduced by dialysis, but without loss of analgesia.[47] However, another case report demonstrated respiratory depression in a dialysis patient who received 5 mg of oxycodone 6 times a day for 8 days. The patient needed a 4-day naloxone infusion.[48] There are no long-term studies of chronic use in CKD and the conflicting case reports mean there is insufficient evidence currently for a recommendation

Tramadol, a centrally acting analgesic, exerts its actions through agonism of the μ-opioid receptor and inhibition of noradrenaline and serotonin re-uptake.[49,50] Tramadol may induce fewer opioid side-effects for a given level of analgesia compared with traditional opioids.[51,52] Only 30% of the analgesic action can be antagonized by naloxone.[53] Tramadol is metabolized in the liver to *O*-desmethyl tramadol (M1) which has a higher affinity for the μ-opioid receptor than the parent drug,[54] but its slow production results in very low and clinically insignificant plasma levels. About 90% of tramadol and its metabolites are excreted in the urine, with 30% as unchanged tramadol.[55] Adjustments are required in patients with renal impairment.[56] Patients with a creatinine clearance of < 30 ml/min or on dialysis should receive a maximal daily dose of 200 mg.[56] If clearance is < 15 ml/min and patients are not being dialyzed, the maximum recommended daily dose is 100 mg (*e.g.* 50 mg b.i.d.).

WHO analgesic ladder: Step 3

Morphine is extensively metabolized by hepatic biotransformation with 5–10% excreted unchanged in the urine. Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are the active metabolites: M6G is approximately twice as potent an analgesic as morphine,[57] accounting for a significant proportion of morphine's analgesic actions with chronic administration.[57–60] Both these metabolites are excreted by the kidney and accumulate in renal failure.[61–66] Chronic administration of morphine is associated with significant toxicity in patients with CKD and, therefore, not recommended.

Hydromorphone is 5–7 times more potent than morphine following oral administration,[67] but may cause less pruritus, sedation, and nausea than morphine.[68] Hydromorphone is primarily metabolized in the liver to hydromorphone-3-glucuronide (H3G) which is excreted in the urine.

A study of 12 anuric haemodialysis patients[69] showed that chronic administration of hydromorphone did not substantially accumulate, most likely due to rapid metabolism to H3G. These patients had been taking a mean daily dose of 20 mg for a mean of 9 months. Conversely, H3G accumulated between dialysis treatments but appeared to be effectively removed during hemodialysis. Importantly, hydromorphone resulted in a 65% reduction in pain over dosing intervals and no clinically significant opioid toxicity was observed. The accumulation of H3G between hemodialysis treatments appeared to be associated with greater sensory-type pain and reduced duration of analgesia suggesting a role of H3G in antagonism of hydromorphone analgesia in patients with CKD. While hydromorphone may be a safe, well tolerated, and effective in selected dialysis patients, it may not be as effective or as well tolerated in conservatively managed, non-dialysis patients or during the final days of life following withdrawal from dialysis. A retrospective audit[70] and our own clinical experience in dialysis patients support the notion that hydromorphone is better tolerated than morphine when normal release preparations are used (see Table 3 for dosing suggestions).

Methadone is a synthetic opioid.[71,72] Clinically, it is used as a substitute opioid in the management of dependence and as an alternative opioid in cancer pain,[73] where some believe it may be more effective for

Table 2 Principles of analgesic dosing

By mouth	Whenever possible, drugs should be given orally
By the clock	When pain is continuous, analgesics should be given regularly. Additional 'breakthrough' medication should be available on an 'as needed' (PRN) basis
By the ladder	Use the World Health Organization (WHO) analgesic ladder
For the individual	There is no standard dose of strong opioids. The 'right dose' is the dose that relieves the patient's pain without causing unacceptable side-effects
Attention to detail	Pain changes over time, thus there is the need for assessment and re-assessment until pain relief is achieved

patients, have been adapted and validated for use in CKD patients: the modified Edmonton Symptom Assessment System (mESAS),[4,13] the Memorial Symptom Assessment Scale Short Form (MSAS-SF), renamed the Dialysis Symptom Index (DSI),[2,20] and the modified Patient Outcome Scale – symptom module (mPOSs).[3] An advantage of utilizing tools common to other patient groups is that relevant and useful comparisons can be made. The mESAS is a simple tool that consists of visual analogue scales with a superimposed 0–10 scale for 10 commonly experienced symptoms, including pain. It has the advantage of being simple, quick, and easily understood by both staff and patients and can be successfully used in patients even as they approach death. The mPOSs includes 17 common symptoms and assesses the degree symptoms affect activities and concentration. The DSI looks at 31 symptoms.

The principles of pain management in CKD

Five principles of analgesic dosing are summarized in Table 2. The World Health Organization (WHO) advocates a step-wise approach to analgesic therapy (Fig. 1) for

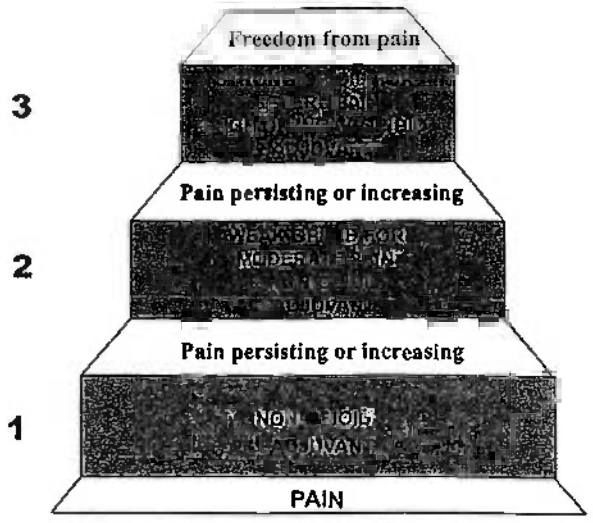

Figure 1 The WHO analgesic ladder

malignant cancer pain. It has been used widely for non-malignant pain and there is preliminary evidence to suggest that this pharmacological approach to pain management may be appropriate and effective in CKD.[21] Initial analgesia is selected according to the severity of pain, starting at the lowest appropriate level. The drug should be used at its full, tolerated dose before moving to the next level. If ineffective, it is unlikely that another drug from the same step will be effective and generally it is necessary to proceed to the next step. Step 1 analgesics at full dose can be added to Step 2 or Step 3 drugs. Adjuvant analgesics can be added to all three steps for specific indications, such as neuropathic pain.

In view of the potential for toxicity, short-acting rather than long-acting preparations should be used until stable pain relief has been achieved. Adverse effects of strong opioids are sufficiently common to prevent effective analgesia and patients should be warned of these and informed of the steps that can be taken to prevent or treat them at the time of opioid initiation. Tolerance to some adverse effects occurs after some days if doses are titrated slowly.

Choice of analgesic and dosing in CKD

Many analgesics and their metabolites are excreted by the kidney. Several handbooks provide guidelines for dose adjustment in renal impairment.[22–24] Data for recommendations are derived from case series or model-dependent changes in clearance, half-life, and volume of distribution.[25–28] Consequently, guidelines are driven in large part by expert opinion and should be regarded only as useful approximations.

WHO analgesic ladder: Step 1

Acetaminophen is metabolized by the liver with only 2–5% excreted unchanged in the urine and does not require dose adjustment in CKD. It is considered the non-narcotic analgesic of choice for mild-to-moderate pain in CKD patients.[29]

Non-steroidal anti-inflammatory drugs (NSAIDs) can cause irreversible reduction in GFR,[30,31] sodium and water retention aggravating hypertension,[32–34] an

Table 3 Dosing suggestions for WHO analgesic ladder Step 3 opioids in dialysis patients

- Start at a low dose, especially if opioid naïve: hydromorphone 0.5–1.0 mg 6-hourly and PRN
- If tolerated, increase frequency to 4-hourly within 24 h if needed
- Titrate dose upwards every 24–48 h according to the number of PRN doses needed
- If 6 or greater doses are required per 24 h, stop regular hydromorphone and replace with transdermal fentanyl 12 μg/h.
- Continue using PRN hydromorphone
- Continue dose titration upwards if needed, remembering to increase the dose of hydromorphone for breakthrough pain if the patch size increases
- Alternative to fentanyl (if 24-h opioid requirement < 12 μg/h or non-dialysis patient) low-dose transdermal buprenorphine starting at 5 μg/h
- If familiar with prescribing methadone for pain consider methadone. There are several ways of switching a patient to methadone. One technique is to start patients on a low dose (*e.g.* 1 mg t.i.d.) and titrate upwards as needed every few days with gradual reduction of previous opioid. Hydromorphone should be available for breakthrough pain
- Monitor closely for toxicity

neuropathic pain than other strong opioids because of its NMDA receptor antagonism. Methadone has high oral bioavailability and is extensively distributed in the tissues where it accumulates with repeated dosing. Slow release from the reservoirs in the tissues can result in prolonged pharmacological action of up to 60 h.[74,75] It is excreted mainly in the feces, with metabolism into pharmacologically inactive metabolites primarily in the liver, although ~20% is excreted unchanged in the urine.[76] It does not appear to be removed by dialysis;[77,78] however, in anuric patients, methadone appears to be exclusively excreted in feces with no accumulation in plasma.[77] These factors would suggest that methadone may be an appropriate analgesic for use in CKD.

Meperidine (Pethidine) is metabolized in the liver mainly to norpethidine, which has twice the proconvulsive activity as its parent compound[79] and accumulates in patients with renal impairment.[80] It should be avoided in CKD patients.

Fentanyl is a potent synthetic opioid with a short onset time and relatively short half-life.[81] Fentanyl has a lower incidence of constipation and affords greater cardiovascular stability than morphine.[82] Fentanyl has poor oral bioavailability; it is usually administered intravenously or transdermally. The latter is only suitable for stable pain or to provide background analgesia while dose titration takes place with a short-acting opioid. There is also extensive experience of subcutaneous use in the UK for end-of-life care for renal patients. It is rapidly metabolized in the liver, with only 5–10% excreted unchanged in the urine.[83] Its metabolites are considered to be inactive. There does not appear to be clinically significant accumulation of fentanyl when administered to patients with renal impairment.[82,84–86] A number of buccal preparations of fentanyl are being developed to contribute to the management of breakthrough pain.

Table 4 Topical analgesics

Topical NSAIDs

These can provide effective pain relief with a number needed-to-treat (NNT) of 3.1 for 50% pain relief.[103] Topical NSAIDs do not appear to be associated with serious side-effects. Where pain is present in joints or non-ulcerated skin, this may be a useful alternative to oral administration

Topical capsaicin

Capsaicin is an alkaloid from chillies that can deplete substance P, which is thought to be associated with the transmission of painful stimuli in local sensory nerve endings. A meta-analysis showed a number needed-to-treat (NNT) of 4 in diabetic neuropathy when compared to placebo and similarly a NNT of 3 in osteoarthritis.[104] Although not as effective as anticonvulsants, it has lower toxicity

Topical opioids

In the presence of inflammation, peripheral opioid receptors are recruited very rapidly.[105] The presence of inflammation appears to be essential for the efficacy of topical morphine[106]

Alfentanil, a derivative of fentanyl, about one-quarter as potent, is extensively metabolized in the liver to inactive compounds. Compared to fentanyl, it has a smaller volume of distribution and a shorter terminal half-life leading to less accumulation.[81] When doses greater than 600 μg/24 h of subcutaneous fentanyl are required, alfentanil can be administered more easily because a smaller total volume is required. Intranasal or buccal administration can be used for breakthrough pain or when additional analgesia is required for short periods such as dressing changes.[87]

Buprenorphine is a semisynthetic opioid with a long duration of action that can be administered sublingually or via a transdermal patch.[88] It is 30–60 times as potent as oral morphine when given sublingually.[88,89] Because of the avidity with which

Table 5 Adjuvant drugs in neuropathic pain

TRICYCLIC ANTIDEPRESSANTS	
Amitriptyline	
Renal handling	Metabolized in the liver (cytochrome P-450); < 5% excreted unchanged in the urine. Unaffected by dialysis
Common side-effects	Antihistaminic: sedation. Anticholinergic: dry mouth, blurred vision, constipation, urinary retention. Central effects: fatigue, dizziness, weakness, tremor, confusion, postural hypotension
Less common, but important, side-effects	Conduction disturbances, especially tachyarrythmias. Weight gain. Reduced libido
Contra-indications	Glaucoma. Concurrent MAOIs. Recent myocardial infarction. Multiple drug interactions
Dose schedule	10–25 mg qhs, increasing every few days to symptomatic relief or toxicity (rarely need to use more than 75 mg)
Comments	Lowers seizure threshold. Dose alteration not usually necessary in renal failure, though may be poorly tolerated
Desipramine	
Renal handling	Metabolized in the liver (cytochrome P-450); < 5% excreted unchanged in the urine. Unaffected by dialysis
Common side-effects	Antihistaminic: sedation. Anticholinergic: dry mouth, blurred vision, constipation, urinary retention. Central effects: fatigue, dizziness, weakness, tremor, confusion, postural hypotension
Less common, but important, side-effects	May have fewer cardiac adverse effects than amitriptyline, especially in the elderly
Contra-indications	Glaucoma. Concurrent MAOIs. Recent myocardial infarction. Multiple drug interactions
Dose schedule	100–200 mg qhs
Comments	Lowers seizure threshold. Dose alteration not usually necessary in renal failure, though may be poorly tolerated
ANTICONVULSANTS	
Carbamazepine	
Renal handling	Metabolized by liver
Common side-effects	Anorexia, nausea, vomiting, ataxia, headaches, dizziness, drowsiness, visual disturbance – may improve with continued treatment
Less common, but important, side-effects	Fluid overload due to antidiuretic action. Interaction with warfarin and oral contraceptive pill
Contra-indications	Concurrent MAOIs
Dose schedule	200 mg daily increasing weekly to effectiveness or toxicity or a maximum dose of 1600 mg
Comments	Effect may occur within 2–3 days. Plasma concentrations reduced by other anticonvulsants
Valporic acid	
Renal handling	Metabolized by the liver and eliminate via the kidneys
Common side-effects	Gastric irritation, nausea, tremor, ataxia, drowsiness, weight gain
Less common, but important, side-effects	Liver toxicity
Contra-indications	Acute liver disease, family history of severe hepatic dysfunction, porphyria
Dose schedule	200 mg daily increasing by 200 mg to pain control or a maximum dose of 1000 mg
Comments	Well tolerated. Interaction with other anticonvulsants
Gabapentin	
Renal handling	Excreted unchanged by the kidney. Accumulates in renal impairment
Common side-effects	Drowsiness, dizziness, ataxia, fatigue. Need to watch closely for signs of toxicity
Less common, but important, side-effects	Instability of blood glucose in diabetics. Antacids reduce absorption
Contra-indications	Lactation
Dose schedule	Creatinine clearance < 15 ml/min 300 mg daily, dose after haemodialysis
Comments	Withdraw dose gradually over 1 week
Pregabalin	
Renal handling	Excreted unchanged by the kidney. Accumulates in renal impairment
Common side-effects	Drowsiness, dizziness, ataxia, fatigue. Need to watch closely for signs of toxicity
Less common, but important, side-effects	Instability of blood glucose in diabetics. Antacids reduce absorption. Weight gain
Contra-indications	
Dose schedule	25 mg p.o. qhs, increase every few days to a maximum of 150 mg qhs if creatinine clearance 15–30 ml/min, and a maximum of 75 mg qhs if creatinine clearance < 15 ml/min; dose after haemodialysis
Comments	Withdraw dose gradually over 1 week
Clonazepam	
Renal handling	
Common side-effects	Sedation
Less common, but important, side-effects	
Contra-indications	
Dose schedule	0.5–1 mg qhs, gradual increase to a maximum of 2 mg daily
Comments	Simple to administer, evidence of efficacy in one study

MAOI, monoamine oxidase inhibitor.

analgesics from all three steps of the WHO analgesic ladder.

Summary

Pain is a significant problem for a substantial number of CKD patients which often goes unrecognized. The WHO analgesic ladder and basic pharmacological principles can be used as a template for the assessment and treatment of pain in CKD patients. There is much still to be learned about the handling of opioids for those needing chronic administration and highlights the need for on-going research and clinical attention in this area of nephrology.

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buprenorphine binds to the μ-opioid receptor, it might be difficult to antagonize the acute effects with opioid antagonists.[90] It is metabolized by the liver[91] with little unchanged drug found in the urine.[92] The two major metabolites, buprenorphine-3-glucuronide (B3G) and norbuprenorphine, are excreted in the urine and accumulate in CKD.[92] B3G is inactive with no analgesic properties. Norbuprenorphine is a less potent analgesic than buprenorphine; the clinical relevance of which is thought to be limited as it does not readily cross the blood–brain barrier. However, it is not known if this remains the case in the presence of uraemia.[93] In a study looking at short-term use of transdermal buprenorphine in 10 dialysis patients, buprenorphine levels were not reduced by dialysis. Norbuprenorphine was only detectable above 0.05 ng/ml in three patients. The median buprenorphine dose was 52.5 μg/h. We are not told the number of patients who could not tolerate buprenorphine and were, therefore, excluded from the study and there are no data from long-term use.[94] Given the minimal changes in kinetics in renal failure, it may be a potentially useful analgesic in CKD; however, until there are longer term studies, the authors remain cautious about any recommendation.[95]

Naloxone, an opioid receptor antagonist, is metabolized in the liver with little excreted unchanged in urine[33] and no dosage alteration is required in CKD. However, it should be remembered that prolonged dosing may be needed to counteract the accumulation of opioid metabolites in CKD patients.

Cannabinoids

Some ESRD patients may be unable to tolerate a sufficient dose of opioid to provide effective analgesia, as they may worsen overall symptom burden by exacerbating cognitive impairment, sleepiness, nausea, vomiting, anorexia, or pruritus. Cannabinoids such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) appear to have therapeutic potential for the treatment of intractable inflammatory and neuropathic pain. THC has analgesia, muscle relaxant, anti-emetic, appetite stimulant, and psycho-active effects. CBD has analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and antipsychotic activity. Sativex, a buccal spray, combines the cannabis-extracts THC and CBD in approximately a 1:1 ratio, as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis and for cancer patients with intractable neuropathic and visceral pain. Sativex has also shown benefits beyond pain control, including improvements in sleep, anorexia, nausea, vomiting, and pruritus.[96–99]

Cannabinoids are metabolized rapidly in the liver by the cytochrome P-450 enzyme system; hence, there is the potential for drug interactions with analgesics such as fentanyl, adjuvant therapies such as amitriptyline, and immunosuppressive therapy with cyclosporine or tacrolimus. THC is metabolized to 11-hydroxy-tetrahydrocannabinol (11-OH-THC), a psycho-active metabolite which is excreted by the kidneys (~13%) and in the faeces (~53%). CBD is extensively metabolized in the liver and more than 33 metabolites have been identified in urine. All cannabinoids have a large volume of distribution as they are highly lipid soluble and accumulate in fatty tissue. They are also highly protein bound. As a result, they are unlikely to be removed effectively by haemodialysis. Since the nature of these metabolites has not been fully elucidated, should they accumulate in CKD, the clinical relevance is unclear.

There are no data of cannabis-based medicine in CKD but tolerability and safety data of cannabinoids, especially Sativex, in other chronically ill populations over a period of 4 weeks to 2 years with mean (SD) daily doses of Sativex ranging from 5.4 (0.84) to 9.6 (6.1) may be better tolerated than conventional therapies for many symptoms in some patients.[100–102] The majority of adverse effects of the THC:CBD buccal spray appear to be mild to moderate and many resolve with chronic use. There is also no evidence to suggest tolerance to their therapeutic effects.[102] For the treatment of intractable pain, a trial of cannabis-based medicine may be warranted, although close observation will be required as data and clinical experience in CKD are lacking.

Topical analgesia

The potential toxicity of analgesics in patients with renal failure makes the possibility of using drugs topically where applicable very attractive. Most drugs appear to act locally rather than through local systemic absorption; thus, there is reduced risk of toxicity (Table 4).

Adjuvant drugs

An adjuvant drug can be defined as any drug that has a primary indication other than pain, but is analgesic in some situations (Table 5). For pure neuropathic pain, adjuvant drugs are often used alone or with analgesics from Steps 1 or 2 of the WHO analgesic ladder. For severe mixed pains they can be used with

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Review

Advance care planning in patients with end-stage renal disease

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This review explores advance care planning within the context of end-stage renal disease and discusses new research that helps define how to initiate and facilitate effective advance care planning for patients with end-stage renal disease.

Keywords: end-of-life care, advance care planning, end-stage renal disease, dialysis, withdrawal of dialysis, palliative care

More than 83,000 long-term dialysis patients die each year in North America with an annual unadjusted mortality rate of 20–25%.[1,2] Approximately 15–25% of these deaths occur after a decision to discontinue dialysis.[1,2] Many patients experience a slowly progressive decline in functional status and patients, family and care providers are often unable to identify a phase in which the patient is clearly recognised as dying. Issues relating to death and dying are, therefore, commonly avoided until late in the illness when patients may no longer be competent to make decisions for themselves. As a result, the quality of the dying experience for patients is suboptimal.[3–8] Advance care planning (ACP) is an important component of comprehensive care for end-stage renal disease (ESRD) patients.[9]

The traditional focus of planning for future end-of-life care has been the completion of advance directives, legal documents with powers and requirements that vary widely between jurisdictions. Advance directives are generally of two types – instructional (*e.g.* personal directive, living will) and proxy (*e.g.* durable power of attorney for health care). Instructional directives specify patients' medical care preferences while proxy directives appoint a surrogate decision-maker. However, the completion of an advance directive does not ensure that the discussion of clinical circumstances and prognosis, and the understanding of patients' values and goals within this clinical context have been undertaken. ACP is the process of on-going discussion, reflection, understanding, and communication between a patient, their family, and healthcare staff, for the purpose of clarifying values, treatment preferences, and goals for end-of-life care.[10] Although encouraged, advance directives are only one optional component within the broader activity of ACP.

ACP is grounded in the ethical principles of patient autonomy and respect for persons. ACP aims to extend patients' control over their medical care at a time when they are not able to voice their preferences by permitting surrogates to make decisions that the patient would have made for themselves.[11] However, the value of ACP extends beyond promoting patient autonomy (Table 1).

This review explores ACP within the context of ESRD and discusses new research that helps define how to initiate and facilitate effective ACP for patients with ESRD.

The current state of advance care planning in end-stage renal disease

Only 6–51% of dialysis patients complete advance directives[12–14] and there are no data indicating how many patients undergo the full process of ACP. Being male, a higher level of education, a poorer perceived quality of life, and being approached in hospital are factors associated with ESRD patients completing an advance directive.[14,15] Although cardiopulmonary resuscitation

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Table 1 Goals of advance care planning in end stage renal disease[10,40,82,88]

- Enhance patient and family understanding about illness and end-of-life issues including prognosis and likely outcomes of alternative plans of care
- Define the patient's key priorities in end-of-life care and develop a care plan that addresses these issues
- Enhance patient autonomy by shaping future clinical care to fit the patient's preferences and values
- Improve the process of healthcare decision-making generally, including patient and family satisfaction
- Specify a proxy for future medical decision-making and help the proxy understand their role in future medical decision-making
- Promote shared understanding of relevant values and preferences between the patient, proxy, and healthcare providers
- Help patients find hope and meaning in life and help them achieve a sense of spiritual peace
- Explore ways to ease emotional and financial burdens borne by patients and families
- Strengthen relationships with loved ones

(CPR) rarely extends survival for dialysis patients,[16–18] most dialysis patients are unaware of their chance of survival following CPR and few dialysis patients choose a 'do not resuscitate' order.[19,20] Duration of dialysis ≥ 4 years and prior experience with CPR increase the probability of refusing CPR by 12 times.[21]

Dialysis patients' advance directives do not typically address withdrawal of dialysis.[22,23] Most chronic dialysis patients report never having discussed with their nephrologist or family the circumstances in which dialysis treatment should be discontinued.[14] Dialysis patients often do not view themselves as having a terminal illness and many assume they can be kept alive indefinitely on dialysis.[14,22,23]

The majority of patients lack decision-making capacity at the time the decision to withdraw dialysis is made.[24] Unfortunately, neither family members nor physicians are accurate in their predictions of patients' desires about life-sustaining treatments, including wishes for on-going dialysis.[25,26] Spouses consistently overestimate patients' desires to continue dialysis across hypothetical health conditions.[27] In a Japanese study of 398 pairs of dialysis patients and a family member, only 50% of family members correctly predicted the patient's current preference for CPR, 44% their wish for dialysis in a severely demented state, and 47% their wish for dialysis if they had terminal cancer. The corresponding figures for physicians were 44%, 47%, and 43%.[28] Most patients who ultimately make the decision to stop dialysis do not seem to be influenced by major depression or suicidal ideation.[29] Up to 83% of ESRD patients request that physicians periodically check with them to determine if their end-of-life care preferences have changed.[21]

Patient and physician-related barriers to effective ACP and advance directives in ESRD are outlined in Table 2. Change in cognitive status appears to be particularly important in predicting a change in end-of-life care preferences.[30–33] Most (85%) patients ≥ 65

Table 2 Barriers to effective advance care planning and advance directive completion

Patient-related barriers

- Inadequate knowledge about ACP and how to complete an advance directive[89]
- Perception that ACP and advance directives are difficult to facilitate and/or execute[90]
- Perception that even if completed, advance directive statements will not be followed by clinicians
- Belief that it is the physician's responsibility to initiate end-of-life discussions
- Reluctance to broach the issue of 'death' and end-of-life planning
- Lack of insight into health status and prognosis and a false sense that ACP is not relevant for their care[89,91]
- View that ACP is unnecessary because one's family or provider will 'know' what to do
- Stability of patients' preferences for end-of-life care. Patients may 'downsize' their perceptions of what is an acceptable quality of life as illness progresses[92]

Physician-related barriers

- Lack of training and comfort with end-of-life decision-making[19,93]
- Lack of familiarity with palliative care and suitable alternatives to aggressive treatment[94]
- Discomfort with the accuracy of prognostic prediction
- Belief that ACP discussions are not needed[94]
- Belief that patients and families do not want these discussions[94]
- Concern that discussing end-of-life issues while embarking on a life-sustaining therapy such as dialysis may destroy hope[89]
- Time constraints[89]
- Postponing end-of-life discussions until patients are too ill to participate in the discussions fully[95]

years of age who choose to forego life-sustaining treatments maintain that choice 2 years later and patients with a living will are less likely to change their wishes (14% vs 41%).[34]

New approaches to facilitate advance care planning in end-stage renal disease

There are no standards about when to initiate or how to conduct end-of-life discussions. The general literature suggests that the majority of end-of-life discussions do not provide the essential information required to inform care at the end of life. Physicians tend to focus on pejorative descriptions of life-sustaining treatments rather than desired outcomes, and fail to articulate a set of positive treatment objectives within which to frame the discussion of forgoing life-sustaining treatment.[35–38] Prognosis, spirituality, religion, and what dying may be like is typically not addressed.[39] Patients' values are rarely explored and discussions do not distinguish between treatments patients may want to forgo now versus treatments they would want to forgo if they were to become worse.[35–37] ESRD patients' perspectives of the salient elements of ACP discussions and their preferences regarding how ACP should be facilitated by the healthcare team have recently been explored.[10,40] Table 3 highlights some of the necessary steps for facilitating effective ACP.

Table 3 Summary of key elements to facilitate effective advance care planning in end stage renal disease[40]

Identify patients who would potentially benefit from ACP
• 'Would you be surprised if this patient died within the next 12 months?' If no, consider ACP
• Patients with Charlson co-morbidity scores ≥ 8, advanced age, low serum albumin ≥ 35 g/dl, low functional status, and low health-related quality of life are likely to benefit from ACP
• Patients with high burden of physical or psychosocial symptoms may benefit from ACP
Timing of ACP
• Initiate early while the patient is relatively well and is competent to participate in the discussions to allow time to discuss and reflect on end-of-life care options, i.e. as soon as the patients as described above are identified
Determine the patient's readiness to participate in ACP
• Assess the patient's cognitive ability to participate in ACP
• Address issues such as depression and anxiety to permit full participation of the patient in discussions
• Determine the patient's interest in and perception of potential benefits of ACP to achieve 'buy-in' for the process. This may include re-assuring the patient that they do have control over future care and can shape that care based on their own values and preferences
Identify whom the patient wishes to engage in ACP
• Family participation is integral to the process for many patients
Decision-making and defining priorities for goals of care
• Ensure the patient has an appropriate understanding of their illness (including prognosis)
• Determine what role patients expect themselves, family, and the healthcare team to have in making decisions
• Explore patient values as they will drive end-of-life care preferences
• Determine specific expectations regarding outcomes of end-of-life care
Information giving
• The majority of patients require clear, honest discussions about prognosis in order to effectively engage in ACP and make informed decisions about their care
• Focus on health states and illness severity
• Discuss how medical interventions will impact patients and their families in their daily lives and whether these interventions are likely to help them achieve their personal goals
• Distinguish between treatments patients may want to forgo now versus treatments they would want to forgo if they were to become worse
• Articulate a set of positive treatment objectives within which to frame the discussion of forgoing life-sustaining treatment
• Include issues of spirituality, religion, and what dying may be like in these discussions
Documentation
• Should be easily identifiable
• Should travel with the patient across healthcare settings so it is available for all professional caregivers involved in the care of the patient (consider POLST)
Quality improvement
• The initiation of a new ACP programme should be accompanied by a comprehensive evaluation process that can guide future programme enhancement

When to initiate advance care planning

ESRD is characterised by progressive physical decline that is often protracted over years and punctuated by episodes of life-threatening complications. ESRD patients, their families, and physicians often have difficulty recognising when a patient is dying and, by implication, when end-of-life decision-making should occur. ACP is, therefore, best initiated early with on-going communication and re-evaluation throughout the illness.[9] Ideally, these discussions should be part of the education process that occurs when patients are presented with dialysis options.[10] Sentinel events (hospitalisations, acute illnesses) present additional opportunities to engage in ACP.

Despite a reluctance of physicians to initiate end-of-life discussions, many patients have already considered their end-of-life options[41–43] and welcome the opportunity to engage in these discussions with their physician.[36,43] In one study, the vast majority of dialysis patients (97%) wanted to be given life-expectancy information, and for the physician to do so without having to be prompted.[44] Physicians need to be aware, however, that not all patients are ready to engage in ACP. In the SUPPORT study, 707 of 1832 seriously ill did not wish to discuss their preferences for resuscitation. These patients perceived they had better prognosis than patients who did wish to discuss their resuscitation preferences.[45] Patients' reluctance to discuss end-of-life issues may reflect a perception that these issues are not yet relevant to their care.

It needs to be recognised that not all dialysis patients will benefit equally from ACP. Patients with minimal co-morbidity and eligible for a kidney transplant are less likely to be interested in ACP. Unfortunately, there are no data to identify clearly which ESRD patients would most benefit from ACP. The recently published palliative care core curriculum for nephrology fellows[46] suggests that, at a minimum, ACP should be considered whenever the healthcare provider would not be surprised if that patient died within the next 12 months.

Who to involve in advance care planning

ESRD patients feel their nephrologists are responsible for initiating and guiding ACP, mainly because physicians are seen as the primary source of information central to this process.[10] However, not all ESRD patients want to talk extensively with their physicians about end-of-life issues and instead view conversations with their loved-ones as the most valuable piece of ACP.[10,31] One study showed that 50% of chronic dialysis patients discussed their preferences for end-of-life care with family members compared to 6% of patients with their physicians ($P < 0.001$) and that more patients wanted to include family members in future ACP discussions than wanted to include physicians (91% compared with 36%; $P < 0.001$).[47] ESRD patients are also comfortable with legislation that grants their family leeway in end-of-life decision making in the event of their own incapacity;[47,48] in a study of 150 dialysis patients, 42% indicated they wanted their surrogates to have leeway to override their advance directives.[33,42] Health professionals, therefore, must be prepared to initiate end-of-life conversations and then step back while these conversations proceed outside of the patient–health professional relationship. However, as outlined below, research in ESRD clearly supports a role for physicians much greater than merely encouraging patients to discuss the salient issues with their families. Dialysis patients acknowledge the therapeutic benefit of empathetic listening and view facilitated ACP as an opportunity to build trusting relationships with the healthcare team. There will be patients who require more active engagement with their healthcare providers to help them reflect on and work through end-of-life issues.[10] Interviewing skills that focus on empathy and strong reflective listening can be taught.[49–52]

Information-giving during the advance care planning process

Dialysis patients want straightforward and honest discussions about how medical interventions will impact their daily lives and help them achieve their personal goals.[10] Health states and illness severity influence end-of-life preferences far more than treatment descriptions.[53] Clear, honest discussions about prognosis and future care promote self-reliance, alleviate fear and uncertainty, help prepare for the future, including death, and give dialysis patients the knowledge to make decisions compatible with their values and beliefs.[10] Varying amounts of time are required for this process to be effective.

How to facilitate advance care planning

Detailed descriptions of the ACP process and important aspects of facilitation have been recently published.[40,54] Determining a patient's readiness to participate in ACP is critical. There is a high incidence of depression, anxiety, and other psychosocial issues in patients with ESRD. These, along with cognitive dysfunction, may prevent meaningful participation in ACP and will need to be addressed prior to making informed decisions. Effective ACP may be jeopardised due to patients' lack of interest or their perception

that their wishes will not alter the end-of-life care they will receive. Determining the perception of potential benefits of ACP for individual patients is perhaps the most under-recognised aspect of patient participation. Patients are much less likely to engage in a process from which no benefit is perceived.[10] ACP facilitators must also identify the patient's support system and the resources required by, and available to, individual patients to enable them to effectively participate in ACP.

In order to plan effectively for end-of-life care, patients and/or families need to understand the overall medical condition and how illness and various treatment options will affect their daily lives. Although physicians should avoid depriving their patients of hope, an unrealistic appraisal of a patient's health status may result in burdensome treatment that will not respect the patient's preferences or achieve his or her goals. Exploring patients' and surrogates' expectations for outcomes of care affords an opportunity to identify unrealistic expectations or misconceptions and re-examine the understanding of their illness. Identifying discordance between patient and care provider expectations allows an opportunity for re-alignment of goals of care and may minimise future conflict surrounding end-of-life decisions.

It is important to understand the role the patient wants in decision-making, realising that the locus of decision-making may shift as events occur. Even patients who wish to maintain significant control over the decision-making still expect health professionals to guide them through the ACP process. Perceiving the full burden of decision-making to be entirely theirs often leads to feelings of isolation and uncertainty.[10] Some dialysis patients have expressed feelings of isolation and hopelessness when they were not able to discuss their hopes and fears for the future openly with loved ones.[10] Facilitators need to provide a platform in which to engage family in these conversations in a supportive environment.

If knowledge is one major driver of patients' end-of-life preferences, values is the other. The questions asked in the process of facilitated ACP should be designed to help the patient explore what they guard most closely and rely upon most heavily. This will be discovery for some and patients will have to work with the healthcare team to discover how their values shape their goals for care. To keep discussions outcome focused, disease-specific scenarios addressing unique health states the patient may experience and the related treatment choices can be used. Through these discussions, patients and their surrogates come to understand what is truly important to the patient. Potential questions that can help explore the various aspects of facilitated ACP in ESRD are described elsewhere.[10,40]

Documentation of ACP is important to communicate salient features and specific treatment decisions that may arise from the process. POLST (Physicians Orders for Life Sustaining Treatment) has been developed in the US to help ensure patients' wishes for end-of-life care are honoured.[56] These documents convert patients' treatment preferences into medical orders and are transferable across health care systems. Most POLST documents address resuscitation status, medical interventions (comfort care only, limited, or aggressive interventions), antibiotics, and artificial hydration and nutrition. POLST orders were universally accepted in a study of 180 nursing home residents and were associated with high levels of comfort care and low rates (15%) of transfer for aggressive life-extending treatments.[57]

Cultural differences that influence advance care planning

Several dimensions involved in end-of-life care vary culturally: concept of autonomy, decision-making models, communication of bad news, and attitudes towards ACP and end-of-life care.[58]

Cultural differences in autonomy and decision-making models

The concept of autonomy varies between Western and many non-Western cultures. Many non-Western cultures, such as traditional Chinese culture, view the person as a 'relational-self' – a self for whom social relationships, rather than individualism, provide the basis for moral judgements.[59] In a similar manner, Hindu and Sikh bioethics is primarily duty based; the person is seen as intimately integrated with family, community, and environment.[60] From these perspectives, an insistence on self-determination may erode the value placed on personal interconnectedness, challenging the assumption that the patient is best suited to plan for his or her own medical decisions. These different views of autonomy result in substantial differences in decision-making models in which the family functions as the decision-maker.[58] North American Aboriginals,[61–63] and Korean Americans and Mexican Americans also tend to operate within a more family-centred model of decision-making compared to European Americans and African Americans. Consequently, healthcare providers must recognise that many patients may prefer that family or community play a dominant role in ACP.

Cultural issues relating to communication of bad news

Some cultures (*e.g.* Aboriginal, Asian) prohibit explicit references to dying based on an interpretative framework in which language has the capacity to create reality.[64] Positive thinking is felt to promote health while truth-telling (of bad news) may shorten the life of the patient. In some contexts, it may be appropriate for family to communicate prognostic information and manage most of the ACP discussions, allowing them to balance hope with the 'bad news'.

Cultural differences in attitudes to advance care planning and end-of-life care

In North America, African Americans, Hispanics, and Whites all appear to agree with the purpose of ACP.[65] However, most studies have found that African Americans and Hispanics are less likely than Whites to engage in ACP or complete advance directives.[66–69] The designation of a healthcare surrogate was the most common form of advance directive in African Americans, Hispanics, and Whites.[65] More African Americans and Hispanics want to involve their physician in end-of-life discussions than Whites.[65] Hispanics were more likely to prefer family-centred decision-making than other racial groups[67] and were more likely to defer decisions to their families.[65] African Americans were more likely to feel that they would receive less care if they had an advance directive than Hispanics, and Whites.[65]

Cultural variations in the concept of autonomy, decision-making, and the meaning of illness clearly have implications for ACP. Given the high prevalence of ESRD in many ethnic minority groups, many dialysis patients will not have discussed end-of-life care preferences and will not have advance directives; their end-of-life care wishes will be unknown. The ACP process must be sensitive to these cultural contexts.

Interventions to increase the use and effectiveness of advance care planning

There is a paucity of data on how to increase the use and value of ACP. The literature has focused primarily on efforts to increase the completion of advance directives, a fundamentally flawed endeavour given that the completion of an advance directive by no means guarantees that the critical components of ACP have been addressed. Educational interventions in isolation have been mostly unsuccessful in altering attitudes or completion of advance directives.[70,71] A randomised, controlled trial of 203 dialysis patients found that peer mentoring increased completion of advance directives, increased comfort discussing advance directives, and improved subjective well-being and anxiety among the African American participants. These benefits of were not observed among White patients.[25]

Health information technology, social marketing, and legal intervention/policy change are three mechanisms proposed to induce the behavioural change required to increase the use of ACP.[72] Information technology may facilitate ACP by providing automated reminders and sharing information across providers with a uniform instrument. Automated physician reminders of advance directives resulted in an almost 8-fold increase in the odds of having an end-of-life discussion with 45% of these discussions resulting in the completion of an advance directive.[73] Another study evaluated a multifaceted automated intervention that not only prompted physicians to have ACP discussions but also sent out educational material on advance directives to patients prior to their appointment with their physician.[74] This resulted in more ACP discussions (64% vs 38%; $P < 0.001$) and more documentation of these discussions (47% vs 24%; $P < 0.001$). Social marketing is the planning and implementation of programmes designed to bring about voluntary social/behavioural change. The 'Respecting Choices' campaign is an example of social marketing that was successful in positively influencing both patient and care provider thinking around ACP and advance directives.[75,76] Legislative changes and the development of policy are typically required to encourage and guide these processes. However, it has yet to be determined how health information technology, social marketing, and policy changes in the context of ACP in ESRD will influence actual end-of-life care.

Outcomes of advance directives

There are numerous limitations to advance directives that could explain their failure to achieve the goals for which they were intended (Table 4). Advance directives have failed to improve surrogate decision-makers' knowledge of patients' values and preferences for end-of-life care[26,77] and have failed to enhance communication between patients and physicians about end-of-life care.[77,78] Most importantly, advance directives have failed to improve the quality of end-of-life care.[79] In the most famous of the many studies of

Table 4 Limitations of advance directives

• Completion of an advance directive in no way ensures that the discussion of patients' values in the context of their clinical circumstances has occurred
• Advance directive documents provide guidance for only a limited set of future medical possibilities[96]
• Preferences for life-sustaining treatment appear to depend on the context in which they are made[97]
• Some patients have limited desire to exert specific control over end-of-life medical decision making and would prefer instead to leave future specific decisions to their families or physicians[42,47,98]
• Proxy decision makers may have difficulty interpreting and converting patients' documented treatment preferences into clinical decisions[99,100]
• Patients have difficulty predicting their future treatment preferences[91]
• Expressed preferences may be subjugated to physician influence concerning the clinical appropriateness of life-sustaining treatment[5,101,102]
• Healthcare providers do not consistently follow advance directives
• Healthcare providers may be unaware of the existence of an advance directive
• The advance directive may not be available to clinicians or the proxy when needed

this, SUPPORT, it was found that an intervention based around the completion of advance directive forms which were then made available to patient's physicians, had no impact on the style of communication between doctor and patient, on the incidence or timing of 'do not resuscitate' orders, or on the knowledge that doctors reported they had about patients' preferences.[77] However, in a study of 182 patients, advance directives were more prevalent among chronic high-dependency patients who withdrew from dialysis in a reconciled fashion than among patients who died suddenly and unexpectedly or who died without a reconciled decision to forego life-sustaining treatment.[80] Patients who had advance directives were more likely to have made their own medical decisions rather than relying on relatives or other agents and tended to be those with a spouse or in a relationship.

Outcomes of advance care planning in end stage renal disease

To my knowledge, there are no published clinical trials of a multidimensional ACP intervention in ESRD. The impact of ACP on important clinical outcomes has yet to be determined. However, there are qualitative data that strongly support the value of ACP in ESRD in that ACP allows patients to prepare for death, strengthen relationships with loved ones, achieve a sense of control, and relieve burdens placed on others.[10,81,82] Facilitated ACP through the provision of timely, appropriate information can positively enhance rather than diminish ESRD patients' hope. ACP discussions may also strengthen patient–physician relationships and provide a closeness that both patients and physicians find rewarding.[10,83]

Knowledge of the impact of ACP on end-of-life care for other groups of patients is also limited. A systematic, community-wide 'Respecting Choices' programme integrated advance directive education and ACP and showed increased congruence in decision-making between patients and care givers, greater satisfaction with and less conflict about end-of-life decisions,[76,84] less willingness to undergo life-sustaining treatments for a new serious medical problem, and less willingness to tolerate poor health states at 2-month follow-up.[85] Implementation of the CHOICES ACP and palliative care programme demonstrated increased hospice length of stay, less time spent in hospital and more deaths occurring at home.[86] In an observational study of advance cancer patients, end-of-life discussions were not associated with higher rates of major depression or worry and were associated with lower rates of ventilation, resuscitation, intensive care unit admission, and earlier hospice enrolment.[87] Although this was not an intervention study and patient self-selection bias will impact data, results are encouraging.

Conclusions

Contemporary investigation into ACP has taught us that end-of-life discussions and planning occur within the patient–family relationship and that patients and families have a much broader view of the goals of ACP. Physicians and dialysis care providers need to continue to facilitate ACP among their patients and families to foster quality care, particularly end-of-life care.

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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 trensferable 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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