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RESEARCH ARTICLE

Conservative Kidney Management and kidney Supportive Care: Essential Treatments for Kidney Failure

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ABSTRACT
Kidney supportive care (KSC) and conservative kidney management (CKM) are essential treatments for kidney failure (KF) but are nonexistent, poorly developed, and/or poorly integrated with kidney care across low-, middle-, and high-income countries. This article reviews the updated definitions and evidence for KSC and CKM and discusses who will most benefit from these treatments. Conservative kidney management involves highly individualized active treatment that comes with its own set of recommendations that focus predominantly on patient-specific goals and health-related quality of life. The recommendations for managing the complications of kidney failure and the symptoms of pain, restless legs, uremic pruritus, nausea and vomiting, poor sleep and fatigue, and breathlessness in people receiving CKM are reviewed. Additional considerations for delivering CKM in low resource settings are discussed.

Keywords: kidney failure, conservative kidney management, kidney supportive care, symptom management, analgesics

The need for kidney supportive care in all active treatments for people with advanced chronic kidney disease

Globally, incident kidney failure (KF) patients (defined as estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2) are becoming older and are presenting with complex comorbidities and substantial physical and cognitive dysfunction.[1] Mortality rates remain high without the progress in preventing mortality that has been seen from other non-communicable diseases such as cardiovascular disease, chronic obstructive pulmonary disease, and cancer.[1] Symptom burden for people with advanced chronic kidney disease (CKD) is also very high across age, sex, race, and geographic location. By the time a person reaches KF and requires kidney replacement therapy (KRT), they will have on average 6-20 symptoms.[2-5] The five most prevalent symptoms across advanced CKD stages and KF tend to be fatigue or lack of energy 81% (49–100%), feeling drowsy 75% (49–82%), pain 65% (38–90%), pruritus 61%, (33–84%) and decreased appetite 57% (9-83%).[4] These symptoms are often multifactorial in etiology, caused by complications of CKD, side effects of medications used to treat these complications, comorbidity, and effects of aging. They increase in prevalence and severity as kidney function declines. Syndromes such as malnutrition, protein energy wasting, and frailty are also common, leading to muscle and fat loss and cachexia.[6] These factors exacerbate symptom burden and together with navigating challenging and shifting family dynamics, end-of-life issues, and a burdensome treatment such as dialysis, they profoundly compromise patients' functional capacity and health-related quality of life (HRQOL).[7] Symptom burden has been shown to account for up to 46% of dialysis patients' reduction in HRQOL.[2,3]

While dialysis may address some uremic symptoms, especially for more robust individuals with limited comorbidity, it appears to do little to address symptoms in older more frail patients or those with multimorbidity. In this subset of patients, dialysis does not necessarily improve HRQOL.[8-12] Rather, for some, dialysis may add to overall symptom burden while chronic inflammation, malnutrition, and frailty continue to progress regardless of whether dialysis is started or not. The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study investigated HRQOL and symptoms at initiation of dialysis and 1 year later.[13] At 1 year, 20%-31% of patients had worsening, 42%-60% had no changes, and 19%-28% had improvement in the eight HRQOL domains of the SF-36. Similarly, 19%-30% had worsening, 50%-65% had no changes, and 16%-24% had improvement in the dialysis-specific symptom domains of assessment after 1 year of dialysis. 101 of 928 (10.9%) of patients had died. Only 24% of patients reported an improvement in energy one year after starting dialysis while 27% reported worsening. The incidence of pruritus is 19% across all pre-dialysis stages of CKD[9] but is reported in up to 84% of people on hemodialysis.[10] Problems with sleep also become more common and severe compared with pre-dialysis; only 19% reported an improvement of sleep symptoms while 24% reported a worsening after 1 year of dialysis.[1] Dialysis had no positive impact on pain and sexual dysfunction became more prevalent.[13] The patients that tend to do the best are those with limited comorbidity; they tend to have low symptom burden until shortly before needing dialysis and experience the more typical uremic symptoms of anorexia, nausea, vomiting, fatigue, and these can quickly improve after starting dialysis. However, at a population level, starting dialysis does not result in an improvement in overall symptom burden or HRQOL. Dialysis withdrawal due to poor HRQOL remains one of the leading causes of death in patients with KF in high-income countries (HICs), where dialysis is readily available.[14] In these high resource settings, older patients are much more likely to withdraw from dialysis compared to younger patients.

Given the high mortality rate and symptom burden associated with advanced CKD and KF, kidney supportive care (KSC) is recognized as a core component of integrated kidney care. Kidney supportive care is "an approach that aims to improve the HRQOL for people for whom kidney disease, either directly or indirectly, substantially impacts their wellbeing, treatment options, or access to care, and that of their families, 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." This definition has its roots in the World health Organization's (WHO's) definition for palliative care and it should be available for all people with advanced CKD according to need, both those receiving KRT (dialysis or kidney transplantation) and those not receiving it. Kidney supportive care should not be reserved solely for people who have withdrawn from dialysis or who are actively dying. It prioritizes the components of care most important to the individual patient and therefore must integrate culturally sensitive shared decision-making and ensure that it guides clinical decisions, even when treatment options are limited. Kidney supportive care involves skilled communication and meticulous

and timely attention to symptom management, crisis planning, advance care planning, integration of community services, terminal/end-of-life care, and bereavement. Many countries are placing increased emphasis on the provision of KSC by nephrologists, "generalists," and community providers as a component of usual care.

Conservative kidney management

Over the last two decades, the international nephrology community has increasingly recognized that the burden of KRT, whether that be dialysis or transplantation, will outweigh the benefits for some patients in whom KRT offers neither a survival nor a HRQOL advantage. These patients may live longer and/or better lives if cared for without KRT. International recommendations state clearly that KRT should not be the default. Where available, receiving KRT is a choice that requires the careful balance of risks and benefits, recognizing that the balance is preference sensitive and will likely involve both HRQOL and survival considerations. If a patient is unlikely to benefit from KRT, a positive alternative in the form of conservative kidney management (CKM) should be provided. Conservative kidney management is defined as "care for people with KF that focuses predominantly on providing KSC to promote HRQOL but does not include KRT." Conservative kidney management is an active treatment that comes with its own set of recommendations and guidelines. It focuses on KSC, but also involves management of CKD progression and complications of CKD in so far as doing so aligns with the individual's priorities. Conservative kidney management should not be confused with pre-dialysis care where the choice for dialysis has been made but has yet to be started. Nor should CKM be bundled with withdrawal of dialysis, in which maintenance dialysis is stopped; these patients typically have only days to weeks to live and therefore require terminal/end-of-life care. Conservative kidney management should also not be defined solely by no KRT as these patients require active treatment that is highly individualized, often for many months or years.

The evidence for CKM and who will most benefit from it

Although there have been no randomized controlled trials in this area, there have been several systematic reviews of cohort studies. A systematic review and meta-analysis of 89 cohort studies published between 1976 and 2014 reported survival on 294 921 elderly patients with KF treated with either CKM or dialysis. Patients receiving CKM were older (79.2 v. 77.4 years).[15] Although there was considerable heterogeneity amongst studies, the combined 1-yr survival rate was similar between those who were dialyzed and those receiving CKM at 73.0% (95% confidence interval (CI) 66.3-79.7%) v. 70.6% (95% CI 63.3-78.0%). Subgroup analyses based on age less than or greater than 80 years, study design, cohort era, or study size made no impact on the main findings. Out of all these studies, only six directly compared survival between dialysis and CKM. All six of these comparative studies showed a small survival advantage with dialysis. Only four of these studies explored factors which predicted survival, three of which demonstrated loss of any survival advantage with high comorbidity (especially ischemic heart disease), deceased functional ability with activities of daily living, or age over 80 years. Of note, there was a difference in the 2-year survival; 62% for dialysis v. 44% for CKM. Limitations included lead-time bias for CKM and a paucity of data as only 724 patients (0.2% of the total patient population) were receiving CKM, most of which were from the United Kingdom.

Subsequently, a retrospective survival analysis of a single-center cohort in The Netherlands from 2004 to 2014 compared the survival of patients > 70 years at the time they made the decision for either dialysis (n = 204) or CKM (n = 107).[16] Results were similar in that there was a survival advantage with dialysis which was no longer observed in patients over 80 years or in patients over 70 years with severe comorbidity. Also consistent was that many people receiving CKM survived several years on a CKM pathway. These cohort studies have also shown that patients receiving CKM spend less time in hospital and die there less often than people receiving dialysis.

A more recent systematic review included 41 cohort studies that documented HRQOL and/or the use of healthcare resources among 5102 patients who made the decision for CKM. Of the eight studies that described HRQOL, mental well-being improved over time, and physical well-being, symptoms, and overall HRQOL were stable until near the end of life. In places that had dedicated CKM and palliative care resources, symptom burden improved. Unfortunately, what is often missing is a coordinated approach and infrastructure to adequately provide CKM, and specifically a lack of coordinated crisis management. This resulted in common use of acute care services including emergency room visits and hospital admissions with a substantial disparity in access to KSC even near the end of life.[17]

Choice-restricted CKM

The rise in CKD is of particular concern in many low- (LICs) and low to middle-income countries (LMICs), particularly in Africa, where there is either restricted or no option for KRT.[18,19] These countries are experiencing an increasing burden of non-communicable diseases, particularly hypertension, heart failure, and diabetes mellitus, all of which are major contributors to KF. [20,21] The evolving epidemic of communicable diseases, particularly human immunodeficiency virus, malaria, tuberculosis, and an explosion of illicit drug use are also contributing to the increased incidence of KF. These factors, compounded by poor access to preventative care, are resulting in people reaching KF with multiple comorbidities and complex psycho-social needs at a much younger age than typically seen in HICs. For example, in Uganda only 4% of the dialysis population is older than 60 years.[22] Priority setting is an essential component of providing healthcare in these low resource regions as kidney care programs work to balance the fundamental human right to health with scare resources due to the expensive nature of KRT.[23,24,25] As a result, physicians and patients in LICs and LMICs face challenges that are significantly different from those experienced by their counterparts in well-resourced countries.[26] Ethically endorsed, transparent criteria to allocate KRT in low resource settings typically use the accountability for reasonableness approach and the overarching ethical principle of utilitarianism.[27] The development of these guidelines involve wide consultation with relevant stakeholders in an iterative process and has withstood the scrutiny of the Human Rights Commission.[28] However, this is not without cost to both patients and decision-makers. As an example, in South Africa the overriding criteria to access KRT for those with irreversible KF is transplantability. Patients need to be assessed as medically and socially able to undergo transplantation before being accepted for dialysis. Dialysis is therefore seen as a bridge to transplantation. In government facilities, dialysis slots are always full, and a new patient can only be accommodated once an existing patient is transplanted or dies. The reality is that many are not accepted into KRT programmes and those that are accepted may die while waiting for an available space. In a retrospective study at Groote Schuur Hospital in South Africa, 54% of 564 patients with KF presenting between 2008- 2012 were deemed not eligible for KRT. Predictors of non-acceptance included age above 50 years (OR 0.3, p = 0.001), unemployment (OR 0.3,p<0.001), substance abuse (OR 0.2, p<0.001), diabetes (OR 0.4, p = 0.016), and a poor psychosocial assessment (OR 0.13, p<0.001).[29]

For patients who are unable to access KRT, the only active treatment option is CKM; when CKM is accessed due to a lack of KRT rather than choice it is referred to as "choice restricted CKM". In an international cross-sectional survey to determine the global capacity to deliver KRT and CKM conducted by the International Society of nephrology (ISN), CKM was reported as available in 124 (81%) of the 154 surveyed countries.[30] However, in 43% (66/154), CKM was associated with a choice-restricted- approach due to lack of resources. Furthermore, in low resource settings there is also limited palliative care capacity. In 2019, only 50% of countries reported having palliative care within their national noncommunicable diseases policy that was operational[31]; this leaves many people with KF untreated and unjustifiably suffering.[32]

The delivery of CKM

The intent of all medical interventions in people receiving CKM is to optimize HRQOL, and individualization is essential. The illness trajectory of people receiving CKM is highly variable; many with an eGFR of 10 – 15 ml/min per 1.73 m^2 or even lower may remain functional and stable for years, although some may deteriorate over a few months. Treatment therefore needs to consider the patient's general condition and prognosis. Earlier in the illness trajectory, maximizing HRQOL likely requires a careful balance between preserving kidney function, optimizing functional status, and reducing symptom burden while in the last weeks to months of life, control of symptoms and overall comfort generally take precedence.

<u>Management of the metabolic complications of kidney failure in CKM</u>

The approach to managing the complications of KF in people receiving CKM represents a shift from disease-focused treatment, which often takes years to accrue benefits such as with statin therapy, to shorter-term symptom- and patient-specific goal-focused interventions. Medications are therefore used primarily with the intention of improving symptoms and protecting kidney function. The recommendations for managing the complications of KF are summarized in Table 1. The full recommendations are available elsewhere.[33,34] Many of these interventions involve dietary restrictions. For patients with significant anorexia and poor oral intake, it is reasonable to remove all dietary restrictions. It is crucial to adapt these recommendations to the specific local context and the resources available, especially in LICs and

LMICs. For example, the use of erythropoiesis stimulating agents and intravenous or oral iron may not be available therefore limiting the need for regular monitoring of haemoglobin and iron studies. It may be feasible to administer a blood transfusion in some settings if the anaemia is very symptomatic and fluid overload is not an issue. As electrolyte monitoring may also be restricted, dietary advice should emphasize low potassium diets. These diets need to take into consideration local food availability and affordability. Educational materials in local languages can assist with the implementation of regional dietary advice. Blood monitoring should be directly in line with management plans. If no alterations in management are to be performed, then monitoring should cease.

Table 1. Summary of CKD Management Recommendations for People receiving CKM[33,34]

Guideline	Treatment Rationale	Recommended Interventions*
Dyslipidemia	People are unlikely to benefit from treating dyslipidemia in the last few years of life but may gain improvement in HRQOL from stopping statin medications.[35,36]	Care providers, in discussion with their patient, can discontinue statin medications.
Blood Pressure	The primary goal of blood pressure management in people receiving CKM is to optimize physical and cognitive function and minimize the risk of falls, while avoiding very high readings as opposed to slowing the progression of kidney disease and reducing cardiac mortality or morbidity. Decisions about specific medications would depend on the patient's co-morbidities. Diuretics are a unique consideration and are aimed primarily at the treatment of volume overload that causes breathlessness or symptomatic peripheral edema.	Blood pressure targets can be relaxed for most people receiving CKM to ≤160/90 mmHg. This applies to patients with diabetes as well.[36-38]
Volume overload	High sodium intake can contribute to volume overload leading to breathlessness and symptomatic peripheral edema. Treatment is aimed at relieving these symptoms. Sodium restriction can negatively influence palatability. Sodium intake should balance symptom management and the patient's priorities for care and other issues such as enjoyment of food and appropriate nutrition. Treatment is recommended only if volume overload is contributing to symptom burden.	Consider diuretics. It is reasonable to offer up to 160 mg twice daily of furosemide. Consider dietary sodium restriction targeting a sodium intake ~2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day). Titrate as needed based on effectiveness.[39] Salt substitutes that are rich in potassium are not appropriate for people receiving CKM because of the potential for hyperkalemia.
Anaemia	Anemia can contribute to fatigue and breathlessness. The purpose of treating anemia is to reduce these symptoms as opposed to reducing cardiac mortality or morbidity.	Iron supplementation to target transferrin saturation > 20% and or ferritin < 200 ng/ml. Use oral iron as a first step if tolerated. If iron replete, consider erythropoiesis stimulating agents to target a haemoglobin between 90 g/l and 120 g/l based on the response in symptom burden.[40] Anemia-related bloodwork (haemoglobin and iron indices) every three - six months is appropriate but should be based on patient preference and symptoms. It is no longer appropriate to manage fatigue and breathlessness by addressing anemia when a patient starts spending most of their time lying down or in the last weeks or days of life. At this time anaemia treatment can be stopped.

Hyperkalemia	Hyperkalemia predisposes patients to cardiac arrhythmias and sudden death. Acute treatment of hyperkalemia is appropriate if consistent with the patient's goals.	Interventions include a potassium-restricted diet and the use of potassium binding resins such as sodium polystyrene sulfonate. Consider decreasing or stopping medications that predispose to hyperkalemia such as angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, potassium-sparing diuretics (consider switching to a loop diuretic), or nonsteroidal anti-inflammatory drugs. If a patient wishes to liberalize their potassium intake, the risks of lifting the restriction must be explained clearly. For those aiming to maintain normal potassium levels, it is reasonable to monitor potassium levels monthly but this should be based on the patient's preference. If monitoring for hyperkalemia, patients should have a potassium binder (e.g. Resonium) available at home as part of their crisis action plan. It is appropriate to stop monitoring and managing potassium levels in the last weeks or days of life.
Acidosis	Treatment of metabolic acidosis in people receiving CKM is aimed at slowing the rate of decline of kidney function. Acidosis may also contribute to fatigue, bone loss and muscle wasting.[41]	Consider bicarbonate supplementation to maintain serum bicarbonate within the normal range, generally ≥ 22 mmol/L and optimally 24–26 mmol/L.[42,43] It is reasonable to monitor bicarbonate every three – six months if patients are being treated. If the patient finds the pill burden too great or is in the last weeks or days of life, treatment should be stopped.
Hyperphosphatemia	There are no clear benefits to normalizing phosphate with respect to bone abnormalities or vascular calcification in patients being cared for conservatively in the last few years of life. Rather, there is a possibility of harm in promoting lower protein intake in patients already at high risk for protein malnutrition. Hyperphosphatemia can contribute to RLS and calcium and phosphorous depositions can lead to myalgias, arthralgias, and pseudogout. Treatment should be aimed at promoting HRQOL through liberalizing diet and maintaining adequate nutrition; dietary restrictions should only be considered to minimize associated symptoms.	Interventions include a phosphorus-restricted diet (being careful to maintain adequate nutrition) and the use of phosphate binders such as calcium carbonate with meals e.g., $CaCO_3$ 500 mg – 1500mg daily to 3 times daily with meals. Bloodwork every three - six months is appropriate if patients are being treated but should be based on patient preference and symptoms. The goal is not to normalize biochemistry but to ameliorate associated symptoms to an acceptable level.
Vitamin D	Vitamin D may have a role in the symptoms of fatigue, weakness, and muscle loss.	Low dose active Vitamin D (vitamin D analogue) e.g., calcitriol 0.25ug every 1 to 2 days, may be beneficial. There is no additional benefit in monitoring parathyroid hormone levels.

Abbreviations: CKM, conservative kidney management; HRQOL, health-related quality of life; RLS, restless legs syndrome.
*Individualization is essential.

Symptom management in CKM

The aim of symptom management is to ameliorate symptoms that cause significant distress. It's typically not necessary nor possible to resolve symptoms completely. It's important to acknowledge this and negotiate with the patient and often the family an acceptable level of symptom control.

Symptom management should ideally follow a stepped approach that first involves ruling out contributing factors, then maximizing the use of non-pharmacological interventions to avoid unnecessary polypharmacy and the adverse effects associated with many medications. Pharmacological interventions should only be considered if symptoms continue to adversely impact the patient's HRQOL. For people with KF most medications should be started at a low dose and titrated slowly to effect while monitoring for adverse effects. Patients require ongoing reassessment for the impact of the treatment on the outcomes that are most important to them. The recommendations for managing symptoms in people receiving CKM are summarized in Table 2. The full recommendations are available elsewhere.[33,34]

The management of pain for people with KF can be particularly challenging as most analgesics, including opioids and their active metabolites, are cleared by the kidneys. Ideally, analgesics should only be used in conjunction with non-pharmacologic therapies such as physical and behavioral therapies that address the psychosocial aspects of chronic pain. There is a very high prevalence of illicit drug use in people receiving CKM in LICs and LMICs. Healthcare workers often fear the divergence of prescribed medication and family support is complicated by previous drug addiction behaviour such as theft, abuse, or homelessness. These patients and their families require specific psycho-social support, which includes the realization that CKM is a palliative pathway, forgiveness of previous abuse, and sometimes containing ongoing addiction.

An adapted WHO analgesic ladder has been advocated for the management of acute and chronic pain in patients with KF and in those receiving CKM.[44-47] It involves the slow introduction and upward titration of analgesics, starting with non-opioids then progressing to opioids as required for pain relief. Table 2 outlines the recommended analgesics in CKM.[46] There is no evidence that weak opioids such as codeine or tramadol are less risky than strong opioids at their lowest effective dose.[48] Given the risks of using weak opioids such as codeine and tramadol in patients with KF, strong opioids at a low dose with careful titration when opioid therapy is required is recommended.[46] For patients with a neuropathic component to their pain, the first step is to introduce an adjuvant. Many pains experienced by people with KF will be of mixed type e.g., pain associated with ischemia. It is important to target the neuropathic component first with an adjuvant to prevent inappropriate opioid use.

Symptom management is complicated in low resource settings due to limited access to essential medications, healthcare facilities, and kidney care or palliative care personnel. For example, 83% of the world's countries have low to non-existent access to opioids[49] and access to even the simplest pain-relieving medication is often limited.[50] Low-income countries and LMICs have the greatest need for CKM and palliative care in general yet these regions account for only 7% of global opioid use.[51,52] Access to medication, particularly opioids, in LICs and LMICs is heavily influenced by national formularies, which are often highly restrictive, leading to overregulation in the prescribing of these medications.[50] This issue becomes even more complex for people with KF who are limited in what they can safely use. There are tremendous differences between the international pharmacological recommendations in KF and CKM and essential medications lists. The WHO lists acetaminophen, codeine, morphine, transdermal fentanyl, and amitriptyline as essential medications; methadone is on the complementary list but only for the management of cancer pain.[53] This list is not fully aligned with the recommended analgesics for people with KF. Only codeine and morphine are typically on formulary across Africa and India with morphine being the preferred opioid for the management of moderate or severe pain.[50-52,54] However, the accumulation of morphine metabolites in KF poses a genuine concern. Despite this, it is important to recognize that leaving a patient in severe pain at the end of life is ethically unacceptable. The reality is that morphine will need to be used for people receiving CKM in low resource settings. In such cases, morphine should be initiated cautiously, starting with small doses of 1.25mg to 2.5mg twice daily and then titrated slowly with close monitoring for adverse effects. There is also a need to continue to advocate for other medications required for the safe and equitable care of people with KF.

Table 2. Symptom Management For People Receiving CKM[33,34]

Restless Legs Syndrome			
Address possible contributing factors	**Non-pharmacologic management**	**Pharmacologic management**	**Additional considerations**
• Decrease or stop medications such as dopamine antagonists, antidepressants, and opioids (some of these drugs are commonly prescribed at end of life e.g., haloperidol and opioids) • Correct iron deficiency, anemia, and hyperphosphatemia	• Trial abstinence from stimulants (e.g., alcohol, caffeine, and nicotine) • Trial mental alerting activities (e.g., puzzles or games) • Promote good sleep hygiene (see Fatigue and Sleep Disturbances below) • If realistic promote aerobic exercise and/or stretching	1st Line: Gabapentin (50mg-300mg daily) 2 hrs before sleep, especially if concomitant pruritus, insomnia and/or neuropathic pain. 2nd Line: Non-ergot derived dopamine agonists 2 hours before sleep (pramipexole 0.125mg – 0.75 mg daily, Ropinirole 0.25mg – 2 mg daily, rotigotine transdermal patch 1-3mg) 3rd Line: Carbamazepine 100-400 mg daily before sleep for up to 5 weeks. Carbamazepine is more readily available than 1st and 2nd line therapies in low resource settings. At the end of life if swallowing is problematic consider midazolam 1 mg subcutaneously q4h PRN. In LICs, diazepam is more readily available and can be given 2mg subcutaneously q4h PRN.	The most common side effects of gabapentin are drowsiness, dizziness, confusion, fatigue, and occasionally peripheral edema. Non-ergot derived dopamine agonists have shown success in reducing symptoms in idiopathic RLS but there are very limited data in uremic RLS. Side effects might include headache, insomnia, and nausea. Augmentation may occur with long-time use. Serious dermatologic reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome can be seen with carbamazepine use; close monitoring for adverse effects is important. Benzodiazepines (e.g., clonazepam 0.25 mg before sleep) are not generally recommended for RLS and carry significant risks including an increased risk of falls, fractures, and decreased cognition. However, there is some limited evidence for their use. If the patient is experiencing refractory RLS causing significant sleep disturbance, or if benzodiazepines may potentially treat concurrent symptoms (e.g., anxiety), or the patient can no longer swallow, they could be considered.
Uremic Pruritus[55]			
Address possible contributing factors	**Non-pharmacologic management**	**Pharmacologic management**	**Additional considerations**
• Correct iron deficiency, anemia, hyperphosphatemia, hypercalcemia • Consider other etiologies or exacerbating factors such as xerosis, drug hypersensitivities, allergies, infestations, contact dermatitis, or inflammation	• Good skin care and moisturizers (e.g., baths with lukewarm water, pat dry and moisturize within 2 minutes, gentle soaps with no fragrances or additives) • Keep skin cool • Humid environment • Avoid scratching – keep fingernails short, encourage gentle massage, wear gloves at night • Consider complimentary therapies: e.g., phototherapy (UVB) three times weekly for a three- week trial; acupuncture. Very little evidence exists for these alternative therapies.	**Topical** • Capsaicin 0.025% or 0.03% ointment • Hydrocortisone 1%/Pramoxine 1% • Menthol/Camphor/ Phenol – 0.3%-1.0% individually in cream or added together with a 0.3% concentration for each. • gamma-linolenic acid cream 2.2%	These agents can be applied two times daily (four times daily for capsaicin). Capsaicin may cause burning to the area initially.
		Systemic 1st Line: Gabapentin (50mg-300mg daily) 2 hrs before sleep 2nd Line: Tricyclic antidepressant such as doxepin 10 mg daily or amitriptyline 10-25 mg daily before sleep	The most common adverse effects of gabapentin are drowsiness, dizziness, confusion, fatigue, and occasionally peripheral edema. Potential adverse effects of tricyclic antidepressants include dizziness, blurred vision, constipation, and urinary retention. There is an

			increased risk of confusion and sedation, particularly in older adults.
Nausea and Vomiting			
Address possible contributing factors	**Non-pharmacologic management**	**Pharmacologic management**	**Additional considerations**
• Gastrointestinal disturbances e.g., constipation, delayed gastric emptying • Decrease or stop medications such as iron supplements, opioids, SSRI antidepressants	• Manage constipation • Encourage good oral hygiene • Smaller, more frequent meals; eat slowly • Avoid alcohol • Avoid foods that are greasy, spicy or excessively sweet • Minimize aromas e.g., cooking odours, perfumes, smoke • Encourage relaxed, upright position after eating to facilitate digestion • Loose fitting clothing • Consider complementary therapies e.g., relaxation techniques, acupressure, the use of ginger	1st Line: Ondansetron 4-8mg every eight hours as needed (unless related to poor gastrointestinal motility) 2nd Line: Metoclopramide 2.5mg every four hours as needed (1st line for poor gastrointestinal motility) 3rd Line: Olanzapine 2.5mg every eight hours as needed OR Haloperidol 0.5mg every eight hours as needed Haloperidol is often the only option available to many individuals in LICs. 4th Line: For persistent and severe nausea, consider increasing Haloperidol to 1.0mg (maximum 5mg in 24 hours) OR replacing with Methotrimeprazine 5mg orally or 6.25mg subcutaneously every eight hours as needed	Ondansetron can be constipating. Haloperidol, metoclopramide, and olanzapine are all dopamine antagonists: avoid prescribing them together. They can also exacerbate RLS. They all cross the blood-brain barrier and extrapyramidal symptoms are possible. Haloperidol has a higher risk of extrapyramidal symptoms than Metoclopramide and Olanzapine. Increasing the dose of Methotrimeprazine may lead to levels of drowsiness that the patient may find unacceptable and should be discussed with the patient and/or family.
Breathlessness			
Address possible contributing factors	**Non-pharmacologic management**	**Pharmacologic management**	**Additional considerations**
• Anxiety • Anemia • Volume overload leading to pulmonary edema • Infection	• Sit in an upright position e.g., 45° • Position by a window or use a fan to blow air gently across the face • Maintain a humid environment • Pursed lip breathing • Supplemental oxygen • Consider complementary therapies e.g., relaxation techniques, music therapy • Consider the role of diet such as sodium and fluid restriction if patient is volume overloaded	If patient is intravascularly overloaded: diuretic such as a loop diuretic - Furosemide Occasionally patients may require combination diuretic therapy – consider adding low dose Metolazone. **Near the end of Life:** low doses of opioids are the most effective treatment. For breathlessness that is episodic and primarily associated with a specific activity, consider Fentanyl 12.5 mcg subcutaneously or sublingually PRN. For shortness of breath that is more constant or unpredictable in nature, consider Hydromorphone 0.5 mg PO (0.2 mg subcutaneously) every four hours around-the-clock and every hour as needed.	Due to the accumulation of metabolites, opioids should always be started at a low dose and monitor closely for adverse effects. Due to its fast action, fentanyl works well in cases where breathlessness is predictable.
Fatigue and Sleep Disturbances			
Address possible contributing factors	**Non-pharmacologic management**	**Pharmacologic management**	**Additional considerations**
Fatigue • Consider correcting vitamin D deficiency, metabolic acidosis, anemia, and hyperphosphatemia	Fatigue • If realistic, exercise • Optimize nutrition and hydration • Promote energy conservation strategies	Sleep Disturbances 1st Line: consider low-dose gabapentin (50-300mg at night), especially if the patient has concomitant neuropathic pain, restless legs syndrome, or uremic pruritus	Reassess medications after two to four weeks. Avoid over the counter sleep aids and benzodiazepines if possible. Specifically, avoid Mirtazapine if taking antidepressants. Monitor Doxepin for anticholinergic side effects e.g.,

• Secondary hypothyroidism • Malnutrition • Mood disorders • Sleep disturbances <u>Sleep Disturbances</u> • Other symptoms e.g., restless legs, pruritus, pain, breathlessness • Cognitive impairment • Medications • Generalized insomnia • Mood disorders • Sleep apnea	such as delegating and setting limits • Promote good sleep hygiene e.g., avoid stimulants before bed, avoid napping during the day, save the bedroom for sleep • Consider cognitive and psychological approaches e.g., relaxation therapy • Consider other complementary treatments e.g., acupressure, massage, acupuncture	2nd Line: Doxepin 10 mg at bedtime, especially if concomitant pruritus or neuropathic pain. 3rd Line: cautiously consider Mirtazapine 7.5mg or Zopiclone 3.75-5mg at night or Melatonin 2-5mg at night.	dizziness, blurred vision, constipation, urinary retention and cardiac arrhythmias. Evidence for Melatonin is limited and inconclusive. Ideally, all these medications should be prescribed for short-term use only.
Nociceptive Pain			
Address possible contributing factors	**Non-pharmacologic management**	**Pharmacologic management**	**Additional considerations**
• Determine cause for pain and consider appropriate investigations.	• Physical therapies e.g., physical therapy, aerobic exercise, stretching, massage, acupressure, acupuncture • Behavioural therapies e.g., cognitive behavioural therapy, biofeedback, relaxation techniques, psychotherapy / individual or group counselling, guided imagery, mindfulness-based stress reduction • Interventional and surgical e.g., ablative techniques, nerve blocks, trigger point injections	Step 1: Acetaminophen (paracetamol), maximum of 3g daily. If pain is localized to a small joint, consider a topical NSAID e.g., Dicofenac gel 5% or 10% two to three times daily Step 2: add an opioid to step 1. e.g., hydromorphone starting at 0.5 mg PO (0.2 mg subcutaneously) every four to six hours; buprenorphine/ Fentanyl/methadone	Trial each step for 1-4 weeks before progressing, depending upon pain severity. Before starting an opioid, consider completing an opioid risk tool and order a bowel routine e.g., PEG 3350. In LICs bisacodyl +/- lactulose is used as more readily available. All opioids should be started at low doses, monitored carefully for adverse effects and overall benefit, and titrated slowly.
Neuropathic Pain			
Address possible contributing factors	**Non-pharmacologic management**	**Pharmacologic management**	**Additional considerations**
• Determine cause for pain and consider appropriate investigations	• As for nociceptive pain	Start with adjuvant therapy. 1st Line: gabapentin, pregabalin (calcium channel alpha 2-delta ligands) 2nd Line: Tricyclic antidepressants, amitriptyline starting at 10-25mg daily or doxepine starting at 10mg daily If additional analgesia is required <u>in addition</u> to adjuvant therapy, add a non-opioid and then proceed stepwise as required to an opioid as described for nociceptive pain.	Opioid medications are second-line agents for most patients with neuropathic pain. Methadone may be effective for severe neuropathic pain because of its activity against NMDA receptor antagonism.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; RLS, restless legs syndrome; SSRI, selective serotonin reuptake inhibitor; UVB, short wave ultraviolet B

Additional considerations for delivering CKM in low resource settings

Delivering CKM in low resource settings requires a comprehensive approach that considers resource optimization. This includes the importance of screening for early detection, risk factor modification, and preservation of residual kidney function in high-risk individuals to reduce the burden of KF and the need for CKM.

Most CKM is overseen in the community by primary care and provide by family members. Engagement with community leaders to strengthen primary care clinics and home-based care nursing is essential. A multidisciplinary approach is needed to optimize CKM delivery and prevent abandonment while acknowledging the unique cultural, religious, and system barriers.[56] This can be very challenging in regions where there is a lack of physicians and allied healthcare professionals and most have little or no knowledge of the principles and practices of palliative care, which is the underpinning for KSC and CKM. Addressing this training gap for those delivering care is a matter of high importance. These care teams need to deal with not only those who have embarked on CKM (typically choice-restricted) but also those on the waiting list for dialysis, many of whom will die before treatment becomes available.

Given the pivotal role of family in delivering CKM, they need to be involved in all management decisions and educational efforts, even when options for care are limited. This includes helping patients and families understand the disease trajectory and the importance of non-pharmacological interventions. Table 3 expands on these discussion points. While they are important for all people receiving CKM, they take on increased relevance in low resource settings.

Table 3. Discussion points around non-pharmacological management of CKM in low resource settings

Ensure understanding of the diagnosis, disease trajectory, and prognosis
• Progression of CKD can be insidious without obvious symptoms. Due to suboptimal monitoring, people with KF often present late. Delivering an unexpected diagnosis of KF requires skilled, compassionate communication using culturally appropriate language and methods to convey the message. • It is common for patients and families to experience emotions like anger and guilt, which require therapeutic care and repeated information sharing through an iterative process.
Discuss treatment options and address issues that will impact adherence
• Adherence to treatment plans – both dialysis and CKM – are challenging due to factors such as distance to clinics, unavailability of medications, and associated costs. • In settings where KRT may be available, but unaffordable, the financial harm to a person and their family may be greater than the short-term benefit of providing dialysis when it needs to be stopped once funds run out. Financial limitation is the main reason for withdrawal from dialysis in low resource settings. In a systematic review in sub-Saharan Africa, only about 10% of adults with incident KF remained on dialysis for more than 3 months.[57] Yet, families may still raise funds for dialysis, even if it can only be sustained for a short period of time, often due to guilt. • It is crucial to consider and explicitly discuss the financial implications to the patient and family when recommending interventions or medications. • Social workers can provide valuable assistance in future care planning, particularly regarding financial considerations and the care of vulnerable family members.
Stress the importance of non-pharmacologic management
• Since many of the pharmacological management strategies are not available, the awareness and implementation of non-pharmacological management is essential. • Education must be adapted to local context to integrate culture considerations and the availability of community resources and local foods. • If pharmacologic interventions are started, they are often not 1st line therapies and are likely to have the potential for increased adverse effects, for e.g., the use of morphine. It is crucial to provide on-going education to the patient and family regarding the signs and symptoms of toxicity.

Abbreviations: CKD, chronic kidney disease; KF, kidney failure; CKM, conservative kidney management; KRT, kidney replacement therapy

Conclusion

Kidney supportive care and CKM are essential treatments for KF but are poorly developed and/or poorly integrated with kidney care across LICs, LMIC, and HICs. For people with KF who are unlikely to derive a survival or HRQOL from KRT, a positive alternative in the form of CKM should be provided. Conservative kidney management is highly individualized active treatment that comes with its own set of recommendations that focus predominantly on providing KSC. In low resource settings, providing choice-restricted CKM should not excuse government bodies from investing in adequate kidney services, including KRT programs, exploring innovative thinking such as public-private partnerships.

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