Kidney Supportive Care: Core Curriculum 2020

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Kidney supportive care is the application of palliative medicine principles and practices to patients with kidney disease. The goal is alleviation of suffering through treatment of symptoms, empathic communication, and support for psychosocial distress. Kidney supportive care includes primary palliative care provided by nephrology teams, as well as referral of patients with complex distress for comanagement by an interprofessional specialty palliative care team, when available. The team may include physicians, nurses, social workers, chaplains, and dieticians. Comanagement with nephrologists offers an additional layer of support to patients and families as prognostic awareness, patient preferences, and care decisions are explored. Kidney supportive care can be offered to patients experiencing acute kidney injury or chronic kidney disease, including those with kidney failure treated by kidney replacement therapy (dialysis and transplantation). Kidney supportive care includes but is not limited to end-of-life care. This installment of the Core Curriculum in Nephrology outlines several practical applications of kidney supportive care, with a focus on the nephrologist's approach to symptom management, active medical management of kidney failure without dialysis (also known as comprehensive conservative care), acute kidney injury in seriously ill patients, and withdrawal from dialysis.

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Am J Kidney Dis. 75(5):793-806. Published online March 12, 2020.

doi: 10.1053/j.ajkd.2019.10.016

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Historical Context and Relevance of Kidney Supportive Care

Kidney supportive care is palliative care for patients with kidney disease. It is a growing subspecialty of the field of nephrology, like transplantation nephrology or onconephrology, but unlike those, it can be applied to all patients living with advanced kidney disease from any cause and on any dialysis modality. Similar to palliative care in oncology, the goal is reduction of suffering throughout the trajectory of illness, including (but not limited to) the end of life. Kidney supportive care is ideally provided through collaboration of nephrologists (who use "primary palliative care" skills) and palliative care specialists, whose approach usually includes an interprofessional team with nurses, social workers, dieticians, and chaplains (Table 1).

Randomized prospective trials in the fields of oncology, heart failure, and others have shown substantial improvements in quality of life, functional status, depression, and anxiety for people treated with palliative care as compared with standard specialty care alone. Though many imagine that palliation in nephrology amounts to stopping dialysis and hospice care, kidney supportive care is much broader, with numerous areas of focus that are applicable to patients across the illness spectrum (Fig 1). This includes intensive physical symptom management, heightened attention to nonphysical dimensions of suffering, iterative and patient-centered explorations of prognostic awareness, elicitation of patient preferences, and in some cases, the option of managing advancing disease without dialysis, which has been called "maximal" or "active" or "nondialytic" medical management, "conservative kidney management," "comprehensive conservative care," or simply "conservative care." These terms are interchangeable, and in this discussion we use "active medical management" and "comprehensive conservative care" for their emphasis on holistic ongoing care.

To understand the relevance of kidney supportive care, it is essential to understand the evolving epidemiology of kidney disease, which is particularly remarkable in the realm of dialysis. Since maintenance dialysis for kidney failure became available in the 1960s (and universally covered in the United States by the Social Security Amendments of 1972), the patient population treated by nephrologists has become older and more ill. In 1978, 25% of incident dialysis patients were 65 years or older and only 10% had diabetes. By 2016, 50% of incident dialysis patients in the United States were older than 65 years, 23% were older than 75 years, and 47% had kidney failure attributed to diabetes. Some also have debilitating and life-limiting illnesses at the time of dialysis initiation, such as cancer, cardiovascular disease, and dementia. Though early legislation may have intended to increase access to dialysis as a bridge to transplantation or renal recovery, today dialysis in the United States is often a

Table 1. Primary and Specialty Palliative Care in Nephrology

Domain of Care	Primary Palliative Care by Nephrology Team	Specialty Palliative Care Consultation
Symptom management	Routine symptom assessment and treatment	Refractory symptom treatment, including pain, neuropathy, itch, nausea, and anxiety/depression
Decision making	Communication about patient priorities, prognosis, dialysis modality options	Assistance with navigation of complex clinical situations or interpersonal dynamics
Interdisciplinary team support	Screening for social, spiritual, or nutritional distress	Access to dieticians, chaplains, and social workers trained in palliation
Conservative care	Medical CKD management with focus on quality of life	Assistance with advance care planning and end of life care

Abbreviation: CKD, chronic kidney disease.
Based on information presented in Quill and Abernethy, 2013 (*N Engl J Med*. https://doi.org/10.1056/NEJMp1215620).

"destination" therapy by which life is prolonged but health and function are not always restored.

In the past 2 decades, recognition has increased that patients with advanced age or comorbid illnesses experience high mortality rates and high symptom burdens on dialysis. Their survival is worse than for many cancers. Patients who start dialysis at age 75 years have on average 1- and 3-year adjusted survivals of 63% and 33%, respectively. Furthermore, among patients older than 80 years, some observational studies have shown no survival benefit with starting dialysis as compared with active medical management. For this reason, the election of a nondialytic approach for patients with advanced age or frailty is gaining acceptance. However, comprehensive conservative care is not yet a well-established component of nephrology fellowship education or routine practice.

To raise awareness and fuel a global effort to develop kidney supportive care, in 2013, international leaders in palliative care and nephrology convened at a KDIGO (Kidney Disease: Improving Global Outcomes) controversies conference on supportive care, where they defined fundamental principles and competence domains. These included: (1) identification of patients most likely to benefit from supportive care, (2) symptom assessment and management, (3) communication of prognosis, (4) shared decision making to advance goal-concordant care, and (5) effective use of local palliative medicine and hospice resources. It is important to emphasize that these domains are applicable to patients across the continuum of illness severity and chronicity, including patients with acute kidney injury (AKI) and chronic kidney disease (CKD) who are not receiving dialysis and patients with kidney transplants.

Kidney supportive care programs are most robust in Canada, the United Kingdom, Australia, New Zealand, and Hong Kong. Limitations to widespread implementation in the United States include misperceptions of palliative medicine, inadequate training and modeling of these skills, limited access to and number of palliative

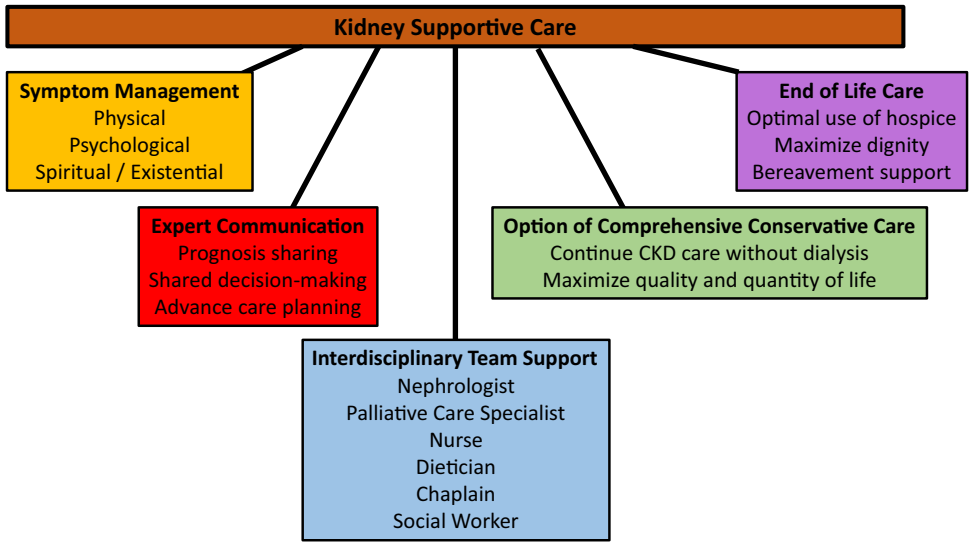

Figure 1. Domains of kidney supportive care. Abbreviation: CKD, chronic kidney disease.

care experts, and financial systems that do not incentivize palliative metrics. However, the serious nature of advanced kidney disease coupled with high mortality and high symptom burden necessitates the inclusion of supportive care as a standard component of all nephrology practice.

Additional Readings

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Symptom Management

> "I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism" – Modernized Hippocratic Oath, revised by Louis Lasagna

Patients with advanced kidney disease experience a high frequency of physical and psychological symptoms, comparable to patients with cancer (Table 2). There is evidence that nephrologists underrecognize and undertreat these symptoms. A cornerstone of kidney supportive care is symptom management, which can be accomplished across a multitude of care settings, including clinics, hospitals, and dialysis units.

Symptom Assessment Tools

Patients underreport symptoms unless asked explicitly about them, and there are robust data that regular assessments with validated tools can reduce symptom burden over time. Options for assessment tools are listed in Box 1. In programs in Australia, the United Kingdom, and Canada, nurses and advanced practice providers conduct periodic symptom assessments with patients and families. In the United States, a few academic centers have devised similar programs, mostly led by nephrologists who are dual trained in nephrology and palliative medicine.

In general, the approach to symptom management should involve evaluation for cause, reversible factors, level of distress or dysfunction caused by symptoms, nonpharmacologic and pharmacologic intervention options, expectation management, and acknowledgement of limitations of therapy. Of note, at this time there are no financial incentives related directly to symptom control among patients receiving dialysis. Although large dialysis organizations require annual symptom assessments such as the Kidney Disease Quality of Life instrument, therapeutic intervention is variable.

Table 2. Symptoms in Patients With End-Stage Kidney Disease on Dialysis and Active Medical Management

Symptom	Prevalence in Patients on HD in the United States	Prevalence in Patients on Comprehensive Conservative Care in the United Kingdom
Fatigue/ weakness	68%	75%
Dry skin	72%	35%
Pruritus	54%	56%
Pain (bone or joint)	50%	56%
Dry mouth	45%	20%
Insomnia	44%	36%
Muscle cramps	43%	NR
Diarrhea	17%	11%
Worrying/anxiety	28%	42%
Shortness of breath	19%	49%
Decreased appetite	29%	58%
Feeling sad or depressed	24%	33%
Restless legs	29%	24%
Nausea	26%	36%
Constipation	21%	42%
Vomiting	11%	25%

Abbreviations: HD, hemodialysis; NR, not reported.
Prevalence data for HD patients based on Weisbord et al, 2005 (*J Am Soc Nephrol.* https://doi.org/10.1681/ASN.2005020157); for comprehensive conservative care patients, on Murphy et al, 2009 (*Nephron Clin Pract.* https://doi.org/10.1159/000183177).

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Box 1. Symptom and Function Assessment Tools

- Edmonton Symptom Assessment Revised: Renal (ESAS-Renal) (http://palliative.org/NewPC/_pdfs/tools/ESASr%20Renal.pdf)
- Integrated Palliative Care Outcome Scale Renal (IPOS-Renal) (https://pos-pal.org/maix/ipos-renal-in-english.php)
- Dialysis Symptom Index (DSI) (www.jpsmjournal.com/article/S0885-3924(03)00517-7/fulltext)
- Karnofsky Performance Status (KPS) score (http://www.npcrc.org/files/news/karnofsky_performance_scale.pdf)
- Eastern Cooperative Oncology Group (ECOG) (https://ecog-acrin.org/resources/ecog-performance-status)

► Weisbord SD, Fried LF, Mor MK, et al. Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol.* 2007;2(5):960-967. ★ **ESSENTIAL READING**

Neuropathy

Case 1: *A 48-year-old man with autosomal dominant polycystic kidney disease who received a deceased donor kidney transplant develops posttransplantation lymphoproliferative disorder. He is treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), which eventually leads to remission of the posttransplantation lymphoproliferative disorder. However, toward the end of his treatment he develops severe pain in his feet and hands. The pain is bilateral, worse at night, and feels like "electric shocks." It prevents him from sleeping. Vincristine-related neuropathy is diagnosed.*

Question 1: Which of the following is NOT a therapeutic tool for the treatment of neuropathy?

a) Gabapentin
b) Subcutaneous lidocaine
c) Methadone
d) Duloxetine
e) Ketorolac

For the answer to the question, see the following text.

Neuropathy is common in patients with kidney disease. Distinct from nociceptive pain, which is triggered by tissue damage and resolves when the tissue has healed, neuropathic pain results from damage to or pathology within the nervous system. Although the most common cause of neuropathic pain in patients with kidney disease is diabetes mellitus, there are a variety of other causes, including degenerative joint diseases, stroke, chemotherapy, and paraneoplastic conditions.

The first step in treating neuropathy is determining the cause. If caused by a nerve root compression, such as lumbar radiculopathy ("sciatica") or median nerve compression (carpal tunnel syndrome), pharmacologic management is usually ineffective and therapeutic options include surgery, steroid injections or neurolytic blocks, and supportive measures (bracing, ice, etc). Neuropathy that affects diffuse distal nerve fibers, including the symmetric distal peripheral neuropathy of diabetes and medication toxicity, is more amenable to pharmacotherapy.

Borrowing from the stepwise treatment approach that has been recommended for neuropathy in the general population and taking into consideration metabolism differences and adverse effects in patients with kidney disease, the first-line pharmacologic treatment for neuropathy is a calcium channel alpha-2-delta ligand (gabapentin or pregabalin). While pregabalin is approved by the US Food and Drug Administration for diabetic neuropathy and data from randomized controlled trials (RCTs) confirm its efficacy, it is not available as a generic and therefore can be prohibitively expensive. Gabapentin, for which there is a generic version, is used off label. Alternatives include selective serotonin-norepinephrine reuptake inhibitors such as duloxetine and tricyclic antidepressants such as amitriptyline. Potential adverse effects and recommended starting doses are outlined in Table 3. In patients with CKD, it is essential to start with low doses and uptitrate slowly because adverse effects can be dangerous. Furthermore, toxicity from inappropriate dosing can cause aversion and mistrust in both the patient and provider toward these effective medications.

For severe or refractory neuropathic pain, referral to a palliative care or pain management specialist may be helpful for access to advanced therapies, including trials of opioids, lidocaine, and ketamine. Of the opioids, hydromorphone, fentanyl, and methadone are safest in the setting of decreased glomerular filtration rate (GFR), and methadone has the most efficacy for neuropathic pain due to its antagonism of the NMDA (N-methyl-D-aspartate) receptor. Of note, heightened awareness of the harms of opioids has led to recommendations by medical societies to avoid or deprescribe opioids in chronic noncancer pain conditions. Among all patients with serious illness, including those with advanced kidney disease, the potential risks and benefits of therapy need to be considered in the individual context of each patient. Close monitoring for adverse effects, functional goal setting, and careful dose titration are all standard parts of specialty palliative care.

Nonsteroidal anti-inflammatory drugs such as ketorolac have no established role in the treatment of neuropathy, but many pain syndromes are a mix of nociceptive and neuropathic pain. Recently, in the context of heightened awareness of the potential harms of opioids, there has been increasing enthusiasm for trialing nonsteroidal anti-inflammatory drugs in select situations. However, they would not be an effective choice for the patient in this case. The correct answer to question 1 is therefore (e).

With specific regard to chemotherapy-related neuropathy, knowing the natural history of the pain syndrome can facilitate shared decision making among nephrologists, oncologists, and patients regarding the need for intervention versus watchful waiting. With vincristine-related neuropathy, symptoms are dose dependent and usually reversible, with improvement seen gradually over months after discontinuation of the drug.

Additional Readings

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Table 3. Treatments for Neuropathy in Patients With Kidney Disease

Class	Agents	Starting Doses	Most Common Adverse Effects
Calcium channel alpha-2-delta ligands[a]	Gabapentin Pregabalin	Gabapentin: 100 mg daily at night (if on dialysis, reduce to 100 mg 3×/wk after dialysis) Pregabalin: 25 mg daily at night (if on dialysis, reduce to 25 mg 3×/wk after dialysis)	Dizziness, drowsiness, edema, ataxia
Serotonin-norepinephrine reuptake inhibitors	Duloxetine Venlafaxine (extended release) Tramadol	Duloxetine: 30 mg daily (if on dialysis, avoid) Venlafaxine: 37.5 mg daily Tramadol: 50 mg every 8-12 h	Headache, drowsiness, dry mouth, nausea, insomnia, withdrawal syndromes
Tricyclic antidepressants	Amitriptyline	10 mg daily at night	Dry mouth, urinary retention, blurred vision, change in libido, dizziness, weight gain, insomnia
Voltage-gated sodium channel blockers	Lidocaine[b] Mexiletene[b]	Lidocaine: weight-based Mexiletene: 150 mg 1-2×/d	Dizziness, ataxia, nervousness, tremor, arrhythmia
Opioids	Methadone[b]	2.5 mg every 8-12 h	Constipation, weight gain, delirium, sexual dysfunction, prolonged QTc
Topical agents	Lidocaine patch Capsaicin	Lidocaine: 1 patch every 12 h; can wear up to 3 patches at a single time Capsaicin: 0.025% ointment, compounded with menthol when available	Numbness (lidocaine), burning (capsaicin)

[a]Caution and close monitoring are recommended with any off-label use of calcium channel alpha-2-delta ligands.
[b]Referral recommended to pain management specialist.

► Finnerup NP, Attai N, Haroutounian, S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14(2):162-173.

Pruritus

Case 2: *A 63-year-old woman with advanced CKD from hypertensive nephrosclerosis presents for follow-up in the clinic. She is active on a waiting list for a kidney transplant. Her energy level is good and she is still working. She is eating well and her weight has been stable, with no hiccups, nausea, vomiting, or dysgeusia. Her main concern is itch, which affects her upper arms, thighs, chest, and back. It is worse at night and after showers. On physical examination, there is no rash. The skin is dry and there are scattered excoriations. Laboratory study results include the following values: serum creatinine, 4.1 mg/dL (corresponding to an estimated GFR of 11 mL/min/1.73 m^2 as calculated using the CKD-EPI equation); potassium, 4.2 mg/dL; bicarbonate, 22 mEq/L; serum urea nitrogen, 39 mg/dL; hemoglobin, 11.1 g/dL on treatment with a monthly erythropoiesis-stimulating agent; serum albumin, 3.9 mg/dL; phosphorus, 5.3 mg/dL; and parathyroid hormone, 95 pg/mL.*

Question 2: What is the best next step?

a) Initiate dialysis
b) Refer to dermatology
c) Treat with topical emollients and low-dose gabapentinoids
d) Treat with evening primrose oil
e) Start UV light treatment

For the answer to the question, see the following text.

Not only is itch common among people living with kidney disease, it is often severe enough to influence mood, sleep quality, interpersonal relationships, and overall health-related quality of life. Among patients receiving dialysis, moderate to severe pruritus has been associated with a 17% higher mortality rate. Although pruritus may not be easy to cure, several small RCTs have shown that it can improve with treatment. Most importantly, decreasing the intensity of itch has shown to correlate with a significant improvement in health-related quality of life.

The pathogenesis of uremic pruritus has been elucidated by recent advances in cutaneous neurophysiology. The sensation of itch is transmitted by myelinated A-delta afferent nerves and unmyelinated C-fibers, of which a minority (10%) are histaminergic and a majority (90%) are histamine-independent. The neurotransmission of itch through these C-fibers is complex and likely related to the uremic alterations in the immunochemical milieu of the epidermal and dermal skin layers.

The therapeutic implications of this complex pathogenesis are important. Antihistamines such as diphenhydramine are commonly prescribed but they do not target the underlying pathophysiology. Although some patients depend on them to "get through" a dialysis treatment, this may stem primarily from their sedative properties rather than actual alleviation of itch. In a recent analysis of DOPPS (Dialysis Outcomes and Practice Patterns Study) data, more than two-thirds of surveyed medical directors in 17 different countries underestimated the prevalence of pruritus among patients in their facilities, and 57% used oral antihistamines as first-line long-term therapy.

A clinical approach to pruritus is outlined in Figure 2. The first step is to confirm the diagnosis by

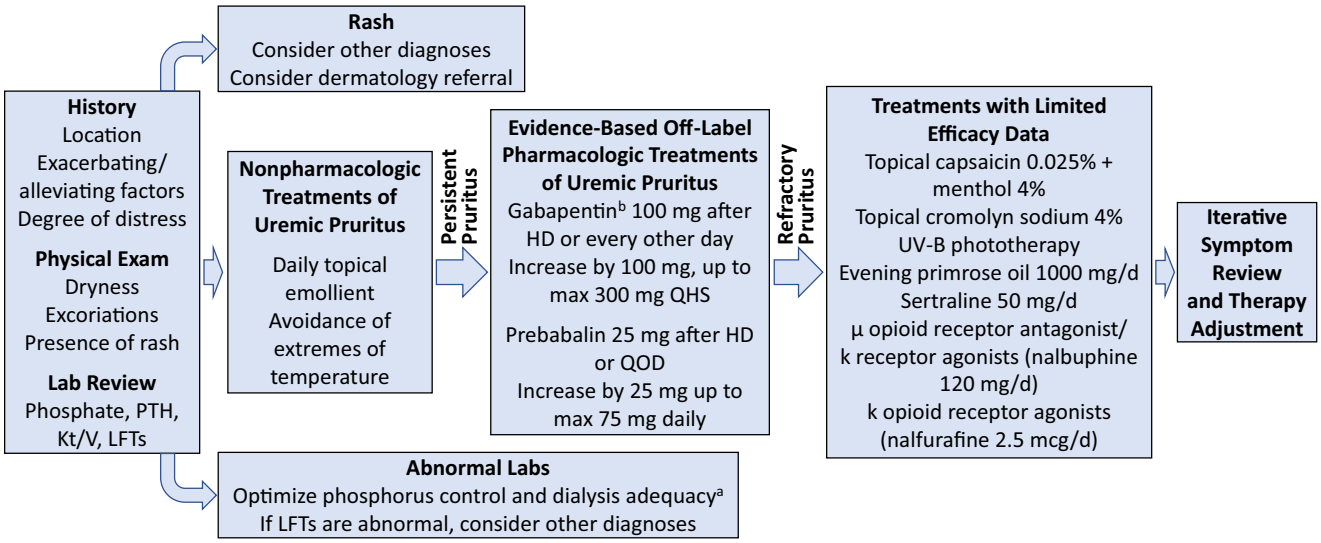

Figure 2. Treatment approach for uremic pruritus. [a]Common clinical practice despite lack of evidence that hyperphosphatemia, hyperparathyroidism, or increasing Kt/V over usual adequacy standards has any relationship to the sensation or alleviation of pruritus. [b]Caution and close monitoring is recommended with any off-label use of calcium channel alpha-2-delta ligands. Abbreviations: HD, hemodialysis; Lab, laboratory; LFTs, liver function tests; PTH, parathyroid hormone; QHS, every bedtime; QOD, every other day.

history and physical examination. The distribution of uremic itch is almost always in large discontinuous bilateral skin areas involving the arms, legs, and torso. On physical examination, the most common skin finding in uremic pruritus is normal epidermis, with possible dryness or superficial excoriations. Presence of a rash suggests a primary dermatologic condition and warrants referral to dermatology. When uremic pruritus is confirmed, treatment options must be tailored to the individual patient. All patients with pruritus, even those without evident xerosis, should be advised to apply a daily over-the-counter emollient and reapply after bathing. Bathing in tepid (rather than hot) water may also reduce itch. In addition to moisturizers, data suggest that lotions with pramocaine (a topical anesthetic, also known as pramoxine) alleviate pruritus better than other moisturizing emollients.

If itch persists, the next step is to try low-dose gabapentin or pregabalin. Although both have been shown to reduce pruritus significantly in small RCTs, it is important to note that neither is approved by the US Food and Drug Administration for this indication. Low doses are appropriate for people with kidney disease. The dosage or frequency can be increased as needed and tolerated, with careful adjustment for GFR. It is essential to monitor for signs of toxicity, including dizziness, changes in mental status, myoclonus, and swelling. There is no superiority of one agent over the other, and their adverse effects are comparable. Patient preference and financial cost should therefore guide initial agent selection. The correct answer to question 2 is (c).

A key component of treating uremic pruritus is setting expectations. It is highly likely that therapy will need to be adjusted after initiation, as in hypertension.

Additional Readings

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Depression

Case 3: *A 71-year-old woman receiving in-center hemodialysis has frequent hospitalizations due to problems with her right arm fistula. She has long-term occlusion of the central vessels on the left and a recurrent central venous stenosis on the right that has required frequent angioplasties. She is ultimately advised to undergo temporary dialysis catheter placement and evaluation for a new vascular access in a*

lower extremity. The hemodialysis unit staff notice that her affect has changed; she is disengaged, terse, and irritable. She is initially reluctant to talk about her mood, but subsequently shares that she feels depressed, like she is "trapped in a nightmare."

Question 3: Which of the following is false?

a) Many patients receiving dialysis attribute their psychological distress to acute and chronic health problems rather than depression
b) It is a national requirement that all dialysis units conduct annual depression screenings and report a therapeutic plan
c) Most antidepressants are metabolized by the liver and are highly protein bound, therefore not highly dialyzable
d) RCTs have shown efficacy of selective serotonin reuptake inhibitors (SSRIs) over placebo for depression in patients receiving dialysis
e) Most nephrologists believe that depression is not treatable in the context of serious illness

For the answer to the question, see the following text.

Mental illness, including depression, is common among patients with kidney disease and associated with poor health outcomes. Among patients receiving dialysis, depression is associated with increased mortality, higher hospitalization rates, longer lengths of stay, and higher rates of suicide. It also often occurs as part of a "symptom cluster" along with pain and fatigue, all of which are consistently rated as highly distressing by patients.

In 2018, the Centers for Medicare & Medicaid Services End-Stage Renal Disease (ESRD) Quality Improvement Program (QIP) mandated reporting of annual depression screening and follow-up plans in all patients receiving dialysis. Many self-reporting tools, such as the Patient Health Questionnaire (PHQ-2 and PHQ-9) and the Beck Depression Inventory, have been validated in patients with CKD, including those with kidney failure. It is noteworthy that some somatic symptoms common in advanced kidney disease, such as fatigue, insomnia, and poor appetite, are nonspecific and may create a "positive screen" without actual dysthymia.

One in 5 patients receiving dialysis will have an episode of major depression, but <25% receive treatment. Barriers include limited access to specialty mental health care, nephrologists' reluctance to treat depression, and patient reluctance to accept treatment. Patients cite many reasons for this, including polypharmacy, skepticism, and unwillingness to spend additional time interfacing with the health care system. In one study, among patients receiving dialysis who screened positive for depression who were not already on therapy, 91% did not accept recommendations to start depression treatment because they attributed their depressed mood to an acute event, chronic illness, or dialysis itself. Furthermore, among patients who agreed to start pharmacotherapy, 61% of renal providers were unwilling to prescribe antidepressants.

Many nephrology providers see the treatment of depression as outside their scope of practice and believe it should be addressed by primary care physicians or psychiatrists. This is problematic because many patients receiving hemodialysis do not have a primary care physician and access to mental health providers is variable. However, therapeutic nihilism is doubtful; in a survey of nephrology fellows, 84% "generally or completely agreed" that depression is treatable in the context of serious illness. The correct answer to question 3 is (e).

SSRIs are considered first-line pharmacotherapy for depression in kidney disease. Most antidepressants are highly protein bound and predominantly metabolized by the liver. In a systematic review of antidepressants in CKD, clearance was noted to be markedly reduced for paroxetine but no other SSRIs, tricyclic antidepressants, or selective serotonin-norepinephrine reuptake inhibitors. No antidepressant was found to be cleared significantly by dialysis.

Efficacy data for depression treatment in patients with kidney disease are mixed (Table 4). Two recent RCTs of SSRIs include CAST (CKD Antidepressant Sertraline Trial), in which sertraline did not significantly improve depression at 12 weeks follow-up in patients with CKD, and ASCEND (A Trial of Sertraline vs Cognitive Behavioral Therapy for ESRD Patients With Depression), in which sertraline conferred a modest but statistically significant benefit for patients receiving dialysis compared with cognitive behavioral therapy, which is psychotherapy that focuses on negative emotions, subconscious associations, and maladaptive behaviors. Other small RCTs have demonstrated the effectiveness of cognitive behavioral therapy and exercise therapy compared to routine dialysis care alone. Unfortunately, many of these therapies are not readily available at nephrology clinics or dialysis centers.

One of the aims of kidney supportive care is to integrate specialty mental health services into nephrology care. This includes increasing access to psychiatrists, therapists, counselors, and integrative medicine services. Additionally, though pharmacotherapy may be appropriate in some cases, it is important to avoid medicalization of suffering that might be soothed by intensification of psychosocial or spiritual support. The multidisciplinary interprofessional approach deployed by most specialty palliative care teams can be very useful in this regard.

Additional Readings

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Table 4. RCTs on Depression Treatments in Kidney Disease

Therapy	RCT	Intervention	Patient Population	Follow-up	Outcome
Selective serotonin reuptake inhibitor (SSRIs)	Hedayati et al, 2017 (*JAMA*. https://dx.doi.org/10.1001/jama.2017.17131)	Sertraline (initial dose 50 mg daily) vs placebo	201 pts with CKD not on dialysis	12 wk	No improvement in depressive symptom severity determined by 16-item QIDS-C score
	Mehrotra et al, 2019 (*Ann Intern Med*. https://dx.doi.org/10.7326/M18-2229)	Phase 1: engagement interview with trained therapist vs control Phase 2: sertraline (initial dose 25 mg daily) vs CBT (10 sessions of 1 h over 12 wk during HD)	Phase 1: 184 pts on HD Phase 2: 120 pts on HD	12 wk	Phase 1: no change in pt willingness to start therapy for depression Phase 2: sertraline more effective than CBT in lowering depressive symptom severity (by QIDS-C score)
Cognitive behavioral therapy (CBT)	Duarte et al, 2009 (*Kidney Int*. https://www.ncbi.nlm.nih.gov/pubmed/19455196)	CBT (12 weekly chairside sessions led by trained psychologist) vs routine care	85 pts on HD	9 mo	CBT reduced depression symptoms
	Cukor et al, 2014 (*J Am Soc Nephrol*. https://doi.org/10.1681/ASN.2012111134)	CBT (10 weekly chairside sessions led by psychologist and supervised psychology trainees) vs routine care	59 pts on HD	6 mo	CBT reduced depression symptoms, overall quality of life, and interdialytic weight gain
Exercise	Giannaki et al, 2013 (*Nephrol Dial Transplant*. https://doi.org/10.1093/ndt/gft288)	Intradialytic cycling vs routine care	24 pts on HD	6 mo	Exercise reduced depression symptoms
	Kouidi et al, 2010 (*Eur J Cardiovasc Prev Rehabil*. https://doi.org/10.1097/HJR.0b013e32833188c4)	Intradialytic cycling vs routine care	44 pts on HD	1 y	Exercise decreased depression symptoms

Note: There are no or minimal data for other drug classes, including tricyclic antidepressants, selective serotonin-norepinephrine reuptake inhibitors, mirtazapine, and bupropion.
Abbreviations: CBT, cognitive behavioral therapy; CKD, chronic kidney disease; HD, hemodialysis; QIDS-C, Quick Inventory of Depression Symptomatology-Clinician Related; RCT, randomized controlled trial.

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Active Medical Management of Advanced CKD in the Outpatient

Case 4: *An 82-year-old man presents for follow-up of advanced CKD. His comorbid conditions include hypertension, coronary artery disease, heart failure with preserved ejection fraction, and peripheral arterial disease. His estimated GFR has declined by 2 to 3 mL/min/1.73 m^2 per year for the last 4 years and is currently 8 mL/min/1.73 m^2. Last year, after discussion with his nephrologist and family, he opted for active medical management over dialysis. Since then, he has been seen every 2 to 3 months by his nephrologist. Currently he feels well, though he notes dry mouth and progressive blandness in the taste of food. He reports that he dislikes "all these pills" and sometimes feels nauseated after taking them. His blood pressure is 158/78 mm Hg and he has ankle edema (1+) that is not bothersome to him. He denies shortness of breath. Serum potassium level is 5.3 mmol/L, bicarbonate level is 17 mmol/L, ionized calcium level is 1.0 mmol/L, phosphorus level is 6.1 mg/dL, intact parathyroid hormone level is 400 pg/dL, and hemoglobin level is 9.7 g/dL. His medications include amlodipine, carvedilol, furosemide, aspirin, atorvastatin, calcitriol, sevelamer, sodium bicarbonate, and darbepoetin every 2 weeks administered at home.*

Question 4: What is most appropriate at this time?

a) Revisit whether he wants to start dialysis
b) Set up regular home intravenous sodium bicarbonate infusions
c) Intensify diuretics to address edema and hypertension
d) Intensify phosphorus control by increasing binders and dietary restrictions
e) Review medications and deprescribe if possible

For the answer to the question, see the following text.

Comprehensive conservative care is an approach to treating advanced kidney disease with tools other than dialysis. This includes traditional CKD therapies that are

known to delay GFR decline, as well as additional palliative tools and services aimed specifically at reducing symptom burden. Although comprehensive conservative care programs vary in resources and infrastructure, the fundamental goals are maximizing quality of life and aligning all care with the patient's priorities.

As a result of historical, political, and financial factors in the United States, comprehensive conservative care is relatively rare. Dialysis is widely understood as the default standard of care for kidney failure that cannot be treated by transplantation. Implicit in this are 2 assumptions common among laypeople and clinicians from fields other than nephrology: that everyone can benefit from dialysis and that the alternative to dialysis is imminent death.

Observational data from the last 20 years challenge these assumptions. Survival with active medical management tends to be on the order of months to a few years for elderly patients, similar to dialysis (Fig 3). In some populations, particularly those with ischemic heart disease and those older than 80 years at dialysis initiation, the survival advantage with dialysis has been shown to be modest or absent. Furthermore, when survival among elderly patients is actually extended by dialysis, much of the "added time" is spent at dialysis, recovering from dialysis, or hospitalized with complications.

Observational analyses are limited by bias and heterogeneity, and it would be catastrophic to use any simple age cutoff, survey response, or comorbidity score to determine which patients would be better suited by comprehensive conservative care than dialysis. It is essential to engage in shared decision making with patients and their closest supports. In large patient surveys, the majority of respondents rank "living longer" as less important than other aspects of life, including independence, dialysis-free time, and ability to travel. For more information on prognostic assessments and communication skills that facilitate dialysis-related decision making, see case 5 and the review by Koncicki and Schell listed in the Additional Readings.

In comprehensive conservative care, how care is delivered will evolve based on changes in patient priorities and needs. Clinic visits and laboratory tests may occur every 2 to 3 months, as they would in usual CKD care. However, as illness progresses, the focus of care may shift entirely to

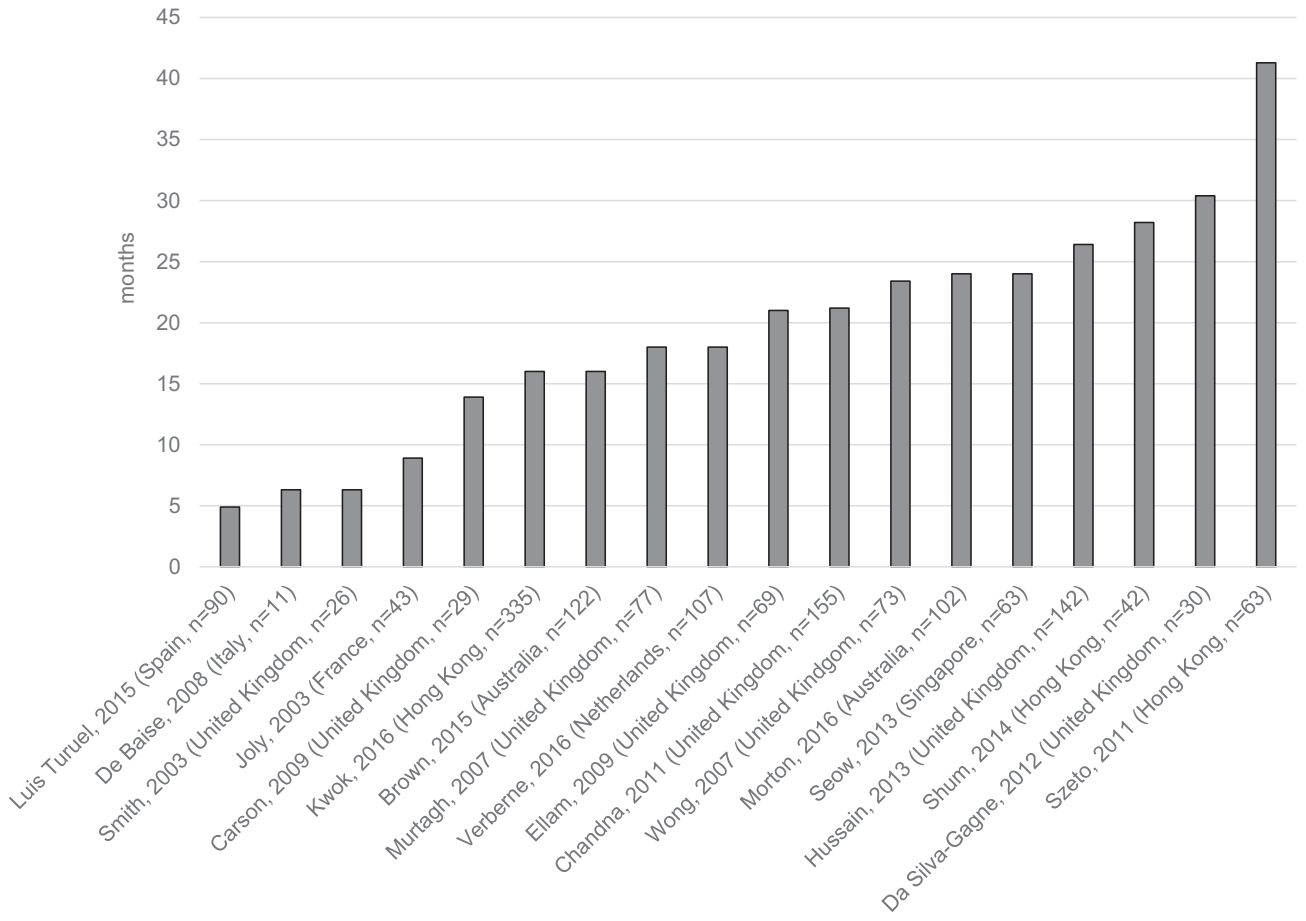

Figure 3. Survival in comprehensive conservative care. Adapted from Wong et al, 2018 (*Am J Kidney Dis.* https://doi.org/10.1053/j.ajkd.2017.11.007); original figure published as a US government work.

symptom management. At that point, while laboratory data may help guide certain interventions, such as in symptomatic anemia, blood tests may be used sparingly and clinic visits or home-based assessments may increase in frequency.

Although it is always possible for patients to change their minds regarding comprehensive conservative care, it is not advisable to reassess this at every visit. In a study from an Australian practice, <2% of patients who selected conservative care changed their minds and initiated dialysis. Recently, in a qualitative study of care practices for patients with advanced kidney disease, doctors were noted to repeatedly assess capacity and urge reconsideration in patients who had opted to forgo dialysis. This was associated with nephrologists' perception that they were "giving up" or had little to offer patients who were not going to start dialysis.

This patient's main concerns include mouth symptoms and pill burden. His acidosis, edema, and suboptimally controlled blood pressure are not causing symptoms and are unlikely to cause acute harm. Although it may be instinctive to titrate diuretics and oral bicarbonate supplements to achieve tighter control, those measures would constitute disease-specific rather than person-centered care in this case. In the absence of dyspnea from metabolic acidosis or hypervolemia, intensification of therapy for the "bad numbers" is not necessary. Similarly, focusing on phosphorus level reduction by increasing binders or dietary restrictions during this visit would be misguided.

In the context of comprehensive conservative care, quality of life and symptom reduction should be the main focus of nutritional advice. Although there is a dearth of literature about nutritional best practices in comprehensive conservative care, dietary recommendations should be modified according to the particular cultural, religious, and social needs of the patient. Many patients have had years of counseling about phosphorus and potassium restriction; new advice may be necessary to mitigate food-related anxiety that may be experienced by the patient or family. It may be helpful to share the rationale for various dietary liberalizations. For example, it can be educational to distinguish biochemical derangements that can be acutely unsafe, such as hyperkalemia, from others that are associated with complications in the long run, such as hyperphosphatemia. The social aspects of eating must also be discussed. This patient's nausea with taking pills, in combination with his dysgeusia, may result in withdrawal from meals and other social activities. Symptoms that impact on oral intake are common in advanced CKD (Table 5).

The most appropriate action to take at this juncture would be to review his medications and consolidate the list if possible. Although cessation of any of these medication treatments could lead to worsening in biochemical parameters, it may be worthwhile to the patient, who is experiencing daily nausea and stress from taking them.

Table 5. Symptoms Related to Eating

Symptom	Intervention
Anorexia	• Liberalize dietary options, no restrictions • Consider eating environment (increase social nature, reduce cooking smells) • Offer low-bulk high-calorie supplements • Trial appetite stimulants including dronabinol
Dry mouth	• Rinse mouth regularly • Trial artificial saliva • Apply lip balm regularly • Stimulate saliva production with lemon juice, hard candies, gum, frozen grapes
Dysgeusia	• Maintain oral hygiene • Rinse with sodium bicarbonate mouthwash • Encourage herbs, spices, and tart flavors to reduce bitter taste • Avoid metal cutlery • Trial cold or tepid foods rather than hot
Nausea, dry-retching, and vomiting	• Trial small regular meals, avoid skipping meals • Avoid strong smells • Trial ginger or ginger products • Address constipation • Trial antiemetic medications

This approach is recommended by global leaders in kidney supportive care after summary of available evidence and expert opinion from nephrologists, geriatricians, and palliative care specialists. The correct answer to question 4 is (e).

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AKI in Patients With Other Serious Illness

Case 5: *A 71-year-old woman with history of cholangiocarcinoma and CKD stage 3 develops sepsis and AKI. One year ago, she underwent surgical resection of the cancer, including cholecystectomy, partial hepatectomy, and hepatico-jejunostomy. She was believed to be cured. She now presents with fever and shortness of breath. She is found to have polymicrobial bacteremia, an ill-defined liver mass, and AKI. On admission, creatinine level is 3.3 mg/dL from a baseline of 1.5 mg/dL and increases to 6.1 mg/dL by hospital day 4, when it plateaus. Urine microscopy shows granular casts. Her bacteremia clears with intravenous antibiotic treatment and she is transitioned to oral antibiotic treatment. Her liver mass is biopsied and cancer recurrence is confirmed. Serum creatinine level remains at 5.9 mg/dL. Serum potassium level is 5.4 mEq/L, pH is 7.31, P_{CO_2} is 30 mm Hg, and bicarbonate level 15 mmol/L. She is edematous (net + 11 L since admission) and making about 800 mL of urine daily with diuretics.*

Question 5: Which of the following is true about this situation?

a) Dialysis will prolong her survival
b) Choosing not to start dialysis means imminent death
c) Dialysis should be started now because not starting dialysis will prolong her hospital stay and delay follow-up with outpatient oncology
d) Shared decision making means contextualizing her priorities and preferences in the setting of her prognosis and therapeutic options
e) Available prognosis estimator tools have been validated for inpatients with AKI

For the answer to the question, see the following text.

In hospitalized patients, AKI is often a reflection of overall severity of illness rather than intrinsic kidney disease. Several domains of kidney supportive care are helpful in developing an appropriate care plan. Empathic patient-centered communication around prognosis (the expected trajectory of illness), exploration of the option of active medical management without dialysis, and psychosocial and spiritual assessments are key (Box 2). The communication tasks can be subdivided into shared decision making about current care choices and advance care planning about anticipated future care choices (advance directives).

Shared decision making is a patient-centered approach to navigating care options. It starts with exploring health literacy and prognostic awareness through the question "What do you understand about your current illness?" Additional discussion ensues, including open-ended prompts about worries, hopes, and priorities in the context of illness. After developing an understanding of a patient's priorities, the medical team then makes an informed recommendation about which treatment plan best aligns with the patient's preferences and goals. In cases in which AKI occurs in the setting of advanced cardiac, liver, or oncologic disease, inclusion of the other specialty teams in the shared decision-making process is essential, if also challenging in the pressurized and fragmented inpatient setting.

A major challenge of shared decision making is prognostic uncertainty. Uncertainties about the renal prognosis are often compounded by uncertainties about the

Box 2. Approach to Shared Decision Making for Inpatients With AKI and Serious Illness

Understand the clinical picture
- Review the medical record and confer with other members of care team to understand the expected trajectory and treatment options for the underlying illness (cancer, cirrhosis, etc)
- Are there disease-specific treatments available for patient's other comorbid conditions?
  - ◇ If so, is patient a reasonable candidate for these treatments at this time?
  - ◇ If not, what is the likelihood of patient being a candidate in the future?

Assess the renal prognosis
- Limited kidney injury (ATN) vs ongoing kidney injury (eg, tumor lysis, toxicity of needed medication, decreased effective arterial blood volume); identify likely short- and long-term effects of KRT vs active medical management in these domains
- Symptoms
- Functional Status
- Quality of life
- Prognosis (expected illness trajectory in terms of time and function)

Arrange meeting with patient, family, and other key members of care team
- Consider assistance through specialty palliative care consultation
- Pre-meet with other care providers to share perspectives
- Review published approaches to family meetings, including SPIKES (see Bailet et al) and REMAP (see Childers et al)
- Start by asking about patient and family's perception of current illness and knowledge of dialysis
- Ask about patient's identity before illness
- Define what patient considers important for quality of life in the context of current illness
- Ask permission to share information and provide a medical update
- Acknowledge prognostic uncertainty
- Address emotion

Align patient goals and values with treatment plan
- Offer a treatment recommendation based on patient priorities, goals, and values
  - ◇ Time-limited trial of dialysis
  - ◇ Active medical management
- Outline "next steps" and expected trajectory for either pathway
- Invite input from other teams on other relevant care decisions

Abbreviations: AKI, acute kidney injury; ATN, acute tubular necrosis; KRT, kidney replacement therapy.
Based on information in Bailet et al, 2000 (*Oncologist.* https://doi.org/10.1634/theoncologist.5-4-302) and Childers et al, 2017 (*J Oncol Pract.* https://doi.org/10.1200/JOP.2016.018796).

underlying illness trajectory. Regardless, being ill enough to require inpatient initiation of dialysis in any clinical context is a poor prognostic sign. According to data from the Health and Retirement Study, of 286 patients who initiated dialysis as an inpatient, 26% died within 30 days, 51% died by 6 months, and 62% died by 1 year. These mortality rates are higher than those derived from the US Renal Data System database, which includes only patients who survive long enough to establish care in an outpatient dialysis unit.

Prognostic assessment tools, including the REIN (Renal Epidemiology and Information Network) score, the Thamer mortality risk score, and the surprise question ("Would I be surprised if this patient died in the next year?") are all validated in patients receiving or transitioning to maintenance dialysis; they are not validated for use at the bedside of a hospitalized patient with AKI.

The main care options for AKI in the context of another serious illness include a time-limited trial of dialysis or nondialytic active medical management of uremia and hypervolemia. During a time-limited trial of dialysis, the nephrology team, other medical teams, and the patient team (including any surrogate decision makers) enumerate potential risks, potential benefits, and intended goals of dialysis. Goals may include "bridging" to expected renal recovery or an important life event, symptomatic relief, or functional improvements in strength or mobility. Purely "prolonging life" is rarely but sometimes a patient goal, and intensive psychosocial and spiritual support can often enhance understanding of this challenging position when encountered. From the outset, it is essential that all teams agree that lack of progress toward the agreed-on goals will be grounds for stopping dialysis. A parallel in oncology is the stopping of a palliative chemotherapy that has not provided intended symptom relief to a patient with cancer.

If a time-limited trial is agreed on, dialysis is provided for a prespecified time, and the patient's progress toward those predefined goals is monitored. Complications of treatment are also acknowledged with the patient, including vascular access problems and hemodynamic instability, both of which are common in the setting of a concurrent serious illness. At the end of the prespecified period, the teams meet to discuss each party's perception of how things are going. When discussing dialysis discontinuation, collaboration with a palliative care team may facilitate a detailed conversation of hospice, including symptom-focused care and disposition options, including home hospice and inpatient facilities.

There are many barriers to time-limited dialysis trials and shared decision making in inpatient settings, including interprofessional team dynamics, misinformation, and inadequate training and skill in communicating. Care fragmentation is common, which means the team that managed dialysis initiation may no longer be present when it comes time to evaluate progress toward the prespecified goals. Additionally, before involvement of the nephrology consulting service, dialysis may already have been discussed with the patient or his or her family. Sometimes options are presented in a dichotomous or oversimplified binary (indefinite dialysis or imminent death). This can prime the patient and family to expect dialysis and may reduce their willingness to engage in nuances of shared decision making. For a thorough discussion of time-limited trials of dialysis, see the review by Scherer and Holley listed in the Additional Readings.

Surveys have repeatedly shown that graduating nephrology fellows feel ill-equipped to navigate difficult conversations related to end-of-life care. Part of the imperative of kidney supportive care is to develop curricular and experiential opportunities to observe and practice these skills. In countries with robust kidney supportive care programs, nephrology fellows rotate in palliative care clinics and inpatient consult services. These types of training experiences equip nephrologists with communication tools necessary for navigating these common complex situations.

The correct answer to question 5 is (d).

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Withdrawal From Dialysis

Case 6: *A 73-year-old man receiving maintenance hemodialysis is hospitalized 5 times during the last 6 months with volume overload. He has aortic stenosis, congestive heart failure (ejection fraction, 10%), transient ischemic attacks, and a below-knee amputation. He now experiences frequent symptomatic intradialytic hypotension and cramping. His nephrologist has tried to improve his tolerance of ultrafiltration by eliminating all antihypertensives, adding midodrine,*

and changing the dialysis prescription, including increased time, ultrafiltration modeling, and low-temperature dialysate. The patient reports distress over the frequent hospitalizations and anxiety that he will be hospitalized during his granddaughter's wedding next month. He says he might want to "call it quits" after that event.

Question 6: Which of the following is false?

a) He can receive kidney supportive care while continuing hemodialysis
b) Elective withdrawal from dialysis is common
c) Completion of an advance directive is one of the ESRD QIP quality metrics through which dialysis units are graded and will be financially penalized for poor performance
d) An alternative dialysis modality might be a palliative option

For the answer to the question, see the following text.

Withdrawal from dialysis is the third most common cause of death of patients with kidney failure after cardiovascular disease and infection. Between 2008 and 2010, more than 50,000 patients in the United States discontinued dialysis before death. Although a patient's right to withdraw has been established in practice guidelines from the Renal Physicians Association and the American Society of Nephrology, it is often challenging and emotionally taxing for patients, families, and providers to discuss. In one study, <10% of patients receiving dialysis reported discussing end of life with their nephrologists in the last year, while 85% to 90% reported it is important to them to receive information about prognosis and all treatment options, including dialysis withdrawal.

Early recognition of those who are more likely to withdraw may improve end-of-life care. Acute medical decompensation and chronic failure to thrive are the 2 most common precedents for dialysis discontinuation. In a retrospective cohort study of more than 17,000 octogenarians receiving dialysis in the United States in 2019, other factors associated with withdrawal included older age, diabetes, dementia, white race, Medicare as primary insurance, and initial access through a central venous catheter. There are also marked regional differences in dialysis discontinuation rates; these variations are not explained by differences in patient characteristics but correlate with overall regional Medicare spending trends. In one study, withdrawal from dialysis was more common in Midwestern and Southwestern states and least common in New York.

Access to hospice remains extremely limited for patients receiving maintenance dialysis under current Medicare policy. The details of these barriers are discussed elsewhere (see the Grubbs editorial in the Additional Readings). Among patients who stop dialysis, approximately half enroll in hospice. Individual survival time varies greatly, with a mean of 7.4 (range, 0-40) days. This is notably lower than the mean survival of patients with nonrenal hospice diagnoses (54 days). Male sex, referral from a hospital, lower functional status, and presence of peripheral edema are all independent predictors of early mortality after dialysis discontinuation.

When considering withdrawal from dialysis, several factors need to be examined: reasons for withdrawal, sources and reversibility of distress, decisional capacity of the patient, and support from family. If hypervolemia and postdialysis fatigue are significant sources of distress, alternative dialysis modalities including nocturnal dialysis and peritoneal dialysis should be considered. Assisted peritoneal dialysis, in which visiting nurses manage the technical aspects of therapy, is a growing option in Canada and Europe though not yet available in the United States. For patients in whom volume is not a significant issue, reduction of in-center dialysis dose, akin to incremental dialysis for incident patients with substantial residual kidney function, should be considered ("decremental dialysis").

It is important to note that in the United States the current ESRD QIP metrics, particularly those related to Kt/V and phosphate goals, may create a barrier for this kind of dialysis customization. The ESRD QIP also does not include any metric related to advance care planning, which is an essential part of caring for seriously ill patients receiving dialysis because it encompasses preferences related to resuscitation attempts (code status) and health care proxy assignments. The correct answer to question 6 is (c).

It is important to emphasize that medical care will continue after stopping dialysis, with a focus on symptom management during the dying process. Expectations should be set for a painless progressive decrease in consciousness and the possibility of treatable dyspnea, nausea, and pruritus. Local hospice resources can be engaged to oversee terminal symptom management in the patient's preferred place of death, if feasible. In a survey of patients with kidney disease, most would rather die at home (36%) or in an inpatient hospice (29%) than a hospital (27%).

Withdrawal from dialysis and end-of-life care should be thought of as a small but important piece of the broad spectrum of kidney supportive care. A successful withdrawal is a dignified death, on a patient's own terms, with the least possible amount of suffering and maximal support for those left behind.

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Conclusion

Palliation, which means reduction of suffering, has always been a cornerstone of the nephrologist's mission. Kidney supportive care encompasses a broad range of skills and services because patients with kidney disease have a broad range of needs, from symptom relief to psychosocial support to intensive communication about complex care choices. Nephrologists must hone their primary palliative skills to craft high-value patient-centered plans of care. When available, collaboration with specialty palliative care teams can provide an additional layer of support for patients, families, and the nephrology team themselves. As dialysis and transplantation practices evolve and as new therapeutic tools emerge, kidney supportive care will remain a way to prioritize, validate, and bear witness to the human experience of illness.

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Support: Dr Scherer acknowledges support from the Cambia Health Foundation and National Kidney Foundation. The funders did not have any role in defining the content of this article.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Peer Review: Received June 27, 2019, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form October 10, 2019.