PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #408
CONSERVATIVE MANAGEMENT OF PATIENTS WITH END STAGE RENAL DISEASE
Antonio Corona MD and April Bigelow PhD, AGPCNP-BC

Background ESRD describes advanced kidney failure (typically a glomerular filtration rate < 15 ml/min/m2) and is the point at which many patients start dialysis if they cannot receive a kidney transplant. Conservative management (CM) refers to the management of the symptoms and signs of ESRD in patients who do not receive dialysis or transplantation, whether due to personal preference or comorbidities (e.g., dementia, advanced frailty). Significant symptom burden is common in patients with ESRD nearing the end-of life, including those receiving CM (1)**.** *Fast Fact* #207 and 208 discuss discontinuation of dialysis. This *Fast Fact* will address the CM of ESRD patients.

Lack of energy Depression (see *Fast Fact* #404), volume imbalance, sleep disorders, poor nutrition, and anemia are common underlying causes of fatigue in patients with ESRD. Blood transfusions have been shown to improve fatigue and self-reported well-being for palliative care patients who are anemic (2). Erythropoietin-stimulating agents are transfusion-sparing interventions that can similarly mitigate fatigue and enhance quality of life for select ESRD patients on CM (3). Psychostimulants do not have supporting evidence in the CKD population and may cause anorexigenic and cardiovascular effects (4).

Itchiness Chronic kidney disease (CKD)-associated pruritus is a common and distressing symptom (5, 6) (See *Fast Fact* # 37). Except for gabapentin, which has been studied in variable doses from 100 mg daily to 400 mg twice weekly in a few trials (7), well-controlled evidence for other effective treatments is lacking. Immunomodulating treatments such as topical tacrolimus (8), ultraviolet light B phototherapy (9), and opioid receptor antagonists have documented efficacy (10). New kappa-opioid receptor antagonists that do not cross the blood brain barrier are being studied with promising clinical results (11).

Dyspnea See *Fast Fact* #27. Optimize volume status and anemia and address any underlying anxiety.

Pain Systemic NSAIDs are not recommended but topical NSAIDs have been shown to be effective in musculoskeletal syndromes. Opioids that are safer in renal insufficiency include (12): fentanyl, methadone, and buprenorphine. Hydromorphone is commonly used, but the neuroexcitatory effect of its metabolite is often overlooked. For patients with calciphylaxis (see *Fast Fact* #325), ketamine (13) and topical morphine (14) have been investigated. For the latter, a morphine 0.125% gel mixture (morphine sulfate 10 mg in 8 g of sterile gel) has been recommended up to three times daily (15); however, the systemic bioavailability of topical morphine seems to be low (16). See *Fast Facts* #161 and 325.

Volume derangements Hypervolemia is common in ESRD, depending on patients' residual renal function, diet, and use of diuretics. The management of volume overload which goes hand in hand with monitoring for renal function and metabolic abnormalities, is contingent on the patient's estimated prognosis. The goal of preserving fluid balance is to manage symptoms such as dyspnea, cramping and debility while minimizing electrolyte derangements. For patients expected to have a more protracted survival, aggressive diuresis with sequential nephron blockade using thiazide diuretics (like metolazone) and aldosterone antagonists (like spironolactone) can be offered (17) while obtaining occasional lab draws. For patients with a shorter life expectancy who do not wish to pursue additional workup, maintenance with a loop diuretic as a single agent is appropriate. In general, oral loop diuretics can be continued in CM if this has been maintaining urine output. Subcutaneous (SQ) or intravenous (IV) furosemide can be used for urgent situations as its onset of action is within 30 minutes. If converting to a parenteral route, divide the oral dose by half; IV and SQ are dosed equally. Keep in mind that patients with advanced CKD often need very high doses to achieve diuresis and in ESRD doses of 80-160 mg IV furosemide at a time are often needed (18). See *Fast Fact* #353.

GI symptoms Renally-dosed haloperidol is a prudent initial step for nausea management, as it may improve other terminal symptoms in patients with ESRD such as agitation (19). Ondansetron and metoclopramide can be considered as well. The diet should be liberalized, despite metabolic concerns. Dysgeusia and anorexia should be assessed regularly. See *Fast Facts* # 100, 304, and 314

Pharmacologic considerations Other interventions that can address electrolyte or acid-base derangements which can potentially cause distressing pain, cramping, or weakness should be discussed with the patient. These include therapies for hyperkalemia, acidemia, and mineral bone disease. Stopping blood pressure medications such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACE/ARB) is recommended as tight blood pressure control only conveys long-term benefits and elevated blood pressure is rarely symptomatic. ACE/ARBs also pose risks of hyperkalemia and symptomatic hypotension complicated by dizziness and falls.

Hospice Prognosis is protracted for patients with ESRD on CM, with survival ranging from around 6 to 23 months (19). This is in sharp contrast to patients stopping dialysis, whose median life expectancy is around 7 days (20). As a result, hospice eligibility varies. In addition to an estimated GFR of <15 ml/min, hospice evaluation for CM patients is warranted for: 1) uncontrolled metabolic derangements such as hyperkalemia and acidemia, 2) uremic symptoms causing frailty or encephalopathy, 3) critical volume overload causing respiratory issues or nephrogenic ascites, and 4) calciphylaxis (21). Early referral to hospice has the potential to reduce healthcare dollar spending and to improve quality of life while effectively managing symptoms as patients approach their end of life (22).

References

1. Murtagh FE, Addington-Hall J, Edmonds P, et al. Symptoms in the month before death for stage 5 chronic kidney disease patients managed without dialysis. *J Pain Symptom Manage.* 2010; 40 (3): 342-352.
2. Chin-Yee N, Taylor J, Rourke K, et al. Red blood cell transfusion in adult palliative care: a systematic review. *Transfusion*. 2017; 58 (1): 233-241.
3. Cheng HWB, Chan KY, Lau HT, et al. Use of erythropoietin-stimulating agents (ESA) in patients with end-stage renal failure decided to forego dialysis: palliative perspective*. Am J Hosp Palliat Care*. 2017; 34 (4): 380-384.
4. Jhamb M, Weisbord SD, Steel JL, Unruh M. Fatigue in patients receiving maintenance dialysis: a review of definitions, measures, and contributing factors. *Am J Kidney Dis.* 2008; 52(2):353-365.
5. Rayner H, Larkina M, Wang M. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. *Clin J Am Soc Nephrol.* 2017; 12(12):2000-2007.
6. Mathur V, Lindberg J, Germain M, et al. A longitudinal study of uremic pruritus in hemodialysis patients*. Clin J Am Soc Nephrol*. 2010; 5:1410–1419.
7. Simonsen E, Komenda P, Lerner B, et al. Treatment of Uremic Pruritus: A Systematic Review. *Am J Kidney Dis*. 2017; 70(5):638-655.
8. Pauli-Magnus C, Klumpp S, Alscher DM, Kuhlmann U, Mettang T. Short-term efficacy of tacrolimus ointment in severe uremic pruritus. *Perit Dial Int*. 2000; 20(6):802-803.
9. Gilchrest BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Ultraviolet phototherapy of uremic pruritus. long-term results and possible mechanism of action. *Ann Intern Med*. 1979; 91(1):17-21.
10. Mettang T, Kremer A. Uremic pruritus. *Kidney International*. 2015; 87(4):685-691.
11. Fishbane S, Jamal A, Munera C, et al. KALM-1 Trial Investigators. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med*. 2020; 382(3):222-232.
12. Davison S. Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. *CJASN.* 2019; 14 (6) 917-931.
13. Polizzotto MN, Bryan T, Ashby MA, Martin P. Symptomatic management of calciphylaxis: a case series and review of the literature. *J Pain Symptom Manage.* 2006; 32(2):186–190.
14. Peppin J, Albrecht P, Argoff C, et al. Skin Matters: A review of topical treatments for chronic pain. Part two: Treatments and applications. *Pain Ther*. 2015; 4:33–50.
15. United Kingdom National Health Service. Topical morphine for painful skin ulcers in palliative care: a treatment guideline. East Lancashire Health Economy Medicines Management Board. Published 2009. Updated April 2016. Available at: http://www.elmmb.nhs.uk/policies-and-guidelines/palliative-care/. Accessed October 21, 2020.
16. Ribeiro M, Joel S, Zeppetella G. The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage.* 2004. 27(5):434-9.
17. Johnson MJ, Booth S. Palliative and end-of-life care for patients with chronic heart failure and chronic lung disease. *Clin Med* (Lond). 2010; 10(3):286-289.
18. Oh SW, Han SY. Loop diuretics in clinical practice*. Electrolytes & Blood Pressure*. 2015; 13(1):17–21.

19. O'Connor N, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. *J Pallit Med.* 2012; 15(2): 228-5.
20. O'Connor N, Dougherty M, Harris P, Casarett D. Survival after dialysis discontinuation and hospice enrollment for ESRD. *Clin J Am Soc Neprol*. 2013; 12:2117-22.
21. Bhambri A, Del Rosso J. Calciphylaxis: a review. *J Clin Aesthetic Derm.* 2008; 1(2):38-41.
22. Shah KK, Murtagh FE, McGeechan K, et al. Health related quality of life and well-being in people over 75 years of age with end stage kidney disease management with dialysis or comprehensive conservative care: a cross-sectional study in the UK and Australia. *BMJ Open.* 2019; 9(5):e027776.

Conflicts of interest: The authors have disclosed no relevant conflicts of interest.
Authors' Affiliations: Northwell Health, Long Island, NY (AC); University of Michigan School of Nursing, Ann Arbor, MI (AB).
Version History: originally edited by Drew A Rosielle MD; first electronically published in October 2020.