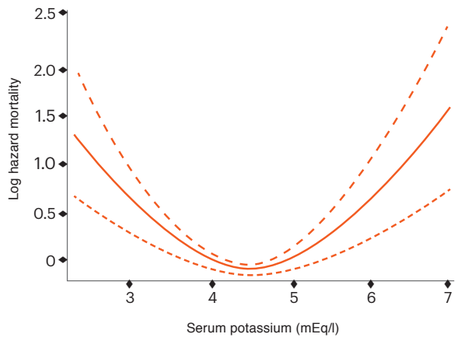
Discussion

Clinical evidence shows that increased serum potassium above the normal range in patients with CKD is associated with a higher mortality rate, especially in patients with advanced age and comorbidities (Figure 2).[26] Hyperkalemia is common in patients with CKD due to multiple risk factors. Management strategies should be based on the degree and cause of hyperkaiemia. Conventional treatments focus on intermittent management of hyperkalemia and may pose safety risks. New agents in the potassium binder class may allow for improved management of hyperkalemia.

Figure 2. **All-Cause Mortality Associated with Serum Potassium Levels in Patients with CKD Not on Dialysis** [26]



Multivariable adjusted log hazards (solid line) and 95% confidence intervals (dashed lines) of all-cause predialysis mortality associated with serum potassium levels in the entire study population (n=1,227).

Adapted with permission from Hayes J, Kalantar-Zadeh K, Lu JL, et al. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron Clin Pract*. 2012;120:c8-c16. Copyright 2012 by Karger Publishers.

References

1. Jain N, Kotla S, Little BB, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *Am J Cardiol*. 2012;109:1510-1513.
2. Moranne O, Froissart M, Rossert J, et al; NephroTest Study Group. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol*. 2009;20:164-171.
3. Espinel E, Joven J, Gil I, et al. Risk of hyperkalemia in patients with moderate chronic kidney disease initiating angiotensin converting enzyme inhibitors or angiotensin receptor blockers: a randomized study. *BMC Res Notes*. 2013;6:306.
4. Yildirim T, Arici M, Piskinpasa S, et al. Major barriers against renin-angiotensin-aldosterone system blocker use in chronic kidney disease stages 3-5 in clinical practice: a safety concern? *Ren Fail*. 2012;34:1095-1099.
5. Johnson ES, Weinstein JR, Thorp ML, et al. Predicting the risk of hyperkalemia in patients with chronic kidney disease starting lisinopril. *Pharmacoepidemiol Drug Saf*. 2010;19:266-272.
6. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppls*. 2013;3:1–150.
7. Inker LA, Astor BC, Fox CH, et al. KDOQI U.S. commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. May 2014;63(5):713-735.
8. ONTARGET Investigators; Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547-1559.
9. Fried LF, Duckworth W, Zhang JH, et al; VA NEPHRON-D Investigators. Design of combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor for treatment of diabetic nephropathy (VA NEPHRON-D). *Clin J Am Soc Nephrol*. 2009;4:361-368.
10. Parving HH, Brenner BM, McMurray JJ, et al; ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367:2204-2213.
11. Vassalotti JA, Centor R, Turner BJ, et al; U.S. Kidney Disease Outcomes Quality Initiative (KDOQI). A practical approach to detection and management of chronic kidney disease for the primary care clinician [Epub ahead of print]. *Am J Med*. September 18 2015.
12. Epstein M. Hyperkalemia as a constraint to therapy with combination renin-angiotensin system blockade: the elephant in the room. *J Clin Hypertens* (Greenwich). February 2009;11:55-60.
13. Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. *Pediatr Nephrol*. March 2011;26:377-384.
14. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol*. 2014;10:653-662.
15. Sarafidis PA, Georgianos PI, Bakris GL. Advances in treatment of hyperkalemia in chronic kidney disease. *Expert Opin Pharmacother*. 2015;16:2205-2215.
16. Kidney Disease Outcomes Quality Initiative (KDOQI). KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43(5 Suppl 1):S1-S290.
17. Kalantar-Zadeh K, Tortorici AR, Chen JL, et al. Dietary restrictions in dialysis patients: is there anything left to eat? *Semin Dial*. 2015;28:159-168.
18. Lepage L, Dufour AC, Doiron J, et al. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol*. December 7 2015;10:2136-2142.
19. Chernin G, Gal-Oz A, Ben-Assa E, et al. Secondary prevention of hyperkalemia with sodium polystyrene sulfonate in cardiac and kidney patients on renin-angiotensin-aldosterone system inhibition therapy. *Clin Cardiol*. 2012;35:32-36.
20. Harel Z, Harel S, Shah PS, et al. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med*. 2013;126:264.e9-e24.
21. U.S. Food and Drug Administration (FDA). FDA drug safety communication: FDA requires drug interaction studies with potassium-lowering drug Kayexalate (sodium polystyrene sulfonate). http://www.fda.gov/Drugs/DrugSafety/ucm468035.htm. Published October 22 2015. Accessed December 15 2015.
22. King RS, Glickman JD. Electrolyte management in frequent home hemodialysis. *Semin Dial*. 2010;23:571-574.
23. Blumberg A, Weidmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int*. 1992;41:369-374.
24. Gutierrez R, Schlessinger F, Oster JR, et al. Effect of hypertonic versus isotonic sodium bicarbonate on plasma potassium concentration in patients with end-stage renal disease. *Miner Electrolyte Metab*. 1991;17:297-302.
25. U.S. Food and Drug Administration (FDA). FDA approves new drug to treat hyperkalemia. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm468546.htm. Published October 22 2015. Updated October 22 2015. Accessed November 24 2015.
26. Hayes J, Kalantar-Zadeh K, Lu JL, et al. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron Clin Pract*. 2012;120:c8-c16.

This publication has been sponsored and developed in collaboration with Relypsa, Inc.

National Kidney Foundation®
30 East 33rd Street
New York, NY 10016
800.622.9010
www.kidney.org

Clinical Update on HYPERKALEMIA

Diagnosis, Evaluation, and Treatment Options for Hyperkalemia in Patients with CKD

National Kidney Foundation®

Introduction

Hyperkalemia is a well-known complication of chronic kidney disease (CKD), since the kidneys are the main route for potassium excretion. Hyperkalemia is associated with increases in all-cause mortality and hospitalizations.[1] Treatment with renin-angiotensin-aldosterone system inhibitors (RAASi) is often associated with increased risk of hyperkalemia in patients with CKD, which may lead to dose reduction or discontinuation. While the main objective for treating hyperkalemia is to induce potassium loss, there have been limited treatment options to accomplish this safely and effectively.

Underlying Risk of Hyperkalemia in CKD

Patients with CKD have a high risk of hyperkalemia, due in part to the effects of kidney dysfunction on potassium homeostasis.[2] Research shows that hyperkalemia is also frequently seen in patients with cardiovascular disease (CVD) who are taking RAASi. Independent predictors of hyperkalemia include advanced age, CKD, diabetes, heart failure, and peripheral vascular disease.[1] Therefore, patients with CKD treated with RAASi, especially at a higher dose or treatment with more than one RAASi, are at very high risk for hyperkalemia.[3] As a result, hyperkalemia is the major barrier against the optimal use of RAASi in patients with CKD.[4, 5]

Importance of RAAS Blockade in CKD

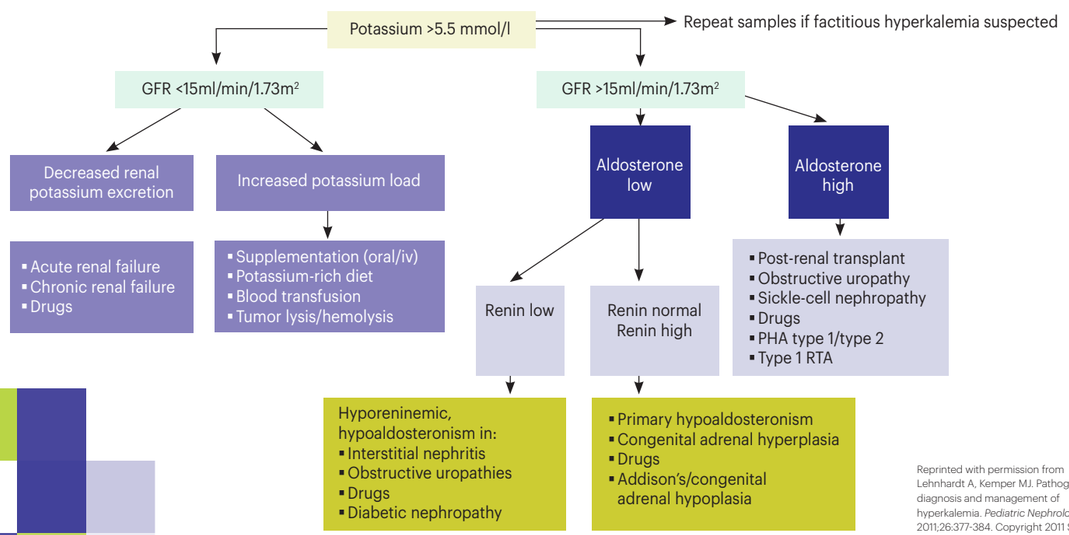
To prevent CKD progression clinical practice guidelines suggest that an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) be used in diabetic adults with CKD and urinary albumin-creatinine ratio 30-300 mg/g (or equivalent), and recommend that an ACE-I or ARB be used in both diabetic and non-diabetic adults with CKD and urinary albumin-creatinine ratio >300 mg/g (or equivalent).[6,7] However, combination therapy with an ACE-I and ARB should not be used in diabetic and non-diabetic patients with CKD and hypertension since studies show more adverse events, including severe hyperkalemia, kidney dysfunction, and hypotension; without any increase in benefits.[8,9,10]

Hyperkalemia and worsening kidney function can develop in some CKD patients after initiating an ACE-I or an ARB since RAASi can lower glomerular filtration rate and can decrease potassium secretion. Therefore, it is important to monitor serum potassium and estimated glomerular filtration rate (eGFR) within several weeks of starting or escalating a RAASi.[11] Discontinuing these drugs is helpful in controlling or treating hyperkalemia, but the disadvantage to doing this is that it increases the risk for kidney disease progression and cardiovascular events.

Diagnosis and Evaluation of Hyperkalemia

The spectrum of hyperkalemia ranges from single episodes of hyperkalemia, sustained hyperkalemia, recurrent hyperkalemia, or severe cases that require dialysis; but what constitutes mild, moderate, or severe hyperkalemia is not consistently defined. Additionally, the cardiotoxic effects of a particular potassium concentration depend on the baseline value, the rate of increase in potassium concentration, as well as the acid-base status, and serum calcium concentration.[12] Pseudohyperkalemia must also be ruled out. Causes of pseudohyperkalemia include release of potassium from red blood cells in the test tube because of venipuncture trauma or prolonged storage before analysis, and very high platelet counts (>500,000 per microL). Pseudohyperkalemia is never accompanied by symptoms or electrocardiogram changes and must be confirmed by repeat analysis using plasma potassium and/or minimizing trauma during venipuncture (minimal use of tourniquet and relaxing the arm).

Figure 1. **Diagnostic algorithm in hyperkalemia[13]**



Mild to moderate hyperkalemia is usually asymptomatic. Patients with moderate to severe hyperkalemia may complain of palpitations, nausea, muscle weakness, or paresthesia. However, moderate and especially severe hyperkalemia can lead to cardiac arrhythmias and conduction abnormalities, and may be fatal.

Emergency diagnostic workup:[13]
1. Assessment of cardiac function, kidneys, and urinary tract
2. Assessment of hydration status
3. Electrocardiogram (ECG)

Elective/etiologic workup:[13]
1. Comprehensive laboratory workup
2. Review of medications

The cause of hyperkalemia has to be determined to prevent future episodes. Figure 1 shows an etiologic workup of hyperkalemia based on GFR and aldosterone levels.[13]

Benefits and Risks of Conventional Management of Hyperkalemia

Non-Emergent Treatment Clinicians should individualize therapeutic strategies by considering the degree and cause of hyperkalemia. Strategies for non-emergent treatment can be divided into four mechanisms of action: (1) restriction – diet, supplements, herbals; (2) excretion – thiazide or loop diuretics, cation exchange resins; (3) removal – dialysis; and (4) redistribution – sodium bicarbonate (does not affect total body potassium levels).[14]

Potassium Restriction The initial management of recurrent hyperkalemia associated with ACE-I or ARB treatment is assessment and restriction of dietary potassium. Potassium restriction has clinical importance, since high dietary potassium intake can counteract the benefits of therapeutic strategies to manage hyperkalemia.[15] Guidelines recommend 2 to 3 grams (approximately 50 to 75 mEq) of potassium per day for patients with a history of hyperkalemia or an eGFR <30 ml/min/1.73m^2.[16]

Clinicians should base the dietary potassium prescription on the serum potassium level. Many potassium-rich foods such as fruits and vegetables are part of a heart-healthy diet, and research shows that a low-potassium diet may contribute to the burden of cardiovascular disease in CKD patients.[17] A balanced and practical approach to dietary potassium restriction includes choosing the sources of potassium which provide the most benefit.

Potassium Excretion Potassium removal can be achieved by enhanced renal excretion using loop or thiazide diuretics. Diuretics such as furosemide inhibit the reabsorption of potassium via Na-K-2Cl cotransporter (NKCC2) in the thick ascending limb (TAL) of Henle's loop.[13] The onset of action varies and the extent of the effect is until diuresis is present, or longer.[14] This approach may not be effective in CKD patients with limited GFR.

Another course of action to increase potassium excretion is ion exchange resins, such as sodium polystyrene sulphonate (SPS), which prevent enteral potassium from being reabsorbed.[13] Oral treatment is more effective with onset of action of 1-2 hours, and the effect lasting for 4-6 hours or more.[14] Concerns about the safety and efficacy of SPS have been raised. A double-blind, randomized clinical trial of 33 mildly hyperkalemic patients with CKD showed that SPS was superior to placebo in reducing serum potassium.[18] In a retrospective chart review of 14 CKD patients, Chernin and colleagues showed that low-dose SPS was safe and effective as a secondary preventative measure for hyperkalemia induced by RAASi in CKD patients with heart disease.[19] In contrast, a systematic review reported that SPS use, both with and without sorbitol, may be associated with fatal gastrointestinal injuries.[20] According to the U.S. Food and Drug Administration (FDA), SPS may bind other medications administered orally. To reduce this potential risk, prescribers and patients should consider separating SPS dosing from other medications taken by mouth by at least 6 hours.[21]

Potassium Removal In patients without residual kidney function, maintenance dialysis is the principal means to control potassium balance. The onset of action takes place within minutes and duration of effect is until the end of the dialysis treatment or longer.[14] Treatment duration, treatment frequency, and potassium dialysate concentration have an impact on potassium clearance. Daily dialysis modalities could enable more physiologic potassium homeostasis, since more frequent dialysis increases the efficiency of small solute clearance by spending more time dialyzing against high solute concentrations.[22] Risks associated with dialysis management of potassium include missed treatments and 2-day interdialytic intervals.

Potassium Redistribution Treatment of metabolic acidosis with sodium bicarbonate may be beneficial to control elevated serum potassium levels.[11] Sodium bicarbonate infusion can shift potassium from the extracellular to intracellular space by increasing blood pH. The onset of action is 5-10 minutes, and the duration of effect is about 2 hours.[14] In general, the efficacy of bicarbonate on hyperkalemia is controversial, and some studies suggest no effect at all.[23, 24] This therapy only has a moderate effect on hemodialysis patients when given as a long infusion, and the sodium load may worsen pre-existing hypertension and heart failure.[15, 23]

Emergency Treatment The life-threatening nature of severe hyperkalemia requires immediate attention, which entails acute medical interventions and occasionally hemodialysis.[14] Details regarding emergency treatment are described elsewhere.

Novel Treatment Options for the Management of Hyperkalemia

New potassium-lowering medications may provide renewed opportunities for improved management of hyperkalemia. A sodium-free, non-absorbed potassium binder for the treatment of hyperkalemia was recently approved by the FDA. A second potassium binder agent, which is an insoluble, non-absorbed cation exchanger, is currently under clinical investigation.[25]