Hyperkalemia management in emergency department; Review

Ahmed Abdulghani Sindi, Turki Muteb S Alotaibi, Faris AbdulAziz Jawmin, Rayan Azeb Alharthi, Saleh Hassan Abdullah Almuntashiri, Mohammed Nawar Awadh Aljuaid, Nasser Awadh Saeed Alshehri

Abstract:

This paper summarizes the outcomes from the INI-CRCT meeting as a guide the emergency management of newly diagnosed, severe hyperkalemia. We conducted a narrative review over the literature using electronic databases as; MEDLINE, and EMBASE for studies involving data on Hyperkalemia management in emergency department, published in English language up to December, 2017. The emergency management of serious hyperkalemia is challenging since patients have an increased risk of death, however the elements (e.g., serum potassium threshold, optimal correction speed, comorbidities, ECG modifications) that affect this risk are unsure. Therefore, physicians are obliged to manage these patients strongly to prevent development to lethal arrhythmias and catastrophic events. Unfortunately, basic treatments are neither without risks or sustained by a compelling body of evidence, and they are used inconsistently. Whether new potassium binders will contribute in the emergency management of serious hyperkalemia remains to be seen, however it is worth investigating their ability to lower potassium in a timely way to decrease the need for insulin with glucose, 2 agonists, and dialysis. Further research is needed to fill existing knowledge gaps, identify remaining unmet needs, and plan definitive clinical tests aiming to enhance results in these patients.

Introduction:

Hyperkalemia is a typical electrolyte problem, particularly among patients with chronic kidney disease (CKD), diabetes mellitus, or heart failure [1], [2].The reported occurrence of hyperkalemia differs (6.0 or > 6.5 mmol/L [3], [4] or electrocardiogram (ECG) manifestations of hyperkalemia (regardless of serum potassium degree) have been recommended as thresholds for initiation of emergency therapy due to the threat of acute serious cardiac rhythm problems [4], [5].

Robust proof is doing not have to lead the emergency management of patients with severe hyperkalemia [5].Emergency therapy techniques are mainly based on tiny researches, anecdotal experience, and commonly approved technique patterns within establishments. The Investigator Network Initiative Cardiovascular and Renal Clinical Trialists (INI-CRCT) is an international company of scholastic cardio and kidney clinical trialists committed to enhancing outcomes among patients with chronic kidney or cardiac disease. To deal with the worry that modern evidence is lacking to guide the emergency situation management of recently identified, serious hyperkalemia, INI-CRCT convened a conference of nephrology, cardiology, and emergency situation medicine global professionals, within the structure of a Cardiovascular Clinical Trialists (CVCT) workshop, to recognize gaps in expertise, set top priorities for future research study, and establish a formula for emergency hyperkalemia management showing experienced opinion in the context of present proof. Chronic or non-emergency management of hyperkalemia was not a focus of this meeting.

This paper summarizes the outcomes from the INI-CRCT meeting as a guide the emergency management of newly diagnosed, severe hyperkalemia.

Methodology:

We conducted a narrative review over the literature using electronic databases as; MEDLINE, and EMBASE for studies involving data on Hyperkalemia management in emergency department, published in English language up to December, 2017. keywords were used in our search as following: “Hyperkalemia”, “emergency department”,” management” We then reviewed the references lists of included studies to find more relevant articles to be for additional evidence.

Discussion:

- **Pathogenesis of hyperkalemia**

The basic pathophysiology of hyperkalemic states involves either extracellular potassium shifts or lowered renal excretion. Common etiologies bring about dimension of hyperkalemia include pseudohyperkalemia, reduced kidney discharging, and unusual potassium circulation. Increased dietary potassium consumption or various other exogenous resources hardly ever trigger greater than short-term hyperkalemic states unless underlying pathology is existing [6].Similarly, throughout enhanced potassium release from endogenous resources, such as high cell turnover or tissue damages, hyperkalemic states are transient, unless concomitant renal pathology exists. Chronic hyperkalemia is always related to kidney potassium discharging problems. It should be kept in mind that often multiple etiologies existing concurrently and might obscure the image.

- **Clinical manifestations of hyperkalemia**

Clinical manifestations of mild to moderate hyperkalemia are normally non-specific and may consist of generalized weakness, exhaustion, nausea, vomiting, digestive colic, and looseness of

the bowels. Serious hyperkalemia may bring about dangerous conditions such as cardiac arrhythmias and muscle mass paralysis.

Potassium and sodium play a crucial duty in the function of the myocardium; as a result, their focus slopes are strictly preserved. Any imbalance of this concentration slope affects the capacity of the heart to preserve a regular rhythm. The concentration gradient is preserved by the sodium potassium ATPase pumps located on the mobile membrane that actively pump sodium exterior and potassium inside the cell. When the potassium degree increases in the extracellular room, the potassium concentration slope across the mobile wall lowers; and this reduces the resting membrane layer potential. The modification in relaxing membrane capacity brought on by hyperkalemia is the concept pathophysiologic mechanism behind most of its signs and symptoms. The decrease in the resting membrane potential decreases the variety of sodium networks turned on that then lower the magnitude of inward sodium current. This creates a long term transmission of the impulse with prolonged depolarization [7].

As the myocardium is very sensitive to any type of modifications in potassium ion concentration, the discrepancy of the potassium focus slope in hyperkalemia could trigger a development of EKG changes such as boosted T wave amplitude (actually peaked T waves), prolongation of the Public Relations period and QRS period, loss of P waves, AV conduction delay, culminating in the combining of the QRS complex with the T wave producing a sine wave pattern, and asystole [7], [8].Scientifically, patients can present with palpatations, syncope, and abrupt cardiac death.

Moreover, hyperkalemia triggers continual spontaneous depolarization of skeletal muscles that brings about inactivation of sodium channels of the muscle mass membrane. These modifications could generate the symptoms of muscular tissue weakness and in severe instances, paralysis [9], [10].

- **Prognostic significance of hyperkalemia in hospitalized patients**

A number of studies have developed the association in between hyperkalemia and all-cause death [11], although whether hyperkalemia is a marker of health problem extent or directly causal is unclear. In one retrospective analysis of 245,808 patients within the United States Veterans Health Administration, the adjusted probabilities proportion for death was 33.4 among inpatients without CKD and 15.8 amongst CKD inpatients within someday of an inpatient serum potassium ≥ 6 mEq/L contrasted to no hyperkalemia (serum potassium < 5.5 mEq/L) [12].Serum potassium was a considerable forecaster of in-hospital, 30, 90, and 365-day all-cause mortality in a retrospective evaluation of 39,705 critical care patients, and the risk boosted as serum potassium values raised [11].Tissue necrosis, hyperkalemia related to potassium supplements, metabolic acidosis, administration of calcium gluconate, acute kidney injury, and period of hyperkalemia have additionally been reported as independent predictors of in-hospital mortality among hospitalized patients with hyperkalemia [13].

- **Impact of hyperkalemia on arrhythmogenicity**

Hyperkalemia destabilizes myocardial conduction [14], [15] by reducing the relaxing membrane potential, leading to raised cardiac depolarization, myocardial excitability, cardiac instability, and arrhythmias, which can proceed to ventricular fibrillation and asystole (Fig. 1) [12], [14].Nevertheless, the specific serum potassium degree and relevant kinetic pattern that incline patients to arrhythmias doubts, and ECGs are aloof signs of the seriousness of hyperkalemia due to the fact that cardiac manifestations could be non-specific or also absent at degrees of serum potassium that are linked with a boosted mortality risk [14], [15].However, cardiac surveillance must be carried out in patients with high levels of serum potassium (i.e., > 6 mEq/L). Heart attack was a providing symptomin43%of 1803 patients hospitalized at a tertiary medical facility with

serum potassium ≥ 6.5 mEq/L, and various other arrhythmias were present in 35%. Amongst 168 cases of hyperkalemia (serum potassium > 6.0 mmol/L) in an emergency situation division, abnormal ECGs were noted in 83%, yet 24% were non-specific [16] Proof of hyperkalemia was observed in 46% of ECGs in one more evaluation of hospitalized patients with serum potassium ≥ 6 mmol/L, and no relationship in between ECG searchings for and potassium level were observed [3].Strict standards defining hyperkalemia-related ECGs were fulfilled in only 16 of 90 hyperkalemia situations from one healthcare facility, whereas 47 instances showed some non-specific ECG adjustments [15].Increasing potassium quintiles and insulin usage were considerably connected with the presence of purely specified ECG changes [15].Patients with CKD or end-stage kidney illness might be much less most likely to show proof of hyperkalemia on an ECG. It has been hypothesized that these patients might establish some degree of tolerance to hyperkalemia [17].

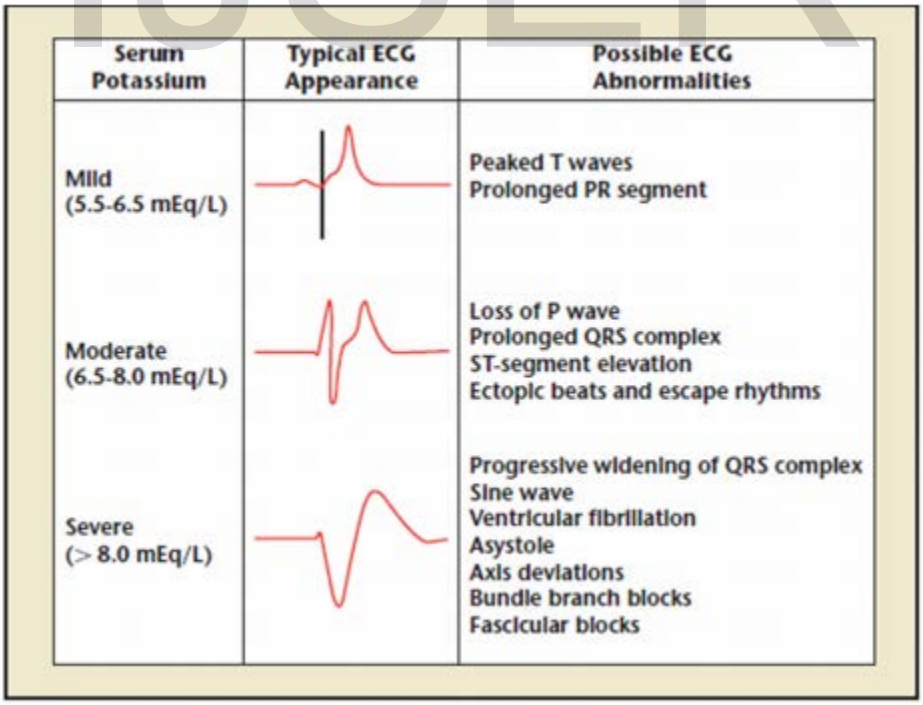

Figure 1. Extracellular concentrations of potassium result in the classic electrocardiographic (ECG) changes.

- **Emergency management of severe hyperkalemia**

Importance of avoiding delays in therapy initiation

Patients with hyperkalemia in acute settings typically existing with non-specific signs. The ECG is often normal, and clinical signs may be absent, every one of which may contribute to under-recognition and treatment hold-ups. Pseudohyperkalemia is an in vitro phenomenon because of the release of potassium from platelet activation, hemolysis, or potassium contamination (i.e. from K+- EDTA or oxalate/fluoride tubes). It has been specified as a serum potassium concentration exceeding that of plasma by > 0.4 mmol/L, provided that examples are accumulated under rigorous strategies, continue to be at room temperature and are checked within 1 h after example collection. Pseudohyperkalemia might result from mechanical injury during or after phlebotomy, potassium contamination by inappropriate tube selection, refrigeration before centrifugation, delay in centrifugation, decreased transport or storage temperature, hemolysis, and clotting. Determining serum potassium is the only dependable approach to determine hyperkalemia, but therapy delays continue also when serum potassium values are readily available, potentially due to the fact that repeat dimensions are purchased to confirm preliminary outcomes and dismiss pseudohyperkalemia in patients without other clinical evidence of hyperkalemia The median time between laboratory results and treatment initiation was 117 min in a retrospective analysis of patients with hyperkalemia (serum potassium > 6 mmol/L) in an emergency division; 25% were dealt with after 196 min [16].An additional study reported a time to treatment of 2.7 ± 2.4 h [3]. Serum potassium level at the moment of therapy initiation was associated with 30-day all-cause death in an important care setting [11].Threat elements that predispose hemodynamically steady patients to create cardiac instability have not been determined. Hence, no data are available to establish whether delaying treatment is

scientifically appropriate in evidently secure patients, or if it puts patients at greater succeeding risk of establishing a deadly arrhythmia.

Summary of existing emergency situation treatments for extreme hyperkalemia.

Fig. 1 summarizes major factors to consider in the emergency situation management of hyperkalemia. The first treatment emphasis is to support the myocardium and protect against or reverse dysrhythmias, followed by interventions to move potassium intracellularly and remove excess potassium [18].Intravenous administration of a calcium salt when any ECG changes exist (other than in the case of digitalis drunkenness or obvious hypercalcemia) is advised to increase the threshold capacity and maintain the myocardium [19].Ten milliliters of a 10% calcium gluconate (or calcium chloride) option must be administered as an intravenous bolus. The start of intravenous calcium is nearly prompt, yet the duration of effect is only 30 to 60 min [23]. Therefore, therapies to move potassium into the cells or get rid of potassium must be instituted as quickly as feasible after intravenous calcium administration [19].Repeat management of calcium might be necessary if the ECG does not normalize or if ECG modifications persist [23].Although information are lacking to support a specific suggestion on repeat calcium administration, it could be duplicated up to 2 times based on professional point of view.

Regular insulin with glucose/dextrose alone, or a mix of nebulized 2 agonist (e.g., albuterol 10-20 mg, salbutamol 20 mg) and regular insulin with glucose [19], [23] can be used as a single dosage to change potassium intracellularly. One potential method to dosing for a 70 kg subject (with weight change of dosages for others) is a 6 device loading dosage of a short-acting insulin (lispro or aspart) complied with by an insulin infusion of 20 units/h with each other with 60 gm of glucose each hour [20], which may be preferable to the typical application (i.e., usually insulin 10 units/glucose 25 g) because of a reduced possibility for hypoglycemia. Insulin and glucose carry

a high threat of hypoglycemia after 1 h, with several case records of deadly as well as fatal hypoglycemia, and need close monitoring [19], [21].Insulin and glucose act within 15 min, top around 30 to 60 minutes, with a total period of 4 to 6 hrs [19].Effects of breathed in 2 agonists on serum potassium levels are typically observed within 30 min and the duration is approximately 2 hours [19], [23].Insulin and glucose or breathed in 2 agonists most frequently bring about reductions in serum potassium levels of ≤ 1 mmol/L. Although sodium bicarbonate has been recommended as a first line method to treat hyperkalemia, data are controversial on the efficiency of intravenous salt bicarbonate to reduced serum potassium in patients with metabolic acidosis [22].A number of research studies reported that salt bicarbonate did not lower serum potassium considerably or promptly [24].Sodium bicarbonate might subject patients to a considerable liquid tons and the associated high concentration of sodium may bring about hypernatremia and metabolic alkalosis. On the other hand, sodium bicarbonate when instilled rapidly might be metabolized to CO2; in patients with respiratory insufficiency, acidosis as well as hyperkalemia could result [25].As such, salt bicarbonate need to not be the very first line technique to deal with hyperkalemia in serious problems. Nevertheless, intravenous sodium bicarbonate may work when patients need fluid loads. Various other crystalloid options could possibly raise serum potassium degree: well balanced services containing potassium, which could additionally boost serum potassium degrees when infused rapidly or in high quantity, or sodium chloride (NaCl 0.9%) could boost serum potassium degree through induced-hyperchloremic metabolic acidosis [26].In these patients, sodium bicarbonate could be taken into consideration to prevent getting worse hyperkalemia when fluid loading is needed.

Emergency dialysis ought to be taken into consideration in patients with relentless ECG changes or those with an insufficient action to 2 agonists or insulin/glucose, largely in patients with renal

insufficiency. Serious AKI (i.e. Stage 2 or 3, specified as serum creatinine 2-- 3 times baseline; or enhance in serum creatinine to ≥ 4.0 mg/dL; or urine result<0.5 ml/kg/h for ≥ 12 h or<0.3 ml/kg/h for ≥ 24 h or anuria for ≥ 12 h) [27] with hyperkalemia is generally considered to be an indication for urgent kidney substitute treatment (renal replacement treatment must be considered at AKI phase 2, no matter of hyperkalemia) [27], although clear-cut evidence to figure out the ideal time to start RRT is lacking. Patients that show up more steady could be started on intravenous loop diuretics ifthey have adequate renal function and normo- or hypervolemia. Sodium or calcium polystyrene sulfonate (SPS or CPS) are cationexchange resins that remove potassiumvia the gastrointestinal system. SPS has long been used to reduce serum potassium, however its tolerability is inadequate, it has been related to colonic necrosis, and its start of activity and level of potassium reducing is unpredictable [28].Moreover, in patients with volume overload, the usage of SPS could be related to volume expansion and the development of manifest heart failing since it exchanges potassium for salt [29].A current randomized, double-blind, placebo-controlled trial in33 outpatients withCKD andmildhyperkalemia (5.0-- 5.9 mEq/L) reported that SPS 30 g by mouth daily for 7 days minimized serum potassium considerably greater than sugar pill (− 1.04 mEq/L, 95% CI − 1.37 to − 0.71), yet the proportion of patients achieving normokalemia at the end of treatment was not significantly different in between treatment groups (73% SPS vs. 38% placebo, P = 0.07) [30] 2 new potassium binders have either recently been authorized or are expected to quickly be offered; patiromer (FDA accepted in October 2015) and sodium zirconium cyclosilicate (ZS-9) (waiting for authorization). The studies carried out with these drugs to this day have omitted patients needing emergency therapy for extreme hyperkalemia. Committed clinical tests need to test whether these novel representatives may have a therapy duty in the emergency situation setup.

Conclusion:

The emergency management of serious hyperkalemia is challenging since patients have an increased risk of death, however the elements (e.g., serum potassium threshold, optimal correction speed, comorbidities, ECG modifications) that affect this risk are unsure. Therefore, physicians are obliged to manage these patients strongly to prevent development to lethal arrhythmias and catastrophic events. Unfortunately, basic treatments are neither without risks or sustained by a compelling body of evidence, and they are used inconsistently. Whether new potassium binders will contribute in the emergency management of serious hyperkalemia remains to be seen, however it is worth investigating their ability to lower potassium in a timely way to decrease the need for insulin with glucose, 2 agonists, and dialysis. Further research is needed to fill existing knowledge gaps, identify remaining unmet needs, and plan definitive clinical tests aiming to enhance results in these patients.

Reference:

1. I. Lazich, G.L. Bakris, Prediction and management of hyperkalemia across the spectrum of chronic kidney disease, Semin. Nephrol. 34 (2014) 333–339.
2. B.F. Palmer, Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system, N. Engl. J. Med. 351 (2004) 585–592.
3.] M.J. Elliott, P.E. Ronksley, C.M. Clase, S.B. Ahmed, B.R. Hemmelgarn, Management of patients with acute hyperkalemia, CMAJ 182 (2010) 1631–1635.
4. L.S. Weisberg, Management of severe hyperkalemia, Crit. Care Med. 36 (2008) 3246–3251.
5. J.C. Hollander-Rodriguez, J.F. Calvert Jr., Hyperkalemia, Am. Fam. Phys. 73 (2006) 283–290.
6. Gennari J. Disorders of potassium homeostasis: Hypokalemia and hyperkalemia. Crit Care Clin. 2002;18(2):273–88.

7. Parham W, Mehdirad A, Biermann KM, Fredman C. Hyperkalemia revisited. Tex Heart Inst J. 2006;33(1):40–7.
8. Spodick D. Effects of severe hyperkalemia. Am Heart Hosp J. 2008;6(1):68.
9. Jurkat-Rott K, Lerche H, Lehmann-Horn F. Skeletal muscle channelopathies. J Neurol. 2002;249(11):1493–502.
10. Kang SY, Kim JS, Choi JC, Kang JH, Lee JS. An unusual pathologic feature and phenotype associated with familial hyperkalemic periodic paralysis. Eur J Neurol. 2008;15(6):47–8.
11. G.M. McMahon, M.L. Mendu, F.K. Gibbons, K.B. Christopher, Association between hyperkalemia at critical care initiation and mortality, Intensive Care Med. 38 (2012) 1834–1842.
12. L.M. Einhorn, M. Zhan, V.D. Hsu, L.D. Walker, M.F. Moen, S.L. Seliger, M.R. Weir, J.C. Fink, The frequency of hyperkalemia and its significance in chronic kidney disease, Arch. Intern. Med. 169 (2009) 1156–1162.
13. J. Khanagavi, T. Gupta, W.S. Aronow, T. Shah, J. Garg, C. Ahn, S. Sule, S. Peterson, Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes, Arch. Med. Sci. 10 (2014) 251–257.
14. W.A. Parham, A.A. Mehdirad, K.M. Biermann, C.S. Fredman, Hyperkalemia revisited, Tex. Heart Inst. J. 33 (2006) 40–47.
15. B.T. Montague, J.R. Ouellette, G.K. Buller, Retrospective review of the frequency of ECG changes in hyperkalemia, Clin. J Am. Soc. Nephrol. 3 (2008) 324–330.
16. K. Freeman, J.A. Feldman, P. Mitchell, J. Donovan, K.S. Dyer, L. Eliseo, L.F. White, E.S. Temin, Effects of presentation and electrocardiogram on time to treatment of hyperkalemia, Acad. Emerg. Med. 15 (2008) 239–249.
17. S. Aslam, E.A. Friedman, O. Ifudu, Electrocardiography is unreliable in detecting potentially lethal hyperkalaemia in haemodialysis patients, Nephrol. Dial. Transplant. 17 (2002) 1639–1642.
18. C.P. Kovesdy, Management of hyperkalemia: an update for the internist, Am. J. Med. 128 (2015) 1281–1287.
19. A.V. Alfonzo, C. Isles, C. Geddes, C. Deighan, Potassium disorders-clinical spectrum and emergency management, Resuscitation 70 (2006) 10–25.
20. R.H. Sterns, M. Grieff, P.L. Bernstein, Treatment of hyperkalemia: something old something new, Kidney Int. 89 (2016) 546–554.
21. S. Schafers, R. Naunheim, A. Vijayan, G. Tobin, Incidence of hypoglycemia following insulin-based acute stabilization of hyperkalemia treatment, J. Hosp. Med. 7 (2012) 239–242.
22. B.A. Mahoney, W.A. Smith, D.S. Lo, K. Tsoi, M. Tonelli, C.M. Clase, Emergency interventions for hyperkalaemia, Cochrane Database Syst. Rev. (2005).
23. L.S. Weisberg, Management of severe hyperkalemia, Crit. Care Med. 36 (2008) 3246–3251.

24. R. Gutierrez, F. Schlessinger, J.R. Oster, B. Rietberg, G.O. Perez, Effect of hypertonic versus isotonic sodium bicarbonate on plasma potassium concentration in patients with end-stage renal disease, Miner. Electrolyte Metab. 17 (1991) 297–302.
25. R.H. Kallet, R.M. Jasmer, J.M. Luce, L.H. Lin, J.D. Marks, The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM), Am. J. Respir. Crit. Care Med. 161 (2000) 1149–1153.
26. E. Potura, G. Lindner, P. Biesenbach, G.C. Funk, C. Reiterer, B. Kabon, C. Schwarz, W. Druml, E. Fleischmann, An acetate-buffered balanced crystalloid versus 0.9% saline in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial, Anesth. Analg. 120 (2015) 123–129.
27. Kidney disease improving global outcomes (KDIGO) working group, KDIGO clinical practice guidelines for acute kidney injury, Kidney Int. Suppl. 2 (2012) 1–138.
28. F. Zannad, P. Rossignol, W.G. Stough, M. Epstein, M.L. Alonso Garcia, G.L. Bakris, J. Butler, M. Kosiborod, L. Berman, A. Mebazaa, H.S. Rasmussen, L.M. Ruilope, N. Stockbridge, A. Thompson, J. Wittes, B. Pitt, New approaches to hyperkalemia in patients with indications for renin angiotensin aldosterone inhibitors: considerations for trial design and regulatory approval, Int. J. Cardiol. 216 (2016) 46–51.
29. B. Pitt, P. Rossignol, Potassium lowering agents: recommendations for physician and patient education, treatment reappraisal, and serial monitoring of potassium in patients with chronic hyperkalemia, Pharmacol. Res. (2016).
30. L. Lepage, A.C. Dufour, J. Doiron, K. Handfield, K. Desforges, R. Bell, M. Vallee, M. Savoie, S. Perreault, L.P. Laurin, V. Pichette, J.P. Lafrance, Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD, Clin. J. Am. Soc. Nephrol. 10 (2015) 2136–2142.