

Original Contributions



REAL WORLD EVIDENCE FOR TREATMENT OF HYPERKALEMIA IN THE EMERGENCY DEPARTMENT (REVEAL-ED): A MULTICENTER, PROSPECTIVE, OBSERVATIONAL STUDY

W. Frank Peacock, MD,* Zubaid Rafique, MD,* Carol L. Clark, MD,† Adam J. Singer, MD,‡ Stewart Turner, PHD,§ Joseph Miller, MD, MS,|| Douglas Char, MD,¶ Anthony Lagina, MD,# Lane M. Smith, MD, PHD,** Andra L. Blomkalns, MD,†† Jeffrey M. Caterino, MD, MPH,‡‡ and Mikhail Kosiborod, MD §§ on behalf of the REVEAL-ED Study Investigators

*Baylor College of Medicine, Ben Taub General Hospital, Houston, Texas, †Beaumont Hospital-Royal Oak, Royal Oak, Michigan, ‡Stony Brook School of Medicine, University Medical Center, Stony Brook, New York, §Arena Pharmaceuticals, San Diego, California, ||Henry Ford Hospital, Detroit, Michigan, ¶Washington University, St Louis, Missouri, #Wayne State University, Detroit, Michigan, **Wake Forest School of Medicine, Winston-Salem, North Carolina, ††UT Southwestern Medical Center, Dallas, Texas, ‡‡The Ohio State University, Columbus, Ohio, and §§Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri

Reprint Address: W. Frank Peacock, MD, FACEP, FACC, Baylor College of Medicine, Ben Taub General Hospital, 1504 Ben Taub Loop, Houston, TX 77030

Abstract—Background: Contemporary emergency department (ED) standard-of-care treatment of hyperkalemia is poorly described. **Objective:** Our aim was to determine the treatment patterns of hyperkalemia management in the ED. **Methods:** This multicenter, prospective, observational study evaluated patients aged ≥ 18 years with hyperkalemia (potassium [K^+] level ≥ 5.5 mmol/L) in the ED from October 25, 2015 to March 30, 2016. K^+ -lowering therapies and K^+ were documented at 0.5, 1, 2, and 4 h after initial ED treatment. The primary end point was change in K^+ over 4 h. **Results:** Overall, 203 patients were enrolled at 14 U.S.-based sites. The initial median K^+ was 6.3 (interquartile range [IQR] 5.7–6.8) mmol/L and median time to treatment was 2.7 (IQR 1.9–3.5) h post-ED arrival. Insulin/glucose (n = 130; 64%) was frequently used to treat hyperkalemia; overall, 43 different treatment combinations were employed within the first 4 h. Within 4 h, the median K^+ for patients treated with medications alone decreased from 6.3 (IQR, 5.8–6.8) mmol/L to 5.3 (4.8–5.7) mmol/L, while that for patients treated with dialysis decreased from 6.2 (IQR 6.0–6.6) mmol/L to 3.8 (IQR 3.6–4.2) mmol/L.

Hypoglycemia occurred in 6% of patients overall and in 17% of patients with $K^+ > 7.0$ mmol/L. Hyperkalemia-related electrocardiogram changes were observed in 23% of all patients; 45% of patients with $K^+ > 7.0$ mmol/L had peaked T waves or widened QRS. Overall, 79% were hospitalized; 3 patients died. **Conclusions:** Hyperkalemia practice patterns vary considerably and, although treatment effectively lowered K^+ , only dialysis normalized median K^+ within 4 h. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords—emergency department; hyperkalemia; observational study; potassium levels; treatment patterns

INTRODUCTION

It is estimated that more than 800,000 hyperkalemia-related emergency department (ED) visits occur annually in the United States (1). Because of the potential for fatal cardiac dysrhythmia, patients with hyperkalemia are often sent to the ED for management (2–4). Several studies have

Presented at the American College of Emergency Physicians 2016 meeting, October 15–19, 2016, Las Vegas, NV.

RECEIVED: 5 March 2018; FINAL SUBMISSION RECEIVED: 21 August 2018;
ACCEPTED: 1 September 2018

shown an increase in the risk of death in patients with potassium levels > 5.0 mmol/L and a steep increase in the risk of death as potassium levels exceed 6.0 mmol/L (5–8). In a retrospective analysis of 2.1 million records from Veterans, Einhorn et al. found that the odds of death within 1 day of a hyperkalemic event for patients without chronic kidney disease (CKD) were up to 33 times greater if the patient's initial potassium level was ≥ 6.0 mmol/L compared to < 5.5 mmol/L (8). Although emergency medicine literature on hyperkalemia epidemiology is sparse, one study by Singer et al. reported that hyperkalemia was observed in 3.6% of ED encounters and elevated presenting potassium levels were associated with increased hospital mortality (9). With the ethical conflict of not treating a potentially fatal pathology, no randomized interventional hyperkalemia treatment trials have been published. Observational data suggest that lowering potassium levels in patients with hyperkalemia is associated with lower mortality (10–12).

Dialysis is effective for the treatment of hyperkalemia, but significant logistical issues must be overcome to initiate this treatment from the ED. Alternative pharmacologic options, more readily available in the ED, have limited data supporting their efficacy. A recent Cochrane review of ED management of hyperkalemia suggested that randomized controlled trials supporting the use of commonly prescribed therapies are lacking, and many of the previously performed trials are methodologically flawed (13). The UK Renal Association has developed recommended clinical practice guidelines for the treatment of acute hyperkalemia, but there are limited data supporting these recommendations (14). The lack of emergency medicine literature and universally accepted guidelines for the management of hyperkalemia has led to inconsistent management practices in the United States (13). Although hyperkalemia is common in the ED and is potentially life-threatening, there is a paucity of documentation outlining the standard of care for hyperkalemia treatment.

The main objectives of this multicenter, prospective, observational study were to describe common causes of hyperkalemia, delineate the variability in treatment patterns, and characterize trends in treatments and outcomes of ED therapies employed to treat hyperkalemia. Because the risk of death is greater with severe hyperkalemia (≥ 6.0 mmol/L), we limited the number of patients recruited with moderate hyperkalemia (≥ 5.5 to ≤ 6.0 mmol/L), so that the main focus of the study would be on severe hyperkalemia (8,9).

MATERIALS AND METHODS

Study Design and Setting

The methodology of the REVEAL-ED (Real World Evidence for Treatment of Hyperkalemia in the Emergency

Department) study has been described elsewhere (15). This study was a multicenter, prospective, observational evaluation of the management of patients presenting to the ED with hyperkalemia. The study was approved by the Institutional Review Board for each site and is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02607085).

Participants

From October 25, 2015 to March 30, 2016, patients aged ≥ 18 years who presented to the ED with a potassium level ≥ 5.5 mmol/L were eligible for study enrollment, after providing informed consent. We conducted the study across 14 sites in the United States (see Supplementary Material). Because the study focused on patients with severe rather than mild hyperkalemia, we limited enrollment of individuals with potassium < 6.0 mmol/L to 50 patients, after which the baseline potassium was required to be ≥ 6.0 mmol/L. Patients were excluded if, in the opinion of the treating physician, they were unable to consent, were participating in another study that could impact serum potassium, or they had been enrolled previously in REVEAL-ED.

Variables and Outcomes

The primary end point of the study was the change in potassium over 4 h after the initial hyperkalemia treatment, or 4 h after the baseline qualifying potassium draw in the event the patient did not receive treatment. We chose 4 h, as this seemed a practical amount of time to ask patients to remain in care in the ED, while > 4 h was deemed as too long for a typical ED visit. Patients who did not have both a baseline and 4-h potassium measurement were excluded from clinical analyses.

Secondary clinical end points included the change in potassium at recorded time points, choice of treatment, timing and details of medical treatment and dialysis relative to ED presentation, other outcome events (e.g., hospital and intensive care unit [ICU] admissions, cardiac dysrhythmias and conduction abnormalities, hemodynamic instability/cardiac arrest, and in-hospital deaths), and the safety and tolerability of treatments. Nephrology consultations were not documented.

Data Sources and Measurements

Patients received treatment at the direction of the attending emergency physician, with no protocol-directed potassium-lowering interventions. The patient's chief complaints were recorded at screening upon arrival at the ED, as well as the treating physician's assessment of the possible cause of hyperkalemia. If the patient had a history of heart failure, the New York Heart Association functional classification assessment was conducted. The treating

physician defined what was considered as a treatment for hyperkalemia. The treating physician ordered potassium levels independently of those mandated by the study protocol, the latter of which were blinded to the treating team. Interventions and study-related potassium levels, primary outcomes, and other clinical outcomes were recorded prospectively using a standardized case report form. In some cases, we performed a chart review for follow-up. Protocol-mandated study potassium measurements began immediately prior to the first medical intervention/treatment (e.g., i.v. calcium, i.v. insulin/glucose, inhaled β_2 -agonists, i.v. diuretics, i.v. bicarbonate, oral sodium polystyrene sulfonate [SPS], dialysis, or other intervention for hyperkalemia) with a baseline measurement and were subsequently obtained at 0.5, 1, 2, and 4 h following the baseline potassium measurement or time of hospital discharge. Patients who received no intervention/treatment during the initial 4-h treatment period but who remained in the ED had protocol-mandated potassium measurements taken in the ED at 4 h after the baseline potassium measurement. Whole blood potassium was determined using a point-of-care device (i-STAT; Abbott Point of Care, Inc, Princeton, NJ). Concomitant medications were recorded from 14 days before until 7 days after enrollment or ED/hospital discharge, whichever came first. Recordable outcomes were limited to pulmonary edema, ventricular tachycardia/fibrillation, pulseless electrical activity, new clinically significant electrocardiogram (ECG) changes (including but not limited to severe bradycardia, advanced heart block, bundle branch block, and tachycardia), palpitations, hypoglycemia (based on clinical judgment and laboratory information, if available), gastrointestinal-related events, and any other event deemed significant by the investigator based on their clinical judgment. Outcomes were recorded from the time of ED admission through ED/hospital discharge, or up to 7 days of hospitalization if the patient was admitted to another hospital location (e.g., in-patient bed or ICU). Recordable outcomes were classified by the *Medical Dictionary for Regulatory Activities* (16). Recordable outcomes resulting in death during hospitalization were also collected for up to 30 days after ED admission. The relationship to hyperkalemia and hyperkalemia interventions, as well as the severity of recordable outcomes, were reported. We adjudicated all cardiac events with an independent review committee before database lock. Standardized case report forms were completed for each patient and sent to a centralized data management group.

Study Size and Statistics

No formal sample size calculation was performed due to the observational, pilot nature of the study. We selected a sample size of 200 patients based on clinical judgment,

which was considered sufficient to adequately characterize the different treatments in this population. We designated all enrolled patients with any post baseline study-related potassium values as the intention-to-treat population, and all patients with any follow-up data as the safety population. Analysis included descriptive statistics for the overall study population, as well as groups stratified by potassium levels at baseline and by treatment.

RESULTS

Characteristics of Study Participants

Overall, 203 patients met all the entry and no exclusion criteria. Of these, one withdrew consent to participate. Deaths occurred in 3 patients at 4, 6, and 13 days post-enrollment; this represents a 1.5% rate of death (95% confidence interval 0.3%–4.3%). The causes of death were acute hypoxemic respiratory failure (n = 1), respiratory failure (n = 1), and cardiac arrest (n = 1).

Descriptive Data

Demographics are presented in [Table 1](#). African Americans and males were most commonly enrolled. In the prior 6 months, 34% of patients had visited their institution for hyperkalemia through an ED visit or hospitalization. The majority of patients had CKD (73%), and 46% were currently receiving dialysis based on their presenting medical history. High rates of other comorbidities were common, with diabetes mellitus and heart failure present in 54% and 38% of patients, respectively. The most common causes of hyperkalemia in this patient population included CKD (67%), acute kidney failure (28%), diabetes (27%), and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (16%).

The four most common chief complaints were dyspnea (32%), nausea/vomiting (24%), weakness/fatigue (22%), and chest pain (12%). A wide range of other complaints were reported but none with an individual occurrence rate > 10%.

Outcomes Data

Of the 203 patients enrolled, 4 did not have a baseline potassium measurement and another 38 did not receive the requisite 4-h potassium measurement; therefore, 42 patients were excluded from potassium analyses. These patients had a baseline potassium level of 6.12 mmol/L (n = 38). The remaining 161 patients had baseline and 4-h potassium values measured and were included in the evaluable potassium patient population (41 had received dialysis and 120 had been managed with medications alone within 4 h of initial treatment). The cohort

Table 1. Patient Demographics, Chief Complaints, and Possible Causes of Hyperkalemia

Characteristics	Patients (n = 203)
Age, y	
Mean (SD)	56.4 (15.8)
Median (IQR)	57.0 (46–65)
Male, n (%)	124 (61)
Race, n (%)	
African American	104 (51)
White	97 (48)
Asian	1 (0.5)
Other	1 (0.5)
Ethnicity, n (%)	
Not Hispanic	172 (85)
Hispanic	31 (15)
ED visit or hospitalization for hyperkalemia in last 6 months, n (%)	69 (34)
No. of hyperkalemia ED visits/hospitalizations in last 6 months, n (%)	
1	32 (16)
2	9 (4)
3	4 (2)
4	4 (2)
≥5	20 (10)
History of heart failure, n (%)	77 (38)
History of diabetes, n (%)	109 (54)
History of CKD, n (%)	149 (73)
CKD stage (as reported by the investigator), n (%)	
2	2 (1)
3	26 (13)
4	20 (10)
5	97 (48)
Currently receiving dialysis, n (%)	94 (46)
Chief complaints,*n (%)	
Dyspnea	64 (32)
Nausea/vomiting	48 (24)
Weakness/fatigue	45 (22)
Chest pain	25 (12)
Asymptomatic hyperkalemia	19 (9)
Diarrhea	12 (6)
CKD–missed dialysis	11 (5)
Possible causes of hyperkalemia,*n (%)	
CKD	135 (67)
Diabetes	54 (27)
Acute kidney failure	57 (28)
ACEIs/ARBs	32 (16)

ACEIs/ARBs = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CKD = chronic kidney disease; ED = emergency department; IQR = interquartile range; SD = standard deviation.

* Occurring in ≥ 5% of patients.

receiving medication alone had an initial median potassium level of 6.3 (IQR 5.8–6.8) mmol/L that declined by –1.0 mmol/L to 5.3 mmol/L (IQR 4.8–5.7 mmol/L) by 4 h after initial treatment (Figure 1A). The initial median potassium level in the dialysis cohort was 6.2 (IQR 6.0–6.6) mmol/L; this decreased to 3.9 (IQR 3.7–4.3) mmol/L within 2 h of initial intervention and remained stable up to 4 h after initial treatment (Figure 1B).

In the overall cohort of patients (n = 203), the median time from ED presentation to first treatment (including dialysis) was 2.7 (IQR 1.9–3.5) h. The median time from receipt of central laboratory potassium

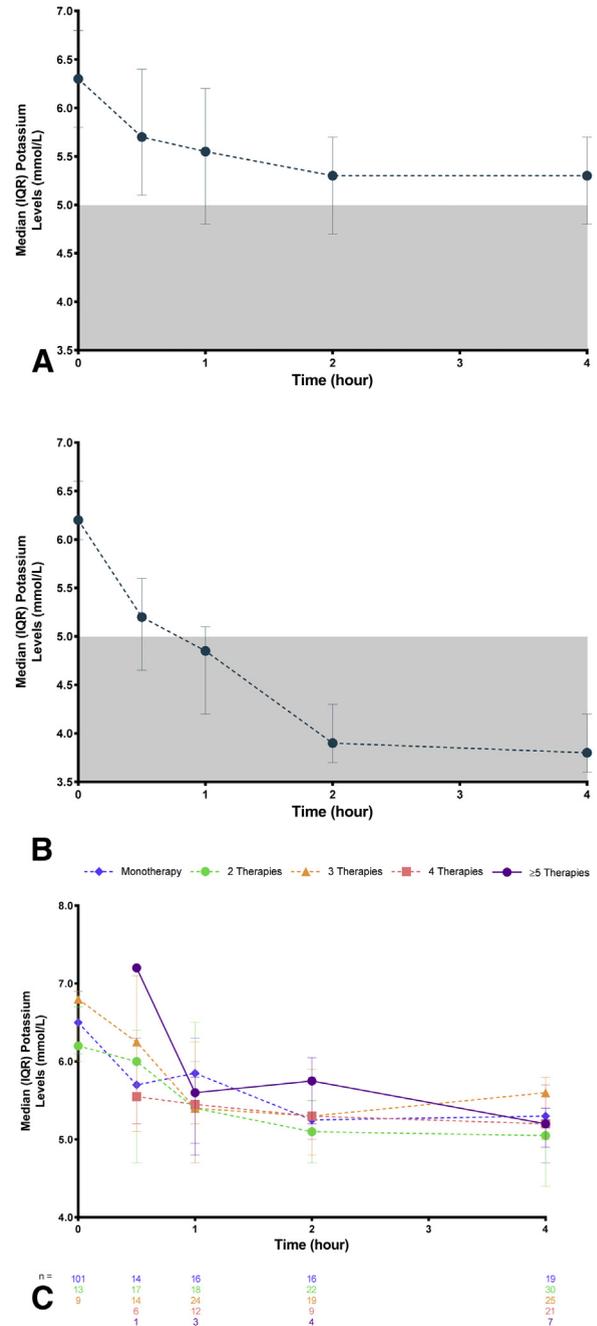


Figure 1. Potassium levels over time following baseline potassium measurement recorded immediately prior to initial intervention* in (A) patients managed only medically,† (B) patients who received dialysis, and (C) patients managed only medically† by the cumulative number of treatments received. *Time of initial potassium measurement did not necessarily occur at precisely the same time as the initial intervention. †Excludes dialysis and non-potassium-lowering medications (saline, dextrose, and sodium chloride). IQR = interquartile range.

measurements to the first treatment was 1.4 (IQR 0.9–2.3) h. There was an inverse relationship between potassium values and time to first treatment among patients with potassium levels < 6.0 or ≥ 6.0 mmol/L. Among

patients with an initial potassium level of ≥ 5.5 to < 6.0 mmol/L, the median time from ED presentation to initial therapy was 3.2 (IQR 2.6–3.9) h. Among patients with potassium levels of ≥ 6.0 – 6.5 , > 6.5 – 7.0 , and > 7.0 mmol/L, therapy was initiated within a median of 2.4 (IQR 1.7–3.5) h, 2.6 (IQR 1.9–3.3) h, and 2.5 (IQR 2.0–3.1) h post-ED presentation, respectively.

Main Results

Treatment choices varied across the spectrum of potassium levels. None of the sites participating in the study reported having a defined hyperkalemia treatment algorithm. Overall, insulin/glucose was the most common therapy employed in the ED setting within the first 4 h and was used alone or in combination with other treatments in 64% of patients. Other treatments used included i.v. calcium (55%), inhaled β_2 -agonists (33%), oral SPS (31%), i.v. bicarbonate (29%), dialysis (24%), and i.v. diuretics (5%) (Table 2). When treatments were stratified by time, the use of a single hyperkalemia agent (i.e., monotherapy) was the most common initial strategy, occurring in 42% of patients at 30 min after first treatment. The use of monotherapy decreased at 1 h after the first treatment and continued to decline at subsequent time points. Physicians appeared to utilize treatment strategies based on initial potassium levels. Patients with an initial potassium level of < 6.0 mmol/L most commonly received no therapy or a single therapeutic agent (66%), while those with higher potassium levels were more likely to receive combination therapy. At the 2-h time point, it appeared that increasing the number of treatment strategies was associated with greater reductions in potassium levels (Figure 1C).

While multiple treatments were implemented for most patients (20% received two therapies, 17% three, 19% four, and 10% received five or more therapies within 4 h), no specific combination of therapies comprised $> 10\%$ of the total treatments used at any single time point (Figure 2). Treatment strategies ranged from no intervention to six simultaneous interventions (Figure 3), with heterogeneity across sites (Supplementary Figure 1). As shown in Figure 3, the three most common treatments

were dialysis, i.v. calcium with insulin/glucose, and i.v. calcium with insulin/glucose in addition to β_2 -agonist and bicarbonate. Overall, 43 different monotherapies and treatment combinations were employed in the first 4 h after first treatment.

One-half of all patients experienced at least one recordable outcome ($n = 104$; 52%). Overall, 10% of patients complained of gastrointestinal disorders occurring during therapy, which most commonly included nausea/vomiting or diarrhea. When complications were stratified by potassium level, patients with the lowest potassium (< 6.0 mmol/L) experienced the fewest complications (34%) compared to those with potassium levels > 6.0 mmol/L (61% overall). Recordable outcomes in patients with potassium levels of > 6.0 – 6.5 , > 6.5 – 7.0 , and > 7.0 mmol/L occurred in 62%, 51%, and 72% of patients, respectively. Clinically relevant hypoglycemia, as determined by the investigator, occurred in 6% of patients overall and in 17% of patients who received insulin/glucose therapy for potassium > 7.0 mmol/L (Table 3).

Of importance, ECG, obtained at each potassium measurement, was not sensitive in predicting hyperkalemia. Hyperkalemia-related peaked T waves, reportedly associated commonly with hyperkalemia, occurred in $< 25\%$ of patients with potassium ≤ 7.0 mmol/L and in only 35% of patients with potassium > 7.0 mmol/L. The presence of a widened QRS occurred in $< 13\%$ of patients with a potassium level ≤ 7.0 mmol/L. Even when the potassium level exceeded 7.0 mmol/L, hyperkalemia-related peaked T waves or widened QRS were found in only 45% of patients.

Patients with hyperkalemia remained in the ED for long time periods, and 79% were admitted to the hospital, with 19% requiring ICU care; mean hospital length of stay among admitted patients was 4.8 (standard deviation 4.4) days. The median ED length of stay was 7.4 (IQR 5.4–10.1) h.

DISCUSSION

The REVEAL-ED study is the first large, prospective, real world hyperkalemia study performed in EDs in the United States to define the clinical presentations, treatments, and outcomes associated with hyperkalemia. We found that there is no standard universally accepted treatment protocol for the management of hyperkalemia in EDs across the United States. We also found that symptoms of hyperkalemia are nonspecific; hence, physicians may order a potassium level to be run based on patient risk factors rather than presenting symptoms.

Despite the lack of a standard of care for hyperkalemia and extreme variability in treatment strategies, overall ED treatment was effective at lowering potassium levels in the short-term. However, it is important to recognize

Table 2. Summary of Hyperkalemia Treatment Options*

Treatment Options
β_2 -agonists (inhaled)
Bicarbonate (i.v.)
Calcium (i.v.)
Dialysis
Diuretics (i.v.)
Insulin/glucose (i.v.)
Sodium polystyrene sulfonate (oral)

* Options were used in 43 unique combinations in this study.

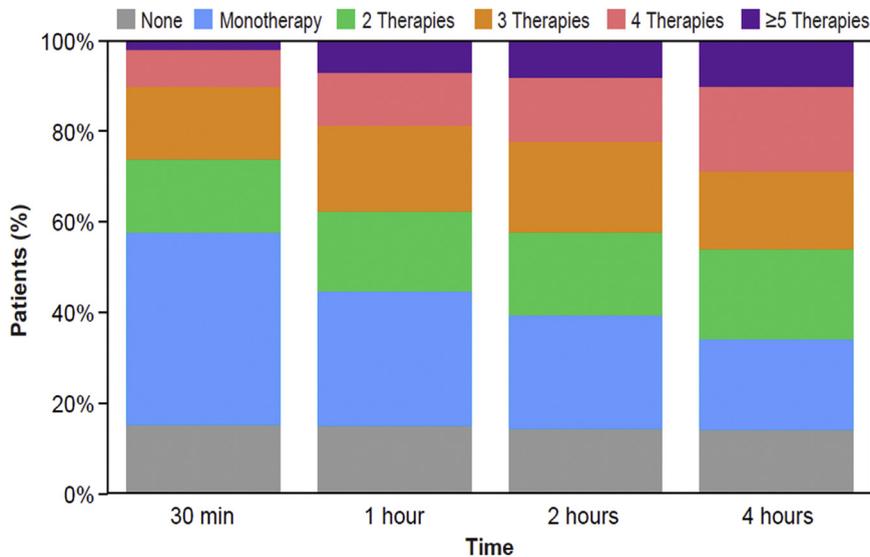


Figure 2. Cumulative number of potassium-lowering treatments over time.

that, although the strategies used appeared to be safe and effective, none of the medical treatments employed except dialysis resulted in a median potassium level < 5.0 mmol/L at 4 h.

ED treatment of hyperkalemia was highly variable and complex. In this study, clinicians applied seven potential therapies (i.v. calcium, β 2-agonists, bicarbonate, dialysis, diuretics, insulin/glucose, and SPS) in 43 different combinations. While it is intuitive that the addition of multiple different therapies would improve the efficacy of potassium lowering, there are no data from prospective, randomized controlled trials to support this treatment approach.

The initial potassium level appears to have dictated the escalated number of combination therapies. Those with an initial potassium level in excess of 6.5 mmol/L typically received four or more different therapies, compared to those with lower potassium levels who usually received one to three different treatments. How this variation impacted outcomes is unclear. It is likely that some of the 43 treatment combinations are less effective than others, and a standard approach to therapy could improve effectiveness, safety, and, possibly, patient outcomes and costs.

Treatments commonly resulted in complications. Of the 43 different treatment strategies, insulin/glucose

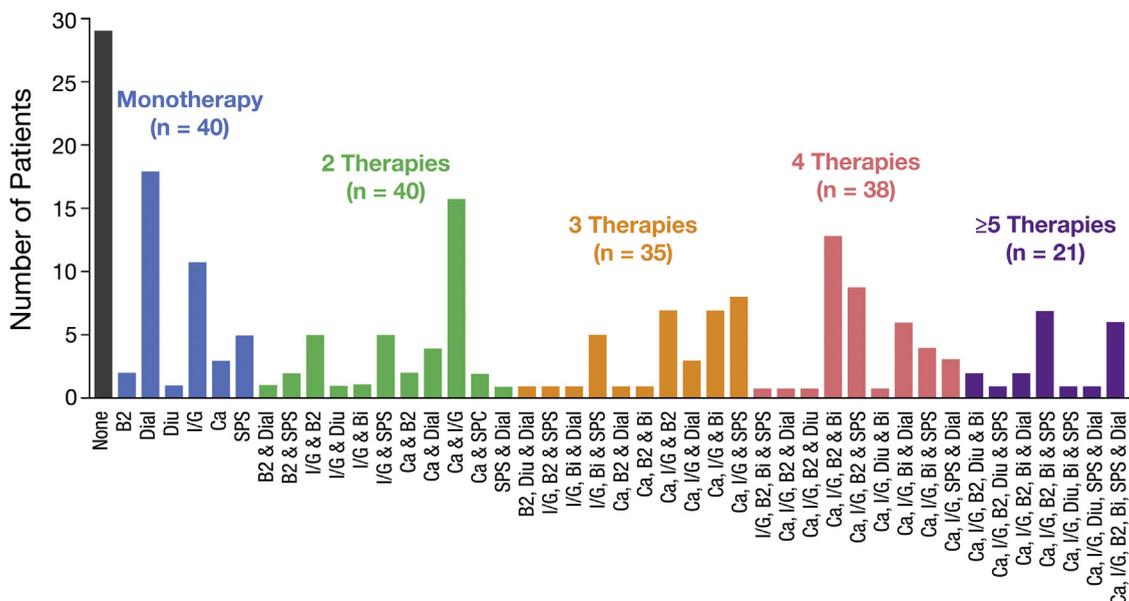


Figure 3. Distribution of the number of potassium-lowering treatments* during the first 4 h after initial treatment. *Excludes non-potassium-lowering medications (saline, dextrose, and sodium chloride). B2 = β 2-agonists; Bi = bicarbonate; Ca = i.v. calcium; Dial = dialysis; Diu = diuretics; I/G = insulin/glucose; SPS = sodium polystyrene sulfonate.

Table 3. Adverse Events and Complications of Treatment Stratified by Baseline Potassium Level

Variable	Baseline Potassium (mmol/L)				All Patients (n = 199)*
	< 6.0 (n = 64)	≥ 6.0–6.5 (n = 63)	> 6.5–7.0 (n = 43)	> 7.0 (n = 29)	
At least 1 AE or complication	22 (34)	39 (62)	22 (51)	21 (72)	104 (52)
Complications of treatment					
GI disorders	6 (9)	9 (14)	4 (9)	1 (3)	20 (10)
Nausea/vomiting	5 (8)	5 (8)	3 (7)	-	13 (7)
Diarrhea	-	3 (5)	1 (2)	1 (3)	5 (3)
GI bleed	1 (2)	1 (2)	-	-	2 (1)
Cholecystitis	-	1 (2)	-	-	1 (0.5)
Hypoglycemia	1 (2)	2 (3)	3 (7)	5 (17)	11 (6)
AEs					
Respiratory failure	4 (6)	3 (5)	1 (2)	1 (3)	9 (5)
Cardiac event	1 (2)	4 (6)	1 (2)	-	6 (3)
Heart failure	1 (2)	3 (5)	-	-	4 (2)
Death	-	-	1 (2)	-	1 (0.5)
NSTEMI	-	2 (3)	-	-	2 (1)
Hemodynamic instability	1 (2)	2 (3)	1 (2)	1 (3)	5 (3)

AE = adverse event; GI = gastrointestinal; NSTEMI = non-ST-elevation myocardial infarction.

Values are n (%).

* Four patients did not have baseline potassium values.

was the most common intervention administered, alone or in combination with other therapies. It was also associated with the greatest rate of complications. Nearly 1 in 6 patients with a potassium level > 7.0 mmol/L and treated with insulin/glucose suffered clinically significant hypoglycemia during therapy. Overall, 6% of all patients and 7% of patients who were treated with insulin (data not shown) experienced hypoglycemia. This incidence of hypoglycemia as a complication of hyperkalemia treatment is consistent with other studies (17,18).

It is important to address the fact that the majority of therapies available to the emergency physicians at the time of this study do not provide definitive treatment of hyperkalemia, as they do not remove potassium from the body. With the exception of SPS, a drug with significant safety and tolerability issues (e.g., colonic necrosis and profound diarrhea), dialysis, and diuretics, the mechanism of action of all acute ED medical hyperkalemia treatments is to translocate serum potassium to the intracellular space where it has less effect on the myocardial conduction system or to stabilize the myocardium (calcium) (19–21). These are temporizing treatments at best. While they achieve the important initial goal of lowering serum potassium and may prevent life-threatening consequences, the length of time for which these strategies are effective is unknown and may contribute to the very high admission rate in patients presenting with hyperkalemia.

Limitations

This study has several potential limitations inherent to its observational design. The method of recording data

during the follow-up period was not mandated in the study protocol. The fact that no institution reported having a hyperkalemia treatment algorithm may explain the marked variability we report. Additionally, the relatively small number of sites, which were mostly academic facilities, and sample size may not be representative of the overall hyperkalemia treatment experience in the United States and may have an urban ED bias. For example, African Americans comprised 51% of the patients recruited for this study, which may be a result of the high recruitment of patients from centers with predominantly African-American populations. The results reported here may also not be representative of treatment practices within each site, because the mean number of patients enrolled per site during the 5-month treatment period was also small, with one-half of the study sites enrolling < 10 patients (Supplementary Material). Limiting the number of patients with a baseline potassium < 6.0 mmol/L to 50 may have resulted in an overrepresentation of patients with more serious hyperkalemia. Due to the observational nature of the study, it is unclear if physicians initially recommended monotherapy for some patients and subsequently added therapy, or if the initial approach of monotherapy was due to delays in the administration of multiple therapies. Finally, our convenience sample may have resulted in “enrollment time” bias, as more patients were enrolled during the day than at night. Dialysis may not be available at all times, so the time of presentation may dictate the interventions available to treat patients. If patients present during hours when dialysis is not available, medical treatment is the only initial option available to the emergency physician. A further treatment-related limitation is that the treating team

was blinded to study-related potassium levels, which may have limited the potassium reductions achieved, because further therapy options may not have been used because of lack of information on the effectiveness of initial therapy.

CONCLUSIONS

The REVEAL-ED study is one of the few real world studies performed to define hyperkalemia treatment practices in EDs in the United States. The study results demonstrate that hyperkalemia practice patterns are variable and highly complex with no clear consistency. Most patients receive multiple therapies depending on the potassium level at the time of ED evaluation; however, the medications most often used do not remove potassium from the body. Clinical presentation and ECG findings are also highly variable and seem to be nonspecific. Although a combination of different medical treatments decreases potassium over 4 h, only dialysis resulted in normalization of potassium within this time frame. In this study, most patients were admitted to the hospital, with 19% requiring ICU admission. Hyperkalemia treatment was not without risk, as hypoglycemia occurred in 17% of patients with potassium levels > 7.0 mmol/L. More studies and evaluation of therapies for the ED management of hyperkalemia are needed.

Acknowledgments—We thank the investigators and patients who participated in this study. Sheridan Henness, PhD, of inScience Communications, Springer Healthcare, prepared the manuscript for submission under the direction of the authors; editorial assistance provided by inScience Communications, Springer Healthcare, was funded by AstraZeneca.

This study was sponsored and funded by ZS Pharma, Inc., a member of the AstraZeneca group. Jessica Mendoza, PhD, an employee of ZS Pharma, Inc., a member of the AstraZeneca group, provided editorial assistance for the preparation of this manuscript. David Morris of Webb Writes provided statistical support for this study and received consulting fees for this work from ZS Pharma, Inc., a member of the AstraZeneca group. Preparation of the manuscript for submission was funded by ZS Pharma, Inc., a member of the AstraZeneca group.

Author contributions: W.F.P. was involved in study conception and design, data collection and interpretation, and drafted the manuscript. Z.R., C.L.C., A.J.S., D.C., A.L., L.M.S., A.L.B., and J.M.C. undertook recruitment of patients at participating centers and were involved in data collection. S.T. was involved in study conception and design, data interpretation, supervised the conduct of the study, and managed the data. J.M. undertook recruitment of patients and was involved in data collection and interpretation. M.K. was involved in study conception and study design, undertook recruitment of patients, and was involved in data collection and interpretation. All

authors contributed substantially to manuscript revisions. W.F.P. takes responsibility for the paper as a whole.

Disclosures

W.F.P. has received grant funding from Abbott, Alere, Banyan, Cardiorentis, Janssen, Pfizer, Portola, Roche, The Medicine's Company, and ZS Pharma, Inc.; has served as a consultant for Alere, Beckman, Boehringer-Ingelheim, Cardiorentis, Instrument Labs, Janssen, Phillips, Portola, Prevencio, Singulex, The Medicine's Company, and ZS Pharma, Inc.; and is a stockholder in Comprehensive Research Associates, LLC and Emergencies in Medicine, LLC. Z.R. served as a clinical trial investigator for ZS Pharma, Inc.; has received a research grant from Relypsa; and has served as a consultant for Instrumentation Laboratory, Relypsa, and ZS Pharma, Inc. C.L.C. has received research funding from Abbott, Biocryst, Cardiorentis, Genentech, GlaxoSmithKline, Ischemia Care, Janssen, Pfizer, Portola, Radiometer, and ZS Pharma, Inc., and has served as a consultant for Janssen, Pfizer, and Portola. A.J.S. served as a consultant and clinical trial investigator for ZS Pharma, Inc. and has served as a consultant for Abbott Point of Care, Alere, and Janssen. S.T. is a former employee of ZS Pharma, Inc. J.M., D.C., L.M.S., and J.M.C. have no conflict of interest to disclose. A.L. served as a consultant and clinical trial investigator for ZS Pharma, Inc. M.K. has received research grants from AstraZeneca, and has served as a consultant, advisory board member, and clinical trial investigator for AstraZeneca and ZS Pharma, Inc.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jemermed.2018.09.007>.

REFERENCES

1. Aggarwal S, Topaloglu H, Kumar S. Trends in emergency room visits due to hyperkalemia in the United States. *Value Health* 2015;18:A386.
2. Freeman K, Feldman JA, Mitchell P, et al. Effects of presentation and electrocardiogram on time to treatment of hyperkalemia. *Acad Emerg Med* 2008;15:239–49.
3. Fisch C. Relation of electrolyte disturbances to cardiac arrhythmias. *Circulation* 1973;47:408–19.
4. Surawicz B. Relationship between electrocardiogram and electrolytes. *Am Heart J* 1967;73:814–34.
5. Krogager ML, Torp-Pedersen C, Mortensen RN, et al. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur Heart J* 2017;38:104–12.
6. Conway R, Creagh D, Byrne DG, O'Riordan D, Silke B. Serum potassium levels as an outcome determinant in acute medical admissions. *Clin Med* 2015;15:239–43.

7. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. *J Am Med Assoc* 2012;307:157–64.
8. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;169:1156–62.
9. Singer AJ, Thode HC Jr, Peacock WF. A retrospective study of emergency department potassium disturbances: severity, treatment, and outcomes. *Clin Exp Emerg Med* 2017;4:73–9.
10. An JN, Lee JP, Jeon HJ, et al. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care* 2012;16:R225.
11. McMahon GM, Mendu ML, Gibbons FK, Christopher KB. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med* 2012;38:1834–42.
12. Grodzinsky A, Goyal A, Gosch K, et al. Prevalence and prognosis of hyperkalemia in patients with acute myocardial infarction. *Am J Med* 2016;129:858–65.
13. Mahoney BA, Smith WA, Lo DS, Tsoi K, Tonelli M, Clase CM. Emergency interventions for hyperkalaemia. *Cochrane Database Syst Rev* 2005;2:CD003235.
14. UK Renal Association. Clinical Practice Guidelines: Treatment of Acute Hyperkalaemia in Adults. 2014. Bristol, UK. Available at: <https://renal.org/wp-content/uploads/2017/06/hyperkalaemia-guideline-1.pdf>.
15. Rafique Z, Kosiborod M, Clark CL, et al. Study design of Real World Evidence for Treatment of Hyperkalemia in the Emergency Department (REVEAL-ED): a multicenter, prospective, observational study. *Clin Exp Emerg Med* 2017;4:154–9.
16. Medical Dictionary for Regulatory Activities (MedDRA). Available at: <https://www.meddra.org/>. Accessed August 22, 2017.
17. Pierce DA, Russell G, Pirkle JL Jr. Incidence of hypoglycemia in patients with low eGFR treated with insulin and dextrose for hyperkalemia. *Ann Pharmacother* 2015;49:1322–6.
18. Schafers S, Naunheim R, Vijayan A, Tobin G. Incidence of hypoglycemia following insulin-based acute stabilization of hyperkalemia treatment. *J Hosp Med* 2012;7:239–42.
19. Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med* 2013;126:264.e9–26424.
20. McGowan CE, Saha S, Chu G, Resnick MB, Moss SF. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. *South Med J* 2009;102:493–7.
21. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol* 2010;21:733–5.

ARTICLE SUMMARY

1. Why is this topic important?

To date, there is a paucity of documentation outlining the standard of care for managing hyperkalemia in the emergency department (ED).

2. What does this study attempt to show?

This study characterizes the treatment for the management of hyperkalemia and the associated outcomes in the ED.

3. What are the key findings?

This study demonstrated that hyperkalemia practice patterns and clinical presentation are variable and highly complex with no clear consistency. Most patients receive multiple therapies depending on their potassium level at the time of ED evaluation. Although a combination of different medical treatments decreases potassium over 4 hours, only dialysis resulted in normalization of potassium within this time frame. Insulin and glucose were commonly administered but associated with a significantly higher rate of iatrogenic symptomatic hypoglycemia.

4. How is patient care impacted?

Emergency physician care is effective for lowering potassium level to a safe but not necessarily normal range. Patients treated with glucose and insulin require close observation for the development of hypoglycemia.