Acute Management of Hyperkalemia: What We Know & What We Need to Know

Patrick Rossignol
Université de Lorraine, Inserm, Centre d’Investigations Cliniques 1433, Inserm U1116; CHRU Nancy; Association Lorraine de Traitement de l’Insuffisance Rénale, and F-CRIN INI-CRCT, Nancy, France
DISCLOSURES

• Personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Corvidia, Grüenthal, Stealth Peptides, Fresenius, Idorsia, Vifor Fresenius Medical Care Renal Pharma, Vifor and CTMA; lecture fees from Bayer and CVRx; cofounder of CardioRenal
What we know

Prognostic significance of hyperkalemia in hospitalized patients

Retrospective analysis of the US VA national cohort

(2,103,422 records/ 245,808 veterans with at least 1 hospitalization and at least 1 inpatient or outpatient serum K record during fiscal year 2005)

odds ratio of death within 1 day of an hyperkalemic event

all adults with eGFR <60 ml/min per 1.73 m² (including dialysis-dependent patients) in Alberta, Canada between April 1, 2010 and March 31, 2011: 111,087 patients had 294,113 emergency department encounters.

What we know

Emergency Department Use among Patients with CKD: A Population-Based Analysis

Paul E. Ronksley, Marcello Tonelli, Braden J. Manns, Robert G. Weaver, Chandra M. Thomas, Jennifer M. MacRae, Pietro Ravani, Robert R. Quinn, Matthew T. James, Richard Lewanczuk, and Brenda R. Hemmelgarn

What we know

How frequent is hyperkalemia in-hospital?

• All patients admitted to Westchester Medical Center, a 647-bed tertiary medical center, from January 1, 2010 to December 31, 2011 with a diagnosis of hyperkalemia based on the ICD-9 either at the time of admission or during hospitalization.

15,608 hospitalizations, 451 (2.9%) had hyperkalemia either at admission or during the hospitalization.

285 patients (70%) had HK at the time of admission, and 123 patients (30%) developed HK during their hospitalization.

What we know

Association between duration of hyperkalemia and outcomes

- All patients admitted to Westchester Medical Center, a 647-bed tertiary medical center from January 1, 2010 to December 31, 2011 with a diagnosis of hyperkalemia based on the ICD-9 either at the time of admission or during hospitalization

15,608 hospitalizations, 451 (2.9%) had hyperkalemia either at admission or during the hospitalization.

285 patients (70%) had HK at the time of admission, and 123 patients (30%) developed HK during their hospitalization.

Table IV. Stepwise logistic regression analysis to determine the predictors of mortality in patients with hyperkalemia

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odds ratio</th>
<th>95% Confidence intervals</th>
<th>Value of ( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue necrosis</td>
<td>4.55</td>
<td>1.74–11.90</td>
<td>0.002</td>
</tr>
<tr>
<td>Potassium supplements</td>
<td>5.46</td>
<td>1.56–19.20</td>
<td>0.008</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>4.84</td>
<td>1.48–15.82</td>
<td>0.009</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>4.62</td>
<td>1.60–13.35</td>
<td>0.005</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3.89</td>
<td>1.14–13.26</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration prior to resolution</td>
<td>1.06</td>
<td>1.02–1.09</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Influence of hyperkalemia on arrhythmogenicity

- Cardiac arrest was a presenting symptom in 43% of 1803 patients hospitalized at a tertiary medical center with serum potassium ≥ 6.5 mEq/L, and other arrhythmias were present in 35% (An et al, Crit Care 2012; 16).
What we know

ECGs are insensitive indicators of the severity of hyperkalemia

- because cardiac manifestations can be non-specific or even absent at levels of serum potassium that are associated with an increased mortality risk
- Among 168 cases of hyperkalemia (serum potassium > 6.0 mmol/L) in an emergency department, abnormal ECGs were noted in 83%, but 24% were non-specific [Freeman et al, Acad. Emerg. Med. 2008; 15:239–249].
- Evidence of hyperkalemia was observed in 46% of ECGs in hospitalized patients with HK≥6 mmol/L, and no relationship between ECG findings and potassium level were observed [Acker et al, Arch. Intern. Med. 1998; 158:917–924].
- Strict criteria defining hyperkalemia-related ECGs were met in only 16 of 90 HK cases from one hospital, whereas 47 cases showed some non-specific ECG changes [Montague et al, Clin. J Am. Soc. Nephrol 2008; 3:324–330].

Electrocardiography is unreliable in detecting potentially lethal hyperkalaemia in haemodialysis patients


Importance of early electrocardiographic recognition and timely management of hyperkalemia in geriatric patients

Exp Clin Cardiol Vol 16 No 2 2011

It is important to note that an ECG is not sensitive for detecting hyperkalemia. In one study (4), nearly one-half of the patients with a serum potassium concentration of greater than 6.5 mmol/L did not exhibit ECG changes; however, ECG changes are predictive of cardiac dysfunction.

ECGs are insensitive indicators of the severity of hyperkalemia... possibly, because ECG alterations associated with HK do not only depend on potassium extracellular concentration,

Being largely influenced by:

- rapid changes of plasma concentration,
- the gradient of potassium across the myocardial cell membrane, the effect of other ions (i.e. sodium, calcium),
- as well as underlying cardiac disease
Hyperkalaemia is the most common electrolyte or drug abnormality to cause loss of capture by a cardiac rhythm device.
The effect of hyperkalaemia on cardiac rhythm devices

S. Serge Barold® and Bengt Herweg

- Hyperkalaemia is the most common electrolyte or drug abnormality to cause loss of capture by a cardiac rhythm device.
- In patients with pacemakers, hyperkalaemia causes two important clinical abnormalities:
  - (i) widening of the paced QRS complex (and paced P-wave if it is seen) on the basis of delayed myocardial conduction
  - (ii) Increased atrial and ventricular pacing thresholds with or without increased latency. Failure to capture is usually seen when the K level reaches 7 mEq/L and occasionally at a lower level especially in the presence of heart disease.
• Oversensing of the T-wave induced by hyperkalaemia has been reported in ICD
Emergency management of severe hyperkalemia

• Importance of ruling out of pseudo-hyperkalemia AND of avoiding delays in therapy initiation

Serum potassium level at the time of therapy initiation was associated with 30-day all-cause mortality in a critical care setting [McMahon et al, Intensive Care Med 2012].

- The median time between laboratory results and treatment initiation was 117min in a retrospective analysis of patients with HK>6 mmol/L in an emergency department; 25% were treated after 196min (Freeman et al Acad. Emerg. Med. 2008).

- Another study reported a time to treatment of 2.7 ± 2.4 h (Acker et al, Arch. Intern. Med. 1998)
Emergency management of severe hyperkalemia

1. Cell membrane “stabilization”
2. Reduction of Serum K⁺
   a. Redistribution into cells
   b. Elimination from the body

   Insulin/glucose, Beta 2 agonists
   Bicarbonates?
   Kidney: Diuretics
   GI tract: potassium binders,
   Extracorporeal: hemodialysis, peritoneal dialysis
What we know?

Emergency management of severe hyperkalemia

- evidence base supporting the current approach to emergency management of severe hyperkalemia is limited

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ngugi et al <em>East Afr Med J</em> 1997;74:503-509</td>
<td>A: glucose 25g i.v. with insulin 10 units i.v.; B: 50 mmol of 8.4% sodium bicarbonate infusion, C: 0.5mg of salbutamol i.v. in 50mls 5% dextrose; D: A + B; E: B + C; F: A + C; G: A + B + C.</td>
<td>10 patients per group</td>
</tr>
<tr>
<td>Lens et al <em>Nephrol Dial Transplant</em> 1989;4(3):228-232</td>
<td>Salbutamol vs. Insulin vs both</td>
<td>44 patients</td>
</tr>
</tbody>
</table>

- clinical events (i.e., arrhythmia, death) were not reported.
Our review (2010), which updates a prior Cochrane systematic review (2005) has highlighted the paucity of evidence to determine the most effective therapy for acute management of hyperkalemia.
We included seven studies (241 participants) in this review (2015).

Meta-analysis of these seven included studies was not possible due to heterogeneity of the treatments and because many of the studies did not provide sufficient statistical information with their results.

Allocation and blinding methodology was poorly described in most studies.

Emergency management of severe hyperkalemia
Evidence for the acute pharmacological management of hyperkalaemia is limited, with no clinical studies demonstrating a reduction in adverse patient outcomes.

Of the studied agents, salbutamol via any route and IV insulin-dextrose appear to be most effective at reducing serum potassium.

There is limited evidence to support the use of other interventions, such as IV sodium bicarbonate or aminophylline.

The effectiveness of potassium binding resins and IV calcium salts has not been tested in RCTs and requires further study before firm recommendations for clinical practice can be made.
The limited data available in the literature shows no statistically significant difference between the different regimens of insulin used to acutely lower serum K+ concentration.
Review

Emergency management of severe hyperkalemia: Guideline for best practice and opportunities for the future

Patrick Rossignol (MD, PhD)\textsuperscript{a,v,1}, Matthieu Legrand (MD, PhD)\textsuperscript{b,1}, Mikhail Kosiborod (MD)\textsuperscript{c}, Steven M. Hollenberg (MD)\textsuperscript{d}, W. Frank Peacock (MD)\textsuperscript{e}, Michael Emmett (MD)\textsuperscript{f}, Murray Epstein (MD)\textsuperscript{g}, Csaba P. Kovessy (MD)\textsuperscript{h}, Mehmet Birhan Yilmaz (MD)\textsuperscript{i}, Wendy Gattis Stough (PharmD)\textsuperscript{j}, Etienne Gayat (MD, PhD)\textsuperscript{k}, Bertram Pitt (MD)\textsuperscript{l}, Faiez Zannad (MD, PhD)\textsuperscript{a}, Alexandre Mebazaa (MD, PhD)\textsuperscript{b}

\textsuperscript{a} Inserm, Centre d'Investigations Cliniques - 1433, and Inserm U1116, CHU Nancy, Université de Lorraine, Association Lorraine pour le Traitement de l’Insuffisance Rénale, F- CRIN INI-CRCT, Nancy, France
\textsuperscript{b} Department of Anesthesiology, Critical Care and Burn Unit, St. Louis Hospital, University Paris 7 Denis Diderot, UMR-S942, Inserm, France and F-CRIN INI-CRCT Nancy, and GREAT network, Paris, France
\textsuperscript{c} Saint Luke's Mid America Heart Institute and University of Missouri – Kansas City, Kansas City, MO, United States
\textsuperscript{d} Divisions of Cardiovascular Disease and Critical Care Medicine, Cooper University Hospital, Camden, NJ, United States
\textsuperscript{e} Baylor College of Medicine, Ben Taub Hospital, Houston, TX, United States
\textsuperscript{f} Baylor University Medical Center, Baylor Scott & White Health Care, Dallas, TX, United States
\textsuperscript{g} Division of Nephrology and Hypertension, University of Miami, Miller School of Medicine, Miami, FL, United States
\textsuperscript{h} Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN, United States
\textsuperscript{i} Department of Cardiology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey
\textsuperscript{j} Departments of Clinical Research and Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, NC, United States
\textsuperscript{k} Département d’Anesthésie – Réanimation – SMUR, Hôpitaux Universitaires Saint Louis – Lariboisière, INSERM – UMR 942, Assistance Publique – Hôpitaux de Paris, Université Paris Diderot, Paris, France
\textsuperscript{l} University of Michigan School of Medicine, Ann Arbor, MI, United States
IN ANY CASE: Treat and cure
1) The cause of hyperkalemia
2) associated disorders (e.g. treatment of shock, correction of hypovolemia or heart failure, or treat the cause of AKI)
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K>=5.1  K>=5.5  K>=6  K>=6.5

Consider pseudohyperkalemia

K-related Changes on EKG?
NO  YES

cardiac monitoring

Ca gluconate or chloride I.v.
IN ANY CASE: Treat and cure
1) The cause of hyperkalemia
2) Associated disorders (e.g., treatment of shock, correction of hypovolemia or heart failure, or treat the cause of AKI)

- K+ > 5.1
  - Consider pseudohyperkalemia
  - K-related Changes on EKG?
    - NO
      - Cardiac monitoring
      - Ca gluconate or chloride IV
    - YES
      - Nebulized β2 agonist OR Insulin + glucose IV

- K+ > 5.5
  - Nebulized β2 agonist OR Insulin + glucose IV

- K+ > 6
  - Nebulized β2 agonist AND Insulin + glucose IV

- K+ > 6.5
  - Nebulized β2 agonist AND Insulin + glucose IV
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K+ => 5.1
K+ => 5.5
K+ => 6
K+ => 6.5

Consider pseudohyperkalemia

K-related Changes on EKG?
NO
YES

cardiac monitoring

Ca gluconate or chloride l.v.

Nebulized β2 agonist
OR
Insulin + glucose l.v.

If Acute hypovolemia and metabolic acidosis, consider sodium bicarbonate l.v.

Nebulized β2 agonist
AND
Insulin + glucose l.v.

K+ excretion/removal
Intracellular K+ shift
Cell membrane stabilization
10 min
30 min
120 min
Sodium polystyrene sulfonate is available but recently developed new drugs (ZS-9 and patiromer) appear promising to lower serum potassium in acute hyperkalemia.
IN ANY CASE: Treat and cure
1) The cause of hyperkalemia
2) associated disorders (e.g., treatment of shock, correction of hypovolemia or heart failure, or treat the cause of AKI)

K+\geq5.1
K+\geq5.5
K+\geq6
K+\geq6.5

Consider pseudohyperkalemia

K-related Changes on EKG?

NO

YES

cardiac monitoring

Ca gluconate or chloride i.v.

Nebulized β2 agonist
OR
Insulin + glucose i.v.

If Acute hypovolemia and metabolic acidosis, consider sodium bicarbonate i.v.

Consider i.v. loop diuretics

if no urinary tract obstruction AND patients with hypovolemia
AND/OR
K-binding agents#

Severe Acute Kidney Injury?

NO

YES

Consider dialysis

Consider semi-urgent Dialysis initiation

Decrease of K+ serum level

YES

NO

ReConsider treatment leading to hyperkalemia***

Discontinue oral and parenteral potassium supplements
What we need to know

Opportunities for research

• Characterizing the relationship between serum potassium and cardiac instability
  a. Defining the threshold potassium level where risk of death or arrhythmia significantly increases is a high priority.
  b. Identifying which ECG changes (i.e., peaked T-waves, conduction system abnormalities, sine wave, or widening QRS) are the greatest predictors of outcome is also a needed area of study.

Rossignol et al, Pharmacological Research 2016
Characterizing the relationship between serum potassium and cardiac instability

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b. Identifying which ECG changes (i.e., peaked T-waves, conduction system abnormalities, sine wave, or widening QRS) are the greatest predictors of outcome is also a needed area of study.

Prospectively designed observational studies that include timed potassium measurement would enable evaluation of the relationship between potassium levels, ECG response, standard interventions, and patient outcomes.

Rossignol et al, Pharmacological Research 2016
Determining the optimal rate for serum potassium correction

The optimal rate of correction for serum potassium is unknown, and the importance of immediately lowering serum potassium in patients without cardiac manifestations of hyperkalemia is uncertain.
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Prospective observational data are needed to characterize the relationship between serum potassium, myocardial conduction, and progression to life-threatening arrhythmias.

Rossignol et al, Pharmacological Research 2016
Prospective, randomized trials of new and existing therapies

These drugs should be tested to determine if they predictably lower serum potassium to a sufficient degree and within an acceptable time frame compared to standard treatment approaches.

Rossignol et al, Pharmacological Research 2016
What we need to know

Opportunities for research

- Prospective, randomized trials of new and existing therapies
- These drugs should be tested to determine if they predictably lower serum potassium to a sufficient degree and within an acceptable time frame compared to standard treatment approaches.
- Relevant study endpoints:
  i. Time to achieve normokalemia (or a specific potassium threshold)
  ii. Incidence of clinically significant arrhythmias
  iii. Need for rescue therapy (i.e. insulin/glucose, inhaled Beta 2 agonists, or hemodialysis)

Rossignol et al, Pharmacological Research 2016
Observational studies

Observational registries conducted in acute settings (e.g., emergency department, in-hospital, or intensive care units) that prospectively evaluate patient demographics (including ethnicity and genetic information), clinical characteristics (including causes of hyperkalemia), presenting symptoms and ECG findings, current standards of care, variation in treatment practices across centers, and clinical outcomes (i.e., death, arrhythmia, need for dialysis, resolution of severe hyperkalemia) would help fill the existing knowledge gaps.
What we need to know

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Rossignol et al, Pharmacological Research 2016
Concomitant medications may matter?

What we need to know

Association between hypo- and hyperkalemia and outcome in acute heart failure patients: the role of medications

Matthieu Legrand1,2,3,4, Pierre-Olivier Ludes1,2, Ziad Massy5,6, Patrick Roggno7, Jiri Parenica8,9, Jin-Joo Park10, Shiro Ishihara11, Khalid F. AlHabib12, Aldo Maggioni13, Óscar Miró14, Naoki Sato11, Alain Cohen-Solal15, Enrique Fairman16, Johan Lassus17, Veli-Pekka Harjola17, Christian Mueller18, Franck W. Peacock19, Dong-Ju Choi10, Patrick Plaisance20, Jindřich Spinar8,9, Mikhail Kosiborod21, Alexandre Mebazaa1,2,3,4, Etienne Gayat1,2,3,4, GREAT (Global Research on Acute Conditions Team) Network and INI-CRCT (Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists) network
• Observational intercontinental study of patients admitted with AHF.
• 15954 patients were included from 12 cohorts in 4 continents.
• Main outcome was 90-day mortality.
• Clinical presentation (medication use, hemodynamics, comorbidities), demographic, echocardiographic, and biochemical data on admission were recorded prospectively in each cohort.

What we need to know:
Concomitant medications may matter?

Legrand M et al, Clin Res Cardiol 2017
| Sub-groups                  | “Normal” range of 
<table>
<thead>
<tr>
<th></th>
<th>kalemia</th>
<th>OR for each 0.1 mmol/l below the lower limit</th>
<th>( P_{interaction} )</th>
<th>OR for each 0.1 mmol/l above the upper limit</th>
<th>( P_{interaction} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients ((n = 15,954))</td>
<td>3.5–4.5</td>
<td>1.03 [0.98–1.09]</td>
<td>–</td>
<td>1.03 [1.02–1.04]*</td>
<td>–</td>
</tr>
</tbody>
</table>
Concomitant medications may matter

**Table 2** Hazard ratio of hyper and hypokalemia for 90-day mortality

<table>
<thead>
<tr>
<th>Sub-groups</th>
<th>“Normal” range of kalemia</th>
<th>OR for each 0.1 mmol/l below the lower limit</th>
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</tr>
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<tr>
<td>All patients ($n = 15,954$)</td>
<td>3.5–4.5</td>
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<td>–</td>
<td><strong>1.03 [1.02–1.04]</strong>*</td>
<td>–</td>
</tr>
<tr>
<td>No RASi ($n = 5,837$)</td>
<td>3.5–4.5</td>
<td>1.05 [0.99–1.12]</td>
<td>&lt;0.0001</td>
<td><strong>1.02 [1.00–1.04]</strong>*</td>
<td>0.005</td>
</tr>
<tr>
<td>RASi ($n = 8,995$)</td>
<td>3.5–4.5</td>
<td>0.98 [0.94–1.02]</td>
<td>–</td>
<td><strong>1.03 [1.02–1.04]</strong>*</td>
<td>–</td>
</tr>
<tr>
<td>No BB ($n = 9,154$)</td>
<td>3.4–4.5</td>
<td><strong>1.08 [1.01–1.16]</strong>*</td>
<td>0.04</td>
<td><strong>1.03 [1.02–1.04]</strong>*</td>
<td>0.009</td>
</tr>
<tr>
<td>BB ($n = 6,015$)</td>
<td>3.6–4.6</td>
<td><strong>0.99 [0.92–1.06]</strong></td>
<td>–</td>
<td><strong>1.01 [0.95–1.08]</strong></td>
<td>–</td>
</tr>
<tr>
<td>No diuretic ($n = 5,020$)</td>
<td>3.3–4.3</td>
<td><strong>1.22 [1.07–1.38]</strong>*</td>
<td>0.001</td>
<td><strong>1.03 [1.01–1.05]</strong>*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretic ($n = 7,156$)</td>
<td>3.5–4.5</td>
<td><strong>1.05 [1.02–1.08]</strong>*</td>
<td>0.91</td>
<td><strong>1.03 [1.02–1.05]</strong>*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No MRA ($n = 11,102$)</td>
<td>3.5–4.5</td>
<td>1.03 [0.99–1.07]</td>
<td>–</td>
<td><strong>1.03 [1.02–1.05]</strong>*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MRA ($n = 3,877$)</td>
<td>3.5–4.5</td>
<td>1.02 [0.91–1.13]</td>
<td>–</td>
<td><strong>1.01 [1.00–1.03]</strong>*</td>
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Legrand M et al, Clin Res Cardiol 2017
CONCLUSIONS

• The emergency management of severe hyperkalemia is challenging because patients have an increased risk of death, but the factors (e.g., serum potassium threshold, optimal correction speed, comorbidities, ECG changes) that influence this risk are uncertain.
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• Thus, physicians are compelled to treat these patients aggressively to prevent progression to life-threatening arrhythmias and fatal events.
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• Thus, physicians are compelled to treat these patients aggressively to prevent progression to life-threatening arrhythmias and fatal events.

• Unfortunately, standard treatments are neither without risks or supported by a compelling body of evidence, and they are applied inconsistently.
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• Thus, physicians are compelled to treat these patients aggressively to prevent progression to life-threatening arrhythmias and fatal events.

• Unfortunately, standard treatments are neither without risks or supported by a compelling body of evidence, and they are applied inconsistently.

• Further research is needed to fill existing knowledge gaps, identify remaining unmet needs, and plan definitive clinical trials aiming to improve outcomes in these patients.

Rossignol et al, Pharmacological Research 2016