GlaxoSmithKline, Forest Laboratories, Pharmacia and Upjohn).

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

C.R.P. is a member of the advisory board of Renalytix AI and owns equity in the same. C.R.P. serves on the Data Safety and Monitoring Board of Genfit. The other authors report no conflicts of interest.

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Serum potassium laboratory reference ranges influence provider treatment behaviors for hyperkalemia

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The prevalence of hyperkalemia in hospitalized patients ranges between 1 and 10% [1] and treatment commonly commences when serum potassium is 5–6 mEq/L [2–4]. Aside from certain cardiovascular diseases [3, 5], the risk of adverse events with serum potassium <5.5 mEq/L is low [2] and treatment has not been shown to mitigate the risk [3]. Serum potassium results are typically reported along with reference ranges, with abnormal results flagged and highlighted. While hyperkalemia treatment guidelines have not changed, laboratory reference ranges have. These ranges are largely based on updates aimed at incorporating a 95% reference population rather than considering adverse event data [6]. Our objective was to discover what effect a reference upper limit change for serum potassium has on pro-

vider treatment behavior for emergency department and hospitalized patients with hyperkalemia.

We performed a retrospective cohort study of all emergency department and hospitalized patients with an order for sodium polystyrene sulfonate (SPS; trade name Kayexalate) at 14 hospitals in a large New York, USA, health system between 2012 and 2018. The reference upper limit for serum potassium changed from 5.1 to 5.3 mEq/L on 23 December 2015. Data were collected from the enterprise electronic health record (EHR; Sunrise Clinical Manager, Allscripts, Chicago, IL) database and included serum potassium results most proximate to an SPS order (up to 12 h prior) and the associated laboratory reference upper limit for that result. We compared SPS ordering patterns

FIGURE 1: Changes in SPS ordering patterns based on serum potassium reference upper limit. (A) The initial spike in SPS ordering occurred earlier, at a serum potassium of 5.2 mEq/L, when the reference upper limit was 5.1 mEq/L, whereas it occurred later when the reference upper limit was 5.3 mEq/L. (B) The maximal difference between the two groups occurred at a serum potassium of 5.3 mEq/L, with a 17.5% difference in cumulative distribution between the two groups. Blue rectangle highlights the area that was designated as hyperkalemia with a reference upper limit 5.1 mEq/L, but normokalemia at 5.3 mEq/L. (C) Interrupted time series examining the change in SPS ordering for a serum potassium level of 5.2–5.3 mEq/L. In the first period, with a serum potassium reference upper limit of 5.1 mEq/L, 9.8% of serum potassium results of 5.2–5.3 mEq/L (flagged as abnormal and high) resulted in an SPS order, whereas in the second period (reference upper limit 5.3 mEq/L), SPS was only ordered 0.9% of the time for the same serum potassium results (flagged as normal).

based on the reference upper limit using a two-sample Kolmogorov–Smirnov test to compare differences in the empirical cumulative distribution function and determine if the two samples were drawn from the same distribution (null hypothesis is that the distribution of orders by serum potassium level should remain consistent regardless of the laboratory-reported reference upper limit). An interrupted time series analysis was further performed to assess the percentage of serum potassium results between 5.2 and 5.3 mEq/L that triggered an SPS order, as this range changed from a hyperkalemia designation (reference upper limit 5.1 mEq/L) to normokalemia (reference upper limit 5.3 mEq/L). This study was approved by the Northwell Health Institutional Review Board.

A total of 43 131 orders for SPS were placed for 6.05 million potassium results during the 7-year period—21 546 orders (49.95%) with reference upper limit 5.1 mEq/L (Period 1) and 21 585 orders (50.05%) with reference upper limit 5.3 mEq/L (Period 2), representing 0.8% and 0.6% of all potassium results, respectively. The initial peak of SPS ordering in Period 1 occurred at a potassium level of 5.2 mEq/L, whereas it occurred at 5.4 mEq/L in Period 2, with a maximum absolute difference between the two cumulative curves occurring at a potassium level of 5.3 mEq/L ($D = 0.17172$, $P < 0.001$), a level that was flagged as elevated (hyperkalemia) in Period 1 but normal in Period 2 (Figure 1A and B). During Period 1, 9.8% of potassium results of 5.2–5.3 mEq/L (flagged as hyperkalemia) led to SPS orders,

whereas in Period 2 (lab-defined normalization of potassium 5.2–5.3 mEq/L) only 0.9% of similar results led to an order for treatment (Figure 1C) ($P < 0.001$).

Despite no change in the physiologic understanding of serum potassium and risk at elevated levels, we found that a simple modification to the default reference upper limit resulted in a significant change in hyperkalemia treatment with SPS. During the study period, no changes were introduced to hospital hyperkalemia protocols and newer potassium-binding agents were not available on the health system formulary. We were unable to ascertain underlying patient comorbidities or use of alternative treatments for hyperkalemia, including sodium bicarbonate, insulin and dextrose or albuterol. Yet the abrupt and sustained change in SPS ordering patterns suggests a reflexive approach to the treatment of hyperkalemia, whereby providers are biased toward treating a serum potassium level based on an ‘abnormal’ value in the EHR rather than clinical indication [7]. Some treatments for hyperkalemia are associated with significant morbidity [3, 8], underscoring the importance of initiating treatment only when patient benefit clearly outweighs the risk. Data on clinically optimal reference ranges are limited [3, 9], with a lack of prospective studies identifying the benefits of treatment at various serum potassium levels [3]. Hence lab-defined reference ranges may also not be optimally established for patient outcomes and closer collaboration and communication between clinical experts, laboratory personnel

and clinical informatics specialists is urgently needed. Educating providers and using appropriate defaults, order sets [4] or alerts [10] can lead to a more evidence-based approach to the management of potassium and other electrolyte disorders.

AUTHORS' CONTRIBUTIONS

J.S.H., R.P., S.F. and K.D.J. contributed to the research idea and study design. J.S.H. and K.R.B. contributed to data acquisition. J.S.H., S.R., V.S., S.F. and K.D.J. contributed to data analysis/interpretation. J.S.H. and V.S. contributed to statistical analysis. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

K.D.J. serves as a consultant for Astex Pharmaceuticals and Natera.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from the corresponding author, J.S.H. The data are not publicly available due to privacy restrictions.

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