Reference Change Values for Sodium Are Ignored by the American and European Treatment Guidelines for Hyponatremia

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Updated revised expert panel recommendations on the evaluation and treatment of hyponatremia were published in the United States in 2013 (1). In 2014, a separate set of guidelines were issued by a group representing the European Society of Intensive Care Medicine, the European Society of Endocrinology, and the European Renal Association–European Dialysis and Transplant Association represented by European Renal Best Practice (2).

US-Based Group

The recommended rates of correction of chronic hyponatremia from the US group are 4–8 mmol/L per day for patients at low risk of osmotic demyelinating syndrome (ODS)4 and 4–6 mmol/L per day if that risk is high. The limits not to exceed are 8 mmol/L in any 24-h period when the ODS risk is high, and when the ODS risk is low, 10–12 mmol/L in any 24-h period and 18 mmol/L in any 48-h period. If 8 mmol/L is exceeded in a 24-h period, there should be no active therapeutic intervention for the next 24 h (1).

Regarding frequency of sodium analysis, serum sodium should be measured at 4- to 6-h intervals until mildly hyponatremic concentrations ≥125 mmol/L have been reached.

The section on counteracting overcorrection of chronic hyponatremia by >6–8 mmol/L in the first 24 h of therapy discusses the uses of 2–4 μg desmopressin with repeated 3-mL/kg infusions of 5% dextrose in water administered over 1 h combined with the measurement of serum sodium after each infusion, i.e., hourly until the therapeutic target for the patient has been reached when the starting serum sodium is <120 mmol/L.

When using vasopressin receptor antagonists (vaptans) and when treating diuretic-induced hyponatremia, measurements of serum sodium are set at a 6- to 8-h minimum until a stable sodium value >125 mmol/L has been reached. When diuretics have caused hyponatremia-induced seizures, hypertonic saline is recommended to raise the serum sodium by 4–8 mmol/L acutely.

Measurements of urine osmolality with volume are also recommended, with frequency not stated.

In active treatment of the syndrome of inappropriate antidiuretic hormone other than fluid restriction, serum sodium measurements should be measured every 4–6 h.

Europe-Based Group

The European guidelines are cognizant of the rigors of laboratory medicine, defining profound hyponatremia as serum sodium <125 mmol/L measured by ion-specific electrode (ISE) (2). The occurrence of pseudohyponatremia when sodium is measured by a major analyzer with sample dilution is noted, as is its absence when a direct-acting ISE is used, usually in blood gas analyzers.

An article on this subject cited in the guidelines reported significant bias between capillary blood analyzed by direct ISE and venous plasma analyzed by indirect ISE, with poor correlation and wide scatter of the data. The SD of the differences was 2.7 mmol/L. The authors of the cited article noted that the 2 methods should not be used interchangeably when monitoring sodium over short time periods, and that a single method should be used for clinical decisions (3). This conclusion is endorsed in the guideline document (2).

The European guidelines distinguish 2 issues, targets and limits for serum sodium in hyponatremia treatment (section 7, G26). The target value is the goal desired when a particular treatment is applied. The limit value is the serum sodium value that should not be exceeded by intervention.

During the treatment of hyponatremia with severe symptoms, whether acute or chronic (Guideline 7.1.1.1), prompt intravenous infusion of 150 mL of 3% hypertonic saline over 20 min is recommended. The serum sodium is to be measured after the 20-min infusion, and then the infusion is to be repeated twice, with serum
sodium remeasured or until a target increase in serum sodium of 5 mmol/L is achieved. The limit value is a change of serum sodium of 10 mmol/L in the first 24 h and an additional 8 mmol/L for every 24 h thereafter until the sodium value reaches 130 mmol/L. Serum sodium should be checked after 6 and 12 h and then daily when the value has stabilized with treatment (Guideline 7.1.2.5).

In Guideline 7.1.3.1, hypertonic saline should be stopped when symptoms improve, when serum sodium increases by 10 mmol/L in total, or when sodium reaches 130 mmol/L. Sodium measurements should be made every 4 h as long as there is hypertonic infusion or similar intervention.

### Overcorrection

The Adrogue–Madias formula is often used to calculate the infusion rate for hypertonic saline infusion treatment \( \frac{1}{2} \). The utility of the formula was studied in a retrospective analysis of the outcomes of hypertonic saline for the treatment of hyponatremia. The guideline of limits of change of serum sodium of 10 mmol/L in the first 24 h and 8 mmol/L for every 24 h thereafter until the sodium value reaches 130 mmol/L. Serum sodium should be checked after 6 and 12 h and then daily when the value has stabilized with treatment (Guideline 7.1.2.5).

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### Serum Sodium in the Clinical Laboratory

The limitations of the performance details of laboratory measurements of sodium were overlooked by both sets of guidelines or recommendations. Could the recommendations of prescribed regular serum sodium measurements have an influence on clinical behavior? The analytical limitations of serum sodium measurements must have an impact on clinical care when rates of change in sodium of 0.5 mmol/L/h are considered maximum values over 24 h, especially when correction formulas have serious limitations. The time intervals for serum sodium analyses described in the treatment protocols varied from 20 min to every 6 h, to 12 h, to daily. The laboratory in our hospital uses a Beckman Coulter AU5400 analyzer. Serum sodium is measured by indirect ISE. There are 4 internal quality assessment checks per day at 3 concentrations of sodium. The accumulated QC values over 6 months are shown in Table 1.

The probability that 2 test results from a single patient are statistically significantly different involves consideration of both analytical \( a \) and biological \( i \) variation. This is known as the critical difference or reference change value (RCV). Desirable biological database specifications are hosted on the Westgard QC database website updated to 2014 (https://www.westgard.com/biodatabase1.htm). The quoted biological variation \( (CV_i) \) for sodium is 0.6%, with a desirable imprecision of 0.3%, inaccuracy of 0.23%, and total error of 0.73%.

The Royal College of Pathologists of Australia lists the analytical quality requirements for serum sodium and point-of-care sodium ≤150 mmol/L as within 3.0 mmol/L and >150 mmol/L within 2%.

The RCV or critical difference is the value that must be exceeded upward or downward over the sum of inherent sources of variation. A recent article \( (5) \) published RCVs for sodium, which were analytical variation \( (CV_a) \) 1.10%, within-person variation \( (CV_i) \) 0.6%, unidirectional RCV 3.05% at \( P < 0.05 \) and 4.31% at \( P < 0.01 \), and bidirectional RCV 3.62% at \( P < 0.05 \) and 4.77% at \( P < 0.01 \).

By a commonly used formula, RCV = \( 2.8 \times \sqrt{CV_a^2 + CV_i^2} \).

Alternatively, RCV can be calculated as \( k \times \sqrt{2 \times CV_1 + CV_2} \), where \( k = 1.65 \) for a 1-tailed test and a probability risk \( \alpha \) of 95%, \( k = 1.96 \) for a 2-tailed test, and \( CV \) is the within-person (or intraindividual) variation.

This formula applied to our laboratory in real time at sodium 121 mmol/L gives RCV = \( 1.96 \times \sqrt{0.99^2 + 0.6^2} = 3.209\% \).

Taking the hyponatremia value of 121.18 mmol/L and 2 analytical SDs above and below the mean reveals a 95% CI of 118.78–123.58 mmol/L; but the RCV is 117.29–125.07 mmol/L. A difference in 2 measurements of sodium at this concentration as large as the upper boundary minus the lower boundary of the 95% CI could occur at random.

The ABL 800 series instrument in our hospital’s Accident and Emergency Department, which uses a direct ISE, shows an analytical SD of 1.0 at a sodium value of 118 mmol/L. These are good performances, but again 2 SDs span values 116–120 mmol/L and the RCV spans 114.214–121.79 mmol/L.

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<th>Table 1. Accumulated QC values over 6 months for 4 internal quality assessment checks per day at 3 levels of sodium.</th>
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had a mean sodium value of 125.5 mmol/L with SD 1.2 and CV 1.0% over 62 participants.

Published values of allowable imprecision from clinical and analytical outcome criteria for serum sodium at 125 mmol/L are 4.0% for medically significant change; CVi 0.8%; clinical maximal allowable imprecision 0.7%–0.9%; Skendzel medically useful CV 1.7%; maximal allowable imprecision 0.6–0.8%; US CLIA proficiency testing criteria 4 mmol/L.

Biological variation derived from the National Health and Nutrition Examination Survey 1999–2002 found that at serum sodium 138.6 mmol/L, the within-person SD was 1.7 and the CVi was 1.0%.

Best practice is that, for disease monitoring, CVi ≤ one-half CVi. For a change in systematic error (Δ SE) during monitoring, Δ SE ≤ one-third CVi. The CVi of serum sodium is 0.7%, resulting in Δ SE ≤ 0.23% (the maximum bias from diagnosis is 0.3%).

Applying the RCV to the therapeutic recommendation and guidelines means that for a serum sodium of 120 mmol/L, the increase in value in the correction of hyponatraemia would have to be ≥ 124 mmol/L to be certain of a real change. The treatment assumptions for the validity of sodium measurements made in the guidelines have clinical and medicolegal implications. Clearly, these issues and calculations should be incorporated into the European and US guidelines and recommendations on hyponatraemia in the next scheduled updates. A best-practice RCV should be recommended as the analytical compromise, and a direct-acting ISE method by use of a single analyzer for each case is the optimum where possible. At a minimum, the same analyzer should be used in individual cases. Multiple replicate analyses within a laboratory are impractical to provide a result in the form of a mean with CIs.

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All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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### References


