Utility and Limitations of the Traditional Diagnostic Approach to Hyponatremia: A Diagnostic Study

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ABSTRACT

BACKGROUND: The differential diagnosis of hyponatremia is often challenging because of its association with multiple underlying pathophysiological mechanisms, diseases, and treatment options. Several algorithms are available to guide the diagnostic approach to hyponatremia, but their diagnostic and clinical utility has never been evaluated. We aimed to assess in detail the diagnostic utility as well as the limitations of the existing approaches to hyponatremia.

METHODS: Each of the 121 consecutive subjects presenting with hyponatremia (serum sodium <130 mmol/L) underwent 3 different and independent diagnostic and therapeutic approaches: inexperienced doctor applying an established Algorithm, intensive care senior physicians acting as Senior Physician, and senior endocrinologist serving as Reference Standard.

RESULTS: The overall diagnostic agreement between Algorithm and Reference Standard was 71% (respective Cohen’s kappa and delta values were 0.64 and 0.70), the overall diagnostic agreement between Senior Physician and Reference Standard was 32% (0.20 and 0.19, respectively). Regarding the therapeutic consequences, the diagnostic accuracy of the Algorithm was 86% (0.70 and 0.72, respectively) and of the Senior Physician was 48% (0.01 and 0.04, respectively). In retrospect, by disregarding the patient’s extracellular fluid volume and assessing the effective arterial blood volume by determination of the fractional urate excretion, the Algorithm improved its diagnostic accuracy to 95%.

CONCLUSION: Although the Algorithm performed reasonably well, several shortcomings became apparent, rendering it difficult to apply the Algorithm without reservation. Whether some modifications may enhance its diagnostic accuracy and simplify the management of hyponatremia needs to be determined.

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KEYWORDS: Algorithm; Differential diagnosis; Hyponatremia; SIADH; Vasopressin

Fifteen to thirty percent of all hospitalized patients feature some degree of hyponatremia, rendering it the most frequent fluid and electrolyte disturbance in clinical medicine.1 Hyponatremia is defined as serum sodium concentration <135 mmol/L and represents an excess of water in relation to existing total body solutes. The underlying cause of hyponatremia may be obvious if a precipitating cause is present as vomiting and diarrhea, acute renal failure, or primary polydipsia. Very often, however, the cause of hyponatremia is less clear. In these cases, the differential diagnosis of hyponatremia frequently is complex and includes a wide range of pathophysiological settings with varying treatment. Because both hyponatremia itself and, importantly, inadequate therapy may substantially raise morbidity, mortality, and health care expenditure,2,3 a careful diagnostic and therapeutic approach to patients with hyponatremia is considered essential in clinical routine.

For this purpose, several diagnostic algorithms have been developed by experts in the field of hyponatremia intending to facilitate the handling of these patients in medical practice.4-6 These algorithms are based on longstanding experience of clinical experts who are aware of the risk of inappropriately being geared by a single laboratory
measurement along the diagnostic workup. Hence, clinical judgment is of utmost importance but cannot necessarily be assumed in younger, less experienced doctors. Of note, the clinical utility of these diagnostic algorithms has never been assessed in a real-life scenario where younger or less skilled clinicians apply these tools. As a result, most clinicians are skeptical or even too unaware to apply these algorithms in clinical practice.

Therefore, in a prospective approach, we examined the diagnostic potential of a diagnostic algorithm to hyponatremia under real-world conditions. The underlying cause of hyponatremia was determined by an expert endocrinologist well versed in this area, and served as the reference standard.

PATIENTS AND METHODS

Study Design and Population

All patients with serum sodium concentration < 130 mmoL/L and serum osmolality < 280 mosm/kg at admission to the University Hospital of Würzburg were consecutively enrolled in this diagnostic study between April and November 2007 (n = 121). Patients aged < 18 years were not eligible. Study design, conduct, and reporting followed the criteria proposed by the “Standards for the Reporting of Diagnostic Accuracy Studies” initiative.8 The study was approved by the Ethical Committee of the University of Würzburg (No. 33/07), and written informed consent was obtained before participation.

Diagnostic Approach

In order to quantify the accuracy of the formalistic diagnostic approach to hyponatremia and the added value of clinical experience, all patients were diagnosed independently using 3 different approaches:

I) Algorithm. We used a diagnostic algorithm based on published approaches to hyponatremia9,8 with minor modifications that we expected to be both feasible and reliable in clinical routine (Figure). This algorithm demands the determination of serum and urine osmolality, renal sodium excretion, and the clinical assessment of the extracellular fluid volume. A young physician with limited clinical experience strictly adhered to this algorithm and was asked to establish a diagnosis within 24 hours after inclusion. Any later correction of the once-documented diagnosis was not considered in the context of this study.

II) Senior Physician. A senior physician with longstanding clinical experience in internal and intensive care medicine, but no particular expertise in the area of hyponatremia, was instructed to categorize the patients according to their underlying cause of hyponatremia at the same time, using all available laboratory tests and diagnostic information collected within the first 24 hours after admission. Again, for the purpose of this study, later correction of the once-documented diagnosis was not considered. The Algorithm and the Senior Physician operated independently.

III) Reference Standard. Because a validated reference standard does not exist, the final diagnosis of the underlying cause of hyponatremia was made after complete diagnostic workup of an expert endocrinologist well versed in the area of hyponatremia. The Reference Standard was free to use whatever diagnostic information he considered necessary, and was allowed to delay the final diagnosis in case of uncertainty until additional imaging or histopathology information had been completed, or until other possible differential diagnoses had been excluded.

Each approach grouped all diagnoses into 1 of 6 etiologic categories: primary polydipsia or potomania, hypervolemia, hypovolemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), diuretic-induced hyponatremia, and adrenal insufficiency. Then, all patients were grouped into 1 of 3 therapeutic categories by each approach: fluid restriction, fluid restoration, and glucocorticoid administration.

Because patients were distributed among different wards of our hospital, during this diagnostic study the treatment remained in the hands of the respective responsible physicians.

Laboratory Measurements

The biochemical evaluation following the Algorithm was performed in samples obtained before any therapeutic intervention and included the following parameters: serum sodium, potassium, chloride, creatinine, glucose, total protein, albumin, triglycerides, osmolality, red and white cell blood count, cortisol, adrenocorticotropic hormone, and thyroid-stimulating hormone.

Routine laboratory measurements were done by automated chemical analyses in the Central Core Laboratory of the University Hospital Würzburg. Specifically, urine
serum samples were analyzed using ion-sensitive electrodes for sodium, potassium, and chloride. A modification of the Jaffé method for creatinine measurement and osmolality was measured directly via determination of freezing point depression. The hexokinase and uricase methods were used for the determination of glucose and uric acid levels. Measurement of cortisol, adrenocorticotropine hormone, and thyroid-stimulating hormone was assessed by using the appropriate assay for the autochemiluminescence system IMMULITE 2000 (Siemens, Medical Solution, Diagnostic GmbH, Bad Nauheim, Germany).

Data Analysis

Indexes of observer agreement are controversially discussed and have individual limitations, one being their dependence on the number of diagnostic categories used. In order to arrive at meaningful statistics, we condensed the multitude of differential diagnoses of hyponatremia into the 6 diagnostic categories described above (here: “etologic diagnoses”).

Because the clinical measures taken after diagnostic categorization of a patient may be of even greater relevance, we also assessed the observer agreement with respect to the therapeutic consequences following from the initial clinical presentation using the 3 therapeutic categories mentioned above. The performances of both Algorithm and Senior Physician were compared with the Reference Standard, and Cohen’s chance-corrected kappa for overall agreement with its standard error was computed. Because kappa has several acknowledged drawbacks, delta with its standard error as an overall measure for conformity, consistency, and agreement was computed additionally following the approach outlined by Andres and Marzo.10

Agreement statistics were computed using DELTA 3.1, which is a freeware tool provided by Andres and Marzo at http://www.ugr.es/~bioest. All other statistics were computed using SPSS 17.0.1 (SPSS Inc., Chicago, Ill).

RESULTS

Baseline Characteristics

In total, 121 hyponatremic patients (53 male, 68 female) were enrolled. Fifteen patients exhibited severe hyponatremia (serum sodium <115 mmol/L; 12.4%) and 62 patients moderate hyponatremia (<125 mmol/L; 51.2%). The mean age was 64 years (range 22-91 years). The causes of hyponatremia according to the Reference Standard were as follows: primary polydipsia 4%, hypervolemia 20%, hypovolemia 32%, SIADH 35%, diuretic-induced 7%, and adrenal insufficiency 2%. In 10 patients (8%), severe or moderate hyponatremia was associated with serious complications such as seizures, coma, or osmotic demyelination syndrome. Two patients died as a consequence of central pontine myelinolysis (Table 1): one patient with advanced alcoholic liver cirrhosis was initially diagnosed with Wernicke encephalopathy and was treated with thiamine. The other patient, presenting with a serum [Na+] of 101 mmol/L, developed myelinolysis syndrome despite correction rates within the recommended range.11,12

The baseline characteristics and the most frequent disorders causing hyponatremia are shown in Table 1.

Comparison of Reference Standard with Algorithm and Clinical Expert

Table 2 shows the performance of the Senior Physician in diagnosing the correct etiology of hyponatremia in all 121 patients. The overall diagnostic agreement between Senior Physician and Reference Standard was 32%, the overall Cohen’s kappa and delta values with its standard errors were 0.20 (0.06) and 0.19 (0.06), respectively. Regarding the therapeutic consequences, the overall agreement between Senior Physician and Reference Standard was 48% and the overall kappa and delta values were 0.01 (0.09) and 0.04 (0.09), respectively, indicating poor agreement and consistency (Table 3).

By comparison, applying the Algorithm, the overall diagnostic agreement with the Reference Standard was 71%, resulting in overall Cohen’s kappa and delta values of 0.64 (0.06) and 0.7 (0.06), respectively (Table 4). Regarding the therapeutic consequences, the overall agreement between Algorithm and Reference Standard was 86%, with overall
kappa and delta values of 0.70 (0.07) and 0.72 (0.12), respectively (Table 5).

**Pitfalls of the Algorithm**

Intake of diuretics was frequent in our study sample (61% of all patients) and has prevented a correct diagnosis in 24/121 patients (20%) applying the Algorithm. Incorrect assessment of patients’ extracellular fluid volume resulted in false diagnoses in 6 patients (5%). In particular, patients with diuretic-induced hyponatremia were often misclassified, because most of them were not hypovolemic but rather euvolemic or even hypervolemic (75% of all patients). Consistently, SIADH was the most frequent false-positive diagnosis, being expected whenever the combination of euvolemia and increased renal sodium excretion (>30 mmol/L) was present. This problem may be ameliorated by using the fractional urate excretion for assessment of the effective arterial blood volume in patients on diuretics. 13 If, in retrospect, the patient’s extracellular fluid volume was disregarded and the effective arterial blood volume was disregarded and the effective arterial blood volume was

![Table 1](http://example.com/table1.jpg)

**Table 1** Characterization of the Study Population (n = 121) and Presentation of the Most Frequent Pathomechanisms and Complications of Hyponatremia*

<table>
<thead>
<tr>
<th>Etiologic Category</th>
<th>Algorithm [n†/n]</th>
<th>Senior Physic. [n†/n] (%)</th>
<th>Ref. Stand.</th>
<th>Sex, Male/Female [n/n]</th>
<th>Age, Years [Mean (SD)]</th>
<th>Number and Type of Complications</th>
<th>Cause of Hyponatremia‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary polydipsia</td>
<td>0/5</td>
<td>1/5</td>
<td>5 (4)</td>
<td>0/5</td>
<td>61 (28)</td>
<td>1× water intoxication (confusion and seizures)</td>
<td>Psychogenic polydipsia</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>15/24</td>
<td>10/24</td>
<td>24 (20)</td>
<td>16/7</td>
<td>66 (13)</td>
<td>1× osmotic demyelination syndrome‡</td>
<td>Congestive heart failure (68%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1× confusion and seizures</td>
<td>Liver cirrhosis (23%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3× stupor/coma</td>
<td>Angioedema (9%)</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>32/39</td>
<td>33/39</td>
<td>39 (32)</td>
<td>19/20</td>
<td>62 (18)</td>
<td>None</td>
<td>Gastrointestinal solute loss (31%)</td>
</tr>
<tr>
<td>SIA DH</td>
<td>70/42</td>
<td>59/42</td>
<td>42 (35)</td>
<td>20/22</td>
<td>66 (14)</td>
<td>1× osmotic demyelination syndrome†</td>
<td>Malnutrition and inappetence (48%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2× confusion and seizures</td>
<td>Neoplastic (48%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3× stupor/coma</td>
<td>Acute bacterial infection (19%)</td>
</tr>
<tr>
<td>Diuretic-induced</td>
<td>3/8</td>
<td>17/8</td>
<td>8 (7)</td>
<td>1/7</td>
<td>71 (13)</td>
<td>None</td>
<td>Nausea and vomiting (18%)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1/3</td>
<td>1/3</td>
<td>3 (2)</td>
<td>2/1</td>
<td>52 (26)</td>
<td>2× coma</td>
<td>AVP and analogues (4%)</td>
</tr>
</tbody>
</table>

SIADH = syndrome of inappropriate antidiuretic hormone secretion; AVP = arginine vasopressin.
*For details, refer to the Methods section.
†Correct diagnosis.
‡Percentages refer to diagnostic categories of the Reference Standard (each category sums up to 100%).

![Table 2](http://example.com/table2.jpg)

**Table 2** Etiologic Diagnosis – Performance of Senior Physician

<table>
<thead>
<tr>
<th>Reference Standard</th>
<th>Senior Physician</th>
<th>Total</th>
<th>Delta per Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary polydipsia</td>
<td>1 0 0 1 3 0 5</td>
<td>5</td>
<td>0.20</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>0 8 6 5 5 0 24</td>
<td>24</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>0 0 13 21 5 0 39</td>
<td>39</td>
<td>−0.06</td>
</tr>
<tr>
<td>SIADH</td>
<td>0 1 13 27 1 0 42</td>
<td>42</td>
<td>0.35</td>
</tr>
<tr>
<td>Diuretic-induced</td>
<td>0 1 1 4 2 0 8</td>
<td>8</td>
<td>0.11</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>0 0 1 0 1 1 3</td>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>Total</td>
<td>1 10 34 59 16 1 121</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

SIADH = syndrome of inappropriate antidiuretic hormone secretion.
*For details, refer to the Methods section.
Overall kappa (SE) = 0.20 (0.06).
Overall delta (SE) = 0.19 (0.06).
assessed using the fractional urate excretion, the overall diagnostic agreement between Algorithm and Reference Standard increased from 71% to 95%.

Another diagnostic problem was evident in patients with primary polydipsia. In 5/5 patients, the Algorithm failed to diagnose primary polydipsia because the definition demanded a urinary osmolality <100 mosm/kg. However, all of our patients with primary polydipsia had a higher urinary concentration and were consequently misdiagnosed as SIADH. By adjustment of the Algorithm through raising the limit of vasopressin suppression to <200 mosm/kg, 4/5 patients with primary polydipsia would have been diagnosed correctly.

DISCUSSION

For a classification to be useful, it must guide the clinician to arrive at the correct diagnosis in due course in order to commence the appropriate therapy. In this study, we analyzed the diagnostic accuracy of a given diagnostic algorithm to hyponatremia, originating from 2 approaches published by Schrier and Verbalis with minor modifications. To the best of our knowledge, this is the first analysis carried out in consecutive hyponatremic subjects within a real-world setting.

Surprisingly, in our data the Algorithm performed clearly superior to the Senior Physician, even though its performance revealed several weaknesses resulting in misdiagnosis in about one third of patients. Most misinterpretations were caused by 2 problems: effect of diuretics on clinical presentation and laboratory markers, and use of information on the extracellular volume status as the decisive discriminating factor.

Previously, we have already pointed to the problem of urine sodium excretion as a diagnostic marker in patients on diuretics. Because most diuretics inhibit the tubular sodium reabsorption, resulting in an increased renal sodium excretion, both U-Na and the fractional sodium excretion have limited diagnostic utility in patients on diuretics.

We have shown that calculation of the fractional urate excretion is an excellent alternative in these patients, probably because the transport mechanisms for urate are localized in the proximal tubus that does not interact with diuretics. The findings in this extensive study sample now seem to support this hypothesis. If confirmed in prospective studies, the calculation of fractional urate excretion may be the preferred method to appropriately estimate the effective arterial blood volume in patients with hyponatremia under diuretics.

The second problem deals with the clinical assessment of the extracellular fluid volume as a discriminating factor. Most hyponatremia algorithms assume that clinicians are able to reliably detect a mild to moderate degree of extracellular fluid volume contraction by physical examination. Our experience and reports from others suggest that this

<table>
<thead>
<tr>
<th>Reference Standard</th>
<th>Fluid Restriction</th>
<th>Fluid Restoration</th>
<th>Steroids</th>
<th>Total</th>
<th>Delta per Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid restriction</td>
<td>44</td>
<td>29</td>
<td>0</td>
<td>73</td>
<td>0.20</td>
</tr>
<tr>
<td>Fluid restoration</td>
<td>28</td>
<td>17</td>
<td>0</td>
<td>45</td>
<td>-0.24</td>
</tr>
<tr>
<td>Steroids</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>47</td>
<td>1</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

Overall kappa (SE) = 0.01 (0.09).
Overall delta (SE) = 0.04 (0.09).

<table>
<thead>
<tr>
<th>Reference Standard</th>
<th>Primary Polydipsia</th>
<th>Hypervolemia</th>
<th>Hypovolemia</th>
<th>SIADH</th>
<th>Diuretic-induced</th>
<th>Adrenal Insufficiency</th>
<th>Total</th>
<th>Delta per Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary polydipsia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>—*</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>0</td>
<td>14</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>0.50</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>0</td>
<td>1</td>
<td>29</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>39</td>
<td>0.66</td>
</tr>
<tr>
<td>SIADH</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>41</td>
<td>0</td>
<td>0</td>
<td>42</td>
<td>0.78</td>
</tr>
<tr>
<td>Diuretic-induced</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>0.28</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>15</td>
<td>32</td>
<td>70</td>
<td>3</td>
<td>1</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

SIADH = syndrome of inappropriate antidiuretic hormone secretion.
Overall kappa (SE) = 0.64 (0.06).
Overall delta (SE) = 0.70 (0.06).
*Not computed because “Algorithm” failed to diagnose “Primary polydipsia.”
assumption is invalid. Rather, the diagnostic accuracy of physical signs for hypovolemia varies greatly if it is not due to blood loss. Furthermore, the hemodynamic response to extracellular fluid volume depletion seems to be dependent on the rate, magnitude, and source of fluid volume loss. Therefore, the clinical assessment of the extracellular fluid volume frequently yields misleading results in hyponatremic disorders. Although the extracellular fluid volume should be routinely assessed in hyponatremic patients, it should be taken into consideration that misjudgment is common.

Further diagnostic problems deserve attention: the missing consideration of relevant aspects of the patient’s medical history, a too-strict definition of “maximally diluted urine” in primary polydipsia, and the tendency to overdiagnose SIADH before adrenal, thyroid, or pituitary insufficiency have been excluded. Two of our patients with adrenal insufficiency were admitted to the neurological intensive care unit with generalized seizures, and one patient with extensive weight loss was admitted to the psychiatry ward with a provisional diagnosis of anorexia nervosa before adrenal insufficiency was eventually diagnosed.

These examples highlight the frequently missing awareness and diagnostic uncertainty concerning endocrine disorders in patients with hyponatremia. It also points to the importance of a detailed patient history (previous craniocerebral injury, radiation of the brain, or pituitary surgery) and allows the conclusion to administer hydrocortisone more deliberately as a first measure whenever therapeutic efforts remain unsuccessful, even if adrenal insufficiency may be excluded later.

Our study has some limitations. First, the sample size is relatively small. Second, the service of only a few Senior Physicians may not be representative for a generalized statement on the diagnostic value of clinical experience in the differential diagnosis of hyponatremia, as other experts may perform differently. To complicate matters further, hyponatremia may be at times multifactorial, which may have contributed to disagreement in individual cases. Third, calculation of the fractional urate excretion is not yet validated as a reliable marker of volume status in patients on diuretics.

CONCLUSION

In conclusion, we demonstrated for the first time the utility of an established hyponatremia algorithm in a real-world clinical setting. Strict adherence to the existing algorithm by a young physician yielded a higher diagnostic accuracy compared with the diagnostic performance of a senior physician.

However, the algorithm revealed several shortcomings, making it difficult to apply in clinical practice. Whether the proposed modifications to this algorithm may enhance its diagnostic accuracy and simplify the management of hyponatremia remains to be shown and is currently investigated in a prospective study.

References