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Classifying Hypotonic Hyponatremia by Projected Treatment Effects - A Quantitative 3-Dimensional Framework

Florian Buchkremer[1], Philipp Schuetz[2], Beat Mueller[3,4] and Stephan Segerer[1]

[1]Division of Nephrology, Kantonsspital Aarau, Aarau, Switzerland; [2]Division of General Internal and Emergency Medicine, Medical University Department, Kantonsspital Aarau, Aarau, Switzerland; [3]Medical Faculty of the University of Basel, Basel, Switzerland; and [4]Division of General Internal and Emergency Medicine, Department of Endocrinology, Diabetology & Metabolism, Medical University Department, Kantonsspital Aarau, Aarau, Switzerland

Introduction: The diagnostic algorithms currently used for hypotonic hyponatremia focus primarily on impaired urinary dilution and often neglect the influence of free water intake and solute excretion. We hypothesized that, in each case of hypotonic hyponatremia different pathophysiological mechanisms play a role simultaneously.

Methods: Using clinical data of the previous observational Co-Med study, we defined each case of hypotonic hyponatremia concurrently in 3 dimensions as follows: (i) high net free water intake (HNFWI), (ii) impaired dilution of the urine (IDU), and (iii) low nonelectrolyte solute excretion (LNESE). For each dimension, a "standard delta sodium" (sdna) was calculated reflecting the expected difference to the serum sodium concentration, that would result from changing a dimension to a specific and equivalent target level.

Results: Results from 279 patients were used for this analysis. With target levels of free water intake and urine osmolality at the fifth percentile, and nonelectrolyte solute excretion at the 95th percentile, median (interquartile range) sdna values were 7.1 (4.8–10.2) for HNFWI, 11.8 (7.0–18.6) for IDU and 2.6 (1.6–4.2) mmol/l per 24 hours for LNESE. Sdna results in individual patients were highest with IDU in 68.5%, HNFWI in 30.8% and 0.7% with LNESE. At an sdna-level of at least 4mmol/l per 24 hours, the prevalence of HNFWI was 78.9%, IDU 87.1%, and LNESE 26.5%. 77.5% of patients had 2 or all 3 mechanisms present. Hyponatremia was mostly multifactorial in subgroups according to classic categories of hyponatremia and typical comorbidities as well.

Conclusion: Hypotonic hyponatremia can be quantitatively defined by 3 dimensions. Most cases should be considered multifactorial.

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Hypotonic hyponatremia is the most common electrolyte disorder encountered in clinical practice.[1–3] Current diagnostic algorithms[3–6] strongly focus on the pathogenesis of impaired urinary dilution. High free water intake and low solute excretion are only considered, usually as "primary polydipsia" or "beer potomania," when urine osmolality is extremely low.

From a treatment perspective, this almost exclusive fixation on urinary dilution is unwarranted.[7–9]

Correspondence: Florian Buchkremer, Kantonsspital Aarau, Tellstr. 25, CH-5001 Aarau, Switzerland. E-mail: florian.buchkremer@ksa.ch
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Case Vignette 1

A 68-year-old patient with chronic kidney disease stage G4 A1 presents with a serum sodium concentration of 123 mmol/l. She is on a thiazide diuretic, blood pressure is 115/82 mm Hg, and she has no peripheral edema. Urine osmolality is 209 mosm/kg and urine sodium concentration is 19 mmol/l.

Using current algorithms, one might call this hypovolemic or diuretic-induced hyponatremia and would probably recommend stopping the diuretic and expanding the extracellular volume to allow excretion of a more dilute urine.

Contrary to this, her hyponatremia was corrected solely by limiting oral water intake.

Moreover, many hyponatremic patients normalize their plasma sodium concentration without any significant changes to their urine osmolality at all.

Case Vignette 2

A 74-year-old lung cancer patient presents with malaise of several days' duration. She has a serum sodium concentration of 124 mmol/l. Her blood pressure is 145/77 mm Hg; she has no peripheral edema, is not on a diuretic, and has normal kidney function. Urine osmolality is 360 mosm/kg and urine sodium concentration 41 mmol/l.

This constellation is consistent with a diagnosis of syndrome of inappropriate antidiuresis (SIAD) by current algorithms. Although high urine osmolality due to inappropriate arginine vasopressin release is allegedly responsible for the hyponatremia, it was corrected by limiting fluid and increasing solute and protein intake, with no relevant change to urine osmolality during follow-up at all.

As an alternative to the traditional classification of hyponatremia, we propose a simple, yet comprehensive diagnostic framework, where each case of hyponatremia is defined concurrently by different degrees of 3 mechanisms, namely HNFWI, IDU, and LNESE.

We have developed a new measure, the sdna, to quantify each mechanism and compare its influence on the serum sodium concentration within and between different patients. We then describe the prevalence of the 3 mechanisms and their combinations in a large cohort of hyponatremic patients.

METHODS

Co-Med study

We used patient data from the Co-Med study,[10] a prospective observational cohort of hospitalized patients with hyponatremia (serum sodium concentration less than 125 mmol/l), that was assembled between June 2011 and August 2013 at the University Hospital Basel and the Medical University Clinic Aarau, both in Switzerland. The primary goal was to analyze the role of copeptin in the differential diagnosis of hyponatremia. Per protocol, a spot urine examination was performed for all patients at the time of inclusion.

From these, we used urine osmolality (in mosm/kg) and urinary concentrations of urea, sodium, potassium, and creatinine (all in mmol/l). When either one of urine osmolality, urea, or sodium plus potassium were not available, we calculated it by solving the formula $Osmolality = 2 * ([Na] + [K]) + [Urea]$ for the missing variable and subtracting a correction factor. Specific correction factors were obtained for each missing quantity by quadratic regression on data from all patients with complete results (Supplementary Methods S1).

Model

Our model of hyponatremia is based on the Edelman equation[11,12]:

$$[Na]_{serum} = 1.03 \times \frac{\left(Na_{exchangeable} + K_{exchangeable}\right)}{Total\ body\ water} - 23.8$$

Accordingly, changes to the serum sodium concentration are determined by the external balance of water, sodium, and potassium or, put together, the electrolyte free water balance.[13,14] The 3 dimensions or mechanisms of our model (Figure 1) specify this balance as a whole: all ins and outs of sodium, potassium, and water apart from urine are covered by net free water intake. Urinary free water excretion is composed of urinary dilution and the amount of nonelectrolyte solutes excreted in the urine.

In general, net free water intake is mainly determined by the amounts of water, sodium, and potassium intake[13]; however, it includes all other possible nonurinary influences on the free water balance as well, such as perspiratio insensibilis, metabolic generation of water, gastrointestinal losses, and sweating. Given that the regulation of urine concentration plays a prominent role in the homeostasis of body tonicity,[16] we retained urine dilution as one mechanism, just as in the traditional algorithms. To completely capture the influence of urine excretion on the electrolyte free water balance, we complemented urine dilution by the nonelectrolyte solute excretion for the following reason: for any given urine osmolality, it is the amount of nonelectrolyte solutes in the urine that determines the magnitude of free water excretion.[17,18]

Given that our model does cover the whole external free water balance, all etiologic factors and treatments of hypotonic hyponatremia were easily fitted into its simple framework (Figure 1). This can be used as a checklist to identify all relevant pathogenetic factors and treatment maneuvers in patients with hyponatremia.[15]

Standard Delta Sodium Method

We used spot urine examinations to quantify these 3 dimensions of hyponatremia (Figure 2) as follows: net free water intake was measured indirectly by calculating the electrolyte free water excretion rate, also known as the "electrolyte free water clearance."[13,14,19] We used the following formula, which has been derived directly from the original Edelman equation[12,20]:

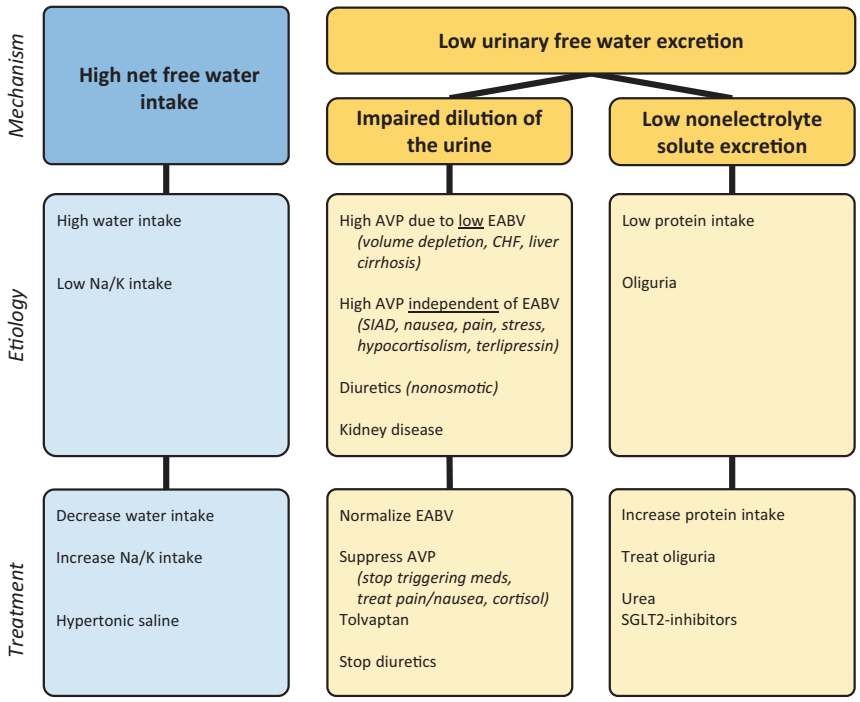

Figure 1. The 3 dimensions of hypotonic hyponatremia with corresponding etiologic factors and treatment maneuvers. To be used as a checklist in the management of hyponatremic patients. AVP, arginine vasopressin; CHF, congestive heart failure; EABV, effective arterial blood volume; K, potassium; Na, sodium; SIAD, syndrome of inappropriate antidiuresis Modified from Buchkremer[15], with permission.

$$\textit{Free water excretion rate} = \textit{Urine flow rate} \times \left(1 - \frac{1.03 \times \left([Na]_{urine} + [K]_{urine}\right)}{[Na]_{serum} + 23.8}\right)$$

Dilution of the urine and nonelectrolyte solute excretion were measured by urine osmolality and urea excretion rate, respectively. Urea and free water excretion were normalized to a creatinine excretion rate of 12.9 mmol per 24 hours, corresponding to the 50th percentile of the US population.[21,22]

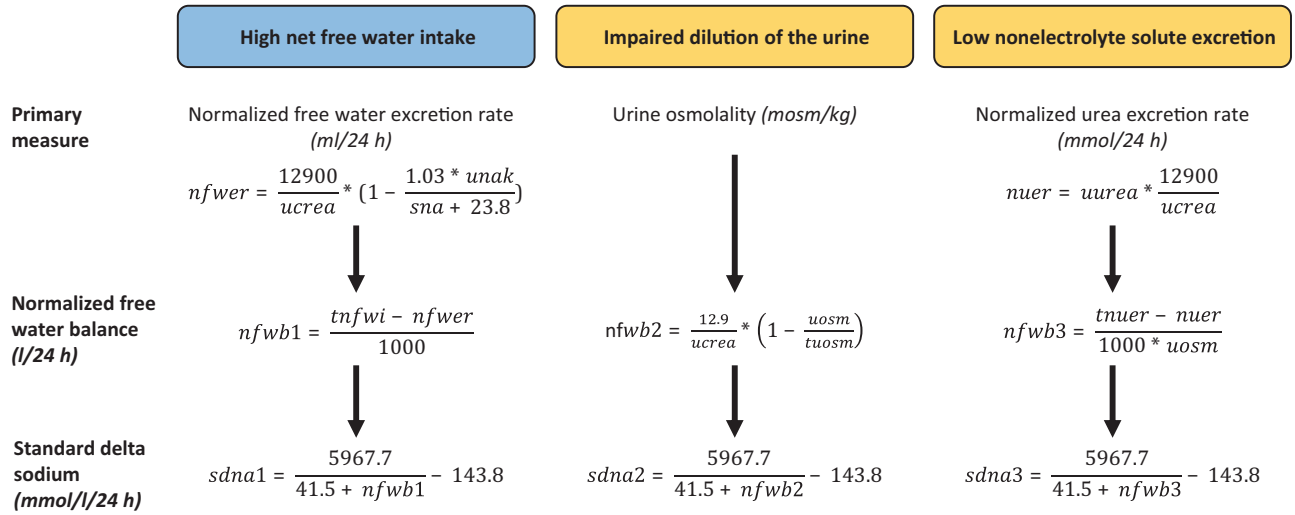

Figure 2. Quantifying the 3 dimensions of hypotonic hyponatremia: (i) High net free water intake, (ii) impaired dilution of the urine, and (iii) low nonelectrolyte solute excretion.
nfwer, normalized free water excretion rate (ml/24 h); nfwb, normalized free water balance (l/24 h); nuer, normalized urea excretion rate (mmol/24 h); sdna, standard delta sodium (mmol/l/24 h); sna, serum sodium concentration (mmol/l); tnfwi, target value for normalized free water intake (ml/24 h); tuosm, target value for urine osmolality (mosm/kg); tnuer, target value for normalized urea excretion rate (mmol/24 h); ucrea, urine creatinine concentration (mmol/l); unak, urine sodium plus urine potassium concentration (mmol/l); uosm, urine osmolality (mosm/kg); uurea, urine urea concentration (mmol/l).

Urine osmolality and these normalized excretion rates enable quantitative comparisons of the 3 mechanisms between different patients, but only for each mechanism separately. To allow quantitative comparisons between the different mechanisms as well, we developed a new measure, the sdna.

The sdna stands for the expected change in the serum sodium concentration due to equivalent treatment effects on either net free water intake, or urine osmolality, or urea excretion rate in a standardized human subject. For example, the sdna value for IDU (at the 5th/95th percentile target, see below) answers, how much the serum sodium would increase, if the urine osmolality would change from an actual value of for example 435 mosm/kg to a target level of 163 mosm/kg, with no changes in the other 2 dimensions (net free water intake and urea excretion rate). Workflow and formulas for the determination of the sdna values are shown in Figure 2. The derivation of the formulas, which are essentially simple applications of the Edelman equation, are described in Supplementary Methods S2.

To ensure comparability of the sdna results between the different mechanisms we defined equivalent target levels for net free water intake, urine osmolality and urea excretion rate, respectively. For that, we used equal percentile levels of the normalized free water excretion rate (5th, 25th, and 50th percentiles), urine osmolality (5th, 25th, and 50th percentiles), and normalized urea excretion rate (95th, 75th, and 50th percentiles) obtained before. With these levels, we first computed the difference in normalized free water balance (Figure 2). We then calculated the resulting change in serum sodium concentration, using standardized values for initial plasma sodium concentration (120 mmol/l) and total body water (41.5 l).

Determining Prevalence of the 3 Mechanisms and Their Combinations

We used specific levels of sdna values to describe the prevalence of the 3 dimensions and their different combinations in the whole cohort and in subgroups defined by classic hyponatremia categories and typical comorbidities, as specified in the original Co-Med study.[10]

We considered primary polydipsia, hypovolemic hyponatremia, diuretic-induced hyponatremia, hypervolemic hyponatremia, cortisol deficiency, and SIAD as hyponatremia categories. As comorbidities, we assessed central nervous system disease, congestive heart failure, pulmonary disease, liver cirrhosis, and kidney disease.

Ethics Statement

The Ethics Committee of Basel/Aarau approved the original study protocol. Informed consent was obtained from all patients or their next of kin before enrollment. It included an approval of subsequent analyses of study data. All our analyses were done in accordance with guidelines laid out by the Declaration of Helsinki and the Declaration of Istanbul.

RESULTS

Patients

From 312 patients originally included into the Co-Med study, 14 patients were excluded for the primary analysis (9 because of missing copeptin levels, 1 because of missing blood and urine values, 3 because of pseudohyponatremia, and 1 because of normal plasma tonicity due to hyperglycemia).[10] From the remaining 298 patients, another 16 patients had missing values needed to calculate normalized free water excretion rate and 1 had an implausibly low urinary creatinine concentration. Overall, we included 279 patients or 93.6% of the primary cohort into our secondary analysis. Their baseline characteristics are shown in Table 1.

Primary Measures

Results for normalized free water excretion rates, urine osmolality, and normalized urea excretion rates are shown in Figure 3 and Table 2. Very similar results were obtained when we limited the analysis to the 214

Table 1. Baseline characteristics

Characteristics	*N* = 279
Female, *n* (%)	183 (65.6)
Median age, yrs (IQR)	72 (60–80)
Median serum [Na], mmol/l (IQR)	120 (116–122)
Classic categories of hyponatremia, *n* (%)	
Primary polydipsia	22 (7.9)
Hypovolemic hyponatremia	54 (19.4)
Diuretic-induced hyponatremia	71 (25.4)
Hypervolemic hyponatremia	27 (9.7)
SIAD	101 (36.2)
cortisol deficiency	4 (1.4)
comorbidities, *n* (%)	
CNS disease	105 (37.6)
Congestive heart failure	38 (13.6)
Pulmonary disease	78 (28)
Liver cirrhosis	20 (7.2)
Kidney disease	58 (20.8)
Medication, *n* (%)	
Any diuretics	167 (59.9)
Thiazide	125 (44.8)
SSRIs	43 (15.4)
NSAIDs	38 (13.6)
Urine data, *n* (%)	
Complete	214 (76.7)
Calculated urine [Na] plus urine [K]	55 (19.7)
Calculated urine osmolality	7 (2.5)
Calculated urine urea	3 (1.1)

CNS, central nervous system disease; IQR, interquartile range; *n*, number; NSAIDs, nonsteroidal anti-inflammatory agents; SIAD, syndrome of inappropriate antidiuresis; SSRIs, selective serotonin reuptake inhibitors.

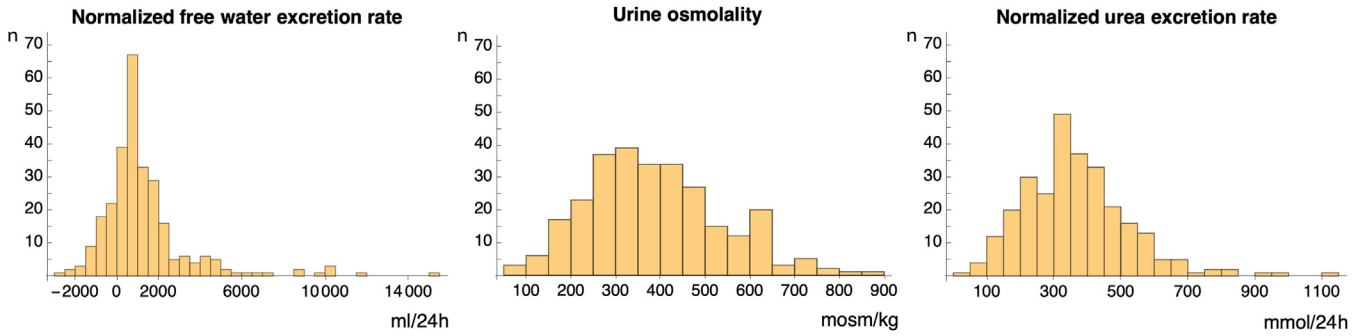

Figure 3. Histogram of normalized free water excretion rate, urine osmolality, and normalized urea excretion rate ($N = 279$). sdna, standard delta sodium.

patients with a complete urine data set (Supplementary Figure S1 and Supplementary Table S1).

Standard Delta Sodium Results

The expected change in the serum sodium concentration due to treatment to the 5th percentile target for HNFWI (sdna1) and IDU (sdna2), and the 95th percentile for LNESE (sdna3) are shown for all 279 patients in Figure 4. The increase in the serum sodium concentration (Table 3) was highest for IDU (sdna2) with a median of 11.8 mmol/l per 24 hours, whereas the median for HNFWI (sdna1) was 7.1 mmol/l per 24 hours and 2.6 mmol/l per 24 hours for LNESE (sdna3). In 68.5% of patients, IDU (sdna2) was quantitatively the most relevant mechanism of hyponatremia, that is, the mechanism with the highest sdna values (Figure 5). HNFWI (sdna1) had the highest sdna values in 30.8% of patients, whereas LNESE (sdna3) was the dominant mechanism of hyponatremia in only 0.7% of patients.

The prevalence of the 3 different mechanisms and their different combinations based on an sdna level of at least 4 mmol/l per 24 hours are shown in Figure 6. Notably, LNESE was present in slightly more than a quarter of patients (Figure 6a), but always in combination with either HNFWI, or IDU, or both (Figure 6b). All 3 mechanisms were present in 15.1% of patients, and half of all patients had a combination of HNFWI and IDU. Less than 25% of patients had only 1 mechanism present, mostly IDU.

Table 2. Distribution of normalized free water excretion rate, urine osmolality, and normalized urea excretion rate ($N = 279$)

Primary measure	min	q5	q25	median	q75	q95	max
Normalized free water excretion rate (ml/24 h)	−2545	−1075	264	884	1684	5094	15,399
Urine osmolality (mosm/kg)	78	163	281	371	484	636	881
Normalized urea excretion rate (mmol/24 h)	44	129	254	346	447	632	1145

min, lowest value; q, percentile; max, highest value.

Unsurprisingly, sdna values were highly dependent on the chosen target levels of net free water intake, dilution of the urine, and nonelectrolyte solute excretion. With less ambitious targets, at percentile levels 25th/75th and 50th, the expected changes in the serum sodium concentration were less pronounced (Supplementary Tables S2 and S3). Whereas the proportion of patients in which HNFWI (sdna1) was the dominant mechanism of hyponatremia remained mostly unchanged, highest sdna results due to LNESE increased progressively from percentiles 5th/95th to 25th/75th and 50th, at the expense of IDU (Supplementary Figure S2).

Prevalence of the 3 different mechanisms and their combinations, based on lower sdna thresholds of 3, 2, and 1 mmol/l per 24 hours with 5th/95th percentile targets are depicted in Supplementary Figure S3. With lower sdna thresholds the proportion of patients with multiple mechanisms increased, so that at a threshold of at least 1 mmol/l per 24 hours, all 3 mechanisms were present in 74.2% of patients.

Traditional Categories and Comorbidities

For subgroups defined by classic hyponatremia categories and typical comorbidities, in Figures 7 and 8, we demonstrate the prevalence of the 3 mechanisms and their combinations, for percentiles 5th/95th and an sdna result of at least 4 mmol/l per 24 hours. In Figure 9, we show for the same subgroups, the frequency of each mechanism having the highest impact on the serum sodium concentration in individual patients.

All patients categorized as having primary polydipsia had HNFWI, but even with the very high threshold of 4 mmol/l per 24 hours, almost 70% exhibited LNESE as well (Figure 7a). The categories of hypovolemic, diuretic-induced, and hypervolemic hyponatremia showed similar distributions of the 3 mechanisms (Figure 7a). In patients classified as SIAD, IDU was present in 97% of patients and was the dominant mechanism in 86.1% (Figure 9a), but HNFWI was also present in 68.3% (Figure 7a). Just 30% of

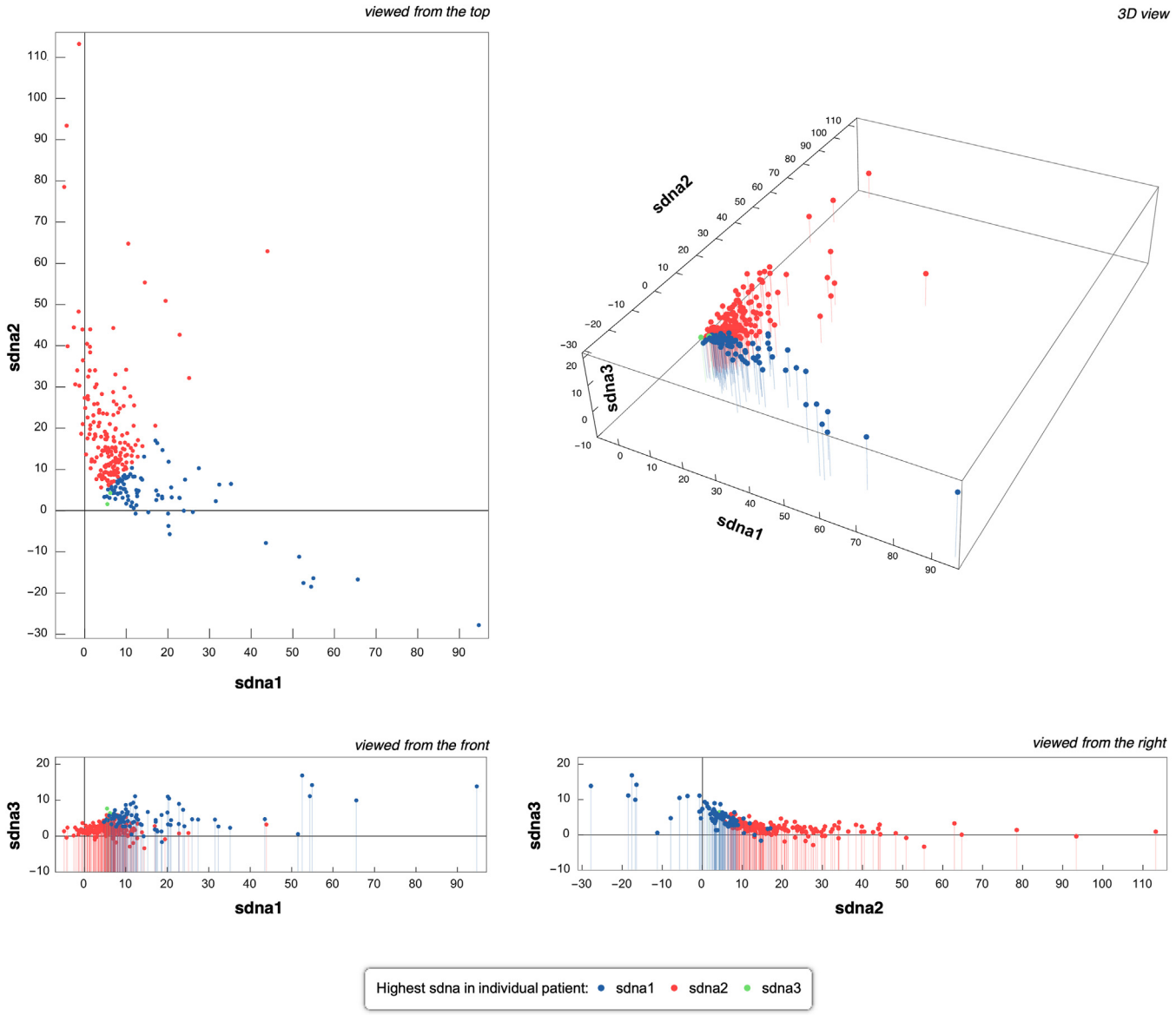

Figure 4. Standard delta sodium values for high net free water intake (sdna1), impaired dilution of the urine (sdna2), and low nonelectrolyte solute excretion (sdna3) for all 279 patients. Each dot represents 1 patient. The highest sdna value in an individual patient is specified by color. All measures in mmol/l per 24 hours and at 5th/95th percentile targets.

SIAD patients showed only impaired urinary dilution (Figure 7b). Rates for only a single mechanism were even less for the other traditional categories (Figure 7b).

Table 3. Distribution of standard delta sodium values[a] ($N = 279$) for high net free water intake (sdna1), impaired dilution of the urine (sdna2), and low nonelectrolyte solute excretion (sdna3)

Sdna values	min	q5	q25	median	q75	q95	max
sdna1, mmol/l/24 h	−4.9	0.0	4.8	7.1	10.2	25.1	94.7
sdna2, mmol/l/24 h	−27.8	0.0	7.0	11.8	18.6	40.4	113.2
sdna3, mmol/l/24 h	−3.3	0.0	1.6	2.6	4.2	7.7	16.9

min, lowest value; max, highest value; q, percentile; sdna, standard delta sodium.
[a]With equivalent treatment targets for net free water intake/normalized free water excretion rate of −1075 ml/24h (5th percentile, see Table 2), for urine osmolality of 163 mosm/kg (5th percentile, see Table 2), and for normalized urea excretion rate of 632 mmol/24h (95th percentile, see Table 2).

Sdna results for the few patients classified as cortisol deficiency ($n = 4$) in the Co-Med study are given in Supplementary Table S4.

In subgroups defined by comorbidities (Figure 8 and Figure 9b), the distribution pattern of the 3 pathomechanism were very similar overall. Notably, patients with liver cirrhosis and kidney disease had very high rates of HNFWI (Figure 8a).

DISCUSSION

Key Finding

Hypotonic hyponatremia should be considered multifactorial in most patients. It can be comprehensively described by different degrees of the following: (i)

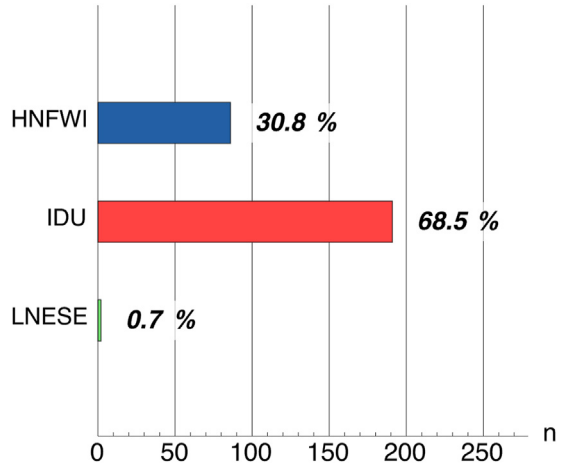

Figure 5. Frequency of each dimension having the highest impact in individual patients (at 5th/95th percentile target). HNFWI, high net free water intake; IDU, impaired dilution of the urine; LNESE, low nonelectrolyte solute excretion.

HNFWI, (ii) IDU, and (iii) LNESE. With the newly developed sdna measure, each mechanisms' influence on the serum sodium concentration can be exactly quantified and compared between and within individual patients.

Diagnosis and Classification

Our results challenge the basic structure of most current diagnostic algorithms of hypotonic hyponatremia.[3–6] These are mostly focused on impaired urinary dilution. HNFWI and LNESE are only considered with very low urine osmolality. This basic dichotomy, based on a certain level of urine osmolality, ignores the continuous nature of the underlying process. The traditional models also depict hypotonic hyponatremia as being due to a single cause.

In contrast to this, we propose a checklist approach to diagnosis and treatment (Figure 1), that acknowledges its multifactorial nature. The 3 basic mechanisms of our model can be uniformly and continuously quantified. We have shown here that LNESE and HNFWI are significant (Figure 4, Table 3) and highly prevalent factors of hyponatremia too (Figure 6). Importantly, this is true for most classic categories of hyponatremia (Figure 7) and typical comorbidities (Figure 8) as well.

Although HNFWI is usually ignored during diagnostic classification by traditional algorithms, limiting oral fluid intake is an integral part of most treatment strategies of hypotonic hyponatremia.[7–9,23] Our approach removes this peculiar disconnect between diagnosis and treatment. Hopefully, it will lead to wider appreciation of the importance of LNESE. We expect that the ability to quantify the 3 dimensions can be used to prospectively tailor treatment strategies to the specific needs of individual patients.

This is exemplified by the case vignettes from the introduction:

Case Vignette 1

Sixty-eight-year-old patient with CKD, thiazide diuretic, and a [Na]serum of 123 mmol/l. Urine osmolality 209 mosm/kg, [Na]urine 19 mmol/l, [K]urine 57.6 mmol/l, [Urea]urine 58 mmol/l, and [Crea]urine 1.4 mmol/l. The sdna values are: sdna1 (HNFWI) 21.2 mmol/l per 24 hours, sdna2 (IDU) 9.6 mmol/l per 24 hours, and sdna3 (LNESE) 1.6 mmol/l per 24 hours.

Current algorithms would classify this patient's hyponatremia as hypovolemic or diuretic-induced. The sdna analysis confirms that urine dilution (i.e., sdna2) is indeed relevantly impaired. But it also demonstrates that

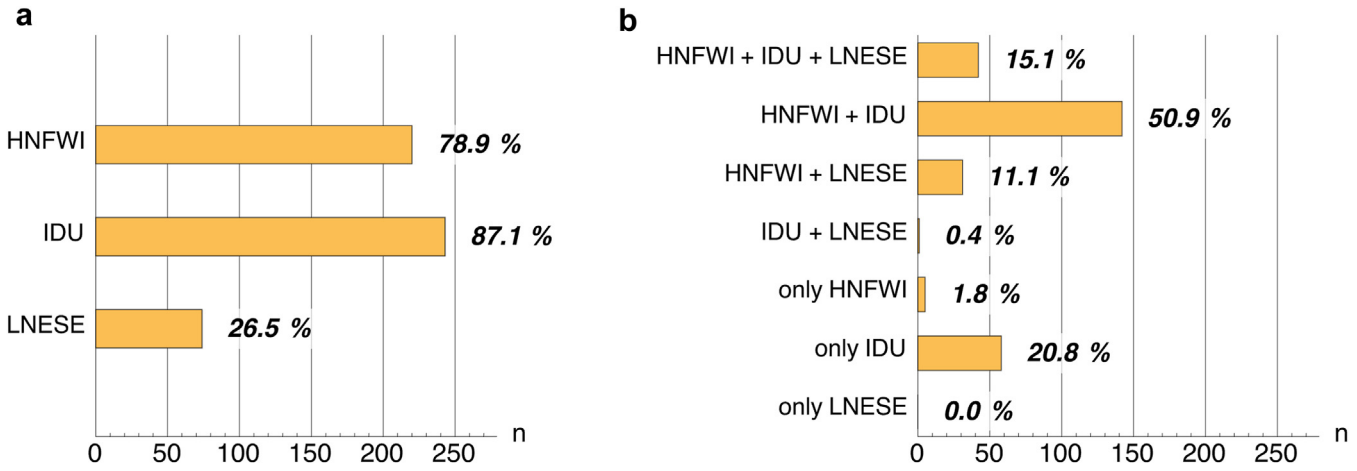

Figure 6. Prevalence of high net free water intake, impaired dilution of the urine, and low nonelectrolyte solute excretion (a) and their different combinations (b) based on a standard delta sodium value of at least 4 mmol/l per 24 hours at 5th/95th percentile targets. HNFWI, high net free water intake; IDU, impaired dilution of the urine; LNESE, low nonelectrolyte solute excretion.

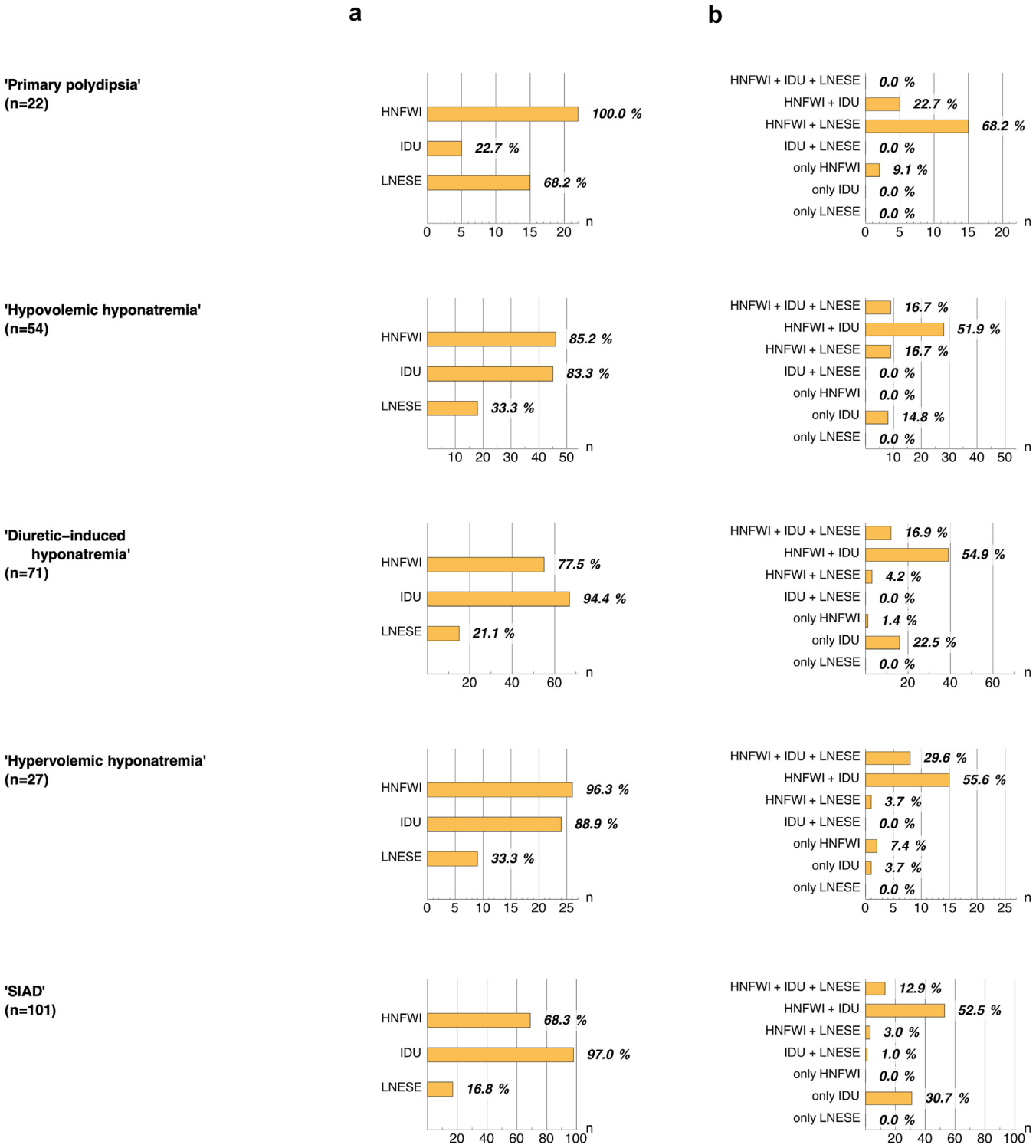

Figure 7. Prevalence of the 3 dimensions (a) and their different combinations (b) in subgroups according to classic hyponatremia categories. Based on standard delta sodium levels of at least 4 mmol/l per 24 hours at the 5th/95th percentile target. HNFWI, high net free water intake; IDU, impaired dilution of the urine; LNESE, low nonelectrolyte solute excretion.

the dominant mechanism of this patient's hyponatremia is by far HNFWI (i.e., sdna1).

Instead of stopping the diuretic and expanding the extracellular volume, limiting oral water intake was all that was needed to correct this patient's hyponatremia.

Case Vignette 2

Seventy-four-year-old lung cancer patient, malaise, and a [Na]serum of 124 mmol/l. Urine osmolality 360 mosm/kg, [Na]urine 41 mmol/l, [K]urine 21.5 mmol/l, [Urea]urine 131 mmol/l, and [Crea]urine 7.63 mmol/l. The sdna values are: sdna1 (HNFWI) 7.4 mmol/l per 24 hours,

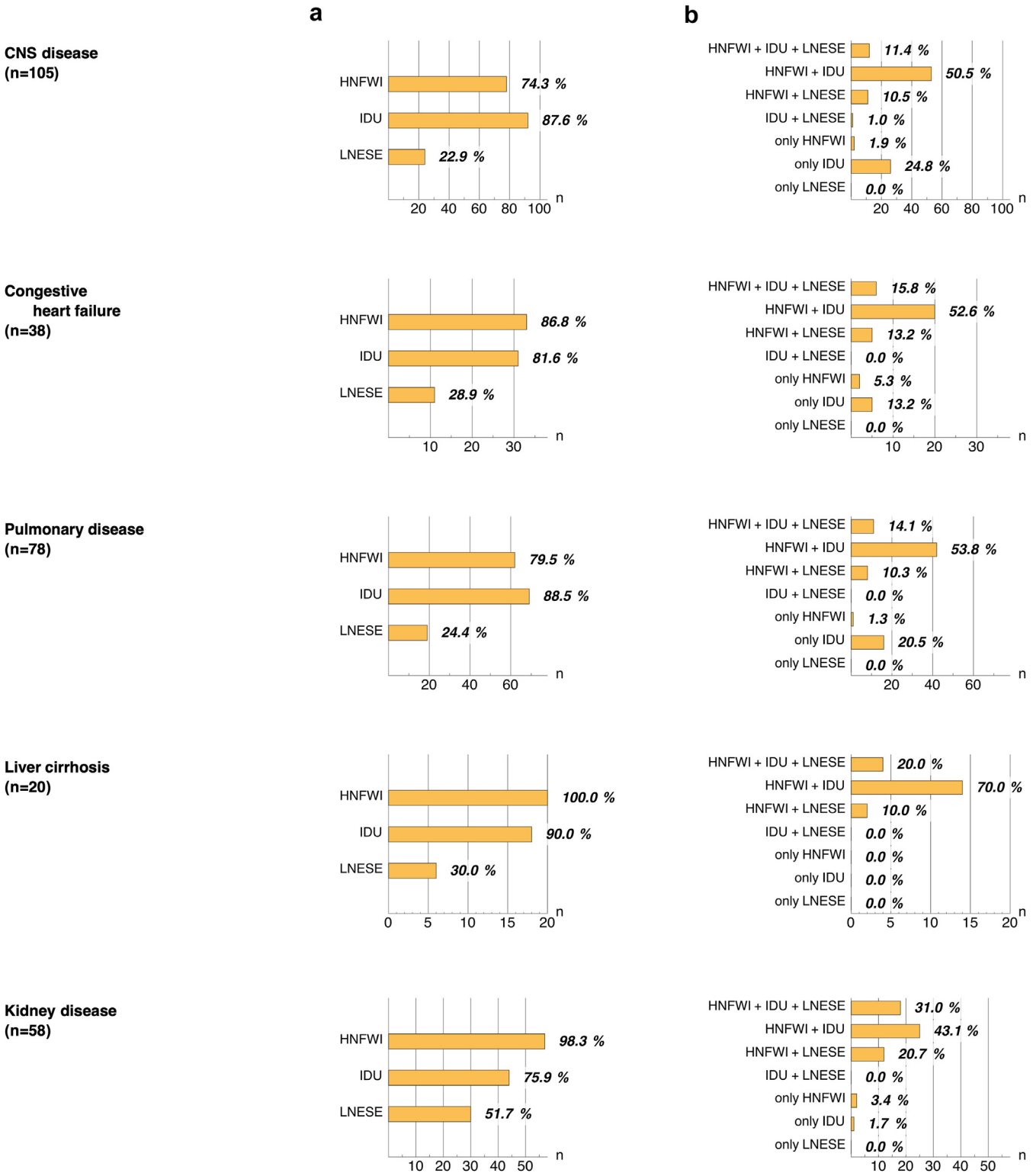

Figure 8. Prevalence of the 3 dimensions (a) and their different combinations (b) in subgroups according to comorbidities. Based on standard delta sodium levels of at least 4 mmol/l per 24 hours at the 5th/95th percentile target. HNFWI, high net free water intake; IDU, impaired dilution of the urine; LNESE, low nonelectrolyte solute excretion.

sdna2 (IDU) 7.4 mmol/l per 24 hours, and sdna3 (LNESE) 4.1 mmol/l per 24 hours.

Traditional algorithms would suggest a diagnosis of SIAD. The sdna values demonstrate the equal importance of HNFWI and a significant contribution of LNESE in this patient as well.

Addressing HNFWI and LNESE thus appeared a promising treatment strategy and therapy with tolvaptan

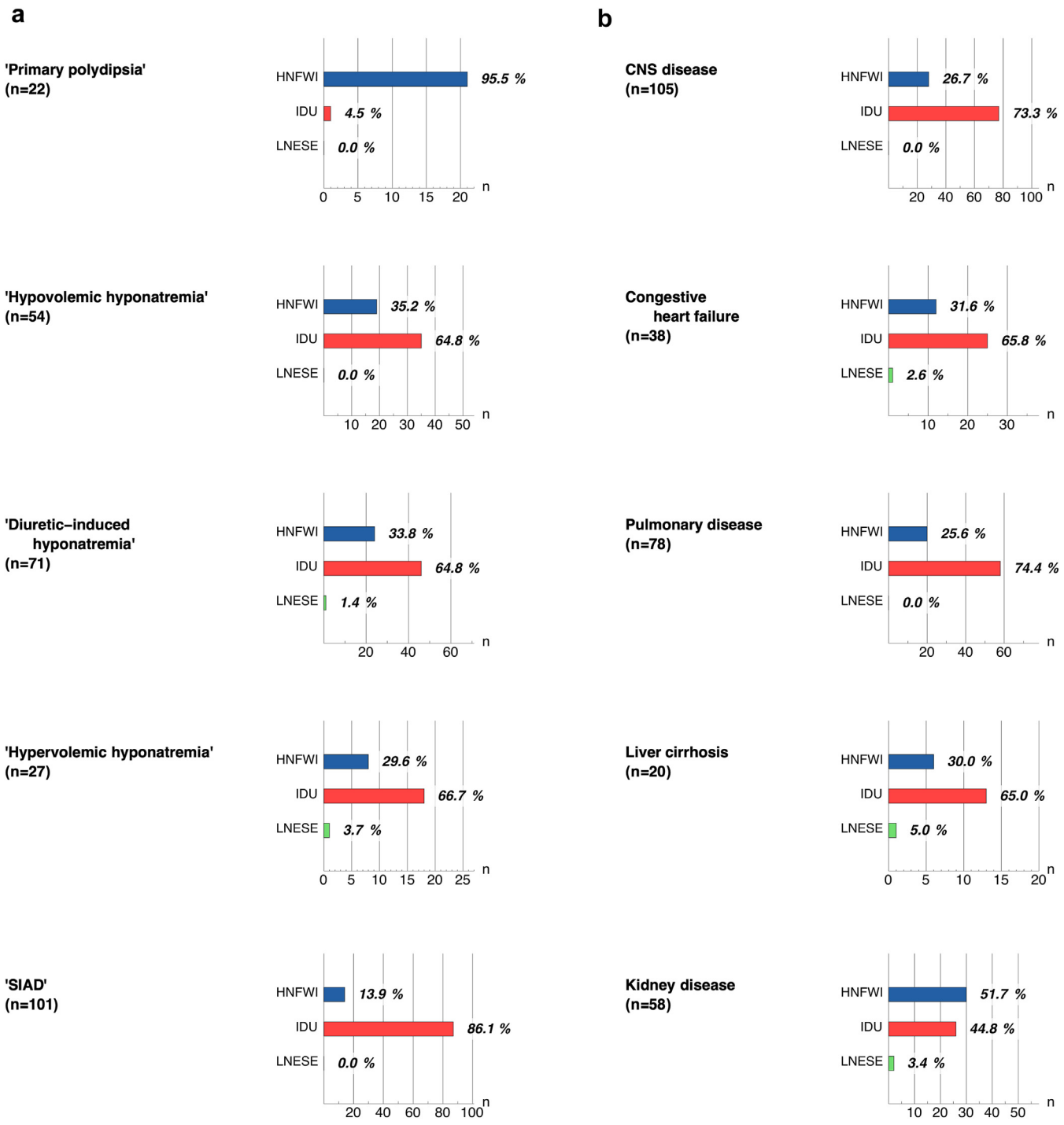

Figure 9. Frequency of each dimension having the highest impact in individual patients in subgroups according to classic hyponatremia categories (a) and typical comorbidities (b) HNFWI, high net free water intake; IDU, impaired dilution of the urine; LNESE, low nonelectrolyte solute excretion.

was deemed unnecessary. Hyponatremia was corrected by limiting fluid and increasing solute and protein intake alone. Urine osmolality did not change significantly during follow-up at all.

To help implement our method into daily clinical practice, we have created an online calculator (Supplementary Figure S4), that provides sdna values for all 3 mechanisms at the 5th/95th percentile levels. The calculator can be used online or downloaded at www.swissnephro.org.

Limitations

The seminal work by Edelman *et al.*[11] has guided the clinical approach to hyponatremia for decades[24] and it is at the core of our method. As is the case with classic models of hyponatremia, we do not consider

possible influences on the serum sodium concentration by shifts in internal balance of sodium, potassium, and water. These modifying processes,[25,26] if they are relevant at all,[27] do not invalidate the overall applicability of the Edelman equation.[28] Moreover, we are not trying to predict an actual future serum sodium concentration. Instead, we calculate theoretical differences, that would result from specific changes to the external free water balance in a standardized human subject.

We want to emphasize again, that the 3 dimensions of our model comprehensively describe the entire electrolyte free water balance and therefore include all influences on the serum sodium concentration due to the balance of sodium, potassium, and water; urinary losses are completely encompassed by osmolality and the amount of nonelectrolyte solutes. Everything else is subsumed under the heading of net free water intake.

Although the theory of our model is valid, the practical assessment does have some limitations. We could only quantify net free water intake indirectly by calculating the urinary electrolyte free water excretion rate. Under steady state conditions the 2 measures would be identical. Therefore, for IDU and LNESE, the calculations are done using the differences between the actual values of urine osmolality and urea excretion rate and their respective targets, whereas for net free water intake, the difference between a steady state intake and the target is used. Although this might underestimate the impact of net free water intake in a patient with rapidly falling serum sodium concentration, and overestimate it with rapidly rising values, the calculations from an assumed steady state situation nevertheless provides an objective and, importantly, clinically usable measure of net free water intake.

We used urinary urea excretion rates to directly evaluate urinary nonelectrolyte solute excretion. The Co-Med study was done in the pre-SGLT2 inhibitor era; however, today glucosuria can contribute regularly and significantly to nonelectrolyte solute excretion.[29,30] Although glucose levels can simply be added to urea for our calculations, the reference values that we used for defining percentile targets might be different today.

We also want to point out that our percentile targets are derived from baseline values and do not necessarily reflect what is achievable during treatment. Such data are currently unavailable. Given that they would obviously be highly dependent on the choice of therapy, it is also unclear whether they would overall be an upgrade to the baseline values we used.

Measures and Standardization

We demonstrated the impact of different percentile targets on the sdna values (Table 3, Supplementary Tables S2 and S3). For further analyses, we chose the 5th/95th percentile level, because its urine osmolality target of 163 mosm/kg is close to the commonly used urine osmolality value of 100 mosm/kg in current hyponatremia algorithms.[4]

We analyzed the effect of different sdna thresholds on the overall prevalence of the 3 mechanisms and their combinations up to a threshold of 4 mmol/l per 24 hours (Supplementary Figure S3). A threshold of 5 mmol/l per 24 hours and higher would have resulted in some patients having no allocated mechanism at all, because the minimum highest sdna result in an individual patient at the 5th/95th percentile target was 4.7 mmol/l per 24 hours (Supplementary Table S5). Even with the highest threshold of 4 mmol/l per 24 hours, we could demonstrate the multifactorial nature of most hyponatremias in the whole cohort (Figure 6) and the different subgroups (Figures 7 and 8).

A central element of our calculations is the use of standardized values for creatinine excretion rate, total body water, and baseline serum sodium concentration. The values for creatinine excretion rate (12.9 mmol/l) and total body water (41.5 l) correspond to median results from population reference data.[21,22] The standard value for serum sodium concentration (120 mmol/l) equals the commonly used upper boundary of severe hyponatremia.[31–33]

It is important to realize, that it is these standardizations that make sdna values a uniform and ubiquitous measure of hyponatremia in all patients, independent of actual creatinine excretion rate, total body water, and serum sodium concentration.

We considered expressing singular sdna values as percentages of the sum of all 3 sdna results in a single patient. We decided against it, because the 3 values are not simply additive physiologically. Instead, they represent expected changes of the serum sodium concentration due to isolated changes of either mechanism. Simultaneous changes in 2 or 3 mechanisms would lead to slightly different results.

Although equivalent percentile targets are essential for gauging and comparing the overall relevance of the 3 mechanisms between different patients, they are not necessary for using sdna values in the care of an individual patient. In fact, attainable percentile targets might be very different for each mechanism in individual patients, and this can be considered when calculating sdna values for treatment planning. We would speculate, for example, that a high percentile target for LNESE (Supplementary Table S6)[34] can be achieved much more easily than an equal lowering of HNFWI (Supplementary Figure S5) or urine osmolality.

CONCLUSIONS

In summary, we present a simple, yet comprehensive model to classify hypotonic hyponatremia from a treatment perspective: We show that most cases of hypotonic hyponatremia should be considered multifactorial and can be objectively defined by 3 exactly quantifiable dimensions.

DISCLOSURE

FB and BM have declared no competing interest. PS reports grants from Nestle, Abbott, Thermofisher, and BmX outside the submitted work. SS reports grants from Fundação Pesquisa e Desenvolvimento Humanitario, during the conduct of the study; personal fees and others from Fresenius; and personal fees from Baxter, Peripal, and Versantis outside the submitted work.

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AUTHOR CONTRIBUTIONS

FB contributed to conceptualization, formal analysis, methodology, writing (original draft, review, and editing). PS and BM contributed to data curation and writing (review and editing). SS contributed to writing (review and editing).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods S1. Derivation of missing urine parameters.

Supplementary Methods S2. Formulas.

Supplementary Reference.

Figure S1. Normalized free water excretion rate, urine osmolality, and normalized urea excretion rate limited to the 214 patients with complete urine data.

Figure S2. Frequency of each dimension having the highest impact in individual patients according to different treatment targets.

Figure S3. Prevalence of high net free water intake, impaired dilution of the urine, and low nonelectrolyte solute excretion based on different sdna thresholds.

Figure S4. Online/downloadable standard delta sodium calculator.

Figure S5. Contour plot of net free water intake dependent on the intake of sodium plus potassium and water.

Table S1. Normalized free water excretion rate, urine osmolality, and normalized urea excretion rate limited to the 214 patients with complete urine data.

Table S2. Standard delta sodium values with 25th/95th percentile targets.

Table S3. Standard delta sodium values with 50th percentile targets/.

Table S4. Standard delta sodium values for the patients categorized as having cortisol deficiency.

Table S5. Distribution of highest standard delta sodium values in individual patients.

Table S6. Normalized urea excretion rate and the corresponding protein intake.

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