Critical Care and Resuscitation 26 (2024) 311–318

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Original Article

Severe intensive care unit–acquired hypernatraemia: Prevalence, risk factors, trajectory, management, and outcome

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ARTICLE INFORMATION

Article history:
Received 7 August 2024
Received in revised form
24 September 2024
Accepted 28 September 2024

Keywords:
ICU-acquired hypernatraemia
Hypernatraemia
Electrolyte-free water clearance
Correction rate

ABSTRACT

Background: Severe intensive care unit–acquired hypernatraemia (ICU-AH) is a serious complication of critical illness. However, there is no detailed information on how this condition develops.
Objectives: The objective of this study was to study the prevalence, risk factors, trajectory, management, and outcome of severe ICU-AH ($\geq$155 mmol·L^{-1}).
Methods: A retrospective study was conducted in a 40-bed ICU in a university-affiliated hospital. Assessment of sodium levels, factors associated with severe ICU-AH, urinary electrolyte measurements, water therapy, fluid balance, correction rate, and delirium was made.
Results: We screened 11,642 ICU admissions and identified 109 patients with severe ICU-AH. The median age was 57 years, 63% were male, and the median Acute Physiology and Chronic Health Evaluation III score was 64 (52; 80). On the day of ICU admission, 64% of patients were ventilated; 71% received vasopressors, and 22% had acute kidney injury. The median peak sodium level was 158 (156; 161) mmolL^{-1} at a median of 4 (1; 11) days after ICU admission. Only eight patients (7%) had urine sodium measurement (median concentration: 17 mmol·L^{-1}). On the day of peak hypernatraemia, 80% of patients were unable to drink due to invasive ventilation; 34% were on diuretics; 25% had fever, and 50% did not receive hypotonic fluids. When available, the median electrolyte-free water clearance was −1.1 L (−1.7; −0.5), representing half of the urine output. After peak hypernatraemia, the correction rate was −2.8 mmol·L^{-1} per day (95% confidence interval: [-2.9 to −2.6]) during the first 3 d.
Conclusions: Severe hypernatraemia occurred in the setting of inability to drink, near-absent measurement of urinary free water losses, diuretic therapy, fever, renal impairment, and near-absent or limited or delayed water administration. Correction was slow.

1. Introduction

Intensive care unit–acquired hypernatraemia (ICU-AH) is a known complication of critical illness and is considered a surrogate for quality of care.[1–3] Hypernatraemia implies a relative deficiency

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https://doi.org/10.1016/j.ccrj.2024.09.004

in total body free water.[4] This often occurs in the context of increased renal and/or extrarenal free water losses, inability to self-regulate free water intake due to sedation, mechanical ventilation, or changes in mental status and decreased renal ability to regulate free water retention.[5–7] ICU-AH is a serious complication associated with alterations in mental status, increased in-hospital length of stay, and hospital mortality.[8–12] Severe ICU-AH (sodium level > 155 mmol·L^{-1}) is associated with a particularly high mortality.[12]

Severe ICU-AH must inevitably first transition through mild and moderate hypernatraemia. Thus, logically, its occurrence represents unsuccessful prevention, diagnosis, and therapeutic response. Consequently, understanding how such severe hypernatraemia develops is critical to its avoidance. Unfortunately, there is no comprehensive published information on the processes and risk factors that should alert clinicians to its likely development, its trajectory towards its peak level, and its return to normal. Additionally, there is a lack of information on how clinicians monitor free water losses and respond or fail to respond to the progressive development of ICU-AH. More specifically, it is unknown whether clinicians use urine measurements to manage free water balance in critically ill patients. Accordingly, we conducted a retrospective cohort study to describe the daily management of hypernatraemia in a general ICU population who went on to develop severe ICU-AH.

We aimed to understand how ICU-AH develops and, in particular, to assess the prevalence of urinary sodium and potassium measurements for the estimation of urinary free water losses. We also aimed to test the hypothesis that severe ICU-AH was partly related to diuretic therapy and to lack of water administration in the 24 h preceding its development. Finally, we aimed to test the exploratory hypothesis that the amount of free water given before and after severe ICU-AH had occurred was insufficient to prevent it and that its correction was slow (defined as a rate of <0.25 mmol·L^{-1}hr^{-1} or <6 mmol·L^{-1} per day).

2. Methods

2.1. Study design and ethical considerations

We conducted a retrospective cohort study in a 40-bed ICU in a university-affiliated hospital. ICU admission policies remained unchanged throughout the study period. This protocol was approved by the Hospital Office of Ethics and Research (Audit/22/Austin/35) and was classified as low risk, with a waiver for the need for individual written consent.

2.2. Patient and data collection

We included all patients admitted to the ICU who experienced severe ICU-AH episodes. Patients admitted to the ICU with hypernatraemia (>145 mmol·L^{-1}) on their first serum sodium measurement were excluded. To avoid confounding variables, we also excluded patients transferred from other ICUs, those under palliative care, or those with a neurological, trauma, fulminant liver failure, or post–cardiac arrest diagnosis, where hypernatraemia might represent a therapeutic intervention aimed at decreasing cerebral oedema. For patients with multiple ICU admissions, only the index episode was considered. Urine and blood measurements including blood gases (arterial oxygen pressure, PaO_2; arterial carbon dioxide pressure, $PaCO_2$ and fraction of inspired oxygen, FiO_2) were exctracted from electronic medical records.

2.3. Definitions

ICU-AH was defined as a serum sodium level above 145 mmol·L^{-1} after ICU admission. Severe ICU-AH was defined by a serum sodium level >155 mmol·L^{-1}. Fever was defined as a recorded body temperature ≥38 °C. Enteral water and dextrose 2.5% or 5% were defined as hypotonic fluids. Five trained intensive care specialists blinded to sodium measurement assessed daily delirium status based on clinical notes using Confusion Assessment Method for the ICU scoring when any mention of hallucination, agitation, disorientation, and/or drug administration for the aforementioned symptoms was reported. Acute kidney injury was diagnosed and staged based on the Kidney Disease: Improving Global Outcomes 2012 definition with the use of Larsen's formula for estimating baseline creatinine function.[13,14] The free water deficit was calculated according to Adrogué and Madias definition.[15] When mentioned, the time of the first hypernatraemia episode refers to the time from ICU admission to the point at which the patient reaches the 145 mmol·L^{-1} threshold. The time of peak sodium level refers to the time from ICU admission to when the peak serum sodium was reached during the ICU admission.

2.4. Urine measurements

Renal electrolyte-free water clearance (*EFWC*) was calculated as follows:[16]

$$EFWC = V \times \left(1 - \frac{U_{[Na+K]}}{P_{[Na+K]}}\right)$$

Table 1
Baseline characteristics.

Variables[a]	**Overall**[b] **(N = 109)**
Demographic	
Age, yr	57 (49; 69)
Sex female	40 (37)
Weight, kg	79 (67; 95)
Admission	
ICU admission source	
Emergency department	28 (26)
Operating theatre/recovery	37 (34)
Other hospital	15 (14)
Ward	26 (24)
Other	3 (3)
Diagnosis	
Cardiovascular	29 (27)
Gastrointestinal	28 (26)
Respiratory	23 (21)
Sepsis	14 (13)
Metabolic	9 (8)
Other	6 (6)
Prognostic scores	
APACHE III score	64 (52; 80)
APACHE III risk of death, %	20 (7; 40)
ANZROD, %	10 (4; 24)
Comorbidities	
Chronic respiratory disease	11 (10)
Chronic cardiovascular disease	4 (4)
Chronic renal disease	8 (7.3)
Immunosuppressed	15 (14)
Chronic liver disease	16 (15)
Lymphoma	4 (4)
Leukaemia	4 (4)
Metastatic cancer	8 (7)
First day in the ICU	
Invasive mechanical ventilation	70 (64)
Vasopressors	77 (71)
Highest serum creatinine, μmol·L^{-1}	123 (80; 168)
Acute kidney injury	24 (22)
Highest white cell count, 10^9L^{-1}	13 (10; 18)

[a] Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ANZROD, Australia New Zealand risk of death; ICU, intensive care unit.
[b] Continuous variables are presented as median (interquartile range). Categorical variables are presented as n (%).

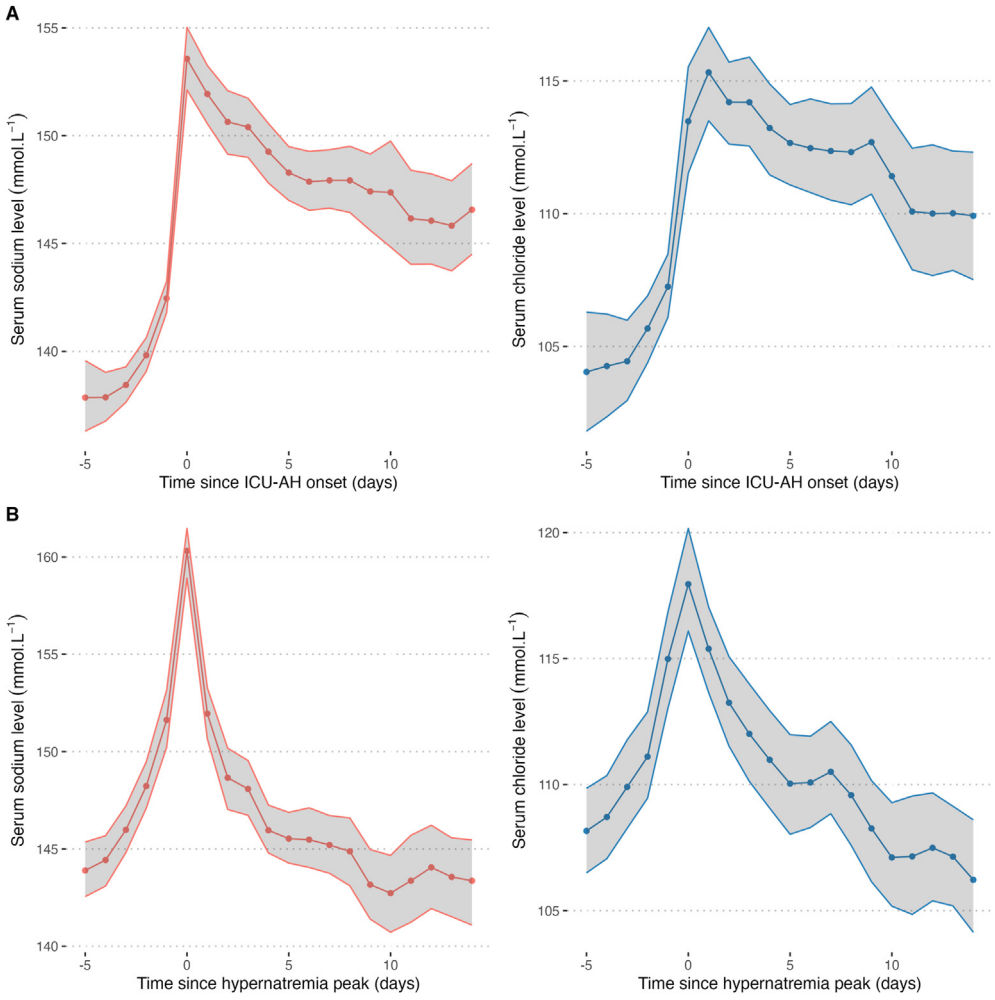

Fig. 1. Time course of serum sodium and serum chloride with respect to **A**: time since ICU-AH onset and **B**: time since peak hypernatraemia. Points represent the daily geometric mean, and shaded areas represent the associated 95% confidence interval (CI). Correction rates were computed using a linear mixed model, with patients treated as a random effect. The correction rate during the 7 days following the first day of hypernatraemia was −0.41 mmol/L per day (95% CI: [-0.48 to −0.34]) mmol·L^{-1} per day. The correction rate during the 3 days following the peak of hypernatraemia was −2.8 mmol/L per day (95% CI: [-2.9 to −2.6]) mmol·L^{-1} per day. Abbreviations: ICU-AH, intensive care unit–acquired hypernatraemia.

where V is the urine output volume, $U_{[Na+K]}$ is the urine [Na + K] molal concentration, and P_{Na+K} is the plasma [Na + K] molal concentration. Plasma [Na + K] molal concentration expressed as mEq per kg of plasma water was derived from the laboratory [Na + K] molar concentration expressed as mEq per L of plasma, assuming the fraction of plasma occupied by water to be 93%.[17,18] Urine [Na + K] molal concentration was considered equal to the laboratory concentration as composed of a relatively small amount of solute dissolved in water. Based on the literature,[19] patients with missing urine potassium measurements had their potassium value imputed at 40 mmol·L^{-1}.

2.5. Outcomes

The primary outcome was the prevalence of urine screening performed from 1 day before to 3 days after the first ICU-AH onset and the peak serum sodium measurement. We chose this period because we reasoned that if clinicians had based their clinical management of ICU-AH on urinary free water losses, such measurements would have been performed during this time.

Secondary outcomes included the amount of hypotonic fluid administered, use of diuretics, and free water administration in the 24 h preceding the development of severe ICU-AH.

Exploratory outcomes included an assessment of the extent to which the amount of free water given before and after severe ICU-AH was insufficient to prevent it and an assessment of whether the speed of its correction was slow (defined as a rate of <0.25 mmol·L^{-1}hr^{-1} or <6 mmol·L^{-1} per day).[20]

2.6. Statistical analysis

Continuous variables are expressed as medians with interquartile range and categorical variables as absolute numbers with percentages. Serum sodium correction rates were computed using a linear mixed model with patients treated as a random effect. Statistical analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna)[21] with the packages dpylr,[22] ggplot2,[23] gtsummary,[24] gt,[25] and nlme.[26]

3. Results

3.1. Study population and baseline characteristics

From July 1, 2015, to December 31, 2021, we screened 11,642 ICU admissions and identified 109 (1.1%) patients with severe ICU-AH (Supplemental Fig. S1). Table 1 summarises their baseline

Table 2
Exposures on the day of the first ICU-AH episode and on the day of peak hypernatraemia.

Variables[a]	On the day of first hypernatraemia episode N = 109[a]	On the day of peak hypernatraemia N = 109[a]
Clinical		
Unable to drink due to invasive ventilation	93 (85)	87 (80)
Diuretic use	43 (39)	37 (34)
Fever	18 (17)	27 (25)
Diarrhoea	20 (18)	33 (31)
Urine output, L	1.9 (0.6; 2.9)	1,5 (0.5; 2,6)
Free water deficit, L	3.6 (2.5; 5.1)	5.7 (4.7; 7.2)
Fluid balance, L	0 (−1,1; +0.7)	0 (−0.9; +0.7)
PaO_2/FiO_2	312 (217; 390)	304 (203; 410)
$FiO_2 > 50\%$	15 (14)	9 (8.3)
Treatment		
Crystalloids given administered		
Administered	52 (48)	54 (50)
Crystalloids volume, mL	0 (0; 760)	0 (0; 710)
Crystalloids intake when administered, mL	800 (340; 1295)	720 (357; 1310)
Hypotonic fluid		
Administered	29 (27)	54 (50)
Enteral water	18 (17)	41 (38)
Dextrose 2.5% or 5%	17 (16)	31 (28)
Total hypotonic volume, mL	0 (0; 18)	0 (0; 910)
Enteral water volume, mL	0 (0; 0)	0 (0; 450)
Dextrose 2.5% or 5%, mL	0 (0; 0)	0 (0; 75)
Total hypotonic volume when administered, mL[b]	500 (100; 755)	950 (525; 1635)
Enteral water volume when administered, mL[b]	205 (80; 600)	680 (300; 1100)
Dextrose 2.5% or 5% when administered, mL[b]	460 (102; 565)	760 (404; 1255)
Total hypotonic volume >200 mL per day	19 (17)	47 (43)
Total hypotonic volume >500 mL per day	14 (13)	42 (39)

Abbreviation: ICU-AH, intensive care unit–acquired hypernatraemia; PaO_2, arterial oxygen pressure; FiO_2, fraction of inspired oxygen.
[a] Continuous variables are presented as median (interquartile range). Categorical variables are presented as n (%).
[b] Total hypotonic volume administered was available for 29 patients on the day of the first hypernatraemia episode and in 54 on the day of peak hypernatraemia. Enteral water volume administered was available for 18 patients on the day of the first hypernatraemia and for 41 patients on the day of peak hypernatraemia. Dextrose 2.5% or 5% administered was available for 17 patients on the day of the first hypernatraemia and for 31 patients on the day of peak hypernatraemia.

characteristics. The median age was 57 years, most patients were male, 69 (63%), and the median Acute Physiology and Chronic Health Evaluation III score was 64 (52; 80). On the day of ICU admission, most patients were mechanically ventilated and on vasopressor, and 22% were admitted with acute kidney injury. None were receiving hypertonic saline or received hypernatraemia as a therapeutic intervention or target.

3.2. Key hypernatraemia timepoints and correction rate

The first hypernatraemia episode occurred at a median of 2 (0; 4) days after ICU admission, at a median sodium level of 147 (146; 156) $mmol \cdot L^{-1}$. The peak sodium level was reached at a median of 4 (1; 11) days after ICU admission, with a median concentration of 158 (156; 161) $mmol \cdot L^{-1}$. The overall correction rate during the 7 days following the first day of hypernatraemia was -0.41 $mmol \cdot L^{-1}$ per day (95% confidence interval: [−0.48 to −0.34]). However, the correction rate during the first 3 days after peak hypernatraemia was -2.8 $mmol \cdot L^{-1}$ per day (95% confidence interval: [−2.9 to −2.6]). The time course for serum sodium and chloride according to the time of first hypernatraemia and the peak hypernatraemia is displayed in Fig. 1.

3.3. Exposures on the first day of ICU-AH and on the day of peak hypernatraemia

On the day of the first hypernatraemia episode, 93 (85%) patients were unable to drink due to invasive ventilation. In addition, 43 (39%) patients were on diuretics, 18 (17%) had a fever, and 20 (18%) had diarrhoea (Table 2). Despite hypernatraemia and ongoing water losses, 80 (73%) patients received 0 mL of hypotonic fluids. The overall median amount of hypotonic fluid administered was 0 mL (0; 18) despite a median urine output of 1.9 L (0.6; 2.9) and an estimated free water deficit of 3.6 L (2.5; 5.1) at that time (Table 2). Enteral water and intravenous hypotonic dextrose (2.5% or 5%) were administered to 18 (17%) and 17 (16%) patients, respectively. When given, the mean enteral water and hypotonic glucose volumes were 205 mL (80; 600) and 460 mL (102; 565), respectively (Table 2). The daily free water balance with respect to the day of ICU-AH onset is displayed in Fig. 2.

On the day before peak hypernatraemia, 91 (84%) patients were already hypernatraemic and 39 (36%) were already in the severe hypernatraemia range. In this setting, the amount of hypotonic fluid administered was 0 for 64% of patients (median of 0 mL [0; 218]), the median urine output was 2.0 L (0.5; 3.3), and the median estimated free water deficit was 3.9 L (2.4; 5.8).

On the day of peak hypernatraemia, 37 (34%) patients were still exposed to diuretics, 54 (50%) received crystalloids, and free water deficit was 5.7 L (4.7; 7.2); 27 (25%) were febrile, and 33 (31%) had diarrhoea (Table 2). The daily free water balance with respect to the day of peak of hypernatraemia is displayed in Fig. 3. The median bicarbonate was 29 $mmol \cdot L^{-1}$ (25; 33), the median base excess was 3.9 $mEq\ L^{-1}$ (0.8; 7.5), the median pH was 7.47 (7.42; 7.51), and the median $PaCO_2$ was 38 mmHg (30; 44). Finally, the median PaO_2/FiO_2 ratio was 304 [203; 410], and the overall fluid balance was 0 L (−0.9; 0.7).

3.4. Urinary electrolyte screening

In the time window from 1 day before to 3 days after the first hypernatraemia episode, only 16 (15%) patients had a urine sample collected. During this time span, 10, eight, and two patients had urine osmolarity, sodium, and potassium measured, respectively. Urinary potassium levels were 42 and 66 $mmol \cdot L^{-1}$. The

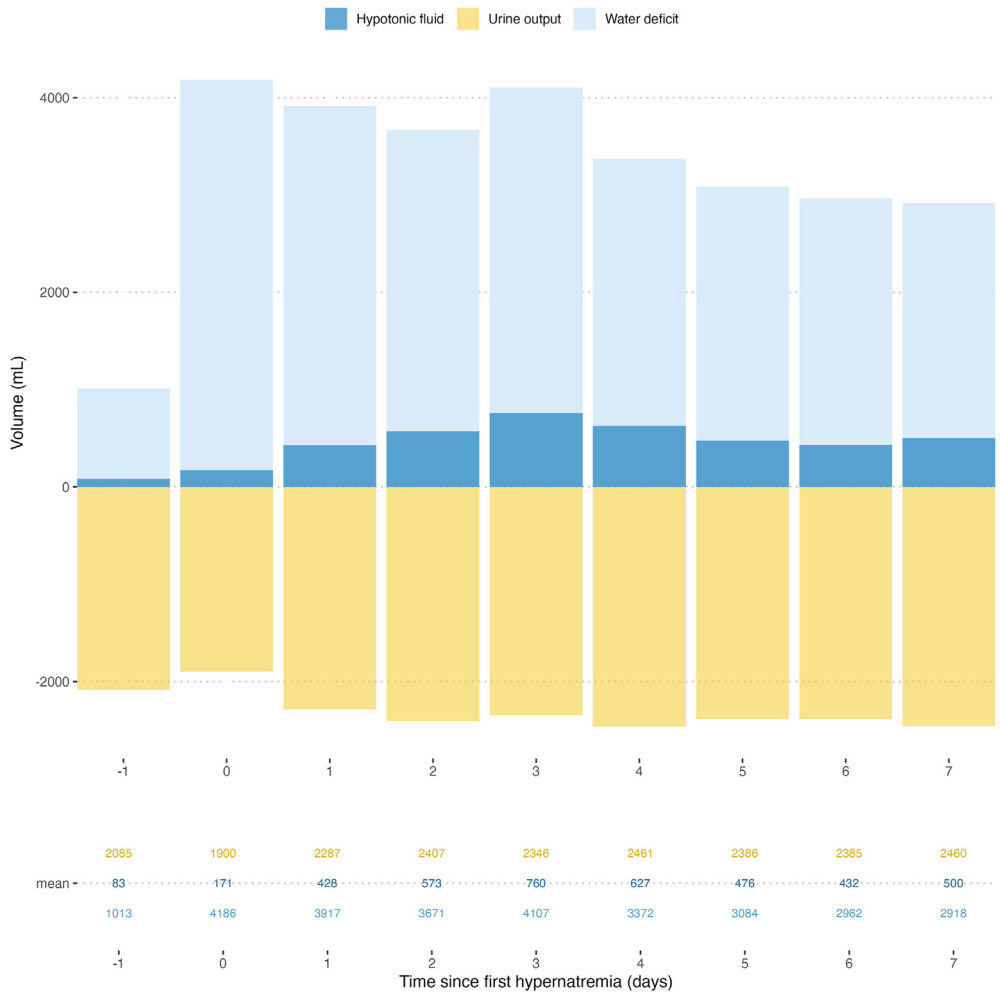

Fig. 2. Free water deficit, hypotonic fluid volume, and urine output from the day when hypernatraemia first developed.

median urine osmolarity was 532 mOsm L^{-1} (512; 608) (Fig. 4). However, the median urine sodium concentration was 17 mmol·L^{-1} (12; 31) (Fig. 4), demonstrating a dissociation between urinary osmolarity and tonicity. The median electrolyte-free water clearance was estimated at −1.1 L per day (−1.7; −0.5), indicating that half of the urine output was electrolyte-free water.

3.5. Treatment and outcome

At 48 h after the first ICU-AH onset, four patients had died, and nine patients were discharged to the ward. Among the 96 patients who stayed in the ICU, by 48 h, 52 (54%) received hypotonic fluids, a total of 820 mL (410; 1420) per day, with enteral water in 37 (39%), 690 mL (400; 1000) per day; and hypotonic dextrose in 27 (28%), 580 mL (337; 1200) per day. Sodium level correction failed in 78 (81%) patients, including 35 (36%) patients who developed severe hypernatraemia. A diagnosis of delirium was made in 27 (28%) patients during this period. The duration of ICU stay was 11 d (4; 23), duration of hospital stay was 24 days (15; 46), and mortality at hospital discharge occurred in 24 (25%) patients.

4. Discussion

4.1. Key findings

Our assessment of the prevalence, risk factors, trajectory, management, and outcome of severe ICU-AH provides several insights. First, it confirms our primary hypothesis that the therapeutic response by clinicians was mostly blind to ongoing urinary free water losses because measurement of urinary electrolyte-free water loss occurred in <10% of patients. Moreover, it demonstrates that, on the day before peak hypernatraemia onset, most patients were already hypernatraemic, and despite a minimally positive median fluid balance and an excellent median PaO_2/FiO_2 ratio, 40% of patients remained exposed to diuretics, yet no free water administration occurred in three out of four patients on the day of first hypernatraemia. Finally, we found that once severe hypernatraemia had occurred; its correction was slow.

4.2. Relationship to previous studies

In 1999, Kees et al. demonstrated that despite frequent sodium level measurements, clinicians commonly handled ICU-AH with nonexistent or inadequate responses.[1] The reason for such non-responsiveness remains unknown. In a comprehensive case–control study, Hoorn et al. demonstrated that ICU-AH was triggered by iatrogenic water losses corrected with too little water or was not treated with free water at all.[5] These results are consistent with our findings and suggest that such lack of free water administration may be common. In ICU patients, only two randomised controlled trials have investigated interventions in hypernatraemic patients. They first assessed the additional effect of spironolactone in attenuating a rise in serum sodium in mechanically ventilated patients.[27] They second compared the effectiveness

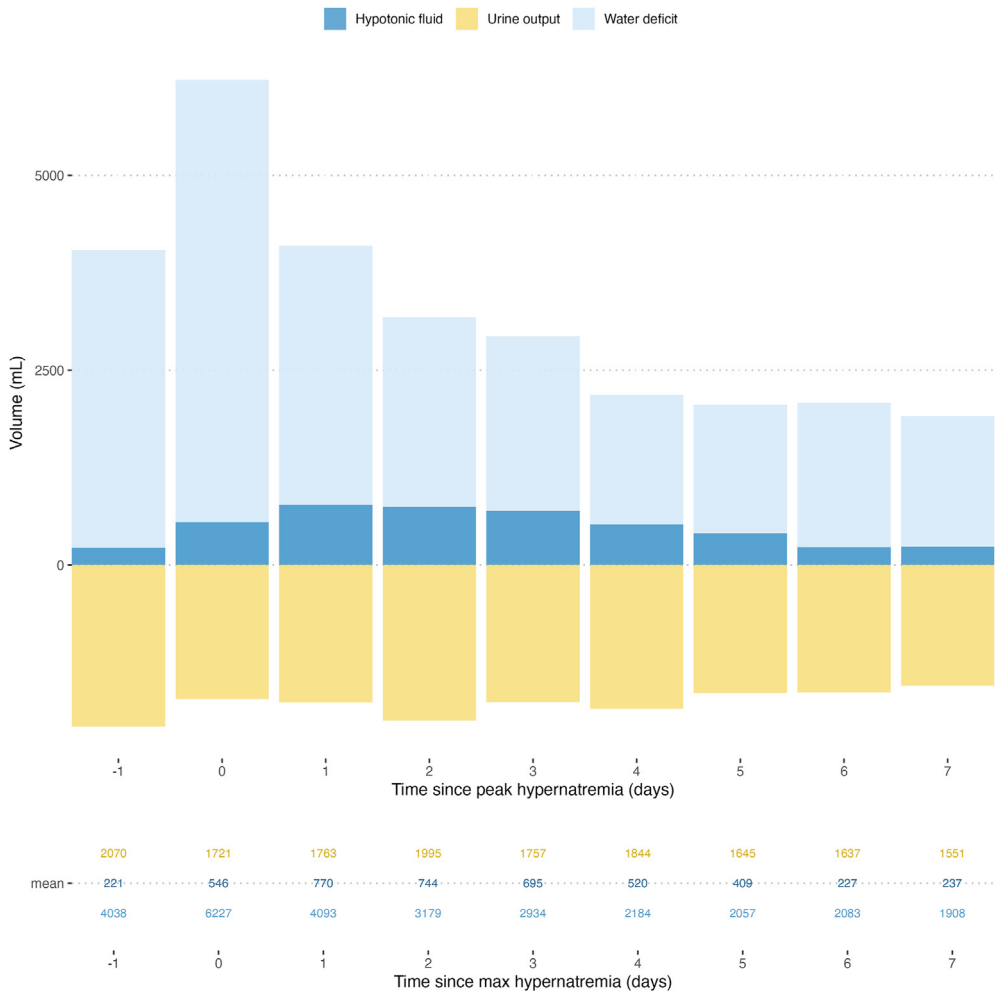

Fig. 3. Free water deficit, hypotonic fluid volume, and urine output with respect to the day when peak hypernatraemia occurred.

of a 25-mg dose of hydrochlorothiazide.[28] Both found no significant impact on serum sodium. These failures may be explained by the small sample size, trial design, and the fixed nature of the intervention. However, blinding to the patient's free water losses may be a key element to explain the failure of such interventions.

To the best of our knowledge, the prevalence of the kind of urinary electrolyte measurements recommended to estimate free water losses[29] has not been previously reported. Lindner et al. demonstrated their usefulness in estimating the amount of free water lost in the urine through electrolyte free water calculations.[6] These investigators reported increased electrolyte-free water losses during ICU-AH development at a median of 1419 mL per day (1052; 1923) or about half of urinary volume. Such observations are consistent with our observations. They also demonstrated how relying on urine osmolarity is misleading in critically ill patients. This is due to the high urinary urea concentration in such catabolic patients, which increases osmolarity but decreases tonicity (electrolyte-free water). Our limited findings of high urinary osmolarity but low urinary sodium are aligned with such notions.

The inadequate amount of free water given in response to ICU-AH has been previously reported and is consistent with our results.[5,30] Recently, in a single-centre retrospective cohort study, Suzuki et al. demonstrated that giving water was an effective treatment for ICU-AH.[31] These results are consistent with previous studies reporting that the mortality rate was consistently lower in patients with rapid hypernatraemia correction (from 0.1 $mmol \cdot L^{-1}$ hr^{-1} to 0.5 $mmol \cdot L^{-1}$ hr^{-1}).[20,32,33] However, to date, no randomised control trial has investigated how best to prevent and treat ICU-AH using such treatments. Our results build upon this current body of literature and highlight the need for such a study.

The association of ICU-AH with mortality has previously been extensively reported.[8–12] However, ICU-AH may contribute to delirium, and its relationship with delirium deserves specific investigation and targeted management.

4.3. Study implications

Our observations suggest that severe ICU-AH follows from a failure in the management of an existing mild or moderate hypernatraemic episode. They also suggest that urine electrolyte measurements are likely not performed often enough to guide the estimation of urinary free water losses. We were able to show that calculating electrolyte-free water is feasible in critically ill patients. This calculation provides an estimate of the amount of free water excreted in the urine, complementing the overall picture with the free water deficit and tonicity of intakes. We propose that this approach could assist clinicians in preventing major iatrogenic events such as severe ICU-AH, although this has yet to be demonstrated in clinical trials. Our results also suggest that consequences of fever and diarrhoea on such losses may not be sufficiently

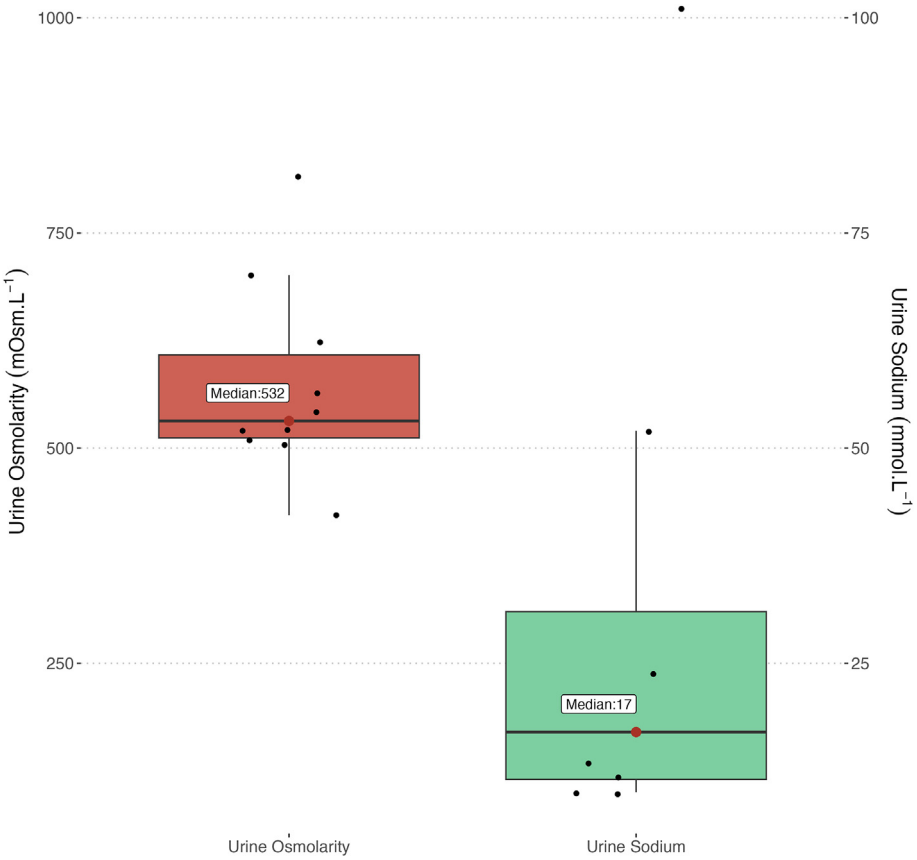

Fig. 4. Urinary sodium and urinary osmolarity when measured.

accounted for. Finally, the findings that the administration of water was absent, insufficient, and/or delayed and that correction was slow, suggesting the need for randomised controlled trials aiming to prevent severe ICU-AH by the systematic estimation of water deficit and losses and their early correction.

4.4. Strengths and limitations

Our study carries several strengths. First, it is the only study of this kind in an ICU setting. Second, the granularity of the data collected allowed us to present a detailed and comprehensive description of the development, risk factors, trajectory, treatment, and monitoring of severe ICU-AH. Third, our findings are highly consistent with previous literature emphasising its likely representativeness to other general ICUs. Finally, the recency of our results and its similarity to previous work from the past century demonstrates the need for fresh investigations and action in the field.

We acknowledge some limitations. First, the retrospective and single-centre nature of our study exposes our results to all the pitfalls of such a design. Therefore, our findings are essentially hypothesis-generating and may not be representative of other settings. Second, it is possible that our ICU medical staff members were uniquely inattentive to the prevention and treatment of severe hypernatraemia. However, the prevalence of severe hypernatraemia in our ICUs was only just above 1% of admissions. Third, although the paucity of urine measurements performed represents one of our key findings, its infrequent assessment also affected the robustness of our estimated free water losses. Nonetheless, our findings of low sodium and high osmolarity are in keeping with the literature.[7] Fourth, we could not measure insensible losses due to perspiration, which are typically low in sodium and represent an additional source of loss of free water.[34] Such water losses typically increase by 2–3 mL kg^{-1} per day with an increase of 1° in temperature and likely contributed to hypernatraemia.[34] Fifth, the retrospective design limited our ability to explore the extracellular compartment (sodium balance) as it relies mainly on clinical symptoms unlikely to be rigorously reported in clinical notes. Finally, the relatively small sample size of our cohort should be taken into consideration when interpreting our results.

5. Conclusion

In a tertiary institution in a resource-rich country, severe hypernatraemia occurred in approximately 1% of ICU patients. Its occurrence was associated with the uncommon measurement of urinary electrolytes, increased urinary loss of free water secondary to diuretics, renal impairment, catabolic urinary urea excretion, and loss of water through fever-associated perspiration and diarrhoea. In this setting, there was near-absent or limited or delayed administration of electrolyte-free water, and when such electrolyte-free water was administered, the amount was only sufficient to correct hypernatraemia at a very slow rate. These findings suggest the need to develop a systematic approach to the prevention and treatment of severe ICU-AH and to conduct trials aimed at finding ways to achieve avoidance of this condition.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediт authorship contribution statement

Conceptualization: A.C and R.B; Methodology: A.C and R.B; Software: A.C; Validation: A.C and R.B; Formal analysis: A.C and R.B; Investigation process: A.C, A.P and R.B; Resources: A.C and R.B; Data Curation: A.C, A.P, O.P, S.R, P.R, A.M, S.S, Y.H, N.P and N.K; Writing - Original draft: A.C and R.B; Writing - Review & Editing: All authors; Visualization: A.C; Supervision: R.B; Project administration: G.E.

Conflict of interest

Rinaldo Bellomo is the Editor-in-Chief of Critical Care and Resuscitation Journal. The other authors do not have any conflict of interest to declare.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2024.09.004.

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