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Original Research

Severe symptomatic hyponatremia in Europe: insights into current clinical practice

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Abstract

Introduction: For the treatment of severe symptomatic hyponatremia, the European Society of Endocrinology (ESE) guidelines (2014) recommend a bolus-wise strategy using hypertonic saline (HTS). However, there are recent controversies regarding the risk of overcorrection and osmotic demyelination syndrome (ODS), leading to significant heterogeneity in practice. The aim of this survey was to evaluate clinical practices and perspectives of endocrinologists across Europe in managing severe symptomatic hyponatremia.

Methods: A web-based anonymous cross-sectional survey (REDCap®), endorsed by ESE, was disseminated from 06, 2024 to 02, 2025. Data were analyzed using R-Studio.

Results: A total of 662 responses were received. After excluding incomplete and non-European responses, 439 responses from 36 countries were analyzed. Most responses were received from university hospitals (68.6%) and senior clinicians (68.1%). Thirty-one percent of clinicians had experience using both bolus and continuous infusions in managing severe symptomatic hyponatremia, while sole bolus or continuous infusion therapy was preferred by 32% and 23%, respectively. Preferred bolus dosage and strength were 3% 100 mL (28%) and 3% 150 mL (19%), while 5% preferred a weight-based dosage. Most (84%) clinicians preferred one bolus infusion followed by a blood test before repeating a second. Thirty-four percent of respondents had encountered ≥1patient with suspected or confirmed ODS in their practice, with 55% reported ODS being associated with sodium overcorrection.

Discussion: This is the first European survey on the management of severe symptomatic hyponatremia, offering valuable insights into real-life clinical practice. Our findings highlight ongoing uncertainties in treatment strategies and underscore the need for future research and evidence-based review of the ESE guidelines.

Keywords: hyponatremia, hypertonic saline, osmotic demyelination syndrome, overcorrection

Significance

Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is associated with adverse clinical outcomes. The European Society of Endocrinology published guidelines to manage hyponatremia in 2015, but practice in the real world varies significantly. This is the first survey to evaluate the perspective and practices of European clinicians on the management of severe symptomatic hyponatremia. The results from this survey demonstrate that there is significant heterogeneity in real-world practice among European physicians. The findings from this survey highlight several uncertainties in the field, which should drive the direction of future research and an evidence-based review of the European guidelines.

Background

Hyponatremia (serum sodium concentration <135mmo/L) is the most frequently encountered electrolyte disorder, occurring in up to 30% of hospitalized patients.[1] Chronic hyponatremia is linked to adverse clinical outcomes, including cognitive impairment, gait instability, and osteoporosis.[2,3] The onset of acute symptomatic hyponatremia is defined as less than 48 hours. In acute settings, biochemical severity is usually moderate (serum sodium <130 mmol/L) to profound (serum sodium <125 mmol/L).[1,4] The rapid onset of hyponatremia can be particularly dangerous, leading to an osmotic influx of water into brain cells. This may result in raised intracranial pressure, cerebral oedema, and severe neurological symptoms.[2] If not recognized and treated urgently, this can progress to cerebral herniation and fatal outcomes.[5,6] Inpatient mortality rates as high as 50% have been observed in some studies of patients with severe hyponatremia (plasma sodium <120 mmol/L).[7,8] Hypertonic saline (HTS) infusion

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can rapidly and effectively increase serum sodium levels, thereby improving the outcomes in patients with severe symptoms due to acute hyponatremia.[9,10] The European Society of Endocrinology (ESE) proposed guidelines in 2014 to standardize the use of HTS.[1] The guidelines recommend a bolus-wise strategy to administer 3% HTS to swiftly increase sodium levels by 5 mmol/L by administering 2 150 mL infusion boluses. The guidelines also limit the maximum correction rate to 10 mmol/L in the first 24 hours to avoid overcorrection to reduce the risk of osmotic demyelination syndrome (ODS). In patients with risk factors for ODS (eg, hypokalemia, malnutrition, alcoholism), a stricter correction limit of a maximum of 8 mmol/L in the first 24 hours is recommended. Desmopressin, a synthetic analog of vasopressin, has been proposed as an option to prevent or reverse overcorrection by promoting water reabsorption in the collecting ducts[11-14] However, the latest guidelines do not recommend routine use due to insufficient evidence at the time of guideline publication.

There are recent controversies regarding acute hyponatremia treatment regimes, leading to significant heterogeneity in practice. First, several observational studies have reported that the risk of overly rapid correction—including in the treatment of severe symptomatic hyponatremia in real-world settings- is substantial, with incidence rates ranging from 17% to 45%.[11,15-17] Second, likely due to concerns regarding overcorrections, a recent UK survey demonstrated a significant heterogeneity in clinical management of severe hyponatremia treatment in general and HTS treatment in particular.[4] In contrast to the latest guidelines, most clinicians preferred a more conservative approach when it came to administering consecutive HTS boluses. Furthermore, a great deal of variation in strength and volume of the HTS was evident.[4] On the other hand, a causal relationship between overly rapid correction and ODS has been questioned lately by McMillan et al. In a retrospective, multi-center, cohort study of 22.858 hospitalized patients, the authors report an ODS rate of only 0.05% despite an overly rapid correction rate of almost 18%.[18]

Given the existing uncertainties in the management of hyponatremia, this project aimed to evaluate the clinical practices and perspectives of endocrinologists across Europe in managing severe symptomatic hyponatremia, and to explore potential variations in clinical practice. This survey provides a comprehensive and contemporary overview of clinical practices across Europe and may inform future guideline development by offering insights into bolus strategy, HTS concentrations, and sodium monitoring protocols.

Methods

A web-based anonymous and cross-sectional survey was employed for this project. This survey was developed by endocrinologists from Sheffield and Basel teams jointly, using insights gained from a preliminary survey for UK endocrinologists.[4] The survey questions were divided into 3 main sections ie, scope of practice, use of HTS, and overcorrection/ODS. A total of 13 multiple-choice-based questions with single-select options were included in the survey, which took approximately 5 minutes to complete. The REDCap® platform was used to develop surveys and accept responses online. The platform supported responses from computers, tablets, and smartphones. The survey participation was voluntary. The full survey questions are available in the Appendix (Figure S3).

The survey was endorsed by the ESE, and invitations to all ESE members were sent out via the ESE monthly newsletter on June, 28, 2024 and via separate email on July, 18, 2024. Link to survey with description was also shared via social media platforms (X formerly called Twitter and LinkedIn) on July, 1, 2024. To get a representative number of further disciplines, the survey was also sent out via an emergency medicine mailing list on October, 3, 2024 and Nephrology mailing list on January, 9, 2025. The responses were recorded anonymously except when the survey participants volunteered to share their email addresses at the end of the survey. All data were stored securely in the database of the University of Basel. Since the survey did not include collecting patient or clinical data and only sought the opinion of healthcare professionals, ethical approval was not required. The research complied with the Declaration of Helsinki.

No formal sample size calculation was required for this survey, however, a target sample size of 500 participants was considered adequate. The data generated from this survey comprised of discrete variables and therefore will be expressed as frequencies and percentages. Missing data from this survey were not replaced or imputed. Comparative analyses were performed using *chi-square* (X^2) test using R 4.4.2 or higher version.

Results

Baseline characteristics

Survey responses were collected from June 2024 to February 2025. A total of 662 unique responses were received. After excluding incomplete and non-European responses, 439 responses were included in the analyses. Responses were available from 36 countries European countries with demographical distribution shown in Figure 1, Figure S1. Clinical specialties represented were endocrinology ($n = 335$, 76.3%), internal medicine ($n = 46$, 10.5%), nephrology ($n = 25$, 5.7%), and intensive care ($n = 6$, 1.4%). Most responses were submitted from University/Tertiary Hospitals ($n = 301$, 68.6%) and by senior clinicians, ie, professors and consultants ($n = 299$, 68.1%, Table 1).

Initial treatment

Thirty-one percent of clinicians ($n = 135$) had experience using both bolus and continuous infusions in managing severe symptomatic hyponatremia, while sole bolus or continuous infusion therapy was preferred by 32% and 23%, respectively (Figure 2). In total, 14% ($n = 63$) based their initial treatment strategy depending on the cause of hyponatremia (Table S1A).

Based on initial treatment strategy, responses for strength of saline infusion were divided into the subgroups "bolus-only strategy" and "continuous infusion only strategy." Strength of saline most often used was 3% in both treatment strategies (bolus only strategy: $n = 107$, 76%, continuous infusion only strategy: $n = 60$, 60%) (Figure 3A and B). Combination of strength/volume most often used was 100 mL of 3% saline bolus ($n = 124$, 28%), followed by 150 mL of 3% saline ($n = 85$, 19%), and 3% saline in a weight-based approach ($n = 21$, 5%, Figure 3C).

Treatment monitoring

Correction targets for sodium rise in first 24 hours were most often stated as ≤8 mmol/L ($n = 170$, 39%) and ≤10 mmol/L

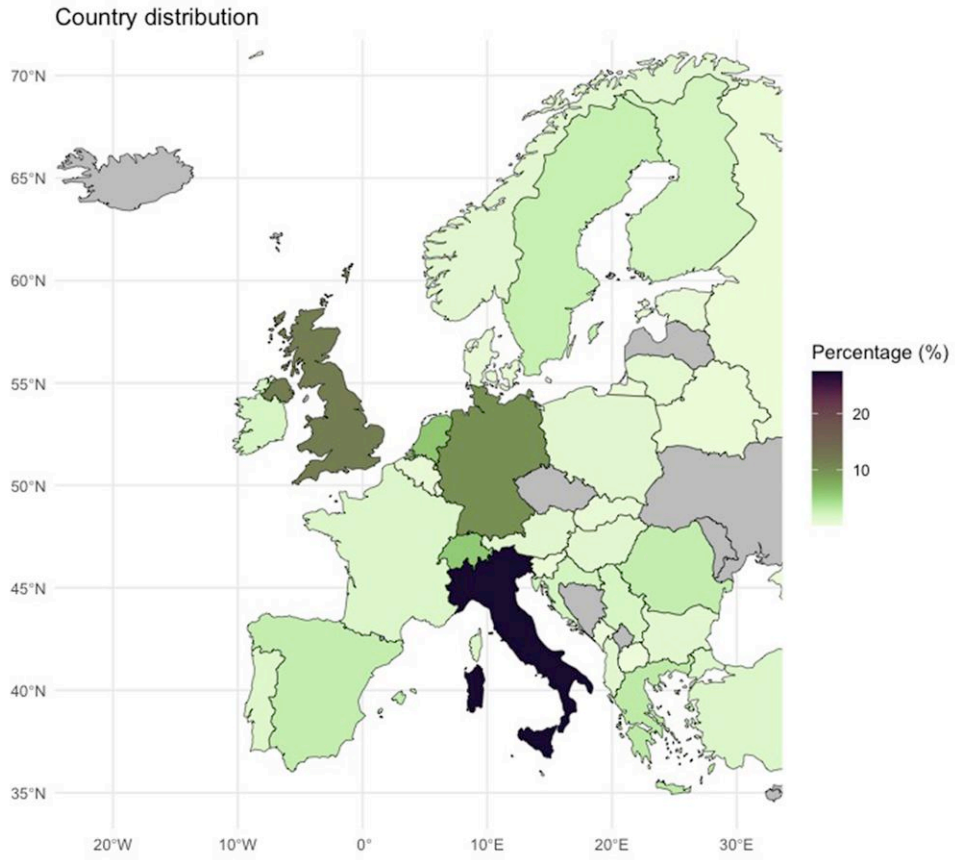

Figure 1. Country distribution across Europe. Distribution of survey responses based on country of residence, expressed as percentage (color gradient, gray = zero response from respective country). Responses were available from total of $n = 36$ different European countries.

Table 1. Baseline characteristics of survey responses.

Overall	
Responses (n)	439
Clinical department	
Endocrinology	335 (76.3)
Internal medicine/other medical department	46 (10.5)
Emergency medicine	26 (5.9)
Nephrology	25 (5.7)
Intensive care	6 (1.4)
Others	1 (0.2)
Type of hospital	
University/tertiary hospital	301 (68.6)
District general/secondary hospital	138 (31.4)
Clinical role	
Consultant/professor	299 (68.1)
Resident/trainee	134 (30.5)
Others	6 (1.4)

Data are expressed as total number and percentage (%).

($n = 162$, 37%, Figure 4A). In the absence of seizures, most ($n = 281$, 84%) clinicians preferred a sodium check after first bolus before repeating a second (Figure 4C). In this context, 86 percent of respondents had at least some experience with using venous blood gas sodium in HTS treatment (sometimes: $n = 188$, 43%, mostly: $n = 126$, 29%, always: $n = 62$, 14%, never: $n = 60$, 14%, Figure 4B). HTS treatment was equally often stated as administered in "intermediate/intensive care only" ($n = 186$, 43%) and "both intermediate/intensive care and general ward" ($n = 188$, 43%, Figure S2)

Overcorrection and osmotic demyelination syndrome

The majority of respondents have infrequently seen overcorrection in clinical practice ($n = 218$, 53%, Figure 5A). In the case of overcorrection, dextrose 5% was administered most often ($n = 203$, 50%, Figure 5B) followed by combined dextrose and desmopressin ($n = 109$, 27%). However, significant experience in using desmopressin for overcorrection was lacking in most respondents ($n = 239$, 59%). If a desmopressin was administered, a reactive approach (administration based on rapid changes in serum sodium concentration or high urine output) was most often used ($n = 96$, 24%, Figure 5C), followed by a rescue approach (administration after overcorrection targets are exceeded or when ODS is imminent) of desmopressin ($n = 50$, 12%). A proactive approach (prophylactic DDAVP clamp) was only rarely used.

Thirty-four percent of respondents had encountered ≥1patient with suspected or confirmed ODS in their practice (Figure 6A). The amount of ODS encounters ranged between one ($n = 60$, 47%) and 2 to 4 encounters in most survey respondents ($n = 60$, 47%, Figure 6B). In case of ODS experience, ODS diagnosis was most often based on both clinical and radiological diagnosis ($n = 86$, 62%, Figure 6C) and associated with sodium overcorrection ($n = 77$, 55%, Figure 6D).

Discussion

This is the first European survey on severe symptomatic hyponatremia, offering insights into real-life practice and management.

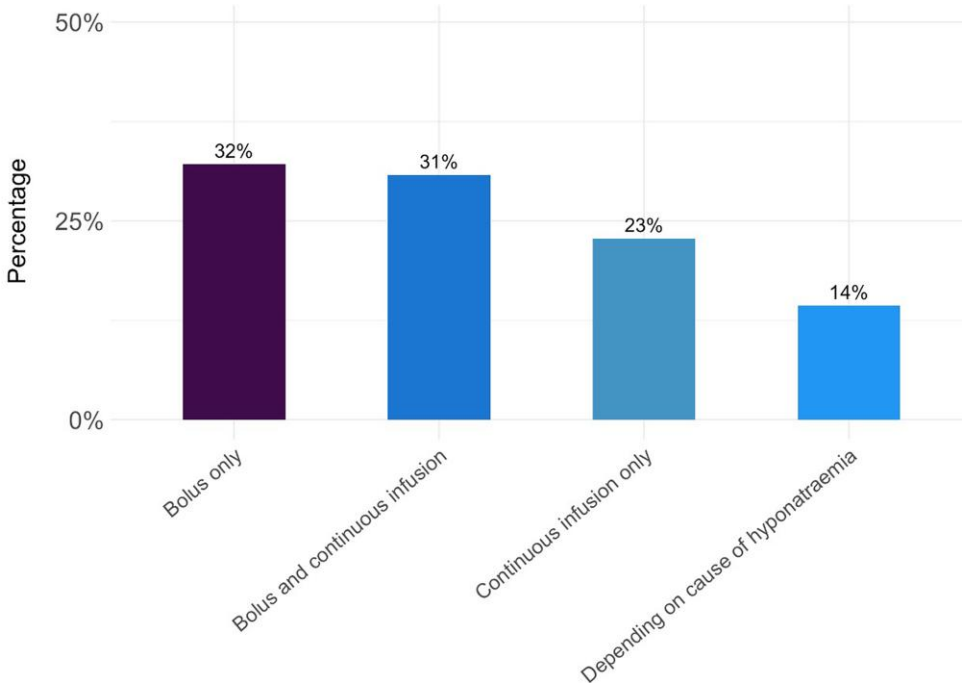

Figure 2. Bolus vs. continuous infusion. Survey responses on initial treatment strategy (expressed as percentage, total $n = 439$).

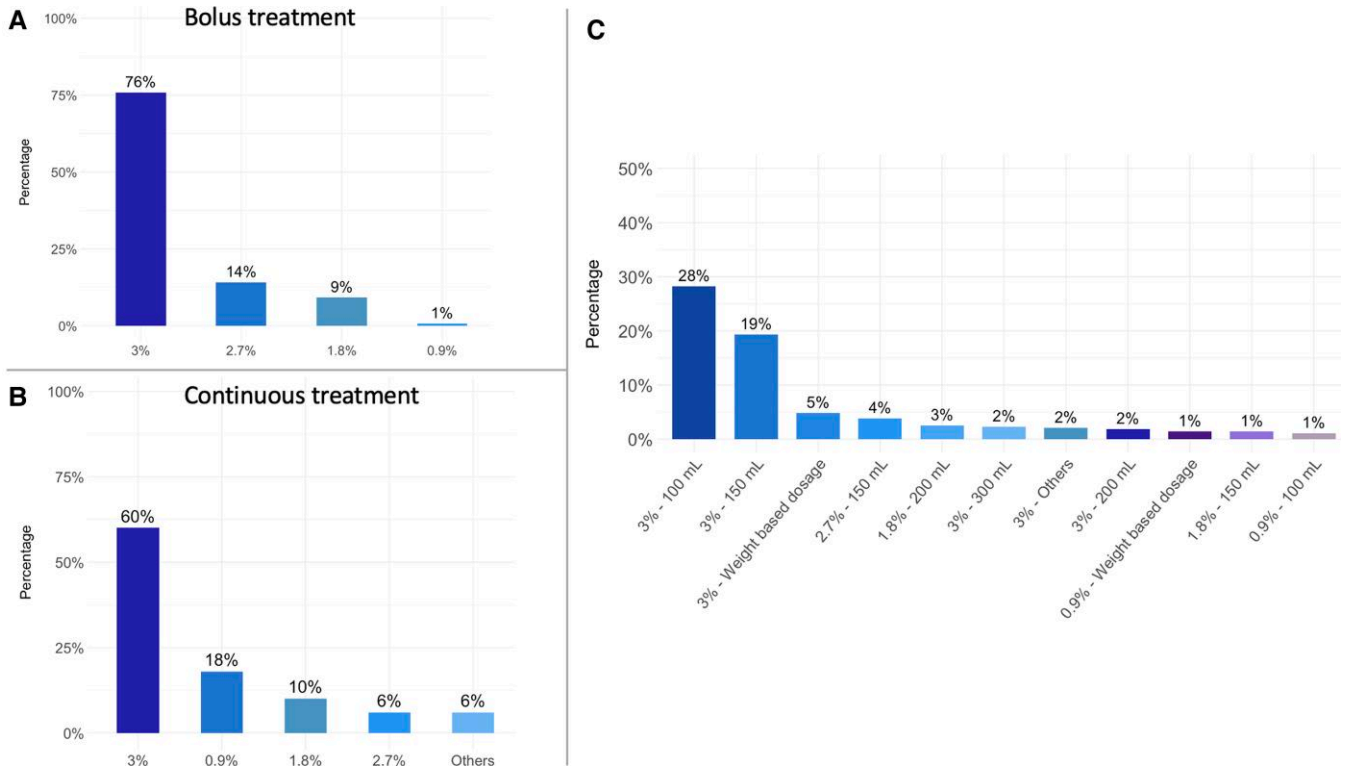

Figure 3. Initial treatment. Survey responses on strength of saline infusion, divided in (A) bolus treatment strategy (total $n = 141$), and (B) continuous infusion (total $n = 100$), expressed as percentage. (C) Dosage and strength combination of saline bolus (expressed as percentage, $n = 335$).

Our survey underlines that first, in clinical practice there is significant variation of managing severe symptomatic hyponatremia, second, most clinicians prefer a more cautious approach than recommended by the current guidelines, and third, one-third of clinicians have encountered clinically suspected or confirmed ODS in their clinical practice.

Severe symptomatic hyponatremia is a life-threatening condition that requires immediate and effective treatment to prevent fatal cerebral herniation and reduce the high risk of mortality. Current guidelines recommend immediate treatment with HTS. As the latest European guidelines for hyponatremia treatment were published more than a decade ago by

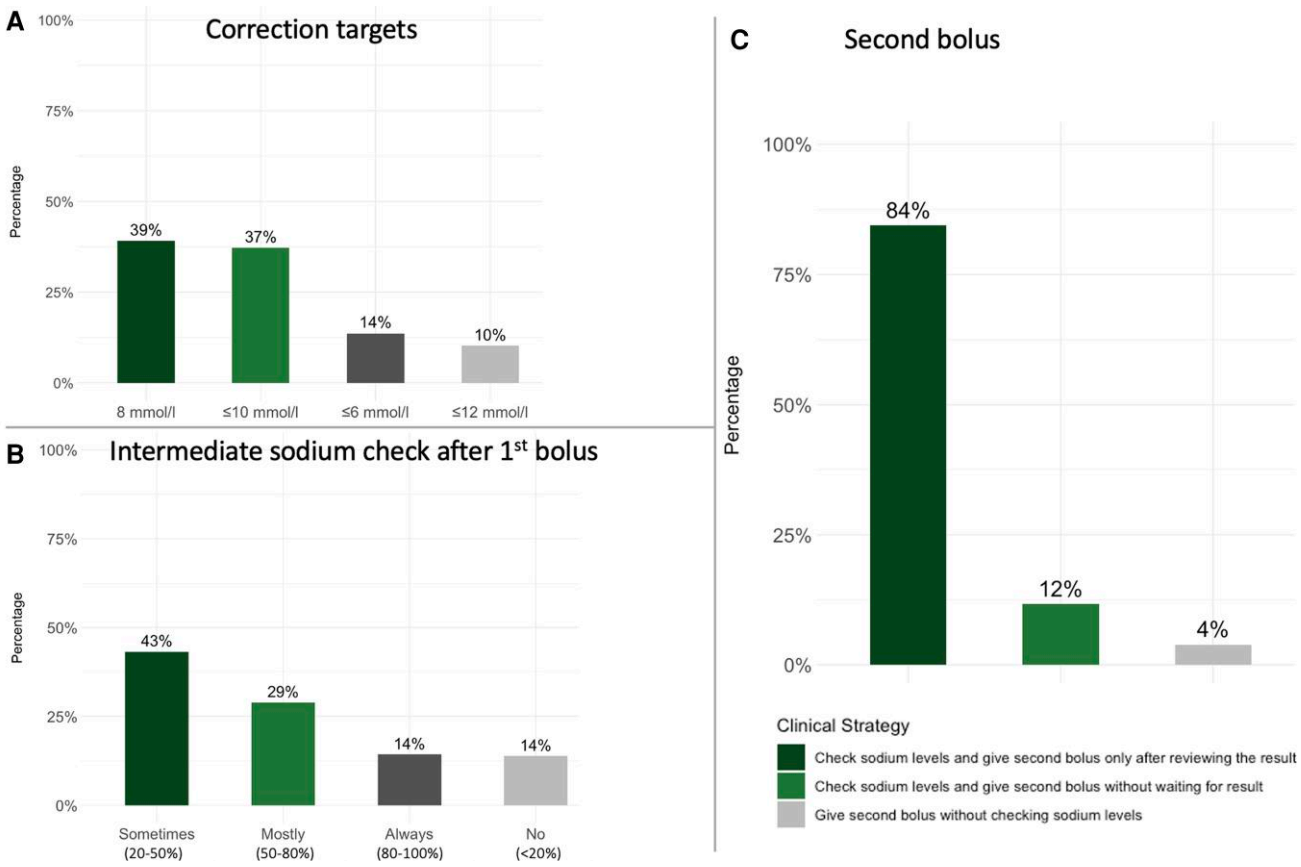

Figure 4. Treatment monitoring. Survey responses, expressed as percentage. (A) Correction targets in first 24 hours in patients without risk factors for ODS ($n = 435$), (B) use of venous blood gas readings after 1st HTS bolus to guide sodium treatment ($n = 436$), and (C) clinical strategy of second bolus ($n = 333$).

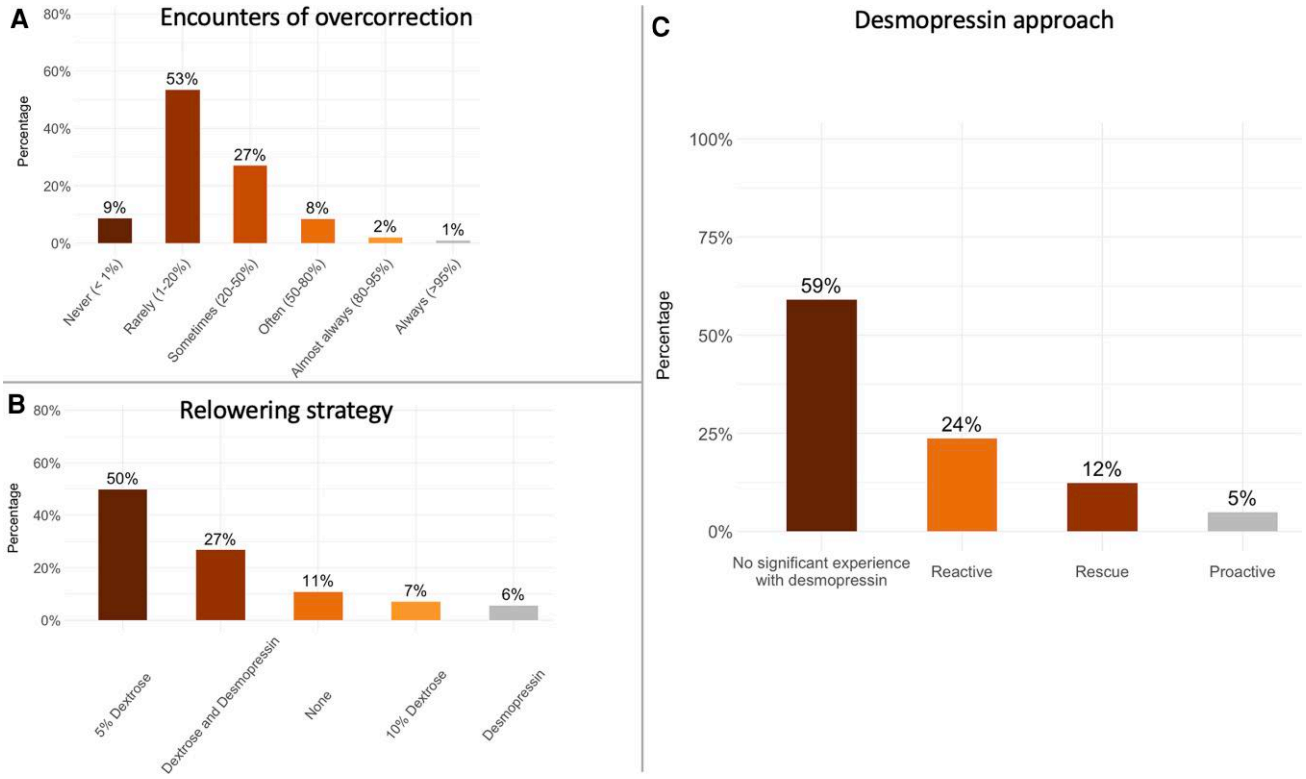

Figure 5. Overcorrection. Distribution of survey responses on (A) overcorrection/too rapid correction frequency in clinical practice (expressed as percentage, $n = 408$), (B) relowering strategy of sodium levels ($n = 408$), and (C) desmopressin approach ($n = 405$).

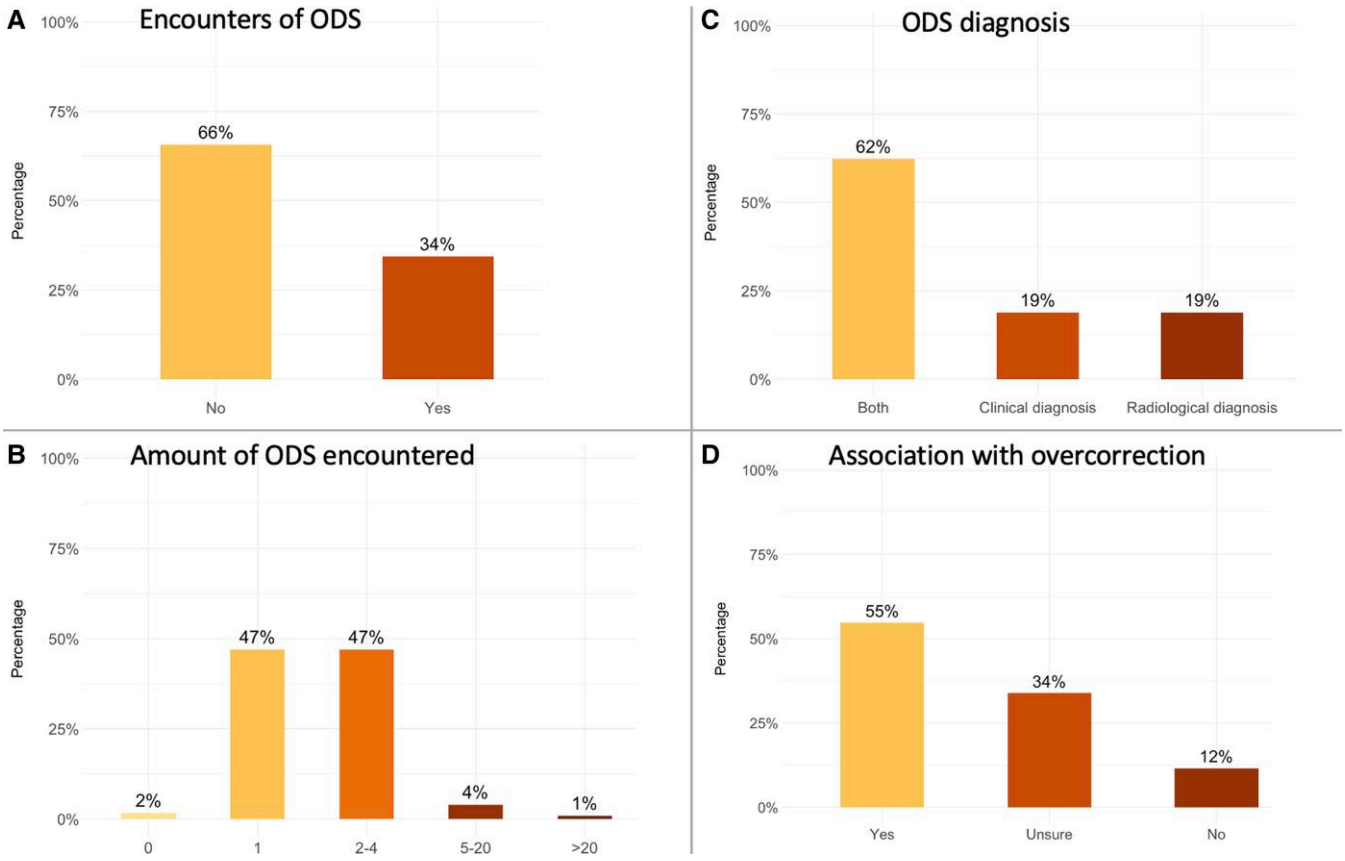

Figure 6. ODS. Distribution of survey responses on (A) any encounter of ODS in clinical practice (expressed as percentage), $n = 405$, (B) amount of ODS encounters ($n = 128$), (C) diagnosis of ODS ($n = 138$), and (D) overcorrection/rapid correction as cause for ODS ($n = 139$).

ESE in 2014,[1] the question arises whether current clinical practice has evolved over time and also if there are uncertainties in the clinical realm, that have not been sufficiently addressed by the guidelines.

Initial treatment

Both European and U.S. guidelines recommend a bolus-wise approach for treating severe symptomatic hyponatremia.[1,19] While evidence supporting the use of HTS as bolus over a slow continuous infusion is limited, some evidence from prospective trials (eg, *SALSA* trial: NCT02887469) exists, demonstrating a more rapid increase in serum sodium levels and better improvement in Glasgow Coma Scale (GCS) for bolus vs. continuous saline infusion.[14,17,20] Interestingly, our survey responses revealed that although one-third of clinicians had experience with both bolus and continuous infusions, only about the same proportion strictly followed the bolus-only approach recommended by current guidelines. This contrasts with a similar survey from the UK, where 85% of respondents preferred bolus therapy alone.[4] A factor for this disparity may be the 2016 UK's Society for Endocrinology (SfE) own guidelines (2016),[21] influencing clinical practice across the UK, whereas implementation across other European countries has been less consistent, contributing to a gap between recommendations and real-world practice. One plausible reason for the limited adoption of 3% saline bolus therapy could be the unavailability of ready-to-use 3% HTS products across some centers,[4] underlined by significant variability in strength and volume combinations reported in our survey, leading to an estimated 3% saline availability among our respondents of only around 60%. In some centers, HTS needs to be manually prepared, a time-consuming process and especially critical in potentially life-threatening emergency situations.

The survey also alludes to possible organizational obstacles within hospitals or reluctance among clinicians as 43% do not administer HTS treatment in general wards, presenting a bottleneck for hyponatremia treatment. ESE guidelines recommend treatment of severely symptomatic hyponatremia in an environment where close supervision can be provided.[1] However, case studies highlight the potential for fatal outcomes due to delays in treatment caused by such restrictions.[22] Also, safety data show that, contrarily to previously suggested data, HTS can be administered safely via peripheral intravenous line without the need for central venous lines.[22,23] However, whether the available data are sufficient to support the use of HTS in non-ICU settings remains to be determined.

Treatment monitoring

Our survey responses indicate a more cautious approach than recommended by current European guidelines. While guidelines advocate for 2 consecutive boluses of 150 mL 3% HTS boluses without intermediate sodium measurement, most respondents preferred checking sodium levels, eg, by venous blood gas analysis, before administering the second bolus. Notably, only 4% followed the recommended approach of giving the second bolus immediately without a sodium check. This cautious approach likely reflects concerns about overcorrection. However, this approach may also

lead to treatment delays, particularly when standard laboratory serum sodium measurements are used instead of rapid venous blood gas analysis. This has paralleled growing recognition of the risks associated with inadequate treatment. A fixed dosing of HTS bolus has shown to lead to more undercorrection in high body weight, while leading to more overcorrection in underweighted patients.[24] Thus, a weight-based approach (eg, 2 mL/kg) and equation formula derived from Edelman equation were recently suggested to calculate the correct hypertonic fluid need in each individual patient,[25,26] an approach that was indeed considered in 6% of our responses. Adequately powered randomized trials are urgently needed to robustly evaluate different treatment modalities in achieving an effective sodium increase while preventing under- and overcorrection.

Overcorrection and osmotic demyelination syndrome

In acute severe symptomatic hyponatremia, the risk of cerebral oedema outweighs the risk of ODS which is rare, and immediate sodium rise is advised as most important treatment goal.[27] However, if hyponatremia symptoms are only moderate and if sodium is biochemically very low, especially in the presence of further risk factors for ODS, a therapeutic challenge arises. In this context, undercorrection can aggravate symptoms, while a rapid increase may increase the risk of ODS. In our survey, most clinicians aimed for a correction target of <8 mmol/L and <10 mmol/L in patients without risk factors for ODS. The 10 mmol/L cut-off is in line with the ESE guidelines, while the 8 mmol/L limit is recommended as per the American expert panel recommendations, albeit in patients with risk factors for ODS only (eg, alcoholism, malnutrition, hypokalemia, advanced liver disease, severe hyponatremia <105 mmol/L).[19] It is important to distinguish between sodium targets and limits, with a target defined as a goal of sodium increase that should be aimed for (5 mmol/L[1]) and a limit of sodium increase that should not be exceeded (10 mmol/L during the first 24 hours and 18 mmol/L during the first 48 hours in patients at normal risk for ODS[1]). If this limit is surpassed, especially in patients with chronic hyponatremia, prompt counter-regulating interventions are recommended.

Overcorrection is a major concern in hyponatremia treatment. However, interestingly, 62% of our respondents have never or only rarely seen overcorrection, which is a low number, considering that real-world data suggest an incidence of overcorrection up to 45%.[11,18] Our results probably reflect underestimation among survey respondents. Potentially, it also hints toward a cautious approach among survey respondents with a self-set treatment goal to avoid overcorrection. If this approach takes into account to accept the risk of undercorrections needs to be assessed in further studies as limited data suggests the prevalence of undercorrection being approximately 20%-30%.[28]

Recently, there is a growing debate that sodium overcorrection only rarely leads to ODS and rapid corrections may actually improve mortality in hyponatremia, therefore, questioning the need for strict correction limits.[18,29] Surprisingly, one-third of our survey respondents have seen confirmed—or at least clinically suspected- ODS. Of those, more than half have seen it in association with overcorrection. Based on recent literature, a much lower incidence of ODS of around 0.05% would have been expected.[18] Importantly, the mentioned study by McMillan et al. based the diagnosis of ODS solely on neuroimaging, while we assessed for confirmed as well as clinically suspected ODS cases. Thus, the high ODS encounters among our respondents may reflect some overestimation due to high awareness caused by the current controversy on ODS. Large, randomized-controlled studies are needed to address this highly debated topic.[26]

Desmopressin

There is growing appreciation of the role of desmopressin in the treatment of hyponatremia.[16,27,30] Notably, the primary cause of an excessive rise in serum sodium is often not the administered dose of HTS, but rather the abrupt excretion of large volumes of dilute urine following arginine-vasopressin (AVP) downregulation during treatment. Therefore, the use of desmopressin, an AVP analog, has been proposed to reverse or prevent overcorrection.[11-14] Three distinct approaches to desmopressin administration can be defined: "proactive" strategy (prophylactic DDAVP clamp), a "reactive" approach (administration in response to rising serum sodium concentration or increased urine output), and a "rescue" strategy (used after overcorrection has occurred or when ODS is imminent). The ESE guidelines endorse the reactive and rescue strategies, especially in patients with chronic hyponatremia and risk factors for ODS. However, current clinical practice in Europe do not seem to reflect this approach as 60% of our survey respondents do not have significant experience with desmopressin treatment. However, those who used desmopressin, mostly used it as a "reactive" approach.

Limitations and strengths

Some limitations of our study design can be addressed. First, the survey study design limited questions and answers to a reasonable degree of detail assessment. Also, our survey mainly represents the perspective of European Endocrinologists with only few perspectives from Emergency medicine and Nephrology. A response rate of approximately 15% hints toward selection bias. However, it needs to be pointed out that 68% respondents were experienced clinicians from tertiary centers, which reflects a broad experience in treating hyponatremia. As 28% of survey responses were submitted by Italy-based physicians, this regional perspective may be somewhat overrepresented. However, our survey includes responses from a total of 36 different European countries, providing a diverse and comprehensive representation of perspectives and reflecting a certain degree of generalizability across Europe.

Conclusion

This is the first European survey focused on the management of severe symptomatic hyponatremia, offering valuable insights into real-life clinical practices and clinician perspectives from across Europe. The findings highlight ongoing uncertainties, even among experienced practitioners, underscoring the need for future research and an evidence-based review of the ESE guidelines. The optimal therapeutic approach to severe symptomatic hyponatremia remains a topic of debate. Future research should include prospective, large-scale clinical studies to evaluate and validate different treatment strategies.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Julia Beck (Conceptualization [equal], Data curation [equal], Formal analysis [lead], Investigation [equal], Project administration [equal], Software [lead], Visualization [lead], Writing—original draft [lead], Writing—review & editing [lead]), Muhammad Fahad Arshad (Conceptualization [equal], Data curation [equal], Formal analysis [supporting], Project administration [equal], Writing—original draft [supporting], Writing—review & editing [equal]), Mirjam Christ-Crain (Conceptualization [supporting], Formal analysis [supporting], Funding acquisition [lead], Project administration [supporting], Supervision [lead], Validation [supporting], Writing—review & editing [supporting]), and Ahmed Iqbal (Formal analysis [supporting], Methodology [supporting], Supervision [supporting], Validation [supporting], Writing—review & editing [supporting])

Conflict of interest: We declare no competing interests. Co-author Mirjam Christ-Crain is on the editorial board of EJE. She was not involved in the review or editorial process for this paper, on which she is listed as author.

Data availability

We may share de-identified, individual participant-level data that underlie the results reported in this Article and related documents, including the detailed responses of the survey. All requests should be sent to the corresponding author.

References

1. Spasovski G, Vanholder R, Allolio B, *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol.* 2014;170(3):G1-G47. https://doi.org/10.1530/EJE-13-1020
2. Warren AM, Grossmann M, Christ-Crain M, Russell N. Syndrome of inappropriate antidiuresis: from pathophysiology to management. *Endocr Rev.* 2023;44:819-861https://doi.org/10.1210/endrev/bnad010
3. Mohan S, Gu S, Parikh A, Radhakrishnan J. Prevalence of hyponatremia and association with mortality: results from NHANES. *Am J Med.* 2013;126(12):1127-37.e1. https://doi.org/10.1016/j.amjmed.2013.07.021
4. Arshad MF, Iqbal A. Use of hypertonic saline in severe symptomatic hyponatraemia; results from a national survey of endocrinologists in the United Kingdom. *Endocrine.* 2024;86(3):1199-1201. https://doi.org/10.1007/s12020-024-03927-9
5. Peri A. Morbidity and mortality of hyponatremia. *Front Horm Res.* 2019;52:36-48. https://doi.org/10.1159/000493235
6. Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ.* 1992;304(6836):1218-1222. https://doi.org/10.1136/bmj.304.6836.1218
7. Crook MA, Velauthar U, Moran L, Griffiths W. Review of investigation and management of severe hyponatraemia in a hospital population. *Ann Clin Biochem.* 1999;36(2):158-162. https://doi.org/10.1177/000456329903600204
8. Gill G, Huda B, Boyd A, *et al.* Characteristics and mortality of severe hyponatraemia–a hospital-based study. *Clin Endocrinol (Oxf).* 2006;65(2):246-249. https://doi.org/10.1111/j.1365-2265.2006.02583.x
9. Garrahy A, Cuesta M, Murphy B, *et al.* Active management of severe hyponatraemia is associated with improved mortality. *Eur J Endocrinol.* 2021;184(1):9-17. https://doi.org/10.1530/EJE-20-0577
10. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. *Semin Nephrol.* 2009;29(3):282-299. https://doi.org/10.1016/j.semnephrol.2009.03.002
11. Lamarche F, Ammann H, Dallaire G, Deslauriers L, Troyanov S. The risk of sodium overcorrections in severe hyponatremia and the utility of desmopressin: a large retrospective study. *Clin Kidney J.* 2025;18(2):sfae386. https://doi.org/10.1093/ckj/sfae386
12. Sood L, Sterns RH, Hix JK, Silver SM, Chen L. Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. *Am J Kidney Dis.* 2013;61(4):571-578. https://doi.org/10.1053/j.ajkd.2012.11.032
13. Perianayagam A, Sterns RH, Silver SM, *et al.* DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol.* 2008;3(2):331-336. https://doi.org/10.2215/CJN.03190807
14. Rondon-Berrios H, Sterns RH. Hypertonic saline for hyponatremia: meeting goals and avoiding harm. *Am J Kidney Dis.* 2022;79(6):890-896. https://doi.org/10.1053/j.ajkd.2021.07.020
15. Arshad MF, Iqbal A, Weeks J, Fonseca I, Munir A, Bennet W. Hypertonic saline for severe symptomatic hyponatraemia: real-world findings from the UK. *Endocr Connect.* 2022;11(5):e220007. https://doi.org/10.1530/EC-22-0007
16. Chifu I, Gerstl A, Lengenfelder B, *et al.* Treatment of symptomatic hyponatremia with hypertonic saline: a real-life observational study. *Eur J Endocrinol.* 2021;184(5):647-655. https://doi.org/10.1530/EJE-20-1207
17. Garrahy A, Dineen R, Hannon AM, *et al.* Continuous versus bolus infusion of hypertonic saline in the treatment of symptomatic hyponatremia caused by SIAD. *J Clin Endocrinol Metab.* 2019;104(9):3595-3602. https://doi.org/10.1210/jc.2019-00044
18. MacMillan TE, Shin S, Topf J, *et al.* Osmotic demyelination syndrome in patients hospitalized with hyponatremia. *NEJM Evid.* 2023;2(4):EVIDoa2200215. https://doi.org/10.1056/EVIDoa2200215
19. Verbalis JG, Goldsmith SR, Greenberg A, *et al.* Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126(10):S1-S42. https://doi.org/10.1016/j.amjmed.2013.07.006
20. Baek SH, Jo YH, Ahn S, *et al.* Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: the SALSA randomized clinical trial. *JAMA Intern Med.* 2021;181(1):81-92. https://doi.org/10.1001/jamainternmed.2020.5519
21. Ball S, Barth J, Levy M. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: emergency management of severe symptomatic hyponatraemia in adult patients. *Endocr Connect.* 2016;5(5):G4-G6. https://doi.org/10.1530/EC-16-0058
22. Ayus JC, Moritz ML. Misconceptions and barriers to the use of hypertonic saline to treat hyponatremic encephalopathy. *Front Med (Lausanne).* 2019;6:47. https://doi.org/10.3389/fmed.2019.00047
23. Madieh J, Hasan B, Khamayseh I, *et al.* The safety of intravenous peripheral administration of 3% hypertonic saline: a systematic

review and meta-analysis. *Am J Med Sci*. 2023;366(2):135-142. https://doi.org/10.1016/j.amjms.2023.04.025
24. Pelouto A, Refardt JC, Christ-Crain M, Zandbergen AAM, Hoorn EJ. Overcorrection and undercorrection with fixed dosing of bolus hypertonic saline for symptomatic hyponatremia. *Eur J Endocrinol*. 2023;188(3):322-330. https://doi.org/10.1093/ejendo/lvad028
25. Nagase K, Imaizumi T, Yamamori A, *et al*. Correction of profound hyponatraemia following rapid bolus therapy: effectiveness of the Barsoum-Levine formula based on the Edelman equation. *Clin Kidney J*. 2025;18(2):sfae402. https://doi.org/10.1093/ckj/sfae402
26. Sterns RH, Rondon-Berrios H, Adrogue HJ, *et al*. Treatment guidelines for hyponatremia stay the course. *Clin J Am Soc Nephrol*. 2024;19(1):129-135. https://doi.org/10.2215/CJN.0000000000000244
27. Rondon-Berrios H. Diagnostic and therapeutic strategies to severe hyponatremia in the intensive care unit. *J Intensive Care Med*. 2023;39:1039-1054. https://doi.org/10.1177/08850666231207334
28. George JC, Zafar W, Bucaloiu ID, Chang AR. Risk factors and outcomes of rapid correction of severe hyponatremia. *Clin J Am Soc Nephrol*. 2018;13(7):984-992. https://doi.org/10.2215/CJN.13061117
29. Ayus JC, Moritz ML, Fuentes NA, *et al*. Correction rates and clinical outcomes in hospitalized adults with severe hyponatremia: a systematic review and meta-analysis. *JAMA Intern Med*. 2025;185(1):38-51. https://doi.org/10.1001/jamainternmed.2024.5981
30. MacMillan TE, Tang T, Cavalcanti RB. Desmopressin to prevent rapid sodium correction in severe hyponatremia: a systematic review. *Am J Med*. 2015;128(12):1362.e15-1362.e24. https://doi.org/10.1016/j.amjmed.2015.04.040