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Clinical Practice Guideline

Clinical practice guideline on diagnosis and treatment of hyponatraemia

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ABSTRACT

Hyponatraemia, defined as a serum sodium concentration <135 mmol/l, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening, and is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Despite this, the management of patients remains problematic. The prevalence of hyponatraemia in widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution- and speciality-based approaches to diagnosis and treatment. To obtain a common and holistic view, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP), have developed the Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia as a joint venture of three societies representing specialists with a natural interest in hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focused on patient-important outcomes and included utility for clinicians involved in everyday practice.

1. FOREWORD

Hyponatraemia is a clinical feature in 15–20% of emergency admissions to hospital. It is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Hyponatraemia is therefore both common and important.

Despite this, the management of patients remains problematic. The prevalence of hyponatraemia under widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution- and speciality-based approaches to diagnosis and treatment. However, the paucity of well-designed, prospective studies in the field has limited the evidence-base to these approaches. Previous guidance has often been based on experience or practice, without a systematic approach to evaluation and lacking a clear, patient-centred focus. Clinicians using previous guidance may have noted a number of problems:

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The guidelines were peer reviewed by the owner societies and by external referees prior to publication.

- It has been difficult to follow the guidance in day-to-day clinical practice, especially by doctors in training who are managing patients in the 'front line'. Here, the requirement is for clear, concise and practical advice on what has to be done, including during the critical 'out-of-office hours' period. Complex diagnostic algorithms and time-consuming investigations are real barriers to implementation in this context.
- The guidance has been over-simplistic and does not reflect the range of clinical problems encountered in day-to-day practice.
- The guidance has been limited by a diagnosis-, mechanism- or duration-based approach to treatment, failing to recognise that establishing the diagnosis, mechanism or duration of hyponatraemia may be difficult. Previous guidance has mostly used duration of hyponatraemia as a key point on which to base management. Yet, duration can be hard to establish, especially in emergency settings. Decisions often have to be made on limited information.
- The guidance has demonstrated an institutional or specialty-specific bias, limiting implementation across sites and clinical disciplines. This is best demonstrated in institution- or speciality-specific approaches to investigations.
- The guidance has used a biochemical focus, failing to prioritise clinical status in decisions on treatment options. Clinicians know that the degree of biochemical hyponatraemia does not always match the clinical state of the patient. Guidance that bases management advice simply on the serum sodium concentration may be counter to clinical experience, risking credibility and engagement.

Together, these factors have limited the utility of previous advice. Two emerging themes require that we revisit the area:

1. The clear recognition of the importance of evidence-based approaches to patient care to enhance quality, improve safety and establish a clear and transparent framework for service development and health care provision.
2. The advent of new diagnostics and therapeutics, highlighting the need for a valid, reliable and transparent process of evaluation to support key decisions.

To obtain a common and holistic view, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP), have developed new guidance on the diagnostic approach and treatment of hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focused on patient-important outcomes and included utility for clinicians involved in everyday practice.

2. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

A steering committee with representatives of all the three societies convened in October 2010 and decided on the composition of the Guideline Development Group, taking into account the clinical and research expertise of each proposed candidate.

Guideline development group co-chairs

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3. PURPOSE AND SCOPE OF THIS GUIDELINE

3.1. Why was this guideline produced?

The purpose of this Clinical Practice Guideline was to provide guidance on the diagnosis and treatment of adult individuals with hypotonic hyponatraemia. It was designed to provide information and assist in decision-making related to this topic. It was not intended to define a standard of care and should not be construed as one. It should not be interpreted as prescribing an exclusive course of management.

This guideline was developed as a joint venture of three societies representing specialists with a natural interest in hyponatraemia: the ESICM, the ESE and the ERA–EDTA, represented by ERBP.

All three societies agreed that there was a need for guidance on diagnostic assessment and therapeutic management of hyponatraemia. A recent systematic review, which included three clinical practice guidelines and five consensus statements, confirmed the lack of high-quality guidelines in this field [1]. The guidance documents scored low to moderate in the six domains of the AGREEII tool – scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence – and the management strategies proposed in the different guidance documents were sometimes contradictory [2].

3.2. Who is this guideline for?

This guideline was meant to support clinical decision-making for any health care professional dealing with hyponatraemia, i.e. general practitioners, internists, surgeons and other physicians dealing with hyponatraemia in both an outpatient and an in-hospital setting. The guideline was also developed for policymakers for informing standards of care and for supporting the decision-making process.

3.3. What is this guideline about?

This section defines what this guideline intended to cover and what the guideline developers considered. The scope was determined at a first meeting held in Barcelona in October 2010 with representatives of ESICM, ESE and ERBP present.

3.3.1. Population. The guideline covers hyponatraemia in adults through the biochemical analysis of a blood sample. It does not cover hyponatraemia detected in children because the guideline development group judged that hyponatraemia in children represented a specific area of expertise. The guideline also does not cover screening for hyponatraemia.

3.3.2. Conditions. The guideline specifically covers diagnosis and management of true hypotonic hyponatraemia. It covers the differentiation of hypotonic hyponatraemia from non-hypotonic hyponatraemia but does not deal with the specific diagnostic and therapeutic peculiarities in the setting of pseudohyponatraemia, isotonic or hypertonic hyponatraemia. These situations are not associated with the hypotonic state responsible for the majority of symptoms attributable to true hypotonic hyponatraemia. The guideline covers diagnosis and management of both acute and chronic hypotonic hyponatraemia in case of reduced, normal and increased extracellular fluid volume. It does not cover the diagnosis or treatment of the underlying conditions that can be associated with hypotonic hyponatraemia.

3.3.3. Health care setting. This guideline targets primary, secondary and tertiary settings dealing with diagnostic testing and the management of hyponatraemia in adults.

3.3.4. Clinical management. This guideline deals with diagnostic tools for improving accuracy of the differential diagnosis of hypotonic hyponatraemia, allowing more specific treatment strategies tailored to the underlying cause and/or pathophysiological mechanism.

This guideline covers the treatment for adults with acute or chronic, symptomatic or asymptomatic hypotonic hyponatraemia, regardless of the underlying condition.

4. METHODS FOR GUIDELINE DEVELOPMENT

4.1. Establishment of the guideline development group

The councils of the three participating societies, ESICM, ESE and ERBP, selected the co-chairs of the guideline development group. The co-chairs then assembled the steering committee with representatives of the three societies involved in this joint venture. This steering committee convened in October 2010 and decided on the composition of the guideline development group, taking into account the clinical and research expertise of the proposed candidates. The guideline development group consisted of content experts, which included individuals with expertise in hyponatraemia, endocrinology, general internal medicine, intensive care medicine and clinical nephrology as well as an expert in systematic review methodology. The ERBP methods support team provided methodological input and practical assistance throughout the guideline development process.

4.2. Developing clinical questions

From the final scope of the guideline, specific research questions, for which a systematic review would be conducted, were identified.

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4.2.1. Diagnosis and differential diagnosis of hypotonic hyponatraemia

1. In patients with hypotonic hyponatraemia, how accurate are various 'diagnostic strategies' in comparison with a reference test of infusing 2 l 0.9% sodium chloride solution for differentiating hypovolaemic from euvolaemic hyponatraemia?
2. In patients with hypotonic hyponatraemia, how accurate are various 'diagnostic strategies' in comparison with a reference test of expert panel diagnosis in differentiating hypovolaemic from euvolaemic hyponatraemia?

4.2.2. Acute and chronic treatment of hypotonic hyponatraemia

1. In patients with hypotonic hyponatraemia, which treatments are effective in improving outcomes?
2. In patients with hypotonic hyponatraemia, does the change in serum sodium concentration per unit time influence outcomes?

4.3. Development of review questions

The methods support team assisted in developing review questions, i.e. framing the clinical questions into a searchable format. This required careful specification of the patient group (P), the intervention (I), the comparator (C) and the outcomes (O) for intervention questions and the patient group, index tests, reference standard and target condition for questions of diagnostic test accuracy [3]. For each question, the guideline development group agreed on explicit review question criteria including study design features (See Appendices 1, 2 for Detailed Review Questions and PICO tables. See section on Appendix given at the end of this article).

4.4. Assessment of the relative importance of the outcomes

For each intervention question, the guideline development group compiled a list of outcomes, reflecting both benefits and harms of alternative management strategies. The guideline development group ranked the outcomes as critically, highly or moderately important according to their relative importance in the decision-making process. As such, patient-important health outcomes related to hyponatraemia and the treatment for hyponatraemia were considered critical. Owing to its surrogate nature, the outcomes 'change in serum sodium concentration' and 'correction of serum sodium concentration' were considered less important than the critically and highly important clinical outcomes (Table 1).

4.5. Target population perspectives

An effort was taken to capture the target population's perspectives by adopting two strategies. First, ERBP has a permanent patient representative in its board. Although he was not included in the guideline development group or in the evidence review process, drafts of the guideline document were sent for his review and his comments were taken into account in revising and drafting the final document.

Table 1. Hierarchy of outcomes.

Hierarchy	Outcomes
Critically important	Patient survival
	Coma
	Brain damage/brain oedema
	Epileptic seizures
	Osmotic demyelinating syndrome
	Respiratory arrest
	Quality of life
	Cognitive function
Highly important	Bone fractures
	Falls
	Length of hospital stay
Moderately important	Serum sodium concentration

Secondly, the guideline underwent public review before publication. The guideline was sent to the council of two different societies for each specialty involved: for ESICM, the Australian and New Zealand Intensive Care Society (ANZICS) and American Society of Critical Care Medicine (SSCM); for ESE, the Endocrine Society of Australia (ESA) and the Endocrine Society (USA); and for ERBP, the Kidney Health Australia–Caring for Australasians with Renal Impairment (KHA–CARI) and the American Society of Nephrology (ASN). Each of these societies was specifically asked to indicate two to three reviewers. Reviewers could use free text to suggest amendments and/or fill in a matrix questionnaire in Microsoft Excel. All members of the ERA–EDTA received an online questionnaire with a standardised answer form in Microsoft Excel. ERA–EDTA members were asked to express to what extent they judged the individual statements were clear and implementable and to what extent they agreed with the content. In addition, a free text field was provided to allow for additional comments.

4.6. Searching for evidence

4.6.1. Sources. The ERBP methods support team searched The Cochrane Database of Systematic Reviews (May 2011), DARE (May 2011), CENTRAL (May 2011) and MEDLINE (1946 to May, week 4, 2011) for questions on both diagnosis and treatment. To identify the limits for the increase in serum sodium concentration above which the risk of osmotic demyelination starts to rise, we searched MEDLINE database from 1997 onwards under the assumption that earlier reports would describe more dramatic increases and would not contribute to helping us set an upper limit. All searches were updated on 10th December 2012. The search strategies combined subject headings and text words for the patient population, index test and target condition for the diagnostic questions and subject headings and text words for the population and intervention for the intervention questions. The detailed search strategies are available in Appendix 3, see section titled Appendix given at the end of this article.

Reference lists from included publications were screened to identify additional papers. The methods support team also searched guideline databases and organisations including the National Guideline Clearinghouse, Guidelines International Network, Guidelines Finder, Centre for Reviews and

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Dissemination, National Institute for Clinical Excellence, and professional societies of Nephrology, Endocrinology and Intensive Care Medicine for guidelines to screen the reference lists.

4.6.2. Selection. For diagnostic questions, we included every study that compared any of the predefined clinical or biochemical tests with infusion of 2 l 0.9% saline as a reference test or with an expert panel for differentiating hypovolaemic from euvolaemic hyponatraemia. For questions on treatment strategies, we included every study in which one of the predefined medications was evaluated in humans. We excluded case series that reported on benefit if the number of participants was ≤5 but included even individual case reports if they reported an adverse event. No restriction was made based on language. For identifying the limits for the increase in serum sodium concentration above which the risk of osmotic demyelination starts to rise, we included all observational studies reporting cases of osmotic demyelinating syndrome and corresponding serum sodium concentration correction speeds.

A member of the ERBP methods support team screened all titles and abstracts to discard the clearly irrelevant ones. All members of the guideline development group completed a second screening. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by group consensus.

The methods support team retrieved full texts of potentially relevant studies and two reviewers examined them for eligibility independently of each other. The reviewer duos always consisted of one content specialist and one methodologist from the ERBP methods support team. Any discrepancies were resolved by consensus. If no consensus could be reached, the disagreement was settled by group arbitrage.

4.6.3. Data extraction and critical appraisal of individual studies. For each included study, we collected relevant information on design, conduct and relevant results through standardised data extraction forms in Microsoft Excel (2010). As part of an ongoing process of introducing software to facilitate the guideline development process, the ERBP methods support team used two formats for data extraction and collation. For detailed methods, see Appendices 4, 5, see section titled Appendix given at the end of this article. Briefly, we used both a simple spreadsheet format and a more sophisticated version, which incorporated user forms programmed in Visual Basic. For each question, two reviewers extracted all data independently of each other. We produced tables displaying the data extraction of both reviewers. Both reviewers checked all data independently of each other. Any discrepancies were resolved by consensus and if no consensus could be reached, disagreements were resolved by an independent referee. From these tables, we produced merged consensus evidence tables for informing the recommendations. The evidence tables are available in Appendices 6, 7, see section titled Appendix given at the end of this article.

Risk of bias of the included studies was evaluated using various validated checklists, as recommended by the Cochrane Collaboration. These were AMSTAR for Systematic Reviews [4], the Cochrane Risk of Bias tool for randomised controlled trials [5], the Newcastle Ottawa scale for cohort and case–control studies [6] and QUADAS for diagnostic test accuracy studies [7]. Data were compiled centrally by the ERBP methods support team.

4.6.4. Evidence profiles. The evidence for outcomes on therapeutic interventions from included systematic reviews and randomised controlled trials was presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The evidence profiles include details of the quality assessment as well as summary – pooled or unpooled – outcome data, an absolute measure of intervention effect when appropriate and the summary of quality of evidence for each outcome. Evidence profiles were constructed by the methods support team and reviewed and confirmed with the rest of the guideline development group. Evidence profiles were constructed for research questions addressed by at least two randomised controlled trials. If the body of evidence for a particular comparison of interest consisted of only one randomised controlled trial or of solely observational data, the summary tables provided the final level of synthesis.

4.7. Rating the quality of the evidence for each outcome across studies

In accordance with GRADE, the guideline development group initially categorised the quality of the evidence for each outcome as high if it originated predominantly from randomised controlled trials and low if it originated from observational data. We subsequently downgraded the quality of the evidence one or two levels if results from individual studies were at serious or very serious risk of bias, there were serious inconsistencies in the results across studies, the evidence was indirect, the data were sparse or imprecise or publication bias thought to be likely. If evidence arose from observational data, but effect sizes were large, there was evidence of a dose–response gradient or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect, we would upgrade the quality of the evidence (Table 2). Uncontrolled case series and case reports automatically received downgrading from low to very low level of evidence for risk of bias, so that no other reasons for downgrading were marked. By repeating this procedure, we would obtain an overall quality of the evidence for each outcome and each intervention. For list of definitions, see Table 3.

4.8. Formulating statements and grading recommendations

4.8.1. Recommendations. After the summary tables were produced and evidence profiles had been prepared, revised and approved by the guideline development group, two full-weekend plenary meetings were held in September 2012 and December 2012 to formulate and grade the recommendations.

Recommendations can be for or against a certain strategy. The guideline development group drafted the recommendations based on their interpretation of the available evidence.

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Table 2. Method of rating the quality of the evidence. Adapted from Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011 64 401–406 [240].

Step 1: starting grade according to study design	Step 2: lower if	Step 3: higher if	Step 4: determine final grade for quality of evidence
Randomised trials = high Observational studies = low	Risk of bias −1 Serious −2 Very serious Inconsistency −1 Serious −2 Very serious Indirectness −1 Serious −2 Very serious Imprecision −1 Serious −2 Very serious Publication bias −1 Likely −2 Very likely	Large effect +1 Large +2 Very large Dose–response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect when results show no effect	High (four plus: ⊕⊕⊕⊕) Moderate (three plus: ⊕⊕⊕◯) Low (two plus: ⊕⊕◯◯) Very low (one plus: ⊕◯◯◯)

Table 3. Grade for the overall quality of evidence. Adapted from Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ & GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008 336 924–926 [8].

Grade	Quality level	Definition
A	High	We are confident that the true effects lie close to that of the estimates of the effect
B	Moderate	The true effects are likely to be close to the estimates of the effects, but there is a possibility that they are substantially different
C	Low	The true effects might be substantially different from the estimates of the effects
D	Very low	The estimates are very uncertain and often will be far from the truth

Judgements around four key factors determined the strength of a recommendation: the balance between desirable and undesirable consequences of alternative therapeutic or diagnostic strategies, the quality of the evidence, the variability in values and preferences. We did not conduct formal decision or cost analysis. In accordance to GRADE, we classified the strength of the recommendations as strong, coded '1' or weak, coded '2' (Table 4; Fig. 1) [8]. Individual statements were made and discussed in an attempt to reach group consensus. If we could not reach consensus, we held a formal open vote by show of hands. An arbitrary 80% had to cast a positive vote for a statement to be accepted. Voting results and reasons for disagreement were specified in the rationale.

4.8.2. Ungraded statements and advice for clinical practice

We decided to use an additional category of ungraded statements for areas where formal evidence was not sought and statements were based on common sense or expert experience alone. They were termed 'statement' to differentiate them from graded recommendations and do not hold an indicator for the quality of the evidence. The ungraded statements were generally written as simple declarative statements but were not meant to be stronger than level 1 or 2 recommendations.

We also provided additional advice for clinical practice. The advice is not graded and is only for the purpose of improving practical implementation. It contains some elaboration on one of the statements, clarifying how the statement can be implemented in clinical practice.

4.8.3. Optimizing implementation

Recommendations often fail to reach implementation in clinical practice partly because of their wording. As part of a research project to evaluate methods for improving guideline development processes, we integrated the GuideLine Implementability Appraisal (GLIA) instrument to optimise the wording of the recommendations [9]. The tool primarily enables structured evaluation of factors such as executability (is it clear from the statement exactly what to do) and decidability (exactly under what conditions) of preliminary recommendations. In addition, the tool is designed to highlight other problems possibly hindering implementation, e.g. recommendations being inconsistent with clinicians' existing beliefs or patients' expectations. The appraisal was done by a panel of target guideline users external to the guideline development group. Comments and remarks were communicated to the guideline development group and used to help refine the recommendations.

4.9. Writing rationale

We collated recommendations and ungraded statements for each of the clinical questions in separate sections structured

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Table 4. Implications of strong and weak recommendations for stakeholders. Adapted from Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ & GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008 336 1049–1051. The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counselling and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger recommendations than level 1 or 2 recommendations.

	Implications		
Grade	Patients	Clinicians	Policy
1. Strong 'We recommend'	Most people in your situation would want the recommended course of action, only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be adopted as policy in most situations
2. Weak 'We suggest'	Most people in your situation would want the recommended course of action, but many would not	You should recognise that different choices will be appropriate for different patients You must help each patient to arrive at a management decision consistent with her or his values and preferences	Policy making will require substantial debate and involvement of many stakeholders

according to a specific format. Each question resulted in one or more specific boxed statements. Within each recommendation, the strength was indicated as level 1 or 2 and the quality of the supporting evidence as A, B, C or D as prescribed by the GRADE methodology (Table 4).

These statements are followed by advice for clinical practice where relevant and the rationale. The rationale contains a brief section on 'why this question' with relevant background and justification of the topic, followed by a short narrative review of the evidence in 'what did we find' and finally a justification of how the evidence translated in the recommendations made in 'how did we translate the evidence into the statement'.

When areas of uncertainty were identified, the guideline development group considered making suggestions for future research based on the importance to patients or the population and on ethical and technical feasibility.

4.10. Internal and external review

4.10.1. Internal review. A first draft of the guideline was sent to a selected group of internal reviewers. Each society nominated experts in hyponatraemia and/or members of their governance body. Internal reviewers were asked to complete a grid-based evaluation of overall appreciation of each individual statement, using a score between 1 and 5. These scores were averaged and colour-coded between red [1] and green [5] to help visualise any problematic part. In addition, internal reviewers were asked to comment on the statements and the rationale within free text fields limited to 225 characters. All these comments and suggestions were discussed during an additional meeting of the guideline development group in June 2013. For each comment or suggestion, the guideline development group evaluated whether it was needed to adapt the statement, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence and the variability in values and preferences.

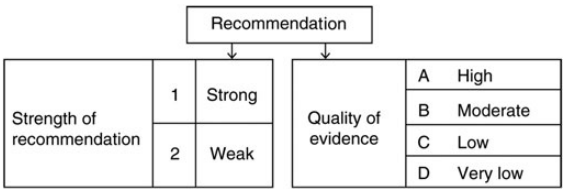


FIGURE 1: Grade system for grading recommendations. Adapted from Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ & GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008 **336** 924–926. [8]

4.10.2. External review. The guideline was sent to the ESA and KHA–CARI for review. Reviewers could use free text to suggest amendments and/or fill in a matrix questionnaire in Microsoft Excel. In addition, all members of the ERA–EDTA received an online questionnaire with a standardised answer form in Microsoft Excel. ERA–EDTA members were asked to express to what extent they believed the individual statements were clear, implementable and to what extent they agreed with the content on a scale from 1 to 5. In addition, a free text field was provided to allow for additional comments. All these valid comments and suggestions were discussed with the guideline development group through e-mail and during a final meeting of the co-chairs of the guideline development group, the methods support team and the chair of ERBP.

4.11. Timeline and procedure for updating the guideline

It was decided to update the guideline at least every 5 years. New evidence requiring additional recommendations or changes to existing statements could instigate an earlier update.

At least every 5 years, the ERBP methods support team will update its literature searches. Relevant studies will be identified and their data will be extracted using the same procedure as for the initial guideline. During a 1-day meeting, the guideline development group will decide whether or not the original statements require updating. An updated version of the

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guideline will be published online accompanied by a position statement in the journals of the three societies describing the changes made.

During the 5-year interval, the guideline development group co-chairs will notify the ERBP chair of new information that may justify changes to the existing guideline. Together, they will consult at least one guideline development group member representing each of the collaborating societies. If they decide that an update is needed, an updated version of the guideline will be produced using the same procedures as for the initial guideline.

5. PATHOPHYSIOLOGY OF HYPONATRAEMIA

5.1. Introduction

Hyponatraemia, defined as a serum sodium concentration <135 mmol/l, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. It occurs in up to 30% of hospitalised patients and can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening [10, 11]. Because hyponatraemia can result from a varied spectrum of conditions, based on different mechanisms, we believed that it would be useful to include an introductory section that outlines some of the pathophysiological principles encountered in hyponatraemia. It was not intended to be a detailed reference section. It was only meant to clarify some of the important concepts to enhance understanding of the rationale of the statements in the guideline.

Hyponatraemia is primarily a disorder of water balance, with a relative excess of body water compared to total body sodium and potassium content. It is usually associated with a disturbance in the hormone that governs water balance, vasopressin (also called antidiuretic hormone). Even in disorders associated with (renal) sodium loss, vasopressin activity is generally required for hyponatraemia to develop. Therefore, after describing common signs and symptoms, we detail the mechanisms involved in vasopressin release.

Changes in serum osmolality are primarily determined by changes in the serum concentration of sodium and its associated anions. It is important to differentiate the concepts of total osmolality and effective osmolality or tonicity. Total osmolality is defined as the concentration of all solutes in a given weight of water (mOsm/kg), regardless of whether or not the osmoles can move across biological membranes. Effective osmolality or tonicity refers to the number of osmoles that contribute water movement between the intracellular and extracellular compartment. It is a function of the relative solute permeability properties of the membranes separating the intracellular and extracellular fluid compartments [12]. Only effective solutes create osmotic pressure gradients across cell membranes leading to osmotic movement of water between the intracellular and extracellular fluid compartment. In most cases, hyponatraemia reflects low effective osmolality or hypotonicity, which causes symptoms of cellular oedema. However, hyponatraemia may also (rarely) occur with isotonic or hypertonic serum if the serum contains many additional osmoles, such as glucose or mannitol. Therefore, we discuss not only how hypo-osmolar but also how isosmolar and hyperosmolar states develop.

Finally, we review the pathophysiology of distinct clinical disorders that can cause hyponatraemia. We have categorised the causes of hyponatraemia in those associated with a reduced, normal or increased extracellular fluid volume. Although the clinical assessment of volume status is often difficult in practice, the concept of volume status has proven useful because it provides a simple framework to understand the diagnosis and treatment of hypo-osmolar disorders.

5.2. Clinical features

Symptoms can vary from mild, non-specific to severe and life-threatening (Table 5). Severe symptoms of hyponatraemia are caused by brain oedema and increased intracranial pressure. Brain cells start to swell when water moves from the extracellular to the intracellular compartment because of a difference in effective osmolality between brain and plasma. This usually occurs when hyponatraemia develops rapidly, and the brain has had too little time to adapt to its hypotonic environment. Over time, the brain reduces the number of osmotically active particles within its cells (mostly potassium and organic solutes) in an attempt to restore the brain volume (Fig. 2). This process takes ~24–48 h, hence the reason for using the 48-h threshold to distinguish acute (<48 h) from chronic (≥48 h) hyponatraemia.

Although the more severe signs of acute hyponatraemia are well established, it is now increasingly clear that even patients with chronic hyponatraemia and no apparent symptoms can have subtle clinical abnormalities when analysed in more detail. Such abnormalities include gait disturbances, falls, concentration and cognitive deficits [13]. In addition, patients with chronic hyponatraemia more often have osteoporosis and more frequently sustain bone fractures than normonatraemic persons [14, 15, 16]. Finally, hyponatraemia is associated with an increased risk of death [17, 18]. Whether these are causal

Table 5. Classification of symptoms of hyponatraemia. The guideline development group wants to underscore that these symptoms can also be induced by other conditions. Clinical and anamnestic data should be taken into account when assessing the causal relationship between hyponatraemia and a certain symptom (i.e. to assess whether the symptom has been caused by hyponatraemia or hyponatraemia by the underlying condition/symptom). The less pronounced (e.g. mild) the biochemical degree of hyponatraemia, the more caution should be taken when considering that hyponatraemia is the cause of the symptoms. This list is not exhaustive, and all symptoms that can be signs of cerebral oedema should be considered as severe or moderate symptoms that can be caused by hyponatraemia.

Severity	Symptom
Moderately severe	Nausea without vomiting
	Confusion
	Headache
Severe	Vomiting
	Cardiorespiratory distress
	Abnormal and deep somnolence
	Seizures
	Coma (Glasgow Coma Scale ≤8)

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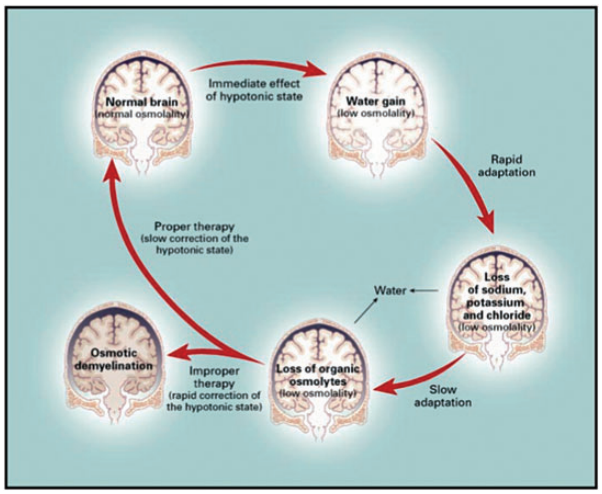


FIGURE 2: Adaptation of the brain to hypotonicity. Reproduced with permission from Massachusetts Medical Society, Copyright © 2000 Adrogue HJ & Madias NE. Hyponatremia. *New England Journal of Medicine* 2000 **342** 1581–1589.

associations or merely symptoms of underlying problems such as heart or liver failure remains unclear [19].

5.3. Regulation of water intake and homeostasis

As the serum sodium concentration is determined by the amount of extracellular water relative to the amount of sodium, it can be regulated by changing intake or output of water. The major mechanisms responsible for regulating water metabolism are thirst and the pituitary secretion and renal effects of vasopressin. Regulation of body water serves to minimise osmotically induced disruptions in cell volume with adverse effects on multiple cellular functions. Osmoreceptive neurons located in the anterior hypothalamus detect changes in cell stretch due to changes in systemic effective osmolality. A decrease in cell stretch increases the firing rate of osmoreceptive neurons, which leads to both increased thirst and increased release of vasopressin from the pituitary gland. Vasopressin in turn increases the re-absorption of water from the primitive urine in the distal tubules of the nephron, which leads to urine that is more concentrated. To prevent persistent thirst, the threshold for releasing vasopressin is lower than that for triggering thirst (Fig. 3) [12].

5.3.1. Osmoregulation and vasopressin release. Under normal circumstances, osmotic regulation of the release of vasopressin from the posterior pituitary primarily depends on the effective osmolality of the serum. Central osmoreceptors, expressing transient receptor potential vanilloid 1 (TRPV1), and peripheral osmoreceptors, expressing TRPV4, relay the information on osmolality [20, 21]. The stretch-inactivating cationic TRPV1 and TRPV4 channels transduce osmotically evoked changes in cell volume into functionally relevant changes in membrane potential. TRPV1 is an osmotically activated channel expressed in the vasopressin producing magnocellular cells and in the circumventricular organs [22, 23]. Recently, afferent neurons expressing the osmotically activated

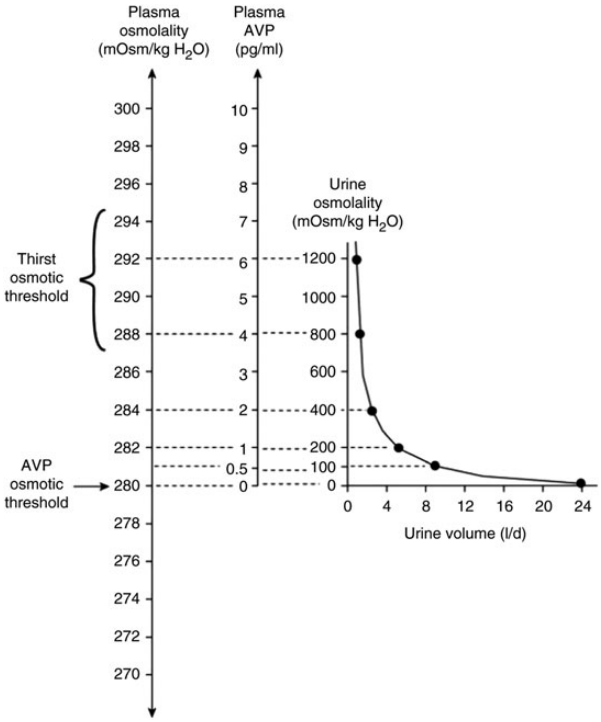


FIGURE 3: Osmotic stimulation of vasopressin release. Schematic representation of normal physiological relationships among plasma osmolality, plasma AVP concentrations, urine osmolality and urine volume in man. Note particularly the inverse nature of the relationship between urine osmolality and urine volume, resulting in disproportionate effects of small changes in plasma AVP concentrations on urine volume at lower AVP levels. Reproduced with permission from Elsevier Copyright © 2003 Verbalis JG. Disorders of body water homeostasis. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2003 **17** 471–503.

ion channel TRPV4 (able to detect physiological hypoosmotic shifts in blood osmolality) have been identified in the thoracic dorsal root ganglia, which innervate hepatic blood vessels [21].

5.3.2. Baroregulation of vasopressin release. Stretch-sensitive receptors in the left atrium, carotid sinus and aortic arch sense circulating volume. When the circulating volume is increased, afferent neural impulses inhibit the secretion of vasopressin [12]. Conversely, when the volume is decreased, the discharge rate of the stretch receptors slows and vasopressin secretion increases [24]. Reductions in blood pressure as little as 5% increase the serum vasopressin concentration [25]. In addition, there seems to be an exponential association between the serum vasopressin concentration and the percentage decline in mean arterial blood pressure, with faster increases as blood pressure progressively decreases.

Because osmoregulated and baroregulated vasopressin secretion are interdependent, renal water excretion can be maintained around a lower set point of osmolality under conditions of moderately decreased circulating volume [26]. As the circulatory hypovolaemia worsens, the serum vasopressin concentration dramatically increases and baroregulation overrides the osmoregulatory system.

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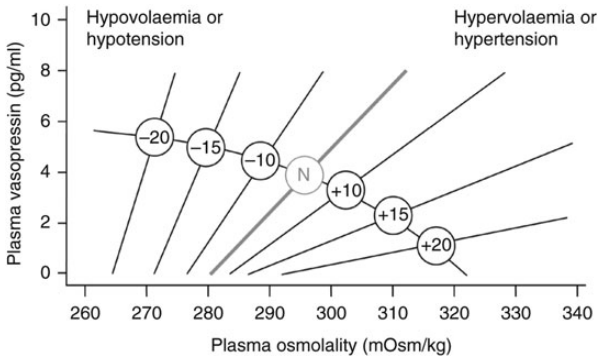


FIGURE 4: Effects of hypovolaemia on osmoreceptor gain. Reproduced with permission from The Endocrine Society Copyright © 1976 Robertson GL & Athar S. The interaction of blood osmolality and blood volume in regulating plasma vasopressin in man. *Journal of Clinical Endocrinology and Metabolism* 1976 **42** 613–620.

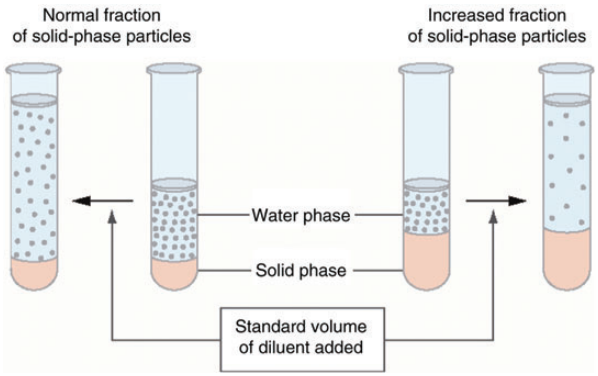


FIGURE 5: Pseudohyponatraemia. Normally, serum contains 7% solids by volume. In order to reduce the volume of blood needed for analysis, serum is frequently diluted before the actual measurement is obtained. The same volume of diluent is always used; the degree of dilution is estimated under the assumption that the serum contains 7% solid-phase particles. When the fraction of solid-phase particles is increased, the same amount of diluent results in a greater dilution, unbeknownst to the laboratory personnel (right side of figure). Consequently, the calculation of an ion level with the use of a degree of dilution that is based on the incorrect fraction of solid-phase particles will lead to an underestimate. Reproduced with permission from Massachusetts Medical Society Copyright © 2003 Turchin A, Seifter JL & Seely EW. Clinical problem-solving. Mind the gap. *New England Journal of Medicine* 2003 **349** 1465–1469.

Osmosensitive neurons are located in the subfornical organ and the organum vasculosum of the lamina terminalis. Because these neurons lie outside the blood–brain barrier, they integrate osmotic information with endocrine signals borne by circulating hormones, such as angiotensin II and atrial natriuretic peptide. The direct angiotensin II effect on osmoregulatory neurons has been termed 'osmoregulatory gain' since Zhang *et al.* [27] have shown that in rats, angiotensin II amplifies osmosensory transduction by enhancing the proportional relationship between osmolality, receptor potential and action potential firing in supra-optic nucleus neurons. Modifications in osmoregulatory gain induced by angiotensin, together with changes in vasopressin secretion induced by baroregulation (see below), may explain why the changes in the slope and threshold of the relationship between serum osmolality and vasopressin secretion are potentiated by hypovolaemia or hypotension and are attenuated by hypervolaemia or hypertension (Fig. 4) [28].

5.3.3. Unregulated vasopressin release. The posterior pituitary is the only organ in which regulated vasopressin release takes place. Under pathological conditions, both pituitary and other cells may also synthesise and secrete vasopressin independent of serum osmolality or circulating volume. Originally, Schwartz & Bartter [29] introduced the term syndrome of inappropriate antidiuretic hormone secretion (SIADH) as an overarching term. We now know that both genetic and pharmacological factors can also increase water permeability in the collecting duct in the absence of vasopressin. Others have previously introduced the term syndrome of inappropriate antidiuresis (SIAD) to cover both situations. We will use it throughout this text.

5.3.4. Renal actions of vasopressin. In order to re-absorb water from the collecting duct, and to concentrate the urine, the collecting duct must become permeable to water. The basolateral membrane is always permeable to water because of aquaporin-3 and aquaporin-4 water channels. Vasopressin regulates the permeability of the apical membrane by insertion of aquaporin-2 water channels through vasopressin-2-receptor activation. The high osmolality of the medulla provides the driving force needed for re-absorption of water from the collecting duct. Thanks to the counter current configuration of the loops of Henle, the kidney is able to create solute gradients from the cortex to the inner medulla. Because of the re-absorption of both sodium and urea from the lumen, the osmolality of the tip of the medulla may reach 1200 mOsm/l in case of water depletion. The medullary osmolality determines maximum urine osmolality and is influenced by vasopressin.

5.4. Pseudohyponatraemia

Pseudohyponatraemia is a laboratory artefact that occurs when abnormally high concentrations of lipids or proteins in the blood interfere with the accurate measurement of sodium. Pseudohyponatraemia was seen more frequently with flame photometric measurement of serum sodium concentration than it is now with ion-selective electrodes, but despite common opinion to the contrary, it still occurs [30], because all venous blood samples are diluted and a constant distribution between water and the solid phase of serum is assumed when the serum sodium concentration is calculated [30] (Fig. 5). Serum osmolality is measured in an undiluted sample and the result will be within the normal range in case of pseudohyponatraemia. If the measurement of serum osmolality is not available, direct potentiometry using a blood gas analyser will yield the true sodium concentration, as this measures the sodium concentration in an undiluted sample too.

5.5. Reset osmostat

In reset osmostat, there is a change in the set point as well as in the slope of the osmoregulation curve [12]. The response

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to changes in osmolality remains intact. We see this phenomenon, for example, in pregnancy where the serum sodium concentration may mildly decrease 4–5 mmol/l.

5.6. Non-hypotonic hyponatraemia

5.6.1. Isotonic hyponatraemia. In the majority of patients that present with hyponatraemia, the serum is hypotonic, i.e. both the sodium concentration and the effective osmolality are low. Sometimes, the serum contains additional osmoles that increase effective osmolality and reduce the serum sodium concentration by attracting water from the intracellular compartment. Examples of such osmoles include glucose (hyperglycaemia due to uncontrolled diabetes mellitus), mannitol and glycine (absorption of irrigation fluids during urological or gynaecological surgery) [31, 32, 33]. The resulting 'translocational' hyponatraemia is often wrongly considered a form of pseudohyponatraemia. However, as described earlier, in pseudohyponatraemia, serum osmolality is normal and no shifts of water occur.

5.6.2. Hypertonic hyponatraemia. In hyperglycaemia-induced hyponatraemia, hyponatraemia is caused by dilution due to hyperosmolality. It is important to make the distinction between measured osmolality and effective osmolality [34].

Effective osmolality may be calculated with the following equations:

Effective osmolality (mmol/kg H_2O) = 2 × (serum Na (mmol/l) + serum K (mmol))+ serum glycaemia (mg/dl)/18

Effective osmolality (mmol/kg H_2O) = 2 × (serum Na (mmol/l)+ serum K (mmol/l)) + serum glycaemia (mmol/l)

This includes only osmoles that are restricted to the extracellular fluid volume. As water returns to the intracellular space during treatment of hyperglycaemia, serum sodium concentration should increase, thus resulting in a constant effective osmolality. If it does not, brain oedema may ensue due to an overly rapid drop in effective osmolality [35].

5.6.3. Ineffective osmoles. High urea concentrations in kidney disease may also increase measured osmolality. However, urea is not an effective osmole because it readily passes across the cellular membrane. It does not change effective osmolality, does not attract water to the extracellular fluid compartment and does not cause hyponatraemia [36].

5.7. Hypotonic hyponatraemia with decreased extracellular fluid volume

Depletion of circulating volume, with or without deficit of total body sodium, can markedly increase the secretion of vasopressin leading to water retention despite hypotonicity. Although the vasopressin release in this case is inappropriate from an osmoregulatory point of view, it happens in order to preserve intravascular volume and can be considered appropriate from a circulatory point of view.

5.7.1. Non-renal sodium loss

5.7.1.1. Gastrointestinal sodium loss. Volume depletion can occur if the body loses sodium through its gastrointestinal tract. In case of severe diarrhoea, the kidneys respond by preserving sodium and urine sodium concentrations are very low. In case of vomiting, metabolic alkalosis causes renal sodium loss as sodium accompanies bicarbonate in the urine despite activation of the renin–angiotensin system. By contrast, in patients with diarrhoea, chloride accompanies ammonium excreted by the kidneys in an effort to prevent metabolic acidosis.

5.7.1.2. Transdermal sodium loss. The body can lose substantial amounts of sodium transdermally due to heavy sweating. This may be caused by impaired re-absorption of sodium in the sweat duct as in cystic fibrosis or by an impaired natural barrier function due to extensive skin burns. It results in increased vulnerability to sodium depletion and volume depletion. The amount of sodium that is lost in sweat varies markedly between healthy individuals, but to date, no link has been found between the sodium concentration in sweat and cystic fibrosis-causing mutations of the cystic fibrosis transmembrane conductance regulator gene [37].

5.7.2. Renal sodium loss

5.7.2.1. Diuretics. Urinary sodium loss can cause volume depletion and, if sufficiently severe, trigger vasopressin release. Diuretics and especially thiazides are frequently implicated as a cause of hyponatraemia. The traditional explanation is that renal sodium loss leads to volume contraction with subsequent release of vasopressin. However, this would require a substantial loss of sodium and body weight, while patients with thiazide-induced hyponatraemia often have increased body weight [38]. It might be reasonable to assume that thiazides directly induce the release of vasopressin or increase the response of the collecting duct to circulatory vasopressin. In any case, there appears to be an individual susceptibility to these effects, as hyponatraemia only occurs in certain patients and usually reoccurs if thiazides are reintroduced [38]. Despite the potential for causing more urinary sodium loss, loop diuretics only rarely cause hyponatraemia because they reduce osmolality in the renal medulla and thus limit the kidney's ability to concentrate urine [39].

5.7.2.2. Primary adrenal insufficiency. In primary adrenal insufficiency, hypoaldosteronism causes renal sodium loss, contracted extracellular fluid volume and hyponatraemia. Although primary adrenal insufficiency usually presents in combination with other clinical symptoms and biochemical abnormalities, hyponatraemia can be its first and only sign [40].

5.7.2.3. Cerebral salt wasting. Renal sodium loss has been documented in patients with intracranial disorders such as subarachnoid bleeding. This renal salt wasting has been rather confusingly named 'cerebral' salt wasting, and increased levels of brain natriuretic peptide have been implicated in its pathogenesis [41]. Because diagnosis may be difficult, and both inappropriate antidiuresis and secondary adrenal insufficiency are actually more common in this clinical setting, cerebral salt wasting may be over diagnosed [42]. Nevertheless, the recognition of cerebral salt wasting is important because its treatment requires volume resuscitation rather than water restriction.

5.7.2.4. Kidney disease. Renal salt wasting can also occur in kidney dysfunction. The so-called salt-losing nephropathies,

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such as tubulopathy after chemotherapy or in analgesic nephropathy, medullary cystic kidney disease and certain pharmacological compounds can inhibit the kidney's ability to re-absorb appropriate amounts of sodium [43].

5.7.3. Third spacing. Bowel obstruction, pancreatitis, sepsis or muscle trauma may markedly reduce effective circulating blood volume through fluid leakage from blood vessels. This causes baroreceptor activation and vasopressin release, which may result in hyponatraemia. Infusion of hypotonic fluids in this case may worsen hyponatraemia.

5.8. Hypotonic hyponatraemia with normal extracellular fluid volume

Euvolaemic hyponatraemia is caused by an absolute increase in body water, which results from an excessive fluid intake in the presence of an impaired free water excretion, either due to inappropriate release of vasopressin or due to a low intake of solutes.

5.8.1. Syndrome of inappropriate antidiuresis. The vasopressin secretion in SIADH is inappropriate because it occurs independently from effective serum osmolality or circulating volume. It may result from increased release by the pituitary gland or from ectopic production. Inappropriate antidiuresis may also result from increased activity of vasopressin in the collecting duct or from a gain-of-function mutation in its type 2 receptor [44]. Throughout this text, we will use the terminology 'SIAD' as an overarching term because management principles are the same for both conditions and any distinction is merely academic and out of the scope of this document [45].

In SIAD, antidiuresis causes progressive hyponatraemia until the expression of vasopressin V2 receptors and aquaporin-2 water channels is down-regulated, a process appropriately called 'vasopressin escape' [46]. Because of the vasopressin activity, urine osmolality will be inappropriately high (usually >100 mOsm/l) and this is one of the criteria required for a diagnosis of SIAD. The criteria are largely the same as originally proposed by Bartter & Schwartz [29]. Importantly, SIAD remains a diagnosis of exclusion (Table 6).

General anaesthesia, nausea, pain, stress and a variety of drugs are non-specific but potent stimuli for the secretion of vasopressin and a frequent cause of SIAD in hospitalised patients. The use of prescribed or illicit drugs may result in either increased vasopressin release or increased effects of vasopressin in the collecting duct. The most frequent causes of increased inappropriate secretion of vasopressin include cancers (e.g. small cell carcinoma of the lung) and diseases of the lung (e.g. pneumonia) or central nervous system (e.g. subarachnoid haemorrhage) (Table 7). Recently, several genetic disorders causing SIAD have been identified. Among them are polymorphisms resulting in a loss-of-function of *TRPV4*, a gene that encodes for an osmosensitive calcium channel expressed in osmosensing neurons [47]. Another is a gain-of-function mutation in the vasopressin 2 receptor, resulting in a constitutively activated receptor causing increased water reabsorption and chronic hyponatraemia [44].

Table 6. Diagnostic criteria for the syndrome of inappropriate antidiuresis. Adapted from Schwartz WB, Bennett W, Curelop S & Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *American Journal of Medicine* 1957 23 529–542 [29] and Janicic N & Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinology and Metabolism Clinics of North America* 2003 32 459–481, vii [242].

Essential criteria
Effective serum osmolality <275 mOsm/kg
Urine osmolality >100 mOsm/kg at some level of decreased effective osmolality
Clinical euvolaemia
Urine sodium concentration >30 mmol/l with normal dietary salt and water intake
Absence of adrenal, thyroid, pituitary or renal insufficiency
No recent use of diuretic agents
Supplemental criteria
Serum uric acid <0.24 mmol/l (<4 mg/dl)
Serum urea <3.6 mmol/l (<21.6 mg/dl)
Failure to correct hyponatraemia after 0.9% saline infusion
Fractional sodium excretion >0.5%
Fractional urea excretion >55%
Fractional uric acid excretion >12%
Correction of hyponatraemia through fluid restriction

5.8.2. Secondary adrenal insufficiency. The production of aldosterone is less impaired in secondary than in primary adrenal insufficiency and renal sodium loss does not contribute to the development of hyponatraemia. Secondary adrenal insufficiency is caused by reduced or absent secretion of adrenocorticotrophic hormone, resulting in hypocortisolism. Under normal circumstances, cortisol suppresses both production of corticotrophin-releasing hormone and vasopressin in the hypothalamus. In secondary adrenal insufficiency, persistently low concentrations of cortisol fail to suppress vasopressin and hyponatraemia results from impaired free water excretion, as it does in SIAD [48].

5.8.3. Hypothyroidism. Although included in many diagnostic algorithms, hypothyroidism very rarely causes hyponatraemia [49]. In 2006, Warner *et al.* [50] observed that serum sodium concentration decreased by 0.14 mmol/l for every 10 mU/l rise in thyroid-stimulating hormone, indicating that only severe cases of clinically manifest hypothyroidism resulted in clinically important hyponatraemia. Development of hyponatraemia may be related to myxoedema, resulting from a reduction in cardiac output and glomerular filtration rate [51].

5.8.4. High water and low solute intake. Under conditions of high water and low solute intake, the excess water intake is primarily responsible for hyponatraemia. Vasopressin activity is absent, which is reflected by an appropriately low urine osmolality, usually <100 mOsm/kg. Patients with primary polydipsia drink more than what the kidneys can eliminate. Primary polydipsia may occur in combination with psychiatric disorders such as schizophrenia. Although excess water intake contributes most to hyponatraemia, renal loss of solutes and an acquired impairment in free water excretion may also occur [52].

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Table 7. Causes of the syndrome of inappropriate antidiuresis. Adapted from Liamis G, *et al.* American *Journal of Kidney Diseases* 2008 52 144–153 [247].

Malignant diseases	Pulmonary disorders	Disorders of the nervous system	Drugs	Other causes
Carcinoma	Infections	Infection	Vasopressin release or action stimulants	Hereditary
Lung	Bacterial pneumonia	Encephalitis	Antidepressants	Gain-of-function mutation of the vasopressin V2 receptor
Oropharynx	Viral pneumonia	Meningitis	SSRIs	Idiopathic
Gastrointestinal tract	Pulmonary abscess	Brain abscess	Tricyclic	Transient
Stomach	Tuberculosis	Rocky Mountain spotted fever	MAOI	Exercise-associated hyponatraemia
Duodenum	Aspergillosis	AIDS	Venlafaxine	General anaesthesia
Pancreas	Asthma	Malaria	Anticonvulsants	Nausea
Genitourinary tract	Cystic fibrosis	Vascular and masses	Carbamazepine	Pain
Ureter	Respiratory failure associated with positive-pressure breeding	Subdural hematoma	Oxcarbazepine	Stress
Bladder		Subarachnoid haemorrhage	Sodium valproate	
Prostate		Stroke	Lamotrigine	
Endometrium		Brain tumours	Antipsychotics	
Endocrine thymoma		Head trauma	Phenothiazides	
Lymphomas		Other	Butyrophenones	
Sarcomas		Hydrocephalus	Anticancer drugs	
Ewing's sarcoma		Cavernous sinus thrombosis	Vinca alkaloids	
Olfactory neuroblastoma		Multiple sclerosis	Platinum compounds	
		Guillain–Barré syndrome	Ifosfamide	
		Shy–Drager syndrome	Melphalan	
		Delirium tremens	Cyclophosphamide	
		Acute intermittent porphyria	Methotrexate	
			Pentostatin	
			Antidiabetic drugs	
			Chlorpropamide	
			Tolbutamine	
			Miscellaneous	
			Opiates	
			MDMA (XTC)	
			Levamisole	
			Interferon	
			NSAIDs	
			Clofibrate	
			Nicotine	
			Amiodarone	
			Proton pump inhibitors	
			MABs	
			Vasopressin analogues	
			Desmopressin	
			Oxytocin	
			Terlipressin	
			Vasopressin	

AIDS, acquired immunodeficiency syndrome; MOAI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

The amount of water that the kidneys can remove on a daily basis depends on solute excretion and hence solute intake. Depending on the kidney's ability to dilute urine, 50–100 mmol of solutes, such as urea and salts, are required to remove 1 l of fluid. If solute intake is low relative to water intake, the number of available osmoles can be insufficient to remove the amount of water ingested. This is seen in patients with anorexia (nervosa), beer potomania and so-called 'tea and toast' hyponatraemia [53].

5.9. Hypotonic hyponatraemia with increased extracellular fluid volume

5.9.1. Kidney disease. When glomerular filtration rate deteriorates, or when there is tubular injury or scarring, the ability to dilute urine and excrete free water decreases. In advanced kidney disease, urine osmolality is usually close to serum osmolality (isosthenuria). Free water removal is no longer regulated by vasopressin but is determined by the number of osmoles excreted in the urine (i.e. solute intake).

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Consequently, hyponatraemia can readily develop if patients do not adhere to fluid restriction. In addition, in patients treated with peritoneal dialysis, the use of icodextrin-based dialysis solutions can cause clinically relevant hyponatraemia [54].

5.9.2. Heart failure. Approximately 20–30% of patients with chronic heart failure New York Heart Association (NYHA) classes III and IV have hyponatraemia [55]. It is associated with more severe heart failure and an increased risk of death, independent of other comorbid conditions [55, 56]. Whether this reflects (unacknowledged) disease severity or has a causal effect remains unclear. Although renal sodium retention tends to increase the extracellular volume, the effective circulating blood volume is generally reduced due to impaired cardiac output. Baroreceptor-mediated neurohumoral activation commonly results in increased secretion of vasopressin by the pituitary. Simultaneous activation of the renin–angiotensin system and increased release of vasopressin reduces urinary sodium excretion and increases urine osmolality. Although simultaneous use of diuretics may contribute to the development of hyponatraemia, loop diuretics have less potential for causing hyponatraemia than thiazides.

5.9.3. Liver failure. Also in liver failure, hyponatraemia is associated with poorer survival [57]. Whether this reflects disease severity or has a direct contributory effect remains unclear [58]. Systemic vasodilation and arteriovenous shunting of blood may reduce the effective arterial blood volume. As in heart failure, this reduction can lead to neurohumoral activation and water retention due to baroreceptor-mediated vasopressin release.

In addition, mineralocorticoid receptor blockers such as spironolactone, which either alone or in combination with loop diuretics, are frequently used to reduce sodium retention in liver failure, can contribute to hyponatraemia [59].

5.9.4. Nephrotic syndrome. In nephrotic syndrome, blood volume may be decreased due to the lower serum oncotic pressure (under-fill hypothesis). If this happens, stimulation of vasopressin secretion can cause patients to develop hyponatraemia. The tendency for water retention is generally balanced by intense sodium retention, but the increased renal reabsorption of sodium usually necessitates a considerable dose of diuretics. The combination of increased vasopressin release and diuretic use may promote moderate hyponatraemia, especially in children with low blood pressure [60].

6. DIAGNOSIS OF HYPONATRAEMIA

6.1. Classification of hyponatraemia

6.1.1. Definition of hyponatraemia based on biochemical severity

6.1.1.1. We define ‘mild’ hyponatraemia as a biochemical finding of a serum sodium concentration between 130 and 135 mmol/l as measured by ion-specific electrode.

6.1.1.2. We define ‘moderate’ hyponatraemia as a biochemical finding of a serum sodium concentration between 125 and 129 mmol/l as measured by ion-specific electrode.

6.1.1.3. We define ‘profound’ hyponatraemia as a biochemical finding of a serum sodium concentration <125 mmol/l as measured by ion-specific electrode.

6.1.2. Definition of hyponatraemia based on time of development

6.1.2.1. We define ‘acute’ hyponatraemia as hyponatraemia that is documented to exist <48 h.

6.1.2.2. We define ‘chronic’ hyponatraemia as hyponatraemia that is documented to exist for at least 48 h.

6.1.2.3. If hyponatraemia cannot be classified, we consider it being chronic, unless there is clinical or anamnestic evidence of the contrary (Table 8).

6.1.3. Definition of hyponatraemia based on symptoms

6.1.3.1. We define ‘moderately symptomatic’ hyponatraemia as any biochemical degree of hyponatraemia in the presence of moderately severe symptoms of hyponatraemia (Table 5).

6.1.3.2. We define ‘severely symptomatic’ hyponatraemia as any biochemical degree of hyponatraemia in the presence of severe symptoms of hyponatraemia (Table 5).

Rationale

- Why did we choose to set definitions?

  Hyponatraemia can be classified based on different parameters. These include serum sodium concentration, rate of development, symptom severity, serum osmolality and volume status. For this guideline, we wanted the

Table 8. Drugs and conditions associated with acute hyponatraemia (<48 h).

Postoperative phase
Post-resection of the prostate, post-resection of endoscopic uterine surgery
Polydipsia
Exercise
Recent thiazides prescription
3,4-Methylenedioxymethamfetamine (MDMA, XTC)
Colonoscopy preparation
Cyclophosphamide (i.v.)
Oxytocin
Recently started desmopressin therapy
Recently started terlipressin, vasopressin

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classification to be consistent and clear so that all users would have a correct understanding of the terminology used. We also wanted to make the classification directly relevant for patient management. However, treatment strategies cannot be adequately classified with reference to a single criterion. Hence, treatment strategies have been classified according to combinations of these criteria.

- What are these definitions based on?

Classification based on serum sodium concentration

Authors mostly use the terms 'mild', 'moderate' and 'severe' [61, 62, 63]. We have chosen to replace 'severe' by 'profound' to avoid confusion with the classification based on symptoms, for which we have reserved the term 'severe'. The definitions of mild, moderate and profound hyponatraemia in published research are variable, especially the threshold used to define profound hyponatraemia for which values have ranged from 110 to 125 mmol/l [64, 65]. Several studies report that when serum sodium concentrations drop below 125 mmol/l, symptoms become more common [61, 66, 67, 68, 69, 70, 71], and the correction to normonatraemia necessitates careful monitoring to avoid overly rapid correction [72].

Classification based on duration and speed of development

Published research suggests using a threshold of 48 h to distinguish 'acute' from 'chronic' hyponatraemia. Brain oedema seems to occur more frequently when hyponatraemia develops in <48 h [73, 74, 75, 76]. Experimental studies also suggest that the brain needs 48 h to adapt to a hypotonic environment, achieved mainly by extruding sodium, potassium, chloride and organic osmoles from its cells [77, 78, 79]. Before adaptation, there is a risk of brain oedema because the lower extracellular osmolality promotes a shift of water into the cells. However, once adaptation is completed, brain cells can again sustain damage if the serum sodium concentration increases too rapidly. Breakdown of the myelin sheath insulating individual neurons can result in what is called the osmotic demyelination syndrome [80, 81, 82, 83]. Consequently, it is important to distinguish between acute and chronic hyponatraemia to assess whether someone is at a greater risk of immediate brain oedema than of osmotic demyelination [84]. Unfortunately, in clinical practice, the distinction between acute and chronic hyponatraemia is often unclear, particularly for patients presenting to the emergency room. It is often unknown when the serum sodium concentration has started decreasing. If classifying hyponatraemia as acute or chronic is not possible, we have decided to consider hyponatraemia as being chronic, unless there are reasons to assume it is acute (Table 9). There is a good reason for this approach. Chronic hyponatraemia is much more common than acute hyponatraemia and should be managed accordingly to avoid osmotic demyelination [85, 86].

Classification based on symptoms

We have divided symptoms of hyponatraemia into 'moderately severe' and 'severe'. The distinction is based on selected observations in acute hyponatraemia; those who subsequently die more often experience what we define as severe symptoms than those who live [73, 74]. Moderately severe symptoms caused by brain oedema are less frequently associated with death. Nevertheless, they may rapidly progress to more severe symptoms associated with an adverse outcome.

We have purposefully omitted the category 'asymptomatic' as we believed this might create confusion. Patients are probably never truly 'asymptomatic' in the strictest sense of the word. Very limited and subclinical signs such as mild concentration deficits are seen even with mild hyponatraemia [13].

A classification based on symptoms aims to reflect the degree of brain oedema and the extent of immediate danger. It allows matching treatment to the immediate risk, with more aggressive treatment for symptoms that are more severe. Nevertheless, a classification based only on symptom severity has several shortcomings. First, symptoms of acute and chronic hyponatraemia may overlap [18]. Secondly, patients with acute hyponatraemia can present without clear symptoms, but go on to develop moderately severe to severe symptoms within hours [73]. Thirdly, symptoms of hyponatraemia are non-specific. Consequently, assessment of symptoms needs to happen with caution. Clinicians need to be wary that symptoms can be caused by conditions other than hyponatraemia, by other conditions in combination with hyponatraemia or by conditions that cause hyponatraemia. In general, one should be particularly careful when attributing moderately severe to severe symptoms to hyponatraemia when the biochemical degree of hyponatraemia is only mild (Table 5).

Table 9. Association between serum glucose concentration, measured serum sodium and corrected serum sodium concentration. Calculated using equation from Hillier TA, Abbott RD & Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. *American Journal of Medicine* 1999 106 399–403 [31].

	Measured (glucose) (mg/dl)							
	True (Na^+) (mmol/l)							
Measured (Na^+) (mmol/l)	100	200	300	400	500	600	700	800
135	135	137	140	142	145	147	149	152
130	130	132	135	137	140	142	144	147
125	125	127	130	132	135	137	139	142
120	120	122	125	127	130	132	134	137
115	115	117	120	122	125	127	129	132
110	110	112	115	117	120	122	124	127
105	105	107	110	112	115	117	119	122
100	100	102	105	107	110	112	114	117
95	95	97	100	102	105	107	109	112
90	90	92	95	97	100	102	104	107
85	85	87	90	92	95	97	99	102
80	80	82	85	87	90	92	94	97
75	75	77	80	82	85	87	89	92
70	70	72	75	77	80	82	84	87

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Classification based on serum osmolality

As this guideline aimed to cover the aspects of diagnosis and treatment specifically of hypotonic hyponatraemia, we needed to define what distinguishes hypotonic from non-hypotonic hyponatraemia. Because this distinction is a necessary first step in the diagnostic evaluation of any hyponatraemia, we have devoted a separate section to this topic (section 6.2). For reasons of completeness, we briefly mention it here. A measured serum osmolality <275 mOsm/kg always indicates hypotonic hyponatraemia, as effective osmolality can never be higher than total or measured osmolality. By contrast, if calculated osmolality is <275 mOsm/kg, hyponatraemia can be hypotonic, isotonic or hypertonic, depending on which osmotically active agents are present and whether or not they are incorporated in the formula.

Classification based on volume status

Patients with hyponatraemia may be hypovolaemic, euvolaemic or hypervolaemic [87]. Many traditional diagnostic algorithms start with a clinical assessment of volume status [88]. However, it is often not clear whether volume status in this context refers to the extracellular fluid volume, to the effective circulating volume or to the total body water. In addition, the sensitivity and specificity of clinical assessments of volume status are low, potentially leading to misclassification early in the diagnostic tree [89, 90]. Therefore, we have used the terms 'effective circulating volume' and 'extracellular fluid volume' throughout the text to reduce ambiguity.

- Note of caution

We wanted the classification of hyponatraemia to be consistent, easy to use and helpful for both differential diagnosis and treatment. Hyponatraemia can be classified according to different factors, each with advantages and pitfalls depending on the clinical setting and situation. We have prioritised the criteria such that we would obtain a classification that would be clinically relevant and as widely applicable as possible.

Nevertheless, the user should keep in mind that differential diagnosis of hyponatraemia is difficult and no classification can be 100% accurate in every situation. We emphasise that the different classifications of hyponatraemia are not mutually exclusive and that classification should always occur with the clinical condition and the possibility of combined causes of hyponatraemia in mind.

Questions for future research

- Is it possible to define thresholds of serum sodium concentration that categorise separate entities in terms of management and outcomes?
- Is 48 h the best threshold to separate acute from chronic hyponatraemia?
- Is it possible to identify symptoms or parameters that can reliably differentiate acute from chronic hyponatraemia?

6.2. Confirming hypotonic and excluding non-hypotonic hyponatraemia

6.2.1.1.	We recommend excluding hyperglycaemic hyponatraemia by measuring the serum glucose concentration and correcting the measured serum sodium concentration for the serum glucose concentration if the latter is increased (1D).
6.2.1.2.	Hyponatraemia with a measured osmolality <275 mOsm/kg always reflects hypotonic hyponatraemia (not graded).
6.2.1.3.	Accept as 'hypotonic hyponatraemia' a hyponatraemia without evidence for causes of non-hypotonic hyponatraemia as listed in Table 10 (not graded).

Advice for clinical practice

Estimates of the serum sodium concentration corrected for the presence of hyperglycaemia can be obtained from the following equations [31]:

$$\text{Corrected serum } (Na^+) = \text{measured } (Na^+) + 2.4 \times \frac{(\text{glucose (mg/dl)} - 100\ \text{(mg/dl)})}{100\ \text{mg/dl}}$$

$$\text{Corrected } (Na^+) = \text{measured } (Na^+) + 2.4 \times \frac{(\text{glucose (mg/dl)} - 5.5\ \text{(mmol/l)})}{5.5\ \text{mmol/l}}$$

Na^+, serum sodium concentration; glucose, serum glucose concentration.

This translates into adding 2.4 mmol/l to the measured serum sodium concentration for every 5.5 mmol/l (100 mg/dl) incremental rise in serum glucose concentration above a standard serum glucose concentration of 5.5 mmol/l (100 mg/dl).

Alternatively, the estimated value of the corrected serum sodium concentration across a range of serum glucose concentrations can be obtained from Table 9.

Rationale

- Why the question?

Non-hypotonic hyponatraemia does not cause brain oedema and is managed differently from hypotonic hyponatraemia. As this guideline covers management of hypotonic hyponatraemia, confirmation of hypotonicity is a prerequisite.

- What are the criteria based on?

There are broadly three categories of non-hypotonic hyponatraemia: hyponatraemia in the presence of a surplus of 'effective' osmoles, hyponatraemia in the presence of a surplus of 'ineffective' osmoles and pseudohyponatraemia (Table 10) [30, 34, 36, 88, 91].

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Table 10. Causes of non-hypotonic hyponatraemia.

Setting	Serum osmolality	Examples
Presence of 'effective' osmoles that raise serum osmolality and can cause hyponatraemia	Isotonic or hypertonic	Glucose [31] Mannitol [32] Glycine [33] Histidine–tryptophan–ketoglutarate [243] Hyperosmolar radiocontrast media [244] Maltose [245]
Presence of 'ineffective' osmoles that raise serum osmolality but do not cause hyponatraemia	Isotonic or hyperosmolar	Urea [36] Alcohols [36] Ethylene glycol [36]
Presence of endogenous solutes that cause pseudohyponatraemia (laboratory artifact)	Isotonic	Triglycerides [97], cholesterol [97] and protein Intravenous immunoglobulins [96] Monoclonal gammapathies [246]

Effective osmoles

Exogenous or endogenous solutes to which cell membranes are impermeable are restricted to the extracellular fluid compartment and are effective osmoles because they create osmotic pressure gradients across cell membranes leading to osmotic movement of water from the intracellular to the extracellular compartment [34, 36]. Because dilutional hyponatraemia results from the water shift from the intracellular to the extracellular compartment, there is no risk of brain oedema. Depending on the serum concentration of effective osmoles, the resulting non-hypotonic hyponatraemia can be isotonic or hypertonic. The prime example is hyperglycaemia [31]. Others include infusion of mannitol or perioperative absorption of irrigation fluids such as glycine [32, 33]. The latter most frequently occurs during transurethral resection of the prostate (TURP) and is therefore also referred to as 'TURP-syndrome'. Although TURP syndrome causes isotonic hyponatraemia and hence does not cause brain oedema, neurological symptoms may develop due to accumulation of ammonia, serine or glyoxylate from the metabolism of glycine [92, 93].

It is important to understand the kinetics of non-hypotonic hyponatraemia in the presence of effective osmoles. When glucose, mannitol or glycine are metabolised or excreted, serum osmolality decreases. This reduces the osmotic gradient, resulting in less water being pulled from the cells and spontaneously limiting the degree of hyponatraemia. It explains why during treatment of diabetic ketoacidosis or the hyperosmolar hyperglycaemic state a decrease in serum glycaemia leads to a 'spontaneous' rise in the serum sodium concentration. If the serum glucose concentration drops to a greater extent than the serum sodium concentration rises, serum effective osmolality will decrease. This can lead to brain oedema [35, 94]. Consequently, calculating 'effective' osmolality during treatment is important [35].

Ineffective osmoles

Solutes to which cell membranes are permeable are ineffective solutes because they do not create osmotic pressure gradients across cell membranes and therefore are not associated with water shifts [36, 91]. Consequently, they do not cause hyponatraemia. In other words, although the presence of ineffective osmoles will make any existing hyponatraemia isomolar or hyperosmolar, the cause of hyponatraemia should be sought elsewhere. The serum is in fact hypotonic and water will still move from the extracellular to the intracellular compartment. It means patients are still at risk of brain oedema if hyponatraemia develops quickly. Examples of ineffective osmoles include urea, ethanol and methanol (Table 10).

Pseudohyponatraemia

Pseudohyponatraemia is a laboratory artefact that occurs when abnormally high concentrations of lipids or proteins in the blood interfere with the accurate measurement of sodium [30, 95, 96, 97]. Pseudohyponatraemia still occurs despite the use of ion-selective electrodes [30]. This is because venous blood samples are always diluted and a constant distribution between water and the solid phase of serum is assumed when the serum sodium concentration is calculated (Fig. 5). This is called indirect ion-selective electrode measurement and used in large-scale analysers, e.g. in central laboratories. Serum osmolality is measured in an undiluted sample, and in case of pseudohyponatraemia (isotonic hyponatraemia), the result will be within the normal range. Other methods for diagnosing pseudohyponatraemia include direct potentiometry using a blood gas analyser (i.e. direct ion-specific electrode measurement) in which case no dilution of the sample occurs, or measurement of serum triglycerides, cholesterol and total protein concentration [30, 97, 98]. Differences between direct and indirect ion-specific electrode measurement of 5–10% have been reported in hypotonic hyponatraemia [99, 100]. Switching between indirect and direct ion-specific electrode measurements should be avoided in this situation.

- How did we translate this into a diagnostic strategy?

Because hyperglycaemia is by far the most common cause of non-hypotonic hyponatraemia, we have added

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excluding hyperglycaemic hyponatraemia in our diagnostic algorithm and detailed how it can be done. In addition, we have added excluding other causes of non-hypotonic hyponatraemia listed in Table 10. How this should be done is beyond the scope of this guideline.

The ability to measure serum osmolality may vary from centre to centre, especially out of office hours. During the discussions within the guideline development group, the importance of measured urine osmolality for the differential diagnosis of hyponatraemia was underscored. Hence, we reasoned it would be illogical not to recommend an additional measurement of serum osmolality because it is not always available. However, although measuring serum osmolality in all patients with hyponatraemia may seem useful, there are no hard data confirming this improves diagnosis or outcome. Hence, we equally accept alternative approaches for ruling out non-hypotonic hyponatraemia. These approaches include evaluating the clinical context (e.g. infusion of mannitol or recent urological surgery), measuring the serum concentration of additional osmoles (e.g. urea, lactate and alcohol) or measuring the serum concentration of analytes that can cause pseudohyponatraemia (e.g. serum triglycerides, cholesterol and total protein).

Questions for future research

- Is the factor with which to correct the serum sodium concentration for glycaemia valid for all ranges of glycaemia and applicable to all patients?
- What is the incidence of pseudohyponatraemia?
- Does measuring serum osmolality in all patients with hyponatraemia improve the diagnostic process and outcomes of hyponatraemia?

6.3. Which parameters to be used for differentiating causes of hypotonic hyponatraemia?

6.3.1.1.	We recommend interpreting urine osmolality of a spot urine sample as a first step (1D).
6.3.1.2.	If urine osmolality is ≤100 mOsm/kg, we recommend accepting relative excess water intake as a cause of the hypotonic hyponatraemia (1D).
6.3.1.3.	If urine osmolality is >100 mOsm/kg, we recommend interpreting the urine sodium concentration on a spot urine sample taken simultaneously with a blood sample (1D).
6.3.1.4.	If urine sodium concentration is ≤30 mmol/l, we suggest accepting low effective arterial volume as a cause of the hypotonic hyponatraemia (2D).
6.3.1.5.	If urine sodium concentration is >30 mmol/l, we suggest assessing extracellular fluid status and use of diuretics to further differentiate likely causes of hyponatraemia (2D).
6.3.1.6.	We suggest against measuring vasopressin for confirming the diagnosis of SIADH (2D).

Advice for clinical practice

- Correct interpretation of laboratory measurements requires contemporaneous collection of blood and urine specimens.
- For practical reasons, urine osmolality and sodium concentration are best determined in the same urine sample.
- If clinical assessment indicates that the volume of extracellular fluid is not overtly increased and the urine sodium concentration is >30 mmol/l, exclude other causes of hypotonic hyponatraemia before implicating SIAD. Consider using the diagnostic criteria listed in Table 6 and look for known causes of SIAD.
- Consider primary or secondary adrenal insufficiency as an underlying cause of the hypotonic hyponatraemia.
- Kidney disease complicates differential diagnosis of hyponatraemia. Besides possibly contributing to hyponatraemia, the ability of the kidneys to regulate urine osmolality and urine sodium is often diminished, much as with the use of diuretics. As urine osmolality and sodium may no longer reflect the effects of regular hormonal axes regulating sodium homeostasis, any diagnostic algorithm for hyponatraemia must be used with caution in patients with kidney disease.
- The water-loading test is generally not helpful for differential diagnosis of hypotonic hyponatraemia and may be dangerous in this setting.

Rationale

- Why this question?

  Hypotonic hyponatraemia has many possible underlying causes. These include, but are not limited to, non-renal sodium loss, diuretics, third spacing, adrenal insufficiency, SIAD, polydipsia, heart failure, liver cirrhosis and nephrotic syndrome (see sections 5.6 and 5.8). Clinicians have traditionally used the clinical assessment of 'volume status' for classifying hyponatraemia as hypovolaemic, euvolaemic or hypervolaemic [87, 101, 102]. However, clinical assessment of volume status is generally not very accurate [90]. Hence, we wanted to know which tests are most useful in differentiating causes of hypotonic hyponatraemia, in which order we should use them and what threshold values have the highest diagnostic value.
- What did we find?

Clinical assessment of fluid status

We found two studies indicating that in patients with hyponatraemia, clinical assessment of volume status has both low sensitivity (0.5–0.8) and specificity (0.3–0.5) [89, 103]. Similarly, it seems that clinicians often misclassify hyponatraemia when using algorithms that start with a clinical assessment of volume status [88]. Using an algorithm in which urine osmolality and urine sodium concentration are prioritized over assessment of volume status, physicians in training had a better diagnostic performance than senior physicians who did not use the algorithm [104].

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Urine osmolality

In the evaluation of hyponatraemia, urine osmolality is used to assess vasopressin activity [84]. Unfortunately, we found no study evaluating the sensitivity and specificity of a particular threshold. Physiologically, one would expect maximally dilute urine, in the presence of hypotonic hyponatraemia, unless hypo-osmolality fails to fully suppress vasopressin release. In hyponatraemia primarily caused by excess water intake, vasopressin release is suppressed resulting in urine osmolality usually <100 mOsm/kg [105]. By contrast, in case of non-suppressed vasopressin activity, urine osmolality usually exceeds serum osmolality [106]. This leaves a 'grey area' for urine osmolalities between 100 mOsm/kg and the value of the serum osmolality [84]. In this range, one cannot be clear about the presence or absence of vasopressin activity and excessive fluid intake may outweigh only moderately suppressed vasopressin activity [85].

Urine sodium concentration

We found five studies assessing diagnostic accuracy of urine sodium concentration for differentiating hypovolaemia from euvolaemia or hypervolaemia. All studies used a rise in serum sodium concentration after the infusion of 0.9% sodium chloride as the reference standard for diagnosing hypovolaemia [89]. Four studies assessed the sensitivity and specificity of a urine sodium concentration >30 mmol/l for diagnosis of euvolaemia vs hypovolaemia [89, 103, 107, 108]. All found similarly high sensitivity estimates ranging from 0.87 to 1.0 but variable specificity estimates ranging from 0.52 to 0.83 [89, 103, 108]. Fenske *et al.* also included hypervolaemic patients. They assessed the same threshold for distinguishing hypovolaemia from euvolaemia and hypervolaemia but analysed patients with and without diuretics separately [107]. A urine sodium concentration >30 mmol/l had high estimated sensitivities of 1.0 and 0.94 respectively in patients off and on diuretics, but low specificities of 0.69 and 0.24 respectively [107]. Others evaluated the diagnostic accuracy of a urine sodium concentration >50 mmol/l [109] and >20 mmol/l [109] but found lower sensitivities and specificities respectively than with a threshold of 30 mmol/l.

Other laboratory tests

Several other diagnostic laboratory tests have been evaluated for their ability to distinguish euvolaemia from hypovolaemia and hypervolaemia in patients treated with and without diuretics. These tests include serum urea concentration, serum uric acid concentration, fractional sodium excretion, fractional uric acid excretion, fractional urea excretion and plasma copeptin concentration [103, 107, 108, 110]. Overall, fractional excretion of uric acid using a threshold of >12% seemed most useful for distinguishing hyponatraemia due to SIAD from non-SIAD hyponatraemia in patients under diuretics with a sensitivity of 0.86 and specificity of 1.0. In comparison with urine sodium concentration, fractional uric acid excretion may be a better test for differentiating hyponatraemia in patients who are also treated with diuretic therapy, but these results need to be confirmed in a separate cohort before this parameter can be recommended for routine use clinically [107].

Diagnostic difficulty with diuretics

The diagnostic difficulty we face with diuretics is that patients on these medications may have increased, normal or decreased extracellular and circulating volume and can have increased or decreased urine sodium concentration, depending on the timing of the most recent tablet, irrespective of their underlying volume status. The natriuresis induced by diuretics may cause 'appropriate' vasopressin release and subsequently hyponatraemia because of a decrease in circulating volume. Finally, diuretics may cause a SIAD-like state characterised by normal or mildly increased extracellular fluid volume [38, 111].

Urine sodium concentration can also be low in patients with heart failure or liver cirrhosis, due to reduced effective circulating arterial volume, even when they are taking diuretics (diuretic resistance) [112] (Appendix 6. Summary tables 1A and 1B).

- How did we translate the evidence into a differential diagnostic strategy?

We translated the diagnostic evidence into a diagnostic decision tree, leading to a point where specific underlying causes can be derived from the clinical setting or history (Fig. 6). However, for obvious reasons, this diagnostic tree is a simplification and does not guarantee completeness in each individual. Of note, severely symptomatic hyponatraemia always requires immediate treatment, which should be prioritised over further diagnostic differentiation.

Urine osmolality

Although there are no diagnostic test accuracy studies assessing optimal thresholds for identifying vasopressin activity, a urine osmolality ≤100 mOsm/kg on a spot urine sample always indicates maximally dilute urine. Hyponatraemia primarily caused by excess water intake or (beer) potomania with low solute intake belongs to this category [53, 113]. Because determining urine osmolality is a simple method for confirming an excess of fluid intake relative to solute intake, we recommend it as a first step in the diagnostic strategy.

Urine sodium concentration

A urine osmolality >100 mOsm/kg should trigger additional diagnostic testing to determine the underlying cause of hyponatraemia: ultimately classified into hyponatraemia with increased, normal or reduced extracellular fluid volume. Because clinical assessment of fluid status is often difficult and may lead clinicians down the wrong path, we have consciously steered away from the traditional approach of including it in the algorithm here. Instead, we recommend determining urine sodium concentration on a spot urine sample.

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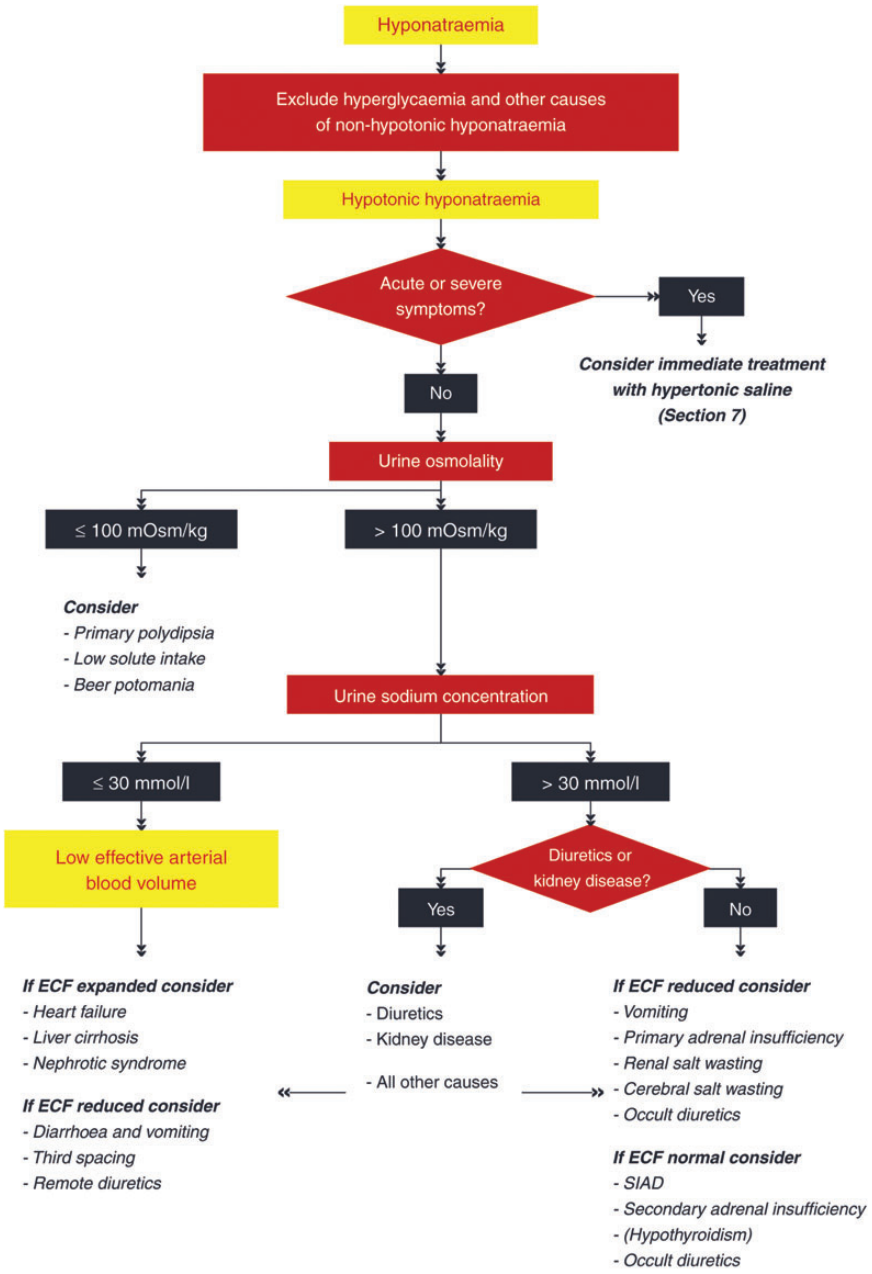


FIGURE 6: Algorithm for the diagnosis of hyponatraemia.

It is important to collect the serum and urine sample around the same time to allow correct interpretation of the values. We have selected a urine sodium concentration threshold of 30 mmol/l because several studies indicated good sensitivity and acceptable specificity in distinguishing hypovolaemia from euvolaemia or hypervolaemia [89, 103, 107, 108]. This means that a urine sodium concentration ≤30 mmol/l suggests low effective arterial blood volume, even in patients on diuretics.

Diagnostic difficulty with diuretics

We suggest interpreting urine sodium concentrations >30 mmol/l with caution if patients are taking diuretics. In patients using diuretics, a fractional excretion of uric acid <12% may be better than urine sodium concentration to differentiate reduced effective circulating volume from SIAD as the underlying cause of hyponatraemia, although this assertion needs further confirmation [107]. We acknowledge that it may also be difficult to obtain the necessary measurements for calculating fractional uric acid excretion. For these reasons, we have refrained from advising to routinely calculate it in clinical practice.

Instead, we have taken a more pragmatic approach. First, we suggest that in patients taking diuretics, the diuretics be considered a contributing factor to hyponatraemia. Keep in mind that patients may not be aware they are taking diuretics or that their use may not have been recorded.

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Although all types of diuretics have been associated with hyponatraemia, thiazide diuretics are most commonly the culprit [39]. Potassium-sparing diuretics such as mineralocorticoid receptor blockers and amiloride may also cause hyponatraemia. It occurs less frequently with loop diuretics because they interfere with the renal concentrating mechanism [17]. Importantly, the use of diuretics does not exclude other causes of hyponatraemia. Other causes require consideration especially if hyponatraemia persists after cessation of the diuretic (unresolved hyponatraemia).

Clinical assessment of fluid status

In the absence of diuretics, a clinical assessment of the volume status may aid further differential diagnosis. Although we have avoided it previously, we feel using it this far down the algorithm is less likely to lead to misclassification. There are fewer possible causes and they are easier to distinguish from one another. Based on the combination of urine sodium concentration and clinical assessment of extracellular fluid volume, we can define four clinical categories that naturally suggest a number of underlying causes (Fig. 6). The pathophysiology of these conditions is detailed in section 5.

Unresolved hyponatraemia

We have labelled hyponatraemia 'unresolved' if it persists after cause-specific treatment (see section 7). If hyponatraemia is unresolved, the initial diagnosis of the underlying cause was probably wrong or only part of the explanation. Reassessment using the diagnostic algorithm may help. One may also want to consider seeking expert diagnostic advice.

A special note on SIAD

SIAD is a diagnosis of exclusion. It fits the category of hyponatraemia with a urine osmolality >100 mOsm/kg, urine sodium concentration ≥30 mmol/l and normal extracellular fluid volume, but formal diagnosis requires exclusion of other possible causes of hyponatraemia. One such possible cause is adrenal insufficiency. In secondary adrenal insufficiency, hypocortisolism stimulates vasopressin release and like in SIAD, hyponatraemia develops through non-suppressed vasopressin activity [114, 115]. Primary adrenal insufficiency can present with hyperkalaemia and orthostatic hypotension but may occur without signs of reduced extracellular fluid volume and indeed resemble SIAD [40, 116, 117, 118]. Hyponatraemia due to hypothyroidism is very rare other than in myxoedema coma, when there is also a decrease in cardiac output and glomerular filtration rate [49, 51]. In 2006, Warner *et al.* [50] did identify a correlation between newly diagnosed hypothyroidism and decreased serum sodium but found this effect to be small and clinically irrelevant.

It is important to consider whether the diagnostic criteria for SIAD are met (Table 6) and look for known causes of inappropriate antidiuresis (Table 7) [29, 45]. In theory, a diagnosis of SIAD requires all essential criteria to be met. If they are not, the presence of supplemental criteria increases the likelihood of SIAD. The original supplemental criteria for SIADH included an inappropriately elevated vasopressin concentration relative to serum osmolality. Although there was no systematic evaluation of the value of plasma vasopressin measurements, the guideline development group believed that it does not contribute to the diagnosis in practice, mainly due to the technical difficulties in measurement, and of interpretation due to the variable relationship between vasopressin concentrations and the resulting electrolyte-free water excretion. The guideline development group therefore feels that measurement of vasopressin cannot be recommended.

The original supplemental criteria for SIADH included an abnormal result of a water-loading test to distinguish it from reset osmostat. However, we did not find data by which we could assess the value of water-loading tests. In addition, during group discussions, a fear of water-loading tests in patients with hypotonic hyponatraemia was expressed, as they may aggravate hypotonicity. Ultimately, it was decided to issue a warning against using it as a diagnostic test in SIAD.

Cerebral salt wasting is a rare condition that has been observed in patients with intracranial disorders such as subarachnoid bleeding [41]. It can reduce extracellular fluid volume due to profound natriuresis. A very high urine sodium concentration, a high serum urea, orthostatic hypotension and a low central venous pressure argue in favour of cerebral salt wasting (Table 11) [42].

Questions for future research

- What is the diagnostic performance of the new diagnostic algorithm included in this guideline?
- Can the addition of newer diagnostic parameters such as uric acid or copeptin or the replacement of the classical parameters by novel ones further improve the accuracy of the diagnosis of hyponatraemia?
- Is it still necessary to exclude hypothyroidism in the differential diagnosis of hyponatraemia?

Table 11. Differences between SIADH and cerebral salt wasting. Adapted from Sherlock M, O'Sullivan E, Agha A, Behan LA, Rawluk D, Brennan P, Tormey W & Thompson CJ. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. *Clinical Endocrinology* 2006 64 250–254 [42].

	SIADH	Cerebral salt wasting
Serum urea concentration	Normal–low	Normal–high
Serum uric acid concentration	Low	Low
Urine volume	Normal–low	High
Urine sodium concentration	>30 mmol/l	≫30 mmol/l
Blood pressure	Normal	Normal–orthostatic hypotension
Central venous pressure	Normal	Low

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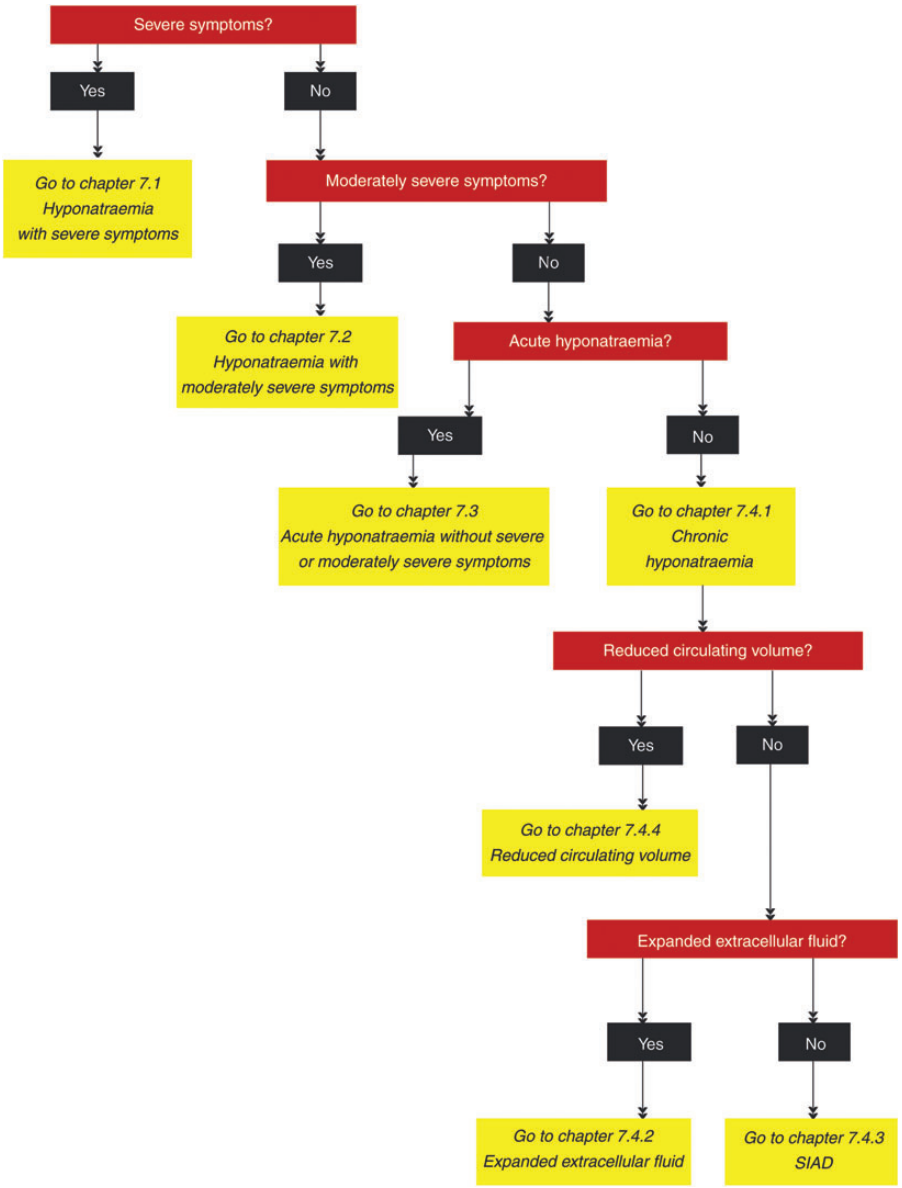


FIGURE 7: Algorithm for the management of hypotonic hyponatraemia.

7. TREATMENT OF HYPOTONIC HYPONATRAEMIA

How to use the treatment recommendations

The advice provided in this section follows a specific hierarchy as illustrated in Fig. 7. Individual recommendations and statements can only be correctly interpreted and implemented if considered within this structure. This is a consequence of the choice to use different classifications for hyponatraemia, as explained in section 6.1.

The guideline development group believed that with severe or moderately severe symptoms, the risk of brain oedema outweighs the risk of osmotic demyelination syndrome. They believed that it justifies urgent treatment in these conditions, irrespective of biochemical degree or timing (acute vs chronic) of hyponatraemia. Conversely, the guideline development group believed that in the absence of severe or moderately severe symptoms, there is time for diagnostic assessment and cause-specific treatment is the most reasonable approach.

For a correct interpretation of the algorithm in question, it is crucial to understand that for correctly classifying symptoms as 'severe' or 'moderately severe', there must be sufficient confidence that the symptoms are caused by hyponatraemia. If hyponatraemia is mild and symptoms are severe or moderately severe (Table 5), the guideline development group advises to only accept causality in exceptional cases. Consequently, generally, sections 7.1, 7.2 and 7.3 are not applicable when hyponatraemia is mild.

It is also essential to understand that the guideline development group distinguishes between targets and limits. A target

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is a goal one is aiming for; it is the change in serum sodium concentration that one wishes and expects to achieve with a particular treatment. By contrast, a limit is a change in serum sodium concentration one does not want to exceed and if surpassed, requires prompt counter-regulating intervention as described in section 7.5. In addition, the reader should bear in mind that the absolute numbers provided as 'targets' or 'limits' should always be interpreted in the clinical context of the individual patient.

7.1. Hyponatraemia with severe symptoms

7.1.1. First-hour management, regardless of whether hyponatraemia is acute or chronic

7.1.1.1. We recommend prompt i.v. infusion of 150 ml 3% hypertonic over 20 min (1D).

7.1.1.2. We suggest checking the serum sodium concentration after 20 min while repeating an infusion of 150 ml 3% hypertonic saline for the next 20 min (2D).

7.1.1.3. We suggest repeating therapeutic recommendations 7.1.1.1 and 7.1.1.2 twice or until a target of 5 mmol/l increase in serum sodium concentration is achieved (2D).

7.1.1.4. Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided (not graded).

7.1.2. Follow-up management in case of improvement of symptoms after a 5 mmol/l increase in serum sodium concentration in the first hour, regardless of whether hyponatraemia is acute or chronic

7.1.2.1. We recommend stopping the infusion of hypertonic saline (1D).

7.1.2.2. We recommend keeping the i.v. line open by infusing the smallest feasible volume of 0.9% saline until cause-specific treatment is started (1D).

7.1.2.3. We recommend starting a diagnosis-specific treatment if available, aiming at least to stabilise sodium concentration (1D).

7.1.2.4. We recommend limiting the increase in serum sodium concentration to a total of 10 mmol/l during the first 24 h and an additional 8 mmol/l during every 24 h thereafter until the serum sodium concentration reaches 130 mmol/l (1D).

7.1.2.5. We suggest checking the serum sodium concentration after 6 and 12 h and daily afterwards until the serum sodium concentration has stabilised under stable treatment (2D).

7.1.3. Follow-up management in case of no improvement of symptoms after a 5 mmol/l increase in serum sodium concentration in the first hour, regardless of whether hyponatraemia is acute or chronic

7.1.3.1. We recommend continuing an i.v. infusion of 3% hypertonic saline or equivalent aiming for an additional 1 mmol/l per h increase in serum sodium concentration (1D).

7.1.3.2. We recommend stopping the infusion of 3% hypertonic saline or equivalent when the symptoms improve, the serum sodium concentration increases 10 mmol/l in total or the serum sodium concentration reaches 130 mmol/l, whichever occurs first (1D).

7.1.3.3. We recommend additional diagnostic exploration for other causes of the symptoms than hyponatraemia (1D).

7.1.3.4. We suggest checking the serum sodium concentration every 4 h as long as an i.v. infusion of 3% hypertonic saline or equivalent is continued (2D).

Advice for clinical practice

- Prompt infusion of hypertonic saline may save lives. However, preparing a 3% hypertonic saline infusion takes time and errors may occur in calculating the required amount of sodium chloride. Therefore, it may be wise for the pharmacy to store pre-prepared 150 ml bags of 3% hypertonic saline. It ensures that solutions are prepared under sterile conditions, by either the pharmacist or the manufacturer, and are available for immediate infusion without having to prepare them on the spot.
- Consider using weight-based (2 ml/kg) rather than the fixed 150 ml infusion volumes of 3% hypertonic saline in case of obviously deviant body composition.
- Do not expect patients with severe symptoms to completely recover immediately, as it may take some time for the brain to fully recover. Be aware that sometimes it may not be possible to assess an improvement in symptoms, e.g. because the patient is intubated and sedated. In these cases, we advise to follow guidance as described under 7.1.2.
- Keep in mind that if hypokalaemia is present, correction of the hypokalaemia will contribute to an increase in serum sodium concentration.
- To achieve the 1 mmol/l per h increase advised in 7.1.2.1, the formula of Adrogué–Madias may be used, but keep in mind that the actual increase may exceed the calculated increase [87]:

$$\text{change in serum } (Na^+) = \frac{\text{infusate } (Na^+) - \text{serum } (Na^+)}{\text{total body water} + 1}$$

$$\text{change in serum } (Na^+) = \frac{\text{infusate } (Na^+) + \text{infusate } (K^+) - \text{serum } (Na^+)}{\text{total body water} + 1}$$

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Na^+, sodium concentration (mmol/l); K^+, potassium concentration (mmol/l). The numerator in formula 1 is a simplification of the expression in formula 2, with the value yielded by the equation (mmol/l). The estimated total body water (l) is calculated as a fraction of body weight. The fraction is 0.6 in non-elderly men and 0.5 in non-elderly women and 0.5 and 0.45 in elderly men and women respectively. Normally, extracellular and intracellular fluids account for 40 and 60% of total body water respectively.

Rationale

- Why this question?

  When hyponatraemia causes severe symptoms, it reflects the presence of brain oedema. If not treated, death may rapidly follow. On the other hand, when hyponatraemia is chronic and the serum sodium concentration increases too rapidly, osmotic demyelination syndrome may develop and permanent brain damage may ensue. Infusion of hypertonic saline can rapidly raise the serum sodium concentration, but for clinicians, the indications, infusion speed and target serum sodium concentration are often unclear.

- What did we find?

  Overall, the body of evidence to base recommendations on this topic was limited. Several early case series reported the use of i.v. hypertonic saline as treatment for hyponatraemia [119, 120, 121, 122, 123, 124, 125]. However, settings, biochemical severity, rate of development, symptoms and co-interventions differed widely both between and within studies and were often difficult to assess. Insufficiently detailed reporting often made it difficult to assess the increases in serum sodium concentration that were attained and to what extent these studies were applicable to patients who present with severe symptoms according to our definitions.

  In a case series published in 1982, seven patients with moderately severe to severe symptoms and profound hyponatraemia (mean serum sodium concentration 99 mmol/l) were treated with a 3% hypertonic saline i.v. infusion, resulting in a mean 2.4 ± 0.5 mmol/l per h increase in serum sodium concentration. Infusion rates differed between patients [120]. In 1986, Worthley *et al.* reported five patients who presented with seizures caused by acute hyponatraemia. They were treated with 250 mmol sodium chloride, infused over 10 min [119]. Serum sodium concentrations increased with a mean of 7.4 ± 1.1 mmol/l after 1 h and neurological symptoms promptly improved in all five cases. In a retrospective chart review of 11 patients with acute hyponatraemia, Hsu saw similar clinical outcomes. After infusion of 250–750 ml 3% NaCl, presenting symptoms of seizures and delirium resolved, although averaged initial increases in serum sodium concentration were limited to 1.6 ± 0.5 mmol/l per h [85].

  Woo *et al.* retrospectively described the results of a fixed protocol for correcting acute hyponatraemia in 49 neurosurgical patients: a 3% hypertonic saline infusion, starting at 20 ml/h and adapted based on 6 h measurements of the serum sodium concentration. Serum sodium concentrations increased a mean 0.4 ± 0.4 mmol/l per h. There was minimal hypernatraemia [121]. The extent and type of symptoms were not reported.

  We found one prospective non-comparative trial including 58 participants with profound hyponatraemia (mean serum sodium concentration 114 mmol/l) and moderately severe to severe symptoms. Patients were treated according to a protocol in which 100 ml 3% hypertonic saline was infused over 4 h with later adjustment according to biochemical response. After the initial infusion, the serum sodium concentration increased a median 2 mmol/l (range 0–6 mmol/l). In 22%, the serum sodium concentration did not increase after the first infusion and 19% required 200 ml while 3% required 300 ml for an initial increase of 1 mmol/l [126].

  Mohmand *et al.* [122] retrospectively reported 62 cases of hyponatraemia treated with 3% hypertonic saline at a median infusion rate of 0.38 ml/kg per h. The treatment resulted in an average increase in serum sodium concentration of 0.5 ± 0.1 mmol/l per h with a mean total increase of 7.1 ± 0.6 mmol/l and 11.3 ± 0.7 mmol/l per h in the first and second 24 h. However, in 11 and 10% of cases, the increase was >12 mmol/l per 24 h and >18 mmol/l per 48 h respectively. Among patients with an initial serum sodium concentration <120 mmol/l, the observed increase in serum sodium concentration exceeded the rise predicted by the Adrogué–Madias formula in 74% of cases, on average 2.4 times the predicted rise. The extent of symptoms at presentation was not reported.

  In another retrospective case series including 23 patients, Castello *et al.* [125] used another formula to calculate sodium deficit in hyponatraemic patients with liver cirrhosis. The sodium deficit was corrected with 3% hypertonic saline. There was a good correlation ($R = 0.98$) between the calculated sodium deficit and the amount of sodium used in correction. Symptoms resolved in all patients, but it is unclear to what extent symptoms were caused by hyponatraemia.

  Forssell *et al.* reported a case series of six patients with chronic hyponatraemia due to heart failure treated with 3% hypertonic saline and i.v. loop diuretics. They observed an increase in serum sodium concentration and no deterioration of heart failure. However, no numeric data with the patient as unit of analysis and no symptomatology were provided [123].

  Musch & Decaux observed 17 patients with chronic asymptomatic hyponatraemia due to SIAD treated with i.v. 0.9% saline. On average, the serum sodium concentration increased only slightly and indeed decreased in up to 1/3 of cases [124].

  Sood *et al.* [127] assessed the efficacy of both 1–2 μg parenteral desmopressin and hypertonic saline for the correction of hyponatraemia in a single centre, retrospective cohort study including 24 patients. Hypertonic saline was infused at rates calculated to keep the increase in serum sodium concentration <6 mmol/l over 24 h (using the

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Adrogué–Madias formula). The combination treatment produced an increase in serum sodium concentration of 5.8 ± 2.8 mmol/l at 24 h and an additional 4.5 ± 2.2 mmol/l at 48 h. None of the patients had an increase in serum sodium concentration exceeding 12 mmol/l during the first 24 h or 18 mmol/l during the first 48 h. There was no significant difference between actual and predicted increases in serum sodium concentration during the first 24 h.

Osmotic demyelination syndrome is a rare but dramatic complication that occurs in chronic hyponatraemia when the serum sodium concentration increases too rapidly [128].

We found 54 cases (63% female, median age 45 years, interquartile range 45–58 years) of osmotic demyelination syndrome published since 1997: 45 individual case reports and three case series including a total of nine patients [72, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175]. In 96% (52/54), the diagnosis of osmotic demyelination syndrome was based on magnetic resonance imaging. Important details such as onset and cause of hyponatraemia, initial symptoms and their evolution, presence of other risk factors for osmotic demyelination syndrome and timing of osmotic demyelination syndrome symptoms in relationship to the increase in sodium concentration were generally poorly reported. In 6% (3/54), data were insufficient to allow estimation of the 24 and/or 48 h correction speed. In 96% (52/54) of cases, the initial serum sodium concentration was <120 mmol/l, in 85% (46/54) <115 mmol/l. In 87% (47/54), the sodium concentration increased ≥12 mmol/l during the first 24 h or ≥20 mmol/l during the first 48 h. Only 7% of cases (4/54) developed osmotic demyelination syndrome at lower correction rates [72, 136, 137, 165]. Two of these patients developed osmotic demyelination syndrome with serum sodium concentration increases of 10– <12 mmol/l during the first 24 h and <18 mmol/l in 48 h [72, 136]. Both patients (men) had a history of alcohol abuse as a risk factor for osmotic demyelination syndrome, and it is therefore unclear whether the neurological condition was caused by the speed of increase in serum sodium concentration. In another case, a woman with a history of alcohol abuse and hypokalaemia developed osmotic demyelination syndrome associated with an increase in serum sodium concentration limited to 2 mmol/l during 24 h and 4 mmol/l during 48 h [137]. Finally, in a further case, a woman developed osmotic demyelination syndrome after the serum sodium concentration increased by 15 mmol/l within the first 48 h of treatment; the 24 h limit could not be calculated. The quality of the reporting did not allow a reasonable assumption of causality [165] (Appendix 6. Summary tables 2A, 2B, 13A).

- How did we translate the evidence into the statement?

First-hour management

Severe symptoms mostly result from brain oedema caused by an acute drop in effective osmolality or by rapid further decrease in pre-existing chronic hyponatraemia [73]. Severely symptomatic hyponatraemia is a dangerous condition, which may lead to permanent brain damage or death if left untreated [73]. Although the available data stem from small series, they do suggest that the situation can be reversed by rapidly increasing the serum sodium concentration in the first hour [85, 119]. Given the immediate risk of severe neurological damage, reducing brain oedema should be prioritised in severely symptomatic hyponatraemia as this threat overrules that of possibly inducing osmotic demyelination or fluid overload.

If severe symptoms are caused by hyponatraemia, then small increases in effective osmolality by small increases in serum sodium concentration may be sufficient to improve them and to prevent brain stem herniation [119]. The infusion of 3% hypertonic saline is an effective way to rapidly increase the serum sodium concentration. Observational data and clinical experience indicate that a 5 mmol/l increase in serum sodium concentration can be sufficient to improve symptoms [176]. Most reports use a total of 500 ml of fluid. Although there is no evidence in published research to support the assertion, the guideline development group believed working with (repeated) 150 ml infusions, given every 20 min, may be a reasonable and safer approach. This approach allows monitoring of the change in serum sodium concentration in relationship to the clinical response and aims to manage the risk of overly rapid correction. We suggest repeating the 150 ml infusions of 3% hypertonic saline until the serum sodium concentration has increased 5 mmol/l, or until the symptoms improve, whichever comes first. There was no consensus in the guideline development group on whether these volumes are best given in continuous infusion (preferred by most) or by a slow i.v. injection. Some guideline development group members argued that the dose should be adapted to the weight of the patient, to avoid both over- and under-correction. Others argued that it may be difficult to assess weight correctly in the clinical environment and that it was unclear whether actual weight or weight adjusted for body composition should be used (e.g. should obese patients have different weight-adjusted treatment regimens from muscular patients or patients with oedema). There was unanimous agreement that weight-dependent dose adaptation should be considered in patients with body composition clearly outside the range commonly seen in practice.

There was some concern regarding the availability of 3% hypertonic saline. The guideline development group agreed that hospitals should make an effort to have this solution available in their pharmacy. Prompt infusion of hypertonic saline may save lives and preparing a 3% hypertonic saline infusion takes time. In addition, errors may occur from having to calculate the required amount of sodium chloride in emergency.

Finally, given the severity of the neurological symptoms and the possibility of requiring airway protection or haemodynamic support, we feel these patients require management in an environment where close supervision can be provided.

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Follow-up management: symptom improvement

If the symptoms improve after a 5 mmol/l increase in serum sodium concentration, we recommend stopping the infusion and starting cause-specific treatment to maintain the achieved serum sodium concentration. Systematic review of the cases of osmotic demyelination syndrome published during the past 15 years generally supports restricting increases in serum sodium concentration <10 mmol/l in the first 24 h and <18 mmol/l in the first 48 h. It is very difficult, if not impossible, to set 'safe' rate limits for correcting hyponatraemia. The risk of developing the osmotic demyelination syndrome seems to depend not only on the rate of increase in serum sodium concentration but also on associated underlying risk factors, such as a history of alcohol abuse, liver disease, use of thiazides or antidepressant medications and the original biochemical degree and duration of hyponatraemia. Although case-based data do not allow incidence or risk estimation, only two cases of osmotic demyelination syndrome have been reported with correction speeds below these limits.

We should reemphasise that limits are different from aims. The capacity of the kidneys to excrete electrolyte-free water can vary substantially during treatment and the actual change in serum sodium concentration may be unpredictable. Correction speeds frequently exceed those predicted by the Adrogué–Madias formula, even by as much as five times that predicted [122]. This reflects interplay between a number of factors: suppression of appropriate endogenous vasopressin secretion by fluid and salt loading, the natural history of the underlying condition and the potential impact of cause-specific treatments. Given the uncertainty in biochemical response to treatment, the guideline development group believes that the increase in serum sodium concentration aimed for initially should be sufficient to allow an appropriate margin of safety. Based on an extensive systematic review of available case reports, the guideline development group agreed that a correction rate of 10 mmol/l during the first 24 h and 18 mmol/l during the first 48 h is probably a safe limit.

We advise close monitoring of serum sodium concentrations during the first 24 h of treatment and daily thereafter. It can be speculated that administering desmopressin makes the Androgué–Madias formula more accurate in clinical practice, as it removes one of the variables during treatment, by clamping urine electrolyte-free water excretion at a constant level. A retrospective observational study has indicated that combined use of 1–2 μg i.v. desmopressin with hypertonic saline may allow gradual increase in serum sodium concentration without risking overcorrection. The study involved physicians with extensive experience in treating hyponatraemia. The guideline development group believes that these results are interesting but require confirmation before advocating it as a general practice. For management in case of accidental overcorrection, we refer to section 7.5.

Follow-up management: no symptom improvement

If the symptoms do not improve after a 5 mmol/l increase in serum sodium concentration during the first hour, other explanations for the symptoms should be explored. Depending on the clinical history, additional neurological investigations such as imaging may be helpful. We advise attempting a further increase in serum sodium concentration of 1 mmol/l by infusing 3% hypertonic saline while additional avenues are explored. If symptoms do not improve after a 10 mmol/l increase in serum sodium concentration, it is (even more) likely they are caused by something other than hyponatraemia. Hence, we believe that serum sodium concentration should not increase >10 mmol/l during the first 24 h (the first 5 mmol included), even if symptoms do not improve. The guideline development group also recommends stopping hypertonic saline if the serum sodium concentration reaches 130 mmol/l. Similar to the reasoning above, it is unlikely that symptoms are caused by hyponatraemia if they persist after the serum sodium concentration has reached 130 mmol/l.

Suggestions for future research

- Development and testing of assessment models (based on easily measurable variables such as height, sex and weight) that would enable accurate and reliable prediction of the expected increase in serum sodium concentration in response to a given i.v. sodium load.
- Prospective, standardised, multicentre registry to collect data relating to the increase in serum sodium concentration and clinical response and to facilitate determining the safe upper speed limit for correcting hyponatraemia.

7.2. Hyponatraemia with moderately severe symptoms

7.2.1.1.	We recommend starting prompt diagnostic assessment (1D).
7.2.1.2.	Stop, if possible, medications and other factors that can contribute to or provoke hyponatraemia (not graded).
7.2.1.3.	We recommend cause-specific treatment (1D).
7.2.1.4.	We suggest immediate treatment with a single i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).
7.2.1.5.	We suggest aiming for a 5 mmol/l per 24-h increase in serum sodium concentration (2D).
7.2.1.6.	We suggest limiting the increase in serum sodium concentration to 10 mmol/l in the first 24 h and 8 mmol/l during every 24 h thereafter, until a serum sodium concentration of 130 mmol/l is reached (2D).
7.2.1.7.	We suggest checking the serum sodium concentration after 1, 6 and 12 h (2D).
7.2.1.8.	We suggest additional diagnostic exploration for other causes of the symptoms if the symptoms do not improve with an increase in serum sodium concentration (2D).
7.2.1.9.	We suggest considering to manage the patient as in severely symptomatic hyponatraemia if

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the serum sodium concentration further decreases despite treating the underlying diagnosis (2D).

Rationale

- Why this question?

  Hyponatraemia with moderately severe symptoms is a dangerous condition. Although the immediate threat to life is less pronounced than for hyponatraemia with severe symptoms, any further decline in serum sodium concentration can cause the clinical situation to deteriorate very rapidly. However, were the serum sodium concentration to increase too rapidly, osmotic demyelination syndrome might develop if hyponatraemia is chronic and permanent brain damage may ensue. For clinicians, it is often unclear which treatments should be used or what increases in serum sodium concentration they should pursue.

- What did we find?

  Overall, the body of evidence on which to base recommendations was very limited and similar to that for hyponatraemia with severe symptoms (see section 7.1).

- How did we translate the evidence into the statement?

  Although hyponatraemia with moderately severe symptoms is a dangerous condition, the immediate threat is less pronounced than for hyponatraemia with severe symptoms. Consequently, in the balance between benefits and harms, the reduced immediate threat from hyponatraemia shifts the priority to preventing a further decrease in serum sodium concentration rather than inducing a rapid increase. The target increase in serum sodium concentration we advise, therefore, is also smaller and the motivation for infusing hypertonic saline is less strong. In our opinion, there is time for diagnostic testing and treatment can be directed towards the specific diagnosis.

Suggestions for future research

None.

7.3. Acute hyponatraemia without severe or moderately severe symptoms

7.3.1.1. Make sure that the serum sodium concentration has been measured using the same technique used for the previous measurement and that no administrative errors in sample handling have occurred (not graded).

7.3.1.2. If possible, stop fluids, medications and other factors that can contribute to or provoke hyponatraemia (not graded).

7.3.1.3. We recommend starting prompt diagnostic assessment (1D).

7.3.1.4. We recommend cause-specific treatment (1D).

7.3.1.5. If the acute decrease in serum sodium concentration exceeds 10 mmol/l, we suggest a single i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).

7.3.1.6. We suggest checking the serum sodium concentration after 4 h, using the same technique as used for the previous measurement (2D).

Rationale

- Why this question?

  We have defined 'acute' hyponatraemia as hyponatraemia that is documented to exist <48 h (section 6.1.2). Although the absence of moderately severe to severe symptoms indicates that the patient is not suffering clinically important brain oedema, adaptation has not occurred and any further decline in serum sodium concentration may rapidly worsen the clinical situation. Because adaptation has not been completed, the theoretical risk of osmotic demyelinating syndrome through overly rapid correction is less of a worry. For clinicians, it is often unclear which treatments should be used or what increases in serum sodium concentration they should pursue.

- What did we find?

  We found one pseudo-randomised trial including eight participants of the 161 km long 2009 Western States Endurance Run, who had a serum sodium concentration <135 mmol/l at the end of their run without neurological symptoms. Participants were randomised based on their registration number to either oral rehydration with 100 ml 3% hypertonic saline solution or a single i.v. infusion of 100 ml 3% saline. After 1 h, the serum sodium concentration was 4.3 mmol/l higher for the participants receiving i.v. fluids than for the patients receiving oral rehydration. Reliability of the results was affected by a 1 mmol/l higher serum sodium concentration at baseline in patients receiving i.v. fluids, inadequate randomisation, lack of untreated controls and the open-label design (Appendix 6. Summary tables 2A and 2B).

- How did we translate the evidence into the statement?

  As is often the case for hyponatraemia, the evidence for a particular management strategy in patients with acute hyponatraemia without moderately severe or severe symptoms is poor. Hence, recommendations are largely based on translation from physiology, laboratory and animal data and clinical experience. The absence of severe symptoms indicates that the brain has not yet developed clinically important brain oedema. Similarly, in hyponatraemia with moderately severe symptoms, it shifts the priority from inducing a rapid increase to preventing a further decrease in serum sodium concentration. Again, the motivation for infusing hypertonic saline is less strong than for hyponatraemia with severe symptoms. In the opinion of the guideline development group, there is time for diagnostic testing. Treatment can be diagnosis specific, although a single infusion of 150 ml 3% hypertonic saline may be wise to avoid a

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further drop in serum sodium concentration regardless of underlying cause.

Because the brain has not had the time to adapt fully to its hypotonic environment when hyponatraemia is acute, we believe the risk of osmotic demyelination after overly rapid increase is less of a concern. The available data on osmotic demyelinating syndrome seem to support that this position is correct. This is why we set no limit nor aim for the correction in acute hyponatraemia. This contrasts with our recommendations for hyponatraemia with moderately severe or severe symptoms because in these settings we advise to initiate treatment regardless of whether hyponatraemia is acute or chronic.

Different techniques to measure serum sodium concentration might result in different results. Therefore, when a sudden decrease in serum sodium concentration between two measurements is observed, it is advisable to first check consistency of measurement.

Suggestions for future research

Prospective, large-scale, registration-based data collection to facilitate impact evaluation of the proposed management strategy on end-points of clinical response and overcorrection rate.

7.4. Chronic hyponatraemia without severe or moderately severe symptoms

7.4.1. General management

7.4.1.1. Stop non-essential fluids, medications and other factors that can contribute to or provoke hyponatraemia (not graded).

7.4.1.2. We recommend cause-specific treatment (1D).

7.4.1.3. In mild hyponatraemia, we suggest against treatment with the sole aim of increasing the serum sodium concentration (2C).

7.4.1.4. In moderate or profound hyponatraemia, we recommend avoiding an increase in serum sodium concentration of >10 mmol/l during the first 24 h and >8 mmol/l during every 24 h thereafter (1D).

7.4.1.5. In moderate or profound hyponatraemia, we suggest checking the serum sodium concentration every 6 h until the serum sodium concentration has stabilised under stable treatment (2D).

7.4.1.6. In case of unresolved hyponatraemia, reconsider the diagnostic algorithm and ask for expert advice (not graded).

7.4.2. Patients with expanded extracellular fluid

7.4.2.1. We recommend against a treatment with the sole aim of increasing the serum sodium concentration in mild or moderate hyponatraemia (1C).

7.4.2.2. We suggest fluid restriction to prevent further fluid overload (2D).

7.4.2.3. We recommend against vasopressin receptor antagonists (1C).

7.4.2.4. We recommend against demeclocycline (1D).

7.4.3. Patients with SIAD

7.4.3.1. In moderate or profound hyponatraemia, we suggest restricting fluid intake as first-line treatment (2D).

7.4.3.2. In moderate or profound hyponatraemia, we suggest the following can be considered equal second-line treatments: increasing solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral sodium chloride (2D).

7.4.3.3. In moderate or profound hyponatraemia, we recommend against lithium or demeclocycline (1D).

7.4.3.4. In moderate hyponatraemia, we do not recommend vasopressin receptor antagonists (1C).

7.4.3.5. In profound hyponatraemia, we recommend against vasopressin receptor antagonists (1C).

7.4.4. Patients with reduced circulating volume

7.4.4.1. We recommend restoring extracellular volume with i.v. infusion of 0.9% saline or a balanced crystalloid solution at 0.5–1.0 ml/kg per h (1B).

7.4.4.2. Manage patients with haemodynamic instability in an environment where close biochemical and clinical monitoring can be provided (not graded).

7.4.4.3. In case of haemodynamic instability, the need for rapid fluid resuscitation overrides the risk of an overly rapid increase in serum sodium concentration (not graded).

Advice for clinical practice

- A sudden increase in urine output to >100 ml/h signals increased risk of overly rapid rise in serum sodium concentration. If vasopressin activity is suddenly suppressed, as happens when intravascular volume is restored in hypovolaemia, free water clearance can dramatically increase, resulting in serum sodium concentrations rising more rapidly than expected. If urine output suddenly increases, we would advise measuring the serum sodium concentration every 2 h until it has stabilised under stable treatment. The implicit advice to monitor urine output does not imply that we advise a bladder catheter solely for this

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purpose. Most patients will be able to void spontaneously and collect urine for output monitoring.

- As a means of increasing solute intake, we suggest daily intake of 0.25–0.50 g/kg urea can be used. The bitter taste can be reduced by combining it with sweet-tasting substances. The pharmacist may be asked to prepare the following as sachets: urea 10 g + $NaHCO_3$ 2 g + citric acid 1.5 g + sucrose 200 mg to be dissolved in 50–100 ml water. This will result in a more palatable, slightly sparkling solution.

Rationale

- Why this question?

  Chronic hyponatraemia is common and associated with an increased risk of death, both in and out of hospital [17]. However, it is unclear whether risk of death further increases as individual sodium concentrations decrease, and data on the exact association between serum sodium concentration and death are contradictory [19]. In addition, it remains unclear whether hyponatraemia itself or the underlying disease explains the higher mortality risk. It is also unclear whether treating hyponatraemia improves patient outcome. Finally, even if we decide to treat, it is often unclear what treatment option is most appropriate.

- What did we find?

  We identified two systematic reviews comparing a vasopressin receptor antagonist (one of conivaptan, lixivaptan, satavaptan or tolvaptan) vs placebo. A first review, published in 2010, included 15 randomised controlled trials and 1619 participants up to 2009 [177]. Overall, vasopressin receptor antagonists modestly increased serum sodium concentration after 3–7 days (mean difference (MD) 5.27 mmol/l, 95% CI 4.27–6.26) and up to 1 month (MD 3.49 mmol/l, 95% CI 2.56–4.41). There was no significant reduction in risk of death and there were similar numbers of adverse and serious adverse events. Although there had been no reports of osmotic demyelination syndrome, risk of a rapid increase in serum sodium concentration was 10% when treated with a vasopressin receptor antagonist and 2.5 times higher than when treated with placebo (relative risk (RR) 2.52, 95% CI 1.26–5.06).

  A second review, published in 2011, included 11 randomised trials and 1094 participants up to May 2010 [178]. Overall, results were consistent with the earlier review. There was a modest increase in serum sodium concentration at 5 days (MD 5.70, 95% CI 4.10–7.40) and up to 1 month (MD 4.60, 95% CI 3.60–5.50). There was no significant reduction in risk of death (odds ratio (OR) 0.67, 95% CI 0.38–1.18), no significant increased risk of adverse events, no reports of osmotic demyelination syndrome but a three times higher odds for rapid increases in serum sodium concentration (OR 3.03, 95% CI 1.82–5.05).

  We identified five additional trials published since 2010, increasing the total sample size to 20 trials and 2900 participants [179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197]. Overall, most participants had only mild to moderate hyponatraemia at onset with average sodium concentrations ranging between 124 and 135 mmol/l. Quality of the evidence was generally reduced by risk of bias due to difficulties with blinding participants, potentially unbalanced use of fluid restriction, incomplete outcome reporting and industry sponsorship. When we updated the earlier meta-analyses by Rozen-Zvi *et al.* with the additional data, we found that compared with placebo, vasopressin receptor antagonists did not reduce the number of deaths (RR 1.08, 95% CI 0.80–1.46). When study results were sub-grouped according to volume status, a signal appeared indicating a possibly increased risk of death for hypervolaemic patients treated with a vasopressin receptor antagonist in comparison with placebo. However, results were not statistically significant and sample sizes were small (Appendix 6, Summary tables 10A and 10B). No study reported a measure of quality of life, validated for hyponatraemia [188]. Combined analysis showed a modest increase in serum sodium concentration in the vasopressin antagonist group vs placebo both at 3–7 days (MD 4.30, 95% CI 3.51–4.95 mmol/l) and up to 7 months (MD 3.49 mmol/l, 95% CI 3.59–5.02). There was no difference in adverse events (RR 1.01, 95% CI 0.94–1.09), serious adverse events (RR 1.04, 95% CI 0.91–1.20) or adverse events requiring drug discontinuation (RR 0.85, 95% CI 0.61–1.19) in patients with hyponatraemia. However, the risk for rapid sodium increase was 60% higher when treated with a vasopressin receptor antagonist (RR 1.61, 95% CI 1.11–2.33), indicating that per 1000 patients treated, 26 more would have an overly rapid correction. Results were consistent across different vasopressin receptor antagonists (tolvaptan, conivaptan, lixivaptan and satavaptan) and thresholds for rapid sodium correction, indicating a class effect. We found no published reports of osmotic demyelination syndrome occurring after an overly rapid increase during treatment with a vasopressin receptor antagonist. In March 2012, however, the company marketing tolvaptan issued a statement saying that there had been reports of neurological sequelae in patients treated with tolvaptan where the correction of serum sodium had exceeded the suggested rate [198]. In April 2013, the U.S. Food and Drug Administration issued a Drug Safety communication based on serious adverse events in a trial where tolvaptan was studied as treatment for delaying the evolution of autosomal dominant polycystic kidney disease [199]. Three patients developed serious liver injury, the earliest case 3 months after initiating tolvaptan. In addition, 42 of 958 participants (4.4%) treated with tolvaptan vs five of 484 (1.0%) treated with placebo developed alanine aminotransferase elevations greater than three times the upper limit of normal [200]. Drug doses administered were higher than those that were used in hyponatraemia.

  We found one trial (nine participants) that compared oral demeclocycline vs placebo, reporting only a modest and non-significant difference in serum sodium concentration increase at 3 weeks (MD 2.7 mmol/l, 95% CI −0.7 to 6.2) [201]. We identified no systematic reviews or randomised controlled trials evaluating the benefits and harms of urea,

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demeclocycline, lithium, mannitol, loop diuretics, phenytoin or fluid restriction. We found several case series demonstrating an increase in serum sodium concentration after 2–7 days for urea [202, 203, 204, 205, 206], demeclocycline [207], loop diuretics in combination with oral NaCl [123, 125, 208], phenytoin [209] and fluid restriction [210]. We also identified case series of patients experiencing an increase in serum sodium over a longer time period of up to 12 months for urea [211, 212, 213], up to 3 weeks for demeclocycline [214, 215, 216, 217, 218, 219], up to 20 weeks for lithium [220], up to 150 days for furosemide with oral NaCl [221] and up to 30 days in phenytoin [220].

We also found several observational reports of acute kidney injury with demeclocycline [214, 215, 218, 219, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232]; a single case report of confusion and somnolence with lithium [220] and unspecified neurological abnormalities with phenytoin [233]. Finally, we identified two reports of adverse events with fluid restriction. The first was a retrospective study using data generated in a randomised controlled trial evaluating tranexamic acid in patients with severe subarachnoid bleeding. In 44 participants with hyponatraemia, 80% developed subsequent cerebral infarction when given <1000 ml of fluids a day vs 33% when not fluid restricted. The very specific setting makes the data of limited value to other settings. The small sample size, lack of adjustment for confounding and the heterogeneity of hyponatraemia within the study group limit its value for causal inference. The second study included two cases of osmotic demyelination syndrome that occurred after restriction of fluid intake to 750 ml daily. The first case occurred in a man with hyponatraemia probably due to polydipsia and low solute intake, the second in a woman with hyponatraemia due to thiazides, which were stopped on admission. In both cases, the serum sodium concentration increased with >19 mmol/l during the first 24 h and causal association between fluid restriction and subsequent demyelination appear to be limited [234, 235] (Appendix 6. Summary tables 3A to 12B).

- How did we translate the evidence into the statement?

General management

Many people take medications that can provoke or contribute to hyponatraemia. It makes sense to check whether patients with hyponatraemia are taking any such medications, to reconsider their necessity and to stop them if perceived benefits do not outweigh perceived harms. Likewise, it seems logical to stop unnecessary fluids, discourage excessive oral water drinking and treat any underlying condition that can be improved.

We found no comparative studies of the different available treatment strategies for chronic hyponatraemia. Taking into account the absence of evidence that treating chronic hyponatraemia results in improvement of patient-relevant outcomes, the guideline development group judged that our primary concern was avoiding harm through treatment.

In patients with chronic mild hyponatraemia, we found no evidence that correcting hyponatraemia itself improves patient-important outcomes. All interventions can cause adverse events. We therefore advise against active interventions with the sole aim of increasing the serum sodium concentration.

One could argue the same holds for moderate or even profound hyponatraemia. For these conditions too, there is little or no evidence to support treatment. However, different members in the guideline development group felt uncomfortable in advocating no treatment for moderate or profound chronic hyponatraemia, highlighting the risk of a sudden, further deterioration leading to severe or moderately severe symptoms. Therefore, it was accepted that the risk–benefit balance for the different biochemical degrees of chronic hyponatraemia, and of the underlying diagnosis, would be evaluated separately.

One important, potential harm is development of osmotic demyelination syndrome when the serum sodium concentration rises too rapidly. Systematic review of the cases of osmotic demyelinating syndrome published during the past 15 years generally support avoiding increases in serum sodium concentration >10 mmol/l in the first 24 h and >18 mmol/l in the first 48 h, regardless of treatment type. It is very difficult, if not impossible, to set 'safe' speed limits for rate of correction. Risk of development of osmotic demyelination syndrome seems to depend not only on the speed of increase in serum sodium concentration but also on associated underlying risk factors: alcohol abuse, liver disease, use of thiazides or antidepressant medications, the original biochemical degree and the duration of hyponatraemia. Although case-based data do not allow incidence or risk estimation, only two cases have been reported with correction speeds below these limits. In the majority of cases, correction speeds largely exceed them. We should be clear that limits are different from aims. As there is no clear evidence that correcting chronic hyponatraemia improves patient-important outcomes, we did not formulate aims. If you wish to avoid surpassing a certain 24-h limit, serum sodium concentration needs to be measured more frequently than once daily to allow adjusting treatment to the observed change. The 6-h measurement is somewhat arbitrary, chosen to manage a balance between allowing change in treatment and practicality. At this point in time, there are insufficient data on incidence of osmotic demyelination syndrome and influence of measurement timing to give a more informed view.

Expanded extracellular fluid volume

There are insufficient data to suggest that increasing serum sodium concentration improves patient-important outcomes in moderate hyponatraemia with expanded extracellular fluid volume, such as seen in liver cirrhosis or heart failure. Given treatments directed solely at increasing serum sodium concentration have inherent risks of overcorrection and other adverse effects, we believed that the balance was in favour of not treating in case of mild or moderate hyponatraemia in patients with expanded extracellular volume. For patients with profound hyponatraemia in this setting, the guideline development group acknowledged that it might be reasonable to avoid further decreases in serum sodium in certain

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patients, although there are no published data to support this view. Hence, the guideline development group refrained from making any statement regarding whether or not to treat this category of patients. Clearly, fluid restriction in this setting can be used as a means to reduce further fluid overload.

On systematic review of data in this specific patient category, there appeared to be an increased number of deaths in those patients treated with vasopressin receptor antagonists in comparison with those treated with placebo. Although results were not statistically significant and sample sizes were small, the guideline development group believed the signal that active treatment may actually worsen outcomes was sufficient to recommend against vasopressin receptor antagonists in this specific category. The side effects reported for demeclocycline and lithium were such that we recommend not using them for any degree of hyponatraemia.

Syndrome of inappropriate antidiuresis

Although there is little to no formal evidence that fluid restriction increases serum sodium concentration more than placebo, clinical experience generally supports its use, provided fluid restriction is strictly adhered to. Similarly, there is no good evidence that fluid restriction is associated with important adverse effects, other than poor patient acceptability. In the cases mentioned above, we believed it was unlikely that fluid restriction played a causal role in the development of osmotic demyelination syndrome. Hence, the guideline development group unanimously preferred fluid restriction as first-line treatment. As a second-line treatment, we suggest an increased intake of osmotic solutes to enhance clearance of water. We agreed that oral urea might be the most practical method to achieve increased solute intake. The guideline group acknowledged the bitter taste of urea, which might reduce acceptability. However, we believed that this could be solved by combining urea with sweet-tasting substances as described in the recipe provided in the advice for clinical practice. The guideline development group did not consider availability of urea a problem as it is used in many other pharmacological preparations.

For demeclocycline and lithium, there is some evidence of possible harm, so we advise against their use for management of any degree of chronic hyponatraemia in patients with SIAD.

Although vasopressin receptor antagonists do increase serum sodium, the guideline development group judged that based on current evidence, these drugs cannot be recommended. Indeed, the risk benefit ratio seems to be negative: there is no proven outcome benefit aside from increase in serum sodium concentrations, while there are increasing concerns on safety. The most prominent safety-related factor is the increased risk for overly rapid correction of hyponatraemia. As this risk is greatest in patients with profound hyponatraemia, the guideline development group wanted to recommend against the use of vasopressin receptor antagonists in this specific patient group. In addition, our concern around the toxicity profile of these compounds was increased by reports from the U.S. Food and Drug Administration warning for hepatotoxicity associated with the use of high tolvaptan doses in autosomal dominant polycystic kidney disease.

Patients with contracted extracellular volume

Hyponatraemia with reduced extracellular fluid volume may require a different approach to other causes of hyponatraemia. Patients with hyponatraemia and a contracted extracellular fluid volume have a combination of a true sodium and water deficit. They also have appropriate vasopressin secretion and hence diminished electrolyte-free water clearance, simultaneously resulting in dilutional hyponatraemia. Although hyponatraemia with reduced extracellular fluid volume is common in clinical practice, we did not find specific studies addressing management from the perspective of treating hyponatraemia. Given the absence of formal evidence in this setting, recommendations are based on direct translation of pathophysiology to clinical practice.

Patients with hyponatraemia and reduced extracellular fluid volume lack water as well as sodium. Consequently, replenishing both deficits with isotonic saline seems logical. However, isotonic saline is characterised by an unphysiologically high concentration of chloride, which may impair renal function. Recent data have indicated that balanced crystalloid solutions might be preferable for restoring volume deficits and these solutions are now commonly recommended in guidelines on volume replacement, although there is no published research specifically for hyponatraemia available [236, 237, 238].

If hyponatraemia is caused by a contracted extracellular fluid volume, restoring this volume will suppress vasopressin secretion causing electrolyte-free water excretion to increase. Therefore, these patients are at high risk of an overly rapid increase in serum sodium concentration. Sudden increases in urine output can act as a warning signal that overly rapid correction of hyponatraemia is imminent.

In patients who are haemodynamically unstable, the immediate risk of decreased organ perfusion is more important than the potential risk of overly rapid increases in serum sodium concentration. Hence, the need for volume resuscitation overrides any concerns for overly rapid correction of hyponatraemia. These patients are best managed in an environment where close monitoring, including frequent and swift sampling of serum and determination of its sodium concentration, is possible. In the case of imminent overcorrection, we suggest to continue fluid loading (if still needed) with free water, e.g. glucose solutions.

Suggestions for future research

More high-quality randomised, head-to-head comparison trial data for all potential treatments using longer term health outcomes such as death, quality of life and cognitive function.

7.5. What to do if hyponatraemia is corrected too rapidly?

7.5.1.1.	We recommend prompt intervention for relowering the serum sodium concentration if it increases >10 mmol/l during the first 24 h or >8 mmol/l in any 24 h thereafter (1D).
7.5.1.2.	We recommend discontinuing the ongoing active treatment (1D).

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7.5.1.3. We recommend consulting an expert to discuss if it is appropriate to start an infusion of 10 ml/kg body weight of electrolyte-free water (e.g. glucose solutions) over 1 h under strict monitoring of urine output and fluid balance (1D).

7.5.1.4. We recommend consulting an expert to discuss if it is appropriate to add i.v. desmopressin 2 μg, with the understanding that this should not be repeated more frequently than every 8 h (1D).

Rationale

- Why this question?

  Interrupting the underlying mechanisms that cause hyponatraemia can lead to sudden and rapid increases in serum sodium concentration. Overly rapid increases in serum sodium concentration can have dramatic consequences if osmotic demyelinating syndrome develops. For clinicians, it is often unclear what to do when overly rapid correction occurs.

- What did we find?

  Although the exact incidence of overly rapid correction is unknown and depends on its definition, overly rapid increases in serum sodium concentration appear to be common. A small retrospective single-centre study including 62 participants treated with hypertonic saline reported correction in 11% at 24 h and in an additional 10% at 48 h [122].

  Among those with a serum sodium concentration <120 mmol/l, the observed increase exceeded the rise predicted by the Adrogué–Madias formula in 74%. In patients with overly rapid correction, the average increase in serum sodium concentration was 2.4 times that of the predicted increase. Inadvertent overly rapid correction was due to documented water diuresis in 40% of cases.

  We found no randomised controlled trials and only two small observational studies on interventions for reversing overly rapid correction of hyponatraemia. In the first of these, a retrospective single-arm cohort study, six patients were given desmopressin after a 24-h increase in serum sodium concentration of 12 mmol/l had already been reached. Correction exceeding a 48-h limit of 18 mmol/l was avoided in five of the six. An additional 14 patients were given desmopressin in an attempt to prevent overcorrection after serum sodium concentration had increased 1–12 mmol/l. All patients had corrections below the 24- and 48-h limits [239].

  The second, a small single-centre single-arm retrospective cohort study included 24 participants [127]. A combination of 1–2 μg parenteral desmopressin and hypertonic saline was infused at speeds calculated (using the Adrogué–Madias formula) to keep the increase in serum sodium concentration <6 mmol/l over 24 h. The combined treatment produced an increase in serum sodium concentration of 5.8 ± 2.8 mmol/l at 24 h and an additional 4.5 ± 2.2 mmol/l at 48 h. None of the patients had an increase in serum sodium concentration exceeding 12 mmol/l during the first 24 h or 18 mmol/l during the first 48 h. There was no significant difference between actual and predicted increases in serum sodium concentration during the first 24 h.

- How did we translate the evidence into the statement?

  The incidence of overly rapid correction of hyponatraemia depends on the thresholds used to define overly rapid correction. The limited data we have seem to indicate that serum sodium concentrations are increased >10 mmol/l during the first 24 h and >8 mmol/l every 24 h thereafter fairly frequently. The incidence of osmotic demyelinating syndrome resulting from overly rapid increases in serum sodium concentration is unknown. As information in this area is still only derived from case reports and small case series, it is probably very low. Given the dramatic consequences of osmotic demyelinating syndrome, it is clear that overly rapid increases should be avoided when treatment for hyponatraemia is started. Similarly, it makes sense to stop the active treatment of hyponatraemia if the increase in serum sodium concentration exceeds the limits we previously defined.

  In established overly rapid correction, the benefits and harms of active treatments to re-lower serum sodium concentration have not been well studied. Nevertheless, the guideline development group feels that the dramatic consequences of osmotic demyelinating syndrome warrant an attempt to re-lower the serum sodium concentration in case of overly rapid correction using an active intervention.

  It is plausible that overly rapid correction occurs more readily in conditions where treatment of the underlying cause results in restoration of the kidneys' capacity to excrete electrolyte-free water. Examples of such conditions include, but are not limited to, volume repletion in hypovolaemia, treatment of glucocorticoid deficiency, withholding thiazides, withholding other drugs known to cause SIADH and lowering fluid intake in primary polydipsia. Based on these theoretical considerations, clinical experience and limited data, we believe that infusing electrolyte-free water (e.g. 5% glucose solutions) and/or injecting desmopressin can be used in experienced hands to re-lower serum sodium concentration in case of overly rapid correction.

  However, the guideline development group was reluctant to advise it strongly without consulting an expert. Large multi-centre trials with these interventions are lacking. Overly rapid correction of hyponatraemia may indicate the presence of a complex case, where the effect of further treatment may be even more difficult to predict. We consider that seeking additional expertise may be the safest option in these conditions.

Suggestions for future research

- Additional prospective studies examining the combination of desmopressin and hypertonic saline to correct hyponatraemia and to avoid further overcorrection in those having already attained the correction limits are needed to further

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evaluate both the outcome benefits and harms of such a strategy.

- The combination of desmopressin and free water to reverse overcorrection needs further study.

8. DECLARATION OF INTEREST

We required all participants in the guideline development group to fill out a detailed 'Declaration of interest' including all the current and future conflicts of interest as well as past interest restricted to the 2 years before joining the guideline development process. Because it was judged that excluding every individual with some degree of potential conflict of interest would make assembling a guideline development group impossible, we allowed members of the guideline development group to have past financial and/or intellectual conflicts of interest. We did not attach any consequences to the stated interests, but rather insisted on transparency. All members of the guideline development group were allowed to participate in all the discussions and have equal weight in formulating the statements. All were allowed equal involvement in data extraction and writing the rationales. The declaration of interest forms are available from www.european-renal-best-practice.org/content/Joint-workgroup-hyponatraemia and are updated on a regular basis.

9. FUNDING

The three participating societies sponsored the production of this guideline. ESE provided an unrestricted grant to cover part of the costs to develop the guideline. The spent amount underwent regular scrutiny by the executive committee of ESE. The ESICM is a scientific society that operates under the leadership of its executive committee and its council. Both structures organise, regulate and control the scientific and educational activities of the society. Statutes and detailed standard operating procedures can be found on the ESICM website (www.esicm.org). ESICM receives funding through membership fees and revenues from its congresses, courses, educational ventures and journals. Activities of ERBP and its methods support team are supervised by an advisory board (see www.european-renal-best-practice.org for details and Declaration of interest). ERBP is an independent part of ERA–EDTA. The council of ERA–EDTA approves and provides the annual budget based on a proposition made by the chair of ERBP. ERA–EDTA receives money and is partly funded by industrial partners, but its council is not involved with and does not interfere with topic choice, question development or any other part of the guideline development process. Neither the societies nor the guideline development group received any funds directly from industry to produce this guideline.

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Co-publication

The guidelines will be co-published in *Nephrology Dialysis Transplantation* and *Intensive Care Medicine*.

Appendix

Appendices are available online at http://ndt.oxfordjournals.org.

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