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# Multicentre study of investigation and management of inpatient hyponatraemia in the UK

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## ABSTRACT

**Purpose** Hyponatraemia is associated with significant morbidity and mortality. The objectives of this study were to evaluate the investigation and management of hyponatraemia and to assess the use of different therapeutic modalities and their effectiveness in routine practice.

**Study design** This multicentre, retrospective, observational study was conducted at three acute NHS Trusts in March 2013. A retrospective chart review was performed on the first 100 inpatients with serum sodium (sNa)  $\leq 128$  mmol/L during hospitalisation.

**Results** One hundred patients (47 male, 53 female) with a mean  $\pm$  SD age of  $71.3 \pm 15.4$  years and nadir sNa of  $123.4 \pm 4.3$  mmol/L were included. Only 23/100 (23%) had measurements of paired serum and urine osmolality and sodium, while 31% had an assessment of adrenal reserve. The aetiology of hyponatraemia was unrecorded in 58% of cases. The mean length of hospital stay was 17.5 days with an inpatient mortality rate of 16%. At hospital discharge, 53/84 (63.1%) patients had persistent hyponatraemia, including 20/84 (23.8%) with sNa  $< 130$  mmol/L. Overall 37/100 (37%) patients did not have any treatment for hyponatraemia. Among 76 therapeutic episodes, the most commonly used treatment modalities were isotonic saline in 38/76 cases (50%) and fluid restriction in 16/76 (21.1%). Fluid restriction failed to increase sNa by  $> 1$  mmol/L/day in 8/10 (80%) cases compared with 4/26 (15.4%) for isotonic saline.

**Conclusions** Underinvestigation and undertreatment of hyponatraemia is a common occurrence in UK clinical practice. Therefore, development of UK guidelines and introduction of electronic alerts for hyponatraemia should be considered to improve clinical practice.

## INTRODUCTION

Hyponatraemia, defined as serum sodium (sNa) concentration below 135 mmol/L, is the most common electrolyte abnormality encountered in hospitalised patients, with a reported incidence of 30–42%.<sup>1–2</sup> Hyponatraemia is an independent risk factor for mortality<sup>3–4</sup> and is associated with an increase in length of hospital stay<sup>5</sup> and hospital resource utilisation.<sup>6</sup>

Accurate diagnosis of hyponatraemia is necessary to guide effective treatment. However, numerous single-centre studies in the UK have consistently reported underutilisation of appropriate biochemical tests in the investigation of hyponatraemia.<sup>7–13</sup> It is unclear to what extent inadequate investigation of

hyponatraemia reflects UK clinical practice in general. There is also a paucity of data about the utilisation of different therapeutic modalities for hyponatraemia and their efficacy in a real world setting.

This study describes current clinical practice in three acute UK hospitals. The objectives were to evaluate the investigation and management of inpatient hyponatraemia and to assess the use of different therapeutic modalities and their effectiveness.

## METHODS

### Study design

This was a multicentre, retrospective, observational study examining the investigation and management of 100 consecutive inpatients with serum sodium (sNa)  $\leq 128$  mmol/L.

Recruitment started on 1 March 2013 and ended on 28 March 2013 when a total of 100 patients were reached. It was conducted simultaneously at three acute NHS Trusts in London: centre 1, an 850-bed teaching hospital; centre 2, including 850 beds across two teaching hospitals; and centre 3, a 450-bed district general hospital. None of the three institutions had local guidelines for the management of hyponatraemia.

### Patient selection

We defined inpatient hyponatraemia as an sNa concentration  $\leq 128$  mmol/L at any point during hospital admission. Patients were identified through an automated laboratory database search. A cut-off of 128 mmol/L was selected because previous data from this hospital cohort showed an upward inflection in inpatient mortality below that threshold.<sup>3</sup> Subjects with hyperglycaemia were included only if their corrected sNa was  $\leq 128$  mmol/L. If venous glucose was 15–24.4 mmol/L, sNa was corrected by 1.6 mmol/L for every 5.6 mmol/L increase in glucose concentration above 7 mmol/L; if glucose was  $> 24.4$  mmol/L, a correction factor of 2.4 mmol/L was used.<sup>14</sup>

### Data collection

Hospital case notes, laboratory results, drug prescription charts and discharge letters were retrospectively reviewed for each patient after hospital discharge. Data were collected on age, gender, speciality responsible for each patient, drug history, admission to the intensive care unit, length of hospital stay, outcome of admission, investigations and documented cause of hyponatraemia, sNa levels at various time points, use of therapeutic modalities, sNa 24 and 72 h after initiation of treatment, and sNa at hospital discharge.



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Adequate investigation of hyponatraemia should include clinical assessment of volume status, measurement of paired serum and urine osmolality and Na, thyroid function tests and serum cortisol measurement. The effectiveness of treatment of hyponatraemia was assessed by sNa concentration at hospital discharge. For the purpose of evaluating the effectiveness of different treatment modalities, 'clear failure' of treatment was defined as a total sNa increase of  $\leq 3$  mmol/L after the 72 h period after initiation of therapy. Over-rapid correction of hyponatraemia, known to risk osmotic demyelination syndrome,<sup>15 16</sup> was defined as an sNa increase of  $> 12$  mmol/L in 24 h.

### Data analysis

All data were recorded on an Access database and then transferred into an Excel spreadsheet. Data were analysed separately for each hospital and for all three hospitals together. Data were summarised using descriptive statistics, with continuous variables being expressed as mean  $\pm$  SD, and categorical variables as percentages.

Adequacy of investigation was assessed by the percentage of patients who underwent each of the recommended tests. The proportion of patients with normonatraemia and different degrees of hyponatraemia (mild/moderate/severe) was used to determine the effectiveness of management of hyponatraemia. The percentage of patients who had 'clear failure' and 'over-rapid correction' determined the effectiveness of each therapeutic modality.

## RESULTS

### Demographic characteristics

Across three hospitals in London, 100 patients (47 male, 53 female) were included with a mean  $\pm$  SD age of  $71.3 \pm 15.4$  years. Centre 1 included 38 patients (19 male, 19 female with a mean age of  $73.6 \pm 15.1$  years), centre 2 contributed 30 patients (13 male, 17 female aged  $68.5 \pm 15.5$  years) and centre 3 contributed 32 patients (15 male, 17 female with a mean age of  $70.4 \pm 15.4$  years).

The mean sNa on admission was  $128.1 \pm 7.1$  mmol/L, and the lowest sNa during hospitalisation was  $123.4 \pm 4.3$  mmol/L. In terms of the time point of onset of hyponatraemia, 58/100 (58%) patients presented on admission with sNa  $\leq 128$  mmol/L in comparison with 42/100 (42%) who developed sNa  $\leq 128$  mmol/L during hospitalisation.

### Speciality distribution

There was a wide distribution of patients within different specialities: 81/100 (81%) patients were under the care of medical specialities including geriatrics (18%), general medicine (11%), respiratory (9%), gastroenterology (9%), oncology (6%), hepatology (6%), cardiology (5%), infectious diseases (5%), endocrinology (4%), nephrology (3%), neurology (3%) and rheumatology (2%); 19/100 (19%) patients were under the care of surgical specialities including general surgery (5%), urology (5%), orthopaedics (4%), cardiothoracic surgery (3%) and gynaecology (2%).

### Drug history

Of the 100 patients, 35 were taking ACE inhibitors, 23 loop diuretics, 22 thiazide diuretics, 15 selective serotonin reuptake inhibitors (SSRIs), 14 potassium-sparing diuretics, 12 angiotensin-II receptor antagonists, and 6 tricyclic antidepressants.

### Outcome of admission

The inpatient mortality rate in our cohort was 16%. The mean length of hospital stay was  $17.5 \pm 14.8$  days with 9/100 (9%) of patients requiring admission to the intensive care unit.

### Diagnostic work-up

Clinical assessment of volume status was documented in 62/100 (62%) cases, while paired serum and urine osmolality and Na were measured in 23/100 (23%). Complete work-up was undertaken in 18/100 (18%) patients, as shown in table 1.

### Aetiology of hyponatraemia

The aetiology of hyponatraemia was unrecorded in the notes of 58/100 (58%) patients. Review of case notes was used to ascertain the aetiology of hyponatraemia in the remaining 42/100 (42%) patients, as summarised in table 2. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was attributed to drugs in three cases (SSRIs in two cases and mirtazapine in one case), to malignancy in two cases (small cell lung cancer in one case and chronic lymphocytic leukaemia in one case) and to miscellaneous causes in two cases (SIADH after transsphenoidal surgery and SIADH of unknown cause).

Only 6/11 (54%) patients diagnosed with SIADH had all the essential tests performed, including clinical assessment of volume status, measurement of paired serum and urine osmolality and Na, and assessment of thyroid and adrenal function.<sup>17 18</sup>

### Effectiveness of treatment of hyponatraemia

Correction of sNa  $\geq 130$  mmol/L was observed in 70/84 (83.3%) patients at some point during admission, but hyponatraemia with sNa  $< 130$  mmol/L recurred in 6/84 (7.1%). A significant proportion of patients (53/84 equal to 63.1%) had persistent hyponatraemia at discharge from hospital, as shown in table 3.

### Utilisation of treatment modalities

Overall, 37/100 (37%) patients did not have any treatment for hyponatraemia. Of the 63 patients treated for hyponatraemia, 53 received one therapeutic modality, 7 received two modalities, and 3 received three treatment modalities. First-line therapy was isotonic saline in 34/63 (54%) cases, discontinuation of potentially offending drugs in 16/63 (25.4%), fluid restriction in 10/63 (15.9%), infusion of human albumin solution in 2/63 (3.2%), and initiation of hydrocortisone replacement in 1/63 (1.5%) cases. Second-line therapy was isotonic saline in 4/10 (40%) cases, fluid restriction in 4/10 (40%), and hypertonic saline in 2/10 (20%). Only three patients received third-line treatment, including two cases of fluid restriction and one case of demeclocycline.

Potentially offending drugs were discontinued in 36/100 (36%) patients, with the most common being ACE inhibitors or angiotensin-II receptor antagonists (18%), loop diuretics (15%),

**Table 1** Investigation of patients with hyponatraemia

Investigation	Total (N=100) (%)	Centre 1 (N=38) (%)	Centre 2 (N=30) (%)	Centre 3 (N=32) (%)
Volume status	62	71.0	53.4	59.4
Serum osmolality	39	39.5	33.3	43.8
Urine osmolality	33	39.5	30.0	28.1
Urine Na	29	34.2	36.6	15.6
Paired osmolality–Na	23	26.3	26.7	15.6
Serum TSH	61	71.0	63.3	46.9
Serum cortisol	31	34.2	26.6	31.2
Full work-up	18	23.7	20.0	9.4
Expert input	16	13.1	13.3	21.8

TSH, thyroid-stimulating hormone.

**Table 2** Classification of cases according to documented aetiology of hyponatraemia

Aetiology	Overall (N=42), n (%)
Hypovolaemic	23 (54.7)
Gastrointestinal Na losses	9 (21.4)
Poor oral intake	7 (16.6)
Diuretics	6 (14.3)
Adrenal insufficiency	1 (2.4)
Euvolaemic	11 (26.2)
SIADH due to pneumonia	4 (9.5)
Drug-induced SIADH	3 (7.1)
Malignant SIADH	2 (4.8)
Miscellaneous causes	2 (4.8)
Hypervolaemic	8 (19.1)
Decompensated cirrhosis	4 (9.5)
Heart failure	4 (9.5)

SIADH, Syndrome of inappropriate antidiuretic hormone secretion.

thiazide diuretics (10%), potassium-sparing diuretics (10%) and SSRIs (3%).

In total, 76 episodes of treatment were recorded, which included isotonic saline in 38/76 (50%) cases, drug discontinuation in 16/76 (21.1%), fluid restriction in 16/76 (21.1%), hypertonic saline in 2/76 (2.6%), human albumin solution in 2/76 (2.6%), hydrocortisone replacement in 1/76 (1.3%) and demeclocycline in 1/76 (1.3%) cases. Use of other drug therapies for SIADH, such as tolvaptan, urea or combination of loop diuretics with oral sodium chloride, was not recorded.

### Effectiveness of isotonic saline and fluid restriction

'Clear failure' of treatment with a total sNa increase of  $\leq 3$  mmol/L after the 72 h period after initiation of therapy was recorded in 4/26 (15.4%) patients treated with isotonic saline compared with 8/10 (80%) individuals managed with fluid restriction, as illustrated in table 4. Fluid restriction was imposed on 16 patients with various volumes prescribed per 24 h (1500 mL in 4 cases, 1000 mL in 9 cases, 750 mL in 1 case and 500 mL in 2 cases). Hypertonic saline was used in two patients, with infusion of 1000 mL saline 1.8% over 18 h increasing sNa by 13 mmol/L, and 300 mL saline 1.8% over 8 h increasing sNa levels by 11 mmol/L.

### DISCUSSION

We found that hyponatraemia was frequently underinvestigated, underdiagnosed and suboptimally managed in routine practice in three hospitals in London. Urine Na, the most important biochemical test<sup>19 20</sup> in investigation of hyponatraemia, was measured in less than one-third of cases. The underlying aetiology

**Table 3** Serum sodium (sNa) concentration at hospital discharge

sNa at discharge	Overall N=84
Patients with sNa <125 mmol/L (%)	4.8
Patients with sNa 125–129 mmol/L (%)	19.0
Patients with sNa 130–134 mmol/L (%)	39.3
Patients with sNa $\geq 135$ mmol/L (%)	36.9
Mean $\pm$ SD sNa (mmol/L)	132.8 $\pm$ 4.7

**Table 4** Effectiveness of isotonic saline and fluid restriction in correcting hyponatraemia in first 72 h

sNa correction after treatment	Isotonic saline (N=26)	Fluid restriction (N=10)
Mean $\pm$ SD change in sNa (mmol/L)	7.3 $\pm$ 5.0	2.8 $\pm$ 3.2
Percentage of patients		
sNa increase <2 mmol/L	7.7	30.0
sNa increase 2–3 mmol/L	7.7	50.0
sNa increase 4–8 mmol/L	50.0	10.0
sNa increase 9–12 mmol/L	19.2	10.0
sNa increase >12 mmol/L	15.4	0

Over-rapid correction of hyponatraemia (sNa increase of >12 mmol/L/day) was recorded in 3/76 (3.9%) therapeutic episodes. All three patients, two treated with isotonic saline and one with hypertonic saline, had an sNa increase of 13 mmol/L within 24 h without any adverse neurological sequelae.

of hyponatraemia, despite being essential to guide appropriate treatment, was unrecorded in more than half of the cases. The limited effectiveness of current management, with 63.1% of patients being discharged with persistent hyponatraemia, was not surprising considering the lack of treatment for hyponatraemia in a substantial proportion of patients. Among patients receiving treatment for hyponatraemia, isotonic saline or fluid restriction were most commonly used, with fluid restriction being ineffective in the majority of cases.

Similar results from all three hospitals indicate that insufficient diagnostic work-up and ineffective treatment of hyponatraemia may reflect UK routine care in general. There are several possible barriers to good clinical practice in this field, such as the diminished provision of undergraduate and postgraduate education in clinical chemistry in recent times,<sup>13 21</sup> the lack of national guidelines, the absence of diagnostic algorithms and treatment pathways in most hospitals or their complexity where they exist, and the limited therapeutic options with little evidence basis for the treatment of SIADH. Besides demonstrating suboptimal standard of care for hyponatraemia, we found that fluid restriction, currently the first-line treatment for SIADH, does not correct hyponatraemia in most cases. Potential reasons are poor patient adherence because of thirst, inadequate rigour in the volume of fluid intake prescribed (which needs to be restricted to at least 500 mL/day less than urine output), and its questionable effectiveness per se given the limited evidence base behind its therapeutic value.<sup>20 22</sup> Therefore, clinicians should pay more attention to appropriate prescription and implementation of fluid restriction and should also have access to alternative therapeutic options such as vaptans and urea.

In comparison with previous UK studies, we recorded a higher frequency of performance of appropriate diagnostic tests. In the subgroup of our cohort with a nadir sNa  $\leq 125$  mmol/L, 40.7% of patients had urine Na and 40.7% had serum cortisol measured compared with 10–18.6%<sup>7–10</sup> and 8–15.2%,<sup>7–9 11</sup> respectively, reported in other UK series using the same cut-off. It is unclear whether these findings represent a widespread rather than a local improvement in the investigation of hyponatraemia in recent years. Regarding the aetiology of hyponatraemia, SIADH was reported in only a quarter of our cases, in contrast with most studies suggesting it as the most common cause,<sup>18 23 24</sup> therefore, SIADH was probably underdiagnosed.

This study has provided insight into the contemporary investigation and management of hyponatraemia in the UK. However, it had a number of limitations. First and foremost, it could not, by its design, test whether undertreatment of hyponatraemia

contributed to adverse patient outcomes and, more importantly, whether correcting hyponatraemia could improve clinical outcomes. Second, the small sample size and the fact that all three hospitals are in London raise the question whether the findings apply to UK clinical practice in general. Third, its retrospective nature made accurate identification of the cause of all cases of hyponatraemia impossible. As a result, its ability to evaluate the effectiveness of different therapeutic modalities was limited because failure of treatment might sometimes reflect misdiagnosis.

In conclusion, this study highlights the need to improve clinical practice. It is essential to develop tools such as electronic alert systems for severe hyponatraemia, similar to electronic alerts for acute kidney injury already introduced in several NHS hospitals.<sup>25–27</sup> By highlighting hyponatraemia and referring to intranet-based guidelines, electronic alerts could prompt optimal investigation and treatment in a timely manner. Another innovative model of care delivery with the potential to improve standard of care is the development of multidisciplinary hospital ‘hyponatraemia teams’ combining the expertise of endocrinologists, nephrologists, chemical pathologists and other physicians. In addition, UK guidelines on management of hyponatraemia are still needed despite the recent publication of clinical practice guidelines by an expert panel<sup>22</sup> and by a joint venture of the European Society of Endocrinology with the European Renal Association.<sup>20</sup> The reason is that clinical practice and experience in the UK differ from that in the USA<sup>22</sup> and continental Europe<sup>20</sup> with regard to the structure of the healthcare system and the availability of treatment options, such as urea and vaptans. Finally, we agree with the authors of both European and US guidelines on the urgent need for studies evaluating the effect of correction of hyponatraemia on patient-important outcomes such as symptoms, quality of life, mortality and length of hospital stay.<sup>20 22</sup>

### Main messages

- ▶ Hyponatraemia is frequently underinvestigated and underdiagnosed in UK clinical practice.
- ▶ Most patients are discharged with persistent hyponatraemia, while a substantial proportion of them have not received any treatment for hyponatraemia.
- ▶ Fluid restriction is often ineffective in correcting hyponatraemia due to SIADH.

### Current research questions

- ▶ Does correction of hyponatraemia improve patient outcomes such as length of hospital stay and mortality?
- ▶ What would be the impact of measures such as introduction of electronic alert systems or widespread provision of expert input on management of inpatient hyponatraemia and patient outcomes?
- ▶ What is the optimal treatment strategy for hyponatraemia due to SIADH with regard to sodium correction and patient outcomes?

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