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Original Article

Hyponatraemia in Hospitalised Children: A Retrospective Survey in Acute Paediatric Admissions in Hong Kong with Focus on Intravenous Fluid Practices

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Abstract ***Purpose:*** Recent intravenous fluid (IVF) guidelines advocate empirical isotonic maintenance fluids in children to prevent potentially dangerous hyponatraemia. To see if this practice is appropriate for Hong Kong, we aimed to review the frequency and nature of hyponatraemia in acute paediatric settings, and its association with hypotonic IVF usage. ***Methods:*** Using Hospital Authority CDARS, we identified all public hospitalisation episodes of children aged 1 month to 18 years with hyponatraemia (Na<135 mmol/L) during 2015. Those with severe hyponatraemia (Na<127 mmol/L) had their clinical details and IVF use analysed. ***Findings:*** Hyponatraemia occurred in 8.8% of

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60,960 paediatric admissions. True severe hyponatraemia occurred in 0.22% of all admissions, with 56% occurring at admission. Five cases had hyponatraemic seizures. Of 110 cases with hypovolaemic or euvolaemic severe hyponatraemia, 22 cases of hospital-acquired hyponatraemia were identified where hypotonic fluids likely contributed, as replacement, hyperhydration or maintenance fluids. ***Conclusions:*** Serious hyponatraemia may occur in association with hypotonic IVF. Paediatricians must prescribe IVF with care. Safe prescription practices are discussed.

Key words Hyponatraemia; Hypotonic fluid; Intravenous fluid; Paediatric

Introduction

The mainstream intravenous fluid (IVF) prescription practice in paediatrics had for years been based on the work of Holliday and Segar in 1950s in healthy children, where the "ideal" maintenance fluids was calculated to be 0.2% sodium and 5% glucose.[1] Since the 1990s, reports of over 100 cases of iatrogenic deaths or permanent neurologic impairment related to hyponatraemia in hospitalised children (including previously healthy children after elective surgery or simple problems like viral infections) have pointed to the dangers of hypotonic fluids, due to the common entity of syndrome of inappropriate ADH (SIADH) in many physiological or disease states, impairing free water excretion.[2]

The UK National Health Service 2007 alert[3] recommended 0.45% saline for maintenance fluids for the majority of children and 0.9% saline for children at risk for hyponatraemia. Since then, there have been many randomised controlled trials (RCT) and metanalyses comparing hypotonic and isotonic fluids, initially in post-operative and paediatric intensive care unit (PICU) children, but recently in general paediatric settings also.[4-6] These trials and metanalyses have all shown isotonic fluids to be protective against hyponatraemia; and is a safer choice than hypotonic fluids. However, the risk of hyponatraemia in general paediatric settings is considered low, and with concerns about hypernatraemia, hyperchloraemic acidosis and fluid overload from isotonic fluids, the recommendations of using isotonic fluids were not widely followed.[7,8]

In 2015, the National Institute for Health and Care Excellence (NICE) published a guideline on intravenous fluid therapy in hospitalised children, recommending initial use of isotonic crystalloids for routine maintenance.[9] This was followed an American Academy of Pediatrics (AAP) clinical practice guideline that strongly recommended the use of isotonic maintenance IVF.[10] An informal survey in 2016 amongst acute paediatric units within the public system (Hospital Authority or HA) in Hong Kong showed 0.45% saline to be the most common empirical choice for IVF, followed by 0.3% saline; while isotonic solution was not a routine. There is thus a need to review IVF use in the local general paediatric setting. A Working Group was commissioned by HA Paediatric Coordinating Committee in 2016 to perform a retrospective survey on hyponatraemia across all acute paediatric units within HA, which looks after ~80% children requiring acute hospital care in Hong Kong. The aim is firstly, to find out the prevalence of hyponatraemia in acute paediatric, non-surgical settings in Hong Kong, and identify the clinical situations where it occurs. The second aim is to see if hypotonic IVF is a contributing factor to hyponatraemia. This information may shed light on the need to modify existing IVF practices.

Methods

Using the HA Clinical Data Analysis & Reporting System, we searched for hospitalisation episodes of children admitted aged 1 month to 18 years into all 12 HA acute paediatric units during the year 2015, with serum sodium (Na) of <135 and <130 mmol/L at any stage during the hospitalisation. To focus on general paediatric cases, neonatal and surgical cases were excluded.

Due to the large number of cases and the preliminary impression that a significant proportion of those with Na 128-129 mmol/L had hyponatraemia at presentation and unlikely to be related to IVF, only those with Na of ≤127 mmol/L (defined as severe hyponatraemia) were systematically studied. We believe this will include all cases of clinically significant hyponatraemia. Each patient's record and intake-output chart was checked by the respective center coordinator. Age; principle and secondary diagnoses; admission sodium level; timing and lowest

sodium level; symptoms of hyponatraemia are noted. The composition, volume and duration of intravenous fluids as bolus, replacement or maintenance; proportion and type of oral fluids are recorded; together with subsequent management and progress of sodium level. Likely causes/contributors to hyponatraemia are noted if known, including dehydration, fluid overload, drugs, laboratory pointers to SAIDH. One investigator (LCKL) went through the case information and selected out those for which IVF are likely contributors to hyponatraemia, seeking consensus with center coordinators and Working Group members. As dilutional hyponatraemia is the cause in fluid overload cases (and the key is fluid restriction and not IVF composition), our analysis mainly focused on euvolaemic or hypovolaemic cases and their relationship with IVF practices. The study is approved by the Hospital Authority Ethics Committees.

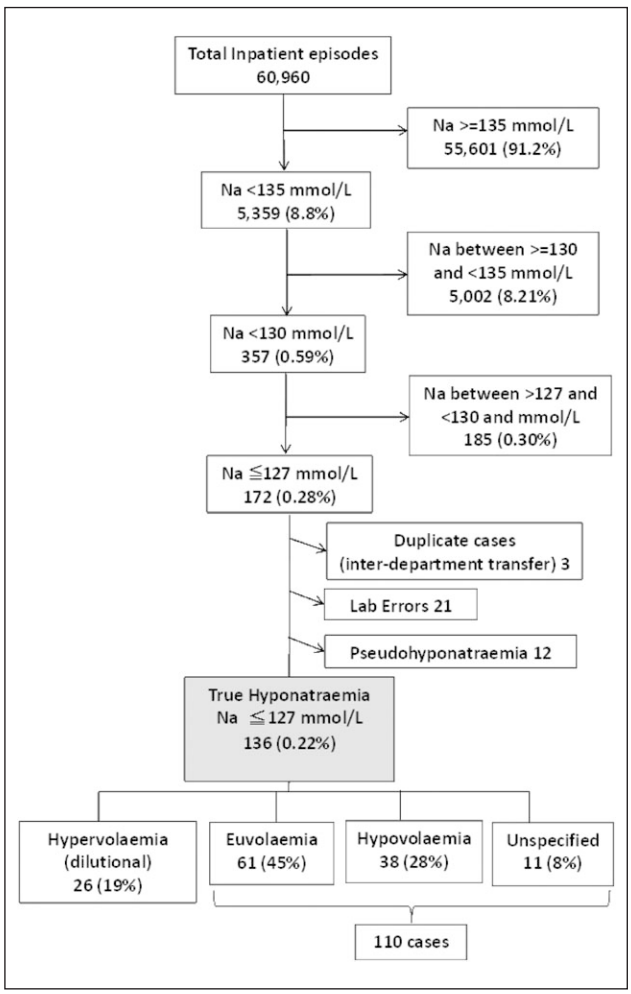

Figure 1 Breakdown of hyponatraemia cases amongst inpatients admitted to HA acute paediatric units in 2015.

Results

Prevalence and Causes of Hyponatraemia

Out of a total of 60,960 paediatric admission episodes in 2015, the number of episodes with Na <135 mmol/L, <130 mmol/L and 127 mmol/L were 5359 (8.8%), 357 (0.59%) and 172 (0.28%) respectively (Figure 1). The 172 severe hyponatraemia (Na ≤127 mmol/L) cases were studied in detail, and 136 episodes were true hyponatraemia. The proportions that were hypovolaemia, euvolaemia and hypervolaemia are illustrated in Figure 2. Hypervolaemic cases are dilutional hyponatraemia and unrelated to IVF, so are not the focus of this survey. Of the remaining 110 hypovolaemia and euvolaemic cases, hypovolaemic hyponatraemia cases mainly included dehydration due to gastro-intestinal loss or poor oral intake; only one case from renal fluid loss. Euvolaemic hyponatraemia cases were likely related to SIADH. Over half had infectious/inflammatory conditions, of which a significant proportion (40%) occurred in children with chronic illness (like neuromuscular diseases, epilepsy). Other euvolaemic cases had central nervous system (CNS) conditions (28%) or cancer related causes (20%).

A breakdown of the diagnoses as related to severity of hyponatraemia is seen in Table 1. Hyponatraemia cases related to hypovolaemia rarely had profound hyponatraemia of Na ≤120 mmol/L. However, 20% (12/61) euvolaemia cases had profound hyponatraemia, showing SIADH related cases are more prone to profound hyponatraemia.

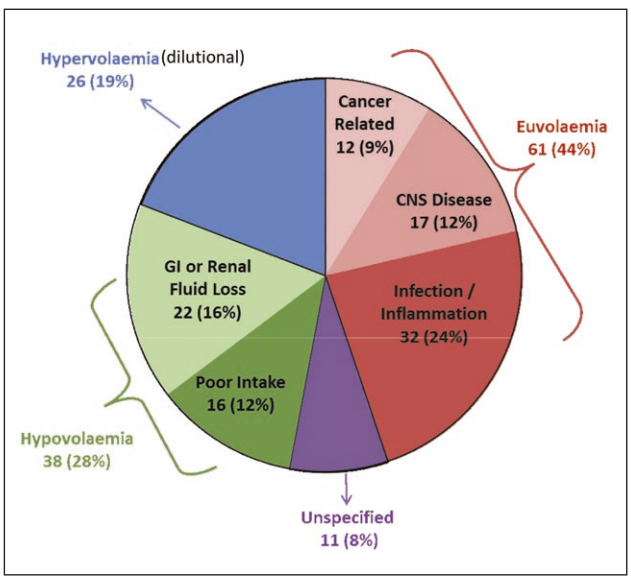

Figure 2 Causes of ALL true severe hyponatraemia (Hypovolaemia, Euvolaemia and Hypervolaemia) *n*=136 cases.

Admission Hyponatraemia and Empirical Fluids Used

Among hypovolaemic or euvolaemic severe hyponatraemia cases, severe hyponatraemia was already present at admission in 56% (Right hand column, Table 1). Young infants with bronchiolitis were particularly at risk, with 2 cases presenting with hyponatraemic seizure (see below). When IVF was used in these severe hyponatraemia cases, 0.45% saline was used in the majority. In 8 cases, fluids ≤0.3% saline was used. None received 0.9% saline.

Hyponatraemic Seizures

Five cases developed seizures associated with hyponatraemia (Table 2 for clinical details). Of note, 3 cases presenting with hyponatraemic seizures were young

Table 1 Breakdown of diagnoses of hypovolaemic and euvolaemic according to severity of hyponatraemia; number with hyponatraemia present at admission

	Na 126-127 mmol/L	Na 121-125 mmol/L	Na ≤120 mmol/L	Total no. = 110 (%)	No. (%) Na ≤127 mmol/L at admission
Hypovolaemia	**22**	**15**	**1**	**38 (35%)**	**28**
GI or renal loss	12	10	0	22	15
Diagnoses include acute gastroenteritis, secretary diarrhoea from graft versus host disease, ulcerative colitis, vomiting, increased gastric aspirate from bowel pathology					
Inadequate intake	10	5	1	16	13
Euvolaemia	**34**	**15**	**12**	**61 (55%)**	**31**
Infection/inflammation	18	7	7	32	20
Diagnoses include pneumonia, tuberculosis, bronchiolitis, influenza, septic shock, septicaemia, neutropenic fever, pneumococcal associated haemolytic uraemic syndrome and haemophagocytic lymphohistiocytosis					
CNS related	9	5	3	17	11
Diagnoses include tumours, hydrocephalus, encephalitis, seizures, intracranial haemorrhage and subdural empyema					
Cancer or drug related	7	3	2	12	
Miscellaneous				**11 (10%)**	
Cranial diabetes insipidus (known-on medication)	2	1	1	4	3
Terminal	2	4	1	7	N/A
Total	**60**	**35**	**15**	**110**	**62 (56%)**

Table 2 Clinical details of 5 patients who developed hyponatraemic seizures

	Na level & timing of seizure and hyponatraemia	Age, diagnosis	Clinical details	Likely contributors to hyponatraemia
A	124 on admission	1 month, RSV bronchiolitis	Admitted with seizure	SIADH risk
B	119 on admission	1 month, RSV bronchiolitis	Admitted with seizure	SIADH risk
C	115 on admission	2 months, ex-prem age 2 weeks	Corrected recent recovery from RSV infection, admitted with seizure.	SIADH risk
D	125 mmol/L 2 days after admission (= Case 3 of Table 3A)	3 years, Non-oliguric CKD from dysplastic Kidneys on peritoneal dialysis	Admitted for GE, dehydration and weight loss. Admission Na 136, Given 0.3% saline "80% maintenance" for rehydration in addition to usual gastrostomy feeds. Developed seizures 2 days later and found Na 125.	Hypotonic fluids given for 'rehydration/maintenance' in addition to full volume oral feeds.
E	118 one day after admission (= Case 11 of Table 3B)	3 months, ex-prem (4.1 kg) with pneumonia	Admission Na 134, given NS bolus then 0.3% saline "150% maintenance" for high fever, tachycardia and diarrhoea (Na 7.6 mmol/kg/day). Status epilepticus at 28 hours after admission and Na found to be 118.	High volume hypotonic fluids given as maintenance fluids; SIADH risk

Abbreviations: CKD=chronic kidney disease; GE=gastroenteritis; RSV=respiratory syncytial virus

infants associated with respiratory syncytial virus (RSV) bronchiolitis (patients A-C). In the other 2 cases (D-E), hyponatraemic seizures occurred 2 days and 28 hours after hyponatraemic fluids (both 0.3% saline) were started.

Hospital-acquired Severe Hyponatraemia

Overall, 31 cases had hospital-acquired severe hyponatraemia, as defined by sodium falling by ≥4 mmol/L from admission to ≤127 mmol/L, or failing to improve adequately above 127 mmol/L during hospital stay. Of these, 22 cases were identified where hypotonic fluid likely contributed to hyponatraemia, based on the time frame and clinical details. In these cases, the clinical situations could be classified into 3 broad categories: 1) those where hypotonic fluids were used in effect as replacement fluid in dehydration (Table 3A); 2) those where hypotonic fluids were used as maintenance fluids in settings at risk of SIADH (Table 3B); 3) those where hypotonic fluids were used for hyperhydration for drugs (Table 3C).

In these 22 patients, empirical 0.45% saline was used in 15 cases, empirical fluids ≤0.3% saline was used in 7 cases. Two patients developed seizures likely related to the hospital-acquired hyponatraemia (patients 3 and 11). The 3 categories are summarised below.

Category 1: Hypotonic Fluids Used as Replacement and Maintenance in Dehydration (Table 3A).

In these 6 cases, hypotonic (0.3% to 0.45% saline) fluid was used as both replacement and maintenance fluid; with or without prior 20-30 ml/kg saline boluses. In three patients, serum sodium decreased from normal values to 125-127 mmol/L over 12 hours to 2 days, including one with hyponatraemic seizure (patient 3). In the remaining three patients (patients 4-6) , severe hyponatraemia at admission failed to improve adequately.

Tables 3A-C Case details of 22 hospital-acquired hyponatraemia where hypotonic fluids likely contributed to hyponatraemia
For simplicity, only saline part of fluid mentioned. Abbreviations: D = Day; O/A = on admission; NS = normal saline.

Table 3A Hospital-acquired hyponatraemia cases related to hypotonic fluid used as replacement fluid for dehydration

	Initial Na/ last normal	Na after IVF	Age, diagnoses	Case details	IVF Given
Related to hypotonic fluids being used as replacement fluids for dehydration					
1	135 O/A	127 after 6 days	11 years, Henoch Schonlein Purpura	NGT fluid loss. Minimal oral for days.	D4 given NS bolus 20 ml/kg then 0.45% saline to replace 5% dehydration + full maintenance. D6: noted Na 127
2	134 O/A	127 after 12 hours	14 years, GE	Severe dehydration.	NS bolus 30 ml/kg, then 0.45% saline to replace 3.3% dehydration + full maintenance.
3	136 O/A (= Case D in Table 2)	125 after 2 days	3 years, Non-oliguric CKD from dysplastic Kidneys on PD	Admitted GE, dehydration and weight loss. Developed seizures 2 days after IVF and found Na 125. Given hypertonic saline and anticonvulsants.	0.3% saline as "80% maintenance" whilst on usual gastrostomy milk feeds.
4	122 O/A	129 after 42 hours	10 years, GE	Poor oral feed, dehydration. Delayed correction of hyponatraemia.	NS bolus, then 0.45% saline to replace 5% dehydration + full maintenance.
5	126 O/A	127 after 12 hours	7 years, GE	Delayed correction of hyponatraemia	0.45% saline "130 ml/kg maintenance" as replacement + maintenance.
6	127 O/A	127 after 30 hours	4 years, Intussusception	Delayed correction of hyponatraemia	0.3% saline full maintenance x 4 hours, then 0.45% saline "140% maintenance" as replacement + maintenance when first Na known.

Abbreviations: CKD= chronic kidney disease; GE=gastroenteritis; NGT=nasogastric tube; PD=peritoneal dialysis.

Category 2: Hypotonic Fluids Used as Maintenance Fluids in Patients at Risk for SIADH (Table 3B)

In these 12 cases at risk of SIADH, the main clinical situations were respiratory (e.g. bronchiolitis, pneumonia), infection or inflammation (e.g. viral illness, sepsis, haemophagocytic lympohistiocytosis), neurological (e.g. blocked VP shunt, intracranial haemorrhage), and cancer. Some patients had multiple factors operating (e.g. patient 17 cancer patient with high stool sodium loss).

As to fluid rates given, none were fluid restricted. Hypotonic fluids both at standard and higher than standard rates were associated with hospital acquired hyponatraemia. Seven patients received hypotonic IVF at higher than standard rates, empirically given for "high fever" or in young infants where a "neonatal pattern" of IVF was prescribed. One young infant (patient 11) developed hyponatraemic status epilepticus. Two patients (patients 12 and 13) received "standard rate IVF" in addition to enteral fluids; which totalled above twice standard volumes. The remaining 5 patients truly received standard rate fluids, and hyponatraemia resolved after increasing sodium in IVF with or without fluid restriction.

Category 3: Hypotonic Fluids Used for Hyperhydration (Table 3C)

In five cases (no. 19-23), hypotonic fluids were used for protocol hyperhydration for cyclophosphamide. Sodium levels decreased from normal down to severe/

Table 3B Hospital-acquired hyponatraemia cases related to hypotonic fluids used as maintenance fluids in patients at risk for SIADH

	Initial Na/ last normal	Na after IVF	Age, dagnoses	Other case details	IVF given
Related to use of hypotonic maintenance fluids, usually in patient at risk for SIADH					
7	Normal	126	16 years, Pneumonia	Long stay PICU, dystonic CP, rhabdomyolysis	0.45% saline, 124% maintenance.
8	126 O/A	120 after 8 hours	4 years, Hydrocephalus blocked shunt	Cerebral salt wasting.	0.3% saline, full maintenance x 2 hours, then 0.45% NS at 136% maintenance→Na 120.
9	142 O/A	127- 7 days after IVF	11 years, AML	Neutropenic fever. Labs showed SIADH.	0.45% saline, 117% maintenance for fever.
10	140 O/A	126 on D9.	2 months, RSV bronchiolitis/pneumonia	3.2 kg, intubated, RSV. Poor feeding. 141 on D2→131 on D6→126 on D9	From D5, fluids with Na 26 mmol/L (calculated as 3 mmol/kg/day Na) given at 120 ml/kg/day.
11	134 O/A (= Case E)	120 at 25 hours, 118 at 28 hours	3 months old, Pneumonia	Ex prem, 4.1 kg. Poor feeding. Status epilepticus at 28 hours.	NS bolus O/A; 0.3% saline at 150 ml/kg/day for high fever, tachycardia, diarrhoea.
12	136 three days before	Then 114/111 on D3	15 years, UTI, paraflu, Norwalk virus	Bedridden, on NSAID for fever.	0.45% saline at 84-90% maintenance. Excessive water intake. Total IV+ oral ~1.9 to 2.67 x maintenance.
13	118 O/A	119 after 11 hours, 124 after 34 hours	5 years, Pneumonia	Severe MR, myoclonic epilepsy, long-stay case. Labs showed SAIDH. Resolved after fluid restricted + oral sodium.	Admission Na118, Urea 8.5, Cr 56→treated as dehydration with NS bolus. 0.3% saline at 80 ml/kg/day + usual milk.
14	137 O/A	126	11 years AVM, ICH	Labs showed SIADH.	0.45% saline, full maintenance.
15	131 O/A	127 after 3 days	10 years, URI	Poor intake	0.45% saline, full maintenance.
16	131 O/A	122 after 6 days	15 years, EBV related HLH	Also incomplete Kawasaki with coronary aneurysm, negligible oral feeding	0.45% saline, full maintenance. Resolved after fluid restriction and increased IVF Na.
17	133 O/A	Na 124 after 1 day	14 years, Gut GVHD	Post BMT for AML	0.45% saline, full maintenance. Resolved after changed IVF to NS.
18	139 O/A	127 after 19 hours	20 months, Scald, septic/hypovolaemic shock	13% Scald	Hartmans 50 ml/kg as bolus - then NS as Parkland + 5% dextrose as full maintenance + 0.3% saline as ongoing loss,

Abbreviations: ALL=acute lymphocytic leukaemia; AML=acute myeloid leukaemia; AVM=arteriovenous malformation; BMT=bone marrow transplant; CKD= chronic kidney disease; CP=cerebral palsy; GE=gastroenteritis; HLH=haemophagocytic lymphohistiocytosis; ICH=Intracranial haemorrhage; MR=mental retardation; PD=peritoneal dialysis; PICU=paediatric intensive care unit; URI=upper respiratory tract infection; UTI=urinary tract infection.

profound levels (118-125 mmol/L) within hours to one day. They included patients on high dose as well as low dose cyclophosphamide.

Discussion

Frequency of Hyponatraemia and Implications of Admission Hyponatraemia

Our cohort shows that in the year 2015, mild (Na <135 mmol/L) and moderate (<130 mmol/L) hyponatraemia is not uncommon amongst paediatric inpatients, representing 8.8% and 0.59% respectively, though there may be some over-estimation from laboratory error or pseudohyponatraemia. Even so, 136 (0.22%) acute hospitalisations had true severe (Na ≤127 mmol/L) or profound (Na ≤120 mmol/L) hyponatraemia; with 5 cases having neurological sequelae. This shows that hyponatraemia is a genuine risk in the acute general paediatric setting.

Not only is hyponatraemia common, but it is also common at admission. Over half (56%) of the 110 hypovolaemic/euvolaemic severe hyponatraemia cases already had Na ≤127 mmol/L at admission. Our findings are consistent with the common risk of hyponatraemia reported in general paediatric patients. Neville[11] found 36% children with gastroenteritis were hyponatraemic at admission. Don[12] found that 45% of children with pneumonia were hyponatraemic and seemed associated with pneumonia severity. Hanna[13] reported that the incidence of admission hyponatraemia in infants with bronchiolitis was 33%, with 11% exhibiting serum sodium <130 mmol/L. Ill patients admitted to PICU may also have admission hyponatraemia ranging from 23 to 33%.[14,15] The common occurrence of admission hyponatraemia has implications on our empirical choice of fluids, as isotonic (but not hypotonic) fluids will normalise low plasma sodium.[11,15,16] In our cases with admission hyponatraemia, hypotonic fluids worsened or delayed improvement in some cases (e.g. cases 2, 4-6, 8, 11, 13, 15-17 in Tables 3A and B). In other cases, usually in those who were also feeding orally (probably indicating the child was not as ill), added oral sodium or fluid restriction may still raise sodium above 130 mml/L despite use of 0.45% saline, though sodium often remained in the mild hyponatraemia range.

Choice of IVF to Replace Volume Deficit

Our survey shows hypotonic fluids when used to replace fluid deficit (sometimes erroneously prescribed as "increased maintenance rates") may lead to hospital acquired hyponatraemia. Dehydration stimulates physiological ADH release which impairs free water excretion. If a volume-depleted child in a hyper-ADH state is given hypotonic fluids, there is risk of hyponatraemia. Neville also showed 0.9% saline reduced hyponatraemia for replacement and maintenance, compared with 0.45% saline, irrespective of rapid or standard rehydration rates in gastroenteritis.[11] According to various guidelines for rehydration in acute gastroenteritis, those with severe normo- or hyponatraemic dehydration without shock may receive replacement of deficit with isotonic fluid over 2-4 hours.[17,18] Once fluid volume is restored, they can be given oral rehydration fluids or dextrose containing IV maintenance fluids, taking into account ongoing losses.

Table 3C Hospital-acquired hyponatraemia cases related to hypotonic fluids used for hyperhydration

	Initial Na/ last normal	Na after IVF	Age, diagnoses	Case details	IVF given
Related to hypotonic fluids used for hyerhydration					
19	139 O/A	124 after 24 hours	8 years, Medulloblastoma	High dose cyclophosphamide	0.45% saline, 160% maintenance (125 ml/m^2/hour as per protocol)
20	139	124 after 9 hours	17 years, Transverse myelitis	Lose dose cyclophosphamide 500 mg/m^2	0.45% saline, 176% maintenance
21	137	125 after 25 hours	10 years, B cell lymphoma	High dose cyclophosphamide	0.45% saline
22	Normal	118	13 years, ALL	High dose cyclophosphamide	0.45% saline at 85 ml/m^2/h x12 hours

Abbreviations: ALL=acute lymphocytic leukaemia

Choice of IVF in Hyperhydration

In our series, 4 cases had hospital-acquired hyponatraemia during hyper-hydration for cyclophosphamide. It is well known high dose cyclophosphamide in malignancy (less commonly low dose in autoimmune disease) is associated with SIADH, water intoxication and seizures.[19] Chemotherapy-induced nausea is also a potent stimulus to ADH release. The risk of hyponatraemia in this setting may be minimised by using isotonic saline rather than hypotonic fluids to maintain a high urine output.

Choice of Maintenance IVF in Children at Risk of SIADH: Tonicity and Rate of Fluid

Amongst the causes of hyponatraemia in our cohort, the largest proportion (Figure 2) and the most severe hyponatraemia (Table 1) can be attributed to diverse conditions at risk for SIADH - the most common being infection/inflammation, CNS and cancer-related causes.

As this study is only a survey of severe hyponatraemia and not IVF prescription, we are unable to attribute a causal link between hyponatraemia and hypotonic fluids. However some points can still be observed when choosing the tonicity and rate of empirical IVF. All of the 12 hospital-acquired hyponatraemia cases related to SIADH (Table 3B) were associated with hypotonic fluids (0.45% saline in 7, ≤0.3% saline in 5 cases), and none received isotonic fluids. Hyponatraemia was successfully treated by increasing sodium orally or in IVF, with or without fluid restriction, suggesting isotonic fluids may have been a better alternative. Indeed, in the 8 patients given ≤0.3% saline in our cohort, hyponatraemia either developed or worsened in 7, the lowest sodium being 118 mmol/L, including two who developed hyponatraemic seizure. So it appears IVF with tonicity of ≤0.3% saline is best avoided, except in special circumstances like renal concentrating defects.

This preference for isotonic versus hypotonic fluids is clear from various systematic reviews[4-6] and evidence based guidelines[9,10] that included 17 RCT and 2455 patients. Isotonic fluid has definitively been shown to protect against hyponatraemia and is a safer choice than hypotonic fluids. In recent years, even the previous lack of RCT in general paediatric patients has been addressed by studies involving children with a broad range of medical diagnoses,[20-23] CNS infections[24] and gastroenteritis.[16] The largest of this is the PIMS trial involving 690 children,[22] showing that an isotonic balanced solution (Plasma-lyte 148) was protective against hyponatraemia compared with 0.45% saline (4% vs. 11%; odds ratio 0.31, 95% CI 0.16-0.61; P=0.001), where median fluid volume of 80% standard maintenance was given. Importantly, there was no difference in hypernatraemia (sodium >150 mmol/L). Other RCTs also confirmed the safety of isotonic IVF as regards to hypernatraemia. However, other side effects like hypervolaemia and hyperchloraemic acidosis (when normal saline is used) have not been well studied.

Despite the strong evidence for isotonic fluids in general, the authors consider the evidence for its use in infants <3 months of age to be less clear. Young infants <3 months old may be at greater risk of hypernatraemia and 5% glucose might be inadequate in this age. Almost all RCTs of general paediatric patients chose 3 months[20,22-24] or 6 months[16] as lower age limit, except Friedman's RCT[21] which included infants from 1 month old, though the numbers are likely small based on the subjects' median and interquartile age ranges. Indeed, in an RCT of term neonates receiving IVF for hyperbilirubinaemia, almost 40% of those on isotonic fluids developed hypernatraemia.[25] Despite the recommendations of empirical use of isotonic saline in well term neonates (NICE guideline) or infants older than 28 days (AAP guideline), we think it is prudent to monitor carefully for hypernatraemia and hypochloraemic acidosis in young infants; and be ready to change to 0.45% saline should hypernatraemia occur.

Besides fluid tonicity, fluid rate is the other important component of IVF prescription, and the two are inter-related. Some authors have argued that fluid restriction with hypotonic fluids would be sufficient to prevent hyponatraemia.[26] Studies have explored the relative importance of fluid tonicity versus rate in general paediatric,[20] PICU[27] and post-operative settings,[28,29] and found that fluid restriction could not prevent hypotonic fluid induced hyponatraemia. However the study numbers were small, and the fluid used in the non-surgical studies was 0.18% saline, which may not be applicable if 0.45% saline is used. Larger studies are needed to clarify the effect of fluid restriction.

Though these is no evidence based recommendations for fluid rate, most recent guidelines recommend empirical isotonic maintenance fluid at 50-80%,[9] or two-thirds standard rates[30-32] for those at risk of SIADH, though some advocate full maintenance rate.[33] In any case, empirical use of hypotonic fluids above standard rates should be avoided. One cannot over-emphasise the importance of ongoing monitoring of fluid and electrolyte balance to adjust both rate and tonicity of IVF.

One other learning point regarding fluid rate from our

survey is that, to avoid retention of electrolyte-free water, one should take into consideration all fluid intake, including gastrostomy, oral intake or medications, with the maintenance IVF rate adjusted down accordingly.

Special Groups of Patients at Risk of SIADH

It is noteworthy that a significant proportion of SIADH cases occurred in children with chronic neurological diseases (e.g. cerebral palsy, epilepsy, myopathy). Such children may be at particular risk of SIADH during acute illness. One explanation is that 50% body water is in skeletal muscle in normal people. Therefore, in patients with marked muscle atrophy or muscle disease, much less electrolyte-free water needs to be retained to cause a rapid decline in sodium levels.[34]

Also noteworthy in our cohort are 5 cases of significant hyponatraemia in young infants with RSV bronchiolitis; three of them presented with hyponatraemic seizures, another fatal case presenting with sodium 126 mmol/L died from ARDS and multi-organ failure. This association of hyponatraemia or hyponatraemic seizures in bronchiolitis has been reported in 2 series. In a retrospective review of severe RSV bronchiolitis requiring intensive care in UK,[35] the incidence of ICU admission hyponatraemia in 91 infants (median age 6 weeks) was 33%, with 11% exhibiting a serum sodium <130 mmol/L. Four infants suffered hyponatraemic seizures at ICU admission (Na 114-123 mmol/L); three had received hypotonic intravenous fluids at 100-150 ml/kg/day before. Another retrospective study[36] showed admission hyponatraemia in 84/233 (36%) children <2 years with bronchiolitis. Seizure occurred in a 29-day-old child with sodium 123 mmol/L while receiving two-thirds volume of 0.18% saline. This suggests that fluid restriction only may not be able to prevent dangerous hyponatraemia, and that empirical isotonic fluids with fluid restriction is safer in young infants with bronchiolitis.

Choice of Fluids in Setting of Hyponatraemia

Even when laboratory results revealed hyponatraemia, our survey revealed a common reluctance among doctors to change to isotonic fluids. Those on 0.3% saline were only changed to 0.45% saline, or had oral sodium added. In two, the rate of 0.45% was increased, thinking that this will increase the total sodium given to the patient, forgetting that free water is also increased and may actually worsen the hyponatraemia. The NICE IVF guidelines advise that if asymptomatic hyponatraemia is found, fluid status should be reviewed. Action taken should include changing a hypotonic fluid to isotonic fluid, and restricting maintenance fluids for patients who are hypervolaemic or at risk of SIADH.

Monitoring of Electrolytes

Another observation from the survey was that electrolytes should be checked more frequently especially in cases with complex pathophysiology (e.g. Case 3, Table 3A) or in young infants (e.g. Case 11, Table 3B). In the latter case, hyponatraemia seizure already occurred at 28 hours. If sodium trend was monitored earlier in these high risk cases (at least by 24 hours), it could have prompted earlier adjustment of IVF prescription before morbidity occurred. In other cases, there was a failure to take appropriate action when decreasing sodium trends were noted. NICE IVF guidelines recommend systematic monitoring when a child is started on IVF, then at least every 24 hours, or more frequently if there are electrolyte disturbances.

Limitations

As our survey is a retrospective study on hyponatraemia and not a survey of IVF prescription, we cannot comment on the incidence of hyponatraemia in those give hypotonic IVF or attribute causal associations to the fluids used. Also, we only looked at cases with Na ≤127, but we believe looking at the severest end of the spectrum will have revealed the most significant learning points in current practices.

Conclusion

This one year survey has shown that in acute general paediatric settings, mild hyponatraemia is common; and true severe hyponatraemia is not rare, including hyponatraemia at admission. Though rare, morbidities including hyponatraemic seizures do occur, and in some cases, preventable. Cases of hospital-acquired hyponatraemia were identified; most associated with the use of hypotonic fluids as replacement, hyperhydration or maintenance fluids at high as well as standard rates. Some safe practice points have been highlighted from our survey:

- The common occurrence of admission hyponatraemia means empirical isotonic fluids is safer.
- Replacement fluids should always be isotonic and calculated separately from maintenance fluids.
- Hyperhydration with hypotonic fluids can lead to rapid development of hyponatraemia; isotonic fluids may be

safer in hyperhydration protocols.

- In children, 0.3% saline is associated with a high risk of severe hyponatraemia and should be avoided except in clinical situations of excessive free water loss.
- Clinicians should be alert to clinical situations where SIADH is common, especially in children with pre-existing neurological, oncological diseases and young infants with bronchiolitis. While fluid restriction is commonly but not universally recommended, isotonic fluids should be the initial fluid in children with SIADH risk, though one should be vigilant about hypernatraemia with its use in young infants under 3 months.
- Calculation of IVF should take into account all oral, gastrostomy intake, fluids from medications, with IVF rate adjusted accordingly. Total maintenance fluids should not be given at higher than standard rates.
- When there is hyponatraemia (Na <135 mmol/L), patient should be changed to isotonic fluids, and reviewed for fluid status and pathophysiology to decide whether child is dehydrated requiring replacement fluids or needs fluid restriction for SIADH risk.
- Frequent monitoring of fluid balance, hydration status and electrolytes is of paramount importance. In high risk cases like unwell children with complex fluid pathophysiology or in young infants, dangerous hyponatraemia can manifest within 24 hours. Care must be taken to readjust composition and rate of IVF appropriately and promptly.

In summary, an individualised approach is needed for IVF prescription (tonicity and rate) in hospitalised children, taking into account age, volume status, pathophysiology (including risk of SIADH or the rare occurrence of increased free water loss through kidney or skin) and sodium result. No single fluid composition or rate is ideal for all children. Nor should it mean isotonic fluids should be default maintenance fluid in all children; or that they are totally without risks especially in those <3 months. To facilitate safe IVF prescription, clinical pathways can be devised. In all fluid choices, frequent and ongoing monitoring of child's fluid balance, hydration and electrolyte status is important. All doctors should treat IVF prescription with care, just as one would prescribe drugs.

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Declaration of Interest

The authors have no conflict of interest regarding this study to declare.

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