Prevalence, prognostic value, pathophysiology, and management of hyponatraemia in children and adolescents with COVID-19

Ploutarchos Tzoulis

Department of Metabolism & Experimental Therapeutics, Division of Medicine, University College London, London, UK

Abstract. Hyponatraemia is frequently encountered in adults with coronavirus disease 2019 (COVID-19) and is associated with poor prognosis. This review aims to describe for the first time the prevalence, aetiology, prognostic value, pathophysiology, and management of hyponatraemia in children and adolescents with COVID-19, taking into account all relevant studies published in PubMed and Cochrane Library studies until 26th September 2021. Literature search did not detect any studies evaluating the prevalence and prognostic value of sodium disorders in paediatric patients with COVID-19. A broader literature review showed a high prevalence of hyponatraemia in children with bacterial pneumonia, while some studies have reported that hyponatraemia is relatively common in Multisystem Inflammatory Syndrome in Children (MIS-C). In adults with COVID-19, an inverse association between sodium and interleukin-6 levels has been found, indicating that hyponatraemia could be used as a surrogate marker for the risk of cytokine storm and may facilitate the identification of patients who could benefit from immunomodulatory agents. Studies are urgently needed to evaluate the frequency and prognostic impact of electrolyte abnormalities in children with COVID-19. In the meantime, clinicians are urged to consider hyponatraemia in children with COVID-19 as a potential red flag, investigate the cause and administer fluids and other therapies accordingly. (www.actabiomedica.it)

Key words: Hyponatraemia, SIADH, sodium, COVID-19, SARS-CoV-2

Introduction

Hyponatremia (defined as serum sodium levels below 135 mmol/l) is the most common electrolyte disorder encountered in hospitals, occurring in approximately 15-30% of hospitalised children (1,2). Hyponatraemia is a well-established independent risk factor for in-hospital mortality and poor clinical outcomes (3-5). The body's main defence against developing hyponatraemia is the kidney's ability to generate dilute urine and excrete free water. The primary reason for development of hyponatremia in children is impairment of renal free water clearance, often in combination with excess water intake or sodium losses. In addition, children are at higher risk than adults for developing hyponatraemic encephalopathy due to the higher brain-to-skull size ratio, leaving less room for brain expansion. A child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age (6). Also, the paediatric brain has much less Na^+-K^+-ATPase activity, the key pathway of sodium extrusion from cells, than the adult brain, limiting brain's capacity to adapt to hyponatraemia (7). Hyponatraemia is a frequent finding in children and adolescents with pneumonia, with its incidence being estimated at 13-35% (8-10). Numerous studies have shown that serum sodium levels in children with respiratory tract infections are inversely correlated with

inflammatory biomarkers, suggesting that hyponatraemia can be a surrogate marker for the degree of inflammation. Similar to paediatric studies, studies in adults with community-acquired pneumonia (CAP) have reported a high prevalence for hyponatraemia, ranging from 28% to 32%, and an independent association with both an excess of in-hospital mortality as well as an increase in the length of hospital stay (11-15).

The COVID-19 pandemic, with a reported 220 million people having so far been infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is the greatest global public health crisis of this generation (16,17). In contrast to adults, the vast majority of children and adolescents with SARS-CoV-2 infection have mild Covid-19 that does not lead to severe illness or hospitalisation (18). In April 2020, the first cases of an emergent life-threatening hyperinflammatory syndrome were reported in children and adolescents (19). Multisystem inflammatory syndrome in children (MIS-C) is a severe postinfectious hyperinflammatory syndrome which involves damage to multiple organ systems, predominantly affecting the gastrointestinal, cardiovascular, haematologic, mucocutaneous and respiratory systems, and occurs on average 25 days after COVID-19 symptoms (20,21). MIS-C resembles Kawasaki disease, but, unlike it, affects predominantly adolescents and children older than 5 years of age (20).

Despite the recent surge in publications related to the prevalence and prognostic impact of hyponatraemia in COVID-19 patients (22-25), there have been sparse reports of this issue in children and adolescents. This is the first review to summarise the literature with regards to the prevalence, aetiology, and prognostic value of hyponatraemia in children and adolescents with COVID-19, supplemented by an overview of the potential pathophysiological mechanisms of hyponatraemia as well as the optimal diagnostic and therapeutic approach.

Methods

We undertook a search via *PubMed* and the Cochrane Library until 26th September 2021 of all studies which included the key words "COVID-19", "SARS-CoV-2", "hyponatraemia", "sodium", "syndrome of inappropriate antidiuretic hormone secretion (SIADH)", "children", "adolescents", and "paediatric". In view of the paucity of data about hyponatraemia in paediatric populations with COVID-19 (i), this review encompasses three relevants topics; hyponatraemia in children with pneumonia in general (ii), hyponatraemia in adults with COVID-19 (iii), and hyponatraemia in children with MIS-C in relation to COVID-19 (iv).

Results

A. Prevalence and prognostic impact of hyponatraemia

(i) Hyponatraemia in children with COVID-19

A review of demographic, clinical, laboratory, and imaging features in 2,597 paediatric patients with COVID-19 did not include any data about serum sodium levels (26). This review reported the most common abnormalities in laboratory parameters in order of frequency; increase in blood levels of creatine kinase-myocardial band (CK-MB), lactate dehydrogenase (LDH), C-Reactive Protein (CRP), aspartate aminotransferase (AST), D-dimer, alanine transaminase (ALT), and leucocytes (26). First reports of laboratory features in children with COVID-19 had already demonstrated a different laboratory profile compared to adult cases (27). A pooled analysis and review of laboratory abnormalities in 624 children with COVID-19 documented a decreased neutrophil count as the most common finding, followed by elevation in levels of CK-MB, LDH, procalcitonin (PCT), and CRP (28). However, the pattern of derangement in white cell count indices in children with COVID-19 was inconsistent, differing from well-described changes reported in adults, such as lymphopenia (28). Interestingly, these reviews did not include serum sodium data in the analysis (27,28). In total, data on laboratory features of paediatric cases with COVID-19 is lacking, with the majority of laboratory data originating from case reports and case series. Therefore, the frequency of hyponatraemia as well as its potential prognostic role are not known yet.

(ii) Hyponatraemia in children with pneumonia

Since the early 1990s, it has become evident that hyponatraemia, not only is common in children with pneumonia, but is also associated with adverse outcomes (8, 29). An observational study of 264 hospitalised children with pneumonia showed that children with hyponatraemia required 60% longer hospital stay and had a 3-fold increase in mortality rate compared to those with normonatraemia (29). Amongst children with pneumonia, those with low serum sodium concentration have longer duration of hospitalisation (8,30). Several studies have documented a high frequency of hyponatraemia (33-45%) and a strong relation to markers of disease severity, with hyponatraemic patients having higher body temperature, white cell count, CRP, and serum procalcitonin than normonatraemic ones (9,10, 31,32). With regards to the pathophysiology of hyponatraemia in children with pneumonia, most studies have attributed the majority of cases with hyponatraemia to the syndrome of inappropriate antidiuretic hormone (SIADH) and the remaining minority to hypovolaemic hyponatraemia (8,29,32). However, a recent prospective study challenged these findings, stating that a significant proportion of cases have instead either pseudohyponatraemia with normal serum osmolality owing to hyperglycaemia / hyperproteinaemia or hypovolaemic hyponatraemia due to non-renal sodium losses (9). In total, the combination of high prevalence and prognostic impact of hyponatraemia has highlighted the importance of establishing the cause of hyponatraemia through history, physical assessment of volume status and laboratory work-up, guiding the choice of appropriate treatment and fluid administration (8, 9, 29,32).

(iii) Hyponatraemia in adults with COVID-19

The emerging data from twelve observational studies (22, 24,25,33-41), confirm that hyponatraemia is frequently observed in patients with COVID-19 (Table 1).

Table 1. Prevalence of hyponatraemia on admission and association with mortality in adults hospitalised with COVID-19

Study	N (COVID-19 patients)	Hyponatraemia Na <135 mmol/l on admission	Na <130 mmol/l on admission	Mortality (versus normal sodium)
Frontera et al. (24)	4,645	30%	7.3%	**26.6% vs 13.2%** P < 0.001 **OR 1.43** 95% CI: 1.08-1.88 P = 0.012
Hu et al. (33)	1,254	9.9%	NR	**16.1% vs 6.3%** P < 0.001
Tezcan et al. (34)	408	35.8%	NR	**OR 10.33** 95% CI: 1.62-65.62 P = 0.01
HOPE-COVID-19 (25)	4,664	20.5%	3.8%	**OR 1.73** 95% CI: 1.28-2.34 P < 0.001
Atila et al. (35)	172	29.1%	NR	**HR: 1.40** 95%CI:1.10-16.62 P = 0.05
Tzoulis et al. (22)	488	24.6%	6.2%	**OR: 2.59** 95% CI 1.44-4.81 P = 0.002 For hypovolaemic hyponatraemia only

Table 1 (Continued)

Study	N (COVID-19 patients)	Hyponatraemia Na <135 mmol/l on admission	Na <130 mmol/l on admission	Mortality (versus normal sodium)
Hirsch et al. (36)	9,946	44.6%	9.1%	**OR: 2.06** 95% CI 1.57-2.70 for Na < 130
De Carvalho et al. (37)	296	31.1%	3.0%	**18% vs 9%** P = 0.042
Sjostrom et al[38]	406	57.0%	NR	Not examined
Berni et al. (39)	380	22.9%	NR	**HR: 2.70** 95% CI:1.13-6.45 P = 0.025
Voets et al[40]	193	34.0%	NR	Not examined
Martino et al. (41)	117	26.5%	NR	Not examined

Legend = NR: not reported.

Recent literature has led the European Society of Endocrinology to publish in Autumn 2021 an update of its previously published guidelines, stating that hyponatraemia in COVID-19 patients is common, similarly with other pneumonia cases (42). All these studies together have examined a population in excess of 20,000 COVID-19 patients who required hospital admission. It is worth emphasising that these studies have included only adults, excluding patients younger than 17 years old. Based on serum sodium concentration at hospital admission of adults with COVID-19, the prevalence of hyponatraemia (serum sodium < 135 mmol/l) has been reported in the vast majority of studies between 20% and 36%, with an estimated 3-9% frequency for moderate to severe hyponatraemia (serum sodium < 130 mmol/l) (23). The most commonly reported risk factors for the development of hyponatraemia in this context have been older age, lower body mass index, larger number of co-morbidities, more severe radiological lung findings (such as bilateral radiological abnormalities), and higher levels of neutrophils and CRP (24,25,33). With respect to the type of hyponatraemia, limited evidence suggests that SIADH and hypovolaemic hyponatraemia are the commonest causes, with similar frequency, in COVID-19 (22,24).

Recent literature shows a strong association of hyponatraemia with poor clinical outcomes in adult COVID-19 patients (23,42,43). Numerous studies have identified hyponatraemia on admission as an independent risk factor for mortality, with odds ratios of 1.40 – 2.70 (24,25,35,36,39). In addition, hyponatraemia is associated with a greater need for invasive mechanical ventilation (IMV) with an odds ratio from 1.83 to 3.30 (24,34,35) and higher ICU admission rates (odds ratio 2.80 – 3.73) (34,35). Finally, most studies have reported that COVID-19 patients with low serum sodium have longer duration of hospital stay than those with normal sodium (33,34,36).

This evidence does not infer causal relationship, but it suggests that hyponatraemia should be considered as an early prognostic marker in adults with COVID-19. It is still unclear whether the relationship of hyponatraemia and clinical outcomes is causal or simply indicative of low sodium being a surrogate marker for disease severity (42). Therefore, the role of serum sodium value may be that of timely identifying those patients at high risk of progression to severe disease in order to intensify monitoring and consider additional therapeutic manouervres (39).

(iv) Hyponatraemia in MIS-C related to COVID-19

A systematic review, including a total of 599 patients with MIS-C, noted hyponatraemia amongst the most prevalent laboratory findings, such as high levels of Erythrocyte Sedimentation Rate (ESR), CRP and ferritin and decrease in leucocytes, lymphocytes and albumin concentration (44). An observational study of critically ill children with MIS-C and myocarditis

reported a median serum sodium of 131 mmol/l (ranging from 122 to 139 mmol/l), with 16 out of 20 children (80%) having hyponatraemia (45). Another observational study of 21 children with a Kawasaki-like multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection reported median serum sodium levels of 130 mmol/l (range 116-135 mmol/l), with 95% of cases having hyponatraemia, across significantly elevated inflammatory markers and interleukin-6 (IL-6) levels (46). A case series of 52 children with MIS-C associated with COVID-19 reported that 59.6% of cases had hyponatraemia on admission with median serum sodium 134 mmol/l, while all patients had at some stage during hospitalisation serum sodium below 135 mmol/l (47). A recent observational study was undertaken in order to identify the differences between active COVID-19 pneumonia and MIS-C in the paediatric population and help clinicians distinguish these two clinical entities[48]. Patients with MIS-C were noted to have significantly lower sodium values on admission [median value (IQR) 133 (131.7-134.2) mmol/l] than patients with COVID-19 [median value (IQR) 139 (136.7-141.2) mmol/l] (48). This study reported hyponatraemia in the vast majority of patients with MIS-C. In line with this difference, inflammatory markers on admission, such as CRP, ESR, and procalcitonin, were significantly higher in MIS-C compared to COVID-19 pneumonia (48). In summary, hyponatraemia is a very common finding, affecting the majority of patients with MIS-C.

B. Pathophysiology of hyponatraemia

In general, hyponatraemia in children can be classified based on extracellular volume status into euvolaemic, hypovolaemic, and hypervolaemic hyponatraemia (49). Sparse data exist on the aetiology of hyponatraemia in children with COVID-19. However, it is speculated that hyponatraemia in children with COVID-19 shares similar pathophysiological mechanisms with children who have other respiratory tract infections.

Euvolaemic hyponatraemia in children with COVID-19 is primarily caused by SIADH via four potential mechanisms. Firstly, increased levels of cytokines, such as IL-6, can directly stimulate non-osmotic release of arginine vasopressin (AVP), as it has been observed in a variety of infectious diseases and other inflammatory conditions (50). Excessive release of AVP as a direct result of significantly elevated inflammatory cytokines is the predominant mechanism, explaining hyponatraemia in patients with MIS-C (51). Secondly, the injury to lung tissue and alveolar cells can result in a ventilation-perfusion mismatch and compensatory hypoxic pulmonary vasoconstriction. Subsequently, this leads to inadequate filling of the left atrium, decreased left atrial stretch and increased AVP secretion (52). Third, patients with COVID-19 pneumonia can have various stimuli, such as pain, nausea and medications, all stimulating the direct release of AVP. Fourth, patients receiving PPV (positive pressure ventilation) can have non-osmotic stimulation of AVP secretion, as pulmonary baroreceptors respond to a reduction in effective arterial blood volume (52). A rare, but important, cause of euvolaemic hyponatraemia which should not go undiagnosed is tertiary adrenocortical insufficiency due to impaired hypothalamus-pituitary-adrenal axis in the context of chronic exposure to exogenous glucocorticoids (53). Long-term use of glucocorticoids in children applies to a broad range of conditions, including respiratory, gastrointestinal, rheumatological and skin diseases. Under normal circumstances, patients with COVID-19 exhibit a marked cortisol stress response, significantly higher compared to other patients with sepsis (54). As a result, mere doubling of glucocorticoid doses according to the standard "sick day rules" may be insufficient and leave those children on long-term glucocorticoids with prolonged periods of hypocortisolaemia (55), resulting in biochemical and clinical picture similar to that of SIADH (56). Finally, another rare aetiology of euvolaemic hyponatraemia is psychogenic polydipsia in children and adolescents with pre-existing psychiatric disease (49).

Hypovolaemic hyponatraemia is characterised by depletion of circulating volume triggering baroreceptor-mediated non-osmotic AVP release (57). Hypovolaemic hyponatraemia in the context of COVID-19 illness in children is most commonly attributed to gastrointestinal sodium losses, as a consequence of vomiting and diarrhoea, in combination with poor oral intake (49). Sodium losses may also be explained by a significant increase in insensible fluid losses due to pyrexia

and tachypnoea or, less often, by renal losses due to renal salt wasting syndrome or diuretic use (24,49). In the paediatric populations with COVID-19, hypervolaemic hyponatraemia should be regarded as a rare occurrence, except for children with coexisting conditions such as nephrotic syndrome, cirrhosis or heart failure (49).

Finally, iatrogenic hyponatraemia, a common problem in hospitalised children, is closely linked to the administration of hypotonic intravenous fluids (IVFs) (58). In contrast to the common use of isotonic IVFs in hospitalised adults, the administration of hypotonic IVFs has been the standard of care in paediatrics since the 1950s, often resulting in hospital-acquired hyponatraemia (2). Several studies have found that the administration of hypotonic maintenance fluids to children compared to isotonic fluids is associated with a significantly greater risk of developing hyponatraemia (2, 58,59). The American Academy of Paediatrics highlighted in a recent clinical practice guideline the link between administration of hypotonic fluids and hospital-acquired hyponatraemia in patients younger than 18 years who are hospitalised in medical or surgical acute care settings (58). Children and adolescents with COVID-19 should be considered at high risk of developing hospital-acquired hyponatraemia due to a high chance of developing excess AVP secretion, impairing free renal water excretion, which combined with supply of free water in the form of hypotonic fluids can lead to euvolaemic hyponatraemia (58,60).

C. Hyponatraemia and inflammation

The main underlying mechanism involved in the development of hyponatraemia associated with inflammatory conditions is that pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and IL-6, induce non-osmotic release of AVP (50,61). Various studies have found an inverse linear relationship between IL-6 levels and sodium concentration (62). Therefore, hyponatraemia tends to reflect the severity of various infections, including pneumonia, tuberculosis, meningitis, encephalitis, HIV infection and malaria (63). In the setting of COVID-19, three studies have evaluated the relationship of serum sodium concentration with IL-6 levels in adult inpatients (24,39,64). Firstly, a retrospective study of 29 adult COVID-19 patients showed that those with levels of IL-6 above the upper normal limit of 10 pg/ml had a significantly lower median serum sodium of 133.1 mmol/l versus 139.6 mmol/l in subjects with normal IL-6 levels (64). In addition, administration of tocilizumab, an IL-6 antagonist, to a small subgroup of hyponatraemic patients with abnormal IL-6 levels led to a significant 48-hour increase in serum sodium from a baseline of 132.4 mmol/l to 139.6 mmol/l, whereas sodium concentrations did not show a significant change in patients not treated with tocilizumab (64). A second, much larger, study of the association of IL-6 and sodium levels in 1,179 COVID-19 patients showed a significant inverse relationship between IL-6 and sodium levels, with median IL-6 levels being progressively higher as the severity of hyponatraemia worsened (24). The majority of patients (82%) with moderate to severe hyponatraemia (serum sodium <130 mmol/l) had abnormally elevated IL-6 levels, with median IL-6 levels of 21 pg/ml versus 14 pg/ml in normonatraemic patients (24). The third study of 441 COVID-19 patients confirmed the inverse correlation of serum sodium with IL-6 levels and reported that median IL-6 levels in patients with hyponatraemia were 20.5 pg/ml compared to 9.5 pg/ml in those with normal sodium (39). In addition, there was a direct correlation between serum sodium and the ratio of partial pressure of oxygen in arterial blood (PaO2) to the inspired oxygen fraction (FiO2), well known as P/F ratio, with patients with low sodium having lower P/F ratio than normonatraemic ones (39). All three studies have confirmed the inverse association of IL-6 with sodium levels, providing evidence in favour of using hyponatremia as a surrogate marker for the magnitude of inflammatory response in COVID-19 adult inpatients. These findings have not been confirmed yet in paediatric populations with COVID-19 since no studies have explored the relationship between serum sodium and IL-6 levels in children.

A proportion of adults with COVID-19 develop a cytokine release syndrome (CRS), also called the cytokine storm, which represents a hyperactive immune response state and is associated with adverse clinical outcomes (65-67). Cytokine storm is caused

by elevated levels of IL-6 and other proinflammatory cytokines (IL-1β, IL-10, interferon γ) in the circulation and leads to secondary organ dysfunction due to inflammation beyond that which could be attributed to an appropriate response to a pathogen (65,68). Since this hyperinflammatory state can be the major driver for morbidity and mortality, it has been argued that blunting the immune response through IL-6 receptor blockade may improve clinical outcomes (69). Therefore, tocilizumab, a recombinant humanised monoclonal antibody that binds human IL-6 receptors, has been evaluated in several studies with critically ill adult COVID-19 patients which overall show better outcomes and lower mortality rates (70-72). Despite the limited information about the benefits and risks of tocilizumab use in children with COVID-19, the US Food and Drug Administration (FDA) issued an Emergency Use Authorisation of tocilizumab for the treatment of COVID-19 in hospitalised children older than 2 years of age who require respiratory support and receive systematic glucocorticoids. It remains to be seen whether sodium measurement should be incorporated in disease severity grading systems in adults with COVID-19 in order to facilitate early identification of patients at high risk of cytokine storm and prompt use of immunomodulatory therapies (73). A similar question arises as to whether serum sodium could be utilised in routine clinical care in order to identify children who would benefit from intensive monitoring and consideration of immunomodulatory therapeutic agents.

D. Investigation of hyponatraemia

The diagnostic approach to a child with COVID-19 and hyponatraemia should follow a similar algorithm with that in the general paediatric patients (Figure 1), necessitating identification of the underlying cause of hyponatraemia in order to guide appropriate treatment (56,57). Since the aetiology of hyponatraemia is expected to be in the majority of children with COVID-19 either SIADH or hypovolaemic hyponatraemia (22,24), the first key step is to distinguish euvolaemic from hypovolaemia (74). A detailed personal history from the child and its carers, including information about fluid balance, weight changes and composition of ingested fluids, along with physical examination, are the first key

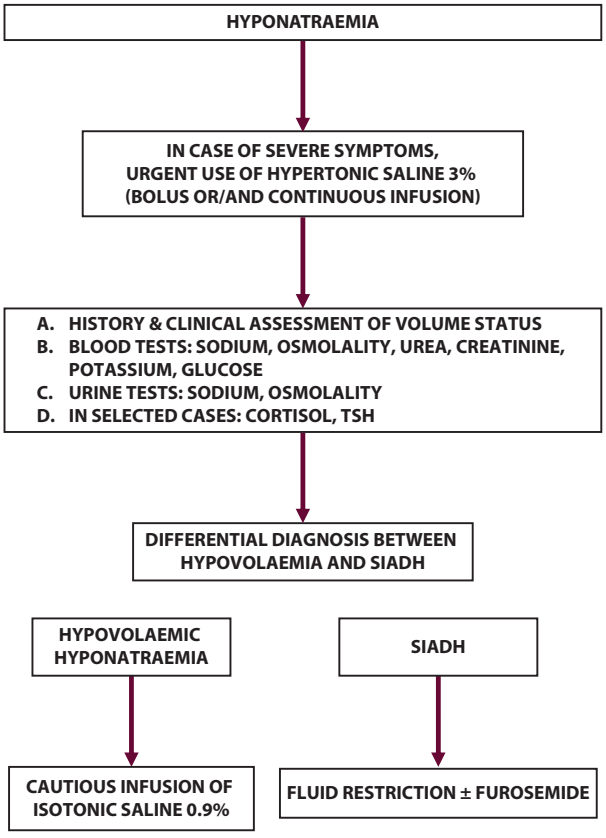

Figure 1. Algorithm for investigation and management of hyponatraemia in children and adolescents with COVID-19.

steps (74). Clinical evaluation of volume status is imperative since children with hypovolaemia may have signs, such as orthostatic changes in blood pressure and heart rate, dry mucous membranes, and poor skin turgor (74). Bearing in mind the low accuracy of clinical evaluation, even by experienced clinicians, for predicting the state of extracellular fluid volume (75,76), laboratory evaluation is of paramount importance. Complete work-up should include measurement of paired serum and urine osmolality and sodium as well as serum glucose, urea, creatinine, potassium(56,57,74,77). Urine dipstick is a very quick, fast and cheap bedside test which provides an instant measure of specific gravity. There is a close direct relationship of urine specific gravity with urine osmolality, with a specific gravity of 1.008 being related to osmolality of 280 mOsm/kg (78). Since hyperglycaemia is frequently reported in COVID-19 patients (79) and in order to exclude hyperglycaemia-related translocational hyponatraemia, it is essential to correct

sodium concentration by an increase of 2.4 mmol/l per 100 mg/dl (5.5 mmol/l) increase in glucose concentration above 126 mg/dl (7.0 mmol/l) (80). In selected cases and if there is a suspicion of adrenal insufficiency or severe myxoedema, serum cortisol and thyroid stimulating hormone (TSH) should be measured respectively.

E. Treatment of hyponatraemia

The key step is to establish the presence or not of severe symptoms, such as seizures, reduced consciousness level, or apnoea. The contemporary guidelines advocate for the management of adult patients with severe hyponatraemic encephalopathy the use of intravenous boluses of hypertonic saline rather than traditional continuous infusion to achieve faster elevation of serum sodium and symptom relief (56,57). Paediatric guidelines have followed a similar approach for children with severe symptoms of hyponatraemic encephalopathy. In order to avoid brain herniation, future deterioration and, even, death, urgent administration of hypertonic saline 3.0% as an intravenous bolus of 2-5 ml/kg of child's body weight over 15-20 minutes is warranted (74). This strategy has been shown in general paediatric populations to be effective, safe and does not require central venous access catheter (81). The initial correction target is a sodium rise of 5 mmol/l and the bolus can be repeated, if needed, to achieve this target which is sufficient to reverse clinical signs of herniation and reduces intracranial pressure by nearly 50% within an hour (82,83). This approach can be lifesaving and is also expected to apply to children with COVID-19 and severely symptomatic hyponatraemia, in line with general paediatric literature.

In the absence of severe symptoms, the underlying cause of hyponatraemia should be sought and treated (74). In the common scenario of hypovolaemic hyponatraemia, treatment consists of intravenous administration of isotonic fluids. In view of concerns about frequent cardiac involvement and subsequent risk of pulmonary oedema in adult with COVID-19, clinicians have been urged to exercise caution in the speed / volume of fluid administration (84). A question arises as to whether the risk of fluid-related pulmonary oedema applies to children with COVID-19. Children with SIADH and without severe symptoms should primarily be treated with restriction of fluid intake. In some cases, fluid restriction can be supplemented by furosemide, promoting water diuresis (74). Pharmacological agents, such as vaptans, which promote aquaresis through antagonism of the action of arginine vasopressin (56,77,85), or urea, which increases solute-free water excretion through increase of the osmotic load (57,85), have not been widely studied and used in children. Therefore, routine use of these agents is discouraged, except for refractory cases under the care of an expert in electrolyte disorders and rigorous monitoring. In total and regardless of therapeutic approach, clinicians should closely monitor electrolytes, daily fluid input and output, and maintain weight chart.

Besides appropriate treatment of hyponatraemia, prevention can be equally important. Following a plethora of reports on the relationship between hypotonic fluids and hospital-acquired hyponatraemia as well as the deleterious effect of hyponatraemia in the acutely ill children, a significant debate emerged in the 1990s about the optimal type of maintenance IVFs to children. Since then, numerous studies have demonstrated that isotonic fluids are superior to hypotonic fluids in preventing hyponatraemia (58). Therefore, the American Academy of Paediatrics recommends that patients younger than 18 years of age should receive isotonic maintenance fluids because they significantly decrease the risk of developing hospital-acquired hyponatraemia (58).

F. Future studies

First of all, studies are urgently needed in children and adolescents with COVID-19 in order to evaluate the prevalence of electrolyte abnormalities and the frequency of different types of hyponatraemia. The high frequency of hyponatraemia in children with pneumonia as well as in adults with COVID-19 raises the question as to whether sodium abnormalities are similarly common in paediatric patients with COVID-19. Second, studies are warranted to explore further the pathophysiological basis of hyponatraemia in paediatric patients with COVID-19 and a potential link to the magnitude of inflammatory response. Third, there is an urgent need to develop more sophisticated risk stratification calculators, incorporating demographic,

clinical, radiologic, and laboratory parameters. It remains to be seen whether serum sodium could be another independent prognostic tool for continuous risk estimate of disease progression and outcomes, not only at the baseline but also during the disease course. Finally, in the era of personalised medicine, studies should examine the potential role of serum sodium as a selection criterion for prompt initiation of immunomodulatory therapy, such as tocilizumab, to the appropriate subgroup of patients.

Conclusions

In conclusion, hyponatraemia is highly prevalent on hospital admission of adults with COVID-19 as well as in children with pneumonia. In addition, hyponatraemia is an independent poor prognostic marker in adults with COVID-19 as well as in all patients, regardless of age, with pneumonia. Several studies have demonstrated that low serum sodium is very frequently observed in COVID-19-related MIS-C. However, there is paucity of data about the frequency and prognostic value of hyponatraemia in children with COVID-19, highlighting the urgent need to undertake relevant studies in paediatric populations with COVID-19. Taking into account the close relationship of sodium with interleukin-6 and the fact that SIADH is the leading cause of hyponatraemia in adults with COVID-19, it could be speculated that serum sodium might also be used for the prompt identification of adults at risk of cytokine storm who may benefit from therapeutic agents, such as IL-6 antagonists. Apparently, the same findings cannot be extrapolated to the paediatric population, necessitating evaluation of the role of sodium as a risk stratification toll and inflammatory marker in children and adolescents with COVID-19. In the interim, hyponatraemia should be investigated and treated in children with COVID-19, following the principles in general paediatric patients.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Moritz ML, Ayus JC. Disorders of water metabolism in children: hyponatremia and hypernatremia. Pediatr Rev. 2002;23:371-380.
2. Carandang F, Anglemyer A, Longhurst CA, et al. Association between maintenance fluid tonicity and hospital-acquired hyponatremia. J Pediatr. 2013;163:1646-1651.
3. Wald R, Jaber BL, Price LL, et al. Impact of hospital-associated hyponatremia on selected outcomes. Arch Intern Med. 2010;170:294-302.
4. Tzoulis P, Bagkeris E, Bouloux PM. A case-control study of hyponatraemia as an independent risk factor for inpatient mortality. Clin Endocrinol (Oxf). 2014;81:401-407.
5. Whelan B, Bennett K, O'Riordan D, et al. Serum sodium as a risk factor for in-hospital mortality in acute unselected general medical patients. QJM. 2009;102:175-182.
6. Moritz ML, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children. Pediatr Nephrol. 2010;25:1225-1238.
7. Ayus JC, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. Am J Physiol Renal Physiol. 2008;295 :F619-624.
8. Park SW, Shin SM, Jeong M, et al. Hyponatremia in children with respiratory infections: a cross-sectional analysis of a cohort of 3938 patients. Sci Rep. 2018;8:16494.
9. Tagarro A, Martin MD, Del-Amo N, et al. Hyponatremia in children with pneumonia rarely means SIADH. Paediatr Child Health. 2018;23:e126-e133.
10. Sakellaropoulou A, Hatzistilianou M, Eboriadou M, et al. Hyponatraemia in cases of children with pneumonia. Arch Med Sci. 2010;6:578-583.
11. Kruger S, Ewig S, Giersdorf S, et al. Dysnatremia, vasopressin, atrial natriuretic peptide and mortality in patients with community-acquired pneumonia: results from the german competence network CAPNETZ. Respir Med. 2014;108:1696-1705.
12. Cuesta M, Slattery D, Goulden EL, et al. Hyponatraemia in patients with community-acquired pneumonia; prevalence and aetiology, and natural history of SIAD. Clin Endocrinol (Oxf). 2019;90:744-752.
13. Nair V, Niederman MS, Masani N, et al. Hyponatremia in community-acquired pneumonia. Am J Nephrol. 2007;27:184-190.
14. Muller M, Schefold JC, Guignard V, et al. Hyponatraemia is independently associated with in-hospital mortality in patients with pneumonia. Eur J Intern Med. 2018; 54:46-52.
15. Zilberberg MD, Exuzides A, Spalding J, et al. Hyponatremia and hospital outcomes among patients with pneumonia: a retrospective cohort study. BMC Pulm Med. 2008;8:16.
16. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382:727-733.
17. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020.

18. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr. 2020;174:882-889.
19. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607-1608.
20. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020;383:334-346.
21. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021;325:1074-1087.
22. Tzoulis P, Waung JA, Bagkeris E, et al. Dysnatremia is a predictor for morbidity and mortality in hospitalized patients with COVID-19. J Clin Endocrinol Metab. 2021;106:1637-1648.
23. Tzoulis P, Grossman AB, Baldeweg SE, et al. MANAGEMENT OF ENDOCRINE DISEASE: Dysnatraemia in COVID-19: prevalence, prognostic impact, pathophysiology, and management. Eur J Endocrinol. 2021;185:R103-R111.
24. Frontera JA, Valdes E, Huang J, et al. Prevalence and Impact of Hyponatremia in Patients With Coronavirus Disease 2019 in New York City. Crit Care Med. 2021; 96:e575-e586.
25. Ruiz-Sanchez JG, Nunez-Gil IJ, Cuesta M, et al. Prognostic Impact of Hyponatremia and Hypernatremia in COVID-19 Pneumonia. A HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry Analysis. Front Endocrinol (Lausanne). 2020;11:599255.
26. Cui X, Zhang T, Zheng J, et al. Children with coronavirus disease 2019: A review of demographic, clinical, laboratory, and imaging features in pediatric patients. J Med Virol. 2020;92:1501-1510.
27. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med. 2020;58:1135-1138.
28. Henry BM, Benoit SW, de Oliveira MHS, et al. Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review. Clin Biochem. 2020;81:1-8.
29. Singhi S, Dhawan A. Frequency and significance of electrolyte abnormalities in pneumonia. Indian Pediatr. 1992;29:735-740.
30. Wrotek A, Jackowska T. Hyponatremia in children hospitalized due to pneumonia. Adv Exp Med Biol. 2013;788:103-108.
31. Don M, Valerio G, Korppi M, et al. Hyponatremia in pediatric community-acquired pneumonia. Pediatr Nephrol. 2008;23:2247-2253.
32. Shann F, Germer S. Hyponatraemia associated with pneumonia or bacterial meningitis. Arch Dis Child. 1985;60:963-966.
33. Hu W, Lv X, Li C, et al. Disorders of sodium balance and its clinical implications in COVID-19 patients: a multicenter retrospective study. Intern Emerg Med. 2021;16:853-862.
34. Tezcan ME, Dogan Gokce G, Sen N, et al. Baseline electrolyte abnormalities would be related to poor prognosis in hospitalized COVID-19 patients. New Microbes New Infect. 2021;16:853-862.
35. Atila C, Sailer CO, Bassetti S, et al. Prevalence and outcome of dysnatremia in patients with COVID-19 compared to controls. Eur J Endocrinol. 2021;184:409-418.
36. Hirsch JS, Uppal NN, Sharma P, et al. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19. Nephrol Dial Transplant. 2021; 36:1135-1138.
37. De Carvalho H, Letellier T, Karakachoff M, et al. Hyponatremia is associated with poor outcome in COVID-19. J Nephrol. 2021;34:991-998.
38. Sjostrom A, Rysz S, Sjostrom H, et al. Electrolyte and acid-base imbalance in severe COVID-19. Endocr Connect. 2021;10:805-814.
39. Berni A, Malandrino D, Corona G, et al. Serum sodium alterations in SARS CoV-2 (COVID-19) infection: impact on patient outcome. Eur J Endocrinol. 2021;185: 137-144.
40. Voets PJ, Frolke SC, Vogtlander NP, et al. COVID-19 and dysnatremia: A comparison between COVID-19 and non-COVID-19 respiratory illness. SAGE Open Med. 2021;9:20503121211027778.
41. Martino M, Falcioni P, Giancola G, et al. Sodium alterations impair the prognosis of hospitalized patients with COVID-19 pneumonia. Endocr Connect. 2021:EC-21-0411.R1.
42. Christ-Crain M, Hoorn EJ, Sherlock M, et al. ENDOCRINOLOGY IN THE TIME OF COVID-19-2021 UPDATES: The management of diabetes insipidus and hyponatraemia. Eur J Endocrinol. 2021;185:G35-G42.
43. Akbar MR, Pranata R, Wibowo A, et al. The Prognostic Value of Hyponatremia for Predicting Poor Outcome in Patients With COVID-19: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021;8:666949.
44. Mardi P, Esmaeili M, Iravani P, et al. Characteristics of Children With Kawasaki Disease-Like Signs in COVID-19 Pandemic: A Systematic Review. Front Pediatr. 2021;9: 625377.
45. Grimaud M, Starck J, Levy M, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care. 2020;10:69.
46. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
47. Tolunay O, Celik U, Arslan I, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19: A Case Series Experience in a

Tertiary Care Hospital of Southern Turkey. J Trop Pediatr. 2021;67:fmab050.
48. Reiff DD, Mannion ML, Samuy N, et al. Distinguishing active pediatric COVID-19 pneumonia from MIS-C. Pediatr Rheumatol Online J. 2021;19:21.
49. Zieg J. Pathophysiology of Hyponatremia in Children. Front Pediatr. 2017;5:213.
50. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr. 2013;56:519-522.
51. Mills T, Trivedi A, Tremoulet AH, et al. Hyponatremia in Patients With Multisystem Inflammatory Syndrome in Children. Pediatr Infect Dis J. 2021;40:e344-e346.
52. Yousaf Z, Al-Shokri SD, Al-Soub H, et al. Covid-19 associated SIADH; a clue in the times of pandemic! Am J Physiol Endocrinol Metab. 2020;318:E882-E885.
53. Garrahy A, Thompson CJ. Glucocorticoid deficiency and syndrome of inappropriate antidiuresis: an underdiagnosed association? Ann Clin Biochem. 2018;55:4-6.
54. Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol. 2020;8: 659-660.
55. Arlt W, Baldeweg SE, Pearce SHS, et al. Endocrinology in the time of COVID-19: Management of adrenal insufficiency. Eur J Endocrinol. 2020;183:G25-G32.
56. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126 (Suppl 1):S1-42.
57. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170:G1-47.
58. Feld LG, Neuspiel DR, Foster BA, et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics. 2018;142:e20183083.
59. Hoorn EJ, Geary D, Robb M, et al. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics. 2004;113:1279-1284.
60. Friedman JN, Canadian Paediatric Society ACC. Risk of acute hyponatremia in hospitalized children and youth receiving maintenance intravenous fluids. Paediatr Child Health. 2013;18:102-107.
61. Park SJ, Oh YS, Choi MJ, et al. Hyponatremia may reflect severe inflammation in children with febrile urinary tract infection. Pediatr Nephrol. 2012;27:2261-2267.
62. Dixon BN, Daley RJ, Buie LW, et al. Correlation of IL-6 secretion and hyponatremia with the use of CD19+ chimeric antigen receptor T-cells. Clin Nephrol. 2020;93:42-46.
63. Swart RM, Hoorn EJ, Betjes MG, et al. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol. 2011;118:45-51.
64. Berni A, Malandrino D, Parenti G, et al. Hyponatremia, IL-6, and SARS-CoV-2 (COVID-19) infection: may all fit together? J Endocrinol Invest. 2020;43:1137-1139.
65. Sinha P, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? JAMA Intern Med. 2020;180:1152-1154.
66. Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol. 2020;20:269-270.
67. Zhu Z, Cai T, Fan L, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:332-339.
68. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020;383:2255-2273.
69. Parr JB. Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia. JAMA Intern Med. 2021;181:12-15.
70. Gupta S, Wang W, Hayek SS, et al. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med. 2021;181:41-51.
71. REMAP-CAP, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384:1491-1502.
72. Rubin EJ, Longo DL, Baden LR. Interleukin-6 Receptor Inhibition in Covid-19 - Cooling the Inflammatory Soup. N Engl J Med. 2021;384:1564-1565.
73. Liu B, Li M, Zhou Z, et al. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2020;111:102452.
74. Zieg J. Evaluation and management of hyponatraemia in children. Acta Paediatr. 2014;103:1027-1034.
75. Musch W, Thimpont J, Vandervelde D, et al. Combined fractional excretion of sodium and urea better predicts response to saline in hyponatremia than do usual clinical and biochemical parameters. Am J Med. 1995;99: 348-355.
76. Chung HM, Kluge R, Schrier RW, et al. Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med. 1987;83:905-908.
77. Grant P, Ayuk J, Bouloux PM, et al. The diagnosis and management of inpatient hyponatraemia and SIADH. Eur J Clin Invest. 2015;45:888-894.
78. Miles BE, Paton A, De Wardener HE. Maximum urine concentration. Br Med J. 1954;2:901-905.
79. Wang S, Ma P, Zhang S, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. Diabetologia. 2020;63:2102-2111.
80. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106:399-403.
81. Brenkert TE, Estrada CM, McMorrow SP, et al. Intravenous hypertonic saline use in the pediatric emergency department. Pediatr Emerg Care. 2013;29:71-73.
82. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. Semin Nephrol. 2009;29:282-299.

83. Koenig MA, Bryan M, Lewin JL, 3rd, et al. Reversal of transtentorial herniation with hypertonic saline. Neurology. 2008;70:1023-1029.
84. Christ Crain M, Hoorn EJ, Sherlock M, et al. Endocrinology in the time of COVID-19: Management of Hyponatraemia and Diabetes Insipidus. Eur J Endocrinol. 2020; 183:G9-G15.
85. Fernandez Martinez A, Barajas Galindo D, Ruiz Sanchez J. Management of hyponatraemia and hypernatraemia during the Covid-19 pandemic: a consensus statement of the Spanish Society for Endocrinology (Acqua Neuroendocrinology Group). Rev Endocr Metab Disord. 2021;22:317-324.

Correspondence:
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Ploutarchos Tzoulis, MD, PhD, FRCP (UK), MSc (Hons)
Department of Metabolism & Experimental Therapeutics
Division of Medicine
University College London
London, UK
Email: ploutarchos.tzoulis@nhs.net