

## Impact of perioperative hyponatremia in children: A narrative review

Cheme Andersen, Arash Afshari

Cheme Andersen, Arash Afshari, Department of Anaesthesiology, Juliane Marie Centre, Rigshospitalet, 2100 Copenhagen, Denmark

Author contributions: Andersen C and Afshari A contributed to this paper.

Correspondence to: Cheme Andersen, MD, Department of Anaesthesiology, Juliane Marie Centre, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. [chemeandersen@gmail.com](mailto:chemeandersen@gmail.com)  
Telephone: +45-20680481

Received: July 19, 2014 Revised: September 13, 2014

Accepted: October 23, 2014

Published online: November 4, 2014

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Children; Fluid; Hyponatremia; Pediatric; Perioperative

**Core tip:** Hospital-acquired hyponatremia is common, particularly among children undergoing surgery. These children tend to develop hyponatremic encephalopathy at higher serum sodium concentrations than adults and they have a poorer prognosis. As the risk is increased by the use of hypotonic fluids, intraoperative fluids for children should be isotonic. Symptomatic hyponatremia should be corrected with 3% sodium chloride and close monitoring of the patient and serum sodium level is mandatory to prevent brain herniation and neurologic damage from cerebral ischemia.

### Abstract

For more than 50 years, hypotonic fluids (crystalloids) have been the standard for maintenance fluid used in children. In the last decade, several studies have evaluated the risk of hyponatremia associated with the use of hypotonic *vs* isotonic fluids, which has led to an intense debate. Children undergoing surgery have several stimuli for release of antidiuretic hormone, which controls renal water handling, including pain, nausea, vomiting, narcotic use and blood loss. The body's primary defense against the development of hyponatremia is the ability of the kidneys to excrete free water and dilute urine. Increased levels of antidiuretic hormone can result in hyponatremia, defined as a plasma sodium level < 136 mmol/L, which causes cells to draw in excess water and swell. This manifests as central nervous system symptoms such as lethargy, irritability and seizures. The risk for symptomatic hyponatremia is higher in children than in adults. It represents an emergency condition, and early diagnosis, prompt treatment and close monitoring are essential to reduce morbidity and mortality. The widespread use of hypotonic fluids in children undergoing surgery is a matter of concern and more focus on this topic is urgently needed. In this paper, we review the literature and describe the impact of perioperative hyponatremia in children.

Andersen C, Afshari A. Impact of perioperative hyponatremia in children: A narrative review. *World J Crit Care Med* 2014; 3(4): 95-101 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v3/i4/95.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v3.i4.95>

### INTRODUCTION

The overall goal of perioperative fluid management is to ensure adequate perfusion of tissue by administering maintenance fluids including electrolytes and glucose to replace preoperative fluid deficits and ongoing losses. Preoperative fluid status in children is affected by various factors, and a deficit is often due to prolonged fasting, dehydration (from diarrhea, vomiting and fever), bleeding and increased levels of stress. Inadequate fluid management may cause reduced cardiac output and oxygen delivery to damaged tissue, which is associated with an increased rate of postoperative complications<sup>[1]</sup>. On the other hand, overhydration can have equally severe consequences, such as acidosis, coagulation deficits and periph-

**Table 1** The 4-2-1 formula for maintenance fluids in children<sup>[10,11]</sup>

| Weight   | Daily fluid requirements                | Hourly fluid requirements                |
|----------|---|--|
| 3-10 kg  | 100 mL/kg                               | 4 mL/kg per hour                         |
| 11-20 kg | 1000 mL + 50 mL for every kilogram > 10 | 40 mL/h + 2 mL/h for every kilogram > 10 |
| > 20 kg  | 1500 mL + 20 mL for every kilogram > 20 | 60 mL/h + 1 mL/h for every kilogram > 20 |

eral and pulmonary edema<sup>[2-5]</sup>.

Children undergoing surgery are at a higher risk for developing hyponatremia, defined as a plasma sodium level < 136 mmol/L, which causes cells to draw in excess water and swell. Accumulating evidence indicates that among those with a serum sodium < 125 mmol/L, more than 50% develop hyponatremic encephalopathy and are at a risk for seizure, respiratory failure and ultimately death<sup>[6-9]</sup>. Thus, correct perioperative fluid management is essential to avoid perioperative hyponatremia. This review discusses the recent evidence concerning this important and often neglected clinical condition in children.

## MAINTENANCE FLUID IN CHILDREN

The calculation of maintenance fluid in children is based on Holliday and Segar's recommendations from 1957<sup>[10]</sup>. They described the physiologic deficits that result from fluid lost from the skin, respiratory tract, and urine, equivalent to approximately 100 mL/100 kcal metabolized per day. Their calculations have since evolved into the widely used "4-2-1 rule" (Table 1)<sup>[11,12]</sup>. However, this formula provides only for water maintenance, and does not consider correction of deficits or replacement of continuous, abnormal water loss. In 1975, Furman *et al*<sup>[13]</sup> suggested calculating the preoperative deficits by multiplying the hourly rate by the number of hours the patient was *nil per os*. Furthermore, they proposed replacing half of this deficit during the first hour of surgery, followed by administration of the other half over the next two hours. This method was simplified in 1986 by Berry<sup>[14]</sup> who proposed delivering a bolus of a 0.9% normal saline solution to otherwise healthy children over the first hour of surgery. Berry concluded that children three years of age and younger should receive 25 mL/kg, whereas children four years and older should receive 15 mL/kg. These methods were based on the assumption that the patients had been under *nil per os* for at least 6-8 h, though recent liberalization of fasting requirements may have decreased preoperative water loss<sup>[15-17]</sup>.

## PERIOPERATIVE HYPONATREMIA IN CHILDREN

Hyponatremia is the most common electrolyte abnormality found in hospitalized children<sup>[18,19]</sup>. The body's primary mechanism to prevent hyponatremia is the generation of

dilute urine and excretion of free water by the kidneys. Renal water handling is generally controlled *via* antidiuretic hormone<sup>[20]</sup>, the release of which is stimulated by pain, nausea, vomiting, narcotic use and blood loss, among others (Table 2), which are experienced by many children undergoing surgery<sup>[21,22]</sup>. Antidiuretic hormone can promote hyponatremia by increasing the permeability of collecting duct cells in the kidney, leading to the retention of free water. Subsequent influx of water into the brain *via* glial cell swelling can lead to cerebral edema, brain stem herniation and death<sup>[23-33]</sup>.

Pediatric patients are more prone to symptomatic hyponatremia<sup>[34-38]</sup>, which is mainly manifested as central nervous system symptoms, including lethargy, irritability, muscle weakness, seizures and coma or even death, in the most severe cases<sup>[39-42]</sup>. Furthermore, children undergoing surgery are also more likely to develop hyponatremic encephalopathy at higher serum sodium concentrations than adults, with an estimated mortality of 8%<sup>[6]</sup>. Symptoms of hyponatremic encephalopathy are often unspecific and may appear as headache, nausea, vomiting and fatigue, which can easily be mistaken for normal symptoms after surgery and general anesthesia<sup>[24,43-47]</sup>, but can rapidly progress to seizures, respiratory arrest and ultimately death or a permanent vegetative state as a complication of severe cerebral edema<sup>[48]</sup>. The associated poorer prognosis is probably due to a combination of physical and physiologic differences between adults and children<sup>[49,50]</sup>. Children have a higher brain:skull size ratio, as their brains reach adult size by six years of age, which is ten years before their skulls attain their final dimensions. One should keep in mind that in older adults, there is a progressive loss of brain volume whilst the volume inside the skull remains constant.

Critically ill children, and those in need of postoperative admission to intensive care units, are particularly at an increased risk for hyponatremia<sup>[51-57]</sup>. Hyponatremia in these children can be caused by normo- or hypervolemic conditions caused by heart failure, such as iatrogenic-induced hyponatremia (secondary to excessive water and/or salt insufficiency), renal insufficiency or a syndrome of inappropriate antidiuretic hormone secretion<sup>[58]</sup>, or by hypovolemia from extra-renal volume loss (gastric, diarrhea, burn wounds, interstitial leakage), renal loss (polyuria after acute kidney failure, adrenocortical insufficiency) or excessive use of diuretics. Children with neurologic diseases, younger children with intracranial neoplasms, and those with hydrocephalus are also more prone to hyponatremia, which can be more complicated<sup>[59-67]</sup>. In a recent study, hyponatremic children with intracranial neoplasms had a five-fold increased risk of moderate or severe disability based on their Pediatric Cerebral Performance Category score at discharge, with hyponatremia independently associated with worse neurologic outcome despite adjustment for age and tumor factors<sup>[68]</sup>. The same group also found an increased risk of postoperative hyponatremia after neurosurgery among children that was independent of the preoperative degree of hyponatremia<sup>[69]</sup>.

**Table 2 Stimuli associated with increased antidiuretic hormone production (adapted from Bailey *et al.*<sup>[15]</sup>)**

|                                     |   |
|-------------------------------------|---|
| Hemodynamic                         |   |
| Hypotension                         | Blood loss, diarrhea, diuretics, vomiting, renal salt wasting, hypoaldosteronism, burns, polyuria   |
| Hypovolemia                         |   |
| Hypervolemia                        |   |
| Non-hemodynamic                     |   |
| Central nervous system disturbances | Meningitis, encephalitis, brain abscess, head injury, hypoxic brain injury, stroke  |
| Pulmonary diseases                  | Asthma, pneumonia, chronic obstructive pulmonary disease, tuberculosis, empyema, bronchiolitis, acute respiratory failure   |
| Cancer                              | Lung cancer (especially small-cell lung cancer), brain tumor, leukemia, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, neuroendocrine tumor, squamous cell carcinoma |
| Medications                         | Selective serotonin reuptake inhibitors, morphine, carbamazepine, cyclophosphamide, vincristine, desmopressin   |
| Other                               | Pain, stress, nausea, emesis, postoperative state, cortisol deficiency  |

**Table 3 Most commonly available crystalloid and human albumin solutions in Europe**

| Fluid   | Na <sup>+</sup><br>(mmol/L) | K <sup>+</sup><br>(mmol/L) | Cl <sup>-</sup><br>(mmol/L) | Lactate<br>(mmol/L) | Acetate<br>(mmol/L) | Glucose<br>monohydrate (g/L) | Osmolarity<br>(mOsm/L) | Tonicity<br>(to plasma) |
|---|-----------------------------|----------------------------|-----------------------------|---------------------|---------------------|------------------------------|------------------------|-------------------------|
| Isotonic NaCl                                 | 154                         | 0                          | 154                         | 0                   | 0                   | 0                            | 308 (iso-osmolar)      | Isotonic                |
| Ringer's lactate                              | 130                         | 4                          | 109                         | 28                  | 0                   | 0                            | 270 (iso-osmolar)      | Isotonic                |
| Ringer's acetate                              | 130                         | 4                          | 110                         | 0                   | 30                  | 0                            | 270 (iso-osmolar)      | Isotonic                |
| Darrow-glucose "SAD"                          | 31                          | 9                          | 26                          | 14                  | 0                   | 55                           | 360 (hyperosmolar)     | Hypotonic               |
| Human albumin 5%                              | 130-160                     | < 3                        | 0                           | 0                   | 0                   | 0                            | 330 (hyperosmolar)     | Isotonic                |
| Human albumin 20%                             | 100-160                     | < 3                        | 0                           | 0                   | 0                   | 0                            | 300 (hyperosmolar)     | Hypertonic              |
| Glucosalin 2:1<br>(Glucose 3.3%/NaCl 0.3%)    | 51                          | 0                          | 51                          | 0                   | 0                   | 33                           | 287 (iso-osmolar)      | Hypotonic               |
| Glucose 2.5%/NaCl 0.45%                       | 77                          | 0                          | 77                          | 0                   | 0                   | 25                           | 293 (iso-osmolar)      | Hypotonic               |
| Glucose 4%/NaCl 0.18%                         | 31                          | 0                          | 31                          | 0                   | 0                   | 40                           | 284 (iso-osmolar)      | Hypotonic               |
| Glucose 5%/NaCl 0.45%                         | 77                          | 0                          | 77                          | 0                   | 0                   | 50                           | 432 (hyperosmolar)     | Hypotonic               |
| Glucose 4.6%/NaCl 0.9%                        | 154                         | 0                          | 154                         | 0                   | 0                   | 46                           | 561 (hyperosmolar)     | Isotonic                |
| Glucose 9.1%/NaCl 0.9%                        | 154                         | 0                          | 154                         | 0                   | 0                   | 91                           | 813 (hyperosmolar)     | Isotonic                |
| Glucolyte<br>(Glucose 5%/NaCl 0.3%/KCl 0.15%) | 51                          | 20                         | 71                          | 0                   | 0                   | 50                           | 420 (hyperosmolar)     | Hypotonic               |

However, there was a greater variation in serum sodium levels among the children with the most severe preoperative hyponatremia. Additionally, obstructive hydrocephalus and < 3.5 years of age were identified as significant independent risk factors for severe hyponatremia among those affected.

The risk for hospital-acquired hyponatremia and hyponatremic encephalopathy have been related to the use of hypotonic intravenous solutions<sup>[6,70-77]</sup>. Wang *et al.*<sup>[78]</sup> found a significantly higher risk for hyponatremia and severe hyponatremia among pediatric patients administered hypotonic solutions compared with isotonic fluids in a systematic review of ten randomized clinical trials involving 855 subjects. Hyponatremia is also a concern in neonates, as intravenous hypotonic and free water intake of more than 6.5 mL/kg per hour during surgery reduces the number of postoperative plasma sodium measurements > 4 mmol/L<sup>[79,80]</sup>. Additionally, there was an adverse association between large (8-13 mmol/L) and very large (> 13 mmol/L) changes in serum sodium levels in the first few weeks of life and the risk of impaired functional outcomes at two years of age, with neuromotor

impairments in particular.

## CORRECTION OF HYPONATREMIA

To prevent brain herniation and neurologic damage from cerebral ischemia, cases of symptomatic hyponatremia require urgent correction of sodium levels to 4-6 mmol/L with 3% sodium chloride<sup>[48,81-86]</sup>. The rate of correction does not need to be restricted in patients with true acute hyponatremia, and modulation of excessive corrections is not indicated<sup>[87]</sup>. However, limits for correction are warranted if there is any uncertainty as to whether the hyponatremia is chronic or acute. It should be noted that correction of hypokalemia will also contribute to an increase in the serum sodium concentration. In the absence of severe or moderately severe symptoms, there is often sufficient time for diagnostic assessment and cause-specific treatment. Although children with severe hyponatremia need urgent, frequent and prolonged monitoring because of the risk of repeated sodium changes<sup>[69]</sup>, correction with hypertonic saline is not indicated in asymptomatic cases<sup>[88,89]</sup>.

## CONCLUSION

As the use of hypotonic fluids is related to a higher risk of hyponatremia compared with isotonic fluids<sup>[90-93]</sup>, it is difficult to justify their widespread use as a standard maintenance fluid in children during surgery. An ideal intraoperative fluid should have a tonicity and sodium concentration close to the physiologic range<sup>[94]</sup>. To avoid lipolysis, hypoglycemia, or hyperglycemia, 1.0%-2.5% glucose (rather than 5%) should be used and should also include metabolic anions (*i.e.*, acetate, lactate or malate) as bicarbonate precursors to prevent hyperchloremic acidosis. Most children need 2-3 mEq/kg per 24 h of sodium chloride, and the target serum sodium is between 135-140 mmol/L.

Monitoring of serum sodium levels in patients maintained by fluid infusion is critical, and certainly in children undergoing surgery as they are more vulnerable to hyponatremia than adults. Indeed, close monitoring is mandatory in symptomatic cases of hyponatremia, as they can rapidly progress to hyponatremic encephalopathy<sup>[95-100]</sup>. This complex problem remains an ongoing clinical challenge and deserves more attention by clinicians, not only in an academic context, but in clinical settings where there is ample evidence to support fluid therapy strategies that can reduce the risk of serious consequences for children. Additionally, the medical industry and researchers should increase their efforts to develop more appropriate and balanced intravenous solutions for children of various ages and conditions, due to the diverse availability of solutions across geographical regions (Table 3).

## REFERENCES

- 1 **Pearse RM**, Ackland GL. Perioperative fluid therapy. *BMJ* 2012; **344**: e2865 [PMID: 22539015 DOI: 10.1136/bmj.e2865]
- 2 **Guidet B**, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D, James M. A balanced view of balanced solutions. *Crit Care* 2010; **14**: 325 [PMID: 21067552 DOI: 10.1186/cc9230]
- 3 **Rosenberg AL**, Dechert RE, Park PK, Bartlett RH. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009; **24**: 35-46 [PMID: 19103612 DOI: 10.1177/0885066608329850]
- 4 **Chappell D**, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723-740 [PMID: 18813052 DOI: 10.1097/ALN.0b013e3181863117]
- 5 **Silva JM**, de Oliveira AM, Nogueira FA, Vianna PM, Pereira Filho MC, Dias LF, Maia VP, Neucamp Cde S, Amendola CP, Carmona MJ, Malbouisson LM. The effect of excess fluid balance on the mortality rate of surgical patients: a multicenter prospective study. *Crit Care* 2013; **17**: R288 [PMID: 24326085]
- 6 **Moritz ML**, Ayus JC. Preventing neurological complications from dysnatremias in children. *Pediatr Nephrol* 2005; **20**: 1687-1700 [PMID: 16079988 DOI: 10.1007/s00467-005-1933-6]
- 7 **Eulmesekian PG**, Pérez A, Mincez PG, Bohn D. Hospital-acquired hyponatremia in postoperative pediatric patients: prospective observational study. *Pediatr Crit Care Med* 2010; **11**: 479-483 [PMID: 20124948 DOI: 10.1097/PCC.0b013e3181ce7154]
- 8 **Dearlove OR**, Ram AD, Natsagdoiy S, Humphrey G, Cunniffe M, Potter F. Hyponatraemia after postoperative fluid management in children. *Br J Anaesth* 2006; **97**: 897-898; author reply 898 [PMID: 17098726 DOI: 10.1093/bja/ael298]
- 9 **Au AK**, Ray PE, McBryde KD, Newman KD, Weinstein SL, Bell MJ. Incidence of postoperative hyponatremia and complications in critically-ill children treated with hypotonic and normotonic solutions. *J Pediatr* 2008; **152**: 33-38 [PMID: 18154895 DOI: 10.1016/j.jpeds.2007.08.040]
- 10 **Holliday MA**, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957; **19**: 823-832 [PMID: 13431307 DOI: 10.1097/01.aco.0000192818.68730.9d]
- 11 **Paut O**, Lacroix F. Recent developments in the perioperative fluid management for the paediatric patient. *Curr Opin Anaesthesiol* 2006; **19**: 268-277 [PMID: 16735810]
- 12 **Murat I**, Dubois MC. Perioperative fluid therapy in pediatrics. *Paediatr Anaesth* 2008; **18**: 363-370 [PMID: 18312509 DOI: 10.1111/j.1460-9592.2008.02505.x]
- 13 **Furman EB**, Roman DG, Lemmer LA, Hairabet J, Jasinska M, Laver MB. Specific therapy in water, electrolyte and blood-volume replacement during pediatric surgery. *Anesthesiology* 1975; **42**: 187-193 [PMID: 1115368]
- 14 **Berry F**. Practical aspects of fluid and electrolyte therapy. In: Berry F, editor. *Anesthetic Management of Difficult and Routine Pediatric Patients*. New York: Churchill Livingstone, 1986: 107-135
- 15 **Bailey AG**, McNaull PP, Jooste E, Tuchman JB. Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? *Anesth Analg* 2010; **110**: 375-390 [PMID: 19955503 DOI: 10.1213/ANE.0b013e3181b6b3b5]
- 16 **Smith I**, Kranke P, Murat I, Smith A, O'Sullivan G, Søreide E, Spies C, in't Veld B. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2011; **28**: 556-569 [PMID: 21712716 DOI: 10.1097/EJA.0b013e3283495ba1]
- 17 **Arun BG**, Korula G. Preoperative fasting in children: An audit and its implications in a tertiary care hospital. *J Anaesthesiol Clin Pharmacol* 2013; **29**: 88-91 [PMID: 23493776 DOI: 10.4103/0970-9185.105810]
- 18 **Cavari Y**, Pitfield AF, Kissoon N. Intravenous maintenance fluids revisited. *Pediatr Emerg Care* 2013; **29**: 1225-1228; quiz 1229-1231 [PMID: 24196097 DOI: 10.1097/PEC.0b013e3182aa4e2a]
- 19 **Moritz ML**, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children. *Pediatr Nephrol* 2010; **25**: 1225-1238 [PMID: 19894066 DOI: 10.1007/s00467-009-1323-6]
- 20 **Ghali JK**. Mechanisms, risks, and new treatment options for hyponatremia. *Cardiology* 2008; **111**: 147-157 [PMID: 18434717 DOI: 10.1159/000121596]
- 21 **Moritz ML**, Ayus JC. Hospital-acquired hyponatremia--why are hypotonic parenteral fluids still being used? *Nat Clin Pract Nephrol* 2007; **3**: 374-382 [PMID: 17592470]
- 22 **Carcillo JA**. Intravenous fluid choices in critically ill children. *Curr Opin Crit Care* 2014; **20**: 396-401 [PMID: 24979714 DOI: 10.1097/MCC.0000000000000119]
- 23 **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-F624 [PMID: 18448591 DOI: 10.1152/ajprenal.00502.2007]
- 24 **Grissinger M**. Hyponatremia and death in Healthy children From plain dextrose and Hypotonic Saline Solutions after Surgery. *P T* 2013; **38**: 364-388 [PMID: 24049421]
- 25 **Fraser CL**, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. *Am J Med* 1997; **102**: 67-77 [PMID: 9209203 DOI: 10.1016/S0002-9343(96)00274-4]
- 26 **Ayus JC**, Arieff AI. Pathogenesis and prevention of hyponatremic encephalopathy. *Endocrinol Metab Clin North Am* 1993; **22**: 425-446 [PMID: 8325296]
- 27 **Moritz ML**, Ayus JC. Prevention of hospital-acquired hypo-

- natremia: a case for using isotonic saline. *Pediatrics* 2003; **111**: 227-230 [PMID: 12563043 DOI: 10.1542/peds.111.2.227]
- 28 **Achinger SG**, Moritz ML, Ayus JC. Dysnatremias: why are patients still dying? *South Med J* 2006; **99**: 353-362; quiz 363-364 [PMID: 16634244]
  - 29 **Sterns RH**, Hix JK, Silver SM. Management of hyponatremia in the ICU. *Chest* 2013; **144**: 672-679 [PMID: 23918113 DOI: 10.1378/chest.12-2600]
  - 30 **Halawa I**, Andersson T, Tomson T. Hyponatremia and risk of seizures: a retrospective cross-sectional study. *Epilepsia* 2011; **52**: 410-413 [PMID: 21314679 DOI: 10.1111/j.1528-1167.2010.02939.x]
  - 31 **Beck CE**, Choong K, Puligandla PS, Hartfield D, Holland J, Lacroix J, Friedman JN. Avoiding hypotonic solutions in paediatrics: Keeping our patients safe. *Paediatr Child Health* 2013; **18**: 94-95 [PMID: 24421665]
  - 32 **Goh KP**. Management of hyponatremia. *Am Fam Physician* 2004; **69**: 2387-2394 [PMID: 15168958]
  - 33 **Nathan BR**. Cerebral correlates of hyponatremia. *Neurocrit Care* 2007; **6**: 72-78 [PMID: 17356196]
  - 34 **Davison D**, Basu RK, Goldstein SL, Chawla LS. Fluid management in adults and children: core curriculum 2014. *Am J Kidney Dis* 2014; **63**: 700-712 [PMID: 24332766 DOI: 10.1053/j.ajkd.2013.10.044]
  - 35 **Choong K**, Arora S, Cheng J, Farrokhlyar F, Reddy D, Thabane L, Walton JM. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. *Pediatrics* 2011; **128**: 857-866 [PMID: 22007013 DOI: 10.1542/peds.2011-0415]
  - 36 **Easley D**, Tillman E. Hospital-acquired hyponatremia in pediatric patients: a review of the literature. *J Pediatr Pharmacol Ther* 2013; **18**: 105-111 [PMID: 23798904 DOI: 10.5863/1551-6776-18.2.105]
  - 37 **Hardesty DA**, Kilbaugh TJ, Storm PB. Cerebral salt wasting syndrome in post-operative pediatric brain tumor patients. *Neurocrit Care* 2012; **17**: 382-387 [PMID: 21822747 DOI: 10.1007/s12028-011-9618-4]
  - 38 **Alves JT**, Troster EJ, Oliveira CA. Isotonic saline solution as maintenance intravenous fluid therapy to prevent acquired hyponatremia in hospitalized children. *J Pediatr (Rio J)* 2011; **87**: 478-486 [PMID: 22170285 DOI: 10.2223/JPED.2133]
  - 39 **Adrogué HJ**, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**: 1581-1589 [PMID: 10824078 DOI: 10.1056/NEJM200005253422107]
  - 40 **Koczmara C**, Wade AW, Skippen P, Campigotto MJ, Streitenberger K, Carr R, Wong E, Robertson K. Hospital-acquired acute hyponatremia and reports of pediatric deaths. *Dynamics* 2010; **21**: 21-26 [PMID: 20333891]
  - 41 **Smith DM**, McKenna K, Thompson CJ. Hyponatraemia. *Clin Endocrinol (Oxf)* 2000; **52**: 667-678 [PMID: 10848869 DOI: 10.1046/j.1365-2265.2000.01027.x]
  - 42 **Halberthal M**, Halperin ML, Bohn D. Lesson of the week: Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001; **322**: 780-782 [PMID: 11282868]
  - 43 **Moran D**, Fronk C, Mandel E. Managing hyponatremia in adults. *JAAPA* 2014; **27**: 23-29; quiz 30 [PMID: 24622398 DOI: 10.1097/01.JAA.0000444730.86174.e8]
  - 44 **Keane M**. Recognising and managing acute hyponatraemia. *Emerg Nurse* 2014; **21**: 32-36; quiz 37 [PMID: 24494770 DOI: 10.7748/en2014.02.21.9.32.e1128]
  - 45 **Reddy P**, Mooradian AD. Diagnosis and management of hyponatraemia in hospitalised patients. *Int J Clin Pract* 2009; **63**: 1494-1508 [PMID: 19769706 DOI: 10.1111/j.1742-1241.2009.02103.x]
  - 46 **Koźniewska E**, Podlecka A, Rafałowska J. Hyponatremic encephalopathy--some experimental and clinical findings. *Folia Neuropathol* 2003; **41**: 41-45 [PMID: 12862395]
  - 47 **Auroy Y**, Benhamou D, Péquignot F, Jouglu E, Lienhart A. Hyponatraemia-related death after paediatric surgery still exists in France. *Br J Anaesth* 2008; **101**: 741 [PMID: 18854387 DOI: 10.1093/bja/aen282]
  - 48 **Verbalis JG**, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013; **126**: S1-42 [PMID: 24074529 DOI: 10.1016/j.amjmed.2013.07.006]
  - 49 **Playfor SD**. Hypotonic intravenous solutions in children. *Expert Opin Drug Saf* 2004; **3**: 67-73 [PMID: 14680463 DOI: 10.1517/14740338.3.1.67]
  - 50 **Arieff AI**, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ* 1992; **304**: 1218-1222 [PMID: 1515791 DOI: 10.1136/bmj.304.6836.1218]
  - 51 **Luu R**, DeWitt PE, Reiter PD, Dobyens EL, Kaufman J. Hyponatremia in children with bronchiolitis admitted to the pediatric intensive care unit is associated with worse outcomes. *J Pediatr* 2013; **163**: 1652-1656.e1 [PMID: 23910686 DOI: 10.1016/j.jpeds.2013.06.041]
  - 52 **Singhi S**, Jayashre M. Free water excess is not the main cause for hyponatremia in critically ill children receiving conventional maintenance fluids. *Indian Pediatr* 2009; **46**: 577-583 [PMID: 19430087]
  - 53 **Choong K**, Bohn D. Maintenance parenteral fluids in the critically ill child. *J Pediatr (Rio J)* 2007; **83**: S3-S10 [PMID: 17486196 DOI: 10.1590/S0021-75572007000300002]
  - 54 **Roberts KE**. Pediatric fluid and electrolyte balance: critical care case studies. *Crit Care Nurs Clin North Am* 2005; **17**: 361-373, x [PMID: 16344206 DOI: 10.1016/j.ccell.2005.07.006]
  - 55 **Singhi S**. Hyponatremia in hospitalized critically ill children: current concepts. *Indian J Pediatr* 2004; **71**: 803-807 [PMID: 15448387 DOI: 10.1007/BF02730718]
  - 56 **Moritz ML**, Ayus JC. Dysnatremias in the critical care setting. *Contrib Nephrol* 2004; **144**: 132-157 [PMID: 15264404 DOI: 10.1159/000078883]
  - 57 **Stelfox HT**, Ahmed SB, Zygun D, Khandwala F, Laupland K. Characterization of intensive care unit acquired hyponatremia and hypernatremia following cardiac surgery. *Can J Anaesth* 2010; **57**: 650-658 [PMID: 20405264 DOI: 10.1007/s12630-010-9309-1]
  - 58 **Peri A**, Giuliani C. Management of euvoletic hyponatremia attributed to SIADH in the hospital setting. *Minerva Endocrinol* 2014; **39**: 33-41 [PMID: 24513602]
  - 59 **Al-Zahraa Omar F**, Al Bunyan M. Severe hyponatremia as poor prognostic factor in childhood neurologic diseases. *J Neurol Sci* 1997; **151**: 213-216 [PMID: 9349678]
  - 60 **Williams C**, Simon TD, Riva-Cambrin J, Bratton SL. Hyponatremia with intracranial malignant tumor resection in children. *J Neurosurg Pediatr* 2012; **9**: 524-529 [PMID: 22546031 DOI: 10.3171/2012.1.PEDS11465]
  - 61 **Hardesty DA**, Sanborn MR, Parker WE, Storm PB. Perioperative seizure incidence and risk factors in 223 pediatric brain tumor patients without prior seizures. *J Neurosurg Pediatr* 2011; **7**: 609-615 [PMID: 21631197 DOI: 10.3171/2011.3.PEDS1120]
  - 62 **Lang SS**, Bauman JA, Aversano MW, Sanborn MR, Vosough A, Heuer GG, Storm PB. Hyponatremia following endoscopic third ventriculostomy: a report of 5 cases and analysis of risk factors. *J Neurosurg Pediatr* 2012; **10**: 39-43 [PMID: 22702328 DOI: 10.3171/2012.4.PEDS1222]
  - 63 **Bettinelli A**, Longoni L, Tammaro F, Faré PB, Garzoni L, Bianchetti MG. Renal salt-wasting syndrome in children with intracranial disorders. *Pediatr Nephrol* 2012; **27**: 733-739 [PMID: 22237777 DOI: 10.1007/s00467-011-2093-5]
  - 64 **Coenraad MJ**, Meinders AE, Taal JC, Bolk JH. Hyponatremia in intracranial disorders. *Neth J Med* 2001; **58**: 123-127 [PMID: 11246111]
  - 65 **Soupart A**, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications.

- Clin Nephrol* 1996; **46**: 149-169 [PMID: 8879850]
- 66 **Betjes MG**. Hyponatremia in acute brain disease: the cerebral salt wasting syndrome. *Eur J Intern Med* 2002; **13**: 9-14 [PMID: 11836078 DOI: 10.1016/S0953-6205(01)00192-3]
- 67 **Tzamaloukas AH**, Malhotra D, Rosen BH, Raj DS, Murata GH, Shapiro JL. Principles of management of severe hyponatremia. *J Am Heart Assoc* 2013; **2**: e005199 [PMID: 23525443 DOI: 10.1161/JAHA.112.005199]
- 68 **Williams CN**, Belzer JS, Riva-Cambrin J, Presson AP, Bratton SL. The incidence of postoperative hyponatremia and associated neurological sequelae in children with intracranial neoplasms. *J Neurosurg Pediatr* 2014; **13**: 283-290 [PMID: 24410125 DOI: 10.3171/2013.12.PEDS13364]
- 69 **Belzer JS**, Williams CN, Riva-Cambrin J, Presson AP, Bratton SL. Timing, duration, and severity of hyponatremia following pediatric brain tumor surgery\*. *Pediatr Crit Care Med* 2014; **15**: 456-463 [PMID: 24777301 DOI: 10.1097/PCC.0000000000000154]
- 70 **Pemde HK**, Dutta AK, Sodani R, Mishra K. Isotonic Intravenous Maintenance Fluid Reduces Hospital Acquired Hyponatremia in Young Children with Central Nervous System Infections. *Indian J Pediatr* 2014; Epub ahead of print [PMID: 24830423]
- 71 **Carandang F**, Anglemeyer A, Longhurst CA, Krishnan G, Alexander SR, Kahana M, Sutherland SM. Association between maintenance fluid tonicity and hospital-acquired hyponatremia. *J Pediatr* 2013; **163**: 1646-1651 [PMID: 23998517 DOI: 10.1016/j.jpeds.2013.07.020]
- 72 **Foster BA**, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr* 2014; **165**: 163-169.e2 [PMID: 24582105 DOI: 10.1016/j.jpeds.2014.01.040]
- 73 **Yung M**, Keeley S. Randomised controlled trial of intravenous maintenance fluids. *J Paediatr Child Health* 2009; **45**: 9-14 [PMID: 18036144]
- 74 **Montañana PA**, Modesto i Alapont V, Ocón AP, López PO, López Prats JL, Toledo Parreño JD. The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: a randomized, controlled open study. *Pediatr Crit Care Med* 2008; **9**: 589-597 [PMID: 18838929 DOI: 10.1097/PCC.0b013e31818d3192]
- 75 **Rey C**, Los-Arcos M, Hernández A, Sánchez A, Díaz JJ, López-Herce J. Hypotonic versus isotonic maintenance fluids in critically ill children: a multicenter prospective randomized study. *Acta Paediatr* 2011; **100**: 1138-1143 [PMID: 21352357 DOI: 10.1111/j.1651-2227.2011.02209.x]
- 76 **Hanna M**, Saberi MS. Incidence of hyponatremia in children with gastroenteritis treated with hypotonic intravenous fluids. *Pediatr Nephrol* 2010; **25**: 1471-1475 [PMID: 20108002 DOI: 10.1007/s00467-009-1428-y]
- 77 **Hoorn EJ**, Geary D, Robb M, Halperin ML, Bohn D. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. *Pediatrics* 2004; **113**: 1279-1284 [PMID: 15121942]
- 78 **Wang J**, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. *Pediatrics* 2014; **133**: 105-113 [PMID: 24379232 DOI: 10.1542/peds.2013-2041]
- 79 **Edjoo Nkilly G**, Michelet D, Hilly J, Diallo T, Greff B, Mangalsuren N, Lira E, Bounadja I, Brasher C, Bonnard A, Malbezin S, Nivoche Y, Dahmani S. Postoperative decrease in plasma sodium concentration after infusion of hypotonic intravenous solutions in neonatal surgery. *Br J Anaesth* 2014; **112**: 540-545 [PMID: 24193323 DOI: 10.1093/bja/aet374]
- 80 **Baraton L**, Ancel PY, Flamant C, Orsonneau JL, Darmaun D, Rozé JC. Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. *Pediatrics* 2009; **124**: e655-e661 [PMID: 19752079 DOI: 10.1542/peds.2008-3415]
- 81 **Moritz ML**, Ayus JC. Management of hyponatremia in various clinical situations. *Curr Treat Options Neurol* 2014; **16**: 310 [PMID: 25099180 DOI: 10.1007/s11940-014-0310-9]
- 82 **Sterns RH**, Hix JK, Silver S. Treatment of hyponatremia. *Curr Opin Nephrol Hypertens* 2010; **19**: 493-498 [PMID: 20539224 DOI: 10.1097/MNH.0b013e32833bfa64]
- 83 **Sarnaik AP**, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. *Crit Care Med* 1991; **19**: 758-762 [PMID: 2055051 DOI: 10.1097/00003246-199106000-00005]
- 84 **Youn KS**, Tokeshi J. Therapy with hypertonic saline in combination with anti-convulsants for hyponatremia-induced seizure: a case report and review of the literature. *Hawaii Med J* 2002; **61**: 280-281 [PMID: 12632826]
- 85 **Decaux G**, Soupart A. Treatment of symptomatic hyponatremia. *Am J Med Sci* 2003; **326**: 25-30 [PMID: 12861122 DOI: 10.1097/00000441-200307000-00004]
- 86 **Moritz ML**, Ayus JC. 100 cc 3% sodium chloride bolus: a novel treatment for hyponatremic encephalopathy. *Metab Brain Dis* 2010; **25**: 91-96 [PMID: 20221678 DOI: 10.1007/s11011-010-9173-2]
- 87 **Spasovski G**, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 2014; **29** Suppl 2: ii-i39 [PMID: 24569496 DOI: 10.1093/ndt/gfu040]
- 88 **Zieg J**. Evaluation and management of hyponatraemia in children. *Acta Paediatr* 2014; **103**: 1027-1034 [PMID: 24862500 DOI: 10.1111/apa.12705]
- 89 **Moritz ML**, Ayus JC. The pathophysiology and treatment of hyponatraemic encephalopathy: an update. *Nephrol Dial Transplant* 2003; **18**: 2486-2491 [PMID: 14605269]
- 90 **Freeman MA**, Ayus JC, Moritz ML. Maintenance intravenous fluid prescribing practices among paediatric residents. *Acta Paediatr* 2012; **101**: e465-e468 [PMID: 22765308 DOI: 10.1111/j.1651-2227.2012.02780.x]
- 91 **Way C**, Dhamrait R, Wade A, Walker I. Perioperative fluid therapy in children: a survey of current prescribing practice. *Br J Anaesth* 2006; **97**: 371-379 [PMID: 16873386]
- 92 **Lee JM**, Jung Y, Lee SE, Lee JH, Kim KH, Koo JW, Park YS, Cheong HI, Ha IS, Choi Y, Kang HG. Intravenous fluid prescription practices among pediatric residents in Korea. *Korean J Pediatr* 2013; **56**: 282-285 [PMID: 23908667 DOI: 10.3345/kjp.2013.56.7.282]
- 93 **Keijzers G**, McGrath M, Bell C. Survey of paediatric intravenous fluid prescription: are we safe in what we know and what we do? *Emerg Med Australas* 2012; **24**: 86-97 [PMID: 22313565 DOI: 10.1111/j.1742-6723.2011.01503.x]
- 94 **Sümpelmann R**, Becke K, Crean P, Jöhr M, Lönnqvist PA, Strauss JM, Veyckemans F. European consensus statement for intraoperative fluid therapy in children. *Eur J Anaesthesiol* 2011; **28**: 637-639 [PMID: 21654319 DOI: 10.1097/EJA.0b013e3283446bb8]
- 95 **Rosner MH**, Ronco C. Dysnatremias in the intensive care unit. *Contrib Nephrol* 2010; **165**: 292-298 [PMID: 20427980 DOI: 10.1159/000313769]
- 96 **Funk GC**, Lindner G, Druml W, Metnitz B, Schwarz C, Bauer P, Metnitz PG. Incidence and prognosis of dysnatremias present on ICU admission. *Intensive Care Med* 2010; **36**: 304-311 [PMID: 19847398 DOI: 10.1007/s00134-009-1692-0]
- 97 **Pokaharel M**, Block CA. Dysnatremia in the ICU. *Curr Opin Crit Care* 2011; **17**: 581-593 [PMID: 22027406 DOI: 10.1097/MCC.0b013e32834cd388]
- 98 **Schrier RW**, Bansal S. Diagnosis and management of hyponatremia in acute illness. *Curr Opin Crit Care* 2008; **14**: 627-634 [PMID: 19005303 DOI: 10.1097/MCC.0b013e32830e45e3]
- 99 **Siragy HM**. Hyponatremia, fluid-electrolyte disorders, and

the syndrome of inappropriate antidiuretic hormone secretion: diagnosis and treatment options. *Endocr Pract* 2006; **12**: 446-457 [PMID: 16901803 DOI: 10.4158/EP.12.4.446]

100 **Sedlacek M**, Schoolwerth AC, Remillard BD. Electrolyte disturbances in the intensive care unit. *Semin Dial* 2006; **19**: 496-501 [PMID: 17150050 DOI: 10.1111/j.1525-139X.2006.00212.x]

**P- Reviewer:** Sterns RH, Tzamaloukas A  
**S- Editor:** Gong XM **L- Editor:** A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

