

REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES

Julie R. Ingelfinger, M.D., *Editor*Maintenance Intravenous Fluids
in Acutely Ill Patients

Michael L. Moritz, M.D., and Juan C. Ayus, M.D.

From the Department of Pediatrics and Division of Nephrology, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center (UPMC), University of Pittsburgh School of Medicine, Pittsburgh (M.L.M.); Renal Consultants of Houston, Houston (J.C.A.); and the Division of Nephrology, Hospital Italiano de Buenos Aires, Buenos Aires (J.C.A.). Address reprint requests to Dr. Moritz at the Division of Nephrology, Children's Hospital of Pittsburgh of UPMC, 1 Children's Hospital Dr., 4401 Penn Ave., Pittsburgh, PA 15224, or at moritzml@upmc.edu.

N Engl J Med 2015;373:1350-60.

DOI: 10.1056/NEJMr1412877

Copyright © 2015 Massachusetts Medical Society.

A CRITICAL ASPECT OF THE CARE OF ACUTELY ILL PATIENTS IS THE ADMINISTRATION of intravenous fluids. Intravenous fluids may be required as a bolus infusion for resuscitation or as a continuous infusion when sufficient fluids cannot be ingested orally.

The goal of maintenance intravenous fluids is to preserve the extracellular volume while maintaining a normal electrolyte balance. An appropriate maintenance fluid provides an adequate quantity of both water and electrolytes to ensure good tissue perfusion without causing complications related to fluid overload or volume depletion. It also prevents the development of hyponatremia, hypernatremia, and other electrolyte imbalances.

Despite the almost ubiquitous need for intravenous fluids in acutely ill patients, there has been little consensus on the most appropriate rate of administration and composition of intravenous fluids, and practice patterns with respect to maintenance fluids vary widely.¹⁻³ In addition, acutely ill patients frequently have conditions that impair normal water and electrolyte homeostasis (Table 1), and choosing the appropriate volume and composition of intravenous fluids requires great care.⁴

Intravenous fluids can be classified, according to the concentration of sodium plus potassium in the fluid, as being either isotonic (approximately equal to the plasma sodium concentration) or hypotonic (less than the plasma sodium concentration). The dextrose content of intravenous fluids has no effect on the tonicity, since the dextrose is rapidly metabolized when it enters the bloodstream and should not produce hyperglycemia.

A prevailing practice has been to administer hypotonic maintenance intravenous fluids in both children and adults.^{1,5,6} This practice has been associated with a high incidence of hospital-acquired hyponatremia and more than 100 reports of iatrogenic deaths or permanent neurologic impairment related to hyponatremic encephalopathy,⁷⁻¹¹ since acutely ill patients may have disease states associated with an excess of arginine vasopressin (AVP) (Fig. 1). This excess impairs excretion of free water and may aggravate hyponatremia.^{15,16}

Over the past decade, many studies have evaluated the association between the composition and quantity of maintenance fluids and the development of hyponatremia. Recent data also suggest that rapid volume expansion with 0.9% saline (normal saline), as compared with balanced electrolyte solutions, may result in untoward complications.¹⁷ The current review considers the physiological principles that guide the appropriate selection of intravenous fluids, as well as the recent literature evaluating the safety of various intravenous fluids with respect to their composition and rate of administration.

AVP AND DISORDERS OF SODIUM AND WATER HOMEOSTASIS

The human body has a remarkable ability to maintain a normal composition of body water and plasma osmolality, despite wide variations in fluid and electrolyte intake.¹⁸ Sodium and water homeostasis is regulated through the actions of AVP, the renin–angiotensin–aldosterone system, and natriuretic peptides. Plasma osmolality is regulated both by thirst and by excretion of free water. In a patient who can ingest nothing by mouth, plasma osmolality is primarily under the control of AVP release, which determines the rate of free-water excretion.¹² Any disease state that results in either excess AVP or impaired AVP action will place a patient at risk for a plasma sodium concentration that is too high or too low.

There are numerous hemodynamic and non-hemodynamic stimuli for AVP secretion; thus, virtually all acutely ill hospitalized patients are at risk for hyponatremia (Fig. 1). Hemodynamic stimuli for AVP production include volume depletion; hypotension; edematous states such as congestive heart failure, cirrhosis, and the nephrotic syndrome; and sepsis.¹³ Nonhemodynamic physiological stimuli for AVP secretion include pain, stress, nausea, vomiting, hypoxemia, hypercapnia, hypoglycemia, and the perioperative state.^{12,14}

These physiological stimuli can result in increased AVP levels in the absence of volume depletion or hyperosmolality.¹² In addition, an ever-expanding list of conditions and medications is associated with the syndrome of inappropriate antidiuresis, in which AVP excess occurs in the absence of any identifiable nonosmotic stimuli for AVP production.¹⁹ The conditions most often associated with this syndrome are cancer, central nervous system (CNS) disorders, pulmonary disorders, and infections.¹⁹ Medications that are frequently associated with this syndrome include narcotics, the chemotherapeutic agents cyclophosphamide and vincristine, selective serotonin-reuptake inhibitors, the antiepileptic agent oxcarbazepine, and the recreational drug “ecstasy” (3,4-methylenedioxymethamphetamine [MDMA]). Thiazide diuretics can also be associated with a condition that resembles the syndrome of inappropriate antidiuresis. The syndrome of inappropriate antidiuresis is now recognized as the most common cause of euvoletic hyponatremia.²⁰

Table 1. Conditions Requiring Special Considerations in Maintenance Fluid Therapy.

Free-water restriction for euvoletic states of AVP excess

CNS disturbances

- Meningitis
- Encephalitis
- Brain tumors
- Head injury
- Cerebritis
- Subarachnoid hemorrhage

Pulmonary disease

- Pneumonia
- Asthma
- Bronchiolitis
- Tuberculosis

Cancer

Postoperative state

Fluid restriction for edematous states

Congestive heart failure

Nephrosis

Cirrhosis

Fluid and sodium restriction for oliguric states

Acute glomerulonephritis

Acute tubular necrosis

End-stage renal disease

Increased free-water requirements for renal concentrating defects

Congenital nephrogenic diabetes insipidus

Sickle cell disease

Obstructive uropathy

Reflux nephropathy

Renal dysplasia

Nephronophthisis

Tubulointerstitial nephritis

Use of lithium

Increased sodium and water requirements for solute diuresis

Diuretic phase of acute tubular necrosis

Postobstructive diuresis

Immediate postoperative renal transplantation

Diabetic ketoacidosis

Bartter's syndrome

Fanconi's syndrome

Cerebral salt wasting

Adrenal insufficiency

Increased free-water requirements for extrarenal free-water losses

Burns

Prematurity in neonates

Fever

Infectious diarrhea

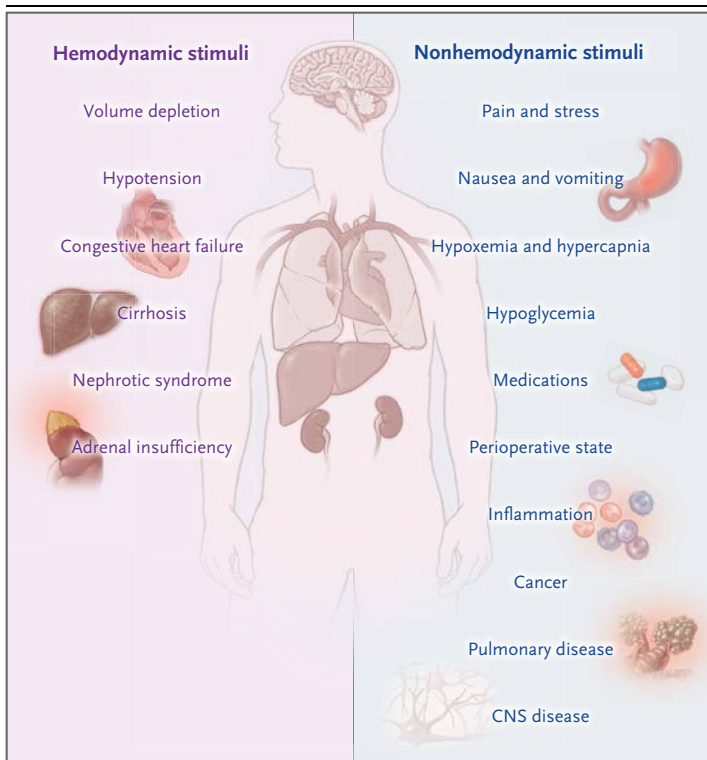


Figure 1. Nonsmotic States of Arginine Vasopressin (AVP) Excess.

Numerous hemodynamic and nonhemodynamic stimuli for AVP secretion place virtually all acutely ill hospitalized patients at risk for the development of hyponatremia. Physiological stimuli can result in an increase in AVP levels in the absence of volume depletion or hyperosmolality. In numerous disease states and medications associated with the syndrome of inappropriate antidiuresis, AVP excess occurs in the absence of any identifiable nonsmotic stimuli for AVP production.¹²⁻¹⁴

The ability to produce concentrated urine depends on both the ability to maintain a concentrated renal medullary interstitium and the water permeability of the collecting duct in response to AVP. Diseases or medications that disrupt the medullary interstitium or interfere with the action of AVP will result in a renal concentrating defect and can lead to hyponatremia in patients with restricted access to free water (Table 1).²¹ Common reasons for a renal concentrating defect include tubulointerstitial renal diseases such as obstructive uropathy and sickle cell disease, genetic disorders such as congenital nephrogenic diabetes insipidus, and the use of lithium.

HOSPITAL-ACQUIRED HYPONATREMIA

Hyponatremia, which is defined as a plasma sodium concentration of less than 135 mmol per

liter, is the most common electrolyte abnormality in hospitalized patients; it affects approximately 15 to 30% of children and adults who are hospitalized.^{22,23} Most hyponatremia in these patients is hospital-acquired and is related to the administration of hypotonic intravenous fluids in patients with elevated AVP levels.^{16,23-26} Virtually all studies evaluating hospital-acquired hyponatremia have shown that it is related to the administration of hypotonic fluids.^{23,24,27-30}

The most serious complication of hospital-acquired hyponatremia is hyponatremic encephalopathy, which is a medical emergency that can be fatal or lead to irreversible brain injury if it is inadequately treated.^{7,10} All large studies of hospital-acquired hyponatremic encephalopathy have involved primarily otherwise healthy children and adults who were receiving hypotonic fluids; in many cases, this condition followed minor surgical procedures.^{7,8,10,11,31} The strong association between the use of hypotonic fluid and hyponatremic encephalopathy and the number of preventable deaths in children that have resulted from the use of hypotonic fluid have drawn the attention of the National Patient Safety Agency in the United Kingdom³² and the Institute for Safe Medication Practices of Canada³³ and the United States.^{34,35} All three organizations have issued warnings about the dangers of administering hypotonic fluids in children and have called for the establishment of and adherence to guidelines for administration of fluid. Similar patient-safety warnings have not, however, been issued for adults.

Patients with hospital-acquired hyponatremia are at particular risk for the development of hyponatremic encephalopathy, which usually develops acutely, in less than 48 hours, leaving little time for brain adaptation. Hospitalized patients who are at particular risk for the development of hyponatremic encephalopathy at even mildly hyponatremic levels include children younger than 16 years of age,⁸ women in their reproductive years,⁷ and patients with hypoxemia³⁶ or underlying CNS disease,³⁷ since these conditions either impair regulation of brain-cell volume or are associated with decreased intracranial capacity for brain expansion (Table 2).

Prevention of hospital-acquired hyponatremic encephalopathy is critical, since the presenting symptoms are nonspecific and can be easily overlooked until advanced symptoms develop.

The most consistent symptoms of hyponatremic encephalopathy are headache, nausea, vomiting, and generalized weakness.^{7,38,39} Advanced symptoms of hyponatremic encephalopathy include seizures, respiratory arrest, noncardiogenic pulmonary edema, and decorticate posturing.^{7,38,39} Symptoms can occur abruptly and do not always correlate with the plasma sodium concentration or the rapidity of development of hyponatremia.^{7,10,38,40}

Failure to recognize and treat hyponatremic encephalopathy with hypertonic saline results in a poor neurologic prognosis.^{7,10} Fluid restriction alone, isotonic fluids, and vaptans have no role in the immediate management of hyponatremic encephalopathy.^{14,39}

Mounting data show that even chronic hyponatremia, which develops over a period of 48 hours or longer, without apparent neurologic symptoms, is deleterious. Chronic hyponatremia has been shown to result in subtle neurologic impairment, which can cause gait disturbances that lead to falls and associated bone fractures in the elderly, with increased bone fragility resulting from bone demineralization.⁴¹⁻⁴⁵

Hyponatremia is an independent risk factor for death in the hospital setting, particularly among patients with end-stage liver disease, congestive heart failure, pneumonia, and end-stage renal disease, and it is associated with increased hospital costs, length of hospital stay, and rates of readmission.⁴⁶⁻⁵⁰ When hyponatremia develops, it can be difficult to correct, since most initial therapies, such as fluid restriction and isotonic fluids, are relatively ineffective in correcting euvolemic and hypervolemic hyponatremia.²⁰ For all these reasons, strategies should be implemented to prevent hyponatremia.

CONCERNS ABOUT HYPOTONIC MAINTENANCE FLUIDS IN CHILDREN AND ADULTS

Hypotonic fluids continue to be recommended as maintenance fluids in acutely ill patients despite the strong association between their use and the development of hospital-acquired hyponatremia.^{6,51} The prevailing practice has been to administer hypotonic fluids (e.g., 5% dextrose in a solution of 0.18 to 0.45% saline) at a rate of approximately 2.0 to 3.0 liters per day in adults. The equivalent amount in children is estimated

Table 2. Risk Factors for Hyponatremic Encephalopathy.

Risk Factor	Pathophysiological Mechanism
Acute hyponatremia (<48 hr)	Decreased time for brain adaptation
Age <16 yr	Increased ratio of brain to intracranial volume
Female sex	Sex steroids (estrogens) inhibit brain adaptation Increased AVP levels Cerebral vasoconstriction Hypoperfusion of brain tissue
Hypoxemia	Impaired brain adaptation Decreased cerebral perfusion
Brain injury	Vasogenic cerebral edema Cytotoxic cerebral edema

as either of the following: 1500 ml per 1.73 m² of body-surface area per 24 hours or, as calculated with the use of the Holliday–Segar formula, 100 ml per kilogram per 24 hours for the first 10 kg of body weight, plus 50 ml per kilogram per 24 hours for a weight of greater than 10 to 20 kg, and an additional 20 ml per kilogram per 24 hours for a weight above 20 kg.^{6,52}

Such recommendations are based on theoretical calculations from the 1950s, before the syndrome of inappropriate antidiuresis was recognized as a common clinical entity. In 1953, Talbot et al. made recommendations regarding the administration of fluids in adults according to a theoretical model of the maximal and minimal amount of sodium and water in parenteral fluids that could be administered without adverse effects.⁵³ In 1957, Holliday and Segar made similar recommendations for children according to average caloric requirements for hospitalized children and electrolyte requirements based on dietary intake.⁵² However, these recommendations lack validation in clinical practice in children or adults. All current recommendations regarding the composition and rate of maintenance fluid therapy in children and adults, regardless of the patient's condition, are predominantly opinion-based.⁵¹

We previously suggested that isotonic fluids should be administered in maintenance intravenous fluids to prevent hospital-acquired hyponatremia in acutely ill children and that the routine practice of administering hypotonic fluids (sodium concentration, <130 mmol per liter) be abandoned because of the increased risk of hyponatremia.⁵⁴ We subsequently extended this recommendation to apply to adult patients.¹⁶

Currently, to our knowledge, there are no formal society-sponsored guidelines for maintenance fluid therapy in hospitalized patients in the United States. Attempts have been made to develop consensus guidelines for children and adults in the United Kingdom.^{6,32,55,56}

The first consensus guideline on fluid therapy was issued by the U.K. National Health Service in 2007. The National Health Service issued a patient-safety alert to remove 0.18% saline from general-use areas (e.g., the emergency department and pediatric ward) for children and recommended 0.45% saline for maintenance fluids for the majority of children and 0.9% saline for children at high risk for hyponatremia.³² These opinion-based recommendations were subsequently adopted for the care of children in Northern Ireland by the Regulation and Quality Improvement Authority and in Australia by the Victorian Paediatric Clinical Network. Preliminary data suggest that these recommendations may have been helpful in reducing the incidence of hyponatremia.⁵⁷

Even though 0.18% saline was essentially banned throughout the United Kingdom for use in children, consensus guidelines still recommend it as a maintenance fluid in adults.^{6,55} The British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients, which were published in 2008 and updated in 2011, recommend 0.18 to 0.45% saline for postoperative maintenance fluids.⁵⁵ In 2013, the National Institute for Health and Care Excellence guidelines for intravenous fluid therapy in adults, which were published in the United Kingdom, recommended 0.18% saline for maintenance fluids.⁶ These guidelines were primarily opinion-based and included low-quality evidence on which to base recommendations. These consensus guidelines lack validation in clinical practice.

ISOTONIC MAINTENANCE FLUIDS
FOR THE PREVENTION OF HOSPITAL-
ACQUIRED HYPONATREMIA

The use of isotonic fluids in maintenance fluids for the prevention of hospital-acquired hyponatremia in acutely ill patients was initially controversial,^{58,59} owing mainly to the potential for unintended consequences. These consequences include the development of hypernatremia, fluid

overload with edema or hypertension, and hyperchloremic acidosis.⁶⁰

More than 15 randomized, prospective trials involving more than 2000 patients have evaluated the safety and efficacy of isotonic fluids as compared with hypotonic fluids for the prevention of hyponatremia.⁶¹⁻⁶⁶ Most of these studies involved children, the majority of whom were surgical and critical care patients. Isotonic fluids were superior to hypotonic fluids for the prevention of hyponatremia in all but 1 small study,⁶⁷ in which 37 patients were followed for approximately 12 hours. Isotonic fluids were not associated with an increased risk of hypernatremia or fluid overload, and there were no apparent serious complications. A meta-analysis of 10 of these studies, involving almost 1000 children, showed that hypotonic fluids were associated with a relative risk of 2.37 for the development of mild hyponatremia (sodium concentration, <135 mmol per liter) and a relative risk of 6.2 for the development of moderate hyponatremia (sodium concentration, <130 mmol per liter).⁶¹ Some physicians have argued that fluid restriction with hypotonic fluids would be sufficient to prevent hyponatremia.⁵⁸ In 4 studies, fluid restriction with hypotonic fluids was not effective in preventing hyponatremia.⁶⁸⁻⁷¹

It has also been argued that isotonic fluids may not be necessary for the prevention of hyponatremia in a general pediatric ward. A study involving almost 700 children showed that the odds ratio for prevention of hyponatremia with an isotonic fluid was similar among surgical patients and nonsurgical patients and among patients who were in intensive care and those who were not in intensive care.⁶²

Taken together, these studies suggest that isotonic fluids are most appropriate for the vast majority of hospitalized patients who are at risk for elevated AVP levels and hospital-acquired hyponatremia. This does not mean that isotonic fluids are appropriate in all clinical settings or that they are without risk. The studies were of short duration (usually <72 hours) and excluded patients with renal disease, heart failure, and cirrhosis. Precautions were taken if complications were developing. It is not certain whether the side-effect profile with isotonic fluids would be as favorable in other patient populations, such as the elderly, as it is in children.

Isotonic fluids may result in hyponatremia in patients with CNS injury in whom cerebral salt wasting develops or in patients with the syndrome of inappropriate antidiuresis in whom the urine osmolality is greater than 500 mOsm per kilogram.⁷² Isotonic fluids could also result in hypernatremia if there is a renal concentrating defect or if there are large extrarenal free-water losses. Any type of intravenous fluid can result in fluid overload if administered in excessive quantities (for example, in patients with end-stage renal disease or heart failure in whom both sodium excretion and water excretion are impaired). In most circumstances, the administration of isotonic fluids should not lead to hypernatremia or fluid overload.⁷³

BALANCED SALT SOLUTIONS AS COMPARED WITH 0.9% SALINE

An area of active investigation focuses on the potential for deleterious effects associated with 0.9% saline (normal saline) as compared with those associated with balanced electrolyte solutions (Table 3).^{17,74} Normal saline (sodium concentration, 154 mmol per liter) has the same sodium concentration as the aqueous phase of human plasma, but it has a supraphysiologic chloride concentration. Saline solutions may also have a pH that is far lower than that of water (range, 3.5 to 7.0). The low pH of 0.9% saline appears to be related to the polyvinyl chloride bags in which it is packaged, since the pH of 0.9% saline in a glass bottle is 7.0.

Deleterious consequences of 0.9% saline have been associated primarily with studies (both in animals and in humans) in which infusion is rapid and with clinical scenarios in which fluid resuscitation or intraoperative fluid management includes administration of a large volume of fluid.⁷⁴ In such circumstances, 0.9% saline, as compared with balanced salt solutions, may produce a hyperchloremic metabolic acidosis, renal vasoconstriction, delayed micturition, an increased incidence of acute kidney injury requiring renal-replacement therapy, and hyperkalemia.

Whether any of these complications will occur when 0.9% saline is used at maintenance rates for less than 72 hours is unclear, but randomized trials that have been sufficiently powered to assess this possibility have not been conducted. Currently, no balanced electrolyte solution

is perfectly matched with plasma (Table 3). Multiple electrolytes injection, type 1, USP, (an infusion fluid) has a supraphysiologic buffer concentration of 50 mmol per liter. Ringer's lactate contains calcium and may be incompatible with blood products and some medications. There are insufficient data to suggest that 0.9% saline is unsafe when used as a maintenance fluid.

SELECTING THE RATE OF ADMINISTRATION AND THE COMPOSITION OF MAINTENANCE INTRAVENOUS FLUIDS

No single rate of administration or composition of maintenance intravenous fluids is appropriate in all circumstances. Thus, intravenous fluids may be viewed as medications that require careful dose adjustment that is specific to the disease state of each patient.

The rate of administration and the composition of intravenous fluids need to be individualized, and while patients are receiving intravenous fluids, they require close monitoring with daily measurement of weight, frequent assessment of vital signs, strict measurements of intake and output, and daily measurement of serum electrolyte levels and physical examination. Many children have died of hyponatremic encephalopathy within 24 hours after the initiation of hypotonic intravenous fluids, so even close observation may be inadequate to prevent this complication.

Table 1 lists a broad range of conditions that require special consideration when maintenance fluid therapy is administered, and Figure 2 shows a practical approach for adjusting maintenance intravenous fluids according to these conditions. This approach is opinion-based, since data are lacking from studies evaluating the most appropriate fluid therapy for all conditions.

Dextrose is provided in maintenance fluids to provide sufficient calories to prevent hypoglycemia and limit tissue catabolism, but it does not provide complete nutritional support. Some dextrose-containing saline solutions are hyperosmolar to plasma, but they are not hypertonic, since the dextrose is rapidly metabolized on entering the bloodstream (Table 3). The default maintenance solution for adults is 5% dextrose in a solution of 0.9% saline administered at a rate of 100 to 120 ml per hour; this is based on the fact that most hospitalized patients are at risk for euvolemic hyponatremia from AVP excess if they

Table 3. Composition of Commercially Available Intravenous Crystalloid Solutions for Fluid Therapy.*

Fluid	Glucose	Sodium	Chloride	Potassium	Buffer†‡	Calcium	Magnesium	pH	Osmolarity <i>mOsm/liter</i>	Osmolality <i>mOsm/kg</i>	Electrolyte-free Water <i>%‡</i>
Human plasma	0.07–0.11	135–144	95–105	3.5–5.3	23–30	2.2–2.6	0.8–1.2	7.35–7.45	308	288	0
5% Dextrose in water	5	0	0	0	0	0	0	3.5–6.5	252		100
4% Dextrose in 0.18% saline	4	30	30	0	0	0	0	3.5–6.5	282		81
5% Dextrose in 0.2% saline	5	34	34	0	0	0	0	3.5–6.5	321		78
5% Dextrose in 0.45% saline	5	77	77	0	0	0	0	3.5–6.5	406		50
5% Dextrose Ringer's lactate	5	130	109	4	28	1.5	0	4.0–6.5	525		13
5% Dextrose in 0.9% saline	5	154	154	0	0	0	0	3.5–6.5	560		0
5% Dextrose multiple electrolytes injection, type 1, USP	5	140	98	5	50	0	1.5	4.0–6.5	547		6
Ringer's lactate	0	130	109	4	28	1.35	0	6–7.5	273	254	13
Ringer's acetate	0	130	112	5	27	1	1	6–8	276		12
Hartmann's solution	0	131	111	5	29	2	0	5.0–7.0	278		12
0.9% Saline	0	154	154	0	0	0	0	4.5–7	308	286	0
Multiple electrolytes injection, type 1, USP§	0	140	98	5	50	0	1.5	4.0–6.5	294		6
Isotonic electrolyte solution¶	0	140	127	4	29	2.5	1	4.6–5.4	304		6

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for calcium to milligrams per deciliter, divide by 0.250. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. USP denotes United States Pharmacopeia.

† The buffer is bicarbonate in plasma, lactate in Ringer's lactate and Hartmann's solution, acetate in Ringer's acetate, acetate (27 mmol per liter) and gluconate (23 mmol per liter) in multiple electrolytes injection, type 1, USP, and acetate (23 mmol per liter) and maleate (5 mmol per liter) in isotonic electrolyte solution.

‡ This percentage is based on a sodium plus potassium concentration in the aqueous phase of plasma of 154 mmol per liter, assuming that plasma is 93% water with a plasma sodium concentration of 140 mmol per liter and a potassium concentration of 4 mmol per liter.

§ Multiple electrolytes injection, type 1, USP, is the generic name for Plasma-Lyte 148, Normosol, and Isolyte.

¶ Isotonic electrolyte solution is the generic name for Sterofundin and Ringerfundin. It has an electrolyte composition that is similar to that of plasma.

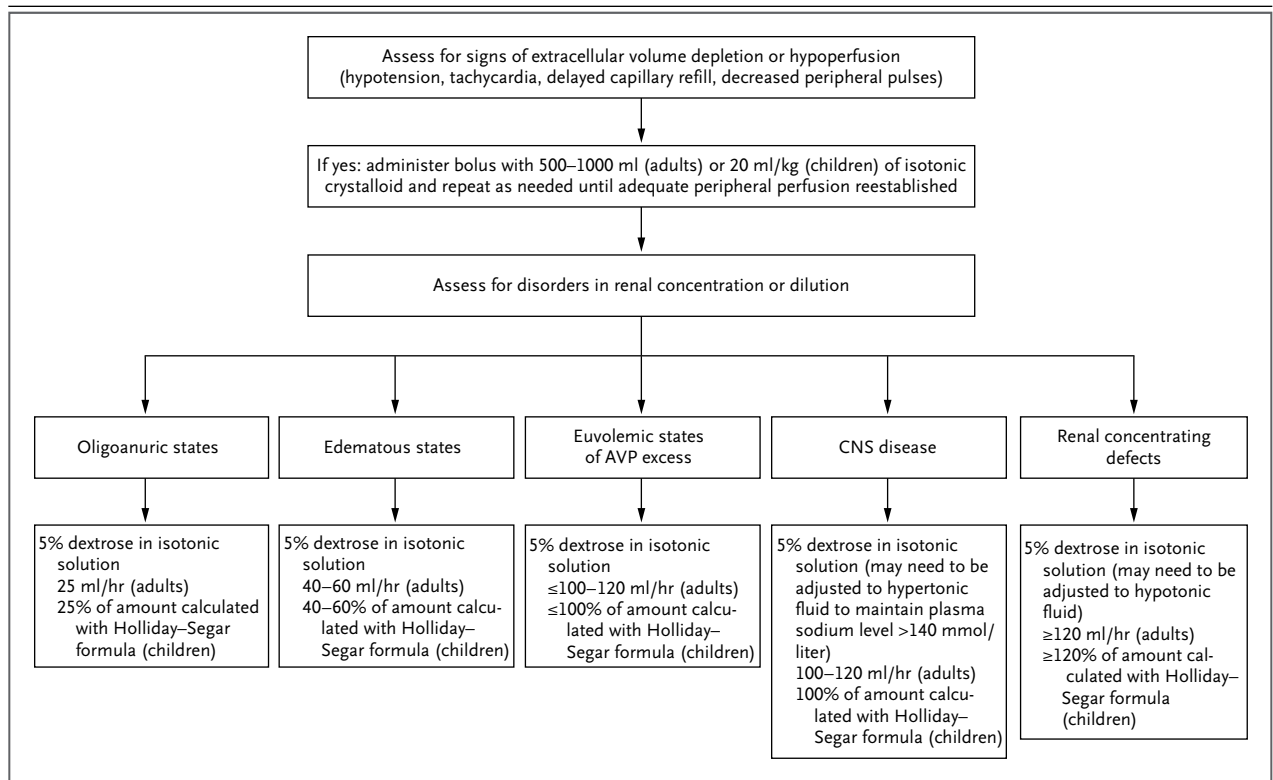


Figure 2. Guide to Maintenance Intravenous Fluid Therapy in Acutely Ill Patients.

Since most hospitalized patients are at risk for hyponatremia from AVP excess, in most acutely ill adults, the safest type of maintenance solution and rate of administration are 5% dextrose in a solution of 0.9% saline at a rate of 100 to 120 ml per hour. In children, the equivalent dose is either 1500 ml per 1.73 m² of body-surface area per 24 hours or an amount calculated with the use of the Holliday–Segar formula (100 ml per kilogram per 24 hours for the first 10 kg of body weight, plus 50 ml per kilogram per 24 hours for weight greater than 10 to 20 kg, and an additional 20 ml per kilogram per 24 hours for weight above 20 kg). The rate and composition of intravenous fluids will need to be adjusted for certain conditions. Patients at risk for fluid overload require fluid restriction. Patients with clinically significant renal concentrating defects require an increased volume of hypotonic fluids to keep up with ongoing urinary free-water losses. Hypotonic fluids should be administered only if there is a specific indication, and they should be avoided if hyponatremia is present. In patients with central nervous system (CNS) diseases who are at risk for cerebral edema, the plasma sodium concentration should be maintained at greater than 140 mmol per liter to prevent cytotoxic cerebral edema.

receive hypotonic fluids. Provision of fluids at a rate greater than or less than this amount is determined according to whether there is a disorder in renal concentration or a fluid overload state, respectively. A hypotonic fluid may be required if there is a clinically significant renal concentrating defect with ongoing free-water losses or to aid in the correction of established hyponatremia.⁴

Studies that evaluate the most appropriate maintenance fluid for edematous states are lacking. It is our opinion that an isotonic fluid administered at a restricted rate would be appropriate, since these patients frequently have hyponatremia.

Administration of potassium is not specifical-

ly addressed in this review article or in the algorithm in Figure 2. A common practice is to add 20 mmol per liter of potassium to maintenance intravenous fluids, but data to support the safety of this approach are lacking, and it is not clear that adding more than a physiologic concentration of potassium (i.e., >5 mmol per liter) is necessary when intravenous fluids are administered for less than 48 hours, unless hypokalemia or malnutrition is present or diuretics are being used.

SUMMARY

The administration of intravenous fluids is an essential component of supportive care for acutely ill patients. Because of limited evidence,

Box 1. Case 1.

Case 1 illustrates the use of perioperative maintenance therapy.

A 28-year-old woman who weighs 65 kg is admitted through the emergency department with a diagnosis of acute appendicitis. Given a history of poor oral intake, she receives a 1-liter bolus of 0.9% saline in the emergency department. Vital signs and serum electrolyte levels are otherwise normal at presentation. What type and rate of maintenance intravenous fluid would you administer while the patient is receiving nothing by mouth both before surgery and postoperatively?

Answer: An appropriate fluid would be 5% dextrose in a solution of 0.9% saline at a rate of 100 ml per hour. Perioperatively, patients have numerous stimuli for AVP production, including pain, stress, nausea, narcotics administered for pain management, and hypovolemia. In addition, women in their reproductive years are at increased risk for hyponatremic encephalopathy.⁷ Administration of 0.9% saline is suitable to maintain the extracellular volume and will reduce the risk of hospital-acquired hyponatremia.

Box 2. Case 2.

Case 2 illustrates maintenance therapy in a patient with CNS disease.

A 75-year-old man who weighs 80 kg presents to the emergency department with symptoms consistent with a stroke. A severe headache develops, followed by confusion and hemiparesis on his left side. He has a long-standing history of hypertension treated with an angiotensin-converting-enzyme (ACE) inhibitor. On examination, he appears euvolemic, with an elevated blood pressure of 150/100 mm Hg and normal serum electrolyte levels. What type and rate of maintenance intravenous fluid would you administer while the patient is receiving nothing by mouth before evaluation and management of a possible stroke?

Answer: An appropriate fluid would be 5% dextrose in a solution of 0.9% saline at a rate of 100 ml per hour. This patient appears to have an acute intracranial process suggestive of a stroke. He is at risk for increased intracranial pressure and cerebral edema. Patients with CNS processes are at high risk for hyponatremia due to the syndrome of inappropriate antidiuresis or cerebral salt wasting. In addition, hyponatremia can have extremely serious consequences in patients with CNS disease, since a small decrease in the serum sodium concentration could result in cytotoxic cerebral edema, thus aggravating vasogenic cerebral edema, which probably is already present.⁷⁵ Administration of 0.9% saline would help to prevent the development of hyponatremia, but the patient's electrolyte levels would need to be monitored closely, since the plasma sodium concentration can decrease in patients with CNS disease who receive 0.9% saline.⁷² The addition of 3% saline may be necessary to maintain a serum sodium concentration above 140 mmol per liter.

Box 3. Case 3.

Case 3 illustrates maintenance therapy in a patient with congestive heart failure.

An 87-year-old man who weighs 70 kg and who has a left-lower-lobe pneumonia is admitted to the hospital from a nursing home. He has a history of myocardial infarctions and well-controlled congestive heart failure managed with an ACE inhibitor, a beta-blocker, a thiazide diuretic, and a sodium-restricted diet. He received 500 ml of 0.9% saline during transport to the hospital. His vital signs are stable, and there is no evidence of pulmonary congestion or peripheral edema on examination. Electrolyte levels are remarkable for a serum sodium concentration of 134 mmol per liter, potassium 3.2 mmol per liter, total carbon dioxide 31 mmol per liter, and creatinine 1.2 mg per deciliter (106 μ mol per liter). Intravenous antibiotics are initiated. He is weak and has tachypnea and clinically significant coughing. There is a concern that he is too ill to be able to drink sufficient fluids. What type and rate of maintenance intravenous fluid would you administer?

Answer: An appropriate fluid would be 5% dextrose in a solution of 0.9% saline plus 20 mmol potassium chloride per liter at a rate of 60 ml per hour. This patient is at risk for both fluid overload and hyponatremia due to congestive heart failure.⁷⁶ Therefore, the rate of intravenous fluids should be restricted. A rate of 60 ml per hour or approximately 1.5 liters per day is probably adequate to maintain good peripheral perfusion without causing fluid overload. This patient has a low serum sodium concentration at 134 mmol per liter, so hypotonic fluids should not be administered. Recent data suggest that sodium supplementation may be beneficial in patients with heart failure.⁷⁷ Potassium should be added to the intravenous fluids, since the patient has hypokalemia, probably from the thiazide diuretic and poor nutrition. In this patient, the volume of intravenous medications needs to be accounted for, since it could contribute to both fluid overload and hyponatremia.

recommendations regarding fluid have historically been opinion-based. It has now become clear that the administration of hypotonic maintenance fluids (sodium concentration, <130 mmol per liter) is associated with the development of hospital-acquired hyponatremia as well as with deaths or permanent neurologic impairment from hyponatremic encephalopathy.

Acutely ill patients have multiple stimuli for AVP that place them at risk for the development of hyponatremia. Numerous prospective studies involving children have shown that isotonic fluids are safe and effective in preventing hospital-acquired hyponatremia. Acutely ill patients can have a variety of conditions that can alter body-water homeostasis, so both the rate and the

composition of intravenous fluid should be prescribed carefully. Isotonic fluids are the most appropriate maintenance fluid in the vast majority of situations. In Box 1, Box 2, and Box 3, we provide three practical cases regarding the most appropriate rate and composition of maintenance intravenous fluid.

Data from studies to determine whether balanced solutions are superior to saline solutions for maintenance fluids and to determine the most appropriate potassium concentration in fluids are

lacking. A solid evidence base from which consensus guidelines for fluid therapy could be built is also needed to better standardize fluid management.

Drs. Moritz and Ayus report receiving consulting fees from Otsuka and a continuing medical education honorarium from the Global Education Group. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Karen Branstetter for editing an earlier version of the manuscript and Kelli Crowley and Kevin Ordons for assistance in preparing an earlier version of Table 3.

REFERENCES

- Freeman MA, Ayus JC, Moritz ML. Maintenance intravenous fluid prescribing practices among paediatric residents. *Acta Paediatr* 2012;101(10):e465-e468.
- Davies P, Hall T, Ali T, Lakhoo K. Intravenous postoperative fluid prescriptions for children: a survey of practice. *BMC Surg* 2008;8:10.
- Chawla G, Drummond GB. Textbook coverage of a common topic: fluid management of patients after surgery. *Med Educ* 2008;42:613-8.
- Moritz ML, Ayus JC. Intravenous fluid management for the acutely ill child. *Curr Opin Pediatr* 2011;23:186-93.
- Intravenous fluid therapy in adults in hospital. London: National Institute for Health and Care Excellence, 2013 (<https://www.nice.org.uk/guidance/cg174>).
- Padhi S, Bullock I, Li L, Stroud M. Intravenous fluid therapy for adults in hospital: summary of NICE guidance. *BMJ* 2013;347:f7073.
- Ayus JC, Wheeler JM, Arief AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992;117:891-7.
- 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;322:780-2.
- Steele A, Gowrishankar M, Abrahamson S, Mazer CD, Feldman RD, Halperin ML. Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann Intern Med* 1997;127:891-5.
- Arief AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ* 1992;304:1218-22.
- Arief AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986;314:1529-35.
- Danziger J, Zeidel ML. Osmotic homeostasis. *Clin J Am Soc Nephrol* 2015;10:852-62.
- Schrier RW. Body water homeostasis: clinical disorders of urinary dilution and concentration. *J Am Soc Nephrol* 2006;17:1820-32.
- Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 2014;29:Suppl 2:i1-i39.
- Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. *Pediatr Nephrol* 2005;20:1687-700.
- Moritz ML, Ayus JC. Hospital-acquired hyponatremia — why are hypotonic parenteral fluids still being used? *Nat Clin Pract Nephrol* 2007;3:374-82.
- Severs D, Hoorn EJ, Rookmaaker MB. A critical appraisal of intravenous fluids: from the physiological basis to clinical evidence. *Nephrol Dial Transplant* 2015;30:178-87.
- Knepper MA, Kwon TH, Nielsen S. Molecular physiology of water balance. *N Engl J Med* 2015;372:1349-58.
- Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007;356:2064-72.
- Greenberg A, Verbalis JG, Amin AN, et al. Current treatment practice and outcomes: report of the Hyponatremia Registry. *Kidney Int* 2015;88:167-77.
- Oster JR, Singer I, Thatté L, Grant-Taylor I, Diego JM. The polyuria of solute diuresis. *Arch Intern Med* 1997;157:721-9.
- Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med* 2006;119:Suppl 1:S30-S35.
- Carandang F, Anglemeyer A, Longhurst CA, et al. Association between maintenance fluid tonicity and hospital-acquired hyponatremia. *J Pediatr* 2013;163:1646-51.
- Chung HM, Kluge R, Schrier RW, Anderson RJ. Postoperative hyponatremia: a prospective study. *Arch Intern Med* 1986;146:333-6.
- Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985;102:164-8.
- Neville KA, Verge CF, O'Meara MW, Walker JL. High antidiuretic hormone levels and hyponatremia in children with gastroenteritis. *Pediatrics* 2005;116:1401-7.
- Aronson D, Dragu RE, Nakhoul F, et al. Hyponatremia as a complication of cardiac catheterization: a prospective study. *Am J Kidney Dis* 2002;40:940-6.
- Nair V, Niederman MS, Masani N, Fishbane S. Hyponatremia in community-acquired pneumonia. *Am J Nephrol* 2007;27:184-90.
- 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;152:33-8.
- Hanna M, Saberi MS. Incidence of hyponatremia in children with gastroenteritis treated with hypotonic intravenous fluids. *Pediatr Nephrol* 2010;25:1471-5.
- Rodríguez MJ, Alcaraz A, Solana MJ, García A. Neurological symptoms in hospitalised patients: do we assess hyponatraemia with sufficient care? *Acta Paediatr* 2014;103(1):e7-e10.
- National Patient Safety Agency (NPSA). Patient safety alert: reducing the risk of hyponatraemia when administering intravenous infusions to children. 2007 (<http://www.nrls.npsa.nhs.uk/resources/?entryid45=59809>).
- Hospital-acquired acute hyponatremia: two reports of pediatric deaths. *ISMP Canada Safety Bulletin* 2009;9:1-4.
- Plain D5W or hypotonic saline solutions post-op could result in acute hyponatremia and death in healthy children. *ISMP Medication Safety Alert* 2009;7:1-4.
- Grissinger M. Hyponatremia and death in healthy children from plain dextrose and hypotonic saline solutions after surgery. *P T* 2013;38:364-88.
- Ayus JC, Armstrong D, Arief AI. Hyponatremia with hypoxia: effects on brain adaptation, perfusion, and histology in rodents. *Kidney Int* 2006;69:1319-25.
- Moritz ML, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children. *Pediatr Nephrol* 2010;25:1225-38.

38. Nigro N, Winzeler B, Suter-Widmer I, et al. Symptoms and characteristics of individuals with profound hyponatremia: a prospective multicenter observational study. *J Am Geriatr Soc* 2015;63:470-5.
39. Ayus JC, Caputo D, Bazerque F, Heuguen R, Gonzalez CD, Moritz ML. Treatment of hyponatremic encephalopathy with a 3% sodium chloride protocol: a case series. *Am J Kidney Dis* 2015;65:435-42.
40. Ayus JC, Arief AL. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. *JAMA* 1999;281:2299-304.
41. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006;119(1):71.e1-78.e1.
42. Ayus JC, Moritz ML. Bone disease as a new complication of hyponatremia: moving beyond brain injury. *Clin J Am Soc Nephrol* 2010;5:167-8.
43. Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA. Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clin J Am Soc Nephrol* 2010;5:275-80.
44. Verbalis JG, Barsony J, Sugimura Y, et al. Hyponatremia-induced osteoporosis. *J Bone Miner Res* 2010;25:554-63.
45. Ayus JC, Negri AL, Kalantar-Zadeh K, Moritz ML. Is chronic hyponatremia a novel risk factor for hip fracture in the elderly? *Nephrol Dial Transplant* 2012;27:3725-31.
46. Hoorn EJ, Zietse R. Hyponatremia and mortality: moving beyond associations. *Am J Kidney Dis* 2013;62:139-49.
47. Mohan S, Gu S, Parikh A, Radhakrishnan J. Prevalence of hyponatremia and association with mortality: results from NHANES. *Am J Med* 2013;126(12):1127.e1-1137.e1.
48. Gankam-Kengne F, Ayers C, Khera A, de Lemos J, Maalouf NM. Mild hyponatremia is associated with an increased risk of death in an ambulatory setting. *Kidney Int* 2013;83:700-6.
49. Corona G, Giuliani C, Parenti G, et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. *PLoS One* 2013;8(12):e80451.
50. Amin A, Deitelzweig S, Christian R, et al. Evaluation of incremental health-care resource burden and readmission rates associated with hospitalized hyponatremic patients in the US. *J Hosp Med* 2012;7:634-9.
51. Shafie MA, Bohn D, Hoorn EJ, Halperin ML. How to select optimal maintenance intravenous fluid therapy. *QJM* 2003;96:601-10.
52. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957;19:823-32.
53. Talbot NB, Crawford JD, Butler AM. Homeostatic limits to safe parenteral fluid therapy. *N Engl J Med* 1953;248:1100-8.
54. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics* 2003;111:227-30.
55. Powell-Tuck J, Gosling P, Lobo DN, et al. British consensus guidelines on intravenous fluid therapy for adult surgical patients. Redditch, United Kingdom: BAPEN, 2011 (http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf).
56. Mythen MG, Swart M, Acheson N, et al. Perioperative fluid management: consensus statement from the enhanced recovery partnership. *Perioper Med (Lond)* 2012;1:2.
57. Drysdale SB, Coulson T, Cronin N, et al. The impact of the National Patient Safety Agency intravenous fluid alert on iatrogenic hyponatraemia in children. *Eur J Pediatr* 2010;169:813-7.
58. Hatherill M. Rubbing salt in the wound. *Arch Dis Child* 2004;89:414-8.
59. Taylor D, Durward A. Pouring salt on troubled waters. *Arch Dis Child* 2004;89:411-4.
60. Holliday MA, Ray PE, Friedman AL. Fluid therapy for children: facts, fashions and questions. *Arch Dis Child* 2007;92:546-50.
61. Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr* 2014;165(1):163.e2-169.e2.
62. McNab S, Duke T, South M, et al. 140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial. *Lancet* 2015;385:1190-7.
63. McNab S, Ware RS, Neville KA, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. *Cochrane Database Syst Rev* 2014;12:CD009457.
64. Friedman JN, Beck CE, DeGroot J, Geary DF, Sklansky DJ, Freedman SB. Comparison of isotonic and hypotonic intravenous maintenance fluids: a randomized clinical trial. *JAMA Pediatr* 2015;169:445-51.
65. Shamim A, Afzal K, Ali SM. Safety and efficacy of isotonic (0.9%) vs. hypotonic (0.18%) saline as maintenance intravenous fluids in children: a randomized controlled trial. *Indian Pediatr* 2014;51:969-74.
66. Bomberger RA, McGregor B, DePalma RG. Optimal fluid management after aortic reconstruction: a prospective study of two crystalloid solutions. *J Vasc Surg* 1986;4:164-7.
67. Saba TG, Fairbairn J, Houghton F, Laforce D, Foster BJ. A randomized controlled trial of isotonic versus hypotonic maintenance intravenous fluids in hospitalized children. *BMC Pediatr* 2011;11:82.
68. Coulthard MG, Cheater LS, Long DA. Perioperative fluid therapy in children. *Br J Anaesth* 2007;98:146-7.
69. Kannan L, Lodha R, Vivekanandhan S, Bagga A, Kabra SK, Kabra M. Intravenous fluid regimen and hyponatraemia among children: a randomized controlled trial. *Pediatr Nephrol* 2010;25:2303-9.
70. Neville KA, Sandeman DJ, Rubinstein A, Henry GM, McGlynn M, Walker JL. Prevention of hyponatremia during maintenance intravenous fluid administration: a prospective randomized study of fluid type versus fluid rate. *J Pediatr* 2010;156(2):313.e2-319.e2.
71. Yung M, Keeley S. Randomised controlled trial of intravenous maintenance fluids. *J Paediatr Child Health* 2009;45:9-14.
72. Musch W, Decaux G. Treating the syndrome of inappropriate ADH secretion with isotonic saline. *QJM* 1998;91:749-53.
73. Moritz ML. Urine sodium composition in ambulatory healthy children: hypotonic or isotonic? *Pediatr Nephrol* 2008;23:955-7.
74. Lobo DN, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury? con. *Kidney Int* 2014;86:1096-105.
75. Moro N, Katayama Y, Igarashi T, Mori T, Kawamata T, Kojima J. Hyponatremia in patients with traumatic brain injury: incidence, mechanism, and response to sodium supplementation or retention therapy with hydrocortisone. *Surg Neurol* 2007;68:387-93.
76. Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. *N Engl J Med* 1988;319:1127-34.
77. Issa VS, Andrade L, Ayub-Ferreira SM, et al. Hypertonic saline solution for prevention of renal dysfunction in patients with decompensated heart failure. *Int J Cardiol* 2013;167:34-40.

Copyright © 2015 Massachusetts Medical Society.