Statement of the 3rd International Exercise-Associated Hyponatremia Consensus Development Conference, Carlsbad, California, 2015

Tamara Hew-Butler,[1] Mitchell H Rosner,[2] Sandra Fowkes-Godek,[3] Jonathan P Dugas,[4] Martin D Hoffman,[5] Douglas P Lewis,[6] Ronald J Maughan,[7] Kevin C Miller,[8] Scott J Montain,[9] Nancy J Rehrer,[10] William O Roberts,[11] Ian R Rogers,[12] Arthur J Siegel,[13] Kristin J Stuempfle,[14] James M Winger,[15] Joseph G Verbalis[16]

For numbered affiliations see end of article.

Correspondence to
Dr Tamara Hew-Butler, DPM, PhD, School of Health Science, Oakland University, Rochester, MI 48309-4482, USA; hew@oakland.edu

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INTRODUCTION

The 3rd International Exercise-Associated Hyponatremia (EAH) Consensus Development Conference convened in Carlsbad, California, in February 2015, with a panel of 17 international experts. The delegates represented four countries and nine medical and scientific subspecialties pertaining to athletic training, exercise physiology, sports medicine, water/sodium metabolism and body fluid homoeostasis. The primary goal of the panel was to review the existing data on EAH and update the 2008 Consensus Statement.[1] This document serves to replace the 2nd International EAH Consensus Development Conference Statement and launch an educational campaign designed to address *the morbidity and mortality associated with a preventable and treatable fluid imbalance*.

The following statement is a summary of the data synthesised by the 2015 EAH Consensus Panel and represents an evolution of the most current knowledge on EAH. This document will summarise the most current information on the prevalence, aetiology, diagnosis, treatment and prevention of EAH for medical personnel, athletes, athletic trainers and the greater public. The EAH Consensus Panel strove to clearly articulate what we agreed on, did not agree on and did not know, including minority viewpoints that were supported by clinical experience and experimental data. Further updates will be necessary to: (1) remain current with our understanding and (2) critically assess the effectiveness of our present recommendations. Suggestions for future research and educational strategies to reduce the incidence and prevalence of EAH are provided at the end of the document; areas of controversy that remain in this topic have also been outlined.

CONSENSUS METHODOLOGY

The 3rd International EAH Consensus Development Conference utilised National Institutes of Health guidelines, amended for a more holistic approach to fit the needs of both the group and the topic. Twenty-two individuals (17 accepted) were invited to participate in the consensus conference who: (1) have made scientific and/or clinical contributions to the topic of water and sodium homoeostasis, and/or hyponatraemia; and (2) represented a specific group (eg, nephrology, endurance medicine, etc) or had unique topical expertise (eg, cystic fibrosis (CF), muscle cramps, fluid balance, etc). The present document is intended to serve as the scientific record of the conference with intent to widely disseminate this information to achieve maximum impact on both current healthcare practice and future medical research.

The methodology governing the conduct of this consensus development conference is summarised below.

- A broad-based expert panel was assembled. Panel members included researchers and clinicians in endocrinology (JGV), nephrology (MHR), emergency medicine (IRR), family medicine (WOR, JMW and DPL), internal medicine (AJS), physical medicine and rehabilitation (MDH), sports medicine (WOR, JMW and DPL), athletic training (SF-G and KCM) and exercise physiology (JPD, SF-G, TH-B, MDH, RJM, SJM, NJR and KJS).
- These experts presented data on EAH in a day long public session, followed by open question/answer and discussion periods with the audience. The panel members met the following day in a closed session to prepare the consensus statement.
- Workgroups were created 3 months prior to the February 2015 meeting to update the following EAH target areas: epidemiology, aetiology and pathophysiology, diagnosis, treatment and prevention. Each workgroup was asked to present updated drafts for discussion during the closed session.
- A systematic, comprehensive and updated literature review was shared by the panel members prior to the February 2015 meeting, using a cloud storage service that was organised into workgroup categories (epidemiology, aetiology and pathophysiology, diagnosis, treatment and prevention). All panel members had unlimited access to the cloud storage service and could add digital versions of published manuscripts to the EAH manuscript section at any time.

The panel chairperson (MHR) was responsible for monitoring the progress of each work group, directing the closed session and guiding the panel's deliberations. Using the previous two EAH consensus statements as a starting point, each work group was asked to: (1) incorporate new data into each assigned section and (2) update any outdated information. All recommendations were graded based on clinical strength, using the grading scale described by the American College of Chest Physicians (table 1).[2] Particular emphasis was placed on

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Table 1 American College of Chest Physicians classification scheme for grading evidence and recommendations used in this statement[2]

Grade	Description	Benefits versus risks and burdens	Methodological quality of supporting evidence
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs with important limitations or exceptionally strong evidence from observational studies
1C	Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	Observational studies or case series
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations or exceptionally strong evidence from observational studies
2C	Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced	Observational studies or case series

RCT, randomised controlled trial.

creating more generalised recommendations so as to prevent and treat EAH across a wider variety of athletic events, rather than the endurance sports focus of the two prior EAH Consensus Statements.

SPONSORSHIP

The travel (except RJM and IRR, who supported their own travel), hotel and meal expenses for the participants were funded by CrossFit, Inc. The open conference was also sponsored by CrossFit, Inc. However, no members from CrossFit, Inc, participated in any of the closed discussions or contributed to the development of the consensus guidelines. Furthermore, no members from CrossFit, Inc, had access to the consensus document prior to publication.

RESULTS AND DISCUSSION

Definition

EAH is used to describe hyponatraemia occurring during or up to 24 h after physical activity. It is defined by a serum, plasma or blood sodium concentration ($[Na^+]$) below the normal reference range of the laboratory performing the test. For most laboratories, this is a $[Na^+]$ less than 135 mmol/L.[1] The main determinants of the serum $[Na^+]$ are the total content of exchangeable body sodium and potassium relative to total body water and thus hyponatraemia can result from loss of solutes (sodium, potassium), a relative excess of total body water or a combination of both.[3 4] However, in most clinical scenarios, the driving force for the development of hyponatraemia is a relative excess of total body water.[5 6] The symptoms associated with EAH depend on both the magnitude of the serum sodium decrease from baseline level along with the rate at which this decrease occurs. Symptomatic EAH can occur if the rate of fall approaches 7–10% within 24 h.[7] Thus, more severe degrees of hyponatraemia (typically <125 mmol/L) as well as more modest serum sodium values (in the range 125–130 mmol/L), that develop over a short period of time, can both be associated with signs and symptoms.[8]

Epidemiology

The vast majority of recreationally active individuals begin endurance races with a blood $[Na^+]$ above 135 mmol/L. Based on data pooled from 27 separate studies, encompassing 2262 participants with a verifiable pre-race blood $[Na^+]$ measurement, only 0.8% (19/2262) presented with hyponatraemia prior to race start.[9–35] These pooled data represent blood $[Na^+]$ measurements collected in seven countries and between 5 min to 72 h precompetition. This 0.8% also includes 16 questionable below-normal $[Na^+]$ values possibly confounded by fingerstick haemolysis[29] and/or outdated techniques.[25] Thus, baseline (pre-event) hyponatraemia in recreational exercisers appears to fall within the expected range for a normal population distribution (1–2%), and at a frequency well below what has been observed in individuals presenting for non-hyponatraemia-related clinical treatment situations[36] or in hospitalised patients.[37] We thereby believe that EAH largely develops *during* or immediately following exercise.

EAH can present in two forms: asymptomatic or symptomatic. Asymptomatic athletes with $[Na^+]$ <135 mmol/L have largely been detected by blood samples taken post-exercise from athletes participating in research protocols or obtained for reasons other than suspicion of EAH. Athletes with the symptomatic form of EAH can present with mild, non-specific symptoms (eg, lightheadedness, nausea) but typically present with headache, vomiting and/or altered mental status (eg, confusion, seizure) resulting from cerebral oedema (termed EAH encephalopathy or EAHE) that may[38–48] or may not[49–52] be associated with non-cardiogenic pulmonary oedema. EAHE is a life-threatening condition that has been observed across a wide variety of activities (box 1). The incidence of asymptomatic and symptomatic cases of EAH varies widely with regard to type and duration of activity, location of the event, characteristics of the participants (see risk factors) and heat or cold stress during the event.

Box 1 Activities in which symptomatic exercise-associated hyponatraemia (EAH) has been reported. Those activities in which known deaths have occurred are noted with an asterisk (*)

Documentation of symptomatic EAH

- Endurance competitions (*marathon*, canoe race*, ultramarathon, triathlon, swimming*)
- Hiking*
- Military exercises*
- Police training*
- American rules football*
- Fraternity hazing*
- Bikram Yoga
- Lawn bowling

Epidemiology of asymptomatic EAH

The reported incidence of asymptomatic EAH has ranged from 0%[30 53] to 51%[54] immediately post-race. In a study of an ultramarathon, 67% of the participants were hyponatraemic (asymptomatic) at some point during the race, but only 27% finished the race with serum [Na^+] <135 mmol/L (40% self-corrected prior to finishing the event).[11] The highest reported incidence of asymptomatic hyponatraemia post-race has been consistently noted in 161 km ultramarathons, in which the reported incidence of EAH has ranged between 5% and 51%.[18 54–56] The incidence of asymptomatic EAH in Ironman triathlons in different environments has been reported to range from negligible,[10] to as high as 18%[57] and 25%.[19] In studies on endurance cyclists, the incidence of asymptomatic EAH has ranged from 0% in a 720 km race,[30] to 12% in a 109 km race.[15] In a 26.4 km swim, 17% of swimmers developed asymptomatic hyponatraemia.[32] The reported incidences at the standard marathon distance run (42.2 km) have ranged from 0%[53] to 12–13% of race finishers.[23 58] Additionally, asymptomatic hyponatraemia was observed in 33% of premier league UK rugby players following an 80 min rugby competition[59] and 70% of elite rowers during a 28-day training camp.[60]

Epidemiology of symptomatic EAH

Symptomatic EAH is rare and occurs with considerably less frequency than asymptomatic EAH, but complications associated with EAH have led to at least 14 athlete-related deaths since 1981.[28 38 47 50 61–69] Symptomatic EAH generally occurs as an isolated case or in small clusters during or following endurance events, with participants reporting to the race medical facilities or to hospital emergency departments within 24 h after participation. In general, participants seek treatment for a constellation of symptoms ranging from feeling unwell to convulsions. Clusters of cases have occurred in military training exercises, marathons, Ironman triathlons and ultramarathons. The incidence of symptomatic EAH has been reported to be as high as 23%[57] and 38%[70] of athletes seeking medical care in an Ironman triathlon and an ultramarathon, respectively, but most endurance events report no cases of symptomatic EAH, especially at the marathon distance and below.

Two studies have examined large compilations of data to help define the incidence of symptomatic and asymptomatic EAH.[55 71] In the first study of 2135 athletes from eight endurance events ranging in length from 42.2 to 161 km,[71] the incidence of symptomatic EAH was 1% (compared to 6% with asymptomatic EAH) among study participants. In the second study of 669 161 km ultramarathon runners,[55 72] only one case (0.1% among study participants) of symptomatic EAH presented during the 5-year sampling period (compared to 13% with asymptomatic EAH), but considering the total number of race participants over this time period, the actual incidence of symptomatic EAH was approximately 0.06%.

Symptomatic EAH has also been reported in hikers[73–75] and military personnel.[75–77] Symptomatic EAH accounted for 16% of Grand Canyon hikers seeking medical care for exercise-associated collapse or exhaustion from 31 May to 31 September 1993, providing an estimated incidence rate between 2 and 4 per 100 000 persons.[73 78] Furthermore, suspected hyponatraemia was found to account for 19% of non-fatal suspected heat-related incidents in the Grand Canyon National Park from April to September during 2004 to 2009 hiking seasons.[74] In the US active duty military, the annual incidence rate of hyponatraemia from 1999 to 2012 has ranged from approximately 4 to 13 cases per 100 000 person-years (averaged 6.7 cases per 100 000 person-years).[77] However, this incidence is probably inflated, as the data were derived from a medical-coded database that does not have a specific designation for EAH and likely includes hyponatraemia from exercise-related as well as non-exercise-related conditions.

Alarmingly, symptomatic EAH is now being reported in a more diverse set of sporting activities. For instance, symptomatic EAH has been reported in shorter distance endurance competitions, such as a half marathon[79] with slower finishers completing the distance in 2–3 h and a sprint triathlon with slower finishers taking approximately 2 h to complete.[80] In addition, EAH has been reported in US professional and college American rules football players,[40 41] and has led to the deaths of three US high school football players between 2008 and 2014.[63 64 69] Symptomatic hyponatraemia has also been reported in a 48-year-old lawn bowler who was heterozygous for the Delta F508 CF mutation, although it is unclear if complete genetic analysis for all possible CF mutations was performed,[81] as well as in a 34-year-old woman following a Bikram Yoga session[82] and in a 39-year-old woman following a 2 h workout including tennis and weightlifting.[83] Cases of symptomatic EAH have also been induced in two separate laboratory studies involving low-intensity exercise conducted in high ambient temperatures.[84 85] Deaths from symptomatic EAH have occurred in a 25-year-old male police officer participating in a 19 km bicycle training ride[68] and at least partially contributed to a case of fraternity hazing involving a male pledge performing callisthenics.[67] It is likely that other cases of symptomatic hyponatraemia have either not been recognised or not been reported.

Risk factors

The major risk factors for developing EAH are listed in box 2. The single most important risk factor is sustained, excessive fluid (water, sports drinks or other hypotonic fluids) intake in volumes greater than loss through sweat, respiratory and renal water excretion so that a positive fluid balance accrues over time.[86 87] Almost all cases of symptomatic EAH have occurred in individuals who have gained or maintained weight during activities in which some weight loss would represent fluid balance and euhydration.[71 72] Body weight losses of <0.75 kg after a standard marathon[35] and <1% after an 80 min rugby match[59] have been associated with asymptomatic EAH. All sports beverages are hypotonic to plasma (typical sodium content in sports drinks are approximately 10–38 mmol/L[88]); thus the magnitude of excessive fluid volume ingestion will overwhelm any protective effect of the beverages' sodium content on maintaining serum [Na^+].[89 90]

Box 2 Risk factors for the development of asymptomatic and symptomatic exercise-associated hyponatraemia (EAH)[1]

Risk factors for EAH
- Overdrinking water, sports drinks and other hypotonic beverages
- Weight gain during exercise
- Exercise duration >4 h
- Event inexperience or inadequate training
- Slow running or performance pace
- High or low body mass index
- Readily available fluids

From a practical standpoint, it is the smaller individuals and those who participate at a slower pace and drink more than sweat losses who are more likely to develop EAH. Although the incidence of women experiencing EAH is greater than that of men,[38 58 61] adjusted for body mass index and racing time, the apparent sex difference is not statistically significant.[58]

Non-steroidal anti-inflammatory drugs (NSAIDs) have been implicated as a risk factor in the development of EAH,[38 91 92] presumably by potentiating the water retention effects of arginine vasopressin (AVP) at the level of the kidney collecting duct.[93 94] However, data are conflicting,[26 58 61] and further investigation is necessary to determine whether NSAID usage—with respect to both classification and dosage—is a risk factor for the development of EAH. The possible pathophysiological contributions of intrinsic renal disease[95] and low solute diets[96–98] on water retention, high sweat sodium concentrations[99] in extreme environments and the potentiation of thirst by non-osmotic stimuli during exercise[72 100–103] warrant further investigation as secondary risk factors for EAH. Whether common medications that are associated with hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the general population, such as selective serotonin reuptake inhibitors, can potentiate the development of EAH is not known and warrants further investigation.[104]

There is a paucity of evidence suggesting that those developing symptomatic EAH have either been a 'salty sweater'[99 105] or a heterozygous carrier of the CF genotype.[106] Athletes with homozygous CF, however, are at risk for developing hyponatraemia, as demonstrated by numerous instances when an individual is diagnosed with CF after the development of hyponatraemia during prolonged physical exertion[105 107] or prolonged exposure to high ambient temperatures.[108–110] As individuals with CF experience a longer lifespan (median predicted survival age in 2012 was 41.1 years[111]) and are encouraged to consider exercise as one of their therapies,[112] this population may be at increased risk for EAH due to the combination of high sweat fluid and sweat [Na^+] loss.

Aetiology and pathophysiology of EAH

The predominant pathophysiology of EAH, and of most serious medical concern, is dilutional hyponatraemia caused by sustained overdrinking and AVP induced impaired water clearance, which overwhelms the ability of the kidney to excrete the excess water load. Dilutional hyponatraemia is the primary pathophysiological variant of clinically symptomatic EAH and largely (if not exclusively) associated with all reported cases of morbidity and mortality listed in box 1. Dilutional EAH is an acute onset form of hyponatraemia, which is now occurring in non-endurance sports, with three deaths recently reported among the approximately 7.5 million American high school football player-years from 2008 through the 2014 seasons.[63 64 69] These football players were encouraged to ingest copious volumes of hypotonic fluids and sports drinks to prevent or relieve exercise-associated muscle cramps (EAMC),[63 64 69] in the belief that EAMC was caused by dehydration and electrolyte imbalance.[113] However, experimental[114 115] and observational[116 117] studies speculate that EAMC may reflect neurological changes due to fatigue rather than uncompensated water and sodium losses incurred during exercise in some cases. Muscle cramping and tremor have also been associated with overdrinking and hyponatraemia in athletes,[82 100 118 119] clinical populations[120] and animals.[121]

Symptoms associated with EAH are due to osmotically induced shifts of water into the intracellular compartment. In the confined space of the cranium, these shifts of water into the central nervous system (CNS) tissues lead to cellular oedema and pathological increases in intracranial pressure. Acutely, this may manifest in symptoms previously described, and in the extreme, may lead to brain stem herniation and death.

Aetiology of euvolaemic/hypervolaemic EAH

Total body water expansion relative to the amount of total body exchangeable sodium is the main pathogenic cause of asymptomatic and symptomatic EAH.[34 41 45 52 57 58 61 71 73 75 76 84 119 122–126] Dilutional EAH can be euvolaemic (total body water expansion without changes in total exchangeable sodium) or hypervolaemic (total body water expansion above concomitant increases in total exchangeable sodium). The primary aetiological factor in dilutional hyponatraemia is consumption of fluids (water, sports drinks or other hypotonic fluids) in excess of total body fluid losses, which includes the sum of insensible (cutaneous, respiratory and gastrointestinal),[127 128] sweat and renal (urine) fluid losses.[34 45 52 57 58 61 73 75 76 84 119 122–125]

Hyponatraemia caused solely by the overconsumption of fluids, above known maximal urine excretory rates of 800–1000 mL,[129] has been demonstrated at rest in athletes with and without a history of EAH.[34 86 87] Although some cases of EAH may be due to pure water intoxication from overconsumption of fluids, non-osmotic AVP secretion is a key contributing factor in most athlete-related symptomatic cases.[5 19] Known stimuli to AVP secretion that are commonly associated with exercise include: nausea/vomiting;[130] interleukin 6 release;[11] plasma volume contraction;[13] hypoglycaemia;[131] elevated body temperature;[132] and/or other hormonal mediators.[16] Even small increases in circulating AVP levels can markedly reduce renal water excretion well below maximal levels,[133] resulting in retained body water not only when drinking rates do not exceed those necessary to prevent excessive dehydration, but also when drinking rates are well in excess of fluid replacement need.[49 134]

Summary statement: The primary aetiology and pathophysiological mechanism underlying EAH—and all known fatalities—is the overconsumption of hypotonic fluids relative to exchangeable sodium likely in combination with non-osmotic AVP secretion (Grade 1A).

Aetiology of hypovolaemic EAH

There is persisting debate as to the relative contribution of under-replaced sodium losses to the lowered sodium concentrations observed in EAH. While in clinical medicine, electrolyte depletion without expansion of total body water or hypovolaemic hyponatraemia is well described,[5 6 135–138] in EAH this variant has been more difficult to define and is much less likely to be encountered except in extreme events usually over prolonged periods (such as ultramarathons),[139] or hot Ironman distance triathlons.[19 20] The data regarding sodium losses during exercise (as measured during recovery) and their potential contribution to the development of symptomatic hyponatraemia in longer and hotter races,[139] have been consolidated in table 2 against data collected from relatively shorter and cooler races[123 140 141] where fluid overload hyponatraemia has been verified. From the standpoint of the clinical literature, hypovolaemic hyponatraemia reflects a loss of total body exchangeable sodium that manifests as volume depletion.[5 6 135 142 143] Hypovolaemic EAH would be predicted[89] to occur in athletes exercising for longer periods of time (such as 161 km ultramarathons; >20 h),[11 54 55 56] and/or in hotter[11 19 20 55 108 109] environments, and/or with higher sweat sodium losses.[99 101] Clinical confirmation of the hypovolaemic form of hyponatraemia is supported by a spot urine sodium concentration (U[Na^+])

Table 2 Comparisons of sodium and fluid balance measured during the recovery period after exercise demonstrating race characteristics and biochemical differences between fluid overload hyponatraemia (Irving *et al*,[123] Speedy *et al*[141] and Speedy *et al*[140]) versus suspected hypovolaemic hyponatraemia (Owen *et al*[139])

Variable	Irving *et al* (*1991*)	Speedy *et al* (*2000*)	Speedy *et al* (*2000: 2 cases*)	Owen *et al* (*2014*)
Number of EAH participants (classification)	8 (symptomatic)	7 (symptomatic)	2 (asymptomatic)	26 (asymptomatic)
Peak race temperature (°C)	NR	21	21	33
Mean exercise duration (h)	<11 (mean NR)	12	13/12 (case 1/case 2)	22
Monitored recovery time (h)	16	11.6	11.7/13	1
Presenting U[Na^+] (mmol/L)	NR	17* (41 controls†)	NR	15 pre-trial (22.3 post-trial)
Presenting BUN (mg/dL)	15.5 pretrial (9.8 post-trial)	NR	NR	31 (pre-trial and post-trial)
Body sodium retained‡ (mean value)	48%	−84 mmol (0 mmol controls†)	34%/0%	96%
Excess fluid excreted§ (mL)	+2953	+1670 (−441 controls†)	+1500/+2500	+20
Presenting serum [Na^+] (mean±SD) (mmol/L)	122±2	127±4	131/130	131±3
Body weight change (post-race—pre-race) (%)	NR	NR	+0.9/+2.5	−2.4±3.1

*All but one of these seven athletes with EAH were released from the hospital with hyponatraemia.
†EAH data compared with control group of normonatraemic triathletes partaking in the same event.
‡This represents the total amount of sodium retained by the body and expressed as a percentage of the total amount of sodium that was administered during the monitored recovery period (sodium deficit/sodium given). In Speedy *et al*,[141] this was expressed as a positive or negative amount (mmol) of sodium administered so that a negative value reflected the amount of sodium retained by the body (U[Na^+] output minus Na^+ input).
§This represents the amount of fluid excreted (urine volume) during the recovery period compared with the amount of fluid that was administered during the recovery period.
BUN, blood urea nitrogen; EAH, exercise-associated hyponatraemia; NR, not reported in the manuscript.

below 30 mmol/L[136 137 144] in conjunction with a serum or plasma [Na^+] below 135 mmol/L. A spot U[Na^+] <30 mmol/L is 100% specific and 80% sensitive for predicting a sustained increase (>5 mmol/L) in serum [Na^+] following isotonic saline administration[136] in clinical patients. Elevated blood urea nitrogen levels (>20 mg/dL)[136 139] and weight loss[19 20 55] may also suggest volume depletion as a pathogenic contributor to EAH. However, these biochemical tests are not always available at the point of care and thus clinical assessment (vital signs, weight change and physical examination) may be the only indication of volume depletion.

Summary statement: Under-replaced sodium losses contribute to serum [Na^+] independent of distance (Grade 1A). However, there is a paucity of data supporting sodium loss as the primary mechanism of symptomatic EAH even in those who exercise for prolonged periods of time and in warm weather (Grade 2C). In these cases, relative overdrinking of hypotonic fluids with sustained non-osmotic AVP secretion is likely involved in the development of symptomatic EAH.

The role of thirst

Since drinking fluid volume above sweat and urinary losses during and after activity is the main pathophysiological mechanism underlying asymptomatic, symptomatic and fatal cases of EAH, prevention is dependent on drinking less. Thirst should provide adequate stimulus for preventing excess dehydration and markedly reduce the risk of developing EAH in all sports. Physiologically driven thirst has been defined as a "generalised, deep-seated feeling of desire for water,"[145] and is an evolutionarily conserved, finely tuned regulatory mechanism serving to protect both plasma osmolality and circulating plasma volume.[146] Osmoreceptors (highly vascularised structures located around the third and fourth ventricles, and characterised by the lack of a blood–brain barrier; they are points of communication between the blood, the brain parenchyma and the cerebral spinal fluid) located within the circumventricular organs of the brain and baroreceptors located within the aortic arch, carotid sinus and great veins provide 'real-time' neural input to higher centres of the brain, which continuously and simultaneously coordinate the regulation of both thirst and AVP secretion. Thus, there are physiological sensing mechanisms in place to prompt when to drink and therefore guard against excessive dehydration. Earlier published recommendations to begin drinking before thirst were largely meant for situations where sweating rates were high, above maximal rates of gastric emptying, and dehydration would rapidly accrue over time. Unfortunately, this advice has fostered the misconception that thirst is a poor guide to fluid replacement, and has facilitated inadvertent overdrinking and pathological dilutional EAH.

Clinical classification and diagnosis of EAH

The diagnosis of EAH is made when the blood, serum or plasma [Na^+] is below the normal reference range of the laboratory performing the test (typically <135 mmol/L), and is associated with a typical clinical constellation of symptoms and signs. In our collective experience, EAH is best classified by clinical severity (symptoms) and not the absolute numerical [Na^+] value to best guide treatment strategies.

Characteristics of asymptomatic EAH

Asymptomatic EAH represents a biochemical finding, diagnosed by blood electrolyte testing for research or unrelated metabolic screening purposes.[10 15 18 19 28 30 32 53–59] This group of participants presents without any discernable symptoms, or may have mild, generalised and transient symptoms commonly experienced by other participants who do not typically seek medical care following exercise. In normally distributed populations, up to 5% of all athletes tested would fall outside of the normal range for [Na^+], with half of those (2.5%) falling in the range of asymptomatic EAH values.

Characteristics of mild EAH

Mildly symptomatic EAH typically presents with non-specific signs and symptoms *without* clear signs of encephalopathy (box 3). Athletes with mild EAH may have normal vital signs and may not have any orthostatic hypotension; also, the symptoms do not resolve after placing athletes in the Trendelenburg position,[147] as would be expected with exercise-associated postural hypotension.[148] The clinical symptoms of mild symptomatic EAH are not specific or sensitive, but should raise the index of suspicion for EAH and necessitate a low threshold for [Na^+]

Box 3 Signs and symptoms of mild and severe (life-threatening) exercise-associated hyponatraemia (EAH). Signs and symptoms related to other conditions associated with exercise-associated collapse noted with an asterisk (*)

Symptoms and signs associated with mild EAH
- Lightheadedness*
- Dizziness*
- Nausea*
- Puffiness
- Body weight gain from baseline

Symptoms and signs associated with severe EAH and EAH encephalopathy (EAHE)
- Vomiting*
- Headache*
- Altered mental status* (*confusion, disorientation, agitation, delirium, feelings of "impending doom", obtundation*)
- Phantom running
- Seizure*
- Coma*
- Signs of impending brain herniation (*decorticate posturing, mydriasis*)
- Dyspnoea (*non-cardiogenic pulmonary oedema*)
- Frothy sputum (*non-cardiogenic pulmonary oedema*)

measurement, as athletes can rapidly progress from mild symptoms to severe and life-threatening EAHE (box 3).

EAH must be differentiated from other causes of collapse that may present with similar signs and symptoms including exertional heat illness,[73] acute mountain sickness,[39] hypernatraemia[149 150] and exercise-associated postural hypotension.[148] It is important for medical staff to perform a rapid history and physical examination to help determine the aetiology of these non-specific symptoms. However, any clinical suspicion of EAH should lead to prompt measurement of [Na^+], if possible. It is common for athletes with EAH to maintain or gain weight during exercise.[58 71 72] However, EAH in the presence of weight loss has been documented in ultraendurance races in the heat.[19 20 55 59] Thus, the presence of weight loss does not necessarily exclude EAH. Weight gain or weight maintenance associated with any symptoms listed in box 3 is an indication to measure the athlete's [Na^+] in order to confirm or exclude the diagnosis of EAH or to consider empiric treatment if on-site [Na^+] cannot be measured, such as in remote settings.[72 118 151]

Characteristics of severe EAH (EAHE)

Severe symptomatic EAH is characterised by neurological signs and symptoms due to cerebral oedema that occur when water flows along the osmotic gradient from the extracellular fluid into the intracellular compartment (box 2).[38–52 152] Severe symptomatic EAH may[38–48] or may not[49–52] be accompanied by the respiratory distress of CNS-triggered non-cardiogenic pulmonary oedema (box 3). EAHE is a life-threatening condition that requires urgent intervention and should be evaluated with an immediate [Na^+] measurement if available.

Summary statement: EAH can present with a wide range of symptoms ranging from non-specific mild symptoms to severe encephalopathy. The severity of symptoms and not the absolute value of the [Na^+] should guide the choice of therapy (Grade 1A). Rapid determination of [Na^+] is critical in confirming clinical suspicion but may not always be available.

Treatment of EAH

Any athlete exhibiting signs or symptoms consistent with acute hyponatraemia (box 3) should be screened for EAH. The capacity for onsite [Na^+] analysis is optimal for management of EAH and is recommended for any large-scale endurance event. However, this capability is not always practical or possible (eg, small or remote events).[118 151] Treatment should be based on the degree of neurological impairment, not simply the [Na^+] level;[5 6] as brain oedema is dependent on both the magnitude and rate of fall of [Na^+], not just the lowest level reached, as stated previously. The following treatment protocols are recommended for EAH and EAHE based either on [Na^+] measurement and clinic assessment or clinical assessment alone if [Na^+] measurement is not available.

Onsite treatment of asymptomatic EAH found via [Na^+] measurement

Asymptomatic hyponatraemia is not normally detected unless an athlete has blood electrolyte concentrations tested for some other reason.[10 15 18 19 28 30 32 53–59] In athletes with this incidental biochemical diagnosis, oral or intravenous hypotonic fluid intake should be restricted until the onset of urination (which suggest that AVP levels have fallen and that the urine is likely dilute) to reduce the risk of further decreasing [Na^+] with continued AVP-mediated water retention.[5 6 120] Furthermore, isotonic intravenous fluids should be administered with great caution or withheld until urination as, in the setting of elevated AVP levels and concentrated urine, these fluids may lower the [Na^+][153] or delay recovery.[91 151 154]

Although there is no compelling reason to actively treat asymptomatic EAH, it is clinically appropriate to administer oral hypertonic saline (HTS) solutions to reduce the risk of progression to symptomatic hyponatraemia;[139 155] this is particularly relevant for those with a [Na^+] <130 mmol/L. On departure from the event site, athletes with asymptomatic EAH should be advised to seek urgent medical attention if any neurological signs or symptoms of EAH develop within 24 h after event completion, since delayed-onset symptomatic EAH may frequently occur.[40 42 46 52 72 80 82 91 100 122 156] Ideally, an athlete with asymptomatic EAH should have a companion on discharge from the medical area to observe the affected athlete for signs and symptoms of evolving EAH, since the neurological impairments associated with EAH may limit the athlete's ability to accurately self-assess his or her own status.

Summary statement: The major clinical relevance of asymptomatic EAH lies in its potential for asymptomatic athletes to quickly transition and progress into symptomatic stages if hypotonic fluids are given intravenously or ingested (Grade 1C). Thus, in patients identified with EAH, hypotonic or isotonic fluids should be withheld until urination is documented (Grade 1C).

Onsite treatment of symptomatic EAH found via [Na^+] measurement

Severe EAH (EAHE)

Acute severely symptomatic hyponatraemia is a rapidly progressing, life-threatening emergency that requires immediate administration of intravenous HTS (such as 3% sodium chloride).[38 42 49 51 72 82 91] Because EAH is an acute rather than chronic process, athletes presenting with symptomatic hyponatraemia can and should be treated with HTS as there is no risk of osmotic demyelination after exposure to HTS, but there is

grave risk of brain herniation and non-cardiogenic pulmonary oedema if HTS is not administered.[5 6 38 47 50 62]

Any athlete with EAH associated with signs or symptoms of encephalopathy should be immediately treated with an intravenous bolus or infusion of HTS to acutely reduce brain oedema, with additional intravenous boluses administered until there is clinical improvement[42 51 72] (box 4). The dose and route of HTS administration should be based on the severity of clinical symptoms and the available HTS formulations, as discussed in box 4. Numerous case reports and case series have validated the efficacy and safety of intravenous HTS administration in symptomatic EAH,[8 38 48 49 52 62 72 82 91 100 122 154] with one runner receiving 950 mL of 3% over a 7 h period without complications[42] and a swimmer receiving 40 mL of 20% HTS[51] without complication.

In the event that an athlete presents with symptoms of severe, life-threatening encephalopathy (eg, seizures, coma or signs of impending brain herniation), it is acceptable and highly recommended to administer the first bolus of HTS before [Na^+] is measured. Confirmed symptomatic dilutional (euvolaemic or hypervolaemic) EAH is a contraindication to the administration of intravenous hypotonic fluids, lactated Ringer's, or isotonic (normal) saline, all of which can worsen the degree of hyponatraemia[41 47 50 134] or delay recovery.[91 118 122 151 154 157]

The efficacy of intravenous HTS as the definitive treatment of acute hyponatraemic encephalopathy has been validated extensively in hospital and in field settings since it was first used successfully in 1938.[158] This treatment is based on the capacity of an intravenous HTS bolus to increase the serum [Na^+] 2–5 mmol/L, resulting in a concomitant decrease of intracranial pressure and improvement in symptoms.[5 6] This approach does not pose any substantial danger to the patient, because osmotic demyelination syndrome has not been associated with either the rapid correction of acute hyponatraemia (ie, <48 h duration) in clinical[159] or exercise settings[8 38 48 49 52 62 72 82 91 100 122 154] or with the limited increase in [Na^+] produced by a single bolus of HTS.[139 160] Also, of note, if the athlete was wrongly assumed to have EAHE, the administration of HTS in small boluses is not associated with any negative consequences and serves as an excellent volume expander.[139]

The goal of this therapy is to stabilise the athlete for transfer to an advanced medical care facility for further evaluation, monitoring and treatment. Ideally, the athlete should be transported with knowledgeable medical personnel from the event who are able to maintain the same level of care en route and to ensure that the treatment is not interrupted for evaluation such as CT of the brain or treatments that may worsen hyponatraemia, such as administration of hypotonic fluids, lactated Ringer's, or isotonic (normal) saline. The diagnosis of EAH or EAHE must be communicated to the receiving physician on transfer of care.

Summary statement: For those athletes presenting with signs and symptoms consistent with EAHE, emergent intravenous treatment therapy with HTS is indicated and should not be delayed pending laboratory measurement or other diagnostic testing (Grade 1B).

Box 4 Recommended treatment for both mild and severe (life-threatening) symptomatic exercise-associated hyponatraemia (EAH) in the field or in the hospital

Treatment of mild EAH

Observation (restrict hypotonic and isotonic fluids until urinating freely)

Administration of intravenous HTS (*see below for severe symptomatology*)

Administration of oral HTS:

- *Concentrated bouillon (4 bouillon cubes in 125 mL, ½ cup of water)*
- *3% NaCl (100 mL), preferably with the addition of a flavouring (eg, Crystal Light, Kool Aid)*
- *Equivalent volumes of other solutions of high sodium concentration (eg, 3–9%)*

Treatment of severe EAH

Administration of intravenous HTS:

- 100 mL bolus of 3% NaCl, repeated twice if there is no clinical improvement (*10 min intervals have been recommended, but this should be determined by the clinical judgement of the treating physician*)
- Comparable amounts of more concentrated Na^+-containing solutions *(eg, 10 mL of 20% NaCl; 50 mL of 8.4% $NaHCO_3$) may be used as an alternative to 3% NaCl.*
- *In some situations (ie, more severe encephalopathic symptomatology such as seizures, coma or signs of impending brain herniation), it may be appropriate to administer larger HTS boluses initially rather than waiting to assess clinical improvement after repeated smaller boluses.*

HTS represents hypertonic saline.

Mild EAH

Any athlete with mild EAH symptoms (box 4) may be treated with an intravenous bolus of HTS as described above. Alternatively, a mildly symptomatic athlete may be treated with oral hypertonic solutions when tolerated,[139 155 160] (box 4) or observation until urination, as seen in clinical settings.[6 120] Oral sodium tablets may not be as efficacious as hypertonic solutions, as suggested in a single case report,[124] and requires further investigation. The efficacy and tolerance of oral HTS has been supported by limited field studies,[139 155] and may offer practical advantages in some settings (eg, where intravenous HTS or intravenous access is not available). In contrast to athletes with severe EAH, those with mild symptoms may be discharged from onsite medical care once symptoms have resolved and spontaneous urination has occurred. Repeat measurement of [Na^+] is generally not required unless the patient has persistent symptoms after the initial treatment. As is recommended for asymptomatic EAH, on departure from the event site, athletes should be advised to seek urgent medical attention if any signs or symptoms of EAH develop after discharge, and ideally should have a companion capable of monitoring for signs and symptoms of which the athlete may not be aware.

Summary statement: Athletes presenting with mild symptoms associated with EAH can be treated with an intravenous bolus of HTS (Grade 1B), oral HTS fluids or observation until the onset of urination, as dictated by clinical symptoms (Grade 2B).

Onsite treatment of EAH suspected clinically but unable to confirm via [Na^+] measurement

The situation may arise where EAH is strongly suspected based on the clinical evaluation of the athlete (ie, history and physical examination showing neurological symptoms or signs of EAH; box 2), but where [Na^+] cannot be determined,[72]

such as in a remote setting.[39 118 151] In this situation, empiric treatment is justified using the same treatment recommendations described above for EAH documented with a [Na^+] measurement (box 4). This empiric approach can be life-saving and is

unlikely to do harm, since: (1) the additional small increase in serum osmolality from a single bolus of HTS will not significantly worsen the neurological status and (2) a bolus of HTS will expand the intravascular volume by increasing the serum [Na^+], partially reducing any hypovolaemic component of the hyponatraemia.[139]

In-hospital treatment of symptomatic EAH

Athletes presenting to a hospital or medical facility, whether primarily or as a transfer from the event site, with signs or symptoms of hyponatraemia, will require immediate measurement of electrolytes and should be treated as described above without delay once EAH is confirmed (box 4). If symptomatic EAH persists or worsens following the initial intervention with intravenous HTS, current treatment guidelines for acute symptomatic hyponatraemia should be instituted and the patient managed in an intensive or critical care setting with care provided or guided by a specialist familiar with this life-threatening condition.[5 6]

Summary statement: Athletes presenting to a medical facility with EAH should be treated as per other settings (Grade 1C). However, diagnostic testing in these scenarios should not delay potentially life-saving therapy with HTS (Grade 1C).

Prevention

Athletes and support crews need to carefully consider fluid and electrolyte supplementation during and after exercise, and the rationale behind those decisions. Excessive fluid replacement beyond thirst (whether water, sports drinks or other hypotonic fluids) is not a panacea for all instances of fatigue, collapse, muscle cramping or exertional heat stroke (table 3). The drinking of fluid volumes sufficiently above sweat and urinary losses before, during and after activity, resulting in the accrual of a positive water balance, is the primary underlying pathophysiological mechanism of symptomatic and fatal EAH cases.[34 41 45 52 57 58 61 71 73 75 76 84 119 122–126 161 162] Therefore, prevention strategies must target drinking behaviour. Fluid intake recommendations suggesting that athletes begin to drink fluids before the onset of the sensation of thirst were targeting those exercising in situations where high sweat rates were present and dehydration could evolve rapidly, with known medical and performance outcomes. Unfortunately, this advice fostered the misconception that thirst is a poor guide to fluid replacement in lower sweat rate situations. We believe that this has facilitated individuals choosing to inadvertently adopt overdrinking and develop

Table 3 Thirteen studies representing 41 cases of symptomatic EAH that provided comment on drinking plan or motivation for chosen drinking behaviours

Study (year)	Subjects, age (years old) sex (♂♀) activity	Serum [Na^+] mmol/L (initial or range)	Symptomatic EAH with drinking above thirst (comments from report)
Frizzell *et al* (1986)[122]	24♂/45♂ *Ultrarunners*	123/118	Runners as a group, are taught to "push fluids" Athletes are instructed to drink more than their thirst dictates, since thirst may be an unreliable index of fluid needs during exercise
Armstrong *et al* (1993)[84]	21♂ *Lab subject*	122	Voluntarily consumed this large volume of fluid because he believed that drinking water copiously would decrease his risk of heat illness
Herfel *et al* (1998)[41]	22♂ *Football player*	121	He was diagnosed with muscle cramps secondary to dehydration. Therefore, five liters (L) of 0.45% normal saline in 5% dextrose was administered intravenously along with 3 L of liquids by mouth over a five hour period
Reynolds *et al* (1998)[189]	6* (4♀/2♂) *Soldiers*	118–134	Consuming large volumes of water as "protection against becoming a heat casualty" predisposed these troops to the physical impairment that they intended to avoid
Backer *et al* (1999)[73]	7* (6♀/1♂) *Hikers*	109–127	Most patients diagnosed as having hyponatremia have a distinct history of high fluid intake… Unlike heat exhaustion patients, few of our hyponatremic patients were thirsty when evaluated, perhaps because they drank more fluids and were hyperhydrated
Garigan *et al* (1999)[45]	18♂ *Soldier*	121	Complained of thirst, drank 3 quarts, then vomited…told to drink 1 quart every 30 minutes With encouragement by unit members, he consumed 10 quarts of water during the next 90 minutes
Hew *et al* (2003)[61]	21* (9♀/8♂) *Marathon runners*	117–134	Advice given to runners was "drink until your urine is clear" and "do not wait until you are thirsty to drink"
Dimeff (2006)[40]	27♂ *Football player*	116	Complained of feeling ill… encouraged to consume sports drinks Admits to drinking 2–3 gallons water every day because he had been taught that "water is the best replacement fluid" and because that is what he was advised to do growing up in Texas
Hew-Butler (2007)[8]	41♂ *Ironman triathlete*	132 (*nadir*)	Subject reports he was never thirsty, but drank to "stay ahead of thirst"
Draper (2009)[49]	37♀ *Marathon runner*	117	She followed a strategy (as advised by fellow experienced marathon runners) to begin the race "well-hydrated" (drinking greater volumes than her thirst dictated) Warnings were issued over the public address system at the race start relating to ensuring a high intake of fluids was maintained
Rothwell and Rosengren (2008)[118]	43♂ *Hiker*	107	Complained of abdominal pains and leg cramps for 24 hours leading up to collapse On the evening before and day of collapse, fellow trekkers and guides encouraged him to drink large amounts of water
Coler *et al* (2012)[151]	85♂ *Hiker*	120	Subject was encouraged to…"Push fluids" above thirst
Rogers (2015)[51]	46♀ *Swimmer*	118	Her intended fluid regimen…was 200 mL of fluid every 20 minutes She reported no sensation of thirst throughout the race Although she did not feel thirsty, she was encouraged to drink by the support staff

*Case reports involving multiple subjects: total number of subjects (number of female/male subjects).
EAH, exercise-associated hyponatraemia.

pathological dilutional EAH, as demonstrated in 41 cases evaluated in table 3.

Modest to moderate levels of dehydration are tolerable and pose little risk to life in otherwise healthy individuals. Laboratory and field studies indicate that fluid deficits less than and up to a volume approximately equal to 3% of normal body mass (or ~5% total body water) can be tolerated without a reduction in endurance performance or muscular power when in cool to temperate (−10°C to 20°C) temperatures.[163] Therefore, aggressive drinking to prevent dehydration is unnecessary and carries with it greater risk of developing symptomatic EAH.

Body weight is a reasonable surrogate measure of hydration state when measured day to day after sleep,[164] and can be used to relatively accurately assess changes in hydration state accompanying upwards to 1–2 h of activity. However, it is a very imprecise measure during those athletic events where EAH is most likely to develop, that is, multiple hours of sustained activity. This is in large part due to body mass changes accompanying energy combustion[128] and unknown amounts of food consumed, bathroom stops, etc. Moreover, consolidation of four studies (786 athletes) comparing body weight changes taken at registration (1–3 days prior) and again within 60 min of race start demonstrate an average of 1% increase in body weight[9 10 12 165] from registration to race start. However, this average value conceals the fact that large gains in weight (up to at least 4% of body mass)[165 166] occur in some individuals while substantial weight losses occur in others over the last day or two before competition. This weight increase further confounds the accuracy of bodyweight as a proxy measure of body water in field events. With that said, a body mass measured after several hours of activity that is equal to or above the individuals' normal body mass, is a positive indicator for the presence of fluid overload.

The safest individualised hydration strategy before, during and immediately following exercise is to drink palatable fluids when thirsty (figure 1). Marathon runners with *hyper*natraemia report 'thirstiness' as a physiologically expected symptom,[149] while a weak but statistically significant relationship has been demonstrated between thirst ratings and plasma [Na^+] immediately following a 161 km race.[167] Studies verify that participants allowed free access to fluids during treadmill walking in the heat[168] or running 30 km under different ambient conditions[169] maintain plasma osmolality by drinking to thirst. Moreover, the cues to drink provided by osmolality and blood volume, persist in hot[101] as well as cold[170] environments. Thus, drinking to thirst will, in most cases, prevent both dilutional EAH and performance decrements due to excessive dehydration.[10] Potential exceptions to this fluid replacement strategy are thirst stimulated by confounding oral variables such as dry mouth (xerostomia),[102 171] genetic influences,[103] known discrepancies between drinking 'ad libitum' versus drinking according to the dictates of thirst,[172] excessive sodium intake and/or other non-osmotic or hypovolaemic factors that are yet to be determined, and require further investigation (table 4).[72 100]

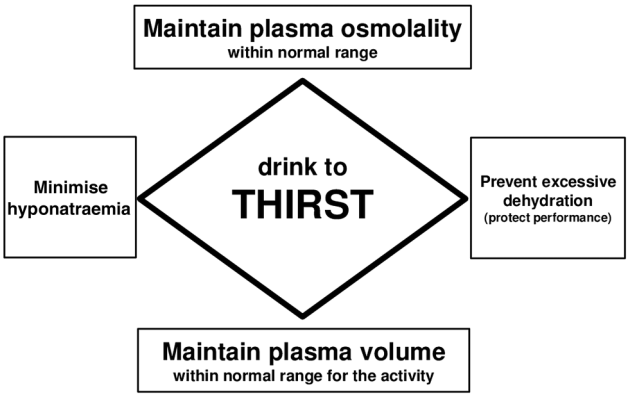

Figure 1 Primary recommended fluid intake strategy to prevent symptomatic exercise-associated hyponatraemia (EAH).

Summary statement: Given that excessive fluid consumption is a primary aetiological factor in EAH, using the innate thirst mechanism to guide fluid consumption is a strategy that should limit drinking in excess and reduce the risk of developing hyponatraemia while providing sufficient fluid to prevent excessive dehydration (Grade 1C).

Additional strategies to prevent EAH

Sodium supplementation

When fluid intake matches or even slightly exceeds sweat losses, the ingestion of sodium-containing sports drinks can attenuate the rate of fall of [Na^+] over the course of 2 h of continuous[173] or intermittent[85] cycling and approximately 4 h of running.[89 174] However, it is critical to emphasise that sodium-containing sports drinks, which are hypotonic, will not prevent EAH in athletes who overdrink during exercise, as all sports drinks have a significantly lower [Na^+] (10–38 mmol/L) than serum (~140 mmol/L). The dilutional effect of volume excess overwhelms any positive effect of sodium and electrolytes in sports drinks.[90] Therefore, while modest salt replacement is likely not harmful and has been associated with significant increases[175] or no change[14 176] in serum [Na^+] during competitive field events, it will be of modest to no benefit in situations where excess fluids are being consumed. The potential detrimental effects of excessive sodium supplementation are not clear.[72 177]

Summary statement: Sodium supplementation is a strategy for attenuating sodium concentration reductions that can develop when fluid intakes approximate sweat losses during prolonged exercise but cannot prevent EAH in the setting of a persistent excessive fluid intake that produces fluid overload (Grade 1C).

Education and event management efforts

Athlete and support team educational strategies should be instituted to improve knowledge of safe hydration practices and reduce the overemphasis on high fluid intakes. For example, an education programme for an Ironman triathlon advising athletes of the risks incurred by overdrinking, coupled with decreasing the number of fluid stations to limit the fluid availability, reduced the incidence of EAH.[178–180] Dissemination of appropriate drinking advice alone has also been shown to reduce the incidence of EAH in a 90 km footrace.[150 181]

Past studies have demonstrated that cycling fluid stations placed 20 km apart in an Ironman triathlon and running fluid stations placed 5 km apart in a standard marathon have reduced or prevented EAH.[53 179] However, this proposed strategy and its effect on the incidence of EAH needs further study to determine the optimal number and spacing of fluid stations in different terrains and ambient temperatures. Furthermore, alternative strategies will be needed in settings where EAH has been noted but aid stations are not provided, or in situations where drinks are freely available and/or athletes transport their own fluids.

Athletes who seek more quantitative guidance are encouraged to weigh themselves before and after training to assess their sweating rates and fluid replacement needs. Some weight loss associated with activity will be unrelated to fluid status, as non-water mass is lost as energy is expended (approximately

Table 4 Four case reports describing symptomatic EAH while drinking either ad libitum (two cases) or in response to thirst (two cases)

Study (year)	Subjects age (years old) sex (♂♀) activity	Plasma [Na^+] mmol/L (initial)	Symptomatic EAH with ad libitum drinking (comments from report)
Baker *et al* (2005)[85]	65♀ *Lab trial*	126	46 kg♀ drank 2.8 L water and gained 2.4 kg in 2.5 h intermittent cycling trial 30°C Subjects were not encouraged to drink but told that more fluid was readily available if needed
Hew-Butler, (2012)[134]	28♀ *cyclist*	114	Subject followed her normal practice of ingesting a GU packet with 200 mL of water every 45 min with Coke and water ad libitum for an estimated fluid consumption rate of ~550 mL/h
			Symptomatic EAH with drinking in response to thirst (comments from report)
Khodaee (2013)[100]	44♂ *Mountain biker*	116	84 kg♂ drank 29 L water and 5.3 g sodium during plus after race (~14 h total) History of muscle cramping after 5–6 h cycling. Felt "very thirsty" after the race Initial labwork in hospital: urine[Na^+]=31 mmol/L and BUN=19 mg/dL Labwork 2 months after hospitalisation: plasma [Na^+]=133 mmol/L, BUN=10 mg/dL
Hoffman (2015)[72]	53♂ *Ultrarunner*	122	Subject began using "regular sodium supplementation" and "very thirsty" at 100 km 2.2% weight gain noted at 126 km and dropped out of race at 145 km (28 h) Initial labwork in hospital: BUN=22 mg/dL 17 h later in hospital (>10.4 L 0.9% saline), plasma [Na^+]=136 mmol/L and BUN=10 mg/dL Subject received 20 L of IV fluids in hospital and discharged with positive fluid balance of 6.6 L

BUN, blood urea nitrogen; EAH, exercise-associated hyponatraemia; IV, intravenous.

0.23–0.24 g/kcal),[128 182] and is increased with increasing duration and intensity of exercise.[128] The presence of weight gain is a positive indicator that fluid intake has been in excess of fluid losses and water overload is present.

Summary statement: Educational efforts regarding the risks of overhydration should be encouraged and disseminated widely to athletes, coaches and event management personnel (Grade 1C). These efforts should include all sporting events where EAH has been encountered. Event management strategies such as limiting access to fluids may be of benefit, but require broader study.

Dissemination of advice for prevention and treatment of EAH

Athletes, coaches, parents

Educational strategies and programmes are needed that effectively communicate to coaches, athletes and parents: rational fluid replacement, avoidance of overconsuming fluids (water, sports drinks or other hypotonic fluids), to recognise the signs and symptoms of EAH, and to understand the critical need for immediate medical attention for suspected casualties. Athletes, coaches and parents must be alert to the risks of excessive fluid consumption and understand that high fluid intakes will not necessarily prevent exercise-associated maladies such as muscle cramps or exertional heat stroke.

On-site medical professionals (medics, paramedics, emergency medical technicians, athletic trainers, physiotherapists and others)

The educational strategies for on-site medical personnel must address the circumstances (during or following events or practices during acclimatisation), identification, evaluation and management of EAH and EAHE, and emphasise that the life-threatening nature of these rare conditions requires immediate intervention. The pathophysiology of EAH and the drinking behaviours involved in the evolution of EAH must be clearly recognised. It should be stressed that: (1) EAH is caused primarily by the consumption of hypotonic fluid in excess of sweat and urinary losses and (2) excessive fluid intake (water, sports drinks or other hypotonic beverages) may not prevent muscle cramps or exertional heat stroke and, in rare cases, may even be associative.[82 100 118–120 183] On-site personnel must understand that oral fluid intake, and intravenous fluid infusion of hypotonic and isotonic fluids, are contraindicated in all suspected cases of EAH and rapid transfer to a hospital is necessary. The potential life-saving role of HTS requires wide-spread education and should be considered the equivalent of automatic external defibrillators and ice/cold water immersion in the 'first aid' of sudden cardiac arrest and exertional heat stroke, respectively.

Team physicians and medical directors of athletic events

Team physicians and medical directors of athletic events should be involved in all decisions regarding medical management, including overseeing medical protocols, medical supplies/equipment, strategies for fluid replacement that optimise safe hydration practices, placement of fluid stations and the use of intravenous rehydration. Important athletic event decisions include spacing and placement of fluid stations, distribution of fluid replacement advice to athletes, and training of the aid station personnel and spectators. Drinking advice distributed to participants by sponsors should be reviewed by and approved by the event medical team to avoid conflict with the official race educational information.

Team physicians and event medical directors should ideally have onsite point of care [Na^+] analysis available and HTS on hand for management of EAH and EAHE. The event organiser/medical director should be in contact with the local emergency medical services to ensure that transportation to an advanced care medical facility is available during events with high risk for EAH (see box 1).

A record of EAH cases should be kept, including follow-up and outcome, to aid in planning for future events, and to establish both incidence and prevalence for different events.

Emergency medical services and hospitals

Prior to the race or athletic event, the medical team should establish a relationship with the local emergency response and transport teams, medical facilities and emergency department physicians. This may include specific collaborative education programmes aimed at all of these groups and pre-event checklists to ensure that the appropriate course of action is taken, and the needed supplies are available in the emergency room when an athlete arrives *in extremis*.

Summary statement: Prevention of EAH requires broad educational programmes with consistent messages that stress the

importance of appropriate hydration practices, recognition of EAH and proper therapy (Grade 1C).

Controversies in EAH

Hypovolaemic hyponatraemia

It is unclear whether the hypovolaemic variant of EAH has medical consequences. At present, we have apparent evidence of hypovolaemic hyponatraemia developing over the course of ultraendurance events, but we lack data regarding: (1) the relative contribution of solute deficits versus fluid status and (2) whether or not the hypovolaemic component is somehow compromising the afflicted individual. Most of the contributions of sweat and urinary sodium losses are negligible to the overall pathogenesis of EAH with the possible exception of volume depleted athletes with low serum sodium levels. Thermoregulatory sweat is hypotonic, with sweat sodium concentrations ranging between 10 and 70 mmol/L,[163] which are well below the normal (isotonic) range of values for serum [Na^+] (135–145 mmol/L). While there will always be some contribution of sodium loss to the pathogenesis of EAH—which will vary significantly in magnitude depending on: exercise intensity, exercise duration, body size and relative ambient temperature[184–186]—it is not clear whether or not sweat sodium losses alone can account for the changes in hypovolaemic hyponatraemia in athletes. The potential role of urinary sodium losses from exercise-induced brain natriuretic peptide secretion contributing to EAH is also unclear.[16 187]

There are three distinct groups of athletes that demonstrate extreme sodium conservation, which may increase the susceptibility towards the development of hypovolaemic hyponatraemia: (1) runners participating in 161 km races under hot conditions;[139] (2) Ironman triathletes participating in hot and humid Ironman triathlons[19 20] and (3) football players during the first week of training camp.[188] These three groups would hypothetically be at greater risk for developing the hypovolaemic variant of EAH from more vigorous and sustained sweating (and associated sweat sodium and potassium losses), coupled with an inability to eat sufficient foods to offset the sodium and potassium losses. Football players may also lack adequate adaptations to heat stress at the onset of pre-season training, which would prevent excessive sweat sodium losses with repeated exposure.

Treatment of hypovolaemic hyponatraemia: Participants with suspected hypovolaemic EAH and developing signs of encephalopathy would be best treated initially with an intravenous HTS bolus to reverse intracerebral oedema and expand the intravascular volume. The initial bolus of HTS can be followed by intravenous 0.9% saline, if neurological symptoms improve. At least one panel member has successfully treated athletes who were clinically volume depleted, with measures of [Na^+] as low as 124 mmol/L, with intravenous normal saline infusion. As in all cases of EAH, it would be harmful to treat with hypotonic intravenous solutions.

Clinical importance of asymptomatic EAH

The clinical relevance of the asymptomatic form of EAH continues to be disputed. We agree that the main clinical relevance of asymptomatic EAH lies in the *potential* for asymptomatic athletes to transition to symptomatic EAH with the continued ingestion of hypotonic fluids.[36 120] Moreover, symptomatic EAH can rapidly progress to life-threatening symptomatic hyponatraemia if large volumes of hypotonic fluids are ingested after identification of asymptomatic EAH,[82] or are administered intravenously[134] during recovery from exercise.

SUGGESTIONS FOR FUTURE RESEARCH

Prospective and controlled clinical trials should be performed both in the laboratory and in the field to best determine optimal preventative and therapeutic strategies. Some of the remaining issues for study include:

- Examining nutritional requirements and/or role of diet on the risk for EAH.
- Examining tolerance versus risk for various forms (tablets vs solution) and amounts of sodium supplementation on health, performance and natraemia status.
- Gathering evidence with regard to the success of the 'drink to thirst' strategy on prevention and/or reduction of the incidence of EAH in athletic events.
- Determining if the development of EAH increases the risk for recurrence and/or long-term health problems.
- Identifying genetic markers that may predispose individuals in developing EAH.
- Additional research is necessary to understand whether individuals consuming NSAIDs are at heightened risk of developing EAH.
- Investigating the efficacy of alternative treatments for non-life-threatening EAH, including oral hypertonic sodium solutions, sodium tablets and vasopressin receptor antagonists.
- Clarifying the aetiology behind the apparent hypovolaemic variant of EAH and the potential for pathophysiological consequences.
- Evaluating the variability in [Na^+] in the days leading up to the event, at event start and during the event.
- Evaluating the variability in body weight in the days leading up to the event and at event start.

SUMMARY OF RECOMMENDATIONS

A. Aetiology of EAH
   1. The primary aetiology and pathophysiological mechanism underlying EAH—and all known fatalities—is the overconsumption of hypotonic fluids relative to exchangeable sodium in likely combination with non-osmotic AVP secretion (Grade 1A).
   2. Under-replaced sodium losses contribute to serum [Na^+] independent of distance (Grade 1A). However, there is a paucity of data supporting sodium loss as the primary mechanism of symptomatic EAH even in those who exercise for prolonged periods of time and in warm weather (Grade 2C). In these cases, relative overdrinking of hypotonic fluids with sustained non-osmotic AVP secretion is likely involved in the development of symptomatic EAH.

B. Clinical classification and diagnosis of EAH
   1. EAH can present with a wide range of symptoms ranging from non-specific mild symptoms to severe encephalopathy. The severity of symptoms and not the absolute value of the [Na^+] should guide the choice of therapy (Grade 1A). Rapid determination of [Na^+] is critical in confirming clinical suspicion but may not always be available.

C. Treatment of EAH
   1. The major clinical relevance of asymptomatic EAH lies in its potential for asymptomatic athletes to quickly transition progression into symptomatic stages if hypotonic fluids are given intravenously or ingested (Grade 1C). Thus, in patients identified with EAH, hypotonic or isotonic fluids should be withheld until urination is documented (Grade 1C).

2. For those athletes presenting with signs and symptoms consistent with EAHE, emergent intravenous treatment therapy with HTS is indicated and should not be delayed pending laboratory measurement or other diagnostic testing (Grade 1B).
3. Athletes presenting with mild symptoms associated with EAH can be treated with an intravenous bolus of HTS (Grade 1B), oral HTS fluids or observation until the onset of urination, as dictated by clinical symptoms (Grade 2B).
4. Athletes presenting to a medical facility with EAH should be treated as per other settings (Grade 1C). However, diagnostic testing in these scenarios should not delay potentially life-saving therapy with HTS (Grade 1C).

D. Prevention of EAH
1. Given that excessive fluid consumption is a primary aetiological factor in EAH, using the innate thirst mechanism to guide fluid consumption is a strategy that should limit drinking in excess and developing hyponatraemia, while providing sufficient fluid to prevent excessive dehydration (Grade 1C).
2. Prevention of EAH requires broad educational programmes with consistent messages that stress the importance of appropriate hydration practices, recognition of EAH and proper therapy (Grade 1C).

Author affiliations
[1]Exercise Science Program, Oakland University, Rochester, Michigan, USA
[2]Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia, USA
[3]Department of Sports Medicine, West Chester University, West Chester, Pennsylvania, USA
[4]The Vitality Group, Chicago, Illinois, USA
[5]Department of Physical Medicine and Rehabilitation, VA Northern California Health Care System and University of California Davis, Sacramento, California, USA
[6]Family Medicine Residency Program, Via Christi Hospitals Wichita, Inc, Wichita, Kansas, USA
[7]Department of Sport and Exercise Nutrition, Loughborough University, Leicestershire, UK
[8]Athletic Training Program, Central Michigan University, Mount Pleasant, Michigan, USA
[9]Military Nutrition Division, United States Army Research Institute of Environmental Medicine, Natick, Massachusetts, USA
[10]School of Physical Education, Sport & Exercise Sciences, University of Otago, Dunedin, New Zealand
[11]Department of Family Medicine and Community Health, University of Minnesota, Minneapolis, Minnesota, USA
[12]Department of Emergency Medicine, St John of God Murdoch Hospital and University of Notre Dame, Perth, Western Australia, Australia
[13]Department of Internal Medicine, Harvard Medical School, Boston, Massachusetts, USA
[14]Health Sciences Department, Gettysburg College, Gettysburg, Pennsylvania, USA
[15]Department of Family Medicine, Loyola University Chicago Stritch School of Medicine, Chicago, Illinois, USA
[16]Department of Endocrinology and Metabolism, Georgetown University Medical Center, Washington DC, USA

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REFERENCES

1 Hew-Butler TD, Ayus JC, Kipps C, *et al*. Statement of the Second International Exercise-Associated Hyponatremia Consensus Development Conference, New Zealand, 2007. *Clin J Sport Med* 2008;18:111–21.
2 Guyatt G, Gutterman D, Baumann MH, *et al*. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006;129:174–81.
3 Edelman IS, Leibman J, O'Meara MP, *et al*. Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest* 1958;37:1236–56.
4 Nguyen MK, Kurtz I. Determinants of plasma water sodium concentration as reflected in the Edelman equation: role of osmotic and Gibbs-Donnan equilibrium. *Am J Physiol Renal Physiol* 2004;286:F828–37.
5 Spasovski G, Vanholder R, Allolio B, *et al*. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol* 2014;170:G1–47.
6 Verbalis JG, Goldsmith SR, Greenberg A, *et al*. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med* 2007;120:S1–21.
7 Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992;117:891–7.
8 Hew-Butler T, Anley C, Schwartz P, *et al*. The treatment of symptomatic hyponatremia with hypertonic saline in an Ironman triathlete. *Clin J Sport Med* 2007;17:68–9.
9 Tam N, Hew-Butler T, Papadopoulou E, *et al*. Fluid intake and changes in blood biochemistry, running speed and body mass during an 89 km mountain trail race. *Med Sport* 2009;13:108–15.
10 Sharwood K, Collins M, Goedecke J, *et al*. Weight changes, sodium levels, and performance in the South African Ironman triathlon. *Clin J Sport Med* 2002;12:391–9.
11 Cairns RS, Hew-Butler T. Incidence of exercise-associated hyponatremia and its association with nonosmotic stimuli of arginine vasopressin in the GNW100 s ultra-endurance marathon. *Clin J Sport Med* 2014. Published Online First. doi:10.1097/JSM.0000000000000144
12 Hew-Butler T, Collins M, Bosch A, *et al*. Maintenance of plasma volume and serum sodium concentration despite body weight loss in Ironman triathletes. *Clin J Sport Med* 2007;17:116–22.
13 Hew-Butler T, Hoffman MD, Stuempfle KJ, *et al*. Changes in copeptin and bioactive vasopressin in runners with and without hyponatremia. *Clin J Sport Med* 2011;21:211–17.
14 Hew-Butler TD, Sharwood K, Collins M, *et al*. Sodium supplementation is not required to maintain serum sodium concentrations during an Ironman triathlon. *Br J Sports Med* 2006;40:255–9.
15 Hew-Butler T, Dugas JP, Noakes TD, *et al*. Changes in plasma vasopressin concentrations in cyclists participating in a 109 km cycle race. *Br J Sports Med* 2010;44:594–8.
16 Hew-Butler T, Jordaan E, Stuempfle KJ, *et al*. Osmotic and non-osmotic regulation of arginine vasopressin during prolonged endurance exercise. *J Clin Endocrinol Metab* 2008;93:2072–8.
17 Stuempfle KJ, Lehmann DR, Case HS, *et al*. Change in serum sodium concentration during a cold weather ultradistance race. *Clin J Sport Med* 2003;13:171–5.
18 Stuempfle KJ, Lehmann DR, Case HS, *et al*. Hyponatremia in a cold weather ultraendurance race. *Alaska Med* 2002;4:51–5.
19 Hiller DB, O'Toole ML, Fortress EE, *et al*. Medical and physiological considerations in triathlons. *Am J Sports Med* 1987;15:164–8.
20 O'Toole ML, Douglas PS, Laird RH, *et al*. Fluid and electrolyte status in athletes receiving medical care at an ultradistance triathlon. *Clin J Sport Med* 1995;5:116–22.
21 Schmidt W, Boning D, Bernal H, *et al*. Plasma-electrolytes in natives to hypoxia after marathon races at different altitudes. *Med Sci Sports Exerc* 1999;31:1406–13.
22 Glace BW, Murphy CA, McHugh MP. Food intake and electrolyte status of ultramarathoners competing in extreme heat. *J Am Coll Nutr* 2002;21:553–9.
23 Cohen I, Zimmerman AL. Changes in serum electrolyte levels during marathon running. *S Afr Med J* 1978;53:449–53.
24 Rose LI, Carroll DR, Lowe SL, *et al*. Serum electrolyte changes after marathon running. *J Appl Physiol* 1970;29:449–51.
25 Dancaster CP, Whereat SJ. Fluid and electrolyte balance during the Comrades Marathon. *S Afr Med J* 1971;45:147–50.
26 Chlibkova D, Knechtle B, Rosemann T, *et al*. The prevalence of exercise-associated hyponatremia in 24-hour ultra-mountain bikers, 24-hour ultra-runners and multi-stage ultra-mountain bikers in the Czech Republic. *J Int Soc Sports Nutr* 2014;11:3.
27 Scotney B, Reid S. Body weight, serum sodium levels, and renal function in an ultra-distance mountain run. *Clin J Sport Med* 2014. Published Online First. doi:10.1097/JSM.0000000000000131
28 Kipps C, Sharma S, Tunstall PD. The incidence of exercise-associated hyponatraemia in the London Marathon. *Br J Sports Med* 2011;45:14–19.
29 Mohseni M, Silvers S, McNeil R, *et al*. Prevalence of hyponatremia, renal dysfunction, and other electrolyte abnormalities among runners before and after completing a marathon or half marathon. *Sports Health* 2011;3:145–51.
30 Rust CA, Knechtle B, Knechtle P, *et al*. No case of exercise-associated hyponatraemia in top male ultra-endurance cyclists: the 'Swiss Cycling Marathon'. *Eur J Appl Physiol* 2012;112:689–97.

31 Mettler S, Rusch C, Frey WO, *et al*. Hyponatremia among runners in the Zurich Marathon. *Clin J Sport Med* 2008;18:344–9.
32 Wagner S, Knechtle B, Knechtle P, *et al*. Higher prevalence of exercise-associated hyponatremia in female than in male open-water ultra-endurance swimmers: the 'Marathon-Swim' in Lake Zurich. *Eur J Appl Physiol* 2012;112:1095–106.
33 Knechtle B, Knechtle P, Rosemann T. Low prevalence of exercise-associated hyponatremia in male 100 km ultra-marathon runners in Switzerland. *Eur J Appl Physiol* 2011;111:1007–16.
34 Galun E, Tur-Kaspa I, Assia E, *et al*. Hyponatremia induced by exercise: a 24-hour endurance March study. *Miner Electrolyte Metab* 1991;17:315–20.
35 Chorley J, Cianca J, Divine J. Risk factors for exercise-associated hyponatremia in non-elite marathon runners. *Clin J Sport Med* 2007;7:471–7.
36 Bissram M, Scott FD, Liu L, *et al*. Risk factors for symptomatic hyponatraemia: the role of pre-existing asymptomatic hyponatraemia. *Intern Med J* 2007;37:149–55.
37 Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. *Semin Nephrol* 2009;29:227–38.
38 Ayus JC, Varon J, Arieff AI. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Ann Intern Med* 2000;132:711–14.
39 Spano SJ, Reagle Z, Evans T. Symptomatic hypotonic hyponatremia presenting at high altitude. *Wilderness Environ Med* 2014;25:69–74.
40 Dimeff RJ. Seizure disorder in a professional American football player. *Curr Sports Med Rep* 2006;5:173–6.
41 Herfel R, Stone CK, Koury SI, *et al*. Iatrogenic acute hyponatraemia in a college athlete. *Br J Sports Med* 1998;32:257–8.
42 Elsaesser TF, Pang PS, Malik S, *et al*. Large-volume hypertonic saline therapy in endurance athlete with exercise-associated hyponatremic encephalopathy. *J Emerg Med* 2013;44:1132–5.
43 Kashyap AS, Anand KP, Kashyap S. Sudden collapse of a young female cross country runner. *Br J Sports Med* 2006;40:e11.
44 Flinn SD, Sherer RJ. Seizure after exercise in the heat. *Physician Sports Med* 2000;28:61–7.
45 Garigan TP, Ristedt DE. Death from hyponatremia as a result of acute water intoxication in an army basic trainee. *Mil Med* 1999;164:234–8.
46 Nelson PB, Robinson AG, Kapoor W, *et al*. Hyponatremia in a marathoner. *Physician Sports Med* 1988;16:78–87.
47 Thompson J, Wolff AJ. Hyponatremic encephalopathy in a marathon runner. *Chest* 2003;124:313S.
48 Stefanko G, Lancashire B, Coombes JS, *et al*. Pulmonary oedema and hyponatraemia after an Ironman triathlon. *BMJ Case Rep* 2009;2009:bcr04.2009.1764.
49 Draper SB, Mori KJ, Lloyd-Owen S, *et al*. Overdrinking-induced hyponatraemia in the 2007 London Marathon. *BMJ Case Rep* 2009;2009:bcr09.2008.1002.
50 Petzold A, Keir G, Appleby I. Marathon related death due to brainstem herniation in rehydration-related hyponatremia: a case report. *J Med Case Rep* 2007;1:186.
51 Rogers IR, Grainger S, Nagree Y. Exercise-associated hyponatremic encephalopathy in an endurance open water swimmer. *Wilderness Environ Med* 2015;26:59–61.
52 Clark JM, Gennari FJ. Encephalopathy due to severe hyponatremia in an ultramarathon runner. *West J Med* 1993;159:188–9.
53 Reid SA, Speedy DB, Thompson JM, *et al*. A study of haematological and biochemical parameters in runners completing a standard marathon. *Clin J Sport Med* 2004;14:344–53.
54 Lebus DK, Casazza GA, Hoffman MD, *et al*. Can changes in body mass and total body water accurately predict hyponatremia following a 161-km running race? *Clin J Sport Med* 2010;20:193–9.
55 Hoffman MD, Hew-Butler T, Stuempfle KJ. Exercise-associated hyponatremia and hydration status in 161-km ultramarathoners. *Med Sci Sports Exerc* 2013;45:784–91.
56 Hoffman MD, Stuempfle KJ, Rogers IR, *et al*. Hyponatremia in the 2009 161-km Western States Endurance Run. *Int J Sports Physiol Perform* 2012;7:6–10.
57 Speedy DB, Noakes TD, Rogers IR, *et al*. Hyponatremia in ultradistance triathletes. *Med Sci Sports Exerc* 1999;31:809–15.
58 Almond CS, Shin AY, Fortescue EB, *et al*. Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 2005;352:1550–6.
59 Jones BL, O'Hara JP, Till K, *et al*. Dehydration and hyponatremia in professional rugby union players: a cohort study observing English premiership rugby union players during match play, field, and gym training in cool environmental conditions. *J Strength Cond Res* 2015;29:107–15.
60 Mayer CU, Treff G, Fenske WK, *et al*. Clinical research paper title: high incidence of hyponatremia in Rowers during a four-week training camp. *Am J Med* 2015. Published Online First. doi:10.1016/j.amjmed.2015.04.014
61 Hew TD, Chorley JN, Cianca JC, *et al*. The incidence, risk factors, and clinical manifestations of hyponatremia in marathon runners. *Clin J Sport Med* 2003;13:41–7.
62 Siegel AJ, Verbalis JG, Clement S, *et al*. Hyponatremia in marathon runners due to inappropriate arginine vasopressin secretion. *Am J Med* 2007;120:461.e11–467.e17.
63 Blevins R, Apel T. Preps sports report. The Clarion-Ledger, 2014. http://www.clarionledger.com/story/prepsreport/2014/08/25/walker-wilbanks-cause-of-death-related-to-over-hydration/14598215/ (accessed 28 Apr 2015).
64 Stevens A. Update: Douglas County football player has died. The Atlanta Journal-Constitution 14 A.D. 11 August 2015. http://www.ajc.com/news/news/family-douglas-county-football-player-has-no-brain/ngy2X/ (accessed 28 Apr 2015).
65 Sydney Morning Herald. Bushwalker died from drinking too much water. Sydney Morning Herald, 2012. http://www.smh.com.au/national/bushwalker-died-from-drinking-too-much-water-20120917-2621c.html (accessed 28 Apr 2015).
66 Baumgarder A. Au Sable River Canoe Marathon pushes paddlers to the limits. The Bay City Times, MLive.com. 16 July 2009. http://www.mlive.com/sports/saginaw/index.ssf/2009/07/au_sable_river_canoe_marathon.html (accessed 28 Apr 2015).
67 Vega C. 8 Charged in Chico hazing death. SFGate. 4 March 2005. http://www.sfgate.com/cgi-bin/article.cgi?file=/c/a/2005/03/04/HAZING.TMP (accessed 28 Apr 2015).
68 Wilber DQ, Brown D. District officer dies after bike ride. Over-hydration cited as factor. Washington Post. 10 August 2005. http://www.washingtonpost.com/wp-dyn/content/article/2005/08/10/AR200508100146 (accessed 28 Apr 2015).
69 Electrolyte Imbalance Blamed in Death of Football Player. Coroner's office says athlete failed to replenish lost sodium. TurnTo23.com. 29 August 2008. http://www.turnto23.com/print/17338293/detail.html (accessed 2 Sep 2008).
70 Lee JK, Nio AQ, Ang WH, *et al*. First reported cases of exercise-associated hyponatremia in Asia. *Int J Sports Med* 2011;32:297–302.
71 Noakes TD, Sharwood K, Speedy D, *et al*. Three independent biological mechanisms cause exercise-associated hyponatremia: evidence from 2,135 weighed competitive athletic performances. *Proc Natl Acad Sci USA* 2005;102:18550–5.
72 Hoffman MD, Stuempfle KJ, Sullivan K, *et al*. Exercise-associated hyponatremia with exertional rhabdomyolysis: importance of proper treatment. *Clin Nephrol* 2015;83:235–42.
73 Backer HD, Shopes E, Collins SL, *et al*. Exertional heat illness and hyponatremia in hikers. *Am J Emerg Med* 1999;7:532–9.
74 Noe RS, Choudhary E, Cheng-Dobson J, *et al*. Exertional heat-related illnesses at the Grand Canyon National Park, 2004–2009. *Wilderness Environ Med* 2013;24:422–8.
75 Zelingher J, Putterman C, Ilan Y, *et al*. Case series: hyponatremia associated with moderate exercise. *Am J Med Sci* 1996;311:86–91.
76 O'Brien KK, Montain SJ, Corr WP, *et al*. Hyponatremia associated with overhydration in U.S. Army trainees. *Mil Med* 2001;166:405–10.
77 Armed Forces Health Surveillance Center. Update: exertional hyponatremia, active component, U.S. Armed Forces, 1999–2013. *MSRM* 2014;21:18–21.
78 Backer H, Shopes E, Collins SL. Hyponatremia in recreational hikers in Grand Canyon National Park. *Wilderness Med* 1993;4:391–406.
79 Glace B, Murphy C. Severe hyponatremia develops in a runner following a half-marathon. *JAAPA* 2008;21:27–9.
80 Shapiro SA, Ejaz AA, Osborne MD, *et al*. Moderate exercise-induced hyponatremia. *Clin J Sport Med* 2006;16:72–3.
81 Morton A. An unusual cause of exercise-induced hyponatremia. *Emerg Med Australas* 2007;19:377–8.
82 Reynolds CJ, Cleaver BJ, Finlay SE. Exercise associated hyponatraemia leading to tonic-clonic seizure. *BMJ Case Rep* 2012;2012:bcr0820114625.
83 Schucany WG. Exercise-associated hyponatremia. *Proc (Bayl Univ Med Cent)* 2007;20:398–401.
84 Armstrong LE, Curtis WC, Hubbard RW, *et al*. Symptomatic hyponatremia during prolonged exercise in heat. *Med Sci Sports Exerc* 1993;25:543–9.
85 Baker LB, Munce TA, Kenney WL. Sex differences in voluntary fluid intake by older adults during exercise. *Med Sci Sports Exerc* 2005;37:789–96.
86 Noakes TD, Wilson G, Gray DA, *et al*. Peak rates of diuresis in healthy humans during oral fluid overload. *S Afr Med J* 2001;91:852–7.
87 Speedy DB, Noakes TD, Boswell T, *et al*. Response to a fluid load in athletes with a history of exercise induced hyponatremia. *Med Sci Sports Exerc* 2001;33:1434–42.
88 Sports Dietitions Australia. Fact Sheet Sports Drinks. 20 April 2011. http://sportsdietitians.com.au/resources/upload/110616%20Sports%20Drinks.pdf (accessed 28 Apr 2105).
89 Montain SJ, Cheuvront SN, Sawka MN. Exercise associated hyponatraemia: quantitative analysis to understand the aetiology. *Br J Sports Med* 2006;40:98–105.
90 Weschler LB. Exercise-associated hyponatremia: a mathematical review. *Sports Med* 2005;35:899–922.
91 Davis DP, Videen JS, Marino A, *et al*. Exercise-associated hyponatremia in marathon runners: a two-year experience. *J Emerg Med* 2001;21:47–57.
92 Wharam PC, Speedy DB, Noakes TD, *et al*. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc* 2006;38:618–22.
93 Baker J, Cotter JD, Gerrard DF, *et al*. Effects of indomethacin and celecoxib on renal function in athletes. *Med Sci Sports Exerc* 2005;37:712–17.
94 Walker RJ, Fawcett JP, Flannery EM, *et al*. Indomethacin potentiates exercise-induced reduction in renal hemodynamics in athletes. *Med Sci Sports Exerc* 1994;26:1302–6.

95 Ayus JC, Olivero JJ, Frommer JP. Rapid correction of severe hyponatremia with intravenous hypertonic saline solution. *Am J Med* 1982;72:43–8.
96 Finkel KW. Water intoxication presenting as a suspected contaminated urine sample for drug testing. *South Med J* 2004;97:611–13.
97 Fox BD. Crash diet potomania. *Lancet* 2002;359:942.
98 Thaler SM, Teitelbaum I, Berl T. "Beer potomania" in non-beer drinkers: effect of low dietary solute intake. *Am J Kidney Dis* 1998;31:1028–31.
99 Brown MB, Haack KK, Pollack BP, *et al*. Low abundance of sweat duct Cl^- channel CFTR in both healthy and cystic fibrosis athletes with exceptionally salty sweat during exercise. *Am J Physiol Regul Integr Comp Physiol* 2011;300: R605–15.
100 Khodaee M, Luyten D, Hew-Butler T. Exercise-associated hyponatremia in an ultra-endurance mountain biker: a case report. *Sports Health* 2013;5:334–6.
101 Brown MB, McCarty NA, Millard-Stafford M. High-sweat Na+ in cystic fibrosis and healthy individuals does not diminish thirst during exercise in the heat. *Am J Physiol Regul Integr Comp Physiol* 2011;301:R1177–85.
102 Brunstrom JM, Tribbeck PM, MacRae AW. The role of mouth state in the termination of drinking behavior in humans. *Physiol Behav* 2000;68:579–83.
103 Saunders CJ, de Milander L, Hew-Butler T, *et al*. Dipsogenic genes associated with weight changes during Ironman triathlons. *Hum Mol Genet* 2006;15:2980–7.
104 Rosner MH. Severe hyponatremia associated with the combined use of thiazide diuretics and selective serotonin reuptake inhibitors. *Am J Med Sci* 2004;327:109–11.
105 Smith HR, Dhatt GS, Melia WM, *et al*. Cystic fibrosis presenting as hyponatraemic heat exhaustion. *BMJ* 1995;310:579–80.
106 Lewis DP, Hoffman MD, Stuempfle KJ, *et al*. The need for salt: does a relationship exist between cystic fibrosis and exercise-associated hyponatremia? *J Strength Cond Res* 2014;28:807–13.
107 Dave S, Honney S, Raymond J, *et al*. An unusual presentation of cystic fibrosis in an adult. *Am J Kidney Dis* 2005;45:e41–4.
108 Augusto JF, Sayegh J, Malinge MC, *et al*. Severe episodes of extra cellular dehydration: an atypical adult presentation of cystic fibrosis. *Clin Nephrol* 2008;69:302–5.
109 Epaud R, Girodon E, Corvol H, *et al*. Mild cystic fibrosis revealed by persistent hyponatremia during the French 2003 heat wave, associated with the S1455X C-terminus CFTR mutation. *Clin Genet* 2005;68:552–3.
110 Priou-Guesdon M, Malinge MC, Augusto JF, *et al*. Hypochloremia and hyponatremia as the initial presentation of cystic fibrosis in three adults. *Ann Endocrinol (Paris)* 2010;71:46–50.
111 Cystic Fibrosis Foundation Patient Registry. 2012 Annual Data Report. Bethesda, MD, 2012:1–32.
112 Wheatley CM, Wilkins BW, Snyder EM. Exercise is medicine in cystic fibrosis. *Exerc Sport Sci Rev* 2011;39:155–60.
113 Stone M, Edwards J, Stemmans C, *et al*. Certified athletic trainers' perceptions of exercise associated muscle cramps. *J Sport Rehabil* 2003;12:333–42.
114 Miller KC, Mack GW, Knight KL, *et al*. Three percent hypohydration does not affect threshold frequency of electrically induced cramps. *Med Sci Sports Exerc* 2010;42:2056–63.
115 Braulick KW, Miller KC, Albrecht JM, *et al*. Significant and serious dehydration does not affect skeletal muscle cramp threshold frequency. *Br J Sports Med* 2013;47:710–14.
116 Schwellnus MP, Allie S, Derman W, *et al*. Increased running speed and pre-race muscle damage as risk factors for exercise-associated muscle cramps in a 56 km ultra-marathon: a prospective cohort study. *Br J Sports Med* 2011;45:1132–6.
117 Schwellnus MP, Nicol J, Laubscher R, *et al*. Serum electrolyte concentrations and hydration status are not associated with exercise associated muscle cramping (EAMC) in distance runners. *Br J Sports Med* 2004;38:488–92.
118 Rothwell SP, Rosengren D. Severe exercise-associated hyponatremia on the Kokoda Trail, Papua New Guinea. *Wilderness Environ Med* 2008;19:42–4.
119 Noakes TD, Goodwin N, Rayner BL, *et al*. Water intoxication: a possible complication during endurance exercise. *Med Sci Sports Exerc* 1985;17:370–5.
120 Schrier RW. Does 'asymptomatic hyponatremia' exist? *Nat Rev Nephrol* 2010;6:185.
121 Helwig FC, Schutz CB, Curry DE. Water intoxication: report of a fatal human case with clinical, pathologic and experimental studies. *JAMA* 1935;104:1569–75.
122 Frizzell RT, Lang GH, Lowance DC, *et al*. Hyponatremia and ultramarathon running. *JAMA* 1986;255:772–4.
123 Irving RA, Noakes TD, Buck R, *et al*. Evaluation of renal function and fluid homeostasis during recovery from exercise-induced hyponatremia. *J Appl Physiol* 1991;70:342–8.
124 Noakes TD, Sharwood K, Collins M, *et al*. The dipsomania of great distance: water intoxication in an Ironman triathlete. *Br J Sports Med* 2004;38:E16.
125 Speedy DB, Rogers IR, Safih S, *et al*. Profound hyponatremia and seizures in an Ironman triathlete. *J Emerg Med* 2000;18:41–4.
126 Rosner MH, Kirven J. Exercise-associated hyponatremia. *Clin J Am Soc Nephrol* 2007;2:151–61.
127 Rehrer NJ. Fluid and electrolyte balance in ultra-endurance sport. *Sports Med* 2001;31:701–15.
128 Maughan RJ, Shirreffs SM, Leiper JB. Errors in the estimation of hydration status from changes in body mass. *J Sports Sci* 2007;25:797–804.
129 Knepper MA. Urinary concentrating mechanism. In: Brenner B, ed. *The kidney*. London: W.B. Saunders, 2003.
130 Rowe JW, Shelton RL, Helderman JH, *et al*. Influence of the emetic reflex on vasopressin release in man. *Kidney Int* 1979;16:729–35.
131 Baylis PH, Zerbe RL, Robertson GL. Arginine vasopressin response to insulin-induced hypoglycemia in man. *J Clin Endocrinol Metab* 1981;53:935–40.
132 Takamata A, Mack GW, Stachenfeld NS, *et al*. Body temperature modification of osmotically induced vasopressin secretion and thirst in humans. *Am J Physiol* 1995;269:R874–80.
133 Verbalis JG. Disorders of body water homeostasis. *Best Pract Res Clin Endocrinol Metab* 2003;17:471–503.
134 Hew-Butler TD, Boulter J, Bhorat R, *et al*. Avoid adding insult to injury—correct management of sick female endurance athletes. *S Afr Med J* 2012;102:927–30.
135 Leaf A. The clinical and physiologic significance of the serum sodium concentration. *N Engl J Med* 1962;267:77–83.
136 Chung HM, Kluge R, Schrier RW, *et al*. Clinical assessment of extracellular fluid volume in hyponatremia. *Am J Med* 1987;83:905–8.
137 Fenske W, Stork S, Koschker A, *et al*. Value of fractional uric acid excretion in differential diagnosis of hyponatremic patients on diuretics. *J Clin Endocrinol Metab* 2008;93:2991–7.
138 Fenske W, Maier KG, Blechschmidt A, *et al*. Utility and limitations of the traditional diagnostic approach to hyponatremia: a diagnostic study. *Am J Med* 2010;123:652–7.
139 Owen BE, Rogers IR, Hoffman MD, *et al*. Efficacy of oral versus intravenous hypertonic saline in runners with hyponatremia. *J Sci Med Sport* 2014;17:457–62.
140 Speedy DB, Noakes TD, Rogers IR, *et al*. A prospective study of exercise-associated hyponatremia in two ultradistance triathletes. *Clin J Sport Med* 2000;10:136–41.
141 Speedy DB, Rogers IR, Noakes TD, *et al*. Exercise-induced hyponatremia in ultradistance triathletes is caused by inappropriate fluid retention. *Clin J Sport Med* 2000;10:272–8.
142 McGee S, Abernathy WB, Simel D. Is this patient hypovolemic? *JAMA* 1999;281:1022–9.
143 Mange K, Matsuura D, Cizman B, *et al*. Language guiding therapy: the case of dehydration versus volume depletion. *Ann Intern Med* 1997;127:848–53.
144 Hato T, Ng R. Diagnostic value of urine sodium concentration in hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion versus hypovolemia. *Hawaii Med J* 2010;69:264–7.
145 Robertson GL. Abnormalities of thirst regulation. *Kidney Int* 1984;25:460–9.
146 Fitzsimons JT. Angiotensin, thirst, and sodium appetite. *Physiol Rev* 1998;78:583–686.
147 Anley C, Noakes T, Collins M, *et al*. A comparison of two treatment protocols in the management of exercise-associated postural hypotension: a randomised clinical trial. *Br J Sports Med* 2011;45:1113–18.
148 Asplund CA, O'Connor FG, Noakes TD. Exercise-associated collapse: an evidence-based review and primer for clinicians. *Br J Sports Med* 2011;45:1157–62.
149 Au-Yeung KL, Wu WC, Yau WH, *et al*. A study of serum sodium level among Hong Kong runners. *Clin J Sport Med* 2010;20:482–7.
150 Hew-Butler T, Boulter J, Godlonton J, *et al*. Hypernatremia and intravenous fluid resuscitation in collapsed ultramarathon runners. *Clin J Sport Med* 2008;18:273–8.
151 Coler C, Hoffman MD, Towle G, *et al*. Hyponatremia in an 85-year-old hiker: when depletion plus dilution produces delirium. *Wilderness Environ Med* 2012;23:153–7.
152 Bunt C, O'Connor F. The 'Phantom Runner'. *Phys Sportsmed* 2004;32:32.
153 Schwartz WB, Bennett W, Curelop S, *et al*. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. 1957. *J Am Soc Nephrol* 2001;12:2860–70.
154 Hew-Butler T, Noakes TD, Siegel AJ. Practical management of exercise-associated hyponatremic encephalopathy: the sodium paradox of non-osmotic vasopressin secretion. *Clin J Sport Med* 2008;18:350–4.
155 Siegel AJ, d'Hemecourt P, Adner MM, *et al*. Exertional dysnatremia in collapsed marathon runners: a critical role for point-of-care testing to guide appropriate therapy. *Am J Clin Pathol* 2009;132:336–40.
156 Ellis C, Cuthill J, Hew-Butler T, *et al*. Exercise-associated hyponatremia with rhabdomyolysis during endurance exercise. *Phys Sportsmed* 2009;37:126–32.
157 Young M, Sciurba F, Rinaldo J. Delirium and pulmonary edema after completing a marathon. *Am Rev Respir Dis* 1987;136:737–9.
158 Helwig FC, Kuhn HP. Water intoxication. *JAMA* 1938;110:644–5.
159 Cheng JC, Zikos D, Skopicki HA, *et al*. Long-term neurological outcome in psychogenic water drinkers with severe symptomatic hyponatremia: the effect of rapid correction. *Am J Med* 1990;88:561–6.
160 Rogers IR, Hook G, Stuempfle KJ, *et al*. An intervention study of oral versus intravenous hypertonic saline administration in runners with exercise-associated hyponatremia. *Clin J Sport Med* 2011;21:200–3.
161 Gardner JW. Death by water intoxication. *Mil Med* 2002;167:432–4.
162 Gardner JW, Gutmann FD. Fatal water intoxication of an Army trainee during urine drug testing. *Mil Med* 2002;167:435–7.

163 Sawka MN, Burke LM, Eichner ER, *et al*. American College of Sports Medicine position stand. Exercise and fluid replacement. *Med Sci Sports Exerc* 2007;39:377–90.
164 Cheuvront SN, Carter R III, Montain SJ, *et al*. Daily body mass variability and stability in active men undergoing exercise-heat stress. *Int J Sport Nutr Exerc Metab* 2004;14:532–40.
165 Hoffman MD, Stuempfle KJ. Hydration strategies, weight change and performance in a 161 km ultramarathon. *Res Sports Med* 2014;22:213–25.
166 Hoffman MD, Stuempfle KJ. Sodium supplementation and exercise-associated hyponatremia during prolonged exercise. *Med Sci Sports Exerc* 2014. Published Online First. doi:10.1249/MSS.0000000000000599
167 Hoffman MD, Fogard K, Winger J, *et al*. Characteristics of those with exercise-associated hyponatremia after a 161-km run. *Res Sports Med* 2012;21:164–75.
168 Armstrong LE, Maresh CM, Gabaree CV, *et al*. Thermal and circulatory responses during exercise: effects of hypohydration, dehydration, and water intake. *J Appl Physiol* 1997;82:2028–35.
169 Cheuvront SN, Haymes EM. Ad libitum fluid intakes and thermoregulatory responses of female distance runners in three environments. *J Sports Sci* 2001;19:845–54.
170 Stricker EM, Verbalis JG. *Hormones and behavior*. Vol. 76. American Scientist, 1988:261–7.
171 Brunstrom JM. Effects of mouth dryness on drinking behavior and beverage acceptability. *Physiol Behav* 2002;76:423–9.
172 Armstrong LE, Johnson EC, Kunces LJ, *et al*. Drinking to thirst versus drinking ad libitum during road cycling. *J Athl Train* 2014;49:624–31.
173 Vrijens DM, Rehrer NJ. Sodium-free fluid ingestion decreases plasma sodium during exercise in the heat. *J Appl Physiol* 1999;86:1847–51.
174 Twerenbold R, Knechtle B, Kakebeeke TH, *et al*. Effects of different sodium concentrations in replacement fluids during prolonged exercise in women. *Br J Sports Med* 2003;37:300–3.
175 Del Coso J, Gonzalez-Millan C, Salinero JJ, *et al*. Effects of oral salt supplementation on physical performance during a half-ironman: a randomized controlled trial. *Scand J Med Sci Sports* 2015. Published Online First. doi:10.1111/sms.12427
176 Speedy DB, Thompson JM, Rodgers I, *et al*. Oral salt supplementation during ultradistance exercise. *Clin J Sport Med* 2002;12:279–84.
177 Luks AM, Robertson HT, Swenson ER. An ultracyclist with pulmonary edema during the bicycle race across America. *Med Sci Sports Exerc* 2007;39:8–12.
178 Sharwood K, Collins M, Goedecke J, *et al*. Weight changes, medical complications and performance during an Ironman triathlon. *Br J Sports Med* 2004;38:718–24.
179 Speedy DB, Rogers IR, Noakes TD, *et al*. Diagnosis and prevention of hyponatremia at an ultradistance triathlon. *Clin J Sport Med* 2000;10:52–8.
180 Reid SA, King MJ. Serum biochemistry and morbidity among runners presenting for medical care after an Australian mountain ultramarathon. *Clin J Sport Med* 2007;17:307–10.
181 Hew-Butler T, Sharwood K, Boulter J, *et al*. Dysnatremia predicts a delayed recovery in collapsed ultramarathon runners. *Clin J Sport Med* 2007;17:289–96.
182 Pugh LG, Corbett JL, Johnson RH. Rectal temperatures, weight losses, and sweat rates in marathon running. *J Appl Physiol* 1967;23:347–52.
183 Nolte HW, Hew-Butler T, Noakes TD, *et al*. Exercise-associated hyponatremic encephalopathy and exertional heatstroke in a soldier: high rates of fluid intake during exercise caused rather than prevented a fatal outcome. *Phys Sportsmed* 2015;43:93–8.
184 Shirreffs SM, Maughan RJ. Whole body sweat collection in humans: an improved method with preliminary data on electrolyte content. *J Appl Physiol* 1997;82:336–41.
185 Fowkes-Godek S, Peduzzi C, Burkholder R, *et al*. Sweat rates, sweat sodium concentrations, and sodium losses in 3 groups of professional football players. *J Athl Train* 2010;45:364–71.
186 Fowkes-Godek S, Bartolozzi AR, Godek JJ. Sweat rate and fluid turnover in American football players compared with runners in a hot and humid environment. *Br J Sports Med* 2005;39:205–11.
187 Harris G, Reid S, Sikaris K, *et al*. Hyponatremia is associated with higher NT-proBNP than normonatremia after prolonged exercise. *Clin J Sport Med* 2012;22:488–94.
188 Fowkes-Godek S, Godek JJ, Bartolozzi AR. Hydration status in college football players during consecutive days of twice-a-day preseason practices. *Am J Sports Med* 2005;33:843–51.
189 Reynolds NC Jr, Schumaker HD, Feighery S. Complications of fluid overload in heat casualty prevention during field training. *Mil Med* 1998;163:789–91.