Exercise-associated hyponatremia

AUTHORS: Mitchell H Rosner, MD, Tamara Hew-Butler, DPM, PhD, FACSM
SECTION EDITOR: Richard H Sterns, MD
DEPUTY EDITOR: John P Forman, MD, MSc

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INTRODUCTION

Severe and potentially life-threatening hyponatremia can occur during or following exercise, particularly in athletes participating in endurance events such as marathons (42.2 km), triathlons (3.8 km swim, 180 km cycling, and 42.2 km running), and ultradistance (100 km) races [1-5]. A similar problem can occur in military operations, desert or recreational hikes, team sport settings, and recreational activities such as yoga [6,7], weightlifting, tennis [8], American football [9], rugby [10], and rowing [11].

Exercise-associated hyponatremia (EAH) was first described in Durban, South Africa in 1981 and in 1985 in four athletes participating in endurance events longer than seven hours [12]. Prior to 1981, athletes were advised to avoid drinking during exercise, leading to the development of hypernatremia in some athletes [13,14]. Subsequently, athletes were advised to consume as much fluid as possible during exercise. Concomitant with these recommendations, the incidence of hyponatremia in endurance athletes appeared to increase, particularly in the United States.

The majority of athletes who develop hyponatremia are asymptomatic or mildly symptomatic (eg, weakness, dizziness, headache, lethargy, nausea/vomiting). However, severe manifestations can occur, including seizures, cerebral edema, noncardiogenic pulmonary edema, and death. (See 'Clinical manifestations' below and "Manifestations of hyponatremia and hypernatremia in adults".)

DEFINITION

The 2019 Wilderness Medical Society Clinical Practice Guidelines and the 2015 Third International Exercise-Associated Hyponatremia Consensus Development Conference defined exercise-associated hyponatremia (EAH) as hyponatremia (serum or plasma sodium <135 mEq/L) occurring during or up to 24 hours after prolonged physical activity [1,9].

INCIDENCE

Prior to the recognition that drinking large volumes of water can lead to potentially fatal hyponatremia, it was not unusual for endurance athletes to be hyponatremic at the end of the race, usually in the absence of overt central nervous system symptoms [2,3,15-23]. The incidence of hyponatremia varies and is still a matter of debate [1]. The approximate incidence ranges from 0 to 18 percent in marathoners and triathletes [3,16,20-22] to 51 percent of runners participating in a 161 km mountain footrace, which suggests that exercise-associated hyponatremia (EAH) may be more prevalent in longer endurance events (like Ironman triathlons and ultramarathons) lasting more than 17 to 24 hours [23]. The incidence of EAH in team sports also appears to be increasing and was reported in 33 percent of rugby players following a match [10], 70 percent of rowers during training camp [11], and four American football players who died [24]. Given that EAH can occur across a wide variety of physical activity, it should be considered in all cases of exercise-associated collapse.

The following observations are illustrative:

- In a prospective study at the 2002 Boston Marathon (26.2 miles, 42.2 km), a sample of 766 runners approached randomly at race registration completed a survey prior to the race and, at the finish line, provided a blood sample and completed a questionnaire detailing their fluid consumption and urine output during the race [2]. Among these runners, 511 reported to the finish line station and an adequate blood sample was obtained from 488. Of these, 13 percent had hyponatremia (defined as a serum sodium concentration ≤135 mEq/L) and three runners (0.6 percent) had what was considered critical hyponatremia (serum sodium concentration ≤120 mEq/L) [2]. If this sample was representative of the almost 15,000 runners who finished the race, then 1900 of all finishers would have some degree of hyponatremia and 90 would have critical hyponatremia.

- The largest experience comes from a review of 2135 athletes in reported endurance events in which both serum sodium and body weight changes after racing were available: 6 percent had a serum sodium between 129 and 135 mEq/L and 1 percent had a serum

sodium below 129 mEq/L [3]. In addition, 13 percent were hypernatremic (serum sodium greater than 145 mEq/L), due to inadequate fluid intake during the race. Hypernatremia has also been noted in other series [25].

- The incidence of hyponatremia may be higher in runners of ultramarathons [26,27] and Ironman triathletes [22] due to increased race distance and exercise time. As an example, 30 percent of runners completing a 161 km mountain race were found to have asymptomatic mild hyponatremia, associated with a loss of body weight in half of cases [26].

Based upon such observations, the recommendations for fluid intake during an endurance event were changed to drinking according to thirst. (See 'Prevention' below.)

RISK FACTORS

A number of risk factors have been linked with the development of exercise-associated hyponatremia (EAH) [1-3,9,19]. The most important is sustained high fluid intake.

High fluid intake — The major risk factor for EAH appears to be a high rate of fluid consumption during and after exercise, leading to water overload and hemodilution [1-3,9,15,18,22,28,29]. The following observations illustrate the range of findings:

- In the report from the Boston Marathon, hyponatremia was independently associated with weight gain during the marathon; 44 of 62 runners who developed hyponatremia gained weight during the race compared with 124 of 426 runners who did not develop hyponatremia (71 versus 29 percent) [2]. This corresponded to the frequency and volume of fluid intake, which was significantly higher in the athletes who developed hyponatremia. Furthermore, the severity of hyponatremia was associated with the amount of weight gained. Of the runners who gained at least 2.0 kg, 17 percent developed severe hyponatremia (defined as a serum sodium less than or equal to 130 mEq/L) compared with 3 percent in runners who gained between 0.0 and 1.9 kg.

- Similar findings were noted in the review of 2135 athletes in endurance events [3]. The mean serum sodium was 136 mEq/L in the athletes who gained weight during the race compared with 141 mEq/L in the athletes who either maintained weight or lost weight. Of the athletes who gained weight, 19 percent had a serum sodium between 129 and 135 mEq/L and 11 percent had a serum sodium below 129 mEq/L. The comparable values in athletes who did not gain weight were 4 and 0.3 percent, respectively.

The authors estimated that athletes who gained more than 4 percent body weight during exercise had an 85 percent probability of developing hyponatremia and a 45 percent probability of developing hyponatremic encephalopathy.

In most athletes who develop EAH, the excessive fluid intake reflects conditioned behavior based upon recommendations to drink fluid during exercise to avoid dehydration. In a study from the 1998 and 1999 Suzuki Rock 'N' Roll Marathons, for example, the 26 runners who developed hyponatremia reported "drinking as much as possible" during and after the race [15].

By contrast, there were no cases of hyponatremia among 134 runners who finished the 2002 City of Christchurch marathon [21]. In this race, aggressive hydration was not promoted, and there were fewer hydration stations than there were in the 2002 Boston Marathon (every 5 versus 1.6 km) [2].

The consumption of a carbohydrate/electrolyte-containing sports drink does **not** provide protection against the development of hyponatremia, since most of these drinks are markedly hypotonic to plasma [2,9,30]. Gatorade, for example, has a sodium plus potassium concentration of only 23 mEq/L (potassium is as osmotically active as sodium) compared with approximately 145 mEq/L in normal plasma. (See 'Prevention' below.)

Other — Other independent risk factors for EAH in different series included longer race time (or the related variable of slower training pace), and a low body mass index [2,9,15,18]. As an example, the following observations were made in the report from the Boston Marathon [2]:

- Fifty-two percent of runners who developed hyponatremia had race times above four hours compared with 13 percent in those who finished the race in less than 3.5 hours. Longer race times probably correlate with increased water consumption and increased sodium losses.

- Thirty-two percent of runners who developed hyponatremia had a body mass index less than 20 kg/m^2 compared with 14 percent in runners whose body mass index was greater or equal to 25 kg/m^2. A possible mechanism is that ingestion of a given volume of water would lead to a greater reduction in serum sodium in individuals with a low body mass index since their total body water is lower at baseline.

Nonsteroidal antiinflammatory drugs (NSAIDs) are used by as many as 50 to 60 percent of marathon runners. Some studies have found an association between NSAID use and the development of hyponatremia [9,15,20,31,32], although NSAID use was not an independent risk factor in the 2002 Boston Marathon study [2].

NSAIDs increase the activity of antidiuretic hormone (ADH, also called arginine vasopressin) by removing the inhibitory effect of prostaglandins. The ensuing decrease in water excretion, which has been demonstrated in athletes [32], could promote the development of hyponatremia. (See "NSAIDs: Electrolyte complications", section on 'Hyponatremia' and 'Sweat sodium loss' below.)

Long-duration exercise may be associated with an increased risk of hyponatremia independent of other factors. In a study of 47 runners completing a 161 km mountain race, 30 percent had a serum sodium less than 135 mEq/L [26]. A gain in weight, longer race time, and use of NSAIDs did not predict the development of hyponatremia.

PATHOGENESIS

Increased fluid intake is necessary but is not the sole explanation for many if not most cases of exercise-associated hyponatremia (EAH) [1,3,28]. The other major factor is impaired urinary water excretion due to persistent secretion of antidiuretic hormone (ADH, also called arginine vasopressin). Other proposed mechanisms of hyponatremia include a failure to mobilize exchangeable sodium stores and sodium losses in sweat [3].

Increased fluid intake — As noted above, increased fluid intake appears to be the primary risk factor for EAH. Another source of water is the breakdown of glycogen during exercise since glycogen associates with "bound" water [33,34]. This release of water would not lead to weight gain.

Despite the water load, individuals on a regular diet who have normal kidney function have a maximum water excretory capacity that, depending upon diet, can exceed 500 to 1000 mL/hour [3,35]. When one adds sweat and insensible fluid losses, which may be as high as 500 mL/hour [3], athletes should be able to consume as much as 1000 to 1500 mL/hour before retaining fluid and becoming hyponatremic. Based upon these calculations, it has been suggested that endurance athletes should not drink more than 1500 mL/hour of fluid during a race [36,37].

Because of the high rate of water loss, water loading alone is not likely to produce more than a modest reduction in serum sodium in most endurance athletes. This was shown in the review of 2135 endurance athletes cited above: only 30 percent of athletes who gained weight during the race developed hyponatremia [3].

Persistent secretion of ADH — Hyponatremia due to water loading alone should suppress the release of ADH (figure 1), leading to a maximally dilute urine with a urine osmolality as low as 30 to 50 mosmol/kg in healthy individuals and a urine output that can exceed 500 to 1000

mL/hour [3,35]. Failure to suppress ADH release can markedly reduce water excretory capacity. As an example, low-level persistence of ADH that results in a urine osmolality of 150 mosmol/kg, which is still hypotonic to plasma, diminishes the rate of water excretion by two-thirds compared with a urine osmolality of 50 mosmol/kg. This is particularly important when there is a marked increase in water intake [3,28]. (See "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)", section on 'Regulation of plasma tonicity'.)

The available data suggest that many patients with EAH have submaximal suppression of ADH secretion, an inappropriately high urine osmolality, and fulfill the criteria for the syndrome of inappropriate ADH secretion (SIADH) [9,28,29,37-41]. (See "Diagnostic evaluation of adults with hyponatremia".)

These features were illustrated in a review of hyponatremia in marathon runners [29]. Among 16 athletes with EAH after the 2004 Boston Marathon, seven had persistent secretion of ADH. In two runners with severe EAH at other marathons who collapsed and were unresponsive, the urine osmolality was inappropriately high (329 and 121 mosmol/kg) and the urine sodium concentration was 81 and 25 mEq/L, findings that are consistent with SIADH.

There are a number of nonosmotic mechanisms by which ADH secretion might be inappropriately stimulated in endurance and team sport athletes [28,39]:

- Intense exercise itself [42-44]
- Nausea and/or vomiting [45]
- Hypoglycemia [46,47]
- Nonspecific stresses such as pain and emotion [48]
- The release of muscle-derived interleukin-6 [29]

In addition to inappropriate ADH release, endurance athletes may develop what has been called appropriate ADH release due, for example, to hypovolemia resulting from sodium loss in sweat (figure 2). (See 'Sweat sodium loss' below and "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)", section on 'Role of ADH in volume regulation'.)

The most comprehensive study of ADH metabolism in endurance athletes evaluated 82 ultramarathon (35 miles, 56 km) runners who ran for a mean of six hours [39]. With ad libitum fluid intake, the plasma sodium was maintained (139.3 versus 138.1 mEq/L at baseline and the end of the race, respectively). Plasma ADH was elevated 3.9-fold at the end of the race, which could be explained at least in part by a mean 3.8 kg weight loss and an 8.5 percent reduction in plasma volume. There was also increased release of other hormones such as oxytocin and,

despite the fall in plasma volume, N-terminal pro-brain natriuretic peptide. Whether these hormonal changes contributed to ADH release could not be determined. A similar study performed in 33 endurance cyclists participating in a 109 km race also documented nonosmotic ADH secretion after roughly five hours of cycling [41].

The applicability of these findings to EAH is uncertain since, as noted above, EAH primarily occurs in endurance athletes who gain weight during the event and would therefore be unlikely to have a hypovolemic stimulus to ADH release [2,3]. The exact nonosmotic stimulus to ADH secretion is unclear [49], but these field investigations suggest that the potential for nonosmotic ADH stimuli during competitive long-distance exercise is higher than previously noted in well-controlled laboratory settings [50,51]. Overall, hyponatremia, particularly severe hyponatremia, is rare in athletes who lose weight during the event [3]. (See 'High fluid intake' above.)

Role of exchangeable sodium stores — In the review of 2135 endurance athletes cited above, 70 percent of athletes who gained weight maintained normal serum sodium concentrations [3]. In some cases, the amount of fluid retained was too small to reduce the serum sodium below 135 mEq/L. It is also possible that, when the serum sodium was measured at the end of the race, some ingested water had not yet been absorbed from the gastrointestinal tract, contributing to weight gain without lowering the serum sodium concentration.

A third possible mechanism for maintenance of normonatremia despite the weight gain is the release of sodium from internal stores [3]. Up to 25 percent of body sodium is bound in bone and, although not osmotically active, is potentially recruitable into an osmotically active form [52,53]. In theory, this pool could minimize the fall in serum sodium induced by overhydration.

The issue of recruiting osmotically active sodium from internal, not osmotically active sources, was addressed in a review of 18 athletes who were hospitalized for encephalopathy due to EAH [3]. Sodium and water balance was estimated at the time of admission and measured during recovery in the hospital. At the time of admission, the predicted serum sodium based upon electrolyte and water balance estimates was higher than the actual measured concentration in 14 athletes, suggesting exchange of sodium from an osmotically active to inactive state, and worsening of rather than protection against hyponatremia. During recovery, eight of the athletes showed evidence of osmotic activation of sodium (ie, the increase in serum sodium was more than could be explained by measured values of sodium and water balance), while 10 showed evidence of osmotic inactivation of sodium (ie, the increase in serum sodium was less than could be explained by measured values of sodium and water balance).

These disparate findings are difficult to explain physiologically, and the following factors could contribute to the observed findings without invoking osmotic activation or inactivation of internally exchangeable sodium:

- Absorption of ingested water still in the gastrointestinal tract would lower the serum sodium without a change in weight, falsely suggesting osmotic inactivation. There is some evidence of delayed gastric emptying during exercise [44].

- The breakdown of glycogen into smaller, more osmotically active molecules (such as lactate) during exercise can increase the cell osmolality, thereby causing the osmotic movement of water into the cells and raising the serum sodium [54]. This effect reverses within five minutes after the cessation of exertion [33].

- Changes in potassium balance, which were not measured, could have influenced the serum sodium concentration without affecting body weight. (See "Overview of the treatment of hyponatremia in adults".)

Sweat sodium loss — There is a variable degree of sodium loss from sweating. The concentration of sodium in sweat may range between 17 to 92 mEq/L [55]. Compared with the general population, fit athletes generally have a lower sweat sodium concentration [56,57], a higher rate of sweat production in proportion to the degree of fitness [58,59], and an earlier onset of sweating [60]. The sweat rate during exercise is primarily determined by the increase in metabolic rate; thus, for athletes of the same body weight, the sweat rate will be higher in those who run faster. By contrast, nonfit athletes, who are at greatest risk of EAH, tend to be heavier and may have a similar rate of sweat loss even though they run more slowly than the thinner fit athletes.

The direct effect of losing hypotonic sweat would be to raise the serum sodium. However, sweat sodium losses could contribute to the development of hyponatremia if the degree of fluid and sweat sodium losses were sufficient to produce significant volume depletion, providing a hypovolemic stimulus to ADH release [61], which, as described above, would impair excretion of ingested water.

The contribution of sweat-induced hypovolemia sufficient to increase ADH release is probably small in endurance athletes based upon the following observations:

- In the review of 2135 endurance athletes cited above, only 3.5 percent of those athletes who lost more than 3 kg during the race (which would have been due in part to sweating) had a serum sodium between 129 and 135 mEq/L at the end of the race and no athlete

had a serum sodium below 129 mEq/L [3]. The rates were much higher (19 and 11 percent) in the athletes who gained weight during the race. (See 'High fluid intake' above.)

- The total body sodium deficit is relatively small in athletes with EAH [3,62,63]. Among 18 athletes hospitalized for hyponatremic encephalopathy, the mean sodium deficit was 104 mEq, which was not significantly different from that in a control group of runners who did not develop hyponatremia (mean 187 mEq) [3]. This observation is consistent with another report in which the plasma volume was maintained in 181 triathletes despite a mean weight loss of 4.9 kg during the race [64].

However, exercise coupled with prolonged heat exposure, particularly in nonacclimatized individuals, may contribute to EAH [65,66].

CLINICAL MANIFESTATIONS

The clinical manifestations of acute hyponatremia due to exercise-associated hyponatremia (EAH) vary with severity and are at least in part related to cerebral edema resulting from osmotic water movement from the extracellular fluid into the brain. Severe manifestations of EAH include seizures, confusion, coma, and death [1,9,15,29,31,36]. Cerebral edema can often be demonstrated on CT scan or at postmortem examination. Although the mechanism is uncertain, noncardiogenic pulmonary edema has also been described in these patients [31,67]. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Clinical manifestations of acute hyponatremia'.)

Relation to serum sodium — The majority of hyponatremic athletes, however, are asymptomatic or mildly symptomatic, with nonspecific manifestations such as weakness, dizziness, bloating, headache, nausea, and/or vomiting [2,3,9,15,29,36]. These athletes usually have serum sodium values ranging from 128 to 134 mEq/L. Headache and vomiting, especially when accompanied by lethargy and/or confusion, should be considered warning signs [29].

Although the likelihood and severity of symptoms attributable to hyponatremia increase with more severe disease, the effect is not predictable, as illustrated in the review of 2135 endurance athletes cited above [3]. Among 24 runners with central nervous system symptoms compatible with hyponatremic encephalopathy, 4 had a serum sodium ≥130 mEq/L, with the highest value being 132 mEq/L. On the other hand, 4 of 15 runners with a serum sodium ≤125 mEq/L were considered asymptomatic.

Some hyponatremic athletes complain only of feeling ill, lie quietly in a corner, often in a fetal position, and want to avoid light and contact with other people. They appear lucid, but cannot

concentrate and may be a little confused. The serum sodium is reduced but is often above 130 mEq/L. Such patients typically respond dramatically to hypertonic saline, but therapy may be delayed because the role of hyponatremia is not recognized [68].

The collapsed athlete — A common scenario for medical personnel staffing endurance athletic events is the care of the "collapsed athlete." Only a minority of these athletes have hyponatremia and a greater proportion have hypernatremia [25,29,36,69,70]. The largest reported experience includes 1319 collapsed runners at the Boston Marathon between 2001 and 2008 [69]. Hyponatremia was present in 5 percent and hypernatremia in 28 percent. Thus, collapsed athletes should **not** be treated for hyponatremia until the diagnosis is confirmed.

The rate of hyponatremia would be higher when athletes were advised to consume as much fluid as possible during exercise. (See 'Prevention' below.)

Rhabdomyolysis — Rhabdomyolysis in association with EAH has been described in occasional ultramarathon runners participating in races greater than 153 km (96 miles) [71,72]. It was suggested in these reports that hyponatremia might increase the susceptibility for muscle cell damage [73].

DIAGNOSIS

Any athlete presenting with signs or symptoms compatible with hyponatremia should be screened by direct measurement of the serum or plasma sodium. The 2019 Wilderness Medical Society Clinical Practice Guidelines and the 2015 Third International Exercise-Associated Hyponatremia Consensus Development Conference recommended that medical facilities at endurance events should have onsite capability for such measurements [1,9].

At endurance events in which the serum or plasma sodium cannot be measured, a presumptive diagnosis of exercise-associated hyponatremia (EAH) is sometimes made in the athlete with severe central nervous system manifestations (eg, seizures and coma) consistent with hyponatremic encephalopathy in whom there is no other obvious cause. As noted below, empiric therapy with hypertonic saline may be initiated in emergency, life-threatening scenarios. By comparison, the presence of EAH should **not** be assumed in collapsed athletes without measurement of the serum or plasma sodium since hyponatremia is present in only a small proportion of these individuals [25,29,70]. (See 'The collapsed athlete' above.)

TREATMENT

Ideally, medical facilities at endurance events should be able to measure the serum or plasma sodium concentration in any athlete manifesting symptoms compatible with exercise-associated hyponatremia (EAH), particularly those with severe symptoms suggesting hyponatremic encephalopathy [1,9]. (See 'Clinical manifestations' above.)

General principles — Most athletes with mild hyponatremia (serum sodium 130 to 135 mEq/L) are asymptomatic and will not be identified unless laboratory testing is performed for some other reason. In such individuals, the recommended approach is restriction of fluid intake or administration of a small concentrated salt broth until the onset of a spontaneous diuresis (see 'Mild to moderate symptoms' below); in addition, these athletes should be advised to seek urgent medical attention if signs or symptoms compatible with hyponatremia develop [1,9]. Some athletes with mild to moderate symptoms and all athletes with severe symptoms should receive hypertonic fluid.

Our approach to the treatment of symptomatic EAH is consistent with the recommendations made by the 2019 Wilderness Medical Society Clinical Practice Guidelines and the 2015 Third International Exercise-Associated Hyponatremia Consensus Development Conference [1,9]. Administration of hypotonic or isotonic fluids should be avoided in all hyponatremic patients since this regimen can exacerbate the hyponatremia.

Mild to moderate symptoms — Endurance athletes with mild to moderate symptoms (eg, headache, dizziness, and/or nausea and vomiting) and **documented** hyponatremia should be treated, at a minimum, with fluid restriction, and should be observed until the onset of a spontaneous diuresis, which will correct the hyponatremia and lead to resolution of the symptoms.

However, fluid restriction may be insufficient in hyponatremic athletes who fail to suppress antidiuretic hormone (ADH) (due, for example, to nausea or hypovolemia). In such patients, an oral or intravenous bolus of hypertonic saline is without harm and has potential benefit, particularly if symptoms seem to be progressing. We would **not** give hypertonic saline if the plasma or serum sodium cannot be measured in individuals with mild to moderate generalized symptoms. Similar symptoms can occur with hypernatremia [25], which would be exacerbated by hypertonic saline, and, as noted above, hypernatremia is more common than hyponatremia [3]. (See 'Use of hypertonic saline' below.)

A possible alternative in patients with suspected EAH if intravenous hypertonic saline is unavailable is oral therapy with a hypertonic broth (120 mL oral bolus of 9 percent saline) [65,69]. As an example, in a small randomized trial of 32 ultramarathon finishers with moderate hyponatremia, oral and intravenous administration of a 100 mL dose of hypertonic saline

produced identical improvements in the serum sodium and may improve symptoms more quickly than intravenous administration when tolerated [74]. Some athletes, particularly those with nausea and vomiting, may be unable to tolerate oral hypertonic saline.

Intravenous isotonic saline should **not** be used, since it may worsen the hyponatremia if the patient is euvolemic and has elevated ADH levels with a urine osmolality above 300 mosmol/kg. Why this occurs is discussed separately. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Intravenous hypertonic saline'.)

The primary indication for isotonic saline is in the infrequent athlete with mild hyponatremia who has signs of volume depletion [9]. As noted above, hyponatremia is less common in patients who lose weight during exercise [3] and the total body sodium deficit is usually relatively small in athletes with EAH. (See 'Sweat sodium loss' above.)

Severe symptoms — Athletes with hyponatremia and severe symptoms (eg, seizures, confusion, coma) should be treated with hypertonic (usually 3 percent) saline [1,9,15,29,31,36,75]. In the largest series, encephalopathy was only seen when the serum sodium was ≤132 mEq/L [29]. However, EAH with encephalopathy has rarely been described at somewhat higher serum sodium concentrations (eg, 134 mEq/L in an Ironman triathlete) [68].

Given the significant risk of delayed therapy in such patients, we recommend treatment in the field by experienced medical personnel with immediate transport to the hospital. If the serum or plasma sodium cannot be measured on site, it is reasonable to empirically initiate hypertonic saline (as described in the next section) if there is no other obvious cause for severe neurologic manifestations [76]. A small elevation in serum sodium can lead to significant symptomatic improvement and should produce no harm [29,68,77]. Furthermore, delaying therapy can lead to worsening of the hyponatremia and possible clinical deterioration due to ongoing absorption of water from the gastrointestinal tract.

Use of hypertonic saline — The potential efficacy of hypertonic saline in severe symptomatic EAH was illustrated in a series of seven previously healthy marathon runners who collapsed after competing in a marathon and had nausea, vomiting, obtundation, cerebral edema (usually detected on computed tomography), noncardiogenic pulmonary edema, and a mean serum sodium of 121 mEq/L (range 117 to 127 mEq/L) [31]. Six were treated with hypertonic (3 percent) saline; all recovered and were well at 3 to 24 month follow-up. One patient died; this patient was not suspected of having hyponatremia, and therefore was not treated with hypertonic saline. An important observation in this report is that noncardiogenic pulmonary edema is **not** a

contraindication to hypertonic saline administration in patients with hyponatremic encephalopathy.

The 2019 Wilderness Medical Society Clinical Practice Guidelines and the 2015 Third International Exercise-Associated Hyponatremia Consensus Development Conference recommend that athletes with hyponatremic encephalopathy (eg, seizures, confusion, coma) and athletes with compatible symptoms (if the plasma or serum sodium cannot be measured) be immediately treated with an intravenous 100 mL bolus of 3 percent saline [1,9,75,78]. This regimen should acutely raise the serum sodium concentration by 2 to 3 mEq/L, thereby reducing the degree of cerebral edema [68]. There is clear potential benefit from this approach with no proven harm, since the sodium load is only 51 mEq.

If neurologic symptoms persist or worsen prior to arrival at the hospital, the Consensus Development Conference recommends that a 100 mL bolus of 3 percent saline can be given one or two more times at ten minute intervals **only** if the plasma or serum sodium has been measured to confirm the presence of hyponatremia [1,9].

All such patients should be transported to a medical center where the serum sodium and neurologic status can be closely monitored; care should be taken to avoid delays in treatment of the hyponatremia while awaiting results of diagnostic imaging tests [9].

Hypertonic saline should be discontinued as soon as the neurologic symptoms resolve, which typically occurs when the serum sodium has risen 3 to 7 mEq/L above the initial value [29,77]. Correction of the remaining hyponatremia will occur spontaneously from a water diuresis once ADH secretion wears off [36]. (See 'Persistent secretion of ADH' above.)

A potential diagnostic problem in patients who have had seizures is that persistent neurologic symptoms may reflect a postictal state rather than persistent hyponatremic encephalopathy. Specific data are limited, but two points deserve emphasis: hyponatremia as the cause of ongoing symptoms is probably unlikely if the serum sodium has risen by 7 mEq/L or more above the initial value [29,77]; and a postictal state probably does not explain symptoms lasting more than 30 to 60 minutes after a single seizure in otherwise healthy individuals.

Rate of correction — A final therapeutic issue is the clinical importance, if any, of the rate of correction of EAH. Among patients with chronic hyponatremia, overly rapid correction (a rise in serum sodium of 10 mEq/L or more in the first 24 hours) can lead to severe and irreversible neurologic complications due to osmotic demyelination. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia".)

The rate of correction should be much less important in EAH, which is a very acute event that does not generate the cerebral adaptations that account for the risk of overly rapid correction in chronic hyponatremia. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Osmolytes and cerebral adaptation to hyponatremia'.)

There are no reported cases of osmotic demyelination in EAH [1,9,29,36], and anecdotal episodes of rapid correction of the hyponatremia have been well tolerated. In a series of six patients with hyponatremic encephalopathy who were treated with hypertonic saline, the serum sodium increased by 10 mEq/L in less than 12 hours, a rate of correction greater than recommended for chronic hyponatremia [31]. In another reported case of EAH with encephalopathy, hypertonic saline therapy was associated with a 13 mEq/L elevation in the serum sodium in 8.5 hours without the development of osmotic demyelination [29]. In all of these athletes, the central nervous system symptoms from EAH resolved, and there were no residua at 3 to 24 month follow-up.

Hypernatremia — In contrast to hyponatremia due to water overload, endurance and team sport athletes can become hypernatremic if they do not drink a sufficient quantity of water during the race or athletic event. The reported incidence of hypernatremia (serum sodium >145 mEq/L) was 13 percent in a review of 2135 endurance athletes [3], 28 percent in a series of 1319 collapsed marathon runners [69], and 54 percent of ultramarathon runners competing in a multistage race [70].

Treatment consists of the administration of hypotonic fluid to lower the serum sodium. Since hypernatremia stimulates thirst, such athletes can replace the water deficit by drinking. Intravenous therapy is required in athletes who cannot take oral fluids [25]. (See "Treatment of hypernatremia in adults".)

PREVENTION

Since consumption of fluid in excess of urinary and sweat losses is the primary mechanism of exercise-associated hyponatremia (EAH), most efforts at prevention of EAH have focused on education about the risks of the overconsumption of fluids. Given the wide variation in sweat production and renal water excretory capacity both between individual athletes and in the same individual depending upon ambient conditions during the race, universal guidelines for prevention are not feasible [9].

In most settings, the regulatory system surrounding the maintenance of plasma sodium is so efficient that the plasma osmolality is maintained within a range of 1 to 2 percent despite wide

variations in sodium and water intake. This depends upon an intact thirst mechanism and appropriate regulation of antidiuretic hormone (ADH) release. (See "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)", section on 'Regulation of water and sodium balance'.)

In the past, some suggested that fluid intake be limited to 400 to 800 mL/hour. However, sweat rates may not be this high, particularly in endurance athletes exercising in the cold. Thus, the risk of EAH would still be present.

We agree with the recommendations from the 2019 Wilderness Medical Society Clinical Practice Guidelines and the 2015 Third International Exercise-Associated Hyponatremia Consensus Development Conference, which concluded that endurance and team sport athletes should **drink according to thirst** during the race or athletic event [1,9]. A prospective study in eight female marathon runners found that such an approach replaced most of the sweat losses with no evidence of overhydration [79].

One method that has been used in an attempt to limit excessive water intake is to have fewer water stations. In the 2002 City of Christchurch marathon, aggressive hydration was not promoted and there were fewer hydration stations (every 5 versus 1.6 km) than in the 2002 Boston Marathon [21]. There were no cases of hyponatremia among 134 runners who finished the race compared to an incidence of 13 percent in the Boston Marathon [2]. For Ironman distance triathlons, hydration stations every 2.5 km when running and every 20 km when cycling have been recommended in addition to education about fluid intake [9,80].

Two additional recommendations have been proposed:

- Onsite analysis of serum or plasma sodium should be available in medical facilities at endurance events [1,9].

- Use of the USA Track and Field (USATF) guidelines [81], or other methods, to estimate hourly sweat losses during exercise and to avoid consuming fluid at greater rates during endurance events. This can be facilitated by serial measurements of body weight during and after exercise in a variety of conditions with a goal of maintenance of or a slight reduction in body weight.

  However, the results during training may not be replicated during the race when ADH secretion may not be suppressed [9], and may be less likely to be followed by casual athletes who are at higher risk of hyponatremia (eg, race time greater than four hours was a significant risk factor in the 2002 Boston Marathon) [2]. Furthermore, the body protects

the plasma sodium, not body weight, during exercise, and drinking according to thirst appears to provide sufficient protection [1,9,82].

The American College of Sports Medicine (ACSM) has recommended an intake of 500 to 700 mg of sodium (22 to 30 mEq) per liter of water ingested as the appropriate level of sodium intake to replace the sodium lost in sweat during endurance events [36]. However, there is insufficient evidence that ingestion of sodium prevents or decreases the risk of EAH [83,84], and consumption of carbohydrate/electrolyte-containing sports drinks does not provide much protection, since most of these drinks are markedly hypotonic to plasma, although they contain roughly the same concentration of cation (sodium plus potassium) as recommended by the ACSM [2,9,30]. (See 'High fluid intake' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hyponatremia" and "Society guideline links: Fluid and electrolyte disorders in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5^{th} to 6^{th} grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10^{th} to 12^{th} grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hyponatremia (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Exercise-associated hyponatremia (EAH) primarily occurs in athletes participating in endurance events, such as marathons, triathlons, and ultradistance races. The incidence of EAH in such events was 6 percent in a large review but has varied among individual studies, ranging from 0 to 51 percent. (See 'Incidence' above.)

- The major risk factor for EAH is a high rate of fluid consumption during and after exercise that is typically associated with weight gain compared with the prerace weight. Other independent risk factors include longer race time (or the related variable of slower training pace), low body mass index, and in some studies, the use of nonsteroidal antiinflammatory drugs (NSAIDs). (See 'Risk factors' above.)

- Fluid intake in excess of fluid loss is the primary pathogenic mechanism underlying EAH. Although excessive fluid consumption is necessary, it is not the sole explanation in many cases of EAH. The other major factor is impaired urinary water excretion due to persistent secretion of antidiuretic hormone (ADH). (See 'Pathogenesis' above.)

- The majority of hyponatremic athletes are asymptomatic or mildly symptomatic, with manifestations such as weakness, dizziness, headache, nausea, and/or vomiting. These athletes usually have serum sodium concentrations ranging from 128 to 134 mEq/L. Severe manifestations of seizures, obtundation, and coma occur primarily in athletes with a serum sodium concentration ≤132 mEq/L. (See 'Clinical manifestations' above.)

- We recommend direct measurement of the serum or plasma sodium in any endurance or team sport athlete with signs or symptoms compatible with hyponatremic encephalopathy, including seizures, obtundation, and coma. If the sodium concentration cannot be measured at an athletic event, a presumptive diagnosis of EAH can be made if an athlete presents with severe central nervous system manifestations consistent with acute hyponatremia in the absence of an obvious alternative etiology. (See 'Diagnosis' above.)

- The presence of EAH should **not** be assumed in the "collapsed athlete" without measurement of the serum or plasma sodium, since hyponatremia is present in only a small proportion of these individuals and hypernatremia is more common and would be made worse with hypertonic saline therapy. (See 'The collapsed athlete' above.)

- Treatment recommendations are based upon the limited data from small, uncontrolled case series, our current understanding of the pathogenesis of hyponatremia, and the treatment of hyponatremia in other settings. (See 'General principles' above.)

- Among athletes with hyponatremia and **mild to moderate** symptoms due to EAH (such as weakness, dizziness, headache, nausea, and/or vomiting), we recommend oral hypertonic saline solutions or fluid restriction and observation until the onset of a spontaneous diuresis rather than administering intravenous hypertonic saline (**Grade 1C**). This will correct the hyponatremia and lead to resolution of the symptoms. (See 'Mild to moderate symptoms' above.)

- Among athletes with hyponatremia and mild to moderate symptoms due to EAH that seem to be worsening, an oral or intravenous bolus of 100 mL of hypertonic saline is potentially beneficial and without potential harm. We would **not** give hypertonic saline if the plasma or serum sodium cannot be measured, and if signs and symptoms are not life threatening, since hypernatremia is more common than hyponatremia in endurance athletes. (See 'Mild to moderate symptoms' above.)

- Among athletes with hyponatremia and **severe** central nervous system manifestations of hyponatremic encephalopathy (eg, seizures, confusion, coma), we recommend the following:

  - Hypertonic saline should be administered by experienced medical personnel in the field. (See 'Severe symptoms' above.)

  - We suggest an initial bolus of 100 mL of hypertonic (3 percent) saline, which should raise the serum sodium by 2 to 3 mEq/L (**Grade 2C**). (See 'Use of hypertonic saline' above.)

  - If the serum or plasma sodium cannot be measured on site, we suggest that this regimen be given empirically by experienced medical personnel to athletes with symptoms compatible with hyponatremic encephalopathy (eg, seizures, confusion, coma) and no other obvious cause (**Grade 2C**).

  - All athletes with severe symptomatic hyponatremia should be promptly transported to a hospital for further evaluation and treatment.

  - Repeat boluses can be given to stabilize the patient prior to arrival at the hospital **only** if the plasma or serum sodium has been measured.

- Intravenous isotonic saline is not necessary in most patients and may **worsen** the hyponatremia. (See 'General principles' above.)

- Prevention of EAH has focused upon education concerning the risks of the overconsumption of fluids during the event. Universal guidelines for prevention are

difficult since there are wide variations in sweat production and renal water excretory capacity both between individual athletes and in the same individual depending upon ambient conditions during the race. We recommend that, during the race, endurance athletes **drink according to thirst** (**Grade 1C**). (See 'Prevention' above.)

- Consumption of carbohydrate/electrolyte-containing sports drinks does **not** provide much protection compared to water alone, since most of these drinks are markedly hypotonic to plasma. (See 'Prevention' above.)

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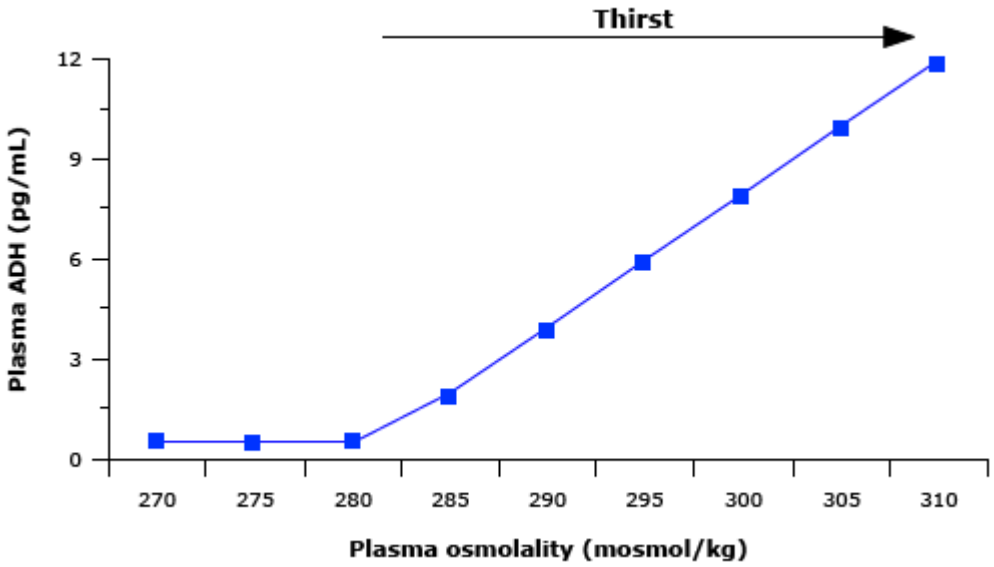
Topic 2290 Version 21.0

GRAPHICS

Osmotic regulation of ADH release and thirst



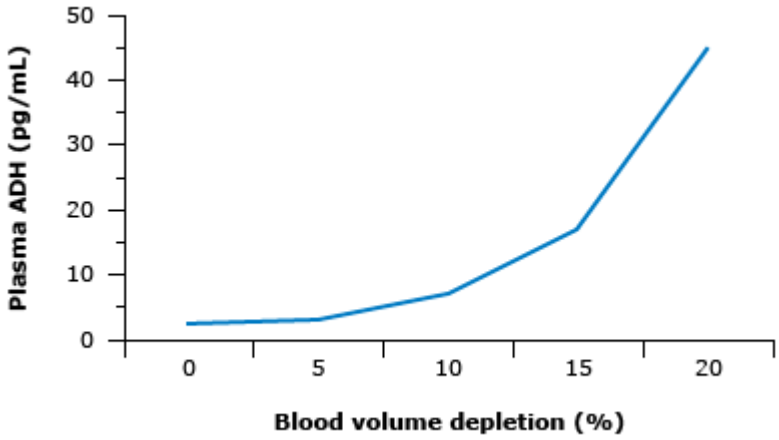
Relation between plasma ADH concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH.

ADH: antidiuretic hormone.

Data from Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. Am J Med 1982; 72:339.

Graphic 65195 Version 5.0

Hypovolemic stimulus to ADH release



Relationship of plasma ADH concentrations to isosmotic changes in blood volume in the rat. Much higher ADH levels can occur with hypovolemia than with hyperosmolality, although a relatively large fall in blood volume is required before this response is initiated.

ADH: antidiuretic hormone.

Data from: Dunn FL, Brennan TJ, Nelson AE, et al. J Clin Invest 1973; 52:3212.

Graphic 58012 Version 3.0