

# Consensus Statement of the 1st International Exercise-Associated Hyponatremia Consensus Development Conference, Cape Town, South Africa 2005

*Exercise-Associated Hyponatremia (EAH) Consensus Panel: Tamara Hew-Butler, DPM,\* Christopher Almond, MD, MPH,† J. Carlos Ayus, MD,‡ Jonathan Dugas, BSc(Hons),\* Willem Meeuwisse, MD, PhD (chair),§ Timothy Noakes, MBChB, MD, DSc,\* Stephen Reid, MBBS, PhD,|| Arthur Siegel, MD,¶ Dale Speedy, MBChB, MD,# Kristin Stuenkel, PhD,\*\* Joseph Verbalis, MD,‡ and Louise Weschler, MAT, PT*

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Over the past decade, exercise-associated hyponatremia (EAH) has emerged as an important complication of prolonged endurance activity.<sup>1–7</sup> Prior to 1985, this condition was not reported, and runners generally finished marathons with weight loss but without serious medical complications. Abnormalities of serum sodium concentrations ( $[Na^+]$ ), when measured, were confined to elevated levels consistent with varying degrees of volume depletion.<sup>8–15</sup>

In March 2005, a panel of twelve international experts on exercise physiology, sport medicine, water metabolism and body fluid homeostasis convened in Cape Town, South Africa, for the 1st International Exercise-Associated Hyponatremia Consensus Development Conference. The primary goal of this panel was to review all of the existing data on EAH and formulate an evidence-based analysis that would define the current understanding of the pathophysiology of EAH. In particular, the panel was constituted to facilitate integration of existing medical and scientific knowledge of other forms of

hyponatremia with the occurrence of this homeostatic imbalance during endurance exercise.

A secondary goal of the EAH Consensus Development Conference was to prepare a statement that would serve to curtail the growing problem of EAH by disseminating the most current information to both medical personnel and the greater public on the prevalence, nature and treatment of this disorder. The panel strived to clearly articulate what we agreed upon, debate issues that we did not agree upon, and describe in detail what we did and did not know, including minority viewpoints that were supported by clinical and experimental data.

The following statement reflects a concise summary of the data deliberated and synthesized by the panel and provides a “snapshot in time” of the current state of knowledge on EAH. New knowledge will continue to advance regarding our understanding of EAH, and will mandate future updates to this consensus statement.

## METHODS

The International Exercise-Associated Hyponatremia Consensus Development Conference (CDC) followed the guidelines set forth by the National Institutes of Health (NIH).<sup>16</sup> The basic principles governing the conduct of a CDC are summarized below:

1. A broad based non-government, non-advocacy panel was assembled to give balanced, objective and knowledgeable attention to the topic. Panel members excluded anyone with scientific or commercial conflicts of interest and included researchers in clinical medicine (C.A., J.C.A., A.S. and J.V.), sports medicine (T.H., T.N., S.R., D.S.) and sports scientists (K.S., J.D.).
2. These experts presented data in a public session, followed by inquiry and discussion. The panel then met in an executive session to prepare the consensus statement.
3. A number of specific questions were prepared and posed in advance to define the scope and guide the direction of the conference. The principle task of the panel was to elucidate responses to these questions.

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4. A systematic literature review was prepared and circulated in advance for use by the panel in addressing the conference questions (see reference list).
5. The consensus statement is intended to serve as the scientific record of the conference.
6. The consensus statement will be widely disseminated to achieve maximum impact on both current health care practice and future medical research.

The panel chairperson (W.M.) did not identify with any advocacy position nor present data on EAH.<sup>16</sup> The chairperson was responsible for directing the plenary session and guiding the panel's deliberations.

There was a strict criterion for invitation to the EAH Consensus Panel: publication of original data on hyponatremia within the last five years. The U.S. Military, which has recently come to its own consensus, was excluded.<sup>17–19</sup> One delegate (L.W.) did not present original data, but has prepared a mathematical model of EAH and was therefore included as an invited participant.<sup>20</sup>

The following focus questions formed the foundation for the EAH consensus statement:

1. What is the definition of exercise-associated hyponatremia (EAH)?
2. Can the severity of EAH be classified by clinical and laboratory criteria?
3. What is the etiology and pathophysiology of EAH?
4. What are the risk factors for the development of EAH?
5. How can EAH be prevented?
6. What are appropriate treatment protocols for EAH?
7. What advice should be disseminated for the prevention and treatment of EAH?
8. What studies should be performed to better understand EAH?

## RESULTS AND DISCUSSION

### What Is the Definition of Exercise-Associated Hyponatremia (EAH)?

EAH is the occurrence of hyponatremia in individuals engaged in prolonged physical activity<sup>1,3–7,21–46</sup> and is defined by a serum or plasma 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,<sup>47</sup> EAH can occur during or after physical activity, and most commonly occurs in events lasting longer than four hours,<sup>1–6,21,23–26,29–35,38–45,48</sup> although at least two cases have been reported in events of shorter duration.<sup>49,50</sup>

### Can the Severity of EAH Be Classified by Clinical and Laboratory Criteria?

EAH should be classified using the same clinical criteria as any acute or rapid onset hyponatremia.<sup>51</sup> As with any acute onset hyponatremia, the most important distinction is determining the presence or absence of clinical signs and symptoms, specifically neurologic manifestations. In general, the lower the serum or plasma  $[Na^+]$ , the more severe will be the

neurologic signs and symptoms.<sup>52</sup> Individual variability is great, however, and the numerical value of  $[Na^+]$  is not a reliable index of the clinical severity of hyponatremia, including EAH.<sup>51</sup>

In general, milder forms of hyponatremia ( $[Na^+]$  between 130–134 mmol/L) are relatively asymptomatic and are likely to resolve spontaneously, although exceptions to this rule have been reported.<sup>1,3,6,31,38,39,41,44</sup> Signs and symptoms of EAH tend to develop when the serum  $[Na^+]$  falls below 130 mmol/L.<sup>3,6,30,31,41</sup> Early signs and symptoms can include: bloating, “puffiness”, nausea, vomiting, and headache. However, many of these signs and symptoms are non-specific and can be present following prolonged exercise in the absence of EAH.<sup>7,21,22,27,30,36,46,53</sup> As the severity of EAH progresses, more serious signs and symptoms can develop as a result of worsening cerebral edema (brain swelling), including altered mental status (confusion, disorientation, and agitation), seizures, respiratory distress (pulmonary edema), obtundation, coma and death.<sup>7,23,25–27,33,34,36,43,45,46,48,53–56</sup> The presence of any of these signs and symptoms represents an absolute indication to measure the serum or plasma  $[Na^+]$ .

### What Is the Etiology and Pathophysiology of EAH?

Current evidence strongly indicates that EAH is a dilutional hyponatremia, caused by an increase in total body water relative to the amount of total body exchangeable  $Na^+$ .<sup>1,4,21–23,26–30,33,35,36,39,46,48,53,55</sup> Although this increase can be relative in nature, in most reported cases of symptomatic EAH, there is body weight gain suggestive of an absolute increase in total body water.<sup>1,4,5,21,23,29,35,39,41,48,53,57</sup> The primary etiologic factor in cases that have been adequately studied appears to be consumption of hypotonic fluids (water or sports drinks) in excess of insensible (respiratory and gastrointestinal), sweat and renal (urine) fluid losses.<sup>1,4,21–23,26–30,33,35,36,39,46,48,53</sup>

Hyponatremia caused solely by the overconsumption of fluids has been demonstrated at rest in athletes with and without a history of EAH.<sup>57,58</sup> Weight gain in these athletes occurred despite an increase in free water excretion and what appeared to be maximally suppressed arginine vasopressin (AVP) levels (as reflected by mean urine osmolalities  $<100$  mOsm/kg  $H_2O$ ). This is consistent with known maximal urine excretory rates of 800–1,000 mL/h in normal adults.<sup>59</sup>

During exercise, however, plasma AVP levels may not be maximally suppressed. This has been demonstrated in a 24-hour field march during which urinary osmolalities failed to reach the minimum concentrations expected in water loaded subjects<sup>29</sup> and in studies of hikers who developed hyponatremia in the Grand Canyon.<sup>22</sup> Plasma AVP levels within “normal ranges” are physiologically *inappropriate* in the presence of hyponatremia and/or hypervolemia.<sup>39–41</sup> Even small increases in circulating AVP levels markedly reduce the maximal kidney excretory capacity,<sup>51</sup> thus increasing the propensity to retain ingested fluids even when rates of drinking do not exceed 800–1,000 mL/h. High urine osmolalities have been measured in athletes hospitalized with critical hyponatremia.<sup>4,22,23,28,46,60</sup> This further implicates inappropriate AVP secretion as an exacerbating factor in the development of dilutional hyponatremia during prolonged physical activity.

Accordingly, hyponatremic athletes can present with a spectrum of urine concentrations, ranging from the ability to excrete dilute urine freely<sup>1,22</sup> to an inability to void despite encouragement.<sup>28,35,53</sup> Thus, the risk of developing fluid overload with previously “normal” or excessive fluid intakes is enhanced when AVP is secreted inappropriately during prolonged exercise, as reflected by increased urine osmolality and decreased urine volume. A lower rate of urine production correlates significantly with a higher rate of serum/plasma  $[Na^+]$  decrease in athletes drinking excessively during exercise.<sup>50</sup> Multiple potential stimuli to AVP secretion can exacerbate fluid retention at any time during prolonged exercise.<sup>21,61</sup> However, given the short half life (6–8 minutes)<sup>61</sup> of AVP, measurement of suppressed AVP levels at time points after the cessation of physical activity do not eliminate the possibility of inappropriate AVP secretion as a contributory factor to the development of EAH.

Excessive  $Na^+$  loss has not been demonstrated to be a primary causative factor in the pathogenesis of EAH. Published data on  $Na^+$  losses in EAH show that sodium loss is no greater in individuals who develop EAH than in individuals who do not.<sup>21,33,40,41</sup> Although symptomatic EAH is largely associated with weight gain, mild or asymptomatic EAH (generally  $[Na^+]$  in the range of 130–134 mmol/L) can be associated with a spectrum of weight change, from weight loss (–9%) to weight gain (+2%).<sup>39</sup> The etiology of asymptomatic EAH with weight loss has not been clearly established.<sup>3,31,39,62</sup> However, in athletes with high sweat sodium concentrations (>100 mmol/L)<sup>63</sup> or high urinary sodium losses from inappropriate AVP secretion and water retention (>400 mOsm/L)<sup>22,23,46</sup> sodium losses may play a *secondary* role in the pathogenesis of EAH by either of two potential mechanisms: 1) hypovolemia produced by losses of sodium and water from sweating can act as a stimulus to AVP secretion, producing a secondary retention of water, as is seen medically in some cases of diuretic-induced hyponatremia<sup>64</sup>; 2) sodium losses themselves can worsen the degree of hyponatremia, although in most cases not nearly as much as water retention<sup>20</sup> when summed up over time. Further studies are needed to fully investigate the role of sodium losses on this group of athletes who develop EAH, particularly those with a weight loss in excess of 3% or with a large volume of sweat over time, in warmer climates and in events lasting over 24 hours.

Ingestion of electrolyte-containing sports drinks does not prevent the development of EAH in athletes who drink to excess.<sup>1,22,32,62</sup> This is due to two factors: 1) all such drinks are hypotonic (<135 mmol/L), and therefore will cause dilution of serum  $[Na^+]$  if water is retained in the body to excess; and 2) it is well known that even administration of isotonic saline will not increase serum  $[Na^+]$  in hyponatremic patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) because in a euvolemic or hypervolemic state, the infused sodium will be excreted in the urine rather than retained.<sup>65</sup> Sodium supplementation does not influence post-exercise  $[Na^+]$  in athletes who either lose<sup>66</sup> or maintain bodyweight.<sup>50,67</sup> However, in athletes who gain weight and develop EAH from excessive fluid intake, the serum  $[Na^+]$  is maintained somewhat better if the sodium concentration of the ingested beverage exceeds the amount present in currently available commercial sports drinks (ie, >20 mmol/L).<sup>44</sup>

## What Are Risk Factors for EAH?

The presence of a risk factor implies a correlation with higher rates of EAH, but not necessarily causation. It is likely that these risk factors interact with each other and, in some cases, may not have an independent association with EAH. Recognized risk factors include:

Low body weight<sup>1,6,40</sup>

Female sex<sup>1,6,7,22,30,39,54</sup>

4 hours exercise duration<sup>1–6,21,23–26,29–31,33–35,38–44,48</sup>

Slow running or performance pace<sup>1,4,7,30</sup>

Race inexperience<sup>30,45</sup>

Excessive drinking behavior<sup>1,4,7,26,30,37</sup>

High availability of drinking fluids<sup>30</sup>

Altered renal water excretory capacity (potentially impaired by drugs, such as nonsteroidal anti-inflammatory agents,<sup>7,23,43,54</sup> intrinsic renal disease or SIADH)

Extreme hot<sup>21,22,25,26,28,32,37</sup> or cold<sup>6</sup> environmental conditions.

In a multivariate analysis, hyponatremia was associated with weight gain, a racing time >4:00 hours and low body-mass-index extremes.<sup>1</sup>

Low sodium ingestion, from the voluntary avoidance of sports drinks, sodium supplements or salty snacks, has not been shown to be a risk factor during events lasting <24 hours.<sup>12,67</sup> Published data on the cystic fibrosis genotype is inconclusive,<sup>68–71</sup> with only one documented case of EAH reported in an infantryman whose fluid intake was high.<sup>63</sup> Further assessment will need to be made before excluding these variables as potential risk factors for EAH.

## How Can EAH Be Prevented?

EAH is caused primarily by the consumption of fluid in excess of urinary and sweat losses. Therefore, it follows that any individual participating in endurance exercise, and particularly those at increased risk for EAH, should avoid over consumption of fluids.<sup>42,72</sup> There is wide variability in sweat rates and renal water excretory capacity\* during exercise, both among individuals and in the same individual depending on ambient environmental conditions during the time of exercise; thus, blanket universal drinking guidelines are not possible. The primary means of preventing EAH is to avoid excess fluid retention, as manifested by weight gain, during or after exercise. There are at least two ways to insure that weight gain does not occur during exercise: 1) drink only according to thirst (ie, *ad libitum*)<sup>73</sup> or 2) use the USATF guidelines, or analogous methods, to estimate hourly sweat losses during exercise and avoid consuming amounts greater than this during endurance exercise events.<sup>74</sup>

Published data show that an education program advising athletes on the risks of overdrinking, together with limiting fluid availability at a race, has been associated with a reduction

\*Sweat rates during sustained endurance exercise can vary markedly between individuals, ranging from as high as >2L/h<sup>27</sup> to as low as <250 mL/h.<sup>77</sup> Under resting conditions, maximum rates of renal water excretion in normal individual can reach levels as high as 1.4 l/h.<sup>21</sup> However, during sustained endurance exercise, rates of renal water excretion can be significantly decreased by antidiuresis due to inappropriate AVP secretion, potentially to as little as 0 to 60 mL/h (resting values).<sup>67</sup>

in the incidence of EAH without deleterious effects.<sup>42,75</sup> Specifically for an Ironman distance triathlon, cycle aid station placement every 20 km, and run stations every 2.5 km are recommended.<sup>42</sup> In a standard marathon footrace, placement of aid stations every 5 km has been associated with an absence of EAH.<sup>72</sup>

There is no currently available evidence to support the suggestion that Na<sup>+</sup> supplementation prevents the development of EAH<sup>66,76</sup> nor is there any evidence that consumption of electrolyte-containing hypotonic fluids (ie, sports drinks) can prevent the development of EAH in athletes who drink to excess.<sup>20,67</sup> Although some studies suggest that ingestion of electrolyte-containing drinks can decrease the severity of EAH,<sup>44</sup> it is clear that this approach will not prevent the occurrence of this disorder in the presence of overdrinking.

### What Are Appropriate Treatment Protocols for Laboratory Confirmed EAH?

Medical facilities at endurance events should include onsite analysis of serum or plasma [Na<sup>+</sup>].<sup>78</sup> Any athlete exhibiting signs and symptoms of acute hyponatremia listed above should be screened for EAH by measuring plasma or serum [Na<sup>+</sup>]. Based on this determination, the following treatment protocols are advised:

#### Asymptomatic EAH

Asymptomatic hyponatremia is not normally detected unless an athlete has blood or serum electrolyte concentrations tested for some other reason.<sup>1,3,6,29,31,38,39,41,44</sup> In athletes with this biochemical diagnosis, oral fluid intake should be restricted until the onset of urination. Athletes should also be advised to seek urgent medical attention if any signs or symptoms of EAH develop within 24 hours. Asymptomatic EAH is a contraindication for the administration of intravenous normal saline, which can worsen the degree of hyponatremia and fluid overload in some cases.

#### Symptomatic—Onsite

Intravenous access must be established in athletes with symptomatic EAH, but care must be taken to avoid the administration of isotonic or hypotonic fluids to prevent worsening the degree of hyponatremia and fluid overload (with the exception of cases where there is evidence of circulatory insufficiency where standard Advanced Cardiac Life Support protocols apply).<sup>55</sup> Oxygen should be administered and the athlete immediately transferred to a definitive medical care facility. The diagnosis of EAH must be communicated to the emergency room physician upon transfer of care.

If the medical staff is experienced in treating hyponatremia in the field, any athlete with EAH who exhibits signs of respiratory insufficiency, confusion, obtundation, nausea and vomiting can be treated with 100 mL of 3% NaCl over ten minutes to acutely raise [Na<sup>+</sup>] and decrease brain edema. This maneuver can raise the [Na<sup>+</sup>] an average of 2–3 mmol/L and should not pose any substantial danger to the patient. This therapy aims to stabilize the athlete prior to hospital transfer without producing complications. The efficacy of hypertonic 3% NaCl infusion treatment has been documented in the

hospital setting<sup>54,79–83</sup> and this approach has been recently proposed in the field.<sup>87</sup>

#### Symptomatic—In Hospital

Both clinical and laboratory reassessment must be performed upon admission, taking care to avoid treatment delays whereas awaiting diagnostic tests such as brain imaging.<sup>7,43,54,60</sup> Administration of hypotonic or isotonic intravenous fluids during this reevaluation is again contraindicated because of the potential to exacerbate hyponatremia and fluid overload.

If symptomatic EAH persists or worsens, current treatment guidelines for acute symptomatic hyponatremia should be followed. These should entail administration of hypertonic solutions of NaCl to immediately decrease brain edema. Several different protocols have been employed to accomplish this goal, including the following: 1) administer either a 100 mL or a 1 mL/kg bolus of 3% NaCl and repeat hourly at a rate of 100 mL/h<sup>7,43</sup> or 2) infuse 3% NaCl at a rate of 1–2 mL/kg/h<sup>84</sup>. Alternatively, if hypertonic NaCl is not immediately available, hypertonic mannitol can be administered to accomplish this goal.<sup>85</sup> Regardless of which method is chosen, treatment should be continued until the patient regains consciousness. Subspecialty consultation is strongly advised (nephrology/endocrinology) with regard to further therapy (eg, loop diuretics, fluid restriction, etc). Plasma or serum [Na<sup>+</sup>] should be monitored every hour until the symptoms subside and the patient is clinically stable with an appropriate urine output. Osmotic demyelination, or central pontine myelinolysis, in association with the rapid correction of an acute hyponatremia (ie, <48 hour duration), has not been reported<sup>86</sup> and should never be an impediment to rapidly correcting hyponatremia in symptomatic EAH.<sup>7,21–23,26,43,46,54,60</sup>

### What Advice Should Be Disseminated for Prevention and Treatment of EAH?

#### Athletes and Coaches

Strategies aimed at preventing the over consumption of hypotonic fluids (water or sports drinks), as outlined above, need to be communicated effectively to coaches and athletes. Furthermore, athletes and coaches must be better educated on the signs and symptoms of EAH regarding when to seek medical attention.

#### Medical Directors and Race Directors

Aid stations should be placed at appropriately distanced intervals. Medical and race directors should strongly consider pre-race weight measurements as a routine part of race registration. The pre-race weights of collapsed athletes should be readily available to medical personnel either electronically or on the athletes' race bib number. Medical directors should ensure the availability of onsite [Na<sup>+</sup>] analysis to screen for EAH before medical treatment is initiated. A self audit regarding the incidence and outcome of EAH cases is strongly advised after completion of each yearly event. Because the condition is preventable, appropriate action should be taken to avert future recurrences.

## Medical Tent Staff

Medical personnel within all medical areas must be educated on the signs, symptoms and treatment strategies of EAH. Mandatory weighing of all participants presenting to the medical tent is strongly advised. Whether symptomatic EAH should be treated with 3% NaCl in the medical tent prior to transfer to a hospital emergency facility has not been critically evaluated at this time. Decisions regarding use of 3% NaCl for treatment of EAH in the field will therefore depend on the level of expertise of the medical staff on site.

## Emergency Medical Services and Hospitals

Prior to the race or event, the medical team should establish a relationship with the local emergency teams, medical facilities and emergency room physicians. The availability of 3% NaCl should be confirmed and the administration of 3% NaCl should be guided by the treatment protocol detailed above.

## Local Media

The media should disseminate the same information that is provided to athletes and coaches.

## What Studies Should Be Performed to Better Understand EAH?

Prospective and controlled clinical trials on fluid replacement during exercise should be performed both in the laboratory and in the field. An international registry of all cases of EAH should be established. The following areas were identified by the Panel as priorities for further study:

- Which cases of symptomatic EAH can be safely monitored and managed on site rather than transferred to hospital emergency rooms?
- What are the appropriate indications for administering hypertonic NaCl in symptomatic EAH? Should initiation of hypertonic NaCl begin onsite in the medical tent when symptoms are severe?
- Are oral hypertonic NaCl solutions of use in mild to moderate EAH? Could they be used when hypertonic NaCl solutions are unavailable (ie, onsite)?
- What is the etiology of EAH when it occurs in association with weight loss?
- What are the mechanisms (renal, cardiovascular, hormonal) responsible for fluid retention during prolonged physical activity?
- What is the etiology/mechanism for inappropriate (ie, non-suppressed) plasma AVP concentrations during endurance exercise?
- What is the rate of endogenous water production or release during endurance exercise, in particular the water complexed to muscle and liver glycogen? How does this reduce the need to ingest fluids to replace sweat losses?

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