[Primary Care]

Athletes at High Altitude

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Context: Athletes at different skill levels perform strenuous physical activity at high altitude for a variety of reasons. Multiple team and endurance events are held at high altitude and may place athletes at increased risk for developing acute high altitude illness (AHAI). Training at high altitude has been a routine part of preparation for some of the high level athletes for a long time. There is a general belief that altitude training improves athletic performance for competitive and recreational athletes.

Evidence Acquisition: A review of relevant publications between 1980 and 2015 was completed using PubMed and Google Scholar.

Study Design: Clinical review.

Level of Evidence: Level 3.

Results: AHAI is a relatively uncommon and potentially serious condition among travelers to altitudes above 2500 m. The broad term AHAI includes several syndromes such as acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), and high altitude cerebral edema (HACE). Athletes may be at higher risk for developing AHAI due to faster ascent and more vigorous exertion compared with nonathletes. Evidence regarding the effects of altitude training on athletic performance is weak. The natural live high, train low altitude training strategy may provide the best protocol for enhancing endurance performance in elite and subelite athletes. High altitude sports are generally safe for recreational athletes, but they should be aware of their individual risks.

Conclusion: Individualized and appropriate acclimatization is an essential component of injury and illness prevention.

Keywords: high altitude pulmonary edema; high altitude cerebral edema; acute mountain sickness; altitude training

Exercise at altitude has been gaining popularity in recent decades. High altitude exercise ranges from casual hiking to highly competitive ultra-endurance races (eg, foot race, mountain biking, cross-country skiing) and even includes team sports. Travel to high altitude has potential significant health consequences. Not only are altitude and environmental factors a concern for the athletes' safety, but access is often a barrier to appropriate medical care. For safety reasons, proper acclimatization is important for those traveling to high altitudes. Altitude training is also thought to be beneficial for athletic performance, though the evidence for this is not clear. The purpose of this article is to review physiologic changes at high altitude, altitude illness, and medical considerations for both recreational and competitive athletes. We will discuss high altitude training for competitive athletes and unique considerations for traveling with teams to high altitude, as well as special groups of athletes such as young athletes, older athletes, and pregnant women.

PHYSIOLOGIC RESPONSE TO ALTITUDE AND MEDICAL CONSIDERATIONS

Regarding human physiology, the most important environmental factors at high altitude are low atmospheric oxygen concentration and low barometric pressure. Other factors to consider are extreme temperature (cold and hot) and increased ultraviolet radiation. The human body responds in different ways to adapt to these changes.

Acute Exposure

The body's first response to high altitude low oxygen concentration (hypoxia) is an increase in ventilatory response triggered by carotid body receptors.[27,64] Acute exposure to high altitude causes multiple compensatory changes, including increase in sympathetic activity with increased heart rate, cardiac output, and blood pressure. These responses eventually play a significant role in acclimatization. Hypoxic ventilatory

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The authors report no potential conflicts of interest in the development and publication of this article.

DOI: 10.1177/1941738116630948

Table 1. Pathophysiologic responses to high altitude[10,21,23,24,27,49,64,73]

System	Acute Exposure	Chronic Exposure
Pulmonary	Hypoxemia, ↑ventilation, ↓arterial oxygen saturation	Hypoventilation, pulmonary hypertension, ↑lung capillary blood volume, ↑lung diffusion capacity, exacerbation of chronic lung disease, HAPE on renascent of altitude residents
Cardiovascular	Transient ↑blood pressure, ↑heart rate, ↑venous tone, ↑cardiac output, peripheral edema	↓Systolic/diastolic blood pressure, right ventricular hypertrophy, right heart failure, arterial oxygen desaturation, ↑plasma triglyceride level, exacerbation of congenital heart disease
Hematologic	↑Hemoglobin concentration, ↓plasma volume, ↑erythropoietin, ↑D-dimer	Polycythemia, ↑O_2 carrying capacity of blood
Renal	↑Bicarbonate excretion, ↓plasma calcium and phosphate, hypocapnic respiratory alkalosis, ↑diuresis	Hyperuricemia, microalbuminuria, ↓renal plasma flow, ↑filtration fraction (preserved or mildly ↓glomerular filtration rate), glomerular hypertrophy
Neuropsychologic	↓Synthesis of neurotransmitters, cerebral vasodilation, mood changes, ↓cognitive function, ↓motor/sensory function	Cerebral hypoxia, biochemical dysfunction, ↓sleep quality, ↑mood disorders, ↓cognitive function
Exercise	↓Maximal oxygen consumption, ↓VO_2max	↓Aerobic exercise capacity
Other	Retinopathy, anorexia	

HAPE, high altitude pulmonary edema.

response causes decreased alveolar CO_2, hypocapnia, and respiratory alkalosis, which has an inhibitory effect on the central respiratory center. This limits further increase in ventilation (Table 1). The renal system responds to these changes by excreting bicarbonate and conserving hydrogen ions.[23] During acclimatization, parathyroid hormone level increases, which causes an increase in plasma calcium and phosphate levels. Altitude-induced diuresis occurs as an early stage of acclimatization.[23,27] There has been some suggestion that short-term high altitude exposure is a risk factor for hypercoagulation.[25,62] There are only a handful of published studies in this area and the majority of them were conducted during long air travel rather than ascent to high altitude. It seems this phenomenon is multifactorial (eg, hypoxia, hemoconcentration, hypohydration, cold temperature, use of constrictive clothing, and relative hypomobility due to extreme weather).[25,62] Athletes with sickle cell trait are also at high risk for sickling during exertion at high altitude.[17]

Chronic Exposure

Increased hemoglobin concentration as a hematologic adaptation to high altitude among highlanders (typically residents at altitude >4000 m) has been reported for over a century (Table 1). This phenomenon is a result of erythropoietin production by the kidneys.[27,64] Effects of chronic exposure to high altitude on other systems are summarized in Table 1.

High Altitude Illness

During certain athletic events such as mountain races, athletes may experience very rapid ascent, which places them at high risk for developing altitude illness (Table 2). Risk factors for developing high altitude illness include previous episodes of high altitude illness, a faster rate of ascent, higher elevation, poor hydration, increased intensity of physical activity, and individual variability.[4,20,26,36]

Slow ascent to altitude is the hallmark of prevention for all acute high altitude illnesses (AHAIs). Guidelines recommend that once above 2500 m, altitude should be increased at a rate of 600 to 1200 m per 24-hour period.[36] Duration of an effective acclimatization also depends on the athlete's residing altitude and the altitude to which the athlete plans to ascend. Methods using hypobaric hypoxic chambers or true high altitude may be more effective for acclimatization than those using normobaric hypoxic conditions.[20] Pharmacologic prevention (Table 2) should be considered as an adjunct to slow ascent and proper acclimatization, or when this is not feasible (eg, during mountain bike and foot races). There are limited data on the effectiveness of agents other than acetazolamide for prevention

Table 2. Acute high altitude illness summary[a]

Condition	Symptoms and Signs	Treatment	Prophylaxis
Acute mountain sickness	Headache, anorexia, nausea, vomiting, dizziness, fatigue, weakness, insomnia	Descent, acetazolamide, dexamethasone, supplemental oxygen	Slow ascent, acetazolamide, dexamethasone
High altitude pulmonary edema	Dyspnea at rest, cough, decreased exercise performance, chest pain/tightness, low pulse oximetry, central cyanosis, tachypnea, tachycardia, rales, wheezing	Descent, supplemental oxygen, nifedipine, phosphodiesterase-5 inhibitors, salmeterol, portable hyperbaric chambers	Slow ascent, nifedipine, phosphodiesterase-5 inhibitors, salmeterol
High altitude cerebral edema	Change in mental status or ataxia in a person with AMS or HAPE	Descent, dexamethasone, acetazolamide, supplemental oxygen, portable hyperbaric chambers	Slow ascent, dexamethasone, acetazolamide

AMS, acute mountain sickness; HAPE, high altitude pulmonary edema.
[a]Adapted from Hoffman et al.[28]

and treatment of acute mountain illness.[36] The adverse effects of acetazolamide are uncommon and include paraesthesia, urinary frequency, and dysgeusia.[54]

Athletes with acute mountain sickness (AMS) should not continue ascent until symptoms resolve and should consider descent if medical management does not resolve symptoms. Medical providers should advise athletes with high altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE) to immediately descend to a lower altitude and be followed for medical management. The preferred rate of deacclimatization has not been well studied.

Chronic mountain sickness (CMS) is an uncommon condition among highlanders. Its prevalence has direct correlation with altitude of residence. CMS is characterized by extreme polycythemia, pulmonary hypertension, severe right ventricular hypertrophy, low systemic blood pressure, hypoventilation, and chronic arterial oxygen desaturation.[27,64]

Ultraviolet Radiation

High altitude athletes are at risk from the deleterious effects of ultraviolet (UV) radiation. With every gain of 1000 m in altitude, there is an increase in UV-A and UV-B exposure by approximately 10% to 20%.[36] Increasing UV exposure is correlated with a greater incidence of skin cancer, seborrheic dermatitis, and cataract formation.[15,36,53,55] Athletes should understand these risks and providers should ensure proper education, including wrap-around sunglasses with UV protection, adequate clothing, and sunscreen with a sun protection factor of at least 30.[36] Snow increases UV exposure risk by providing a reflective surface, and radiation is at its highest between 10 AM and 2 PM during the summer months.[36,53] This may cause snow blindness (UV keratitis).[55]

Sleep Hygiene

At high altitude, athletes often complain of insomnia, frequent awakening, and restless sleep.[8,61,63] Unacclimated athletes may be more prone to poor sleep quality.[8,61] Subjectively, this is characterized by the sensation of suffocation or apnea and relieved by wakening and several deep breaths, resulting in restless sleep.[8,63] Physiologically, athletes have a cycle of hyperventilation secondary to high altitude–associated hypoxia, subsequent hypocapnia, and decreased respiratory drive, which is followed by apnea and resumption of the cycle.[61,63] Appropriate sleep hygiene and pretravel management of jetlag are recommended.[36] In athletes requiring treatment of sleep disturbance, both acetazolamide and sleep medications (eg, low-dose benzodiazepines) have been effective.[36,63] Risks of taking medications such as benzodiazepine include ataxia, cognitive impairment, and fatigue, and should be weighed against the potential benefits.

Nutrition

There are a few nutritional concerns for athletes at high altitude. First, there is an association between chronic high altitude exposure and significant weight loss.[69] This seems to be primarily due to loss of fat-free mass, which may have significant negative effects on physical performance.[69] Factors possibly contributing to this weight loss are decreased physical activity, hypoxia, irregular sleep pattern, cold exposure, and nutritional imbalance related to protein metabolism.[1,19,34,50,69] Based on a few small studies, it seems that increasing caloric intake is not the best way to retain fat-free mass at altitude.[69] Increasing protein intake, particularly leucine, may be a more practical strategy.[69] Significant weight loss occurs at altitude

above 5000 m. However, mild to moderate weight loss may occur with a shorter duration stay at lower altitude (3000-5000 m) due to increased basal metabolic rate, increased exertion, hypoxia-related appetite suppression, and restricted food availability.[19,34] There is also a tendency for hypohydration at high altitude.[36] This is likely multifactorial (eg, diuresis, decreased fluid intake). Adequate fluid intake is essential to avoid underperformance due to hypohydration particularly in warm climates. Because of strong demand for erythropoiesis, athletes should increase dietary and supplemental iron before traveling to high altitude.[36]

Overall, at high altitude, an athlete's nutritional strategy should include adequate caloric intake, which is usually difficult to achieve mainly because of difficult access to food and decreased appetite.[34] Inadequate caloric intake may cause significant weight loss for athletes staying at high altitude for more than 3 weeks.[34] To prevent glycogen storage deficit, a diet should consist of about 60% carbohydrates, 25% fat, and 15% protein.[34] This is particularly important for athletes staying at high altitude for more than a couple of weeks.[34]

MEDICAL CONSIDERATIONS FOR SPECIAL POPULATIONS

The majority of research on risks of and patient care at high altitude is focused on healthy adults. However, it is also important to consider the particular risks faced by young athletes, pregnant women, and older athletes.

Young Athletes

Children are not at greater risk of altitude illness than adults and may actually be at lower risk.[37,38,71] In addition, children do not experience altitude illness of greater severity than adults.[38] Male children and children with a greater body mass index may be at greater risk for altitude illness compared with other children, though there is no correlation between altitude illness and physical fitness.[70]

Certain underlying medical conditions including a history of prematurity with respiratory distress syndrome, pulmonary hypertension, congenital cardiovascular or pulmonary abnormalities, current respiratory infection, trisomy 21, and obstructive sleep apnea increase a child's risk of AMS.[32,47] Children who develop severe altitude illness including HAPE should be evaluated for underlying cardiopulmonary abnormality.[32,47]

Diagnosis of AMS can be more difficult in children than in adults. Fussiness is a common symptom of AMS in preverbal children, as well as symptoms of decreased appetite, gastrointestinal symptoms, and lack of playfulness.[71,72] The Lake Louise Age-Adjusted Symptom Score is available for use in verbal children and uses more age-appropriate language for assessment of symptoms.[60]

As for adults, treatment of altitude-related illness in children consists primarily of descent to lower altitude. Medications for treatment and prevention of altitude-related illnesses in children are the same as used for adults. It is important to remember that use of these medications is based on clinical experience not on primary studies in children.[32]

Pregnant Women

Pregnant women who live at high altitude are known to have increased rates of intrauterine growth restriction (IUGR) and preeclampsia.[12,33,48] Women who are at high risk for IUGR or preeclampsia are advised to avoid travel to high altitude.[30]

However, less data are available about the risks of pregnant women traveling from sea level to high altitude. Pregnant women are not believed to be at increased risk of altitude illness.[46] Acetazolamide is contraindicated in the first trimester and after 36 weeks gestation.[30,31] A higher rate of spontaneous abortion has been suspected but not consistently supported by evidence.[32] However, women at increased risk of spontaneous abortion are advised to avoid travel to high altitude.[30]

Increased risk of IUGR and preeclampsia at high altitude are thought to be related to relative hypoxia. Exercise also has the potential to cause fetal hypoxia in the case of compromised uteroplacental circulation.[30,31] Pregnant women should allow 2 to 3 days for acclimatization before exercising at all over 2500 m and 2 full weeks before strenuous exercise.[30]

Because of the lack of data on exercise in pregnancy at high altitude, formal recommendations vary. The American College of Obstetricians and Gynecologists endorses exercise at altitudes up to 1830 m.[16,18,32] The Society of Obstetricians and Gynaecologists of Canada cited no adverse effects with moderate exercise at 1800 to 2500 m and recommends acclimatization prior to exercise above 2500 m.[18,32] These recommendations are for healthy women with healthy pregnancies; women with high-risk pregnancy conditions such as hypertension, preeclampsia, IUGR, anemia, diabetes, and maternal smoking should avoid exercise at high altitude.[31]

Given the lack of data in this area, pregnant women should be cautious regarding exercise and should be sure to make any decisions in consultation with their obstetric provider.[32]

Older Athletes

Aging is not a risk factor for altitude illness, and in fact, may be protective against severe altitude illness.[51,52] The reason for this is not well understood, but it may be due to the known decrease in brain size with aging, which results in an increase in cranial compliance.[51,52]

Adults with controlled, stable chronic lung disease can do well at high altitude but should be prepared for exacerbation. If on oxygen, an individual will likely have to increase the FiO_2 at altitude. A portable pulse oximeter can be a guide. Patients with chronic obstructive pulmonary disease should be prepared with medications and possibly oxygen in case of exacerbation.[13,44] Though the obstructive component of obstructive sleep apnea does not worsen at altitude, hypoxia can be worsened by concomitant relative central sleep apnea or increase in sleep-disordered breathing.[13] Acetazolamide improves the apnea-hypopnea index and oxygen saturation in obstructive sleep

apnea patients with or without continuous positive airway pressure use.[39]

Individuals with unstable cardiovascular disease should be cautious at altitude, while those with well-controlled disease usually do well. In patients with labile or resistant hypertension, nocturnal O_2 at altitude may help with blood pressure control.[13] However, patients with stable hypertension should not have to adjust their medications.[43] Individuals with a history of congestive heart failure should be cautious for development of AMS as this is associated with fluid retention.[13] An older adult's prognosis related to high altitude is based on his or her medical conditions and general physical fitness.

CONCERNS FOR ATHLETIC TEAMS TRAVELING TO HIGH ALTITUDE

Physicians of athletic teams traveling to relatively high altitude locations (eg, Denver at 1610 m and Mexico City at 2250 m) should be familiar with prevention and management of AHAI as well as special considerations for specific conditions and populations. Athletes with sickle cell trait should be counseled about the potential risk of acute sickling with exertion. If possible, early arrival to the event is highly recommended, and the medical team should discuss the importance of adequate hydration and caloric intake for better performance. Athletic teams often question the need for and utility of supplemental oxygen for athletes at high altitude, but in reality, this should not be necessary for healthy children and adults. If an athlete is so hypoxic as to require supplemental oxygen, HAPE or another pulmonary problem should be considered.

ALTITUDE TRAINING

Altitude training has emerged as a way to gain a tactical advantage over the competitor. It entails breathing in a reduced percentage of oxygen (hypoxia), either natural or simulated, with a goal of improved athletic performance. The optimal altitude for this type of training is unknown; however, most research studies have been conducted at moderate altitudes (2000-3000 m). At these elevations, a reliable erythropoietin response has been observed with minimal side effects.[11,14,42,57,58]

There are 3 basic models for altitude training: live high, train high (LHTH); live low, train high (LLTH); and live high, train low (LHTL). In locations where training at altitude is not always geographically possible, simulated altitudes are often employed. Altitude training can be simulated (normorbaric hypoxia) through an altitude simulation room, tent, or hypobaric chamber.[66]

Live High, Train High

Some team sports also have facilities at altitudes in the 1800- to 2500 m range. LHTH is often utilized because of a general consensus among athletes that it improves endurance performance.[22] There is a dose-response relationship with the degree of hypoxia resulting in increased red cell mass. However, there is concern that elevations higher than 3000 m can result in loss of training intensity and subsequent muscle wasting,[42] excess ventilatory work, and increased likelihood of acute mountain sickness. These side effects may cause stress on the athletes and can outweigh any positive erythropoietic benefits.[11,57] While training at altitude does allow for acclimatization, endurance athletes often are not able to train at the same intensity as compared with sea level training.[65] Performance outcomes at LHTH are equivocal, and some positive results in uncontrolled studies can be explained by placebo effect.[6] Another drawback of living at persistently high altitudes and returning to sea level is the challenge of heat acclimatization back at sea level after being at a cooler high altitude temperature.

Live Low, Train High

LLTH is a model of altitude training where athletes live in a natural environment (normobaric normoxic) and are exposed to short intervals (5-180 minutes) of simulated normobaric hypoxia or hypobaric hypoxia.[65] The hypoxic exposures can be done at rest or during exercise training. Intermittent hypoxic exposures are effective in preacclimatization in athletes before ascending to high altitude. However, the effect seen on performance has been mixed, and this strategy does not seem to improve endurance capacity any more than training in the natural environment.[65]

Live High, Train Low

With LHTL, athletes either live/recover at moderate altitude (2000 to 3000 m; hypobaric hypoxia) or use simulated altitude (normobaric hypoxia) and train at lower altitude or sea level. In addition to acclimatization, LHTL methods enhance exercise performance at altitude and sea level as athletes gain physiological benefits at altitude while maintaining workout volume and intensity training at a lower altitude.[65] To sustain a hypoxic erythropoietic effect with altitude training, the athlete must accumulate approximately 300 to 400 hours by living at a minimum altitude of 2000 m for more than 14 to 16 hours per day for at least 19 to 20 days.[22,41,66,67] The response to altitude training is individualized, and not everyone benefits the same.[14] Furthermore, the potential physiological response seems to be reduced in athletes with high red cell volume, such as elite endurance athletes.[45] However, the degree of physiologic response does not necessarily predict performance, as larger physiological responses are expected during preseason and in less fit individuals.

In a meta-analysis, hypobaric hypoxia LHTL offers the best chance for enhancing endurance performance in elite and subelite athletes.[9] In a second study, there were significant differences in the responses to LHTL training camp in hypobaric hypoxia groups compared with normobaric hypoxia groups.[56] There was greater performance enhancement in the hypobaric hypoxia group 3 weeks after LHTL and increased hematological changes, although some of the differences were thought to be secondary to increased exposure time in the hypobaric hypoxia group.[56] In a double-blind, placebo-controlled study of 16

endurance cyclists, there was no difference in time trials or changes in measured physiologic variables after 4-week exposure to normobaric hypoxia at 2500 m versus placebo.[59] Alternatively, a second study comparing hypobaric hypoxia to normobaric hypoxia with acute exposure at 4300 m in cyclists concluded that exposure to normobaric hypoxia may not induce the same hypoxic stimulus and training benefit as exposure to hypobaric hypoxia.[3]

The development of hypoxic facilities (eg, hypoxic dormitories or tents, hypobaric chambers) increases the opportunity for hypoxic altitude training, especially when geographically challenged. Altitudes of around 2500 m can be simulated by reducing the oxygen content from the normal 21% down to about 15% by diluting the oxygen with nitrogen. These are often called hypoxic/nitrogen houses. Hypoxic tents are easy to use and very portable. Tents can simulate altitudes up to 4000 m. Large and small barometric steel chambers are available, but these are high in cost and are limited in availability. Respiratory masks increase respiratory muscle strength rather than resulting in physiologic changes. Respiratory muscle training has resulted in benefit to exercise performance in less fit individuals.[29] Although studies have shown mixed results, there is some evidence that suggests nitrogen dilution may enhance sea level performance in elite athletes, provided a sufficient dose of simulated altitude is applied (12-16 hours for 4 weeks at an elevation of 2500-3000 m).[40,68]

The optimal altitude for an athlete depends on the athlete's sport, current residing altitude, and altitude of the event.[22] Athletes that may derive the most benefit from altitude training are those that cover long distances with repeated high-intensity effort.[2,22] There are divergent data on whether physiologic responses of hypobaric hypoxia and normobaric hypoxia are similar or different. Hypobaric hypoxia LHTL currently provides the best protocol for enhancing endurance performance in elite and subelite athletes, while some normobaric hypoxia protocols are effective in subelite athletes.[9] When geographically challenged, hypoxic/nitrogen houses or tents are an alternative and can help with acclimatization.

CONCLUSION

Appropriate acclimatization duration varies among athletes. General consensus is that athletes should arrive at moderate altitude at least 2 weeks before a given event.[4,35,36] Physiologic changes of altitude typically improve with acclimatization and resolve with descent to lower altitude.[32] Because of the potentially dangerous nature of high altitude illnesses, conservative management, including prompt descent to lower altitude, is essential to prevent life-threatening conditions. Altitude training is a popular training method particularly among elite athletes. Effects of altitude training on athletic performance seem to be at best minimum and temporary. Most studies were conducted on individual endurance athletes; hence, the effects on team-sport athletic performance is unknown.[5,7]

REFERENCES

1. Armellini F, Zamboni M, Robbi R, et al. The effects of high altitude trekking on body composition and resting metabolic rate. *Horm Metab Res.* 1997;29:458-461.
2. Aughey RJ. Applications of GPS technologies to field sports. *Int J Sports Physiol Perform.* 2011;6:295-310.
3. Beidleman BA, Fulco CS, Staab JE, Andrew SP, Muza SR. Cycling performance decrement is greater in hypobaric versus normobaric hypoxia. *Extrem Physiol Med.* 2014;3:8.
4. Bergeron MF, Bahr R, Bartsch P, et al. International Olympic Committee consensus statement on thermoregulatory and altitude challenges for high-level athletes. *Br J Sports Med.* 2012;46:770-779.
5. Billaut F, Gore CJ, Aughey RJ. Enhancing team-sport athlete performance: is altitude training relevant? *Sports Med.* 2012;42:751-767.
6. Bishop D, Edge J. Determinants of repeated-sprint ability in females matched for single-sprint performance. *Eur J Appl Physiol.* 2006;97:373-379.
7. Bishop DJ, Girard O. Determinants of team-sport performance: implications for altitude training by team-sport athletes. *Br J Sports Med.* 2013;47(suppl 1):i17-i21.
8. Bloch KE, Buenzli JC, Latshang TD, Ulrich S. Sleep at high altitude: guesses and facts. *J Appl Physiol (1985).* 2015;119:1466-1480.
9. Bonetti DL, Hopkins WG. Sea-level exercise performance following adaptation to hypoxia: a meta-analysis. *Sports Med.* 2009;39:107-127.
10. Brito J, Siques P, Leon-Velarde F, De La Cruz JJ, Lopez V, Herruzo R. Chronic intermittent hypoxia at high altitude exposure for over 12 years: assessment of hematological, cardiovascular, and renal effects. *High Alt Med Biol.* 2007;8:236-244.
11. Buchheit M, Simpson BM, Garvican-Lewis LA, et al. Wellness, fatigue and physical performance acclimatisation to a 2-week soccer camp at 3600 m (ISA3600). *Br J Sports Med.* 2013;47(suppl 1):i100-i106.
12. Buekens P, Canfield C, Padilla N, Lara Lona E, Lozano R. Low birthweight in Mexico: a systematic review. *Matern Child Health J.* 2013;17:129-135.
13. Campbell AD, McIntosh SE, Nyberg A, Powell AP, Schoene RB, Hackett P. Risk stratification for athletes and adventurers in high-altitude environments: recommendations for preparticipation evaluation. *Clin J Sport Med.* 2015;25:404-411.
14. Chapman RF, Karlsen T, Resaland GK, et al. Defining the "dose" of altitude training: how high to live for optimal sea level performance enhancement. *J Appl Physiol (1985).* 2014;116:595-603.
15. Cheng I, Kiss A, Lilge L. An observational study of personal ultraviolet dosimetry and acute diffuse reflectance skin changes at extreme altitude. *Wilderness Environ Med.* 2013;24:390-396.
16. Committee opinion no. 650 summary: physical activity and exercise during pregnancy and the postpartum period. *Obstet Gynecol.* 2015;126:1326-1327.
17. Eichner ER. Sickle cell considerations in athletes. *Clin Sports Med.* 2011;30:537-549.
18. Entin PL, Coffin L. Physiological basis for recommendations regarding exercise during pregnancy at high altitude. *High Alt Med Biol.* 2004;5:321-334.
19. Friedlander AL, Braun B, Marquez J. Making molehills out of mountains: maintaining high performance at altitude. *ACSM Health Fitness J.* 2008;12:15-21.
20. Fulco CS, Beidleman BA, Muza SR. Effectiveness of preacclimatization strategies for high-altitude exposure. *Exerc Sport Sci Rev.* 2013;41:55-63.
21. Gao YX, Li P, Jiang CH, et al. Psychological and cognitive impairment of long-term migrators to high altitudes and the relationship to physiological and biochemical changes. *Eur J Neurol.* 2015;22:1363-1369.
22. Girard O, Amann M, Aughey R, et al. Position statement—altitude training for improving team-sport players' performance: current knowledge and unresolved issues. *Br J Sports Med.* 2013;47(suppl 1):i8-i16.
23. Goldfarb-Rumyantzev AS, Alper SL. Short-term responses of the kidney to high altitude in mountain climbers. *Nephrol Dial Transplant.* 2014;29:497-506.
24. Groepenhoff H, Overbeek MJ, Mule M, et al. Exercise pathophysiology in patients with chronic mountain sickness exercise in chronic mountain sickness. *Chest.* 2012;142:877-884.
25. Gupta N, Ashraf MZ. Exposure to high altitude: a risk factor for venous thromboembolism? *Semin Thromb Hemost.* 2012;38:156-163.
26. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med.* 2001;345:107-114.
27. Hackett PH, Roach RC. High-altitude medicine and physiology. In: Auerbach PS, ed. *Wilderness Medicine.* 6th ed. Philadelphia, PA: Mosby; 2012:2-33.
28. Hoffman MD, Pasternak A, Rogers IR, et al. Medical services at ultra-endurance foot races in remote environments: medical issues and consensus guidelines. *Sports Med.* 2014;44:1055-1069.
29. Illi SK, Held U, Frank I, Spengler CM. Effect of respiratory muscle training on exercise performance in healthy individuals: a systematic review and meta-analysis. *Sports Med.* 2012;42:707-724.

30. Jean D, Leal C, Kriemler S, Meijer H, Moore LG. Medical recommendations for women going to altitude. *High Alt Med Biol*. 2005;6:22-31.
31. Jean D, Moore LG. Travel to high altitude during pregnancy: frequently asked questions and recommendations for clinicians. *High Alt Med Biol*. 2012;13:73-81.
32. Joy E, Van Baak K, Dec KL, et al. Wilderness preparticipation evaluation and considerations for special populations. *Clin J Sport Med*. 2015;25:443-455.
33. Julian CG. High altitude during pregnancy. *Clin Chest Med*. 2011;32:21-31, vii.
34. Kechijan D. Optimizing nutrition for performance at altitude: a literature review. *J Spec Oper Med*. 2011;11:12-17.
35. Khodaee M, Ansari M. Common ultramarathon injuries and illnesses: race day management. *Curr Sports Med Rep*. 2012;11:290-297.
36. Koehle MS, Cheng I, Sporer B. Canadian Academy of Sport and Exercise Medicine position statement: athletes at high altitude. *Clin J Sport Med*. 2014;24:120-127.
37. Kriemler S, Burgi F, Wick C, et al. Prevalence of acute mountain sickness at 3500 m within and between families: a prospective cohort study. *High Alt Med Biol*. 2014;15:28-38.
38. Kriemler S, Radtke T, Burgi F, Lambrecht J, Zehnder M, Brunner-La Rocca HP. Short-term cardiorespiratory adaptation to high altitude in children compared with adults [published online February 3, 2015]. *Scand J Med Sci Sports*. doi:10.1111/sms.12422.
39. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, et al. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. *JAMA*. 2012;308:2390-2398.
40. Levine BD, Stray-Gundersen J. "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. *J Appl Physiol (1985)*. 1997;83:102-112.
41. Levine BD, Stray-Gundersen J. Dose-response of altitude training: how much altitude is enough? *Adv Exp Med Biol*. 2006;588:233-247.
42. Levine BD, Stray-Gundersen J, Mehta RD. Effect of altitude on football performance. *Scand J Med Sci Sports*. 2008;18(suppl 1):76-84.
43. Luks AM. Should travelers with hypertension adjust their medications when traveling to high altitude? *High Alt Med Biol*. 2009;10:11-15.
44. Luks AM, Swenson ER. Travel to high altitude with pre-existing lung disease. *Eur Respir J*. 2007;29:770-792.
45. Lundby C, Millet GP, Calbet JA, Bartsch P, Subudhi AW. Does 'altitude training' increase exercise performance in elite athletes? *Br J Sports Med*. 2012;46:792-795.
46. Mieske K, Flaherty G, O'Brien T. Journeys to high altitude—risks and recommendations for travelers with preexisting medical conditions. *J Travel Med*. 2010;17:48-62.
47. Niermeyer S. Going to high altitude with a newborn infant. *High Alt Med Biol*. 2007;8:117-123.
48. Palmer SK, Moore LG, Young D, Cregger B, Berman JC, Zamudio S. Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 meters) in Colorado. *Am J Obstet Gynecol*. 1999;180:1161-1168.
49. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation*. 2007;115:1132-1146.
50. Pulfrey SM, Jones PJ. Energy expenditure and requirement while climbing above 6,000 m. *J Appl Physiol (1985)*. 1996;81:1306-1311.
51. Richalet JP, Larmignat P, Poitrine E, Letournel M, Canoui-Poitrine F. Physiological risk factors for severe high-altitude illness: a prospective cohort study. *Am J Respir Crit Care Med*. 2012;185:192-198.
52. Richalet JP, Lhuissier FJ. Aging, tolerance to high altitude, and cardiorespiratory response to hypoxia. *High Alt Med Biol*. 2015;16:117-124.
53. Rigel EG, Lebwohl MG, Rigel AC, Rigel DS. Ultraviolet radiation in alpine skiing: magnitude of exposure and importance of regular protection. *Arch Dermatol*. 2003;139:60-62.
54. Ritchie ND, Baggott AV, Andrew Todd WT. Acetazolamide for the prevention of acute mountain sickness—a systematic review and meta-analysis. *J Travel Med*. 2012;19:298-307.
55. Sasaki H, Sakamoto Y, Schnider C, et al. UV-B exposure to the eye depending on solar altitude. *Eye Contact Lens*. 2011;37:191-195.
56. Saugy JJ, Schmitt L, Cejuela R, et al. Comparison of "live high-train low" in normobaric versus hypobaric hypoxia. *PLoS One*. 2014;9:e114418.
57. Saunders PU, Pyne DB, Gore CJ. Endurance training at altitude. *High Alt Med Biol*. 2009;10:135-148.
58. Schommer K, Menold E, Subudhi AW, Bartsch P. Health risk for athletes at moderate altitude and normobaric hypoxia. *Br J Sports Med*. 2012;46:828-832.
59. Siebenmann C, Robach P, Jacobs RA, et al. "Live high-train low" using normobaric hypoxia: a double-blinded, placebo-controlled study. *J Appl Physiol (1985)*. 2012;112:106-117.
60. Southard A, Niermeyer S, Yaron M. Language used in Lake Louise Scoring System underestimates symptoms of acute mountain sickness in 4- to 11-year-old children. *High Alt Med Biol*. 2007;8:124-130.
61. Tseng CH, Lin FC, Chao HS, Tsai HC, Shiao GM, Chang SC. Impact of rapid ascent to high altitude on sleep. *Sleep Breath*. 2015;19:819-826.
62. van Veen JJ, Makris M. Altitude and coagulation activation: does going high provoke thrombosis? *Acta Haematol*. 2008;119:156-157.
63. Weil JV. Sleep at high altitude. *High Alt Med Biol*. 2004;5:180-189.
64. Whayne TF Jr. Cardiovascular medicine at high altitude. *Angiology*. 2014;65:459-472.
65. Wilber RL. Application of altitude/hypoxic training by elite athletes. *Med Sci Sports Exerc*. 2007;39:1610-1624.
66. Wilber RL, Stray-Gundersen J, Levine BD. Effect of hypoxic "dose" on physiological responses and sea-level performance. *Med Sci Sports Exerc*. 2007;39:1590-1599.
67. Wilbur RL. Live high + train low: thinking in terms of an optimal hypoxic dose. *Int J Sports Physiol Perform*. 2007;2:223-238.
68. Wille M, Gatterer H, Mairer K, et al. Short-term intermittent hypoxia reduces the severity of acute mountain sickness. *Scand J Med Sci Sports*. 2012;22:e79-e85.
69. Wing-Gaia SL. Nutritional strategies for the preservation of fat free mass at high altitude. *Nutrients*. 2014;6:665-681.
70. Wu SH, Lin YC, Weng YM, et al. The impact of physical fitness and body mass index in children on the development of acute mountain sickness: a prospective observational study. *BMC Pediatr*. 2015;15:55.
71. Yaron M, Niermeyer S, Lindgren KN, Honigman B. Evaluation of diagnostic criteria and incidence of acute mountain sickness in preverbal children. *Wilderness Environ Med*. 2002;13:21-26.
72. Yaron M, Waldman N, Niermeyer S, Nicholas R, Honigman B. The diagnosis of acute mountain sickness in preverbal children. *Arch Pediatr Adolesc Med*. 1998;152:683-687.
73. Zhang G, Zhou SM, Yuan C, Tian HJ, Li P, Gao YQ. The effects of short-term and long-term exposure to a high altitude hypoxic environment on neurobehavioral function. *High Alt Med Biol*. 2013;14:338-341.

Hyponatraemia – presentations and management

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ABSTRACT

Hyponatraemia is the most common electrolyte disturbance encountered in clinical practice. It is associated with significant morbidity and mortality, thus appropriate investigation and treatment is essential. Hyponatraemia presents with a spectrum of clinical presentations ranging from no symptoms to life-threatening neurological sequelae. Hyponatraemia has multiple aetiologies and distinguishing the underlying aetiology facilitates appropriate treatment. This review provides an overview of the presentations and approaches to management of this common clinical condition.

Introduction

Hyponatraemia (defined as serum sodium <135 mmol/L) is the most common electrolyte abnormality and is encountered in all areas of clinical practice.[1] Hyponatraemia is associated with increased morbidity and mortality.[2] The assessment of patients with hyponatraemia can pose a clinical challenge and strategies for its management are often suboptimal. In recent years, expert guidance and recommendations have been published that provide an evidence-based approach to diagnosis and treatment of hyponatraemia[3,4] although it should be highlighted that high-quality evidence is lacking for many aspects of hyponatraemia management. Additionally, new therapies have emerged promising a more targeted approach to regulating body water and sodium balance in certain patients with hyponatraemia.

Epidemiology

Hyponatraemia occurs in approximately 15–30% of hospitalised patients, with 1–2% of patients having a serum sodium level <125 mmol/L.[5,6] In addition, hyponatraemia is often underreported in the hospital setting.[7] In the intensive care unit, approximately 25–30% of patients will have a serum sodium <134 mmol/L.[8,9] In neurosurgical units, hyponatraemia is reported in up to 50% of patients with subarachnoid haemorrhage in retrospective[2] and prospective studies.[10] Hyponatraemia is also a common occurrence in heart failure with an incidence of approximately 20% in patients hospitalised for heart failure.[11] Age-related changes and chronic diseases are often associated with abnormalities in water homeostasis. Miller *et al*[12] have reported that more than 50% of nursing home residents had at least one episode of hyponatraemia over a 12-month study period.

Morbidity and mortality associated with hyponatraemia

Hyponatraemia is associated with increased morbidity and mortality. Acute severe symptomatic hyponatraemia is a medical emergency that carries a high mortality rate if not addressed acutely. A recent prospective observational study found a positive correlation of serum sodium and mortality, with a serum sodium <125 mmol/L associated with a substantial 1-year mortality, recurrence of hyponatraemia and rehospitalisation rate.[13] 'Asymptomatic' chronic mild hyponatraemia has previously been thought to be clinically insignificant; however, recent evidence shows that mild chronic 'asymptomatic' hyponatraemia, particularly in an older population, may contribute to impaired cognition,[14] increased risk of falls[15] and fractures.[16] Recent studies suggest

Key Points

Hyponatraemia is the commonest electrolyte abnormality in hospitalised patients and is associated with increased morbidity and mortality

Assessment of volume status and urinary sodium are key steps in the appropriate diagnosis and treatment of hyponatraemia

Symptomatic hyponatraemia is a medical emergency and needs to be treated acutely in order to reduce neurological sequelae

During the treatment of hyponatraemia careful and regular monitoring of sodium is required in order to avoid rapid overcorrection with the risk of osmotic demyelination syndrome

Many patients with syndrome of inappropriate antidiuresis may not respond to fluid restriction and will need second line therapy

KEYWORDS: Hyponatraemia, plasma osmolality, syndrome of inappropriate antidiuresis, urine sodium, vasopressin ■

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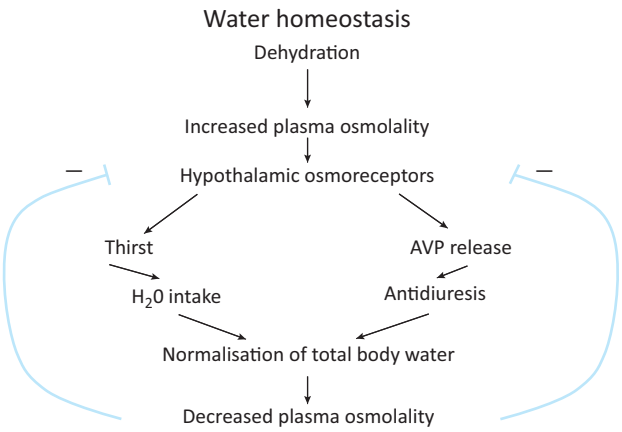

Fig 1. Normal regulation of salt and water balance. Adapted from Hannon MJ *et al.*[10] AVP = antidiuretic hormone vasopressin

the predisposition to fractures in patients with hyponatraemia not only exists because of a higher falls risk, but also as a result of associated osteoporosis.[17,18] In addition to the above, inappropriate management of hyponatraemia can lead to significant morbidity.[19]

Physiology of water balance

In healthy humans, plasma sodium concentrations are maintained within a narrow range, despite wide variations in water and salt intake.[20] Plasma sodium concentration rarely varies by more than 1–2% off baseline in normal physiological conditions, when access to water is normal. In health, plasma osmolality is very closely regulated by the sophisticated interaction between the secretion and action of the antidiuretic hormone vasopressin (AVP) and the sensation of thirst, which promotes water intake (Fig 1). Changes in plasma osmolality are detected by specialised magnocellular neurons in the anterior hypothalamus. When plasma osmolality rises, there is stimulation of synthesis and secretion of AVP. AVP binds to V2 receptors in the collecting ducts of the renal tubules, stimulating an intracellular cascade that leads to migration of vesicle bound aquaporin-2 to the luminal membrane of the collecting duct.[21] This renders the cells of the collecting duct permeable to water, enabling reabsorption of water from the urine to the blood, such that adequate urine concentration can occur. Simultaneously, the thirst centre in the cerebral cortex is stimulated, promoting water intake. Thus, AVP-mediated restriction of water excretion combined with thirst-driven water intake leads to an increase in plasma water and normalisation of plasma osmolality.[22] Changes in plasma sodium concentration are therefore a reflection of abnormal water balance, rather than the dysregulation of sodium intake and excretion.

Aetiology and classification of hyponatraemia

There are a number of aetiologies of hyponatraemia, which can be divided into:

1 hypotonic hyponatraemia (which is divided into hypovolaemic, euvolaemic and hypervolaemic causes)
2 pseudohyponatraemia
3 non-hypotonic hyponatreamia.

Other important sub-classifications include whether the hyponatraemia has developed acutely or chronically and is symptomatic or asymptomatic.

Table 1. Causes of hyponatraemia according to volume status and urinary sodium

Volume status	Clinical signs	Urinary $Na^{=}$ ≤30 mmol/L	Urinary $Na^{=}$ ≥40 mmol/L
Hypovolaemic	Dry mucous membranes	GI losses	Diuretics
	Decreased turgor	Mucosal losses	Addison's disease
	Tachycardia	Pancreatitis	Cerebral salt wasting
	Hypotension (orthostatic)	Sodium depletion post diuretics	Salt wasting nephropathy
	Raised urea, renin		
Euvolaemic	Underlying illness	Hypothyroidism	SIAD
		SIAD with ongoing fluid restriction	ACTH deficiency
Hypervolaemic	Peripheral oedema	Cirrhosis	Cardiac failure with diuretic therapy
	Ascites	Cardiac failure	
	Raised JVP	Nephrotic syndrome	
	Pulmonary oedema	Primary polydipsia	
	Underlying illness		

ACTH = adrenocorticopic hormone; GI = gastrointestinal; JVP = jugular venous pulse; SIAD = syndrome of inappropriate antidiuresis

Adapted from Smith et al.[23]

Hypotonic hyponatraemia

Hypotonic hyponatraemia can be classified, based on the estimation of extracellular volume status of the patient, as hypovolaemic, euvolaemic or hypervolaemic hyponatraemia (Table 1). In clinical practice, evaluation of volume status may be challenging and is often suboptimal.[23]

Hypovolaemic hyponatraemia

Hypovolaemic hyponatraemia occurs when there is depletion of both water and body sodium with a relative excess of sodium loss. Solute loss can be classified as renal and non-renal. Thiazide diuretic-induced hyponatraemia is the leading cause

of drug-induced hyponatraemia requiring hospital admission, and can affect up to one third of older patients taking thiazide diuretics.[24] Risk factors for the development of thiazide-induced hyponatraemia include increasing age,[25] low body mass index,[26] hypokalaemia[27] and female gender.[28] Other causes of hypovolaemic hyponatraemia include gastrointestinal losses, skin losses (burns and perspiration) and renal salt loss due to salt wasting nephropathy or mineralocorticoid deficiency (eg Addison's disease).

Euvolaemic hyponatraemia

Euvolaemic hyponatraemia is caused by a relative absolute increase in body water. It is the most heterogeneous and common cause of hyponatraemia among hospitalised patients and the syndrome of inappropriate antidiuresis (SIAD) is the most frequent underlying disorder. Most hyponatraemic patients who appear to be euvolaemic by physical examination have SIAD. However, such patients may occasionally have hyponatraemia due to true volume depletion, primary polydipsia, malnutrition, glucocorticoid deficiency or severe hypothyroidism.

Syndrome of inappropriate antidiuresis

SIAD is the most common cause of euvolemic hyponatraemia in hospitalised patients.[29] It is a common complication of a wide range of clinical disorders and drug therapies. The most common causes of SIAD are malignancy, pulmonary disorders, central nervous system disorders and medications.[30,31] SIAD has been reported as an adverse effect of many drugs, including psychotropic medications[32] and chemotherapeutic drugs.[33]

The cardinal diagnostic criteria for SIAD, originally described by Bartter and Schwartz in 1967, are outlined in Box 1.[34]

Glucocorticoid deficiency

An important cause of euvolaemic hyponatraemia, which must be differentiated from SIAD, is adrenocorticotropic hormone (ACTH) deficiency leading to cortisol deficiency (this is different to patients with Addison's disease who are also lacking mineralocorticoids). The biochemical presentation is identical to that of SIAD. Patients with ACTH deficiency and hyponatraemia have elevated plasma vasopressin concentrations,[35] which may be partially baroregulated because of an associated decrease in blood pressure. In addition, cortisol is required for free water excretion, which also contributes to the development of euvolaemic hyponatraemia. In a large, prospective and well-defined cohort of euvolaemic hyponatraemia in a tertiary centre, undiagnosed secondary adrenal insufficiency co-occurred in 3.8% of cases initially diagnosed as SIAD.[36] Acute glucocorticoid insufficiency should also be considered as the cause of hyponatraemia in any patient with acute neurotrauma and in patients who have been receiving long-term glucocorticoid therapy.

Box 1. Essential diagnostic criteria for SIAD[37]

1 Plasma hypoosmolality (<275 mOsm/kg)

2 Inappropriate urine concentration (Uosm >100mOsm/kg H20)

3 Urine sodium >30mmol/L, with normal salt and water intake

4 Clinical euvolaemia

5 Exclusion of glucocorticoid deficiency or hypothyroidism (rare)

Supplementary criteria are not included as these are not used routinely in clinical Practice.

Hypothyroidism

Determination of thyroid-stimulating hormone is important for evaluation of a patient with hyponatraemia as the exclusion of hypothyroidism is one of the prerequisites for the diagnosis of SIAD.

However, the relationship between hypothyroidism and hyponatraemia is inconsistent,[37] although they often coexist, and recent data suggest that hypothyroidism-induced hyponatraemia is extremely rare and probably occurs only in severe hypothyroidism and myxoedema, with reduction in cardiac output and nonosmotic stimuli to AVP release.

Hypervolaemic hyponatraemia

In hypervolaemic hyponatraemia, there is an increase in both total body water and total body sodium, with a relative excess of total body water, leading to dilutional hyponatraemia. In both cardiac failure and cirrhosis there is a fall in mean arterial pressure (particularly within the splanchnic circulation). This stimulates baroregulated vasopressin secretion, baroregulated activation of the renin-angiotensin-aldosterone axis and increases sympathetic tone. Increased AVP leads to water retention, and the activation of the renin-angiotensin axis promotes sodium and water retention.[38]

Pseudohyponatraemia

Pseudohyponatraemia, originally described in the 1950s,[39] is caused by a displacement of serum water by significantly elevated concentrations of serum lipids or proteins. It occurs when blood specimens with high concentrations of either lipid or protein are analysed by either a flame photometer or an ion-selective electrode that requires sample dilution before assay.[40]

Non-hypotonic hyponatraemia

Hyponatraemia with normal or increased effective osmolality can occur when the serum contains additional osmoles, which reduce serum sodium concentration by attracting water from the intracellular compartment. Hypertonic hyponatraemia may occur as a consequence of hyperglycaemia. Hyperglycaemia will result in an osmotic shift of water from the intracellular to the extracellular fluid compartment, thus diluting serum sodium levels, which can be calculated by correcting the measured serum [Na^+] for the glucose elevation.[41] It is imperative to control the rate at which plasma glucose is lowered, to minimise the associated risk of cerebral oedema that can occur.[42]

Clinical presentation of hyponatraemia

The symptoms associated with hyponatraemia are varied and are related to the severity and rapidity of the fall in the plasma sodium concentration as well as the coexistence of neurological disease or other electrolyte abnormalities. Symptoms are

far more likely if the fall in plasma sodium is rapid, whereas chronic hyponatraemia (hyponatraemia of >72-hour duration) may present as a relatively asymptomatic condition, even in cases where hyponatraemia is biochemically significant. In acute hyponatraemia, the main pathological consequence is the development of cerebral oedema, which leads to raised intracranial pressure with the risk of cerebral herniation, hypoxia and even death.[43] In chronic hyponatraemia there is a lower risk of acute neurological symptoms because of the presence of chronic cerebral adaptive mechanisms.[44]

Diagnosis and investigations

The initial diagnostic approach to the adult patient with hyponatraemia consists of a directed history and physical examination, supported by laboratory tests. There should be a focus on assessment of extracellular fluid volume status, symptoms and signs of hyponatraemia, the rate at which hyponatraemia developed and the biochemical severity of hyponatraemia. Measurement of urinary sodium is crucial in the distinction of hyponatraemia aetiology (Table 1). In hypovolaemic hyponatraemia, urinary sodium allows differentiation between renal (high urine sodium; >30 mmol/L) and extra-renal (low urine sodium; <30 mmol/L) salt loss. These are not absolute values; they are a guide as they may also be determined by solute intake. In euvolaemic hyponatraemia, urinary sodium levels are high in SIAD and glucocorticoid insufficiency, but low in hyponatraemia associated with hypotonic fluid replacement or in patients with low solute intake. However, low urinary sodium is also an early feature of the recovery phase from diuretic use (within hours) or SIAD, highlighting the complexities in forming a diagnostic algorithm for hyponatraemia. Recent studies have focused on the use of a novel parameter, co-peptin, as a surrogate marker for vasopressin and its potential role as a diagnostic parameter in the differential diagnosis of hyponatraemia has been discussed.[45] However, as AVP is elevated in almost all causes of hyponatraemia co-peptin is unlikely to be of significant clinical utility at present. In patients with primary polydipsia, a low co-peptin may be a useful diagnostic tool.[46] Fenske *et al*[47] have also recently reported that measurement of fractional excretion of urea (FEurea) or uric acid (FEUA) levels were valuable parameters for discriminating between SIAD and other hyponatraemia aetiologies, irrespective of diuretic use.[47]

Management of hyponatraemia

Management of hyponatraemia needs to be targeted to the underlying aetiology. The urgency of intervention is determined by the severity of symptoms and the potential for an adverse outcome.

Management of acute symptomatic hyponatraemia

There is a high mortality associated with symptomatic hyponatraemia given the risk of cerebral oedema and brain herniation and, as such, plasma sodium needs to be elevated acutely (the risk of not increasing the plasma sodium needs to be weighed against the risk of osmotic demyelination syndrome).[48] Evidence available in the literature regarding the treatment of acute severe hyponatraemia is limited. Recently, a number of guidelines, which differ slightly in their approach to the management of severe symptomatic hyponatraemia in adult patients, have been published.[3,4,49]

The US consensus guidelines recommend an initial rise in serum sodium of 4–6 mmol/L over 4 hours, using intravenous boluses of hypertonic (3%) sodium chloride.[3] This is based on published experience with hypertonic saline to treat cerebral oedema in normotraemic patients with neurosurgical conditions, where a 5 mmol/L rise in serum sodium reversed the clinical signs of herniation and reduced intracranial pressure by almost 50% within the first hour.[50]

The Society for Endocrinology guidelines recommend 150 mL bolus of hypertonic saline, aiming for a rise of 5 mmol/L in serum sodium within the first hour.[49]

For severe symptoms, a 100 mL bolus of 3% saline infusion should be given over 10 minutes and repeated up to three times, if necessary, depending on clinical improvement. For mild to moderate symptoms with a low risk of cerebral herniation, 3% saline infusion is again recommended but at a slower rate of 0.5–2 mL/kg/h. Patients who are treated with hypertonic saline need to be managed in a critical care setting to allow for frequent monitoring of plasma sodium in order to ensure that there is not a rapid overcorrection of hyponatraemia.

In true acute hyponatraemia (where the decrease in plasma sodium has been documented to be in the prior 24–48 hours), the rate of correction need not be restricted as tightly as in chronic hyponatraemia as there is a lower risk of osmotic demyelination. However, if there is any uncertainty as to the rapidity of onset of hyponatraemia (chronic verses acute), then the target limits for correction of chronic hyponatraemia should be adhered to.

Management of chronic hyponatraemia

Rapid overcorrection of chronic hyponatraemia can lead to neurological sequelae due to osmotic demyelination syndrome (ODS; previously known as pontine or extra-pontine myelinolysis). This syndrome manifests clinically as progressive quadriplegia, opthalmoplegia or with extrapyramidal features such as ataxia. The mainstay of diagnosis is clinical suspicion and examination, aided by T1-weighted magnetic resonance imaging, which may have the classic appearances of a hypointense pons on sagittal imaging but a hyperintense pons on coronal imaging. Prognosis is variable but usually poor, with many patients developing persistent neurological deficit.

Current recommendations suggest a target rise in serum sodium concentration in patients with chronic hyponatraemia stratified by the risk of developing ODS (Table 2). They suggest a target maximum rise of 4–8 mmol/L per day in patients with low risk of ODS, with a target maximum limit not to exceed 10–12 mmol/L in any 24 hours or 18 mmol/L in any 48 hours. For those at high risk of ODS, they suggest a lower maximum target rise of 4–6 mmol/L per day, with a maximum target limit not to exceed 8 mmol/L in any 24-hour period. Factors that place a patient at high risk of developing ODS with correction of chronic hyponatraemia include starting serum sodium concentration ≤105 mmol/L, hypokalaemia, alcoholism, malnutrition and advanced liver disease (Table 2).[3]

Table 2. Targets for elevation in plasma sodium in hyponatraemic patients

	Goal of minimal correction of plasma sodium in first 24 hours (mmol/L)	Limits not to exceed in plasma sodium per 24 hours (mmol/L)
Normal risk patient	**4–8**	**10–12***
High risk of ODS	**4–6**	**8**
Patients with pNa^+ <105 mmol/L, hypokalaemia, alcoholism, malnutrition, liver disease		

*Not >18 mmol/L in 48 hours in normal risk patients.
ODS = osmotic demyelination syndrome

Management of hypovolaemic hyponatraemia

In hypovolaemic hyponatraemia, the aim is to correct plasma sodium and also restore intravascular volume. Most cases will respond to intravenous infusion of physiological saline. Diuretic therapy should be discontinued and any other underlying causes sought and treated.

The diagnosis of Addison's disease is suggested by history, examination and the presence of hyperkalaemia. Although the biochemical abnormalities of Addison's disease will respond to high-dose corticosteroids, patients are often profoundly fluid deplete and require intravenous saline to expand blood volume and replace body sodium. Current guidelines recommend a rapid intravenous infusion of 1,000 mL of isotonic saline infusion within the first hour, followed by further intravenous rehydration as required (usually 4–6 L in 24 hours, with careful monitoring for volume overload in the elderly or in renal impairment).[51] Intravenous dextrose may also be needed if the patient if hypoglycaemic (close monitoring is required as dextrose can exacerbate hyponatraemia).

Management of SIAD

Owing to a relative lack of randomised controlled trials, the treatment of SIAD is largely based on expert opinion. The current European guidelines and US consensus recommendations diverge in relation to the use of interventions after fluid restriction has failed.

Fluid restriction

The first-line therapy for mild to moderate asymptomatic hyponatraemia secondary to SIAD is fluid restriction. Several factors may predict failure of fluid restriction, including high urine osmolality (>500 mOsm/kg H_2O), low 24-hour urine volume (<1,500 mL/day) and a urinary sodium and potassium that are greater than plasma sodium. In addition, failure of fluid restriction may prompt reconsideration for the presence of underlying causes, such as malignancy, or the presence of clinically unapparent hypovolaemia.

Fluid restriction of 800–1,200 mL/day is generally advised, according to severity of hyponatraemia. As long as background water losses from the kidney, skin and lungs exceed this amount, there is progressive depletion of total body water and a gradual rise in plasma sodium concentration. The principle drawback is that patients find it extremely difficult to maintain fluid restriction, as thirst in SIAD is inappropriately normal because of a downward resetting of the osmotic thirst threshold.[15] Hospitalised patients who can be supervised tend to do better with fluid restriction than outpatients. However, hospitalised patients who are receiving intravenous fluids, as part of cytotoxic or antibiotic regimens, often find it hard to comply with fluid restriction.

Demeclocycline

Demeclocycline is a tetracycline derivative that is utilised in the treatment of SIAD because it causes nephrogenic diabetes insipidus in about 60% of patients. The degree of vasopressin resistance is not predictable; in a significant proportion of patients, it does not work. When it does work, the onset of action is also unpredictable, usually occurring after 2–5 days, but occasionally taking longer. In some patients, polyuria can be profound and patients can become markedly symptomatic, occasionally developing hypernatraemia if access to water is compromised. Nephrotoxicity can arise, particularly in patients with cirrhosis, and although renal impairment is usually reversible with discontinuation, cases with permanent renal failure have been reported.[16] It has also been associated with photosensitive skin rash and appropriate UV protection is recommended.

Urea

A relatively small number of centres have experience in the use of urea. It is recommended for use in the recent European hyponatraemia guidelines; however, it is unavailable in many countries. Human studies have shown that long-term (5-year) treatment of hyponatraemia with urea is effective[24] and the same group have published data in a rat model of SIAD that suggest that treatment of hyponatraemia with urea may protect against brain complications, such as osmotic demyelination syndrome.[25,26]

Frusemide

Frusemide was shown some years ago to be effective in the rapid correction of hyponatraemia in SIAD,[27] but it is of limited efficacy in long-term treatment as the diuresis that it induces includes a natriuresis, which can occasionally worsen hyponatraemia.

Vaptans

The development of specific vasopressin receptor antagonists (vaptans) represents a novel therapeutic option in euvolaemic hyponatraemia. The vaptans are vasopressin receptor antagonists with V1a (relcovaptan) or V2 (tolvaptan, lixivaptan) selectivity or non-selective activity (conivaptan), which may be advantageous in some disorders. The V2 receptors located primarily in the collecting tubules mediate free water absorption while the V1B receptors are located in the anterior pituitary and mediate ACTH release.[52]

The V1a/V2 non-selective vasopressin antagonist conivaptan was the first vaptan approved by the US Food and Drug Administration for the treatment of euvolaemic and hypervolaemic hyponatraemia as an intravenous infusion. Its efficacy for the treatment of hyponatraemia has been assessed in several double-blind, placebo-controlled clinical trials.[53,54] Like other vasopressin antagonists, its use is contraindicated in patients with hypovolaemic hyponatraemia.

Tolvaptan is an oral, selective non-peptide V2 receptor antagonist. The results of two large multicentre, randomised, placebo-controlled, double-blind trials of oral tolvaptan have been reported in patients with hyponatraemia (due to chronic heart failure, cirrhosis and SIAD).[55] Approximately 55% of patients in the tolvaptan group had normal serum sodium concentrations after 1 month of treatment (without the need for water restriction) compared with 25% in the placebo group. However, the benefit on serum sodium was more effective in SIAD patients compared with heart failure and cirrhotic patients. Excessive correction of serum sodium concentrations was noted in this study (>12 mmol/L per day in 3%). The SALTWATER trial, an extension of the SALT study (Study of Ascending Levels of Tolvaptan in Hyponatremia), showed that the effect of tolvapton was sustained for the duration of the observation period, a maximum of 214 weeks.[56]

The US consensus recommendations suggest certain precautions with the use of vaptans to avoid overcorrection and subsequent ODS. Clinicians should monitor serum sodium levels frequently during the active phase of correction of the hyponatraemia. In addition, fluid restriction should not be recommended, thereby allowing the patient's own thirst mechanism to compensate for the induced aquaresis. Goals and limits for safe correction are similar to those described above in the treatment of chronic hyponatraemia. Hepatotoxicity with tolvaptan is a concern based on the TEMPO trial (this trial examined the effect of tolvaptan, at high dose, on the progression of polycystic kidney disease);[57] it is therefore recommended to check liver enzymes in patients taking tolvaptan. Another potential limitation to the use of vaptan therapy is that its cost may be prohibitive.

Saline infusion in SIAD

There is data to suggest that plasma sodium concentration will rise in some patients with SIAD who are treated with intravenous normal (0.9%) saline.[28] However, treatment with normal saline is reserved for patients in whom the differentiation between hypovolaemia and euvolaemia is difficult. In this situation, intravenous saline is a safer first-line treatment than fluid restriction, but careful monitoring is required in order to ensure improvement in sodium concentrations while on saline.

Management of hypervolaemic hyponatraemia

In hypervolaemic hyponatraemia, therapy is aimed at treating the underlying cause. In congestive cardiac failure and cirrhosis, the mainstays of therapy are a combination of dietary sodium restriction, diuretics and fluid restriction to restore total body water to normal, in combination with inhibition of the renin angiotensin aldosterone system using angiotensin converting enzyme inhibitors, angiotensin receptor blockers or spironolactone. The use of vasopressin receptor antagonists in hypervolaemic hyponatraemia results in increased solute-free excretion without activation of the neurohumoral systems, as compared with loop diuretics. This provides a rationale for substitution in the management of heart failure. This was recently demonstrated in normonatraemic heart failure patients. The efficacy of vaptans in hypervolaemic hyponatraemia and cirrhosis is limited[58] and, given the potential hepatotoxicity seen with tolvaptan, it is recommended that tolvaptan should not be given to patients with chronic liver disease.

Conclusion

Hyponatraemia is the commonest electrolyte abnormality encountered in clinical practice and is a biochemical manifestation of a spectrum of illnesses. It is associated with a significant morbidity and mortality. The aetiology of hyponatraemia needs to be systematically determined and is the critical step to ensure adequate treatment. SIAD is the most common cause of euvolaemic hyponatraemia in hospitalised patients. Clinical practice guidelines and consensus statements provide recommendations to help evidence-based practice. Acute hyponatraemia should be promptly managed to protect from neurological sequelae, while chronic hyponatraemia should be investigated to establish aetiology and cautiously treated to avoid overcorrection. ■

Conflicts of Interest

CJT and MS have received honoraria for lectures from Otsuka. RD has no conflicts of interest to declare.

References

1 Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med* 2006;119(Suppl 1):S30–5.
2 Sherlock M, O'Sullivan E, Agha A *et al.* The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. *Clin Endocrinol* 2006;64:250–4.
3 Verbalis JG, Goldsmith SR, Greenberg A *et al.* Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013;126(Suppl 1):S1–42.
4 Spasovski G, Vanholder R, Allolio B *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med* 2014;40:320–31.
5 Asadollahi K, Beeching N, Gill G. Hyponatraemia as a risk factor for hospital mortality. *QJM* 2006;99:877–80.
6 Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. *Nephrol Dial Transplant* 2006;21:70–6.
7 Marco J, Barba R, Matia P *et al.* Low prevalence of hyponatremia codification in departments of internal medicine and its prognostic implications. *Curr Med Res Opin* 2013;29:1757–62.
8 DeVita MV, Gardenswartz MH, Konecky A, Zabetakis PM. Incidence and etiology of hyponatremia in an intensive care unit. *Clin Nephrol* 1990;34:163–6.
9 Oude Lansink-Hartgring A, Hessels L, Weigel J *et al.* Long-term changes in dysnatremia incidence in the ICU: a shift from hyponatremia to hypernatremia. *Ann Intensive Care* 2016;6:22.
10 Hannon MJ, Finucane FM, Sherlock M, Agha A, Thompson CJ. Clinical review: Disorders of water homeostasis in neurosurgical patients. *J Clin Endocrinol Metab* 2012;97:1423–33.

11 Grodin JL. Pharmacologic approaches to electrolyte abnormalities in heart failure. *Curr Heart Fail Rep* 2016;13:181–9.
12 Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. *J Am Geriatr Soc* 1995;43:1410–3.
13 Winzeler B, Jeanloz N, Nigro N *et al.* Long-term outcome of profound hyponatremia: a prospective 12 months follow-up study. *Eur J Endocrinol* 2016;175:499–502.
14 Gunathilake R, Oldmeadow C, McEvoy M *et al.* Mild hyponatremia is associated with impaired cognition and falls in community-dwelling older persons. *J Am Geriatr Soc* 2013;61:1838–9.
15 Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006;119:71.e1–8.
16 Hoorn EJ, Rivadeneira F, van Meurs JB *et al.* Mild hyponatremia as a risk factor for fractures: the Rotterdam study. *J Bone Miner Res* 2011;26:1822–8.
17 Verbalis JG, Barsony J, Sugimura Y *et al.* Hyponatremia-induced osteoporosis. *J Bone Miner Res* 2010;25:554–63.
18 Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. *J Biol Chem* 2011;286:10864–75.
19 Singh TD, Fugate JE, Rabinstein AA. Central pontine and extrapontine myelinolysis: a systematic review. *Eur J Neurol* 2014;21:1443–50.
20 Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. *BMJ* 2006;332:702–5.
21 Knoers NV, van Os CH. The clinical importance of the urinary excretion of aquaporin-2. *N Engl J Med* 1995;332:1575–6.
22 Thompson CJ, Bland J, Burd J, Baylis PH. The osmotic thresholds for thirst and vasopressin release are similar in healthy man. *Clin Sci* 1986;71:651–6.
23 Smith DM, McKenna K, Thompson CJ. Hyponatraemia. *Clin Endocrinol* 2000;52:667–78.
24 Liamis G, Filippatos TD, Elisaf MS. Thiazide-associated hyponatremia in the elderly: what the clinician needs to know. *J Geriatr Cardiol* 2016;13:175–82.
25 Sharabi Y, Illan R, Kamari Y *et al.* Diuretic induced hyponatraemia in elderly hypertensive women. *J Hum Hypertens* 2002;16:631–5.
26 Elliott WJ, Weber RR, Murphy MB. A double-blind, randomized, placebo-controlled comparison of the metabolic effects of low-dose hydrochlorothiazide and indapamide. *J Clin Pharmacol* 1991;31:751–7.
27 Liamis G, Mitrogianni Z, Liberopoulos EN, Tsimihodimos V, Elisaf M. Electrolyte disturbances in patients with hyponatremia. *Intern Med* 2007;46:685–90.
28 Al Qahtani M, Alshahrani A, Alskaini A *et al.* Prevalence of hyponatremia among patients who used indapamide and hydrochlorothiazide: a single center retrospective study. *Saudi J Kidney Dis Transpl* 2013;24:281–5.
29 Baylis PH. The syndrome of inappropriate antidiuretic hormone secretion. *Int J Biochem Cell Biol* 2003;35:1495–9.
30 Verbalis JG, Greenberg A, Burst V *et al.* Diagnosing and treating the syndrome of inappropriate antidiuretic hormone secretion. *Am J Med* 2016;129:537.e9–537.e23.
31 Shepshelovich D, Leibovitch C, Klein A *et al.* The syndrome of inappropriate antidiuretic hormone secretion: distribution and characterization according to etiologies. *Eur J Intern Med* 2015;26:819–24.
32 Lange-Asschenfeldt C, Kojda G, Cordes J *et al.* Epidemiology, symptoms, and treatment characteristics of hyponatremic psychiatric inpatients. *J Clin Psychopharmacol* 2013;33:799–805.
33 Atas E, Kesik V, Karaoglu A, Kalkan G. Inappropriate antidiuretic syndrome hypersecretion after a single dose of cisplatin. *J Cancer Res Ther* 2015;11:1032.
34 Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967;42:790–806.
35 Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med* 1989;321:492–6.
36 Cuesta M, Garrahy A, Slattery D *et al.* The contribution of undiagnosed adrenal insufficiency to euvolaemic hyponatraemia: results of a large prospective single-centre study. *Clin Endocrinol* 2016;85:836–44.
37 Warner MH, Holding S, Kilpatrick ES. The effect of newly diagnosed hypothyroidism on serum sodium concentrations: a retrospective study. *Clin Endocrinol* 2006;64:598–9.
38 Oren RM. Hyponatremia in congestive heart failure. *Am J Cardiol* 2005;95:2b–7b.
39 Albrink MJ, Hald PM, Man EB, Peters JP. The displacement of serum water by the lipids of hyperlipemic serum; a new method for the rapid determination of serum water. *J Clin Invest* 1955;34:1483–8.
40 Hussain I, Ahmad Z, Garg A. Extreme hypercholesterolemia presenting with pseudohyponatremia - a case report and review of the literature. *J Clin Lipidol* 2015;9:260–4.
41 Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. *Am J Med* 1999;106:399–403.
42 Donnelly H, Connor S, Quirk J. Central pontine myelinolysis secondary to hyperglycaemia. *Pract Neurol* 2016;16:493–5.
43 Ellis SJ. Severe hyponatraemia: complications and treatment. *QJM* 1995;88:905–9.
44 Hyponatraemia Thompson CJ.: new associations and new treatments. *Eur J Endocrinol* 2010;162 (Suppl 1):S1–3.
45 Nigro N, Winzeler B, Suter-Widmer I *et al.* Evaluation of copeptin and commonly used laboratory parameters for the differential diagnosis of profound hyponatraemia in hospitalized patients: 'The Co-MED Study'. *Clin Endocrinol* 2016;86:456–62.
46 Fenske W, Stork S, Blechschmidt A *et al.* Copeptin in the differential diagnosis of hyponatremia. *J Clin Endocrinol Metab* 2009;94:123–9.
47 Fenske W, Stork S, Koschker AC *et al.* Value of fractional uric acid excretion in differential diagnosis of hyponatremic patients on diuretics. *J Clin Endocrinol Metab* 2008;93:2991–7.
48 Sterns RH, Silver SM. Brain volume regulation in response to hyposmolality and its correction. *Am J Med* 2006;119(Suppl 1):S12–6.
49 Ball S, Barth J, Levy M. Society for Endocrinology Endocrine Emergency Guidance: emergency management of severe symptomatic hyponatraemia in adult patients. *Endocr Connect* 2016;5:G4–g6.
50 Koenig MA, Bryan M, 3rd Lewin JL *et al.* Reversal of transtentorial herniation with hypertonic saline. *Neurology* 2008;70:1023–9.
51 Arlt W. Society for Endocrinology Endocrine Emergency Guidance: emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. *Endocr Connect* 2016;5:G1–g3.
52 Decaux G, Soupart A, Vassart G. Non-peptide arginine-vasopressin antagonists: the vaptans. *Lancet* 2008;371:1624–32.
53 Zeltser D, Rosansky S, van Rensburg H *et al.* Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *Am J Nephrol* 2007;27:447–57.
54 Ghali JK, Koren MJ, Taylor JR *et al.* Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab* 2006;91:2145–52.
55 Schrier RW, Gross P, Gheorghiade M *et al.* Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006;355:2099–112.
56 Berl T, Quittnat-Pelletier F, Verbalis JG *et al.* Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol* 2010;21:705–12.
57 Torres VE *et al.* Effect of tolvaptan in autosomal dominant polycystic kidney disease by CKD stage: results from the TEMPO 3:4 Trial. *Clin J Am Soc Nephrol* 2016;11:803–11.
58 Pose E, Sola E, Piano S *et al.* Limited efficacy of tolvaptan in patients with cirrhosis and severe hyponatremia. Real-life experience. *Am J Med* 2016;130:372–5.

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