Hyponatraemia

Dr. Peter Allan
Foundation Doctor, Royal Cornwall Hospitals NHS Trust, UK

Dr. Saibal Ganguly
Intensive Care Registrar, Royal Cornwall Hospitals NHS Trust, UK

Edited by **Dr William English**

Correspondence to atotw@wfsahq.org

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QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article, together with an explanation. **Please answer True or False:**

Regarding hyponatraemia:

a. Hyponatremia is an independent risk factor for increased mortality
b. 99% of the sodium filtered by the kidney is reabsorbed in the distal tubule
c. Malnourished patients and alcoholics are at increased risk of osmotic demyelination
d. A urinary sodium level below 20 mmol/l is suggestive of an extra renal cause of hypovolaemic hyponatremia
e. Disorientation, weakness and confusion are typically seen in chronically hyponatremic patients with sodium levels between 130-125 mmol/l

SUMMARY

- Sodium disorders are the most common electrolyte abnormalities seen in hospitals.
- Hyponatremia is often iatrogenic in in-patients and severe sodium disturbances are associated with considerable morbidity and mortality. Disorders of sodium balance can be confusing.
- Categorisation based on fluid status aids diagnosis of the underlying cause and helps guide treatment.
- The speed with which hyponatremia develops is important as it both influences presenting symptoms and dictates initial management. In acute cases there is a greater risk of cerebral oedema and rapid correction is beneficial, especially in the presence of coma or convulsions.
- Rapid correction can be dangerous, however, in patients with chronic hyponatremia as osmotic demyelination is a greater risk in these patients. Here slower, careful correction of sodium is usually indicated and serum sodium should not be increased by more than 4-8 mmol/l/day

INTRODUCTION

The presence of hyponatremia has been demonstrated to be an independent risk factor for increased mortality in hospital inpatients.[1] As hyponatremia is the most common electrolyte disturbance encountered in clinical medicine,[1] it is vital that doctors and nurses know how to appropriately manage this condition. Severe hyponatremia has long been recognised to be associated with adverse outcomes.[2] It is also increasingly being recognised that even mild hyponatremia can be associated with patient harm, with even relatively minor derangements having been shown to be associated with increased falls and fractures.[3–5]

Appropriate management of hyponatremia is often challenging due to both numerous pathophysiological mechanisms and multiple underlying pathological conditions.[6] After revising the normal control of sodium balance this article will review the causes, classification, diagnosis and management of hyponatremia. An algorithm for investigations and treatment is provided at the end of this article.

CONTROL OF SODIUM BALANCE

Sodium is the most prevalent cation in the extracellular fluid (ECF). Total body sodium is therefore proportional to ECF volume. Under normal circumstances serum sodium levels are maintained within a tight physiological range of between 135-145mmol/l. Despite great variation in the intake of both sodium and water, close control of serum sodium is

maintained via control of the excretion of water and sodium.[7] Over 99% of the sodium filtered by the kidney is reabsorbed in the proximal tubule and loop of Henle. This reabsorption occurs at a relatively fixed rate, regardless of total body sodium. It is the smaller proportion of sodium, reabsorbed in the distal tubule and collecting ducts that exert the most influence on total sodium balance,[8] but serum sodium levels reflect water balance under the influence of antidiuretic hormone (ADH).

THE ROLE OF ANTIDIURETIC HORMONE

The majority of hyponatremic states involve inappropriately elevated levels of anti-diuretic hormone.[9] This causes disproportionate water retention compared to sodium. The secretion of ADH is influenced by multiple factors such as plasma osmolality and circulating volume. Failure to suppress ADH production in lowered osmolality states is a feature of SIADH. By contrast, continued production of ADH despite a lowered serum osmolality is a feature of oedema forming conditions such as heart failure and liver disease.[10] In these latter conditions ADH production continues because reduced renal perfusion causes excess aldosterone production.

CAUSES OF HYPONATREMIA

"True hyponatremia" is regarded as a low sodium level in the presence of hypo-osmolality

Hyponatremia in the presence of normal or high serum osmolality can occur. This is known as pseudohyponatraemia

Further classification of true hyponatremia by volume status, although difficult, aids diagnosis and guides management.

True hyponatremia

As sodium and its accompanying anions are the major effective plasma solutes in the ECF, hyponatremia and hypo-osmolality almost always co-exist. "True hyponatremia" is regarded as a low sodium level in the presence of hypo-osmolality. The situations in which hyponatremia can occur without hypo-osmolality are discussed later.

True hyponatremia is characterised by hypo-osmolality. This is because sodium in the ECF and potassium in the ICF (along with their associated anions) determine osmolality, with water moving freely between fluid compartments, in order to maintain the same osmolality between compartments. As a result, plasma hypo-osmolality and therefore hypotonic hyponatremia, indicates a relative excess of water to sodium regardless of volume status.

It is an oversimplification to regard hypo-osmolar states as produced by either water excess or solute depletion as often components of both are involved.[11] It can be useful though to classify hyponatraemia on the basis of fluid status. This can facilitate understanding of the processes involved in the development of hyponatremia and also help guide management.

Categorisation into one of three clearly defined groups based on volume status is not always possible due to multiple aetiologies and patient co-morbidities. However inappropriate categorisation of hyponatremia and subsequent mismanagement has been shown to lead to poor clinical outcomes,[12] whilst following a simple algorithm for the diagnosis and treatment of hyponatremia has been shown to be associated with improved outcomes.[13]

Hypovolaemic hyponatremia

In hypovolaemic hyponatraemia total body water and total body sodium are both low, but there is disproportionate loss of sodium compared with water. This is a result of the increased ADH secretion seen in hypovolaemic states causing increased water reabsorption. Hyponatremia is often compounded by thirsty patients consuming hypotonic fluids at a level inadequate to try to restore circulating volume.

Sodium loss can be renal or extra- renal and establishing the urinary sodium level is important in making this distinction. A urinary sodium level below 20mmol/l is suggestive of an extra renal cause.[14,12] Extra renal causes are commonly of gastrointestinal origin. Other causes include exercise-associated hyponatremia (also commonly seen in people working in hot conditions), burns, trauma and pancreatitis. Renal causes include diuretic excess, renal failure, salt wasting nephropathy, aldosterone deficiency, chronic pyelonephritis, nephrocalcinosis, proximal renal tubular acidosis and ketonuria.[12]

Euvolaemic hyponatremia

Euvolaemic hyponatremia is the most common category of hyponatremia seen in hospital in-patients.[12] SIADH is the most common cause of euvolaemic hyponatremia and it is associated with many different disorders. These can be divided into several major etiologic groups but this is beyond the scope of this article. If SIADH is suspected it can be useful to measure urine osmolality as a urine osmolality >100 mOsm/kg in the presence of hyponatraemia reflects inappropriate antidiuresis. As SIADH remains a diagnosis of exclusion other potential causes must be investigated and excluded first.

Table 1: Table showing some important causes of SIADH with examples of major groups of causes and descriptions of specific causes.

Cause	Description
Drugs	Commonly thiazide diuretics, vincristine and cyclophosphamide. Many others including SSRIs, sodium valproate and haloperidol. For a more comprehensive list see Binu et al, 2011.[15]
CNS disorders	Infection, trauma, ischemia, haemorrhage and psychosis can increase the release of ADH.[16,17]
Malignancies	Commonly of the lung, particularly small cell carcinoma.[18] Other tumours can less frequently have a similar effect. These include head and neck, duodenal and pancreatic cancers.[15,19]
Pulmonary disease	Pneumonia, asthma and acute respiratory failure have been known to cause SIADH.[15]
Surgery	Major surgery can lead to increased secretion of ADH.[2021] This is thought to involve a pain afferent mediated response.
Nephrogenic SIADH	Due to aV2 receptor gene gain of function mutation. This leads to excess water reabsorption in the renal collecting duct.[22]
Infective	Acquired immune deficiency syndrome.[23,24]

CNS= central nervous system. SIADH= Syndrome of inappropriate anti-diuretic hormone secretion. SSRI= selective serotonin reuptake inhibitor.

Other common causes of euvolaemic hyponatremia include:

- Glucocorticoid deficiency - cortisol deficiency may lead to failure of ADH suppression
- Hypothyroidism- hyponatremia secondary to hypothyroidism is rare. It is thought to result from impaired water excretion due to decreased glomerular filtration rate (GFR) secondary to the systemic effects of thyroid hormone deficiency on peripheral vascular resistance and cardiac output
- Low Solute Intake- e.g. beer potomania where the primary abnormality is not one of water balance but sodium balance due to reduced intake
- In the vast majority of cases excessive water intake in isolation is insufficient to overwhelm the capacity of the kidneys to excrete water. Therefore severe hyponatremia due to excess water intake alone is rare in the presence of normal renal function. If water intake exceeds 20 l/day, as seen in psychogenic polydipsia, it is possible to achieve a transient hyponatremia, but in the absence of other dysfunction this is rapidly corrected on cessation of fluid intake.[12] It is more likely that patients with high fluid intakes and accompanying hyponatremia have a concurrent impairment of water excretion which has previously gone unnoticed during periods of normal water ingestion. In patients with known psychiatric disorders who consume large volumes of water this is often a result of iatrogenic SIADH, for example as a side effect of selective serotonin reuptake inhibitors. Acute psychosis has also been shown to increase ADH secretion

Hypervolaemic hyponatremia

This is a situation characterised by a paradoxical increase in total body sodium, but a simultaneous and proportionally larger increase in total body water leading to a dilutional hyponatremia. This reduction in water excretion is secondary to either an excess of ADH secretion or an element of renal impairment limiting the maximal excretion of free water.
Underlying pathologies include nephrotic syndrome, congestive cardiac failure (CCF) and cirrhosis (although rarely in the absence of ascites).[10] In all of these situations there is oedema secondary to impairment of the kidney's ability to excrete water maximally. This results from either inappropriate ADH secretion leading to water retention or an inappropriate distribution of fluid within the body, preventing intravascular fluid elimination.

Hyponatraemia without hypo-osmolality

As stated previously, hyponatremia and hypo-osmolality almost always co-exist and this is referred to as "true hyponatremia." Hyponatremia occurring without hypo-osmolality is referred to as pseudohyponatremia. Pseudohyponatremia can occur with a normal or elevated serum osmolality. Pseudohyponatremia with normal serum osmolality occurs when grossly elevated levels of lipids or proteins lead to an artificial apparent decrease in measured

serum sodium. This is because sodium normally distributes in the aqueous phase of plasma which accounts for 93% of the plasma volume. A correction factor for whole plasma can be rendered incorrect if the non-aqueous phase is increased due to hypertriglyceridemia or paraproteinemia.[17] The use in laboratories of direct ion-sensitive electrodes eliminates this potential error. Hypertonic hyponatremia refers to hyponatremia with an increased osmolality. This occurs when sodium and its associated anions are no longer the major effective solutes present in the plasma. This "translocation hyponatraemia" is the due to osmotically active solutes in the plasma which are unable to cross the cell membrane. While many solutes such as urea and ethanol can enter cells and so cause hyper-tonicity without cell dehydration, other molecules such as glycine cannot. Glucose normally diffuses freely into cells but when insulin is deficient, such as in diabetic ketoacidosis (DKA), glucose is effectively confined to the ECF. When the concentration of glucose rises, water is displaced across the membrane from inside to outside the cell. As well as dehydrating the cell, this leads to a dilutional hyponatremia. In diabetic ketoacidosis, the "true" corrected serum sodium can be estimated from the formula: $[Na^+]$ corrected= $[Na^+]$ measured +{(glucose-5.6) x 0.288}. It is an important axiom of treatment of DKA, especially in children, that the corrected sodium concentration should rise slowly as glucose falls, to avoid the risk of cerebral oedema secondary to plasma hypo-osmolality.

SYMPTOMS AND SIGNS OF HYPONATREMIA

The symptoms and signs associated with hyponatremia relate to both the degree of imbalance and the time course over which the imbalance has developed. Neurological symptoms can occur as a result of an osmotic gradient between the intra-cellular and extra-cellular fluid compartments. This gradient causes water to move into cells resulting in tissue oedema.[27,28] This process is clinically most important in the brain as, due to the exhaustion of adaptive mechanisms and confinements of the skull, cell swelling here can lead to raised intracranial pressure and neurological damage. This situation occurs most often when hyponatremia develops over a short time frame.

If severe hyponatraemia develops over the course of hours or a few days, rather than over many days or weeks, then the ability of the brain to adapt to osmotic changes and cell swelling is more rapidly exceeded. This leads to the development of cerebral oedema.[29] Patients in whom acute severe hyponatremia has developed in under 48 hours can present with alarming neurological findings such as coma and convulsions. Additionally they are at risk of death as a result of cerebral herniation.[30]

Rapidly evolving severe hyponatraemia is a different disease entity from slowly evolving hyponatremia. Brain adaptation seen in slowly evolving hyponatraemia may prevent cerebral oedema. This occurs via the transport of sodium, chloride, and potassium to the ECF. This compensatory mechanism maintains ICF osmolality equal to equal ECF osmolality and thereby avoids large shifts of water into the cells.[31] Over a period of time organic solutes such as glutamine, glutamate and taurine follow into the ECF to maintain this osmotic stability. These molecules are known as "organic osmolytes". The clinical result of this compensation is that these patients experience fewer and less severe symptoms and generally do not die as a result of brain herniation.[31]

Slowly evolving hyponatraemia is frequently asymptomatic but there are limits to how low levels can get before physiological processes are affected, regardless of the chronicity of the process.[12] Non-specific symptoms generally develop when serum sodium levels drop below 120 mmol/l. These symptoms include fatigue, lethargy, weakness and confusion. Seizures and coma are uncommon. As well as time frame, symptoms are also dependant on the patients' pre-morbid state. Certain groups, such as children, hypoxic patients and premenopausal women, are all at increased risk of cerebral oedema.[32]

INVESTIGATION

The diagnosis of underlying cause is difficult and should be carried out with the help of an endocrinologist. A careful history with particular reference to the patient's recent medications and fluid intake should be taken. A clinical examination, looking for indicators of volume status, e.g. oedema, jugular venous pressure; signs of adrenocortical insufficiency including pigmentation, postural hypotension; stigmata of hypothyroidism; or any signs related to chest or central nervous system disease, in particular underlying neoplasia, should be carried out.

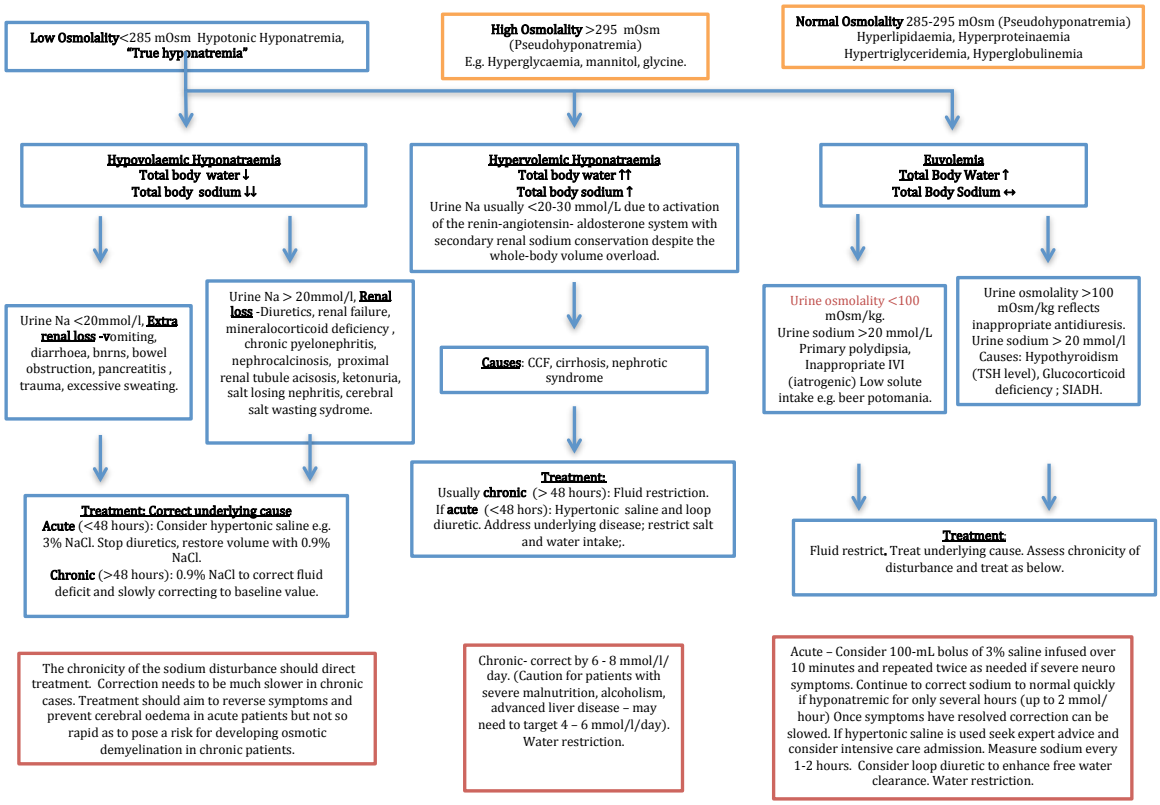
Assessment of volaemic status using clinical examination is notoriously unreliable, however and must be made in conjunction with the history and blood and urine tests.

Radiological investigations where indicated might include CT of brain, thorax, abdomen and pelvis.

Urine osmolality and electrolytes, thyroid function tests, random cortisol and/or short synacthen test, lipids, and serum electrophoresis are required.

The algorithm below provides a useful structure for investigating and managing hyponatremia.

Hyponatraemia treatment Algorithm



MANAGEMENT

General advice

Because there are inherent risks associated with both hyponatremia and its rapid correction, appropriate management of hyponatremia involves balancing these risks. Patients, who have developed a sodium imbalance over a longer period of time are likely to have made appropriate compensatory changes.[31] They are therefore better able to tolerate severe hyponatremia. Additionally in these patients slow correction is much safer as discussed later. In contrast, in patients who have developed hyponatremia over a short timeframe, a faster resolution may be appropriate, particularly if there are signs of neurological compromise.

The major risk associated with excessively rapid sodium correction is osmotic demyelination.[33] This can result in severe and permanent neurological impairment or death. Certain patient groups such as the malnourished, alcoholics, those with burns and those with hypokalemia are at increased risk of osmotic demyelination.[12] Osmotic demyelination occurs as a result of the failure of the adaptations that prevent chronically hyponatraemic patients from developing cerebral oedema. Over-rapid correction in these patients prevents the brain from replacing organic osmolytes at an appropriate speed. The resultant osmotic stress leads to osmotic demyelination.[33,34] This condition has previously been known as central pontine myelinolysis, due to its tendency to affect the pons, which has a dense concentration of heavily myelinated ascending and descending tracts which are particularly vulnerable to osmotic stress. However these changes have been reported in extra-pontine sites also.[35] The key features of osmotic demyelination are shown below. While it is known that resolution of hyponatremia should be tailored to the speed of the acquisition of the imbalance, there is no clear consensus on the absolute safe rate, and it may be that none exists.

Over-rapid correction is extremely common, despite the use of formulae to guide sodium correction. This is because volume repletion, irrespective of the fluid's actual sodium content, can switch off ADH production and cause a rapid rise in sodium level.

Importantly, there are case reports of successful treatment of osmotic demyelination treated by acutely relowering the serum sodium with dextrose and/ or desmopressin in cases of overshoot correction, thereby buying time for organic osmolytes to recumulate. [44]

Osmotic demyelination

- Presentation is usually delayed by 2-5 days following correction
- Diagnosis may be very difficult in sedated and ventilated patients
- Clinical features are varied, including bulbar problems, paraplegia, quadriplegia and locked-in syndrome
- Changes are often irreversible but re-lowering of serum sodium has anecdotal efficacy in the event of overly rapid correction.
- Where indicated, MRI is the imaging modality of choice.

Management of acute hyponatremia

Recommendations for the rate of correction of acute hyponatremia are based on avoiding brain herniation, something that is almost exclusively seen in acute hyponatremia.[12,36,37] These patients have the greatest risk of cerebral oedema but a lower risk of demyelination when compared with chronically hyponatraemic patients. Therefore prompt partial correction of hyponatremia is indicated. Limited available literature suggests that an increase in serum sodium of 4-6 mmol/l or to exceeed the seizure threshold of 120 mmol/l is adequate to reverse the most severe manifestations of acute hyponatremia.[37]

In acute hyponatremia severe neurological symptoms may be treated with a 100 ml bolus of 3% hypertonic saline.[32,38] This can be given intravenously over 10 minutes. This bolus may be repeated twice if severe neurological symptoms persist.[12] The aim of this emergency treatment is to address neurological complications such as cerebral oedema, hyponatremic seizures or reduced level of consciousness. Importantly the aim is not to return serum sodium levels to within the normal range. In acute hyponatremia once symptoms have resolved, it becomes less important to rapidly correct the sodium level, and in these instances an increase in serum sodium rates of up to 2 mmol/l/hour may be appropriate.[39]

If hypertonic saline (3% sodium chloride) is used in acute symptomatic patients, specialist advice should be sought. Very close (1-2 hourly) monitoring of plasma sodium should be performed. These patients should be admitted to a critical care unit, if such facilities are available. Some authors advocate the use of a loop diuretic in combination with hypertonic saline in order to enhance free water clearance, however extreme caution is required as this may lead to too rapid a rise in sodium.[39]

Management of chronic hyponatremia

It is widely accepted that patients with chronic hyponatremia are susceptible to adverse neurological outcomes when sodium levels are rapidly corrected due to iatrogenic brain damage.[12,29,33,34,37,40-42] Current guidance suggests the desired increase in serum sodium in chronic hyponatremia should be 4-8 mmol/l/day for those at low risk of osmotic demyelination syndrome.[12] In patient groups where the risk of osmotic demyelination syndrome is high, it has been suggested that an even lower goal of 4-6 mmol/l/day be targeted.[12] For patients with severe symptoms, the entire 6mmol/l can be achieved during the first 6 hours of therapy, with subsequent treatment delayed until the next day. Sterns et al. have described a rule of sixes that some may find helpful: six a day makes sense for safety; so six in six hours for severe symptoms and stop.[43]
As the precise time course of the disturbance is often not clear it is often safer to adopt slow correction for all patients unless adverse neurological symptoms and signs mandate a more rapid correction or there is absolute certainty about the time course. Specific tips for the management of the different subtypes of true hyponatremia are given below.

Hypovolaemic hyponatremia
In hypovolaemic hyponatremia, the aim is to correct the volume deficit, as the relative water excess will correct itself via a water diuresis once circulating volume is restored. Fluids such as 0.9% should be administered until blood pressure is restored and the patient has clinical euvolemia.[12] Hypovolaemic hyponatremia is almost always an example of chronic hyponatremia, so slow correction should be employed.

Euvolaemic hyponatremia
In euvolaemic hyponatremia, as with all hyponatremia, management is dictated by the underlying cause, the chronicity or acuteness of the imbalance and the presence or absence of neurological symptoms. Water restriction of 1–1.5 l/day may be used. Drugs that may have caused SIADH should be discontinued and any underlying causes addressed.

Hypervolemic hyponatremia
In hypervolemic hyponatremia, fluid restriction is the mainstay of treatment. Strict restriction is often necessary to achieve a negative solute-free water balance. Typical initial fluid restriction for a normal sized adult should be around 1–1.5 litres per day. Loop diuretics are sometimes used to remove excess fluid with urine usually hypotonic to plasma.[12]

CONCLUSION

Hyponatremia is a condition associated with significant morbidity and mortality. Treatment is guided by the underlying cause, speed of onset and the presence of adverse neurological signs. In the absence of severe neurological signs, current guidance suggests that correction of serum sodium should not exceed 4-8 mmol/l/day in patients with chronic hyponatremia. Lower rates of correction may be indicated in patients with chronic hyponatremia who have additional risk factors for osmotic demyelination. More rapid correction should only be targeted in cases where there is certainty that the hyponatremia is acute or if the hyponatremia is causing severe neurological symptoms. Too rapid correction of hyponatremia may risk permanent severe neurological damage or death.

Answers to questions

a) **True**. It is associated with increased mortality along with prolonged hospital stays and increased falls.
b) **False**. Over 99% of the sodium filtered by the kidney is reabsorbed in the proximal tubule and loop of Henle. The proportion of sodium reabsorbed in the distal tubule is much smaller but exerts the most influence on total sodium balance
c) **True**. Patients with advanced liver disease are also at increased risk.
d) **True**. It is often gastrointestinal in origin.
e) **False**. Such signs are usually only seen when serum sodium levels reach 115-120 mmol/l.

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