Hyponatraemia in clinical practice

M Biswas, J S Davies

Hyponatraemia is defined as a serum sodium concentration below 135 mmol/l. It causes major diagnostic and management problems in practice. Hyponatraemic disorders are divided into euvoalaemic, hypervolaemic and hypovolaemic. In the evaluation of the hyponatraemic patient, history taking should focus on identifying the potential cause, duration and symptomatology. Clinical examination should include assessment of volume status. Acute hyponatraemia of less than 48 h duration requires prompt correction. Treatment may involve hypertonic saline, isotonic saline and appropriate hormone replacement therapy depending on the aetiology. Chronic hyponatraemia should be treated with caution because of the risk of central pontine myelinolysis.

Hyponatraemia is the electrolyte disorder most commonly encountered in clinical practice, with a reported incidence of 15–30%. It poses considerable diagnostic and management problems for clinicians. The condition has a multifactorial aetiology, and multiple causes of hyponatraemia may be identified in individual patients. In the acute setting, treatment often has to be initiated before a confirmatory diagnosis can be made and results of supportive biochemical investigations are available. Both over-correction and under-treatment can produce devastating effects on cerebral function.

In this review, we will update the physiology of sodium and water balance and present a classification system of hyponatraemic disorders. Specific clinical scenarios and appropriate management strategies are provided.

REGULATION OF SODIUM AND WATER BALANCE

Water homeostasis is closely related to serum osmolarity and sodium concentration and is controlled by thirst, arginine vasopressin and the kidneys. The normal plasma osmolarity is 275–295 mosmol/l. Osmolarity is a measure of the osmotic pressure exerted by a solute in the presence of a semi-permeable membrane, which allows free passage of water without solute. As cell membranes are highly permeable to water, lipids, anions and cations, the term “tonicity” is often used to mean “effective osmolarity” and the ability of a solution to result in a transmembrane shift in water. Total plasma osmolarity does not always equal “effective plasma osmolarity”. For example, organic solutes such as urea, methanol and ethanol might increase serum osmolarity but can move freely in and out of cells and therefore do not induce a transcellular shift of water.

The principle determinants of plasma osmolarity are sodium and anions such as bicarbonate and chloride. This total concentration of anions and cations is roughly calculated as follows:

\[2 \times (\text{sodium mmol/l} + \text{potassium mmol/l}) + \text{urea mmol/l} + \text{glucose mmol/l}\]

If plasma osmolarity rises, antidiuretic hormone (ADH; also known as arginine vasopressin, AVP), a nonapeptide hormone synthesised in the hypothalamus and stored in the posterior pituitary, is released and thirst is activated. AVP binds to the V2 receptor in the renal collecting ducts, which stimulates the synthesis of cyclic AMP which then activates protein kinase A. Protein kinase A induces the phosphorylation of the aquaporin 2 water channel. Aquaporins are proteins which consist of membrane-spanning domains joined by connecting loops that fold back on to the membrane to form a pore, which allows water to pass. Phosphorylation results in the translocation of intracytoplasmic aquaporin 2 water channels to the apical cell membrane and tubular water reabsorption. In contrast, in healthy people, a large water load results in an acute fall in plasma AVP concentration and the excretion of large volumes of dilute urine.

With an intact diluting mechanism, the kidney can excrete in excess of 10 litres per day, resulting in a maximally dilute urine of less than 100 mosmol/l, protecting against hyponatraemia. Thus the consumption of excessive volumes of water does not usually cause hyponatraemia unless intake exceeds 10–15 l/day, overwhelming the renal diluting mechanism.

The renin–angiotensin–aldosterone system also regulates sodium balance, through its effect on aldosterone. This mineralocorticoid hormone stimulates sodium reabsorption in the distal nephron and the distal colon via the amiloride-sensitive sodium channel and Na/K ATPase, the sodium pump. Urinary excretion of sodium can vary from 1 mmol/day to up to 400 mmol/day depending on the amount of sodium ingested.

CLASSIFICATION OF HYPONATRAEMIA

Hyponatraemia is defined as a serum sodium concentration of <135 mmol/l after the exclusion of “pseudo-hyponatraemia”. In the latter, increases in the non-aqueous components of plasma such as in hypertiglyceridaemia or hypo-proteinenaemia result in a spuriously low sodium

Abbreviations: ADH, antidiuretic hormone; AVP, arginine vasopressin; CCF, congestive cardiac failure; EABV, effective arterial blood volume; SIADH, syndrome of inappropriate ADH secretion
concentration. Hyponatraemic disorders are divided into euvolaemic, hypovolaemic and hypervolaemic (Box 1).

A confusing number of descriptive terms such as hypotonic hyponatraemia and hypertonic hyponatraemia are also used in the literature in association with hyponatraemia. Hypertonic hyponatraemia refers to the translocation of water from the intracellular compartment into the extracellular compartment, because of the presence of an osmotically active “hypertonic” solute in the plasma, which cannot enter cells. This is seen after mannitol administration after transurethral resection of the prostate or insulinopenic states resulting in hyperglycaemia.

Hypotonic hyponatraemia is also termed dilutional hyponatraemia and reflects water retention. Patients with hypotonic hyponatraemia can have normal or high serum osmolarity and be either euvolaemic or hypervolaemic.

**EUVOLAEMIC HYponatraemia**

This is the most commonly encountered form of hyponatraemia in hospital patients, and the syndrome of inappropriate ADH secretion (SIADH) is a diagnosis that is often made; but it is important to stress that the latter is a diagnosis of exclusion. The diagnostic criteria for SIADH are hyponatraemia with low serum osmolarity (<270 mosmol/l) and an inappropriately high urine osmolarity of >100 mosmol/kg in a euvolaemic patient in whom hypopituitarism, hypoadrenalism, hypothyroidism renal insufficiency and diuretic use have been excluded.

In SIADH, excessive ADH release produces renal water reabsorption, and the body’s intracellular and extracellular fluid compartments are expanded, resulting in hyponatraemia. Despite the expansion of fluid compartments, the patient is not oedematous clinically and therefore the term euvolaemic is applied. SIADH is often caused by drugs (Box 2).

Plasma AVP measured by radioimmunoassay would be increased in such cases, but this is of limited use in clinical practice because of the lack of availability.

**HYPOVOLAEMIC HYponatraemia**

Diuretic-induced hyponatraemia is one of the most common causes of hypovolaemic hyponatraemia and is associated with high urinary sodium. Hyponaetraemia occurs more commonly with thiazide diuretics, although it has also been
described in association with furosemide and spironolac-
tone.[14] Thiazide diuretics act at the distal tubule. Mecha-
nisms postulated for thiazide diuretic-induced hypona-
traemia include hypovolaemia-stimulated ADH and interfer-
ence with urinary dilution in the cortical diluting segment.3
Some studies have identified specific risk factors for the
development of hyponatraemia and these include: institu-
tionalised elderly patients, low serum potassium concentra-
tion, low total body weight and indapamide use.[13, 15]
Salt-losing nephropathy occurs in patients with advanced
chronic renal disease who are unable to conserve sodium and
also in patients with proximal renal tubular acidosis and mild
renal insufficiency. Salt-losing nephropathy may be seen in
medullary cystic disease, polycystic kidney disease, analgesic
nephropathy and obstructive uropathy.5

Hyponatraemia with extracellular fluid volume contraction
and urine sodium >20 mmol/l in association with hyperkala-
emia may also be due to mineralocorticoid deficiency. It is
noteworthy that hyperkalaemia is not present in one-third of
patients with Addison's disease.3

Cerebral salt wasting was first reported in 1950 by Peters
et al24 in three patients with neurological disorders, hyponatrae-
mia, and clinical evidence of volume depletion and renal
sodium wasting without disturbance of the pituitary adrenal
axis. It is increasingly recognised in disorders of the central
nervous system, particularly in the field of neurosurgery.[12,
17, 18] This phenomenon has often been reported in patients
with subarachnoid haemorrhage who are found to be hypona-
traemic, with raised urine sodium (>25 mmol/l) and high urine
osmolarity.19,24 Such patients fulfill laboratory criteria for
SIADH, but have clinical signs of volume depletion, including
low central venous pressure.25 In one report total blood volume
was measured and shown to be reduced.17 The likely candidate
hormones mediating renal sodium loss are brain natriuretic
peptide and ouabain-like peptide.19

Gastrointestinal and third space losses may cause hypona-
traemic hypovolaemia, but there is avid sodium retention by
the kidneys. Urine sodium concentration is <10 mmol/l, and
the urine is hyposmolar.

HYPERVOLAEMIC HYponatraemia

The three main causes of hypervolaemic hyponatraemia are
congestive cardiac failure (CCF), cirrhosis and renal disease. In
these cases, total body sodium is increased, but total body water
(intracellular and extracellular fluid) is disproportionately
expanded resulting in hyponatraemia and oedema.20

In CCF a fall in cardiac output and mean arterial pressure
reduces effective arterial blood volume (EABV). This activates
the sympathetic nervous system, decreases renal blood flow,
and triggers release of AVP leading to water reabsorption in the
collecting ducts.25 Decreased renal blood flow stimulates the
renin–angiotensin–aldosterone system, which enhances
sodium reabsorption.[22] Hyponatraemia associated with CCF
may also be exacerbated by diuretic therapy. Numerous studies
have demonstrated that the development of hyponatraemia in
this condition is a poor prognostic indicator.[23, 24]

In cirrhosis, many factors lower EABV and lead to hypona-
traemia through similar mechanisms to those described above.
Portal hypertension leads to fluid migration into the peritoneal
cavity (ascites), and decreased serum albumin lowers plasma
oncotic pressure. The damaged liver fails to degrade vasodilating
factors, which reduces total peripheral resistance and causes
splanchic vasodilatation, reducing EABV. Diuretic administra-
tion, gastrointestinal haemorrhage and large volume para-
centesis may exacerbate hyponatraemia in cirrhosis.[25, 26] Hyponatraemia is also indicative of poor prognosis and such
patients are at higher risk of hepatorenal syndrome.[27]

In renal disease, proteinuria may lower plasma oncotic
pressure and reduce EABV, triggering activation of the renin–
angiotensin and aldosterone system and ADH release.5
Hyponoentic hyponatraemia may also result from defective
renal salt and water excretion.5

SPECIFIC CLINICAL SETTINGS

Alcohol abuse

Hyponatraemia in this setting is beer potomania syndrome, and
the diagnostic criteria include a history of binge drinking, poor
dietary solute intake, and decreased sodium concentrations in
the absence of other causes.26 Urine osmolarity is <100 mosm/
kg in this situation, indicating ADH suppression.26 In addition
to alcoholic liver disease, traumatic cerebral injury plus all the
other disorders mentioned above may affect the alcoholic
patient.

Hyponatraemia in psychiatric disorders

SIADH can occur in the setting of acute psychosis and also after
use of psychotropic medication.29 Excessive water intake is
often seen in association with psychiatric illness and is
commonly referred to as psychogenic polydipsia.29 High-volume
water intake eventually overburdens the renal diluting
mechanism. It is unclear what causes such compulsive
drinking, but proposed mechanisms include hyperactivity of
the hypothalamic thirst centre, neuroleptic drugs and resetting
of the hypothalamic osmostat.30

Marathon runners

Marathon-induced hyponatraemia is now emerging as a cause
of race-related death. Hyponatraemia is caused by the
consumption of high volumes (>3 litres) of fluid in excess of
sodium losses.31

Postoperative hyponatraemia

Careful assessment of admission notes, premedication, intrao-
perative records, fluid balance charts and anaesthetic records is
imperative. Drug therapy, surgical procedures and pain are all
causes of SIADH. Sodium picosulphate bowel preparation
before colonic surgery may cause dehydration and electrolyte
disorders, including hyponatraemia.32 As previously mentioned,
irrigation solutions such as mannitol, sorbitol and glycine may
cause hypertonic hyponatraemia when absorbed.3 The intrave-
nous administration of large volumes of 5% dextrose is a
common cause of postoperative hyponatraemia.

Hyponatraemia in primary adrenal insufficiency
(Addison’s disease) and secondary adrenal insufficiency

Primary adrenal insufficiency is associated with glucocorticoid
deficiency, which impairs renal water excretion and miner-
alarcoloid deficiency, which causes renal sodium loss.3
Secondary adrenal insufficiency may be due to hypopituitarism.
Glucocorticoid deficiency is the predominant cause of hypona-
traemia in this setting, as mineralocorticoid activity is
preserved. In addition, SIADH induced by hypothyroidism
may contribute.3 Hyponatraemia may resolve after correction of
cortisol deficiency.33

Symptoms of hyponoentric

The symptoms are primarily neurological and relate to the
rapidity of fall of serum sodium.34 Acute hyponatraemia is
defined as occurring within <48 h. There are usually no
symptoms if serum sodium is 130–135 mmol/l. Nausea and
malaise are seen if serum sodium falls to 125–130 mmol/l.
Headaches, nausea, vomiting, muscle cramps, restlessness,
disorientation and depressed reflexes can be seen if serum
sodium falls below 125 mmol/l.35 When severe hyponatraemia
evolves over a period of hours, seizures, coma, permanent brain
damage, respiratory arrest, brain-stem herniation and death may occur.4 5

In sharp contrast, patients with chronic hyponatraemia are often asymptomatic irrespective of the degree of hyponatraemia.1 Symptoms may only occur if there is acute exacerbation of hyponatraemia, or if serum sodium falls below 110 mmol/l.1 In chronic hyponatraemia present for >48 h, the brain adapts to protect itself against cerebral oedema: a rapid increase in plasma sodium can lead to a decrease in brain cell volume with resultant demyelination.6 7 It may not be apparent until 2–6 days after correction of sodium, and most patients are left with permanent neurological dysfunction including quadriplegia, pseudobulbar palsy and seizures.8 9 Coma and death may occur. Individuals at particular risk include elderly patients on thiazides, alcoholics and patients with primary polydipsia.1

Management of hyponatraemia

The treatment of hyponatraemia depends largely on its onset, aetiology and symptomatology. Initial evaluation of any patient with hyponatraemia involves identification of the onset of the condition (acute or chronic), the presence of symptoms and assessment of volume status.

A clinical history of renal, liver or cardiac disease should be noted, as well as previous electrolytes to distinguish acute from chronic hyponatraemia. Any loss of blood or extracellular fluid should be determined. A precise drug history, which includes recreational drug use, is necessary. Symptoms of headache, nausea, seizures and confusion suggest raised intracranial pressure.

On physical examination, an accurate recording of the patient’s volume status is critical. The biochemical parameters in salt-wasting conditions and those in SIADH can be identical and are differentiated by determining volume status (box 3). For example, distinguishing cerebral salt wasting from SIADH is of vital importance, as fluid restriction in a volume-depleted patient may worsen ischaemic cerebral injury in subarachnoid haemorrhage.10 Measurement of central venous pressure may be required.

The presence or absence of oedema, skin turgor and postural drop in systolic blood pressure of >20 mm Hg should all be recorded. When the patient cannot stand upright, sitting blood pressure can be used as an estimate. Examination may also reveal signs of an underlying illness causing hyponatraemia such as hypoadrenalism, hypopituitarism, chronic liver disease or nephrotic syndrome.

Acute symptomatic hyponatraemia

It is agreed that in acute hyponatraemia (<48 h duration) prompt correction of serum sodium is required to reduce cerebral oedema. The risk of cerebral oedema from hyponatraemia in this setting is greater than the risk of central pontine myelinolysis from overcorrection.11 It is also generally agreed that the correction of sodium should not exceed 1–2 mmol/h and 8 mmol/day on any given day of treatment.12 13 The target should not be to normalise serum sodium, but to raise it to safe levels (>120 mmol/l) after which conservative measures such as fluid restriction can be deployed.1

Hyponatraemia from endocrine causes is treated with appropriate hormone replacement therapy. Management of hypertonic hyponatraemia secondary to hyperglycaemia should focus on insulin and isotonic fluid administration (table 1). Intravenous hydrocortisone (100 mg intravenously/intramuscularly four times a day for 24–48 h) is given to correct hyponatraemia when adrenal insufficiency is suspected, after blood samples for cortisol have been sent. Patients with hypovolaemic hyponatraemia should be treated with isotonic saline.1 5

In other situations where acute hyponatraemia develops in a euvoalaemic or hypervolaemic patient with neurological symptoms, 3% sodium (3% NaCl) can be used.1 5 Opinions differ with regard to its use, and there is no evidence for its superiority. If given, serum electrolytes should be measured hourly along with urine output and cardiovascular status. This regimen enables the rapid correction of hyponatraemia, with smaller volumes of fluid. Solute-free water should be completely withheld. Furosemide (40 mg intravenously) can be given in addition to promote solute-free water excretion.1 5 Isotonic saline is unsuitable for correcting hyponatraemia in euvoalaemic or hypervolaemic states, as the resulting rise in sodium is small and there is a net retention of water, potentially worsening hyponatraemia.16

The rate of infusion can be started at 1–2 ml/kg/h, with repeated hourly estimates of serum sodium. The Adrogue–Madias formula5 may assist in providing “the anticipated change in serum sodium” following the administration of 1 litre of any infusate containing sodium:

\[\text{Change in Na mmol/l} = \frac{(\text{Na in infusate} - \text{serum Na})}{(\text{total body water} + 1)}\]

Total body water is estimated from body weight and expressed in litres; it is roughly 0.5 × female weight in kg and 0.6 × male weight in kg. This equation has been evaluated recently in a large series of patients with dysnatremias and accurately predicted changes in serum sodium in most patients, but underestimated the degree of sodium rise in certain cases.16

Chronic hyponatraemia

Caution is advised in the treatment of chronic hyponatraemia, as the risk of osmotic demyelination is high because of brain adaptation; it may even develop with water restriction alone.15–36 The goal of treatment of chronic asymptomatic hyponatraemia is to remove the underlying cause. If chronic hyponatraemia becomes symptomatic, treatment involves slow, gradual correction of sodium, largely with fluid restriction (800 ml/day) once hypovolaemia has been excluded.3 5 If sodium fails to rise with fluid restriction, a reassessment of the patient’s volume status should be made, and, if euvoalaemic, demeclocycline 600–1200 mg/day can be given.1 5 Most drug-induced hyponatraemia responds to withdrawal of the offending agent with or without fluid restriction.9

Table 1 Sodium content of infusates

<table>
<thead>
<tr>
<th>Infusate</th>
<th>Infusate sodium (mmol/l)</th>
<th>ECF distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>855</td>
<td>100</td>
</tr>
<tr>
<td>3%</td>
<td>513</td>
<td>100</td>
</tr>
<tr>
<td>0.9%</td>
<td>154</td>
<td>100</td>
</tr>
<tr>
<td>Ringer’s lactate</td>
<td>130</td>
<td>97</td>
</tr>
<tr>
<td>0.45% NaCl in water</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>5% dextrose in water</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

ECF, extracellular fluid.

www.postgradmedj.com

Box 3 Biochemical parameters in hyponatraemia

<table>
<thead>
<tr>
<th>Blood parameter</th>
<th>EABV low</th>
<th>EABV normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Na &gt;20 mmol/l</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>High osmolality</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Low serum osmolality</td>
<td>SIADH</td>
<td>Cerebral salt wasting</td>
</tr>
<tr>
<td>High serum osmolality</td>
<td>SIADH</td>
<td>Low</td>
</tr>
<tr>
<td>Diuretics</td>
<td>SIADH</td>
<td>Low</td>
</tr>
<tr>
<td>Salt-losing nephropathy</td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Mineralocorticoid deficiency</td>
<td>SIADH</td>
<td></td>
</tr>
<tr>
<td>EABV, effective arterial blood volume; SIADH, syndrome of inappropriate ADH secretion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hyponatraemia in clinical practice

**Key references**


**Oedematous states with low EABV**

In severe cardiac failure, treatment should focus on sodium and water restriction and the administration of loop diuretics, which will reduce the action of ADH on the collecting tubules and limit water reabsorption.[14] Spironolactone may promote the excretion of oedema fluid while maintaining potassium.[14] Thiazide diuretics should be avoided, as they impair urinary dilution and can paradoxically worsen hyponatraemia.3

In cirrhosis, hyponatraemia is usually treated with salt and water restriction. When overdiuresis is causative, diuretics are temporarily terminated. Some have treated sodium deficits with 3% saline, furosemide-induced diuresis, and re-infusion of solute.39

**FUTURE THERAPIES**

The aquaretics are a new line of agents which hold promise for future use in the treatment of euvoalaemic and hypervolaemic hyponatraemia. Vasopressin receptor antagonists block AVP from binding to V2 receptors in the distal nephron and promote the excretion of electrolyte-free water.40 In recent randomised trials, tolvaptan, an orally active V2 receptor antagonist, has been effective in raising serum sodium in euvoalaemic and hypervolaemic subjects.41 Conivaptan is another agent that shows activity at both the V2 receptor and the V1a receptor, which is responsible for AVP-mediated vasoconstriction. Dual receptor activity reduces cardiac preload and total peripheral resistance, which are both of benefit in CCF.42

**MULTIPLE CHOICE QUESTIONS (ANSWERS AFTER THE REFERENCES)**

Choose the best response out of the five options provided.

1. Which of the following statements best describes the mechanism by which mannitol causes hyponatraemia?
   
   (A) hypotonic hyponatraemia
   
   (B) isotonic hyponatraemia
   
   (C) reducing renal free water clearance
   
   (D) hypertonic hyponatraemia
   
   (E) increased urine sodium excretion

2. In which one of the following situations is urine sodium excretion likely to be less than 20 mmol/day?
   
   (A) SIADH
   
   (B) renal disease
   
   (C) acute diarrhoea
   
   (D) hyperglycaemia
   
   (E) hypothyroidism

3. An elderly lady presents to A&E with an acute confusional state. She is pyrexial. Blood pressure is 140/90 and there is no postural drop. She takes carbamazepine for trigeminal neuralgia. Serum sodium is 123 mmol/l (135–145). Which of the following statements best applies to the diagnosis and management?
   
   (A) acute hyponatraemia is the most probable cause of her confusion
   
   (B) carbamazepine is an unlikely cause of hyponatraemia
   
   (C) hypertonic saline should be used to correct hyponatraemia
   
   (D) she may have acute on chronic hyponatraemia
   
   (E) fluid restriction is the only treatment required in this setting

4. Which of the following best describes the mechanism of hyponatraemia in secondary adrenal insufficiency?
   
   (A) renal sodium wasting
   
   (B) extra-renal sodium loss
   
   (C) hypovolaemic hyponatraemia
   
   (D) hypertonc hyponatraemia
   
   (E) impaired renal water excretion

5. Which of the following best describes the action of the aquaretics agents?
   
   (A) they bind to V1a receptors
   
   (B) they act at the proximal convoluted tubule
   
   (C) they bind to V2 receptors in the distal nephron and promote the excretion of sodium and water
   
   (D) tolvaptan binds to the V2 receptor in the distal nephron
   
   (E) tolvaptan demonstrates activity at the V1a receptor and the V2 receptor

***************

**Authors’ affiliations**

M Biswas, Department of Medicine, Royal Gwent Hospital, Newport, Wales, UK

J S Davies, Department of Medicine, University Hospital of Wales, Heath Park, Cardiff, Wales, UK

Competing interests: None.

**REFERENCES**


www.postgradmedj.com
Submit an eLetter, and join the debate

eLetters are a fast and convenient way to register your opinion on topical and contentious medical issues. You can find the “submit a response” link alongside the abstract, full text and PDF versions of all our articles. We aim to publish swiftly, and your comments will be emailed directly to the author of the original article to allow them to respond. eLetters are a great way of participating in important clinical debates, so make sure your voice is heard.
Hyponatraemia in clinical practice

M Biswas and J S Davies

Postgrad Med J 2007 83: 373-378
doi: 10.1136/pgmj.2006.056515

Updated information and services can be found at:
http://pmj.bmj.com/content/83/980/373.full.html

These include:

References
This article cites 37 articles, 5 of which can be accessed free at:
http://pmj.bmj.com/content/83/980/373.full.html#ref-list-1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/