Electrolytes and Homeostasis
Skills and techniques

Update 2011 (pdf)

Module Authors (Update 2011)

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Electrolytes and Homeostasis
Learning objectives:

After studying this module on Electrolytes and Homeostasis, you should be able to:

1. Diagnose and determine appropriate management for acute disorders of sodium and potassium balance
2. Recognise the manifestations of hypoglycaemia and hyperglycaemic syndromes and institute optimal therapy
3. Identify simple and complex acid-base disorders and appropriately treat the aetiology
4. Diagnose and manage acute adrenal and thyroid conditions.

FACULTY DISCLOSURES
The authors of this module have not reported any disclosures.
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INTRODUCTION

Competent analysis and management of electrolyte, acid-base and hormonal homeostasis plays a crucial role in the provision of quality care to critically ill patients. The key to managing electrolyte and acid-base imbalances as well as hormonal disturbances is prompt recognition, identification of the underlying process and correction proportional to the acuity and severity of the derangement. Disturbed serum electrolyte levels are not always indicative of the total body stores but may reflect a pathological process that requires definitive treatment. Furthermore, iatrogenic causes of disturbed homeostasis are commonplace. Intensive care physicians should therefore be familiar with the causes and manifestations of these disorders and the various treatment strategies that can be employed. Some particularly useful reviews are mentioned below. While established ‘recipes’ for correcting electrolyte abnormalities serve as a starting point, they cannot replace repeated clinical examination and sequential measurement of electrolyte levels.


1/ ACUTE DISORDERS OF SODIUM HOMEOSTASIS

Hyponatraemia


Recognition

Hyponatraemia reflects relative excess of free water to solute and is usually accompanied by a decrease in plasma osmolality. Hypo-osmolality can be considered to be dangerous when the effective plasma osmolality falls to ≤240 mOsm/kg, regardless of aetiology. Both the rate of decrease and the magnitude of change in plasma sodium are important in the generation of symptoms. Commonly patients with hyponatraemia present with neurologic symptoms that can vary from confusion and lethargy to stupor, convulsions and coma.

Although hyponatraemia is most commonly found on routine lab work, it should be specifically looked for in critically ill patients with:

- New-onset confusion, convulsions, stupor and/or coma, particularly in a patient known to be at risk of water intoxication e.g. following transurethral resection of prostate (TURP), laparoscopic irrigation, or the utilisation of hypotonic fluids for resuscitation.
- History of known predisposing causes, such as hypothyroidism, cirrhosis, chronic heart failure, conditions known to cause the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and adrenal insufficiency.

Q. What is the cause of hyponatraemia following TURP?

A. Transurethral resection of the prostate or a bladder tumour is occasionally associated with the use of large volumes of flushing solutions containing glycine, sorbitol or mannitol.

Q What volume of fluid enters the circulation to cause hyponatraemia?

A Variable quantities of this fluid enter the circulation (sometimes as much as 3 litres) leading to a dilutional reduction in the plasma sodium concentration that may fall below 100 mmol/L (mEq/L).

Though previously a relatively common occurrence, increased awareness now means that this cause of hyponatraemia is less common. A similar complication is being increasingly recognised with the use of glycine irrigation solutions during hysteroscopy in women. Risk factors for severe hyponatraemia are prolonged duration of surgery, excess height of the irrigation solution reservoir (which introduces the fluid under high pressure) and large tissue resection. A clue to the diagnosis of this disorder is the history and the presence of an osmolar gap.
**Resuscitation**

If the patient is stuporous and/or convulsing, assessing and establishing the airway is a priority. Control of convulsions and correction of any hypotension should be initiated immediately after securing the airway.

**Diagnosis**

- Plasma osmolality is key to categorising the aetiology of hyponatraemia.
- Urine osmolality: in those patients with hypotonic hyponatraemia, the urine osmolality can be used to distinguish between impaired water excretion, which is present in almost all cases (indicated by a high urine osmolality), and primary polydipsia, in which water excretion is normal but intake is so high that it exceeds excretory capacity (despite low urine osmolality).
- Plasma osmolar gap (difference between the calculated and measured osmolar gaps) of >10 mmol suggests the presence of ‘unmeasured osmoles’ in the plasma, like mannitol and alcohols.
- Plasma uric acid level: the initial water retention and volume expansion in the SIADH leads to hypouricaemia, another frequent finding that is the opposite of that typically seen with volume depletion which is increased serum uric acid levels and increased uric acid excretion. The only exception to this rule is that in patients with cerebral salt wasting, despite intravascular volume depletion, the serum uric acid levels stay low.
- Confirm normal renal, adrenal and thyroid function (prerequisite for diagnosis of SIADH).
- Look for and identify diseases and/or drugs associated with SIADH (see table).

**Causes of SIADH**

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Categories of hyponatraemia

Key to the determination of the aetiology of hyponatraemia is the measurement of plasma osmolality and assessment of the effective total body water volume.

Hypotonic hyponatraemia – Commonest type
Patients can have either a decreased intravascular volume (with or without oedema) or a normal intravascular volume. Congestive heart failure, cirrhosis and nephrotic syndrome cause an oedematous state with decreased intravascular volume. The two major conditions causing euvoalaemic hyponatraemia are SIADH and primary psychogenic polydipsia. These two conditions can be readily differentiated using urine osmolality values (as discussed above).

Isotonic hyponatraemia – ‘Pseudo’ hyponatraemia
Occurs with severe hyperlipidaemia or hyperproteinaemia. Plasma sodium (PNa) is determined by measuring the concentration of sodium per litre of the whole plasma. Therefore, when the non-water component of plasma (lipids or proteins) increases, PNa decreases spuriously.

Hypertonic hyponatraemia – ‘Dilutional’ hyponatraemia
Occurs due to hyperglycaemia or mannitol administration, both of which induce osmotic water movement out of the cells and lower the plasma sodium concentration by dilution.

Q. How do you correct (roughly) the measured plasma sodium for hyperglycaemia?
A For every 5.5 mmol/L (100 mg/dL) increase in plasma glucose over the normal levels, plasma sodium decreases by 1.6 mmol/L (1.6 mEq/L). Or for every 3.5 mmol/L (62.5 mg/dL) increase in plasma glucose above normal, plasma sodium decreases by 1 mmol/L (1 mEq/L).
Q Please give the formula for correcting the sodium for the plasma glucose level in hyperglycaemic patients.

A
Corrected PNa = Measured PNa + \([\text{Change in plasma glucose (mmol/L)} / 3]\) or
Corrected PNa = Measured PNa + \([\text{Change in plasma glucose (mg/dL)} / 62]\)


Calculate the actual serum sodium concentration of all your patients with serum glucose >16.6 mmol/L (>300 mg/dL) using the correction formula until you achieve familiarity with using this formula.

Aetiology of neurological dysfunction

In hypotonic hyponatraemia of acute onset, brain swelling occurs due to fluid shift into the cells. However, the degree of brain swelling and therefore the likelihood of neurologic symptoms are much less with chronic hyponatraemia. This is due to the following reversible protective mechanisms:

- Extracellular fluid movement out of the brain into the cerebrospinal fluid (due to increase in the interstitial hydrostatic pressure due to the initial cerebral oedema).
- Loss of solutes from the brain cells, leading to the osmotic movement of water back out of the cells. This is initially mediated by extrusion of intracellular sodium and potassium. Subsequently, over the next few days, loss of organic solutes occurs thereby restoring brain size. In chronic hyponatraemia, in which the excessive brain volume has returned toward normal, rapid correction of severe hyponatraemia can lead to the development of a neurologic disorder called osmotic demyelination or central pontine myelinolysis.

Q. What is the mechanism of injury in osmotic demyelination syndrome (ODS)?

A. Severe hyponatraemia, if acute in onset, leads to brain swelling (due to osmotic movement of water into the brain) and can potentially cause irreversible neurologic damage and death. The brain tries to adapt by mobilising intracellular water by extruding sodium and potassium salts and certain organic solutes (called osmolytes), thereby lowering the brain volume toward normal. In this setting (in which the increased brain volume has returned towards normal), rapid correction of severe hyponatraemia can lead to the development of a neurologic disorder called central pontine myelinolysis or osmotic demyelination.

The symptoms of osmotic demyelination include dysphagia, dysarthria, quadriparesis, lethargy, seizures and coma. Most of these symptoms are irreversible or only partially reversible. This disorder has been associated with a rate of rise of serum sodium concentration.
of as little as 12 mmol/L per 24 hours. For this reason, the rate of correction recommended in patients with acute severe hyponatraemia is no more than 10–12 mmol/L/day (mEq/L/day) on the first day of treatment. Osmotic demyelination syndrome is associated with alcoholism and middle-age and, although more common in males, is also recognised in premenopausal women and in the paediatric population.

**Clinical management**

Severe, acute symptomatic hyponatraemia is a medical emergency and therapy should be initiated with intravenous hypertonic saline. The goal of therapy is to correct the [Na] by no more than 2 mmol/L/hr for the initial 6 hours, but not to exceed a change of >10–12 mmol/L/day. During correction, plasma electrolytes should be closely monitored and hypertonic saline should be discontinued when the patient becomes asymptomatic.

In patients with asymptomatic hyponatraemia, [Na] can be corrected more slowly at a rate of around 0.5 mmol/L/hr. This can be safely achieved by water restriction in euvaloemic patients. Drugs associated with SIADH need to be discontinued.

In hyponatraemic patients who are hypovolaemic with haemodynamic compromise, correction of volume depletion by normal saline resuscitation is a prerequisite to the normalisation of plasma sodium, since both intravascular volume and plasma osmolality regulate antidiuretic hormone (ADH) secretion.

**NOTE** The main considerations during the treatment of hyponatraemia are the acuity of its onset, the tonicity of the plasma and the presence and severity of symptoms.

**Outcome**

The initial outcome for hyponatraemia is usually favourable with careful electrolyte correction and treatment of underlying disorder but dysnatraemia itself is an independent prognostic factor for long-term survival. Furthermore, when a patient with hyponatraemic encephalopathy experiences respiratory arrest, some degree of brain damage is common. The complications resulting from treatment of symptomatic hyponatraemia (especially with hypertonic saline) include congestive heart failure and osmotic demyelination syndrome (ODS), which has a poor outcome. You can read more about ODS in the following references.

Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. J Neurol Neurosurg Psychiatry 2004; 75(Suppl III); 22–28. PMID 15316041


Hypernatraemia


Recognition

Hypernatraemia in the ICU patient is most often an incidental finding and may be difficult to detect clinically because it frequently occurs in the setting of coexistent pathological processes. Nevertheless, hypernatraemia should be suspected in critically ill patients with hyperreflexia, coma and/or seizures, especially if a water losing circumstance pertains – see aetiology below.

Resuscitation

As in the patient with hyponatraemia, assessment and management of airway and haemodynamics are crucial, especially if the patient has neurologic symptoms, such as decreased level of consciousness or convulsions.

Diagnosis

The cause of the hypernatraemia is usually evident from the history e.g. polyuria of >10 L/day suggests a diagnosis of diabetes insipidus (DI). If, however, the aetiology is unclear, the correct diagnosis can usually be established by evaluation of the integrity of the ADH-renal axis via measurement of the plasma and urine osmolality. Increased plasma osmolality is a potent stimulus of ADH and if both hypothalamic and renal secretion function are intact, maximal ADH secretion occurs leading to very concentrated urine. However in the presence of impaired ADH secretion (central DI) or resistance to ADH (nephrogenic DI) the urine is inappropriately hypotonic in the setting of plasma hypertonicity.

Q. What is the total water deficit in a 70 kg man with a plasma sodium of 165 mmol/L?

A. Water deficit = [(Actual PNa – 140) / 140 × 0.6 × Body weight (in kg)].
In a 70 kg man with serum sodium of 165 mmol/L (mEq/L), the water deficit is: (165–140) / 140 × 0.6 × 70 = 7.5 l.

Aetiology/categories of hypernatraemia

Hypernatraemia indicates (relative) water depletion and can occur with decreased, increased or normal total body sodium (TBNa+):

- In the setting of decreased TBNa+, both sodium and water have usually been lost, but water loss exceeds sodium losses leading to hypernatraemia. This can be a result of renal losses (loop diuretics or DI) or extra-renal losses (commonly seen in diarrhoea and vomiting).
- Hypernatraemia with increased TBNa+ is less common and occurs due to exogenous administration of large volumes of normal saline, hypertonic saline or excessive sodium bicarbonate during correction of metabolic acidosis.
Loss of relatively salt-free water can lead to hypernatraemia with normal TBNa+. However, water losses alone do not culminate in hypernatraemia unless either they are very large (as in diabetes insipidus) or are aggravated by decreased water intake. Examples are central (brain death, neurotrauma, neurotumours and neurosurgery) or nephrogenic DI of varied aetiology – congenital, hypercalcaemia, hypokalaemia and drugs such as lithium, demeclocycline and amphotericin B.


In acute hypernatraemia, plasma hypertonicity shifts fluid from within the cells to the extracellular space causing brain ‘shrinkage’. However, in chronic hypernatraemia, the brain compensates by synthesising ‘idiogenic osmoles’, bringing fluid back into the cells and reversing some of the brain shrinkage.

**Clinical management**

The principles of correction of hypernatraemia are similar to those of hyponatraemia in that the rate of correction should depend on the acuity and degree of the derangement and the presence or absence of symptoms.

- The goals of management of hypernatraemia are to correct the plasma volume and plasma tonicity.
- In hypovolaemic patients with impaired haemodynamics, isotonic fluids to correct volume status should be administered first. Once haemodynamics are stabilised, correction of the tonicity should be performed either by administration of water enterally or by giving intravenous hypotonic fluids (0.45% saline or dextrose water).
- The recommended rate of correction of hypernatraemia is usually 1 mmol/L/hr or not more than half the calculated free water deficit in the first 24 hours. In patients with DI, all underlying causes should be corrected, offending drugs stopped and desmopressin administered if the patient has central DI.

THINK What would be the fluid of choice for correcting hypernatraemia in a diabetic patient presenting with a blood glucose of 63.7 mmol/L (1158.2 mg/dL), serum sodium of 155 mmol/L (155 mEq/L), and a blood pressure of 78/50 mmHg? Explain your reasoning.

**Outcome**

Response to treatment in a patient with hypernatraemic encephalopathy is usually slow. However, care must be taken not to correct the plasma sodium rapidly, since this carries the risk of inducing brain swelling.
2/ Acute Disorders of Potassium Homeostasis

Hypokalaemia


Recognition

Symptoms usually occur when the serum potassium (K+) level falls to <3 mmol/L (3 mEq/L). Although hypokalaemia is usually found incidentally in the critically ill, it should be looked for in ICU patients:

- With any arrhythmia, especially during the postoperative period
- During or immediately after aggressive correction of acidosis (especially if sodium bicarbonate was administered)
- Receiving diuretics
- With large volumes of nasogastric aspirate or diarrhoea
- Manifesting fatigue, myalgia and muscular weakness with or without hypoventilation
- With end-stage liver disease and of hepatic encephalopathy
- Receiving frequent beta-stimulant inhalers/nebulisations (such as salbutamol).

Resuscitation

Airway compromise caused by hypokalaemia is rare; management of any arrhythmias and the associated hypotension should take priority over the evaluation of the cause of hypokalaemia.

Diagnosis

Usually the aetiology of K+ depletion can be determined from a careful history. Diuretic and laxative abuse and surreptitious vomiting should be excluded when severe hypokalaemia is seen in the emergency department. In patients with a marked leukocytosis (e.g. acute leukaemia) and low serum K+, ‘pseudohypokalaemia’ due to intracellular uptake of K+ by WBCs should be considered and plasma potassium should be measured, after rapid separation of plasma from serum. Rule out precipitating causes for renal (e.g. diuretic use, osmotic diuretics, hypomagnesaemia, amphotericin B, ticarcillin,) or extra-renal K+ losses (vomiting, diarrhoea, ‘fistula’ losses and or NG aspiration).

- Check for metabolic alkalosis – a frequent complication of medium or long-term hypokalaemia.
- In patients with severe hypokalaemia, do an ECG to look for specific changes (see question below).
- Check plasma magnesium levels because hypomagnesaemia leads to renal potassium wasting. Correction of hypokalaemia will not be sustainable until hypomagnesaemia is also corrected.

[10]
- Type I and Type II renal tubular acidosis is usually associated with hypokalaemia which may be extreme. Blood gas and electrolyte analysis will exclude these abnormalities.
- Rarely, measuring 24-hour urine K⁺ may be necessary to differentiate renal and extra-renal K⁺ losses. However urine K⁺ levels must be interpreted in the light of total urine volume and its osmolality.

**Anecdote**

A 32-year-old patient was admitted to the hospital with alcohol intoxication, dehydration and a serum K⁺ of 2.2 mmol/L (2.2 mEq/L). The patient’s K⁺ remained persistently <2.5 mmol/L (<2.5 mEq/L) despite replacement with a total of 100 mmol (100 mEq) of potassium chloride (KCl) over the first hospital day. Serum magnesium when measured the next day was only 0.4 mmol/L (0.8 mEq/L). After supplementing the patient with 4 g (1 g Magnesium sulphate = 4.1 mmol) of intravenous magnesium per day, the patient’s hypokalaemia responded to replacement therapy.


**Q. What are the ECG changes associated with hypokalaemia?**

A. ECG changes associated with hypokalaemia include flattening and/or inversion of the T waves (panel A), prominent U waves (panel B), ST segment depression and prolongation of the QT interval. As hypokalaemia becomes more severe, decreased voltage and widening of the QRS complex, prolonged PR interval and ventricular arrhythmias can occur.
Q. Are the ECG changes of hypokalaemia related to serum potassium level?

A. No, it is important to appreciate that the ECG changes of hypokalaemia do not correlate with plasma potassium levels.

**Aetiology**
- Decreased ingestion
- Redistribution into the cells – alkalosis, insulin, β2-adrenergic agonists, hypothermia
- Increased losses – renal (diuretics, hypomagnesaemia, amphotericin B, salt-wasting nephropathies, primary mineralocorticoid excess) and extra-renal (diarrhoea, vomiting, laxative abuse and NG drainage).

**Clinical management**

The degree of whole body K⁺ depletion does not correlate closely with the plasma K⁺ concentration. The route and rapidity of correction depends on the presence or absence of life-threatening cardiac arrhythmias due to hypokalaemia.

- When the GI tract is available, it is safer to correct hypokalaemia using the oral route.
- In severe hypokalaemia, intravenous route can be used. The recommended rate of intravenous administration of K⁺ is 10 mmol/hr (10 mEq/hr) in a peripheral line or 20 mmol/hr (20 mEq/hr) using a central venous catheter, usually accompanied by ECG monitoring.
- Serum K⁺ levels must be monitored repeatedly during intravenous therapy.
- Saline rather than a dextrose-based solution is preferred for initial therapy, since the administration of dextrose stimulates insulin release and as a consequence can lead to an initial transient reduction in the plasma K⁺ concentration.
- If the patient is alkalotic, KCl should be administered. However, if the patient is acidotic and/or hypophosphataemic (diabetic ketoacidosis), phosphate salt of potassium should be used.
- All offending drugs should be stopped and precipitating causes treated simultaneously.
- Correction of co-existing hypomagnesaemia should be performed.
simultaneously to achieve effective and sustainable correction of hypokalaemia.

- In patients with K⁺ wasting disorders, long-term treatment with oral potassium supplements will be required.


**Outcome**

The effects of hypokalaemia are usually transient and are reversible. However, hypokalaemia at hospital admission has been associated with poorer outcomes.

### Hyperkalaemia


**Recognition**

Clinical manifestations of hyperkalaemia usually occur only when serum K⁺ levels are >6 mmol/L (>6 mEq/L), but clinicians should react when K⁺ levels rise above 5 mmol/L (5 mEq/L). It should be suspected in critically ill patients with:

- Acute oliguric renal failure
- Severe acidosis
- Conditions predisposing to rhabdomyolysis e.g. polytrauma
- History compatible with tumour lysis syndrome
- Digitalis toxicity
- Acute cardiac conduction disturbances and asystolic cardiac arrest
- Generalised symmetrical weakness with decreased reflexes.

The rapidity with which hyperkalaemia occurs, varies depending on the cause. Conditions causing release of intracellular potassium due to cellular breakdown (e.g. bowel necrosis and rhabdomyolysis) and conditions that lead to extracellular shift of potassium (metabolic acidosis, digitalis toxicity and severe insulin deficiency) usually cause acute hyperkalaemia that manifests within hours of onset of the inciting process. When there is a rapid (hours) rise in serum potassium, renal function should be assessed and clinical and biochemical evidence of rhabdomyolysis should be sought. Serum calcium is low, but phosphate (also) released from within the cells is elevated in this syndrome. However, conditions causing decreased renal excretion of potassium (e.g. acute renal failure, hypoaldosteronism, NSAIDs) generally cause a gradual (days to weeks) onset of hyperkalaemia.
**Resuscitation**

In a hyperkalaemic patient with a cardiac arrhythmia, management of the arrhythmia and establishment of an airway and haemodynamic stability is the first priority.

**Diagnosis**

Occasionally ‘pseudohyperkalaemia’ can occur due to mechanical trauma during venopuncture, haemolysis, prolonged tourniquet application, prolonged storage of a blood sample and severe leukocytosis or thrombocytosis. The presence of pseudohyperkalaemia should be suspected in an asymptomatic patient and whenever there is no apparent cause for the elevation in the plasma K⁺ concentration. Acute oliguric renal failure, chronic renal insufficiency and precipitating causes of rhabdomyolysis (trauma, alcohol) should be ruled out by history. Conditions that predispose to the movement of K⁺ out of the cells into the extracellular space (insulin deficiency, acidosis) should be sought. In critically ill patients with relevant past history (e.g. steroid-dependence, recent anticoagulation, sepsis) be on the alert for signs and symptoms of adrenal insufficiency (hypotension, hypoglycaemia, hyponatremia).

Apart from the evaluation of acute oliguric renal failure (commonest cause of hyperkalaemia in the ICU), serum creatinine kinase level, random cortisol level or an adrenocorticotropic hormone (ACTH) stimulation test may be warranted in the appropriate settings. Although hyperkalaemia can cause specific ECG changes, they do not correlate well with serum potassium levels.

**Q. What is the earliest ECG manifestation of hyperkalaemia?**

A. As in hypokalaemia, ECG changes associated with hyperkalaemia do not correlate closely with plasma potassium levels. The earliest ECG change is tall peaked T waves. Other changes that occur with more severe hyperkalaemia include: prolonged PR and QRS duration, AV conduction delays and finally a sine wave pattern terminating in ventricular fibrillation or asystole.

**Aetiology**

- Extracellular potassium shift (metabolic acidosis, insulin deficiency (DKA), exercise, β-adrenergic blockade, digitalis toxicity)
- Decreased excretion
Acute oliguric renal failure

Drugs – ACE inhibitors, NSAIDS, trimethoprim/sulphamethoxazole, heparin

Type IV renal tubular acidosis (RTA)

Impaired sodium reabsorption (primary and secondary hypoaldosteronism).

Look routinely at the ECGs of all patients with electrolyte abnormalities and familiarise yourself with the ECG changes of hyperkalaemia. Also check for yourself whether the serum potassium levels correlate with ECG manifestations in these patients.

Clinical management

If hyperkalaemia is associated with physiological effects such as cardiac arrhythmias, intravenous calcium should be administered immediately. The usual dose is 10 mL of 10% calcium gluconate given fairly rapidly intravenously. This dose can be repeated up to a total of 30 mL. It is important to note that intravenous calcium acts as a physiological antagonist and does not cause a significant change in the serum potassium concentration.

Intravenous insulin lowers the serum potassium concentration by approximately 0.6 to 1.0 mmol/L (mEq/L) and is widely used to treat patients with hyperkalaemia. However, insulin promotes potassium uptake into the cells by mechanisms independent of glucose entry and hence glucose should also be administered to prevent hypoglycaemia. A commonly used regimen is 10 units of regular insulin as an intravenous bolus, followed by 50–100 mL 50% dextrose solution given through a peripheral line (or CVC, if available) as a rapid infusion. In some countries, insulin/dextrose is given simultaneously over 20–30 minutes.

Nebulised β2-agonists may be valuable when intravenous access is difficult. The usual adult dose is 10–20 mg of salbutamol by nebuliser over 10 minutes. The dose of salbutamol recommended for acute management of hyperkalaemia is 3–4 times that of the dose used for bronchodilation. The transcellular shift of potassium into the cells by salbutamol may be attenuated in patients receiving beta-blockers.

It is generally recommended that dual therapy with both insulin/dextrose and salbutamol be used for acute management of hyperkalaemia in critically ill patients since dual therapy reduces serum potassium more than mono therapy.

Alkalisation with either sodium bicarbonate or hyperventilation to drive potassium into the cells can rapidly reverse the adverse physiological effects of hyperkalaemia. However recent studies have not demonstrated reliable reductions in the serum potassium concentration with bicarbonate therapy and hence this approach is not recommended as the first line of therapy in patients with hyperkalaemia. In patients who are not acidic, administration of sodium bicarbonate has little or no effect on serum potassium levels and should be reserved for patients with significant acidosis.

Once some or all of the above measures have been initiated, provided the GI tract is available, cationic-exchange resins can be given orally or as an enema to sustain lower serum potassium levels.
In patients with adequate renal function, loop diuretics can be administered to enhance renal potassium excretion. However, in the critically ill patient with renal impairment or with refractory hyperkalaemia, haemodialysis or haemofiltration may be necessary. Furosemide is generally avoided in those with rhabdomyolysis as it induces an acid diuresis and urinary acidity is associated with myoglobin precipitation in the renal tubules and possible worsening the renal insult. (See the PACT modules on Acute kidney injury – parts I and II for further information.)

The underlying cause of hyperkalaemia if any (e.g. dietary modification, correction of acidosis, resection of dead bowel, exogenous mineralocorticoid administration, rhabdomyolysis) should be treated and offending drugs e.g. spironolactone, amiloride, ACE inhibitors be discontinued. In patients with suspected adrenal insufficiency, steroid supplementation should be initiated immediately while the diagnosis is being confirmed.


**Outcome**

If hyperkalaemia is unrecognised or not corrected, it may lead to fatal arrhythmias. However, in most clinical circumstances one or more of the above measures is usually effective but haemodialysis or haemodiafiltration may be indicated acutely thus affecting the patient mortality categorisation. Once acute hyperkalaemia is controlled, the outcome will depend on the underlying cause.
3/ ACUTE DISORDERS OF GLUCOSE HOMEOSTASIS

Hypoglycaemia


Recognition

Although hypoglycaemia is an uncommon occurrence in non-diabetic patients, it should be considered in any patient who presents with:

- Confusion
- Altered level of consciousness
- Seizures
- Tachycardia and diaphoresis (in ventilated and sedated ICU patients).

Hypoglycaemia should also be actively looked for in patients with acute liver failure or end-stage liver disease and in patients with clinical suspicion of adrenal insufficiency or severe hypothyroidism (because of the possibility of hypopituitarism).

Resuscitation

Assessment and establishment of a patent airway should take priority in patients with seizures, unconsciousness or altered mental status. Glucose should be administered immediately in all patients with suspected hypoglycaemia. Intravenous Thiamine 100 mg should also be given to all patients with a history of extensive alcohol use prior to glucose administration. Immediate restoration of blood pressure (in patients with adrenal insufficiency or myxoedema coma) is a priority.


Q. What are the manifestations of Wernicke’s encephalopathy?

A. The condition is characterised by confusion, nystagmus, ataxia, peripheral neuropathy and ophthalmoplegia.

Q. Is there a risk of precipitating or aggravating the condition by hospital therapy?

A. Wernicke’s encephalopathy can occur when glucose is administered to correct hypoglycaemia without thiamine administration (more common in alcoholics).
Q. How is the condition treated?

A. Patients at risk should receive 50–100 mg of thiamine intravenously or intramuscularly.

Q. How is Wernicke’s encephalopathy diagnosed?

A. In the above clinical context, the diagnosis is supported by the response to treatment, but indices of thiamine deficiency such as red cell transketolase or thiamine pyrophosphate activity may be available in your laboratory to confirm the diagnosis (retrospectively).

**Diagnosis**

It is important to differentiate hypoglycaemia in diabetics from that in non-diabetics (see algorithm, below). A history of recent fasting or worsening renal function in a diabetic patient, along with any changes in medication usually establishes the cause of the hypoglycaemia. In non-diabetics, a history and clinical clues of alcohol use, liver or kidney disease, prescribed drugs (e.g. pentamidine, quinidine) or factitious drug use (insulin, sulphonylurea), should be sought. The temporal relationship of hypoglycaemia to food intake (fasting vs post-prandial) may help in establishing the cause of hypoglycaemia.

The extent and need for investigations to establish the cause of hypoglycaemia is variable. In patients with clear precipitants (fasting, sepsis, liver disease, alcohol) no further investigations are necessary. In a patient with no obvious precipitating factors, a plasma insulin level and a simultaneous plasma C-peptide level during the episode of hypoglycaemia might help to make the diagnosis. C-peptide is a protein secreted along with insulin and in conditions of excessive endogenous insulin secretion (insulinomas, sulphonylurea overdose), plasma levels of both insulin and C-peptide are high. However if hypoglycaemia is due to exogenous insulin overdose, C-peptide levels are depressed.

**Aetiology**

- **Endogenous hyperinsulinism**
  - Insulinoma
  - Sulphonylurea
  - Auto-immune
- **Organ failure (liver, kidney, sepsis)**
- **Drugs (pentamidine, quinidine, salicylates**
- **Ectopic insulin secretion from tumours (rhabdomyosarcoma, hepatoma)**
- **Endocrine deficiencies (adrenal, thyroid, growth hormone)**
- **Post-prandial (alcohol, post gastric surgery)**


**Clinical management**

Critical care management entails prompt glucose administration for hypoglycaemia. In adult patients, initiation and maintenance of full nutritional support with minimal interruptions will minimise the incidence of hypoglycaemia. In patients with, for example, prolonged fasting or alcohol use, give thiamine (100 mg i.v.) prior to glucose administration—see above. In diabetics, with hypoglycaemia, knowledge of the patient’s treatment regimen will help to determine the duration for which glucose replacement will be required. Alcoholics and malnourished patients (in whom glycogen stores are depleted) may need sustained glucose infusions to prevent recurrent hypoglycaemia.

Self-injection or injection by a close friend or family member of glucagon can be life-saving in severe hypoglycaemia. Training the patient and a family member to inject glucagon should be provided as part of diabetes education and support. In patients with sulfonylurea-induced hypoglycaemia, octreotide along with dextrose increases blood glucose levels and minimises the number of hypoglycaemic episodes.


**Outcome**

In critically ill patients, several studies have suggested that hypoglycaemia impacts negatively on outcome. The absence of survival benefit in medical ICU patients in whom strict glycaemic control was implemented, is partly explained by the high rates of hypoglycaemia in this patient population. The duration of hypoglycaemia determines the long-term neurological outcome. In most cases the outcome is favourable, unless there is a protracted hypoglycaemic episode.
Algorithm for the approach to the diagnosis and supplementary management of hypoglycaemia

Hyperglycaemic Emergencies – Diabetic Ketoacidosis and Hyperglycaemic Hyperosmolar State


Recognition

Hyperglycaemia should be considered in the differential diagnosis of patients manifesting
- Altered mental status
- Coma
- Seizures
- Tachypnoea
- Increased minute ventilation and/or increased work of breathing

Hyperglycaemic emergencies are usually precipitated by non-compliance of diabetic patients with their treatment regimen in the presence of a precipitating factor (diarrhoea and vomiting, sepsis, alcohol binge etc.). Not uncommonly, hyperglycaemic coma can be the presenting manifestation of new-onset diabetes mellitus. It can also be a marker of an acute catastrophic event such as sepsis, myocardial dysfunction, stroke, pancreatitis causing or complicating critical illness.
**Resuscitation**

As in any other condition causing altered level of consciousness and/or seizures, assessment and establishment of a patent airway is a priority. Since almost all patients with hyperglycaemic emergencies also have moderate to severe dehydration, resuscitation with isotonic fluids to correct hypovolaemia and any co-existing haemodynamic instability should be performed immediately.

Initial clinical evaluation in patients with any episode of hyperglycaemia should also be directed towards addressing the following key issues:

- Mental status
- Precipitating factor.

**Note** Since almost all these patients have severe intravascular dehydration, isotonic fluids should be used for initial resuscitation and maintenance irrespective of serum sodium levels.

**Diagnosis (approach)**

Diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) represent a continuum of metabolic derangements associated with insulin deficiency. The diagnosis is usually suggested by a history of non-compliance with their treatment regimen (insulin or oral hypoglycaemic agents) in a diabetic patient or with recent onset of a precipitating illness e.g. urinary tract infection (UTI), myocardial infarction (MI), pancreatitis. Differentiation between these two disorders can often be made by obtaining an arterial or venous blood gas and, when acidosis is present, by calculating serum anion gap and measuring urine or plasma ketones.

**Note** However, one must be aware that both (raised) anion gap acidosis and positive plasma ketones are extremely non-specific markers and under some circumstances (e.g. in an alcoholic patient with decreased oral intake) can be present even in hyperosmolar non-ketotic states.

**Diagnosis (aids)**

**Plasma Glucose:** Elevated plasma glucose is seen in both these conditions. The blood sugar values are often higher in patients with HHS than in DKA, since these patients often present later in the illness (due to the absence of warning signs induced by the ketoacidosis).

**Plasma/Urine ketones:** The key difference between the two hyperglycaemic states is the presence of ketonaemia (and ketonuria) in DKA and its absence in HHS. However, as discussed above, one must remember that ketonaemia (starvation ketosis), can occur in some patients with HHS. Ketones may also be negative initially in patients with DKA – see warning below.
Testing for ketones: This is generally done with tablets of nitroprusside which react with acetoacetate and acetone, but not with β-hydroxybutyrate (the major serum ketone in DKA). Hence the serum ketone levels (measured by this test) can actually rise as a normal response to treatment (due to conversion of β-hydroxybutyrate back to acetone and acetoacetate). Secondly, some drugs containing sulfhydryl groups (captopril) interact with the nitroprusside reagent, leading to false positive ketone tests.

Plasma anion gap should be followed serially in these patients to assess the response to treatment and guide insulin therapy. Plasma electrolytes should be closely monitored (especially potassium) in these patients. Most patients with DKA and HHS are mildly hyponatraemic. However, patients with HHS who may have had a marked osmotic diuresis may have a normal or even elevated serum sodium concentration despite a serum glucose concentration that can exceed 55 mmol/L (1000 mg/dL). Irrespective of serum potassium and phosphate levels, most patients with DKA and HHS have depletion of total body potassium and phosphate.

Hyperamylasaemia, hyperlipasaemia and leukocytosis are frequently and non-specifically seen in patients with DKA. Although leukocytosis is common in patients with DKA and HHS, the presence of fever should prompt the search for infection.

**Aetiology**

Hyperglycaemic emergencies can be precipitated by:
- Non-compliance with oral hypoglycaemic agents/insulin regimen or inadequate insulin administration
- Infections (UTI, Abscesses)
- Pancreatitis
- Infarction (Myocardial, Cerebral)
- Drugs (Steroids) including illicit drugs e.g. Cocaine
- Pregnancy.

**Clinical management**

The goals of therapy in hyperglycaemic emergencies include aggressive rehydration, correction of acidosis and elimination of ketonaemia, normalisation of blood glucose, correction of electrolyte abnormalities and prevention of complications.

The average fluid deficit in DKA is about 4–6 L and in the region of 8–10 L in HHS. Most authors advocate the use of 0.9% saline (or Lactated Ringer’s) during the initial resuscitation, at a rate of 1 L/h over the first 2–3 hours, subsequently guided by the degree of dehydration and an assessment of organ perfusion. Administration of an isotonic fluid e.g. 0.9% saline not only repletes the extracellular volume more rapidly but also prevents rapid decreases in plasma osmolality, thereby avoiding cerebral oedema. Once the acute resuscitation is completed, half-normal saline can be used to decrease plasma osmolality further, especially if serum sodium remains > 150 mmol/L. Fluids should be changed to a dextrose-containing solution, when plasma glucose reaches 250 mg/dL (14 mmol/L).
During the initial resuscitation care must be taken to avoid saline-induced hyperchloraemic acidosis, if necessary by using other fluids such as Hartmann’s solution or dextrose-saline.

Insulin needs to be administered in hyperglycaemic emergencies to:

- Decrease glucagon release from the pancreas
- Counteract the ketogenic actions of glucagon
- Inhibit lipolysis and deplete the substrate needed for ketogenesis
- Decrease plasma glucose by increasing tissue (muscle and fat) utilisation of glucose.

Regular insulin should be used and the intravenous route is preferable. The recommended dosing regimen is usually 0.1 units/kg regular insulin bolus, followed by 0.1 units/kg/hr infusion. This dose appears to saturate the insulin receptors adequately without substantially increasing the risk of hypoglycaemia. Plasma glucose should be measured hourly and plasma potassium should be determined every 2 hours during the insulin infusion. The target should be a 70–120 mg/dL [3.89–6.66 mmol/L] reduction of plasma glucose per hour.

Some patients are insulin-resistant and in these cases, the insulin infusion rate should be doubled. Insulin infusion should be continued until the anion gap normalises. Subcutaneous insulin should be given 1 hour prior to discontinuation of intravenous insulin. In HHS, when serum glucose reaches 300 mg/dL (16.65 mmol/L), the insulin dose can be decreased to 0.02–0.05 units/kg/hr with the goal of maintaining blood sugars within that range until the patient is mentally alert. A 5% dextrose infusion should also be initiated at this stage in patients with HHS.

Irrespective of serum potassium levels, total body potassium is depleted in all patients with DKA. As insulin is administered, serum potassium levels often fall due to both correction of acidosis and influx of potassium into the cells. It is therefore important to anticipate this fall and initiate potassium replacement in non-oliguric patients with serum potassium levels in the normal range.

As with potassium, total body phosphate is often depleted because of urinary losses. In patients with low serum phosphate levels, supplementation of phosphate is recommended. Phosphate salt of potassium can be given to correct both potassium and phosphate depletion simultaneously.

The use of bicarbonate in DKA has been controversial. The available data indicate that there is no clear benefit from bicarbonate administration in patients with DKA, although some authors recommend bicarbonate therapy in patients with pH <7.0 and in the presence of life-threatening hyperkalaemia.

Finally, assessment, further evaluation and treatment of the precipitating cause is essential.

**Outcome**

Hyperglycaemic emergencies generally have a favourable prognosis. Outcome depends largely on the nature of the precipitating cause. Cerebral oedema occurs in about 1% of patients and is more common in children. Thrombosis including the
serious complications of cavernous sinus thrombosis can occur rarely as a result of hyperviscosity and dehydration. This complication is more common in patients with HHS than DKA. Other complications include ARDS, pancreatitis and acute gastric dilatation.


Hyperglycaemia: stress-induced hyperglycaemia in the critically Ill.

Recognition

Stress-induced hyperglycaemia occurring in critical illness is usually recognised as a result of routine glucose monitoring at the bedside, is often termed 'stress hyperglycaemia' and is a consequence of several hormonal factors, including increased cortisol, glucagon, catecholamines and growth hormone leading to enhanced gluconeogenesis and glycogenolysis.

Stress-induced hyperglycaemia occurs both in diabetics and non-diabetics and, even though it is not usually associated with acidosis or a hyperosmolar state, adds significantly to the morbidity and mortality of critical illness. Hence all ICU patients should have their blood sugar measured routinely on admission and then at a frequency based on whether or not they are diabetic, the presence of co-morbidities and the severity of the acute illness.

Resuscitation

Initial clinical evaluation in patients with hyperglycaemia of any cause should be directed towards addressing and managing the following key issues:

- Airway, breathing and circulation if necessary
- Mental status
- Precipitating factor
- Intravascular volume status.
**Diagnosis**

The optimal technique to monitor blood sugar at the bedside is unclear. Capillary blood sugar checks have been shown to be error prone and should not be relied upon when values are extremely high or low – see Critchell reference below.


**Clinical management**

This section deals with the management of hyperglycaemia in the acutely ill ICU patient. These recommendations do not apply to hospitalised patients who are less ill and can take an oral diet.

The goals of therapy of hyperglycaemia in the ICU include intravascular volume repletion when warranted, identification of the underlying cause and treatment, normalisation of blood glucose without inducing hypoglycaemia and minimising fluctuations in blood glucose levels.

When required, an intravenous infusion of insulin with frequent monitoring of blood sugar and titration based on blood sugar values is recommended. Subcutaneous insulin should not be used in acutely ill patients in the ICU as absorption and effect may vary with level of tissue (hypo)perfusion. The level of blood sugar that should be targeted in critically ill patients varies depending on the patient population. Several studies have provided conflicting results. A summary of the key studies/references and a final recommendation is provided below:

**Surgical patients:** One large single-centre study of 1548 surgical ICU patients predominantly consisting of cardiothoracic ICU patients (around 2/3rds) randomised patients to either intensive insulin therapy (IIT) (blood sugar maintained between 80–110 mg/dL (4.44 mmol/L–6.1 mmol/L) or conventional glycaemic control (target blood sugar values 180–200 mg/dL) (9.9–11.1 mmol/L). IIT significantly reduced ICU mortality, hospital mortality and decreased the incidence of several ICU-related complications including acute renal failure, transfusion requirement, polyneuropathy and blood stream infections compared to conventional glycaemic control. However hypoglycaemia was more common in the IIT group than in the conventional glycaemic control arm (5.1 versus 0.8 per cent).

**Medical patients:** The same group of investigators performed a randomised study in 1200 medical ICU patients comparing IIT (blood sugar maintained between 80–110 mg/dL (4.44 mmol/L–6.1 mmol/L) and conventional glycaemic control (target blood sugar values 180–200 mg/dL) (9.9–11.1 mmol/L). However, in this study IIT did not alter hospital mortality, but decreased ICU length of stay, hospital length of stay, duration of mechanical ventilation and acute kidney injury. The incidence of hypoglycaemia was more than 3-fold higher in this study compared to the surgical study (18.7 versus 3.1 per cent) perhaps partly explaining the lack of mortality benefit. The increased incidence of hypoglycaemia also suggests that medical ICU patients may be more prone to this complication. Both the surgical and medical
studies used early total parenteral nutrition which limits the generalisability of these studies across all ICU patients.

**Mixed medical and surgical patients:** Several studies have evaluated the benefit of tight glycaemic control in mixed ICU patient populations and have failed to confirm these positive results.

The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, a multicentre two-by-two factorial trial was conducted in medical and surgical ICU patients with severe sepsis. It compared IIT (target blood glucose 80 to 110 mg/dL or 4.44 mmol/L–6.1 mmol/L) to conventional glucose control (target blood glucose 180 to 200 mg/dL or 9.9–11.1 mmol/L), and also compared two different fluids for resuscitation. The IIT arm of the trial was stopped after interim analysis because IIT significantly increased the rate of hypoglycaemia (12.1 versus 2.1 per cent) and the incidence of serious adverse events (10.9 versus 5.2 per cent). No significant differences in 28 day mortality, morbidity or organ failures were found between groups.

Another multicentre European study randomised 1101 critically ill medical and surgical patients to IIT (target blood glucose 80 to 110 mg/dL or 4.44 mmol/L–6.1 mmol/L) and conventional glucose control (target blood glucose 140–180 mg/dL or 7.77 mmol/L–9.99 mmol/L). The trial was terminated early because of a high rate of unintended protocol violations. IIT significantly increased the rate of hypoglycaemia (8.7 versus 2.7 per cent) but did not improve ICU or hospital mortality.

The largest multicentre trial that evaluated tight glycaemic control in mixed medical-surgical ICU patients is the Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial that randomised 6104 ICU patients to either IIT (target blood glucose 81 to 108 mg/dL or 4.3–6.0 mmol/L) or conventional glucose control (target blood glucose of <180 mg/dL or < 9.99mol/L). The IIT group had a significantly higher 90-day mortality (27.5 versus 24.9 per cent) and a higher incidence of hypoglycaemia. IIT was associated with a higher mortality even in the subgroup of surgical patients.

In summary, in most critically ill mixed medical-surgical patients, a blood sugar level target of 6–10 mmol/L (140 to 180 mg/dL) is recommended.

In the subset of cardiothoracic ICU patients a tighter glycaemic control with a blood sugar target of 80–110 mg/dL (4.44 mmol/L–6.1 mmol/L) might, on the basis of one study, be considered appropriate. However, a generally accepted approach to blood sugar control has not yet been agreed. Hypoglycaemia has been shown to be an independent risk factor for death and hence careful monitoring of blood sugars to prevent hypoglycaemia is warranted in all ICU patients in whom glycaemic control is undertaken. Wide fluctuations in blood glucose levels have been associated with worse outcomes and should be avoided. Both serum glucose and potassium levels need to be closely monitored during insulin therapy.

**Outcome**

Several observational studies have demonstrated that hyperglycaemia is associated with poor clinical outcomes in critically ill patients. Trauma patients who are hyperglycaemic have been shown to have an increased mortality rate, hospital length of stay, ICU length of stay, and incidence of nosocomial infections. Similarly
hyperglycaemia is associated with worse outcomes in patients with stroke and acute myocardial infarction.


4/ ACUTE DISORDERS OF ACID-BASE HOMEOSTASIS


Acid-base homeostasis is defined by the pH of blood and by the conditions of the acid-base pairs that determine it. Normally, arterial plasma pH is maintained between 7.35–7.45. The determinants of blood pH can be grouped into two broad categories, respiratory and metabolic. Respiratory acid-base disorders are disorders of carbon dioxide (CO₂) homeostasis whereas metabolic acid-base disorders comprise all other conditions affecting the pH.

The terms alkalosis and acidosis refer to physiological (or pathophysiological) processes that result in acidaemia or alkalaemia, conditions defined by the arterial blood pH. Metabolic acid-base disturbances seem to be associated with more adverse effects than respiratory acid-base disturbances; these are listed in the table below:

**Recognition**

In practice, acid-base disorders are usually recognised by the ‘blood gas’ stat lab result but critically ill patients may be affected not only by their acid-base disorder, per se, but also by their body’s response to the condition e.g. increased respiratory rate. Thus work of breathing in response to metabolic acidosis may induce respiratory failure. See table below for summary of effects on other organ systems.

**Potential clinical effects of acid-base disorders**

<table>
<thead>
<tr>
<th>ACIDOSIS</th>
<th>ALKALOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Decreased inotropy</td>
<td>Increased inotropy (Ca++ entry)</td>
</tr>
<tr>
<td>Conduction defects</td>
<td>Altered coronary blood flow*</td>
</tr>
<tr>
<td>Arterial vasodilatation</td>
<td>Digoxin toxicity</td>
</tr>
<tr>
<td>Venous vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>Oxygen delivery</td>
<td></td>
</tr>
<tr>
<td>Decreased oxy-Hb binding</td>
<td>Increased oxy-Hb affinity</td>
</tr>
<tr>
<td>Decreased 2,3 DPG (late)</td>
<td>Increased 2,3 DPG (delayed)</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Neuromuscular excitability</td>
</tr>
<tr>
<td>Decreased sensorium</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
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<tr>
<td>Protein wasting</td>
<td>Hypokalaemia</td>
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<tr>
<td>Bone demineralisation</td>
<td>Hypocalcaemia</td>
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<tr>
<td>Catecholamine, PTH, and</td>
<td>Hypophosphataemia</td>
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<td>aldosterone stimulation</td>
<td>Impaired enzyme function</td>
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<td></td>
</tr>
<tr>
<td>GI effect</td>
<td></td>
</tr>
<tr>
<td>Emesis</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

*Animal studies have shown both increased and decreased coronary artery blood flow
Classifying acid-base disorders

There are four broad categories of acid-base disorders:

- Metabolic acidosis
- Metabolic alkalosis
- Respiratory acidosis (acute and chronic)
- Respiratory alkalosis (acute and chronic).

Acid-base disorders are further divided into simple, denoting a single process, and complex (or mixed), denoting a condition where two, three or even four processes are occurring simultaneously.

Typical values seen in simple acid-base disorders are shown in the Table

![Table of values indicating changes in acid-base balance](image)

Simple acid-base disorders

Simple acid-base disorders result in predictable changes both in terms of carbonic acid equilibrium and physiologic compensation. The table above outlines the observed changes in pCO₂, bicarbonate and arterial standard base excess (SBE) seen with simple acid-base disorders. When measured acid-base variables fall outside the ranges shown in the table, the acid-base disorder should be considered complex. The table also shows the expected compensatory changes that accompany simple acid-base derangements. A failure of normal compensation leads to the development of a complex acid-base disorder.

⚠️ It is possible, though rare, that a mixed disorder might develop such that opposing processes (alkalosis and acidosis) are completely balanced, giving the impression that acid-base balance is normal.

Complex acid-base disorders

A complex acid-base disorder is diagnosed by first examining the pH. If the pH is <7.35, at least one type of acidosis is present and if the pH is >7.45, at least one type of alkalosis is present.

The values of compensatory changes shown in the above table should be used to determine if a complex disorder is present. Examples:

- A simple metabolic acidosis will manifest as a SBE < –3 mmol/L, a plasma bicarbonate concentration < 22 mmol/L and \( pCO_2 = 1.5 \times \text{bicarbonate} + 8 \) or = 40 + SBE (either formula has a range of ± 2). If the arterial pCO\(_2\) is outside this range, a secondary respiratory acid-base disorder is present (respiratory alkalosis if pCO\(_2\) is lower than expected and respiratory acidosis pCO\(_2\) is higher than expected).

- A simple chronic respiratory acidosis will manifest as a pH < 7.35, a pCO\(_2\) > 6 kPa (45 mmHg). The plasma bicarbonate concentration should be equal to \( [(pCO_2 – 40) / 3] + 24 \) and the SBE should equal 0.4 × (pCO\(_2\) – 40). The ranges are again ±2.

**Note**: Chronic respiratory acid-base disorders are those that have been present long enough to permit metabolic (primarily renal) compensation, a process that generally takes 2–5 days. In general, the decrease in pH with chronic respiratory acidosis is approximately half that seen with acute respiratory acidosis. A patient may present at a time point somewhere between acute and chronic, making classification difficult.

**The anion gap (AG)**: This is used to sub-classify a metabolic acidosis. The AG is determined by the formula:

\[ \text{AG} = \text{Na}^+ + K^+ – \text{Cl}^- – \text{HCO}_3^- \]. (The AG is often calculated without including potassium).

The normal range for the AG is 8–12 mmol/L (mEq/L) and reflects the unaccounted negatively charged species present in the blood under normal (e.g. proteins, PO\(_4^–\)) and pathophysiologic (e.g. lactic acid, ketones, SO\(_4^–\)) conditions. However, if the patient’s albumin and phosphate concentrations are low, the normal range of AG will be reduced.

**Note**: Beware of a falsely normal AG in a patient with hypoalbuminaemia or hypophosphataemia. The normal AG is made up predominantly by albumin and phosphate and can be estimated from the following equation: \( \text{AG} = 2 \times \text{albumin g/dL} + 0.5 \times \text{phosphate mg/dL} \). For international units: \( \text{AG} = 0.2 \times \text{albumin g/L} + 1.5 \times \text{phosphate mmol/L} \).

Clues to the existence of a balanced complex disorder include the emergence of imbalance on repeated measurements or the presence of an abnormal anion gap.

**Q.** What acid-base disorder(s) does the following arterial blood gas suggest: pH 7.07; pCO\(_2\) 28 (3.7kPa); HCO\(_3^-\) 8; SBE –20?
A. This patient has a pH <7.35 and a pCO₂ <5.3 kPa (40 mmHg). Hence the primary abnormality is a metabolic acidosis. Secondly, the patient’s pCO₂ should be 2.6 kPa (20 mmHg), if complete respiratory compensation had occurred (see above table on observational acid-base patterns for formulae to calculate compensation). However, since the pCO₂ is 3.7 kPa (28 mmHg), it means that the patient has a second acid-base disorder, which in this case is a respiratory acidosis. This kind of mixed acid-base disorder often occurs in patients with diabetic ketoacidosis (AG metabolic acidosis) and respiratory depression (respiratory acidosis).


The appendix includes material which interprets acid-base disorders in terms of the concept of strong ion difference (SID).

The following reference summarises the difference between this physicochemical (Stewart’s) versus the ‘traditional’ and more commonly used (Henderson–Hasselbalch) approach. The ‘Acidbase’ website includes the full text of Stewart’s ‘How to Understand Acid-Base’ textbook; the ‘Anaesthetist’ website includes a discussion and bibliography of the relative merits of the two systems.


http://www.acidbase.org/
http://www.anaesthetist.com/index.htm

**Metabolic acidosis**

**Recognition**

Although occasionally the history and clinical signs will suggest the presence of an acid-base disturbance (Kussmaul’s breathing, ketotic smell on a patient’s breath), such abnormalities are most often detected by a blood gas/acid-base analysis.

Except when part of a complex (mixed) disorder, metabolic acidosis is manifest by acidaemia (arterial pH <7.35), decreased bicarbonate (HCO₃⁻ <22 mmol/L), hypocarbia (pCO₂ <5.3 kPa (40 mmHg)) and a reduced SBE (<–3 mmol/L).

**Resuscitation**

Metabolic acidosis may induce a variety of adverse clinical effects (see table on clinical effects of acid-base disorders) some of which can be life-threatening. Although tachypnoea is the normal response to metabolic acidosis, respiratory
depression and altered sensorium can occur as a consequence of severe acidemia. When alterations in mental status or respiratory function occur, control of the patient’s airway is advisable. Metabolic acidosis may contribute to hypotension and resuscitation with volume and/or vasoactive medications may be necessary.

Caution is required when treating acidosis with sodium bicarbonate, particularly if ventilation is compromised. The CO2 generated as a result of the therapy can worsen intracellular acidaemia and precipitate hypercarbic/acute respiratory failure.

**Diagnosis**

When metabolic acidosis is diagnosed, the anion gap (Na+ + K+– Cl–– HCO3-) should be calculated. See cautions and table above regarding the calculation of the AG.

Increased AG metabolic acidosis is due to acids whose anions are not normally measured by routine electrolyte determinations (e.g. lactate, ketones, toxins) whereas normal anion gap acidosis is due to abnormalities in chloride homeostasis. In the case of an increased AG, the change in SBE should be equal to the increase in the AG from its normal value.

If the change in SBE is larger than the change in the AG, a concomitant hyperchloraemic acidosis is also present. If the AG is increased, the putative anion should be sought and when possible, its concentration compared to the change in the AG. Strong ions such as lactate produce a 1:1 decrement in the AG for each mmol/L (mEq/L) increase in their concentration. When the increase in the AG is larger than the increase in strong ions, other acids must be present.

Calculate the expected anion gap for the patient’s serum albumin and phosphate in all your ICU patients. In those whose anion gap is greater than expected, determine if the gap is explained by predicted but not measured anions (e.g. lactate, uraemia, ketosis).

**Q. Would you calculate an anion gap in a patient with a pH of 7.5?**

A. AG is often calculated in all patients routinely to avoid missing a concealed metabolic acidosis. However alkalaemia can increase the AG by as much as 3–5 mmol/L (mEq/L) by altering the charges on plasma proteins. Alkalaemia may also induce mild hyperlactataemia by stimulating phosphofructokinase activity.

If a normal AG (hyperchloraemic) metabolic acidosis is present, the cause can be determined by examining the urine strong ion difference (SID). Strong ions are those that are present in the dissociated state at physiological pH. Strong cations include Na+ and K+ and major strong anions include Cl-. The difference between strong cations and anions make the strong ion difference (SID). In conditions of acidosis, the normally functioning kidney excretes more Cl– than Na+ and K+. Hence if the kidneys are functioning normally in a patient with a metabolic acidosis, the urine SID should be negative.

If a patient has an increased AG metabolic acidosis, looking for an osmolar gap might help determine the aetiology. Osmolar gap is the difference between the measured
serum osmolarity and the calculated serum osmolarity. A gap of more than 10 mOsmol/l is indicative of the presence of a toxin that increases osmolarity. Alcohols (methanol and ethylene glycol) typically cause (raised) anion gap metabolic acidosis with an increased osmolar gap.

Determine if a respiratory disorder is also present. The expected arterial pCO₂ in response to a metabolic acidosis can be determined either using the bicarbonate concentration or the SBE. A measured pCO₂ of greater than 0.26 kPa (2 mmHg) higher than expected indicates a concomitant respiratory acidosis while measured pCO₂ of <0.26 kPa (2 mmHg) less than expected indicates a respiratory alkalosis.

\[ pCO_2 = 1.5 \times HCO_3^- + 8 \]
\[ pCO_2 = 40 + SBE \]

**Q. How do you calculate the osmolar gap?**

**A. Osmolar gap = Measured serum osmolarity – Calculated serum osmolarity**

The formula for calculating the serum osmolarity is

\[ 2 (Na^+ + K^+) + \text{Glucose (mmol/L)} + \text{BUN (mmol/L)} \]

In the US, the formula is: \[ 2 \times Na^+ \text{glucose/18} + \text{BUN/2.8 mg/dL} \]

**Q. What is the expected AG for a patient with an albumin of 20 g/l (2 g/dL) and a phosphate of 0.65 mmol/L (2 mg/dL)? What would produce an AG of 12 in such a patient?**

**A. The normal difference between cations and anions is made up predominantly by albumin and phosphate. In a critically ill patient with hypoalbuminaemia and or hypophosphatæmia, the upper limit of expected AG will hence be reduced. Therefore in any ICU patient, the observed AG should be compared with the expected upper limit of AG based on these variables. The expected upper limit of expected AG can be corrected for the serum albumin and phosphorus using the following equation:**

\[ AG = 2 \times \text{albumin g/dL} + 0.5 \times \text{phosphate mg/dL}. \]

For international units: \[ AG = 0.2 \times \text{albumin g/L} + 1.5 \times \text{phosphate mmol/L}. \]

In this patient with albumin and phosphate concentrations of 2, the corrected upper limit for expected AG would be 5. Hence an AG of 12 in this patient is clearly abnormal and one has to look for causes of metabolic acidosis, such as the presence of ketones, lactic acid, methanol, ethylene glycol or salicylates.

**Beware of interpreting the AG in a patient with alkalaemia. Alkalaemia may increase the AG by as much as 3–5 mmol/L (mEq/L) by altering the charges on plasma proteins. Alkalaemia may also induce mild hyperlactataemia by stimulating phosphofructokinase activity.**

**Aetiology**

Conditions causing metabolic acidosis can be divided into those associated with an increased anion gap and those in which the anion gap is normal. Some conditions can be associated with either e.g. renal failure.
Acid-base disorder may be understood in terms of the traditional Henderson–Hasselbalch or Stewart’s strong ion difference (SID) concepts, which is utilised in this module. The appendix provides further detail and the above links provide background information and analysis.

**Differential diagnosis of metabolic acidosis (decreased SID)**

<table>
<thead>
<tr>
<th>Increased Anion Gap</th>
<th>Toxic Ingestions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogenous Acids</strong></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>Ethylene glycol</td>
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<tr>
<td>Ketoses – diabetic, alcohol, starvation</td>
<td>Salicylate</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>Paraldehyde</td>
</tr>
<tr>
<td>Unknown anions: Liver failure, Sepsis</td>
<td>Methanol</td>
</tr>
<tr>
<td>Toluene</td>
<td>Iron*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal Anion Gap</th>
<th>Non-Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Tubular Acidosis</strong></td>
<td>urine SID (Na + K - Cl) &gt; 0</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal diarrhoea</td>
</tr>
<tr>
<td></td>
<td>small bowel/pancreatic drainage</td>
</tr>
<tr>
<td><strong>Renal Tubular Acidosis</strong> (Type I)</td>
<td>urine pH &gt; 5.5</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td>intravenous saline infusions</td>
</tr>
<tr>
<td><strong>Renal Tubular Acidosis</strong> (Type II)</td>
<td>urine pH &lt; 5.5/low serum K</td>
</tr>
<tr>
<td></td>
<td>Aldosterone Deficiency (Type IV)</td>
</tr>
<tr>
<td></td>
<td>urine pH &lt; 5.5/high serum K</td>
</tr>
</tbody>
</table>

* Iron overdose causes metabolic acidosis by multiple mechanisms, including lactic acidosis due to circulatory collapse, direct cellular injury and by causing proximal tubular damage.

**Q. What is the most likely aetiology for a mixed respiratory alkalosis and increased AG metabolic acidosis.**

A. The most common cause of mixed respiratory alkalosis and increased AG acidosis is sepsis. Another important cause is salicylate overdose.


**Clinical management**

In many cases, a metabolic acidosis is a manifestation of an underlying pathology. Routine administration of sodium bicarbonate to rectify the acidaemia is not recommended. Identify and treat the underlying cause of metabolic acidosis whenever it is possible – in particular shock should be excluded in patients with lactic acidosis. Specific antidotal therapy is required for toxic ingestions (e.g. methanol, ethylene glycol).
See the PACT module on Major intoxication.

The physiological response to a metabolic acidosis is to hyperventilate and reduce pCO₂. This is generally the safest way to treat acute metabolic acidosis. Treatment of acute metabolic acidosis with sodium bicarbonate has not been shown to be beneficial and may be harmful. Sodium bicarbonate by infusion rather than bolus injection induces less hypercarbia and may be safer. Non-bicarbonate buffers such as tris hydroxymethyl aminomethane (TRIS or THAM) have occasionally been used for severe metabolic acidosis, although published reports are limited. Severe metabolic acidosis may require treatment with renal replacement therapy.

Chronic metabolic acidosis (e.g., chronic renal failure) requires therapy to increase the SID. Oral sodium bicarbonate therapy is most commonly used. Patients with proximal or Type IV RTA rarely develop life-threatening acidosis, while patients with distal RTA may. In addition, distal RTA may be associated with hypokalaemia, sometimes severe.

The combination of hypokalaemia and acidosis is particularly dangerous. These patients have profound total body K⁺ depletion. K⁺ must be administered before the pH is corrected (whether by decreasing pCO₂, or alkali therapy) since serum K⁺ will fall further as the pH is increased.


Outcome

Metabolic acidosis is associated with a worse outcome in a variety of patient subsets (trauma, sepsis, respiratory failure), emphasising the need for prompt treatment of the underlying cause. The outcome depends on the type, degree and aetiology of the acidosis. Although, many clinicians correct severe acidosis, there is little evidence that such treatment improves outcome.

Metabolic alkalosis

Recognition

In ICU, patients with intravascular volume depletion, or those who are slow to wean secondary to depressed respiratory drive (resulting in compensatory hypercarbia) may have a metabolic alkalosis. Metabolic alkalosis can be sub-divided into two broad categories: chloride-responsive and chloride-unresponsive.
**Resuscitation**

Seizures and respiratory depression may occur when arterial pH is more than 7.6. Serious cardiac arrhythmias may be precipitated by the alkalosis itself or by electrolyte disturbances. When severe alterations in mental status or respiratory function occur, control of the patient’s airway is likely to be advisable.

**Diagnosis**

A history and physical exam will reveal most causes of metabolic alkalosis. Chronic metabolic alkalosis is unusual and is usually the result of mineralocorticoid excess or chronic diuretic use. Most cases of acute metabolic alkalosis are due to losses of acid from the GI tract (vomiting, or gastric drainage), to volume contraction, or to the administration of non-chloride containing sodium salts (e.g. acetate, citrate, lactate). Often metabolic alkalosis patients have underlying post-hypercarbic states and the alkalaemia is aggravated by salt-depleted hypovolaemia.

Except when part of a complex (mixed) disorder, metabolic alkalosis is manifest by alkalaemia (arterial pH >7.45), a high bicarbonate (HCO₃⁻ >26 mmol/L), hypercarbia (pCO₂ >5.3 kPa (40 mmHg)) and an increased SBE (>3 mmol/L).

The urine Cl⁻ concentration can be used to help narrow the differential diagnosis.

- In so-called chloride-responsive metabolic alkalosis, Cl⁻ losses in excess of Na⁺ increase the SID. The urine Cl⁻ concentration is usually <10 mmol/L. GI loss, post-diuretic use and post-hypercarbic states are chloride-responsive.
- Chloride-unresponsive alkalosis results in a urine Cl⁻ concentration >20 mmol/L and is caused by mineralocorticoid excess or active diuretic use.

Determine if a respiratory disorder is also present. The expected arterial pCO₂ in response to a metabolic alkalosis can be determined either using the bicarbonate concentration or the SBE. Measured pCO₂ >0.26 kPa (2 mmHg) more than expected indicates a concomitant respiratory acidosis while measured pCO₂ <0.26 kPa (2 mmHg) less than expected indicates a respiratory alkalosis.

\[
pCO₂ = (0.7 \times HCO₃⁻) + 21 \\
pCO₂ = 40 + (0.6 \times SBE)
\]

**Q. What is the normal response of the kidney to metabolic alkalosis?**

A. The normal response of the kidney to alkalosis is to retain chloride, thereby narrowing the SID and increasing water dissociation leading to more hydrogen ion generation to counteract the alkalosis.

**Aetiology**

As outlined in the section on metabolic acidosis above, the aetiology of disorders of acid-base homeostasis is discussed in terms of the strong ion difference (SID) concept in this module. The appendix and the above links provide explanatory detail.
Metabolic alkalosis results from an increase in the SID. There are four mechanisms:

- Severe depletion of free water inducing a parallel increase in Na\(^+\) and Cl\(^-\). Since the concentration of Na\(^+\) > Cl\(^-\), the difference between them increases.
- Cl\(^-\) is lost from the GI tract or urine (diuretic use or abuse) in excess of Na\(^+\).
- Na\(^+\) is administered in excess of Cl\(^-\).
- There is a severe deficiency of intracellular cations such as magnesium or potassium. This decreases intracellular Cl\(^-\) and secondarily total body Cl\(^-\).

Common causes are:

- Diuretic use (or abuse) is perhaps the most common cause of metabolic alkalosis.
- Gastrointestinal losses of Cl\(^-\) may be due to vomiting, gastric drainage, and rarely, chloride wasting diarrhoea (villous adenoma).
- Administration of non-chloride sodium salts can occur with massive blood transfusions (sodium citrate), parenteral nutrition (sodium acetate), plasma volume expanders (acetate or citrate), Ringer’s solution (sodium lactate) or overzealous use of sodium bicarbonate.
- For several hours (or longer) following recovery from chronic, renally compensated hypercarbia, metabolic alkalosis (chloride-responsive) will persist.
- Mineralocorticoid excess: primary hyperaldosteronism (Conn’s syndrome), secondary hyperaldosteronism, Cushing’s syndrome, Liddle’s syndrome, Bartter’s syndrome, exogenous corticosteroids, and excessive liquorice intake.

**Clinical management**

As with other acid-base disorders, the first rule of clinical management is to treat the underlying disorder. This is especially true for the large number of chronic conditions associated with metabolic alkalosis. Metabolic alkalosis secondary to administration of non-chloride containing sodium salts is usually self-limited. When additional i.v. fluids are needed, saline should be used. Parenteral nutrition formulae should be adjusted to maximise chloride and minimise citrate and acetate.

**Chloride-responsive alkaloses**

- For patients with diuretic-induced metabolic alkalosis, 0.45% saline is effective for reversing free water deficit and treating alkalosis. Also consider expanding the circulating volume and stopping diuretics.
- For patients with volume overload and metabolic alkalosis, KCl can be administered along with loop diuretics. Alternatively, K\(^+\) sparing diuretics (which will also spare Cl\(^-\)) can be used.
- Acetazolamide (250–500 mg bid), inhibits carbonic anhydrase and can induce excretion of Na\(^+\) in excess of Cl\(^-\) and thus reduce the SID.
- For patients with renal failure and at risk of volume overload, dilute (0.1N) HCl acid can be administered through a central venous line. Each litre of this solution contains 100 mmol of Cl\(^-\), and it is advisable to recheck the acid-base status after each litre. However, it is important to remember this treatment has potential risks and may not be licensed in many jurisdictions.
See the following reference for more information about intravenous hydrochloric acid use.


- Due attention should be paid towards correcting electrolyte changes occurring along with or secondary to alkalosis (hypokalaemia, hypomagnesaemia).
- In patients with ongoing gastric losses, H2- blockers or proton pump inhibitors may prove a useful adjunct to therapy.

**Chloride–unresponsive alkaloses**

Chloride-unresponsive alkaloses are often more difficult to treat. For neoplastic diseases such hyperaldosteronism, or Cushing’s syndrome, spironolactone may be helpful but surgery is usually required. ACE inhibitors such as captopril are often effective for secondary hyperaldosteronism. Triamterene may be tried in cases of Bartter or Liddle syndromes though with varying success.


**Outcome**

Metabolic alkalosis is usually mild and not life-threatening. However when it is severe or develops quickly, the condition can produce seizures and respiratory depression. Although case-reports of mortality from acute severe metabolic alkalosis exist, no large studies have explored the relationship between metabolic alkalosis and outcome in critically ill patients.

**Respiratory acidosis**

**Recognition**

Hypercarbia may cause somnolence (CO₂ narcosis), worsen respiratory depression and precipitate acute respiratory arrest. Hypercarbia secondary to respiratory muscle fatigue is a clear sign of respiratory deterioration.

**Resuscitation**

Unless supplemental oxygen is given, hypoventilation results in life-threatening hypoxaemia before causing dangerous respiratory acidosis. Intubation and mechanical ventilation should be instituted early in patients with worsening respiratory acidosis, in order to avoid respiratory arrest.
**Diagnosis**

Pure respiratory acidosis is easily diagnosed; the pCO₂ will be elevated and arterial pH decreased. Respiratory acidosis may also complicate metabolic acid-base disorders. In metabolic acidosis, the arterial pCO₂ should decrease (respiratory compensation). When the pCO₂ fails to decrease (>0.26 kPa (2 mmHg) more than the expected pCO₂), respiratory acidosis is also present. For metabolic acidosis, the expected pCO₂ can be calculated from either of the following formulae.

\[
\text{pCO}_2 = 1.5 \times \text{HCO}_3^- + 8 \\
\text{pCO}_2 = 40 + \text{SBE}
\]

Unlike respiratory compensation, metabolic compensation takes time (up to 5 days). Therefore, acute and chronic respiratory acid-base disorders will have different patterns of SBE and bicarbonate. In acute respiratory acidosis, SBE will be within the normal range and bicarbonate will be determined by the pCO₂ using the following relationship.

\[
\text{HCO}_3^- = \frac{(\text{pCO}_2 - 40)}{10} + 24
\]

When there is an acute respiratory acidosis, a metabolic acid-base disorder is also present if the SBE is < -3 (acidosis) or > 3 (alkalosis) or if the measured bicarbonate is different (±2) from expected.

When respiratory acidosis is chronic, the expected SBE and bicarbonate can be estimated from the following formulae.

\[
\text{SBE} = 0.4 \times (\text{pCO}_2 - 40) \\
\text{HCO}_3^- = \frac{(\text{pCO}_2 - 40)}{3} + 24
\]

Without knowing the history, a patient with a pCO₂ of 60 mmHg (8 kPa) and an SBE of +5 might have either a pure chronic respiratory acidosis or an acute respiratory acidosis with a superimposed metabolic alkalosis.

**Q. What is first thing you should do when encountering a patient with respiratory acidosis?**

A. Assess the airway and breathing and initiate supportive treatment which may include mechanical ventilation. If the cause of respiratory depression is reversible, non-invasive ventilation (NIV) can be used to support gas exchange whilst specific treatment (e.g. reversal of narcotic overdose) takes effect.

**Aetiology**

Respiratory acidosis occurs when CO₂ production exceeds CO₂ elimination.

- Decreased CO₂ elimination results from either alveolar hypoventilation e.g. due to respiratory depression (CNS disease, narcotics), neuromuscular disease, or airway obstruction, or from increased dead space effect (pulmonary
embolism or dynamic hyperinflation).

- With fixed minute ventilation e.g. during general anaesthesia, increases in CO₂ production can result in respiratory acidosis. This may be seen with shivering and fever. Large amounts of exogenous CO₂ administration (typically from sodium bicarbonate administration) can result in hypercarbia when minute ventilation is fixed.

Rapid infusion of NaHCO₃ in patients with respiratory acidosis can induce acute respiratory failure if alveolar ventilation is not increased to account for the increased CO₂ production.

Chronic respiratory acidosis is most often caused by chronic lung disease (e.g. COPD) or chest wall distortion (e.g. kyphoscoliosis). Rarely, the cause is central hypoventilation or chronic neuromuscular disease. A cause of acute hypercarbia is increased CO₂ production due to fever, seizures or increased caloric intake.

**Clinical management**

When the underlying cause of respiratory acidosis can be addressed quickly (e.g. reversal of narcotics with naloxone), it may be possible to avoid tracheal intubation. However, more often this is not the case and mechanical ventilation is required. Mechanical ventilatory support is indicated when the patient is unstable or at risk of instability, or when CNS function deteriorates. Furthermore, in patients who are exhibiting signs of respiratory muscle fatigue, mechanical ventilation should be instituted before respiratory failure occurs. A trial of NIV with careful monitoring can be considered. Thus, it is not the absolute pCO₂ value that is important, but rather the clinical condition of the patient.

See the PACT modules on Mechanical ventilation and Acute respiratory failure.

Chronic hypercapnia requires treatment when there is an acute deterioration. In this setting it is important not to try to restore the pCO₂ to normal but rather to tailor treatment according to the patient’s baseline pH or pCO₂ if known. Other options for treatment of hypercarbia include non-invasive ventilation using a BiPAP system. This technique can be useful in the management of sedated patients, particularly when their sensorium is not impaired.

Occasionally, it is useful to reduce CO₂ production. This can be accomplished by reducing the amount of carbohydrate in nutritional support, controlling temperature in the febrile patient and sedation of the anxious or combative patient. Treatment of shivering in the postoperative period can also reduce CO₂ production. However, it is unusual to be able to control hypercarbia with these techniques alone.

In recent years there has been considerable interest in reducing ventilator associated lung injury. One strategy to reduce lung stretch is to reduce tidal volume and to tolerate a reduced minute ventilation and hence an elevated pCO₂. This practice is often referred to as lung protective ventilation including permissive hypercapnia or controlled hypoventilation when indicated. Recent RCTs suggest that this method may reduce mortality in patients with severe ARDS. However, permissive hypercapnia is not without risks. Intracranial pressure increases, as do pulmonary artery pressures making this technique unsuitable for patients with brain injury and right ventricular dysfunction.

See the PACT module on Acute respiratory failure for more information on this topic.

**THINK** What happens to respiratory acidosis in a non-intubated patient when sodium bicarbonate is given to correct the acidosis?

**Outcome**

Unlike metabolic acidosis, respiratory acidosis per se does not appear to be associated with increased mortality. Indeed, controlled respiratory acidosis (permissive hypercapnia) is routinely used to control airway pressures in patients with acute lung injury. Outcome appears to be related to the underlying disease process but the added risks (or benefits) of respiratory acidosis per se have not been adequately evaluated.

**Respiratory alkalosis**

**Recognition**

Hyperventilation may be evident clinically in a ventilated or non-ventilated patient. Hypocarbia causes light-headedness, tetany and if severe, unconsciousness and convulsions.

**Resuscitation**

Respiratory alkalosis may be the presenting manifestation of many serious disorders including sepsis and pulmonary embolism. The underlying cause should be treated and any accompanying hypotension aggressively corrected.

**Diagnosis**

Pure respiratory alkalosis is easily diagnosed, as the pCO₂ will be reduced and arterial pH increased.

Respiratory alkalosis may also complicate metabolic acid-base disorders. In metabolic acidosis, the arterial pCO₂ should decrease (respiratory compensation). However, when the measured pCO₂ is decreased >0.26 kPa (2 mmHg) below the estimated pCO₂, respiratory alkalosis is also present. For metabolic acidosis, the expected pCO₂ can be calculated from either of the following formulae.

\[
pCO₂ = 1.5 \times HCO₃^- + 8 \\
pCO₂ = 40 + SBE
\]

[41]
In cases of metabolic alkalosis, CO₂ retention occurs and the expected pCO₂ is increased. When the pCO₂ fails to increase as expected (>0.26 kPa (2 mmHg) less than the estimated level), respiratory alkalosis is also present. For metabolic alkalosis, the expected pCO₂ can be determined from either of the following formulae.

\[
pCO₂ = (0.7 \times HCO₃^-) + 21 \\
pCO₂ = 40 + (0.6 \times SBE)
\]

Unlike respiratory compensation, metabolic compensation takes time (up to 5 days). Therefore, acute and chronic respiratory acid-base disorders will have different patterns of SBE and bicarbonate. In acute respiratory alkalosis, SBE will be within the normal range and bicarbonate will be determined by the pCO₂ using the following relationship.

\[
HCO₃^- = [(40– pCO₂) / 5] + 24
\]

When there is an acute respiratory alkalosis, a metabolic acid-base disorder is also present if the SBE is <-3 (acidosis) or >3 (alkalosis) or if the measured bicarbonate is different (±2) from expected.

When respiratory alkalosis is chronic, the SBE and bicarbonate can be estimated from the following formulae:

\[
SBE = 0.4 \times (pCO₂– 40) \\
HCO₃^- = [(40– pCO₂) / 2] + 24
\]

**Aetiology**

- Central nervous system stimulation – pain, anxiety, fever, pregnancy, CNS disease (meningitis, tumour, cerebrovascular accident), hypoxia
- Drugs – salicylates, progesterone, nikethamide
- Stimulation of chest receptors – cardiac failure, pulmonary embolism
- Miscellaneous – sepsis, hepatic failure.

**Clinical management**

Treatment should be directed towards the underlying cause. Most often simple reassurance, anxiolytics, rebreathing from a bag or treating the underlying psychological stress is enough to alleviate respiratory alkalosis. In some clinical circumstances, resolution of tachypnoea will serve as a marker for successful treatment (e.g. sepsis) and may indicate that the patient is ready for a trial of weaning from the ventilator.

- Control of fever, seizure activity and sepsis will minimise hypocapnia.
- Sedatives or neurodepressants should not be given to decrease ventilatory drive prior to evaluation of the underlying cause.
- Severe alkalosis is associated with electrolyte disturbances such as hypokalaemia, hypophosphataemia and hypomagnesaemia. One should look for these disturbances and correct them to avoid/treat accompanying arrhythmias.

[42]
Outcome

Outcome depends on the nature and severity of the underlying cause. However, hypocapnia appears to be a particularly bad prognostic indicator in critically ill patients, especially those with sepsis. Chronic hypocapnia appears to have minimal risk for the health of patients.

5/ ACUTE DISORDERS OF ADRENAL FUNCTION

Hypoadrenalism


Recognition

Hypoadrenalism can present in various non-specific ways ranging from vague generalised weakness and malaise (chronic hypoadrenalism) to cardiovascular collapse in the acute setting. In this module, adrenal insufficiency relevant to the intensive care unit (ICU) setting will be discussed. Critical illness (sepsis, head injury etc) impairs the hypothalamic pituitary axis (HPA) and cortisol production often fails to meet the demands of the stress. HPA axis suppression during critical illness happens irrespective of whether patients have been previously exposed to long-term steroids. In addition drugs such as etomidate and phenytoin may inhibit cortisol synthesis.

Relative adrenal insufficiency is a more common condition and should be considered in any ICU patient with:

- Severe vasodilatory shock refractory to vasopressor therapy
- Persistent shock despite adequate resuscitation, antibiotics and source control in a septic patient
- Unexplained or recurrent hypoglycaemia
- Unexplained fever
- Protracted hyperkalaemia combined with hyponatraemia
- Overwhelming sepsis, HIV infection and severe stress if the patient has been previously exposed to corticosteroids.

Q. What kind of haemodynamic picture does adrenal insufficiency cause?

A. Adrenal insufficiency usually causes a distributive shock, with high cardiac output and decreased systemic vascular resistance, similar to that seen in sepsis and liver failure.

Resuscitation

Adrenal insufficiency in the ICU can present as a life-threatening emergency and hence a high index of suspicion, prompt recognition and immediate evaluation and therapy are critical for survival. Immediate measures include assessment and management of airway, breathing and circulation, and aggressive correction of hypovolaemia is indicated in all patients whose physiology permits. Glucocorticoids should be administered as soon as adrenal insufficiency is suspected and not delayed until diagnostic test results are available.
Diagnosis

Most often, relative adrenal insufficiency in the ICU is diagnosed and treated based on clinical suspicion. In the critical care setting, it is diagnosed by demonstrating low serum cortisol (inadequate cortisol production) and an inability of the adrenal glands to produce more cortisol on stimulation with ACTH (absence of adrenal reserve).

Plasma cortisol level: A basal plasma cortisol level of less than 10 µg/dL (276 nmol/L) strongly suggests the diagnosis of primary hypoadrenalism in non-ICU patients. However, no consensus exists in critically ill patients on the cut-off cortisol value for the diagnosis of relative adrenal insufficiency. Moreover, a single cortisol value is often misleading due to the extremely variable and pulsatile nature of the response of the hypothalamic-pituitary-adrenal axis to stress.

Since systemic hypotension maximally stimulates the HPA axis, the finding of a random serum cortisol <20 µg/dL (541.2 nmol/L) in the setting of systemic hypotension (MAP<60 mmHg) is considered by some to be presumptive evidence of relative adreno-cortical insufficiency. However, neither cortisol levels nor their response to ACTH stimulation predict relative adrenal insufficiency or the likely response to replacement doses of steroids. Hence routine measurement of serum cortisol levels is not recommended prior to initiating therapy with stress dose steroids in patients with refractory septic shock.

In critically ill patients, loss of cortisol binding globulin (CBG) results in decreased protein-bound cortisol and increased free cortisol (which is the physiologically active molecule). Therefore standard assays for plasma cortisol (which measure total plasma cortisol) underestimate HPA axis activity in critical illness. Hence, it has been proposed that free cortisol measurement may identify patients with relative adrenal insufficiency more accurately than total serum cortisol levels, but this assay is not widely available and is not recommended in critically ill patients.

Short ACTH stimulation test: This test involves the intravenous administration of 250 µg of ACTH and measurement of plasma cortisol levels before, 30 minutes and 60 minutes afterwards. A normal response to the high-dose (250 µg as an i.v. bolus) ACTH stimulation test is a rise in serum cortisol concentration after 30 or 60 minutes of >9 µg/dL (248.4 nmol/L). A subnormal response supports the diagnosis of relative adrenal insufficiency.

Some experts believe that, because 250 µg of ACTH is a supranormal dose and can stimulate even a suppressed adrenal gland, some cases of (relative) adrenal insufficiency may be missed. Hence 1 µg ACTH dose has been advocated by some investigators.

In summary, there is no consensus about the criteria that should be used to diagnose relative adrenal insufficiency in critically ill patients. All available tests are unreliable and have their limitations e.g. variability between different laboratories. Treatment is often instituted on the basis of clinical suspicion. Although controversial, many experts favour a diagnosis of relative adrenal insufficiency in critically ill patients if a random total plasma cortisol level is <20 µg/dL (541.2 nmol/L) or the increase in serum cortisol with 250 µg of ACTH stimulation is ≤9 µg/dL (248.4 nmol/L).
Cortisol levels are often not available for a few hours to days. Hence it is important that steroid therapy is begun as soon as the diagnosis is clinically suspected and the blood tests have been sent.

**Aetiology**

Causes of adrenal insufficiency in the ICU include:
- Sepsis (Tuberculosis, HIV, Disseminated fungal infections, bacterial infections including meningococcaemia)
- Metastatic Cancer (Primary from lung, breast and stomach)
- Adrenal haemorrhage and infarction
- Drugs (Ketoconazole, Etomidate, Phenytoin, Rifampicin)

**Clinical management**

Two large randomised studies have evaluated the role of steroid supplementation in patients with septic shock and have produced discordant results:

In a French, multicentre study, 300 patients were randomly assigned to placebo or hydrocortisone (50 mg intravenously every six hours) plus fludrocortisone (50 µg enterally once a day) within eight hours of the onset of septic shock. High-dose (250 µg) ACTH stimulation test was performed in all patients irrespective of randomisation and the patients were classified as responders (delta increase in serum cortisol of >9 mcg/dL (248.4 nmol/L)) or non-responders (delta increase in serum cortisol of ≤9 µg/dL (≤248.4 nmol/L). The study treatment was continued for one week. In non-responders, steroid administration significantly improved 28 day, ICU and hospital mortality. However no survival benefit was seen in the responders. Vasopressor withdrawal rates at 28 days were higher in the steroid group compared to placebo.

The Corticosteroid Therapy of Septic Shock (CORTICUS) trial randomised 499 patients with septic shock to receive hydrocortisone (50 mg) or placebo intravenously every six hours for five days, followed by a tapering regimen. The patients were classified as responders and non-responders using similar cut-off values of delta rise in serum cortisol after 250 µg ACTH administration. However in this study, there was no survival difference between the groups, irrespective of their adrenal reserve. Shock reversal was faster in the patients receiving steroids compared to placebo. However, there were more episodes of superinfection, including new sepsis and septic shock in the patients who received steroids.

The French study’s favourable outcome has been attributed to sicker patients, a higher proportion of non-responders and earlier initiation of steroids (within 8 hours of onset of shock compared to the CORTICUS study where steroids were initiated within 72 hours).

In summary, corticosteroid therapy should be considered within 24 hours in septic patients with persistent shock despite adequate resuscitation, appropriate antibiotics and source control. Corticosteroid therapy has been shown to lead to faster resolution of shock and vasopressor withdrawal in these patients, especially if begun within eight hours of the onset of shock. Response to ACTH testing should not be used to select patients for corticosteroid therapy.
Hydrocortisone at a dose of 200–300 mg/day is used when therapy is being initiated; higher doses should not be used. In a recent (COITTS) trial, the addition of fludrocortisone did not add any further benefit to hydrocortisone alone in critically ill patients with refractory septic shock. The treatment regimen should be continued for 5–7 days or until resolution of shock, followed by a gradual tapering of the dose. Blood sugars need to be closely monitored and controlled in patients who are receiving corticosteroid therapy.

**Outcome**

The outcome of relative adrenal insufficiency in itself is usually good if recognised early and treatment initiated. However, the overall outcome will depend on the underlying cause.


Hyperthyroidism


Recognition

Hyperthyroidism should be thought of in critically ill patients presenting with one or more of the following:

- New-onset arrhythmias, especially atrial fibrillation
- Acute confusional state
- Severe fever and persistent tachycardia
- Anxiety, tremors and palpitations
- Diarrhoea or unexplained weight loss
- Muscle weakness.

However, all these signs and symptoms are non-specific and a multitude of conditions can manifest with similar features especially in the critically ill patient. Nevertheless a combination of one or more of these manifestations should suggest the possibility of this diagnosis. The presence of eye changes (e.g. exophthalmos, lid retraction) and a goitre, along with one or more of the above clinical features increases the likelihood of hyperthyroidism. Rarely, patients can present with ‘thyroid storm’, necessitating ICU admission and urgent treatment. Thyroid storm is a life-threatening exacerbation of hyperthyroidism, usually manifested by high fever, delirium, severe cardiac arrhythmias and failure, seizures and jaundice. This presentation carries a mortality of about 30%. Thyroid storm is usually precipitated by an infection.

In elderly patients, manifestations of hyperthyroidism can be subtle. Also, elderly patients often present mainly with fatigue, lethargy and weight loss, a variant called apathetic hyperthyroidism.

Resuscitation

Patients with hyperthyroidism most commonly present with hypertension and tachycardia. However, attention must be paid to any associated arrhythmias, haemodynamic instability or hyperthermia.

Diagnosis

A thorough history and careful clinical examination are key to making the diagnosis. Thyroid function tests confirm the diagnosis and help to establish the aetiology of hyperthyroidism. The most cost-effective screening test for hyperthyroidism is a serum thyroid-stimulating hormone (TSH) level. If the TSH level is normal,
hyperthyroidism is unlikely. If TSH is low, serum free T4 levels should be determined to establish the diagnosis and quantify the degree of hyperthyroidism.

In overt hyperthyroidism, plasma TSH levels are low (due to suppression) and free T3 and T4 levels are high. The exception to this rule is T3 toxicosis, where there is isolated free T3 level elevation with normal free T4 levels and T4 toxicosis where free T4 levels are elevated with normal free T3 levels. In an outpatient setting, radioactive iodine uptake (RAIU) might be helpful in delineating the aetiology of hyperthyroidism. In most instances of hyperthyroidism, the RAIU is increased. Exceptions to this rule include subacute thyroiditis and factitious hyperthyroidism. However, this test is seldom performed in the ICU setting.

In critically ill patients with hyperthyroidism, serum T3 and T4 levels are often normal or even low. In critical illness, both T3 formation from T4 and protein binding of T3 are decreased leading to lower serum T3 levels. Decreased serum T4 levels in critical illness is mainly due to decreased protein binding. Due to alterations in T3 formation and protein binding, thyroid function tests in critical illness are often inconclusive and difficult to interpret. However an elevated free T4 suggests hyperthyroidism, whilst elevated reverse T3 (rT3) suggests the 'sick euthyroid syndrome'.


**Aetiology**

Causes of hyperthyroidism include:

- Excess thyroxine from the thyroid gland
  - Grave’s disease
  - Autonomous thyroid hormone production from the thyroid gland (adenoma, toxic multinodular goitre)
  - Increased thyroid hormone release (thyroiditis)
  - TSH secreting pituitary tumours
  - Ectopic TSH production (choriocarcinoma)
- Excess thyroxine from non-thyroid source
  - Thyrotoxicosis factitia and deliberate overdose
  - Ectopic thyroxine secretion (ovarian teratoma)

**Clinical management**

Hyperthyroid manifestations are sympathetically mediated and hence can be attenuated by β-blockade. However, the main approach to management of the underlying condition is to reduce thyroid hormone synthesis and release (antithyroid medications) and/or to decrease the amount of functioning thyroid tissue (radioactive iodine).
β-blockers are very useful and should be initiated early. Antithyroid medications take a few weeks to act; hence β-blockers are often used to alleviate symptoms during this latent period. Propranolol is preferred, since it can also inhibit peripheral conversion of T4 to T3. Propranolol is usually given orally at a dose of 60 to 80 mg every four hours.

Thionamides are the major class of antithyroid drugs and should be initiated along with the β-blockers. In patients with thyroid storm, propylthiouracil (PTU) is the antithyroid drug of choice since it also blocks peripheral conversion of T4 to T3. The dose of thionamide given to patients with thyroid storm is higher than that required to block thyroid hormone synthesis. The dose of PTU used is 200 mg every four hours, orally.

Various drugs and regimens can be used for less severe hyperthyroidism where thyroid function tests are performed every 3–4 weeks and the dose titrated based on serum free T4 levels.

Radioactive iodine causes slow destruction of thyroid follicles and inhibits peripheral conversion of T4 to T3. It releases thyroid hormone from the gland and hence administration of radioactive iodine should always be preceded by treatment with antithyroid drugs for at least a month. However, in patients with thyrotoxic crisis, stable iodide can be administered one hour after giving the loading dose of PTU to inhibit the synthesis of thyroid hormone.

Iodine elixirs, such as saturated solution of potassium iodide (SSKI) or Lugol’s solution, are generally used in hyperthyroid emergencies. SSKI is usually given in a dose of 10 drops daily in divided doses. Iodine-containing oral radiocontrast agents, ipodate and iopanoic acid, which are also potent inhibitors of thyroxine conversion, may be preferable to iodide in the treatment of hyperthyroid emergencies. Doses in most studies have ranged from 500 mg to 1000 mg as a single daily dose. Patients unable to take oral medication can be treated with sodium iodide, 500 mg every 12 hours intravenously.

Glucocorticoids are administered in patients with ‘thyroid storm’. They reduce T4 to T3 conversion, and may have a direct effect on the underlying auto-immune process if the thyroid storm is due to Grave’s disease. Hydrocortisone is the usual drug of choice and is given at a dose of 100 mg intravenously every eight hours in patients with thyroid storm.

Partial or total thyroidectomy may be necessary in some cases. However, patients should be maintained euthyroid prior to surgery by antithyroid medications.
**Outcome**

The outcome of hyperthyroidism depends on the aetiology. Mortality is usually related to the underlying aetiology rather than the hyperthyroidism itself. However, patients presenting with ‘thyroid storm’ carry a high mortality due to malignant arrhythmias and cardiac failure.


**Hypothyroidism**


**Recognition**

Hypothyroidism is usually caused by decreased thyroid hormone synthesis and/or release from the thyroid gland. It can also be secondary to decreased TSH release as a result of pituitary or hypothalamic dysfunction. Hypothyroidism should be suspected in critically ill patients presenting with:

- Unexplained bradycardia
- Unexplained hypothermia
- Altered mental status and/or coma
- Obstructive sleep apnoea (due to macroglossia) and hypercapnia
- Unexplained pleural and pericardial effusions.

These findings alone are extremely non-specific and insensitive. However, the presence of one or more of these manifestations in a patient with other classical physical findings such as dry, coarse skin, puffy facies, macroglossia, periorbital oedema increase the likelihood of this diagnosis.

**Resuscitation**

Hypothyroidism per se is very rarely the presenting illness in critically ill patients. Very occasionally, patients present with ‘myxoedema coma’, a severe form of hypothyroidism characterised by hypothermia, bradycardia, hypotension, hypoglycaemia and coma. The key to management of myxoedema coma is early suspicion and diagnosis. In these patients, the priority is to secure the airway, expand the circulating volume and re-warm actively. Hyponatraemia is a common feature; when present, fluid resuscitation should be cautious, and the rate of increase in serum sodium should be closely monitored.
**Diagnosis**

The diagnosis of hypothyroidism is usually clinical. However, measurement of TSH and free T4 help to determine the specific aetiology and differentiate primary from secondary hypothyroidism. Increased TSH in the presence of normal or low free T4 suggests primary hypothyroidism (intrinsic thyroid abnormality). On the other hand decreased TSH in the presence of low free T4 suggests secondary (pituitary origin) hypothyroidism.

- TSH is an excellent screening test for hypothyroidism in the outpatient setting. However, in critically ill patients, this is not the case since plasma TSH levels can be affected by various factors. Commonly a transient elevation in plasma TSH is seen in patients recovering from non-thyroidal illness. These patients seldom become hypothyroid. Also some drugs such as amiodarone and metoclopramide can increase plasma TSH levels.
- For an accurate diagnosis in critically ill patients plasma levels of free T4 should be measured along with TSH.
- Other tests such as thyroid peroxidase antibody and thyroglobulin level, help to identify the specific cause of hypothyroidism, but are seldom useful in the acute setting.


**Aetiology**

- Primary hypothyroidism
  - Decreased functioning thyroid tissue
    - Auto-immune thyroiditis
    - Infiltrative disorders (amyloidosis)
    - Iatrogenic (radioactive iodine)
  - Decreased thyroid hormone synthesis
    - Congenital enzyme deficiencies
    - Iodine deficiency
    - Drugs (thionamides, lithium and sulphonamides)
- Secondary hypothyroidism (pituitary or hypothalamic dysfunction)
- Peripheral thyroid resistance.

**Clinical management**

Most patients with hypothyroidism will need life-long thyroxine replacement. Oral T4 is usually used and can be given once a day due to its long half-life. The usual dose is 1.5 µg/kg/day. However, patients with myxoedema coma should be treated aggressively, even before a definitive diagnosis is made because the associated mortality is about 70–80%. Glucocorticoids should always be administered along with thyroxine in patients suspected to have myxoedema coma, since adrenal reserve is decreased in severe hypothyroidism.

In myxoedema coma, levothyroxine (T4) or liothyronine (T3) should be administered
intravenously. If the intravenous drug is not available, oral forms of thyroxine can be given via a nasogastric tube. Since peripheral conversion of T4 to T3 is impaired in myxoedema coma, some experts advocate initial replacement of both T4 and T3. However, such recommendations are still controversial and treatment with T3 has been shown to be associated with an increased risk of cardiac toxicity, especially in elderly patients.

The recommended dose of T4 is 500 µg as a loading dose intravenously followed by 50–100 µg/day. If T3 is used, 10–25 µg can be given intravenously followed by 5–10 µg every eight hours. Supportive measures to counteract hypothermia, hypercapnia and hypotension should be undertaken.

Vasoactive agents may be ineffective and can induce dangerous cardiac arrhythmias in patients with myxoedema coma. Also drugs like digitalis are not adequately metabolised, often leading to toxic plasma levels.

Q. How often should you monitor TSH levels in a hypothyroid patient undergoing therapy with oral thyroxine?

A. Thyroxine has a long half-life and changes in TSH concentrations in response to therapy can take 4–6 weeks to reach a steady state. It is therefore suggested that TSH levels should not be measured more frequently than once every 4–6 weeks to guide the dose of oral thyroxine replacement therapy.

Outcome

Outcome of patients with hypothyroidism is good. However, myxoedema coma carries a high mortality. Old age, presence of hypotension and delayed diagnosis are associated with worse outcomes.


CONCLUSION

Disorders of electrolytes, acid-base balance, cortisol and thyroid function represent fundamental metabolic stresses in the critically ill and at least one of these disturbances is likely during the care of each critically ill patient. Such imbalances complicate the management of single organ-system failures and produce protean manifestations and generalised organ-system dysfunction. Timely recognition of dysfunctional signs, appreciation of their importance and the appropriate correction of both the immediate hazard where it exists and of the underlying disorder are key to the role of the critical care physician.
This Appendix contains additional information on understanding acid-base disorders and Hyperadrenalism.

**Aetiology of acid-base disorders: Metabolic acidosis**

According to Stewart’s approach to understanding acid-base disorder (see AcidBase link and other references), metabolic acidosis results from a decrease in the strong ion difference (SID) or an increase in total weak acid (ATOT) or both.


The SID is the net charge on all ions in the plasma and is predominantly determined by Na⁺ and Cl⁻. ATOT is made up of weak acids, predominantly albumin and phosphate. Standard base excess (SBE) quantifies the change in both SID and ATOT relative to equilibrium. Thus, for a given ATOT, changes in SID produce a 1:1 change in SBE. Increases in strong anions (e.g. Cl⁻, lactate) decrease the SID and make the SBE negative; increases in weak acids (e.g. phosphate) increase ATOT and have a small effect on SBE.

When the SID is decreased (or ATOT is increased) as a result of anions other than Cl⁻, the anion gap (AG) increases. This occurs as a result of both endogenous and exogenous acids.

A decreased SID will force the equilibrium point for CO₂ away from HCO₃⁻ (HCO₃⁻ will decrease) and this can be interpreted as indicating a metabolic acidosis. However the decrease in HCO₃⁻ per se is an effect, not a cause of the acidosis. The classical metabolic acidosis of renal failure is an early hyperchloraemic acidosis, usually with a SBE not less than −10, followed by a gradual increase in the AG as the accumulation of sulphate, phosphate and other organic acids accumulate. Although some of these substances are strong ions (e.g. sulphate) peak concentrations are relatively low and therefore even in untreated end-stage renal disease, the AG rarely exceeds 5 mmol/L (mEq/L) above predicted.

**Increased anion gap**

Lactic acidosis is perhaps the most common cause of an increased AG metabolic acidosis. Lactic acidosis in patients with shock often represents inadequate resuscitation; while lactic acidosis occurring in well-perfused patients generally represents increased glucose metabolism, decreased lactate utilisation, oxidative stress, or in association with acute lung injury.

Ketones from diabetic ketoacidosis induce an increased AG metabolic acidosis that may be profound. Starvation ketosis may also cause acidosis but it is usually quite mild.
Unknown anions can be responsible for large AGs occasionally seen in patients with sepsis, liver failure and hyperosmolar hyperglycaemic coma.

Severe toxins which induce an increased AG metabolic acidosis include methanol, ethylene glycol, paraldehyde, and toluene. The presence of an osmolar gap along with an anion gap acidosis suggests intoxication by one of these alcohols.

Salicylate toxicity classically induces a mixed picture of increased AG metabolic acidosis and respiratory alkalosis.

Some patients can develop lactic acidosis (Type B lactic acidosis) without any clinical evidence of organ hypoperfusion. Common causes include metformin when continued in patients with renal failure, some malignancies such as leukaemias and lymphomas and anti-retroviral drugs such as zidovudine.

**Normal anion gap**

Metabolic acidosis associated with a normal AG can be due to abnormalities in Cl⁻ homeostasis. This may occur either as a consequence of abnormalities in Cl⁻ handling by the kidneys or the intestinal tract or as a result of chloride accumulation.

When metabolic acidosis is caused by non-renal disease (e.g. diarrhoea) the kidney excretes Cl⁻ in excess of Na⁺ and K⁺ and the urine SID becomes negative (NH⁺ is also excreted). Failure by the kidney to excrete urine with a negative SID results in renal tubular acidosis (RTA) and will be manifest by a positive urine SID. Different forms of RTA can be further differentiated on the basis of urine pH and plasma K⁺ concentration (see table differential diagnosis of metabolic acidosis).

Type I (Distal) RTA can be caused by: inherited disease, drugs (amphotericin B, lithium, toluene), nephrocalcinosis, idiopathic hypercalciuria, hypervitaminosis D, hyperthyroidism, hyperparathyroidism, auto-immune disorders, hypergammaglobulinaemia, or interstitial nephropathies.

Type II (Proximal) RTA can be due to: Wilson’s disease, drugs (heavy metals, carbonic anhydrase inhibitors) hyperparathyroidism, amyloid, nephrotic syndrome, renal transplant, myeloma, hypervitaminosis D, vitamin D deficiency, chronic active hepatitis, outdated tetracycline, or scleroderma.

Type IV RTA is an imprecise category including all other forms of RTA. It can be due to selective aldosterone deficiency, usually associated with interstitial disease, especially lead poisoning or diabetes. Drugs, especially non-steroidal anti-inflammatory agents and cyclosporin, have also been reported to cause Type IV RTA.

Diarrhoea or small bowel/pancreatic drainage impairs electrolyte reabsorption from the gastrointestinal tract such that Na⁺ is lost in excess of Cl⁻. The result is a decrease in the SID and a hyperchloraemic metabolic acidosis.

Chloride accumulation occurs when large volumes of non-physiologic solutions such as saline are given intravenously. HCl infusion will also produce the same effect, albeit more rapidly.


Hyperadrenalism

Recognition

Although hyperadrenalism denotes an excess of one or more of the many hormones produced in the adrenals, in this section the discussion will be confined to glucocorticoid and mineralocorticoid excess. Hyperadrenalism should be considered in hypertensive patients with the classical physical findings of moon facies, weight gain, abdominal striae, hyperpigmentation and oedema. Clues to the presence of hyperadrenalism include hypokalaemic metabolic alkalosis, glucose intolerance, hirsutism and proximal muscle weakness. However, these findings are neither sensitive nor specific for hyperadrenalism.

Rarely, adrenal masses are found incidentally on CT scans done for other purposes (‘incidentalomas’) but should be considered in critically ill patients with otherwise unexplained hypokalaemia and/or resistant hypertension.

Resuscitation

When patients present as an emergency with hypertension, hypokalaemia or arrhythmias, consider the diagnosis of hyperadrenalism.

Diagnosis

The presence of hypokalaemic metabolic alkalosis in a patient suspected of having hyperadrenalism suggests a diagnosis of excess mineralocorticoid activity, since this finding is uncommon in glucocorticoid excess. In contrast, the presence of hyperpigmentation, violaceous striae, moon facies, glucose intolerance and proximal muscle weakness suggest a diagnosis of glucocorticoid excess. Increased 24-hour urinary free cortisol reflects an elevation in the plasma levels of bioactive cortisol and serves as a good screening test for glucocorticoid excess.

Plasma ACTH levels help to distinguish ACTH-dependent cortisol excess versus ACTH-independent states (primary adrenal disease).

- If the patient has ACTH-independent hypercortisolism (increased plasma and urinary cortisol with a decreased plasma ACTH level), adrenal imaging with thin-section CT scan or MRI is indicated.

- In patients with ACTH-dependent hypercortisolism (increased plasma and urinary cortisol levels with increased plasma ACTH levels), further testing using high-dose dexamethasone-suppression tests can differentiate excessive ACTH of pituitary (adequate suppression) versus non-pituitary origin.

In patients suspected of having excessive mineralocorticoid activity, plasma aldosterone levels, along with plasma renin activity (PRA) should be measured to differentiate renin-dependent hyperaldosteronism (renovascular hypertension) from renin-independent hyperaldosteronism (suppressed PRA).
**Aetiology**

Glucocorticoid excess
- ACTH-dependent causes (ACTH secreting tumours – pituitary and ectopic)
- ACTH-independent causes (Adrenal adenoma and carcinoma, factitious or surreptitious glucocorticoid ingestion).

Mineralocorticoid excess
- Renin-angiotensin dependent causes (vomiting, diuretics, renovascular hypertension, Bartter’s syndrome)
- Renin-independent causes (aldosterone secreting adenoma, congenital adrenal hyperplasia).

**Clinical management**

In patients with ACTH-dependent hypercortisolism, transsphenoidal resection of pituitary microadenomas is the initial treatment of choice. This has a 70–90% initial cure rate, with recurrence rates of 5–20%. In patients with recurrence, pituitary radiation can be attempted. In patients, refractory to the above modes of therapy, medical (mitotane, ketoconazole) or surgical adrenalectomy are indicated.

In patients with ACTH-independent hypercortisolism, adrenalectomy is the treatment of choice.

In primary aldosteronism, if the cause is adrenal adenoma, surgical resection (laparoscopic) is the preferred treatment. If there is bilateral hyperplasia, patients can usually be managed medically with spironolactone or amiloride, while surgery is usually reserved for patients with refractory hypokalaemia and or alkalosis.

**Outcome**

Outcome is generally good once the underlying disorder is treated
SELF-ASSESSMENT

EDIC-style Type K

1. Hypertonic hyponatraemia may occur in the following circumstances:
   A. Hyperglycaemia
   B. Hyperlipidaemia
   C. Hyperproteinaemia
   D. Administration of mannitol.

2. In order to avoid central pontine myelinolysis (osmotic demyelination) the recommendations during correction of symptomatic hyponatraemia are:
   A. Correct the serum Na by no more than 2 mmol/hour in the first 6 hours
   B. Correct serum Na by 10–12 mmol/day
   C. If seizures are part of the clinical picture, a rapid normalisation of serum Na within 12 hours is the goal
   D. Avoid any infusion of glucose.

3. Hypernatraemia is commonly found in the following clinical conditions:
   A. Diabetes insipidus
   B. Syndrome of inappropriate ADH secretion (SIADH)
   C. Vigorous use of loop diuretics
   D. Acute renal failure with anuria.

4. The consequences of rapid correction of hypernatraemia include:
   A. Hypoglycaemia
   B. Cerebral oedema
   C. Decreased GCS
   D. Increased (improved) GCS.

5. Hypokalaemia is associated with:
   A. Respiratory alkalosis
   B. Ventricular arrhythmias
   C. Tenting of the T-waves
   D. Renal tubular acidosis.

6. When hypokalaemia is being treated by the administration of K+, this is best done by:
   A. Always utilising the intravenous route
   B. Not giving more than 10 mmol/hr, if using a peripheral i.v. cannula
   C. Never exceeding a rate of 20 mmol/hr
   D. Concurrent correction of hypomagnesaemia, if present.
7. ECG changes are common in hyperkalaemia; what is/are correct statements in this context:
   A. There is a linear relation between rise in s-K⁺ and ECG changes
   B. Tall peaked T-waves are late ECG changes
   C. Shortened PR interval is not a usual change
   D. Prolonged QRS complex is a feature.

8. The acute treatment of life-threatening hyperkalaemia includes:
   A. Intravenous magnesium
   B. Intravenous calcium
   C. Glucose/Insulin infusion
   D. Intravenous lidocaine.

9. Common symptoms of severe hypoglycaemia include:
   A. Coma
   B. Seizures
   C. Ventricular arrhythmias
   D. Excessive sweating (diaphoresis).

10. Aetiology of hypoglycaemia include:
    A. Severe liver disease
    B. Septic shock
    C. Hyperthyroidism
    D. Insulinoma.

11. Insulin deficiency can cause both diabetic ketoacidotic (DKA) and hyperosmolar non-ketotic (HONC) coma. Clear differentiation is afforded by:
    A. The level of serum glucose
    B. Arterial blood gas analysis
    C. Calculation of serum anion gap
    D. Measurement of urine ketones.

12. The cornerstones of therapy of hyperglycaemic emergencies include:
    A. Fluid restriction
    B. Correction of acidosis
    C. Normalisation of blood glucose with insulin
    D. Correction of electrolyte levels.

13. The most appropriate initial fluid therapy in hyperglycaemic emergencies includes:
    A. Isotonic glucose with insulin
    B. Isotonic crystalloid solution
    C. Hypertonic saline
    D. Albumin 4 mg/mL.
14. Supplementary therapy for diabetic ketoacidosis includes:
   A. Correction of potassium deficits
   B. Treatment of hyperphosphatemia with magnesium
   C. Use of alkalinization therapy if pH < 7.20
   D. Treatment of infections

15. In stress-induced hyperglycaemia of the critically ill, the precise, optimum blood sugar level is not fully determined. On the basis of current evidence, reasonable recommendations for target blood sugar levels are:
   A. Below 12 mmol/L
   B. 6–10 mmol/L
   C. Normoglycaemia (4.5–6 mmol/L) in all ICU patients
   D. No specific target

16. The anion gap (AG)
   A. Is calculated as the sum of Na⁺ + K⁺ minus the sum of Cl⁻ and HCO₃⁻
   B. The AG represents ‘other’ unaccounted (unmeasured) anions
   C. The normal AG range is 12–16 mmol/L
   D. In the case of a low serum albumin, the normal AG is reduced

17. Symptomatic treatment of metabolic acidosis includes:
   A. Renal replacement therapy
   B. Hypoventilation
   C. Sodium bicarbonate infusion
   D. Enteral resonium.

18. In chloride-responsive alkaloses treatment may include:
   A. Azetazolamide
   B. Ringer’s Acetate
   C. K⁺ sparing diuretics (spironolactone)
   D. HCl through a central venous catheter.

19. Regarding the diagnosis of hyperthyroidism in a critically ill patient:
   A. Clinical signs are frequently non-specific
   B. Hypotension is often present
   C. Measurement of T₃ and T₄ is diagnostic
   D. Diarrhoea and unexplained weight loss are features.
20. The danger of hyponatraemia is linked to the degree of plasma hypo-osmolality. What level of hypo-osmolality represents the start of the ‘danger zone’?
   A. < 280 mOsm/kg  
   B. < 260 mOsm/kg  
   C. < 240 mOsm/kg  
   D. < 220 mOsm/kg  
   E. < 200 mOsm/kg

21. An 88-year-old female, previously healthy apart from hypertension (treated with a thiazide diuretic), is admitted to hospital after a three-week heat-wave with ambient air temperatures around 35 °C in the city. She has been caring for herself until the morning of her hospital admission. At admission she is unconscious and has a history of seizures in the last few hours. What is the most likely cause of her condition?
   A. Hypoglycaemia  
   B. Hyponatraemia  
   C. Hypocalcaemia  
   D. Status epilepticus  
   E. Senility-associated seizures

22. The following clinical circumstances are associated with hypokalaemia EXCEPT?
   A. Diuretic therapy  
   B. Aggressive correction of acidosis  
   C. Salbutamol therapy  
   D. Postoperatively – after major surgery  
   E. Rhabdomyolysis

23. The following clinical conditions are accepted as risk factors for developing hyperkalaemia with the EXCEPTION of:
   A. Acute renal failure  
   B. Severe metabolic alkalosis  
   C. Rhabdomyolysis  
   D. Digitalis toxicity  
   E. Tumour lysis syndrome

24. Common causes of metabolic alkalosis includes all EXCEPT:
   A. Vomiting  
   B. Diuretic use  
   C. Nasogastric drainage  
   D. Diarrhoea  
   E. Hyperaldosteronism
25. A patient arrives in the hospital after resuscitation from a cardiac arrest. On arrival he is spontaneously breathing. His HCO₃⁻ is 10 mmol/L, what should his expected pCO₂ be?
   A. 2.9 kPa
   B. 3.1 kPa
   C. 3.3 kPa
   D. 3.5 kPa
   E. 3.7 kPa

Self-assessment answers

Type K

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PATIENT CHALLENGES

A 24-year-old female presents to the emergency room complaining of increased urinary frequency, vomiting, decreased oral intake for two days and severe crampy abdominal pain for one-day. Her breath has a ‘fruity’ odour. There is no history of diarrhoea, fever, haematemesis or melaena. The patient has no other past medical history. Her menstrual and social histories are unremarkable. She is very drowsy and lethargic, with a weak gag and cough. Her current vital signs are a pulse rate of 128/min, regular, supine BP of 80/50 mmHg, respiratory rate of 35 breaths/min and temperature of 38.3 °C (101 °F). Pulse-oximetry reveals an oxygen saturation of 90% on room air that improves to 96% on 40% venturi mask oxygen. There are crackles at the right lung base. Her sister says that the patient has been shivering intermittently for the past three days.

Q. What immediate actions should you take?

A. ABCs first. Her neurological and respiratory status (despite oxygen) warrant consideration of intubation and ventilation. Her hypotension likely reflects hypovolaemia (and perhaps sepsis) and warrants large bore i.v. cannulation and fluid resuscitation e.g. with 2–3 Litres of normal saline or Ringer’s lactate.

ABCs always first
Measurement of capillary blood glucose

PACT modules on Airway management and Hypotension

Q. What is the underlying diagnosis? Do any conditions warrant immediate exclusion?

A. A variety of causes of acute drowsiness and hypotension may pertain (see PACT module on Altered consciousness) but a rapid near-patient test of blood sugar is warranted to rule out disorders of glucose metabolism.

Q. Given that the patient has abdominal pain, what other findings would point towards the diagnosis of DKA?

A.
Tachypnoea with increased minute ventilation
History of Polyuria
‘Fruity’ odour of the breath.

The finger prick blood sugar is markedly elevated (over the upper limit of the glucose meter scale) and you suspect DKA with an unknown (as yet), underlying aetiology. You continue resuscitation, request urine dipstick and arrange for the patient to be transferred to your ICU.

Q. Which urine testing would you specifically request to further support DKA?
A. Glycosuria and ketonuria testing. Urgent microscopy might also be requested to rule out an underlying UTI.

Diabetic ketoacidosis

Q. What is your differential diagnosis for a likely underlying precipitating cause?

A. Differential diagnosis (other than community-acquired pneumonia) will include:
   - Urosepsis
   - ‘Acute abdomen’ including perforation of viscus, ischaemic bowel, severe acute pancreatitis etc.
   - Ectopic pregnancy – possibly ruptured
   - Other causes of intra-abdominal bleeding e.g. ruptured ovarian cyst
   - Drug intoxication.

Further lab work reveals a normal WBC, serum sodium of 115 mmol/L, chloride of 84 mmol/L, bicarbonate of 7 mmol/L and serum glucose of 77 mmol/L (1400 mg/dL). Her haematocrit was 45%. Her amylase was 360 U/L (<60 U/L) and lipase was normal. Urine microscopy does not reveal pyuria and urine gram stain does not reveal any bacteria. The abdomen is soft on clinical examination with minimal tenderness that resolved over time. No guarding or rigidity is noted.

Q. How would you interpret the measured hyponatraemia?

A. This patient likely has hypertonic hyponatraemia (dilutional hyponatraemia from the increased plasma glucose levels).

Q. What is the corrected serum sodium level and does it account for her encephalopathy?

A. This patient’s serum sodium when corrected for serum glucose is around 130 mmol/L, which is unlikely to be the reason for this patient’s encephalopathy.

Q. How do you manage the hyponatraemia? Would you institute specific corrective measures?

A. The result does not warrant any correction. Controlling the blood glucose will correct the serum sodium.

Management of hyponatraemia
Correction of plasma sodium

After the patient has received 1L fluid bolus with 0.9% saline, a 12-lead ECG was obtained as she developed a run of sustained ventricular tachycardia without haemodynamic compromise. The ECG is as shown.
Q. What is the likely cause of the patient's arrhythmia?

A. ECG reveals tall peaked T waves and wide QRS complexes, suggestive of moderate-severe hyperkalaemia.

Q. How do you interpret this finding?

A. Irrespective of serum potassium levels, the total body potassium in patients with DKA is always low. This patient’s hyperkalaemia is predominantly because of transcellular shift to outside the cell secondary to acidosis.

Q. The acidosis-related hyperkalaemia is confirmed, 6.4 mmol/L (mEq/L). How would you treat it?

A. Since this patient has ECG manifestations of hyperkalaemia, the patient should receive intravenous calcium gluconate immediately to antagonise the physiological effects of hyperkalaemia. The most appropriate ongoing treatment option in this patient would be to correct the acidosis using intravenous insulin infusion to decrease plasma glucose and the potassium simultaneously.

Q. Would you start ion exchange resin therapy?

A. No. Care must be taken not to use long-acting agents to decrease serum potassium since precipitous fall in serum potassium levels can occur once acidosis is corrected.

Management of hyperkalaemia in DKA
Total body potassium is ALWAYS LOW in these patients irrespective of serum levels.


The likely need for intubation and ventilation is kept under constant review and an arterial blood gas analysis revealed a pH of 7.02, pCO₂ 3.3 kPa (25 mmHg), HCO₃⁻ 6 mmol/L, pO₂ 9.6 kPa (72 mmHg) and BE –23.

**Learning issues**

Arterial blood gas analysis
Acid-base disorders

Q. What is the primary acid-base abnormality?
A. Metabolic acidosis.

Q. The anion gap was 30. How do you analyse this acid-base picture?
A. First of all you need to ascertain whether the data are internally consistent

\[
[H^+] = \frac{24 \times pCO_2}{[HCO_3^-]}
\]

\[
[H^+] = 24 \times 25 / 6
\]

\[
[H^+] = 100 \text{ (corresponds to a pH of about 7.0)} \text{ and hence the data are internally consistent}
\]

pH is acidaemic.
It is a primary metabolic acidosis since serum bicarbonate is low and pCO₂ is low.
Given the elevated anion gap, this is an (increased) anion gap metabolic acidosis.

**Learning issues**

Metabolic acidosis
Estimation of appropriate pCO₂
Anion gap

Q. Is there another acid-base disorder?
A. Yes, there is also a respiratory acidosis.

Q. Is the disorder well compensated?
A. If fully compensated, the PaCO$_2$ should be 2.4 kPa (18 mmHg). Given that the PaCO$_2$ in this case is 3.3 kPa the patient is not fully compensated and therefore has a relative respiratory acidosis.

**Respiratory acidosis**

**Insulin infusion**

The patient had been started on an insulin infusion and vigorous i.v. hydration is continued. Six hours after initiation of treatment, a repeat set of electrolytes shows serum sodium of 124 mmol/L, potassium of 4.5 mmol/L, chloride of 92 mmol/L, bicarbonate of 10 mmol/L and serum glucose of 13 mmol/L (234 mg/dL).

Q. How would you manage this patient’s insulin treatment now?

A. The insulin infusion should be continued until the anion gap normalises.

Q. When would you change from saline/Ringer’s and start a glucose containing solution?

A. When the blood glucose level reaches a value <13.9 mmol/L (250 mg/dL), a dextrose containing fluid should be substituted for saline and the insulin infusion should be continued with close monitoring of blood glucose levels and the anion gap.

**Close the (anion) gap before discontinuation of insulin infusion**

**Hypoglycaemia**

The next day, the patient’s blood sugar is 8.2 mmol/L (148 mg/dL) and the anion gap is normal. The insulin infusion is discontinued and subcutaneous insulin initiated. However, the patient remains tachypnoeic with a respiratory rate of 35 breaths/min. A repeat blood gas analysis reveals a pH 7.24, pCO$_2$ of 3.7 kPa (28 mmHg), pO$_2$ of 12.2 kPa (92 mmHg) and bicarbonate of 12 mmol/L. Morning labs reveal serum sodium of 135 mmol/L, potassium of 2.2 mmol/L, chloride of 119 mmol/L and bicarbonate of 11 mmol/L. On reviewing the intake output chart, the patient appears to have received 8 L of 0.9% saline and 2 L of 0.45% saline and 1 L of Lactated Ringer’s solution on the previous day.

Q. What acid-base disorder does this patient have and why?

A. This patient has a normal anion gap acidosis caused by saline-induced hyperchloraemia.

**Saline-induced acidosis**

**Strong ion difference**

[67]
The patient’s initial chest X-ray was normal, she is now afebrile and after aggressive rehydration and correction of her ketosis, she is transferred to the general medical floor the next day.

Seven hours after the transfer, she develops progressive shortness of breath, fever and hypoxaemia and is readmitted to the ICU with the chest X-ray which is shown below. An upright X-ray of the abdomen, requested on the ward to evaluate the abdomen, did not show any evidence of free-air in the peritoneum.

Q. What is the most likely diagnosis?
A. This patient’s infiltrate appears to be unilateral and hence suggests a pneumonia rather than pulmonary oedema.

Q. Antibiotic therapy is started after blood and sputum cultures are taken but what would you do now from a ventilatory support perspective?
A. Although non-invasive ventilation can be tried, it is unlikely to benefit this patient. The patient is likely to need intubation and mechanical ventilation.

See PACT module on Mechanical ventilation for role of NIV

The patient does not tolerate non-invasive ventilation and hence she is intubated and mechanically ventilated. She develops progressive hypotension, which does not respond to fluid resuscitation and the initial broad-spectrum antimicrobial therapy which has been started.

A PA catheter is then placed, which reveals a cardiac output of 9.0 l/min and a cardiac index of 6.0 l/min/m². The patient is started on dopamine to maintain a mean arterial pressure of >65 mmHg. But over the next 24 hours, the patient’s hypotension continues to worsen despite increasing doses of dopamine. The patient also develops a marked tachycardia (135–140/min) and is therefore switched to a norepinephrine infusion. The patient’s norepinephrine requirement continues to increase over the next 12 hours, with haemodynamic changes typical of distributive shock.
Q. What else apart from sepsis could contribute to the resistant hypotension in this patient?

A. In any patient with sepsis, in whom shock is refractory to volume resuscitation, appropriate antibiotics and adequate source control, ‘replacement doses’ of steroids (hydrocortisone 200–300 mg/day) should be considered within 24 hours of onset of shock. Relative adrenal insufficiency may be considered.

Considering the refractory shock, hydrocortisone (50 mg i.v. Q 6H) was initiated. Serum cortisol levels were not measured before starting steroids. Within 12 hours of initiating treatment, the patient’s norepinephrine requirement decreased and she was successfully weaned from vasopressor support over the next 24 hours. The patient continued to improve clinically and was extubated and transferred from the ICU two days later.

Q. Is the responsiveness to steroid therapy related to the patient’s cortisol levels?

A. Serum cortisol levels and the response to a short synacthen do not predict the haemodynamic response to treatment with corticosteroids. However steroids hasten resolution of septic shock.

Role of ‘replacement dose’ steroid therapy in septic shock
Possible ‘relative adrenal insufficiency’


On reflection, precipitating causes of acute diabetic ketoacidosis should be actively sought in any patient with DKA. Pneumonia and UTI are the two most common infections precipitating DKA. The chest X-ray is often normal initially and patients with DKA can be normothermic despite infection. Repeat chest X-ray after aggressive rehydration should be performed in all patients with a suggestive history. Blood cultures are usually warranted.

Abdominal pain is a common clinical manifestation in patients with DKA, but usually resolves with correction of acidosis. Abdominal pain which does not subside in a few hours of resuscitation and correction of acidosis, especially in the presence of guarding and rigidity needs further evaluation with abdominal imaging and surgical consultation.

In this case, the centre of attention was on the metabolic abnormalities which were well managed but there was inadequate focus on the underlying illness which precipitated the DKA in the first place. This occurred initially when the patient had fever, shortness of breath, hypoxaemia and hypotension and would have benefited from blood cultures and early empiric antibiotics to treat the likely clinical pneumonia and subsequently when discharged from ICU to the ward.