BAPEN

Acid-base Problems in Patients with Intestinal Failure

Sheldon Cooper, Jeremy Nightingale and the BIFA Committee

Acid-base issues are not often recognised in patients with intestinal failure (IF) and needing parenteral support (PS), despite there being a significant amount of acid and bicarbonate produced and reabsorbed by the gut. The stomach can produce 2.0 L of gastric juices including hydrochloric and ascorbic acid, whilst the hepato-biliary/pancreatic secretions amount to about 1.5 L and includes bicarbonate and bile acids. Small bowel fluid additionally contains bicarbonate. Any disruption to the anatomy, motility and absorption, and thus normal gut physiology, can result in disturbances of the acid-base balance. Patients with a short bowel (SB) and receiving PS have a strain placed upon the homeostatic processes. Normal physiology buffers changes in acid-base balance well providing normal lung (CO_2 excretion) and kidney (H+ excretion) function. The normal blood pH of 7.35-7.45 is necessary for homeostasis (including enzymic function and oxygen delivery). Metabolic acidosis (low serum bicarbonate) with a normal or raised anion gap is the most common acid-base problem. This can arise from the underlying illness or the treatments.

Key points

1. Serum bicarbonate (HCO_3) and chloride (Cl) and urinary sodium concentration, should be regularly measured.
2. The serum anion gap (sodium [Na] + potassium [K]) – (HCO_3 + Cl) in mmol/L (normal range 12-17 mmol/L) should be calculated.
3. Metabolic acidosis with a raised anion gap may result from L and D-lactic acidosis, ketosis, uraemia and toxins/drugs (e.g. methanol, glycols/ethanol or aspirin).
4. Metabolic acidosis with a normal anion gap (usually hyperchloremia) is often due to excess intravenous fluids containing Cl and sometimes due to gastrointestinal or renal losses of HCO_3.
5. Stopping/changing an oral rehydration solution that contains Na Cl, stopping a proton pump inhibitor (PPI), giving adequate thiamine and phosphate may be considered in a patient who has a metabolic acidosis with a normal anion gap.
6. D-lactic acidosis may occur in short bowel patients with jejunum in continuity with all or part of the colon.
7. Prolonged acidosis causes bone mineral loss (osteopaenia/osteoporosis) and muscle loss.
8. Metabolic alkalosis may occur after excessive gastric acid loss (e.g. vomiting or aspiration including from a venting gastrostomy), from consuming excessive antacids or a carbonic anhydrase inhibitor diuretic.
9. Acid-base affects serum K levels. Generally, acidosis is associated with hyperkalaemia (except renal tubular acidosis [types 1 and 2]) and alkalosis with hypokalaemia.
10. PS formulations are usually acidic, bespoke compounded infusions that can be adjusted to create a more alkaline formulation (e.g. acetate salts to replace Cl salts).
11. As hydration affects acid base balance, the fluid balance for both inpatients and outpatients should be reviewed to detect under or over hydration.
12. Respiratory acidosis is rare but can be associated with feeding glucose to a patient with CO_2 retention (due to type 2 respiratory failure).

Explanations

1. **Assessment**

Increasingly the serum HCO_3 and Cl are not being measured routinely on venous blood samples; however, we recommend this is performed at least twice weekly on inpatients receiving PS, and as part of the routine blood monitoring for patients receiving home PS at least annually or if the patient develops confusion/falls. In addition, the serum Na, K and albumin should be measured.

The measurement of fluid balance including urine and stoma/fistula/stool output is essential for inpatients and correct replacement may be enough to reverse disturbances in acid-base balance.

Measuring the urinary Na concentration is a good indicator of Na (and associated volume) depletion in patients with IF (in the absence of kidney disease or taking diuretics) with levels of <20 mmol/L indicative of renal conservation of Na. Even a patient with IF receiving PS and having a normal serum Na concentration and a low urine Na concentration represents inadequate replacement of Na and thus also of volume.

PS and/or sepsis can cause stress to glucose homeostasis, so it is important to measure the capillary blood glucose and if significantly raised (>20mmol/L) measure the urine for ketones, to exclude diabetic ketoacidosis.

Over-vigorous use of 0.9% saline and/or gut HCO_3 losses can lead to a hyperchloraemic acidosis. It is important to consider the effect of 0.9% Na Cl containing 154 mmol/L of Na and Cl, higher than the serum Cl levels (95-108 mmol/L). Excessive overuse can lead to hyperchloraemic acidosis.

An arterial blood gas measurement in the acute setting may provide more information (e.g. pH, pCO_2 [and pO_2], base excess/deficit, glucose and lactate) about acid-base balance and compensatory mechanisms. However, it is a painful and skilful procedure. If the patient is not on critical care and without an arterial line, then a venous sample will commonly suffice.

2. **Anion gap**
The anion gap is the sum of the major cations (Na and K) less the sum of the major anions (HCO_3 + Cl); though the calculation may be done without including K as its contribution is small. Most commonly the anion gap is calculated when there is a low serum HCO_3 suggesting acidosis. Albumin is negatively charged (an anion) and its value should be taken into account when interpreting the anion gap. If low it can falsely appear that an anion gap is normal.

3. **Metabolic acidosis with raised anion gap**
A high anion gap is considered to be greater than 17 mmol/l (with K included) and means there are unmeasured anions present (e.g. lactate, ketones or toxins). Lactic acidosis (L isomer) is most commonly found in very sick patients including those with all shock states (septic, cardiogenic, hypovolemic), regional ischaemia (limb, mesenteric), seizures/convulsions and obstruction. Sepsis in IF patients is commonly intra-abdominal or a catheter-related blood stream infection (CRBSI). Hence measuring the temperature, examining the patient, reviewing the white cell count, CRP, albumin (negative inflammatory marker) and a lactate are all good starting points. Hypovolaemia may be present with excess losses in IF patients or occur in conjunction with sepsis. Patients receiving metformin are also at risk of lactic acidosis.

Ketones are important anions and may indicate diabetic keto-acidosis, starvation, re-feeding problems (hypophosphataemia). Drugs in overdose, particularly salicylates (aspirin) and paracetamol, may also cause a metabolic acidosis with a raised anion gap. Patients who develop renal and liver failure are also highly likely to develop varying degrees of metabolic acidosis.

4. **Metabolic acidosis with normal anion gap**
Normal anion gap metabolic acidosis occurs where there is a loss of HCO_3 or an increase in Cl. In IF patients the causes include fistula/stoma losses/diarrhoea, refeeding problems (hypophosphataemia), and excessive intravenous solutions containing Cl (especially 0.9% saline). Urinary diversion to the colon (ureterosigmoidostomies) can also cause this.

The common causes of a normal gap acidosis can be remembered with the American acronym HARD-ASS: hyperalimentation, Addison's disease, renal tubular acidosis, diarrhoea, acetazolamide, spironolactone, or saline infusion.

5. **Oral rehydration solutions**
Rehydration solutions not based on Na Cl (e.g. sodium citrate) should be considered in IF patients at risk of acidosis. Oral rehydration solutions with high Na Cl content can induce hyperchloremic metabolic acidosis. This condition arises because Cl ions displace HCO_3 ions, resulting in decreased HCO_3 levels and subsequent acidosis. PPIs and H_2 antagonists inhibit gastric acid secretion, potentially leading to hypochlorhydria (reduced stomach acid), which can disrupt the body's acid-base homeostasis. Thiamine (vitamin B_1) is critical for carbohydrate metabolism; its deficiency can precipitate lactic acidosis due to impaired pyruvate metabolism, causing an accumulation of lactate. Phosphate is essential for numerous cellular functions, including acid buffering. A deficiency in phosphate can compromise the body's buffering capacity, leading to acidosis.

6. **D-lactic acidosis**
D(-) lactic acidosis only occurs in patients with a short bowel and a preserved colon. Colonic bacteria may degrade a surplus of fermentable carbohydrate to form D(-) lactate which is absorbed but not easily metabolised. This may cause confusion and ataxia. In addition to a metabolic acidosis with a large anion gap, increased concentrations of D(-) lactate are found in blood and urine. Treatment involves restricting mono and oligosaccharides and encouraging the more slowly digestible polysaccharides (starch), thiamine supplements and broad-spectrum antibiotics. In rare cases the patient may need to fast while receiving PS.

7. **Problems of chronic acidosis**
Metabolic acidosis can lead to hyperventilation (attempted respiratory compensation to excrete CO_2). Chronic metabolic acidosis is harmful to bone health, with the development of metabolic bone disease and impairment of renal vitamin D conversion with subsequent vitamin D insufficiency or deficiency.

Metabolic acidosis is also associated with worsened control of hyperglycaemia, thyroid hormone dysfunction, skeletal muscle atrophy, impaired cardiac function, arrhythmias, decreased sensitivity to circulating catecholamines, vasodilatation leading to hypotension, hyperkalaemia, impaired immune function and an increased risk of progressive chronic kidney disease. There is an increased mortality associated with uncorrected acute metabolic acidosis.

8. **Metabolic alkalosis**
A low HCO_3 is associated with acidosis whilst being raised with alkalosis. Metabolic alkalosis, typically represented by a raised pH >7.45 and a raised HCO_3, but with respiratory compensation can be nearer to normal. It is a less common scenario than metabolic acidosis in those with IF but can be seen when much gastric hydrochloric acid is loss due to excessive vomiting (especially if gastric outlet obstruction) or with the treatment of gastric drainage/venting. Excessive losses of K or magnesium through the gastro-intestinal tract can promote metabolic alkalosis and should be reviewed and replaced.

Metabolic alkalosis can predispose to hypokalaemia, hypomagnesaemia and together with increased binding of ionised calcium to albumin, muscle irritability, cramps, tetany and convulsions. In severe cases there can be coma, arrythmias and an increased mortality.

9. **Hyperkalaemia and hypokalaemia**
In acidosis, hydrogen ions accumulate in the extracellular fluid. To maintain electrochemical balance, K ions move from the intracellular to the extracellular space. Acidosis impairs the kidneys' ability to produce ammonia, which is crucial for buffering and excreting hydrogen ions. Hyperkalaemia increases the amount of K filtered by the kidneys. Since K and hydrogen ions share the same transport mechanisms (such as the H/K-ATPase pump), increased K levels reduce hydrogen ion excretion, exacerbating acidosis.

In alkalosis, there is a decrease in hydrogen ions in the extracellular fluid. To maintain balance, K ions move from the extracellular to the intracellular space, leading to hypokalaemia. Conditions such as vomiting, nasogastric (NG) tube losses, excess stomal losses, or diuretic use can cause volume and Cl depletion. This depletion can lead to metabolic alkalosis. In response to alkalosis, the kidneys attempt to retain hydrogen ions, further promoting K excretion and contributing to hypokalaemia.

These mechanisms illustrate the intricate relationship between K levels and acid-base balance in the body.

10. **PS formulation**
The stability of the PS formulation is essential, particularly due to the number of constituent ingredients and the need for a suitable shelf life. To achieve this, the pH is usually maintained between 5-6 and thus is slightly acidic. This pH is a balance, as calcium-phosphate precipitation will occur more readily in alkaline conditions. Lipids, however, are more stable in alkaline conditions. Glucose solutions are acidic and amino acid solutions, which act as buffers are also mildly acidic. While some amino acids (e.g. aspartate and glutamate) are acidic and others (e.g. arginine, histidine and lysine) are basic it is not generally possible to alter their ratios.

In bespoke compounded bags of PN, the ratio of Cl to acetate can be altered to adjust the acid-base balance. When blood HCO_3 levels are low, additional acetate may be administered to correct the imbalance. If the Na HCO_3 concentration is approximately 12 mmol/L (normal range: 22-29 mmol/L), it is recommended to add 100 mmol of acetate (equivalent to 100 mmol of HCO_3). The source of acetate can be either Na acetate or K acetate. Acetate, which is metabolised to HCO_3, on an equimolar basis, by the skeletal muscle and liver cells. It is crucial to ensure that the patient does not have restrictions on Na or K intake before administration.

The patient's medication chart should be reviewed to determine if they are receiving oral or intravenous HCO_3.

11. **Fluid balance**
Once all other causes of disturbances in acid-base balance have been reviewed and a prescription change is deemed appropriate, the primary consideration should be optimising fluid volumes to ensure euvolemia. Dehydration/sodium depletion leads to increased aldosterone levels and hence reabsorption of Na (and water) in the kidneys. In exchange K and magnesium are excreted resulting in alkalosis. Euvolemia can be achieved by adjusting infusion volumes or modifying the number of nights on PS.

Attention should be given to any recent initiation or discontinuation of medications that can alter body fluid losses, such as diuretics, recent changes in PS prescriptions, modifications in oral rehydration solutions, or the commencement of a glucagon like peptide-2 (GLP-2) agonist (e.g. teduglutide). Additionally, during foreign travel to very hot climates or local heatwaves, extra fluids and electrolytes may be required to replace excessive insensible (e.g. sweat) losses.

This approach ensures that fluid and electrolyte balance is maintained, thereby preventing disturbances in acid-base homeostasis.

12. **Respiratory acidosis**
Limiting respiratory causes, however, is important so that this buffering system is available for compensation should there be metabolic acidosis. A respiratory acidosis may occur (e.g. when a type 2 respiratory failure patient is very unwell or ventilated) and it may resolve if the glucose energy is changed to lipid.

Suggested reading

- Allan P, Nightingale J, Javaid K and the BIFA committee (2024). BIFA Guidelines for the prevention and treatment of metabolic bone disease in patients with chronic intestinal failure. Accessible online: **www.bapen.org.uk/pdfs/bifa/guidelines-for-metabolic-bone-disease-in-if.pdf**
- Berne RM, Levy MN. Physiology, 3rd Edition. Mosby Year Book 1993.
- BAPEN (2011). GIFTASUP Guidance. Accessible online: **www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf**
- Forsythe SM, Schmidt GA (2000). Sodium bicarbonate for the treatment of lactic acidosis. Chest.; 117(1): 260.
- Gurukripa Kowlgi N, Chhabra L. (2015). D-Lactic Acidosis: An underrecognized complication of short bowel syndrome. Gastroenterol Res Pract.; 2015: 476215.
- Jones BJM, Acid-base disturbance. In Nightingale J M (ed), Intestinal Failure 2nd Edition, Springer 2023; Vol 1: 377-390.
- Kumar PJ, Clark ML. Clinical Medicine 2nd Edition. Bailliere Tindall 1990.
- Lee Hamm L, Hering-Smith KS, Nakhoul NL. (2013). Acid-base and potassium homeostasis. Semin Nephrol.; 33(3): 257-64.
- Lote CJ. Principles of Renal Physiology 2nd Edition. Croom Helm, 1987.
- Neavyn MJ, et al. (2013). Sodium acetate as a replacement for sodium bicarbonate in medicaltToxicology: a review. J Med Toxicol.; 9: 250–254.