8.4: Hyperchloraemic Metabolic Acidosis

8.4.1: Is this the same as normal anion gap acidosis?

In hyperchloraemic acidosis, the anion-gap is normal (in most cases). The anion that replaces the titrated bicarbonate is chloride and because this is accounted for in the anion gap formula, the anion gap is normal.

There are TWO problems in the definition of this type of metabolic acidosis which can cause confusion. Consider the following:

What is the difference between a "hyperchloraemic acidosis" and a "normal anion gap acidosis"?

These terms are used here as though they were synonymous. This is mostly true, but if hyponatraemia is present the plasma [Cl\(^-\)] may be normal despite the presence of a normal anion gap acidosis. This could be considered a 'relative hyperchloraemia'. However, you should be aware that in some cases of normal anion-gap acidosis, there will not be a hyperchloraemia if there is a significant hyponatraemia.

In a disorder that typically causes a high anion gap disorder there may sometimes be a normal anion gap!

The anion gap may still be within the reference range in lactic acidosis. Now this can be misleading to you when you are trying to diagnose the disorder. Once you note the presence of an anion gap within the reference range in a patient with a metabolic acidosis you naturally tend to concentrate on looking for a renal or GIT cause.
Now how could this happen?

1. **One possibility is the increase in anions may be too low to push the anion gap out of the reference range.**

   In lactic acidosis, the clinical disorder can be severe but the lactate may not be grossly high (eg lactate of 6mmol/l) and the change in the anion gap may still leave it in the reference range. So the causes of high anion gap acidosis should be considered in patients with hyperchloraemic acidosis if the cause of the acidosis is otherwise not apparent. Administration of IV saline solution may replace lost acid anion with chloride so that treatment may result in the acidosis converting to a hyperchloraemic type.

2. **Another possibility is intracellular movement of acid anions in exchange for chloride**

   In lactic acidosis, the movement of lactate intracellularly in exchange for chloride occurs via an antiport. It has been found that when lactic acidosis occurs in association with grand mal seizures then as many as 30% of this group of patients may present with a hyperchloraemic component to their acidosis. This is an interesting situation because the lactic acidosis is due solely to muscular over-production, occurs rapidly & can be severe BUT it also resolves rapidly. This should therefore be a pure lactic acidosis initially without any respiratory compensation or evidence of other acid-base problem. So if we find a hyperchloraemic component this clearly suggests that the lactate is being taken up by some cells in exchange for chloride. This movement of the acid anion intracellularly is one mechanism responsible for a hyperchloraemic component in some types of high anion gap acidosis.

3. **The situation may also be due to the wide normal range of the anion gap.**

   This could result in a situation where the anion gap is only elevated slightly or still within the normal range due to the combination of small errors in the measurement of the component electrolytes.

**8.4.2: Causes of Hyperchloraemic Acidosis**

Some of the causes are listed in the Table in Section 5.2 and some of these are discussed below. Renal tubular acidosis is discussed in the next section.

A review of these causes shows that the predominant mechanism is **loss of base** (bicarbonate or bicarbonate precursors) and this may occur by either GIT or renal mechanisms. A gain of acid can occur with certain infusions but this situation can be diagnosed easily on history.

In general then the diagnosis of a normal anion gap acidosis is just to look for evidence of one of only two mechanisms:

- GIT loss of base
- Renal loss of base

A key question is to distinguish GIT causes from renal causes. In most cases, this will be obvious from the history. In some cases though some factors may be involved or there may be some doubt as to which cause is the most significant.
8.4.3: GIT Bicarbonate Loss

Secretions into the large and small bowel are mostly alkaline with a bicarbonate level higher than that in plasma. Excessive loss of these fluids can result in a normal anion gap metabolic acidosis.

Some typical at risk clinical situations are:

- severe diarrhoea
- villous adenoma
- external drainage of pancreatic or biliary secretions (eg fistulas)
- chronic laxative abuse
- administration of acidifying salts

Severe diarrhoea

This can cause either a metabolic acidosis or a metabolic alkalosis. Development of a significant acid-base disturbance requires a significant increase in stool water loss above its normal value of 100 to 200 mls/day. The more fluid and anions lost, the more marked the problem.

Hyperchloraemic metabolic acidosis tends to be associated with acute infective diarrhoea. This is the classical finding in patients with cholera. The problem is an excessive loss of bicarbonate in the diarrhoeal fluid. Diarrhoeas which are caused by predominantly colonic pathology may cause a metabolic alkalosis: this includes chronic diarrhoeas due to ulcerative colitis, colonic Crohn's disease and chronic laxative abuse.

The acid-base situation with severe diarrhoea can be complicated by other factors (see Table below) and it may not be possible to completely sort out all the factors in the acid-base disturbance in an individual case.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infective diarrhoea (small bowel origin)</td>
<td>Normal anion gap(hyperchloraemic) metabolic acidosis due loss of bicarbonate</td>
</tr>
<tr>
<td>Chronic colonic diarrhoea</td>
<td>May be metabolic alkalosis due predominant loss of Cl^-</td>
</tr>
</tbody>
</table>

Multiple Factors which affect Acid-Base balance in patients with Severe Diarrhoea
<table>
<thead>
<tr>
<th>Hypovolaemia causing prerenal renal failure</th>
<th>High anion gap acidosis due to renal retention of phosphate &amp; sulphate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia causing peripheral circulatory failure</td>
<td>Type A lactic acidosis</td>
</tr>
<tr>
<td>Hypovolaemia causing an increase in plasma protein concentration (increased unmeasured anion)</td>
<td>Increased anion gap</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Metabolic alkalosis due loss of gastric HCl</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Hyperventilation (respiratory alkalosis)</td>
</tr>
</tbody>
</table>

**Villous adenoma**

This can cause hypokalaemia. Acid-base disorders may also occur: this is:

- a hyperchloraemic acidosis if bicarbonate is the principal anion lost, *or:*
- a metabolic alkalosis if chloride is the predominant anion lost.

If hypovolaemia occurs, this may cause a metabolic acidosis. Plasma bicarbonate levels of less than 10 mmol/l have been recorded.

**Drainage of pancreatic or biliary secretions**

Loss of these secretions can cause a hyperchloraemic acidosis due to the high bicarbonate levels in these secretions. The frequency and severity depend on the daily volume of secretions lost. Low output fistulae don't cause a problem. Pharmacological treatments (eg somatostatin) which decrease the volume lost by high output fistulae are effective at preventing the acidosis.

**Losses via a nasogastric tube**

In patients with a small bowel obstruction, these losses can be predominantly of bile and pancreatic secretions and cause an acidosis (rather than an alkalosis as is usual with severe vomiting). Patients on proton pump inhibitors or H2-blockers may also be more likely to lose predominantly alkaline secretions.
8.4.4: Urinary Diversions

Implantation of the ureters into the sigmoid colon or a vesicocolic fistula can result in a hyperchloraemic acidosis due to absorption of Cl⁻ in exchange for HCO₃⁻ across the bowel mucosa. Absorption of urinary NH₄⁺ in the sigmoid colon may also contribute to the development of acidosis as metabolism of the ammonium in the liver results in production of H⁺. Some of these patients develop renal failure related to infection, stones or urinary obstruction. This can result in uraemic acidosis or renal tubular acidosis as well.

Acidosis is much less of a problem with an ileal conduit (acidosis incidence 2 to 20%) than it was with the older procedure of ureterosigmoidostomy (incidence 30-80%). (Incidence data from Cruz, 1997) This is because the continuous external drainage from the ileal conduit usually results in a short dwell time in the conduit with minimal time for Cl⁻-HCO₃⁻ exchange.

The presence of urinary diversion operations will usually be obvious from the history.

8.4.5: Other Causes

Recovery Phase of Diabetic Ketoacidosis

Hyperchloraemic metabolic acidosis commonly develops during therapy of diabetic ketoacidosis. The mechanisms involved have been discussed in Section 8.2. The mechanism is effectively renal loss of base even though it is not bicarbonate which is lost in the urine. The actual loss is of ketoacids (keto-anions) and water. When therapy commences, the ketoacids are metabolised in the liver resulting in the production of equal amounts of bicarbonate. If excessive ketoacids have been lost in the urine and fluid therapy is initially with normal saline, there is a deficiency of bicarbonate precursors and a surfeit of chloride to replace bicarbonate. Correction of the acidosis will now involve renal excretion of chloride and its replacement with bicarbonate. This is a slower process than metabolism of ketoacids to regenerate bicarbonate. The net result then is that full correction of the acidosis is much slower when a hyperchloraemic acidosis develops.

Chronic Administration of Carbonic Anhydrase Inhibitors

Normally 85% of filtered bicarbonate is reabsorbed in the proximal tubule and the remaining 15% is reabsorbed in the rest of the tubule. In patients receiving acetazolamide (or other carbonic anhydrase inhibitors), proximal reabsorption of bicarbonate is decreased and distal delivery is increased. The distal tubule has only a limited capacity to reabsorb bicarbonate and when exceeded bicarbonate appears in the urine. This results in a hyperchloraemic metabolic acidosis. This can be considered as essentially a form of proximal renal tubular acidosis (see section 8.5) but is usually not classified as such.
Oral Ingestion of Acidifying Salts

Oral administration of CaCl$_2$ or NH$_4$Cl is equivalent to giving an acid load. Both of these salts are used in acid loading tests for the diagnosis of renal tubular acidosis. CaCl$_2$ reacts with bicarbonate in the small bowel resulting in the production of insoluble CaCO$_3$ and H$^+$. The hepatic metabolism of NH$_4^+$ to urea results in an equivalent production of H$^+$. 