'Ammonia, lactate and blood gases – A user's guide'

James E Davison

Abstract
Basic biochemical tests are frequently obtained in acutely unwell neonates and children, as well as in some elective situations. Correct interpretation can be invaluable in identifying rare inherited primary metabolic disorders, but secondary causes of hyperammonaemia, elevated blood lactate or blood gas derangement are more common and require appropriate treatment of the underlying cause. This *Personal Practice* guide provides an overview of these tests and their interpretation.

Keywords ammonia; lactate; blood gas; acid-base balance; metabolic disorders

Ammonia

Basic biochemistry
Ammonia is the normal end product of nitrogen-containing protein and amino acid catabolism. It is highly toxic and is rapidly removed by the **urea cycle** in the liver (Figure 1), which converts ammonia to the renally-excreted non-toxic urea. Elevated blood ammonia (hyperammonaemia) results in progressive neurologic dysfunction with lethargy, vomiting, coma and seizures, and leads to cerebral oedema that is fatal if untreated.

When to test
As the clinical features of hyperammonaemia are non-specific, ammonia should be tested in any sick neonate, and in any child with unexplained encephalopathy. It should also be tested if there is unexplained respiratory alkalosis, and also in the known metabolic patient who is unwell.

How to test
Correct sampling is essential. Ammonia must be tested only on free flowing venous samples; capillary samples will generate a spuriously high result as tissue ammonia levels are ten-fold higher than in blood. Samples should be transported rapidly on ice to the laboratory for prompt processing.

How to interpret
Any sick neonate may have ammonia levels up to 150–180umol/L. Levels above 200 umol/L in the neonate are suggestive of a primary metabolic disorder. In older infants and children, a level above 100umol/L is suggestive of a possible metabolic disorder. An elevated level should be confirmed with an urgent repeat sample.

Secondary causes of hyperammonaemia include severe liver failure, persistent patent ductus venosus in the neonate, drug effects (some chemotherapy agents, sodium valproate) and due to increase muscle activity (but usually <180umol/L). Primary metabolic causes of hyperammonaemia include primary disorders of the urea cycle itself, organic acidurias (with secondary urea cycle dysfunction) and long-chain fatty acid oxidation defects.

What to do next
An elevated ammonia is a metabolic emergency and should be discussed with a metabolic specialist centre immediately. Emergency investigations include other basic biochemistry (blood gas, lactate, glucose, ketones) together with liver function tests and coagulation profile. First line metabolic tests include plasma amino acids, urine organic acids and bloodspot acylcarnitine profile.

First steps in treatment are to stop protein intake (discontinue all milk and solid feeds, and any parenteral nutrition), commence intravenous fluids containing 10% glucose (dextrose), and consider need for specific therapy with ammonia scavenger drugs and potentially haemofiltration, as directed by the metabolic specialist centre (See also emergency guidelines at www.bimdg.org.uk).

Lactate

Basic biochemistry
Lactate is the end-product of glycolysis and anaerobic respiration, being reversibly converted from pyruvate by lactate dehydrogenase (Figure 2). Further metabolism of pyruvate through the Krebs cycle and the respiratory chain requires oxygen (aerobic respiration) and results in additional generation of high-energy adenosine triphosphate (ATP). Lactate generated in muscles can be converted in the liver back to glucose by the Cori cycle. Blood lactate levels will be increased during anaerobic respiration for example if there is tissue hypoxia, if there is reduced removal from the blood due to liver dysfunction, or if there is primary or secondary dysfunction of the Krebs cycle or respiratory chain in the mitochondria.

When to test
Lactate is frequently measured by standard blood gas analysers as it is an important biochemical marker in any critically ill patient. Lactate should be measured in any sick neonate or child specifically if they have a metabolic acidosis. Lactate may also be measured in the stable child as part of investigation of neurodevelopmental or neuromuscular disorders, or when there is a suspected metabolic disorder including those affecting glucose metabolism.

How to test
Lactate can be measured on venous or free-flowing capillary samples. A "difficult" sample from a struggling child will often cause a spurious elevated lactate result. Alanine, measured as part of the plasma amino acid profile, reflects the lactate level and is not affected by sampling issues and can be helpful in interpretation. Pre- and post-prandial lactate levels (together with ketones and glucose) can be helpful in differentiating primary causes.

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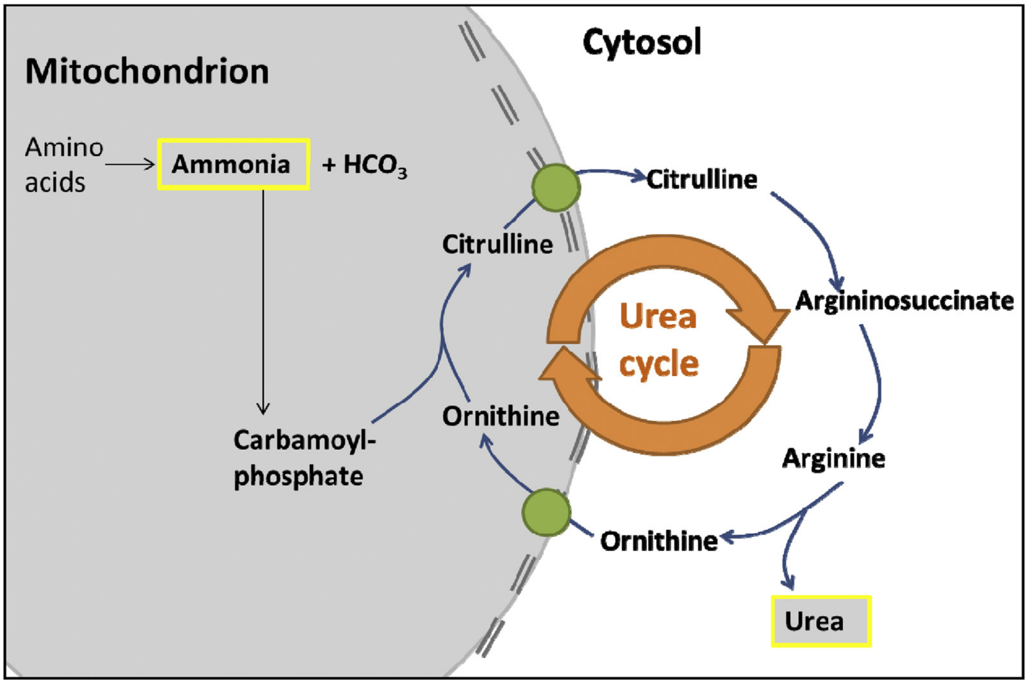

Figure 1 The urea cycle converts ammonia through a series of chemical conversions to urea.

How to interpret

Secondary causes of lactic acidaemia should be sought, in particular any severe systemic disease including hypoxia or ischaemia, shock and cardiac failure, sepsis or surgical pathology. In the neonate with elevated lactate, the perinatal history should be reviewed for evidence of hypoxia-ischaemia, as lactic acidaemia from hypoxia during delivery can persist for 48 hours or more post-partum. Other important causes of lactic acidosis in the neonate include sepsis, necrotising enterocolitis and duct-dependent cardiac disease. An elevated lactate in a systemically

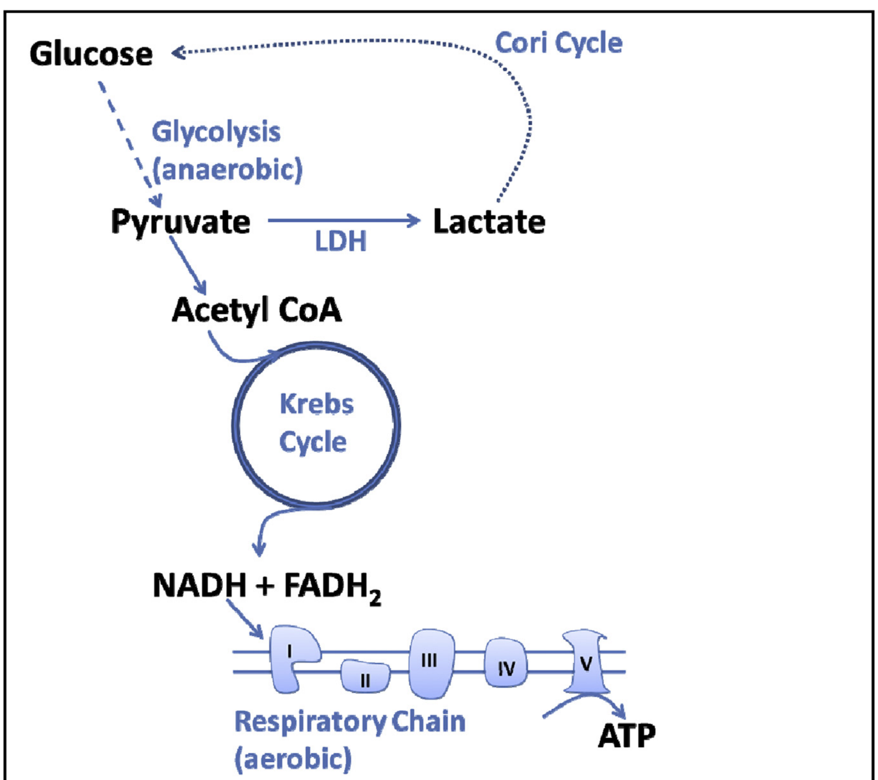

Figure 2 Overview of anaerobic and aerobic respiration pathways. (LDH – lactate dehydrogenase; NADH - Nicotinamide adenine dinucleotide (reduced); $FADH_2$ - Flavin adenine dinucleotide (reduced). I-V indicate the five complexes of the respiratory chain. ATP – adenosine triphosphate.

well child from an easily obtained sample needs further investigation for possible primary metabolic causes.

What to do next

Secondary causes of lactic acidaemia should be sought and treated accordingly. Further investigation for primary metabolic causes including mitochondrial disorders, long-chain fatty acid oxidation defects, organic acidurias, biotinidase deficiency, glycogen storage diseases and disorders of gluconeogenesis should be considered, with guidance from a specialist metabolic team. Initial investigations will include blood gas analysis, urine or blood ketones, plasma amino acids, bloodspot acylcarnitine profile, biotinidase activity and urine organic acids. Treatment of a primary lactic acidaemia should be discussed with a metabolic specialist team, and may include empiric trial of biotin (for biotinidase deficiency) and thiamine (pyruvate dehydrogenase deficiency). Dichloroacetate is sometimes indicated if there is a persistent severe acidosis caused by the hyperlacticacidaemia.

Blood gas

Basic biochemistry

Blood gas analysis provides a bedside assessment of general acid-base balance. Homeostatic mechanisms maintain tight control of cellular and blood pH to provide a stable environment for biochemical processes. Deranged acid-base balance will lead to biochemical dysfunction. The blood gas analysis measures blood acid-base (pH), together with carbon dioxide, oxygen and bicarbonate levels. An acid (e.g. lactic acid) consists of the base (lactate) associated with hydrogen ions (H^+). The pH (hydrogen ion concentration) of the blood depends on the degree of dissociation of the hydrogen ions from the base.

The "base excess" is a derived value that provides a measure of the normal acid-base buffering systems; a very positive base excess suggests there is additional base (bicarbonate) in the blood, whereas a very negative base excess suggests a deficiency of base (bicarbonate).

When to test

A blood gas analysis should be obtained in any critically ill neonate or child, including where there is respiratory distress, or suspected metabolic disorder, poisoning, or renal disorder.

How to test

Blood gas can be measured from arterial, venous or free-flowing capillary samples, but must be interpreted according to source of the sample. In particular the pO_2 will only be reliable from an arterial sample, and pCO_2 will be relatively higher in capillary and venous samples. A sample obtained from a struggling child or a "difficult" sample may give artefactual results.

Parameter	pH	pCO_2	pO_2	HCO_3	BE	Lactate
	Acidity / alkalinity	Carbon dioxide	Oxygen	Bicarb-onate	Base excess	Lactate
Units		kPa	kPa	mmol/L	mmol/L	mmol/L
Normal range	7.35-7.45	4.5-6.0	12-14	22-28	-2 - +2	<2.0
Metabolic Acidosis…	7.20	5.5	13	18	-10	8.7
…Respiratory compensation	7.35	2.1	13	17	-10	8.7

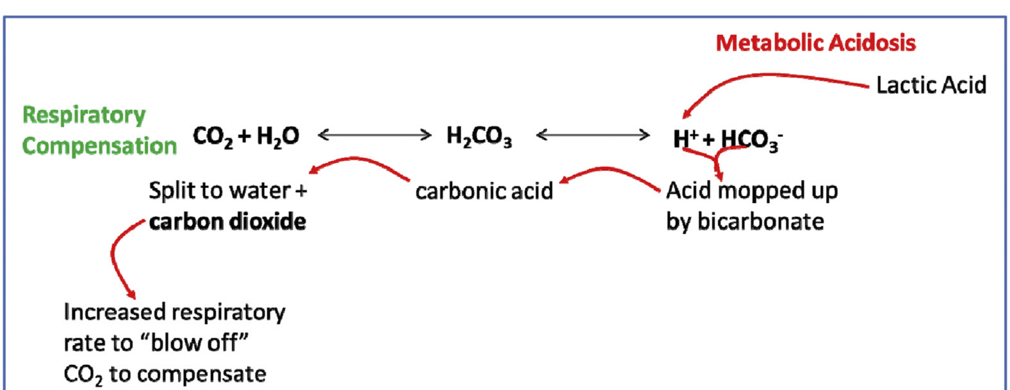

Figure 3 Blood Gas analysis. Normal values, and example of metabolic acidosis due to lactic acidaemia with subsequent respiratory compensation.

How to interpret (Figure 3)

First look at the pH: a decreased pH indicates an acidosis, an elevated pH indicates alkalosis. The pCO_2 and bicarbonate (and base excess) then determine whether there is an underlying metabolic or respiratory cause.

Acidosis: increased pCO_2 indicates a respiratory acidosis (and an elevated bicarbonate suggests metabolic compensation).

A low bicarbonate and negative base excess indicates a metabolic acidosis (and a low pCO_2 indicates respiratory compensation, and may clinically appear as tachypnoea/Kussmaul breathing).

Alkalosis: a low pCO_2 indicates respiratory alkalosis, which may be due to hyperventilation (e.g. in a struggling child), but can be due to elevated ammonia which is a respiratory stimulant.

An elevated bicarbonate and increased base excess suggests a metabolic alkalosis; a hypochloremic metabolic alkalosis in an infant with recurrent vomiting suggests possible pyloric stenosis.

Metabolic Acidosis: a metabolic acidosis can be secondary in any acutely unwell child and results should be interpreted in the clinical context.

The "anion gap" is routinely measured by some blood gas analysers, but may require separate calculation including measurement of chloride. The anion gap ($[Na^+ + K^+] - [\text{Bicarbonate} + \text{Chloride}^-]$, normally <18mmol/L) can help in interpretation of a metabolic acidosis. A "normal anion gap metabolic acidosis" indicates that the acidosis is caused by a primary loss of bicarbonate (e.g. in a renal tubular acidosis or gastrointestinal losses of bicarbonate), whereas a "raised anion gap metabolic acidosis" indicates that the acidosis is caused by an accumulation of an excess acid (e.g. an organic acid in an organic aciduria).

What to do next

Clinical management should be instigated to address the underlying cause of the abnormal blood gas result, for example respiratory support for respiratory acidosis, and addressing systemic illness.

Persistent metabolic acidosis not responding to initial fluid resuscitation and supportive measures may require treatment with bicarbonate half correction. A raised anion gap metabolic acidosis suggestive of a metabolic disorder should prompt further investigation to identify the causative acid. General biochemistry (renal and liver function, glucose, lactate, ammonia blood and urine ketones) should be analysed. Specific first- line metabolic tests (plasma amino acids, urine organic acids, bloodspot carnitine profile) should be sent. Further management should be discussed with a specialist metabolic unit. ◆

FURTHER READING

Grunewald S, Davison J, Matinelli D, Duran M, Dionisi-Vici C. Emergency diagnostic procedures and emergency treatment. In Physician's guide to the diagnosis, treatment and follow-up of inherited metabolic diseases. Blau N et al Eds.

Saudubray Jean-Marie. In: Baumgartner Matthias R, ed. John Walter Inborn metabolic diseases: diagnosis and treatment. 6th ed, 2016.

British Inherited Metabolic Disease Group, Emergency Guidelines available at: www.bimdg.org.uk.

Practice Points

- Ammonia, lactate and blood gas analysis should be measured in any sick neonate or child.
- Deranged results can be secondary to systemic illness or other factors, but can indicate a primary metabolic disorder.
- Specific investigations for secondary and primary metabolic causes will be required; a basic metabolic panel will include bedside ketones, urine organic acids, plasma amino acids and bloodspot acylcarnitine profile.
- Management of a suspected primary metabolic disorder should be discussed urgently with a specialist metabolic centre.