Type A Lactic Acidosis: Clinical Evidence of Inadequate Tissue Oxygen Delivery
(Anaerobic muscular activity (eg sprinting, generalised convulsions))
(ii) Tissue hypoperfusion (eg shock - septic, cardiogenic or hypovolaemic; hypotension; cardiac arrest; acute heart failure; regional hypoperfusion esp mesenteric ischaemia)
(ii) Reduced tissue oxygen delivery or utilisation (eg hypoxaemia, CO poisoning, severe anaemia)
- If hypoxaemia is the only factor present, it needs to be severe (eg paO2 <35mmHg) to precipitate lactic acidosis because of the protection afforded by the body’s compensatory mechanisms which increase tissue blood flow. Similarly anaemia needs to be severe (eg Hb <5g/dl) if present alone because tissue blood flow is increased in compensation.

Type B Lactic Acidosis: No Clinical Evidence of Inadequate Tissue Oxygen Delivery
- refers to situations in which there is no clinical evidence of reduction in tissue oxygen delivery. Carbohydrate metabolism is disordered for some reason and excess lactic acid is formed. Research using more sophisticated methods to assess tissue perfusion have now shown that occult tissue hypoperfusion is present in many cases of Type B acidosis.
  (i) type B1: Associated with underlying diseases
    - LUKF leukaemia, lymphoma
    - TIPS thiamine deficiency, infection, pancreatitis, short bowel syndrome
  (ii) type B2: Assoc with drugs & toxins (eg phenformin, cyanide, beta-agonists, methanol, adrenaline, salicylates, nitroprusside infusion, ethanol intoxication in chronic alcoholics, anti-protore drugs, paracetamol, salbutamol, biguanides, fructose, sorbitol, xylitol, isoniazid)
  (iii) type B3: Assoc with inborn errors of metabolism (eg congenital forms of lactic acidosis with various enzyme defects eg pyruvate dehydrogenase deficiency)

- The condition is often suspected on the history and examination (eg shock, heart failure) and is easily confirmed and quantified by measuring the blood lactate level.
- It may be associated with other causes of a high anion gap acidosis (eg ketoacidosis, uraemic acidosis).
- Concurrent lactic acidosis and metabolic alkalosis may result in minimally altered plasma bicarbonate level. A high anion gap may be a clue in this later situation but the anion gap is not invariably elevated out of the reference range.

- The principles of management of patients with lactic acidosis are:
  (i) Diagnose and correct the underlying condition (if possible)
  (ii) Restore adequate tissue oxygen delivery (esp restore adequate perfusion)
  (iii) Ensure appropriate compensatory hyperventilation where possible

Use of bicarbonate:
- two randomised controlled studies of bicarbonate in lactic acidosis and shock found no beneficial effects on cardiac function or any other effects of pH correction
- potential adverse effects include:
  (i) acute hypercapnia
  (ii) ionised hypocalcaemia
  (iii) intracellular acidosis due to CO2 crossing cell membranes rapidly
  (iv) acute intravascular overload
  (v) bicarbonate increases lactate production by increasing the activity of the rate limiting enzyme phosphofructokinase, shifts Hb-O2 dissociation curve, increased oxygen affinity of haemoglobin and thereby decreases oxygen delivery to tissues
- potential indications:
  (i) patients with pulmonary hypertension in whom pulmonary vasconstriction may be worsened by acidosis
  (ii) patients with significant ischaemic heart disease in whom severe acidosis lowers the threshold for arrhythmia

Carbicarb:
- Carbicarb is an equimolar combination of sodium bicarbonate & sodium carbonate which generates less CO2 than HCO3 & may have less adverse effects. It is not in clinical usage

Dichloroacetate: DCA stimulates the activity of phosphat dehydrogenase complex, the rate limiting enzyme that regulates entry of pyruvate into the TCA cycle. It increases intracellular pH and decreases lactate concentrations; however, a large multicentred study found no haemodynamic benefit or improvement in patient outcome in treatment of patients with lactic acidosis
- it is not commercially available

Tris / THAM:
- Tris-hydroxymethyl aminomethane is a weak alkaline which is rarely used because of concerns about side effects. Namely,
  (i) hyperkalaemia
  (ii) hypoglycaemia
  (iii) extravasation necrosis
  (iv) neonatal hepatic necrosis

Diagnosis & significance:
- Definitions differ concerning the blood level at which a lactic acidosis is regarded as significant but as a guide:
  Hyperlactaemia: a level from 2 mmol/l to 5 mmol/l
  Severe Lactic Acidosis: when levels are greater than 5 mmol/l
- As levels rise above 5mmol/l, the associated mortality rate can become very high.
- The brief and often very high lactate levels that occur with severe exercise or generalised convulsions (eg up to 30 mmol/l) are associated with an extremely low mortality rate so the absolute lactate level (alone) is not a good predictor of outcome unless the cause of the high level is also considered.

Pathophysiology of Lactic Acidosis:
- Lactic acidosis can occur due to:
  (i) excessive tissue lactate production
  (ii) impaired hepatic metabolism of lactate
- In most clinical cases it is probable that both processes are contributing to the development of the acidosis. The liver has a large capacity to metabolise lactate so increased peripheral production alone is unlikely to lead to other than transient acidosis.
- In situations where lactic acidosis is clearly due to excessive production alone (such as severe exercise or convulsions), the acidosis usually resolves (due to hepatic metabolism) within about an hour once the precipitating disorder is no longer present. In severe exercise, lactate levels can rise to very high levels up to 30 mmol/l.
- A continuing lactic acidosis means that there is continuing production of lactate that exceeds the liver’s capacity to metabolise it. This may be due to clearly very excessive production (eg convulsions) with a normal liver at all extremes, or to increased production in associated with greatly impaired hepatic capacity to metabolise it (eg due to cirrhosis, sepsis, hypoperfusion due hypovolaemia or hypotension, hypothermia, or some combinations of adverse factors) at the other extreme.
- Lactic acidosis in sepsis has been attributed to:
  (i) impaired regional microvascular blood flow & autoregulation
  (ii) mitochondrial dysfunction with impaired pyruvate oxidation
  (iii) excess catecholamines may impair hepatic lactate extraction
  (iv) lactate clearance is decreased because pyruvate dehydrogenase activity is reduced in both skeletal muscle and liver.

Management:
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NB:
- Tissue hypoxia may not be a major mechanism & NMR spectroscopy suggests that hyperlactaemia may occur without tissue hypoxia
- net lactate production from the hepatosplanchnic bed is uncommon in sepsis

Tissues Producing Excess Lactate
- At rest, the tissues which normally produce excess lactate are:
  (i) skin - 25% of production
  (ii) red cells - 20%
  (iii) brain - 20%
  (iv) muscle - 25%
  (v) gut - 10%
- During heavy exercise, the skeletal muscles contribute most of the much increased circulating lactate.
- During pregnancy, the placenta is an important producer of lactate which passes into both the maternal and the foetal circulations.

Lactate metabolism:
- Lactate is metabolised predominantly in the liver (60%) and kidney (30%).
- Half is converted to glucose (gluconeogenesis) and half is further metabolised to CO2 and water in the citric acid cycle. The result is no net production of H+ (or of the lactate anion) for excretion from the body.
- Other tissues can use lactate as a substrate and oxidise it to CO2 and water but it is only the liver and kidney that have the enzymes that can convert lactate to glucose.
- The balance between release into the bloodstream and hematopoietic uptake maintains plasma lactate at about one mmol/l.
- The renal threshold for lactate is about 5 to 6 mmol/l so at normal plasma levels, no lactate is excreted into the urine. The small amount of lactate that is filtered (180mmol/day) is fully reabsorbed.

Causes of Lactic Acidosis
- (Cohen & Woods classification)

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