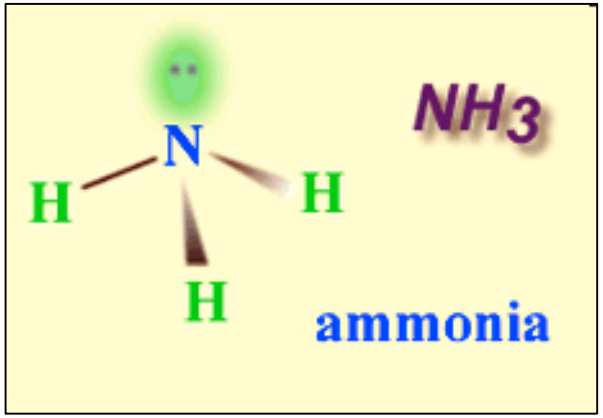
A Case of Neonatal Hyperammonaemia

Presentation

- Male, born full term.
- Presented to A&E at 9 days old, was:
  - jaundiced
  - hypotonic
  - sleepy
- Lost 9% of birth weight
- Significant biochemistry:



Ammonia: 299 µmol/L (normal for term neonate <100 µmol/L)

Ammonia:

- Formed in the liver, muscle, kidneys, gut (bacteria) mainly due to the deamination of amino acids.
- Mainly as NH_4^+ at physiological pH. Removed by the urea cycle.
- Neurotoxic at 5-10 x normal concentrations.
- Presentation of hyperammonaemia varies: behavioural changes, developmental delay, poor feeding, vomiting, hypoglycaemia, convulsions, coma.

First Line Biochemistry Results

Ammonia: hyperammonaemia confirmed

U&E: Normal except for a slightly raised urea

LFT: ALT 22 U/L (0-45)

GGT 104 U/L (0-55)

ALP 303 U/L (100-400)

Total bilirubin 250 umol/L (0-22)

Conjugated bilirubin <1 umol/L (0-4)

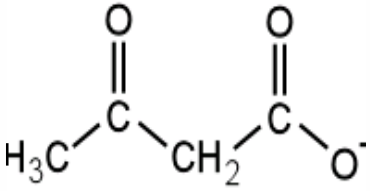
Acid base: Slight metabolic acidosis (later results showed a slight respiratory alkalosis)

Lactate: 1.46 mmol/L (0.5-2)

Glucose: 5.7 mmol/L (3-6)

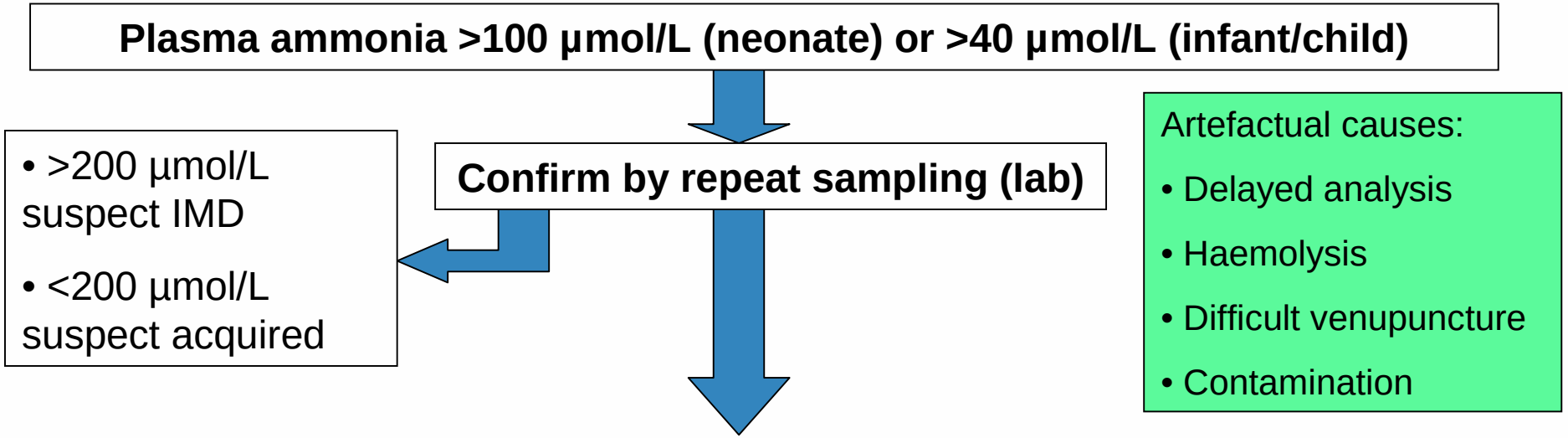
CRP: <5 ug/L(0-12)

Urine ketones: Positive



acetoacetate

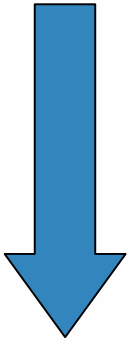
Diagnostic Algorithm for Hyperammonaemia (MetBioNet Guidelines)



First line biochemical investigations

- **Blood gases**: NH_3 is a respiratory stimulant which may cause respiratory alkalosis. Metabolic acidosis may suggest an organic acid or fatty acid oxidation disorder
- **U&E**: Urea may be inappropriately low in UC disorders.
- **LFT & clotting**: Severely deranged in some acquired causes, mildly deranged in urea cycle or organic acid disorders.
- **Glucose**: hypoglycaemia in e.g. fatty acid oxidation defects, hyperinsulinaemia, liver failure
- **Lactate**: raised in a number of IEMs & liver failure.
- **Calcium**: hypocalcaemia in some organic acid disorders.
- **Urine ketones**: often increased in organic acid disorders, sometimes absent in liver failure & fatty acid oxidation defects..

Diagnostic Algorithm for Hyperammonaemia (MetBioNet Guidelines)



Specialist Metabolic Investigations:

- Urine & plasma amino acids: HPLC
- Urine organic acids: GC-MS
- Urine orotic acid: GC-MS
- Blood spot/plasma acylcarnitines: LC-MS/MS

But treatment often has to be started before the diagnosis is made!

Treatment

• Enteral feed was discontinued immediately (**stopping protein intake** to reduce catabolism and the production of ammonia and any other metabolites)

• Started on **IV glucose** with:

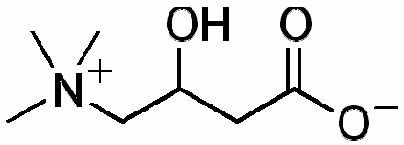
• **sodium benzoate** (benzoate combines with glycine to form hippuric acid which is cleared by the kidneys) This pushes the conversion of ammonia into glycine and hence ultimately leads to its excretion

Benzoate + Glycine

Hippuric acid

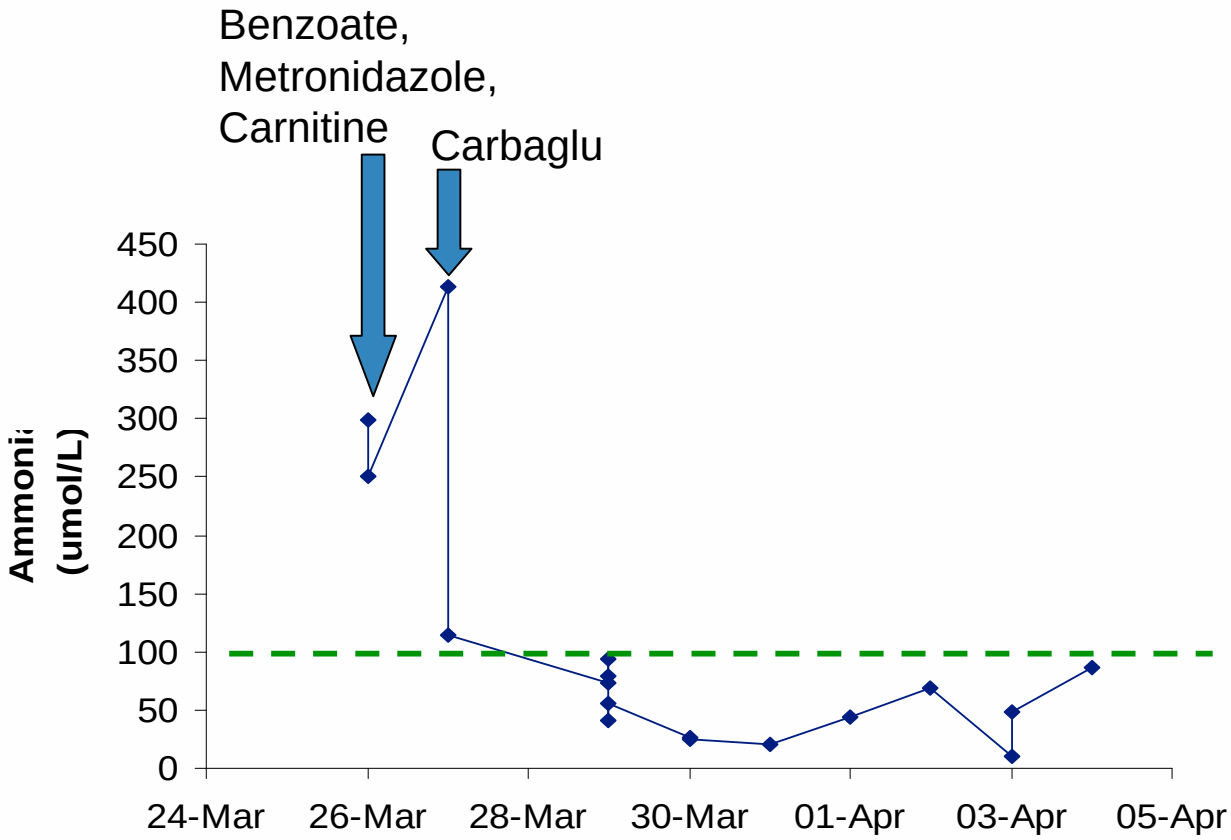
• **metronidazole** (antibiotic: reduces the numbers of bacteria in the gut that produce ammonia)

• **carnitine** (replenishes carnitine and conjugates with some accumulating organic acid metabolites)



Treatment

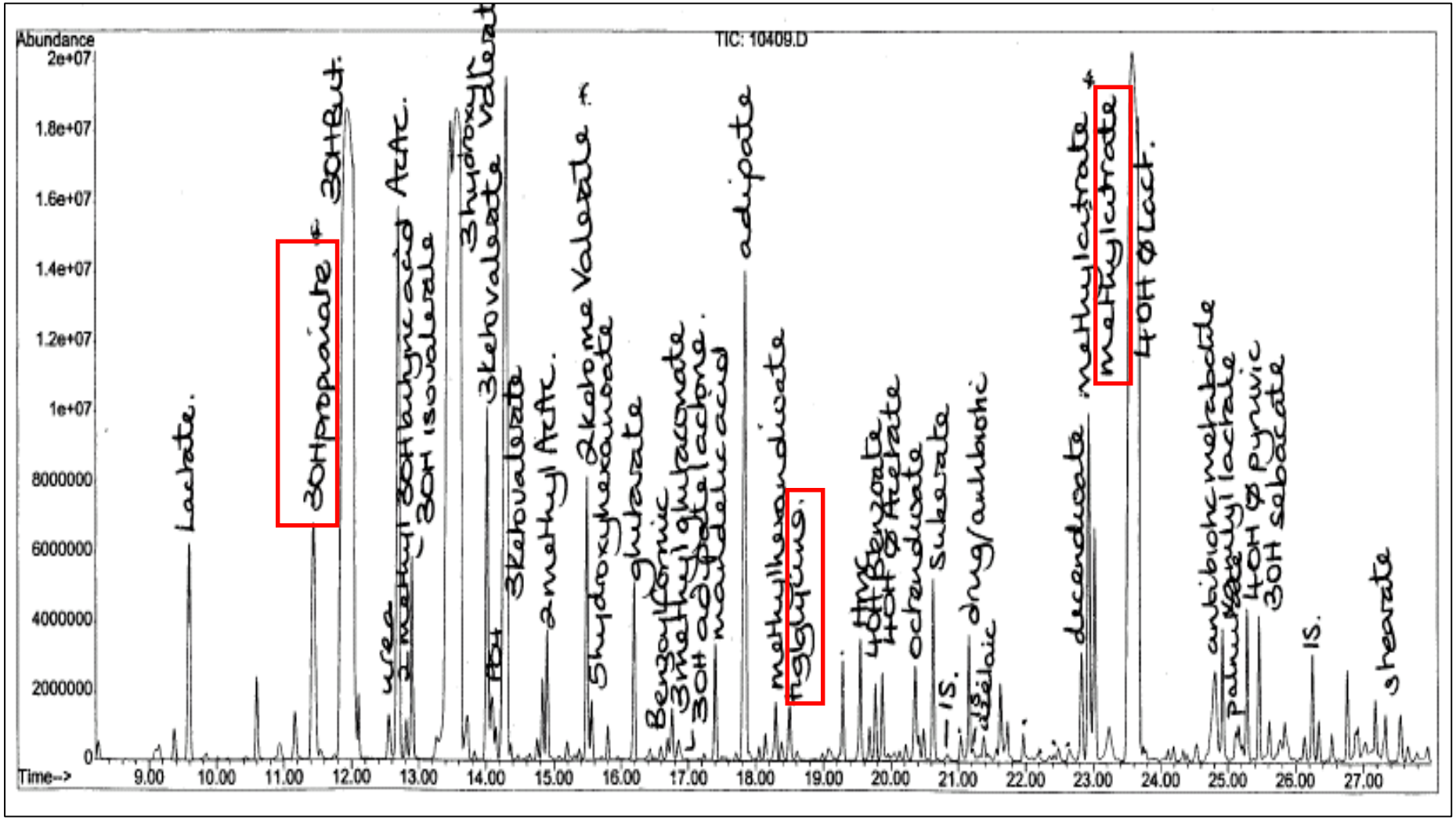
- Ammonia levels continued to rise and peaked at **487 µmol/L**, started:
  - **carbaglu** (analogue of N-acetylglutamate, activates carbamoyl phosphate synthase I (1st enzyme in urea cycle) hence increasing ammonia conversion to urea.



Secondary metabolic screen results:

Urine Organic Acids:

Increased excretion of 3OH propionate, tiglylglycine, methylcitrate, 3-OH valerate, ketotic metabolites and lactate



Characteristic of PROPIONIC ACIDAEMIA

Secondary metabolic screen results:

Plasma amino acids:

Increased glycine consistent with propionic acidaemia and elevated lysine secondary to hyperammonaemia.

Urine amino acids:

Increased lysine secondary to hyperammonaemia and slightly increased cystine, ornithine, arginine probably reflecting the acute episode or renal immaturity.

Blood spot acylcarnitines:

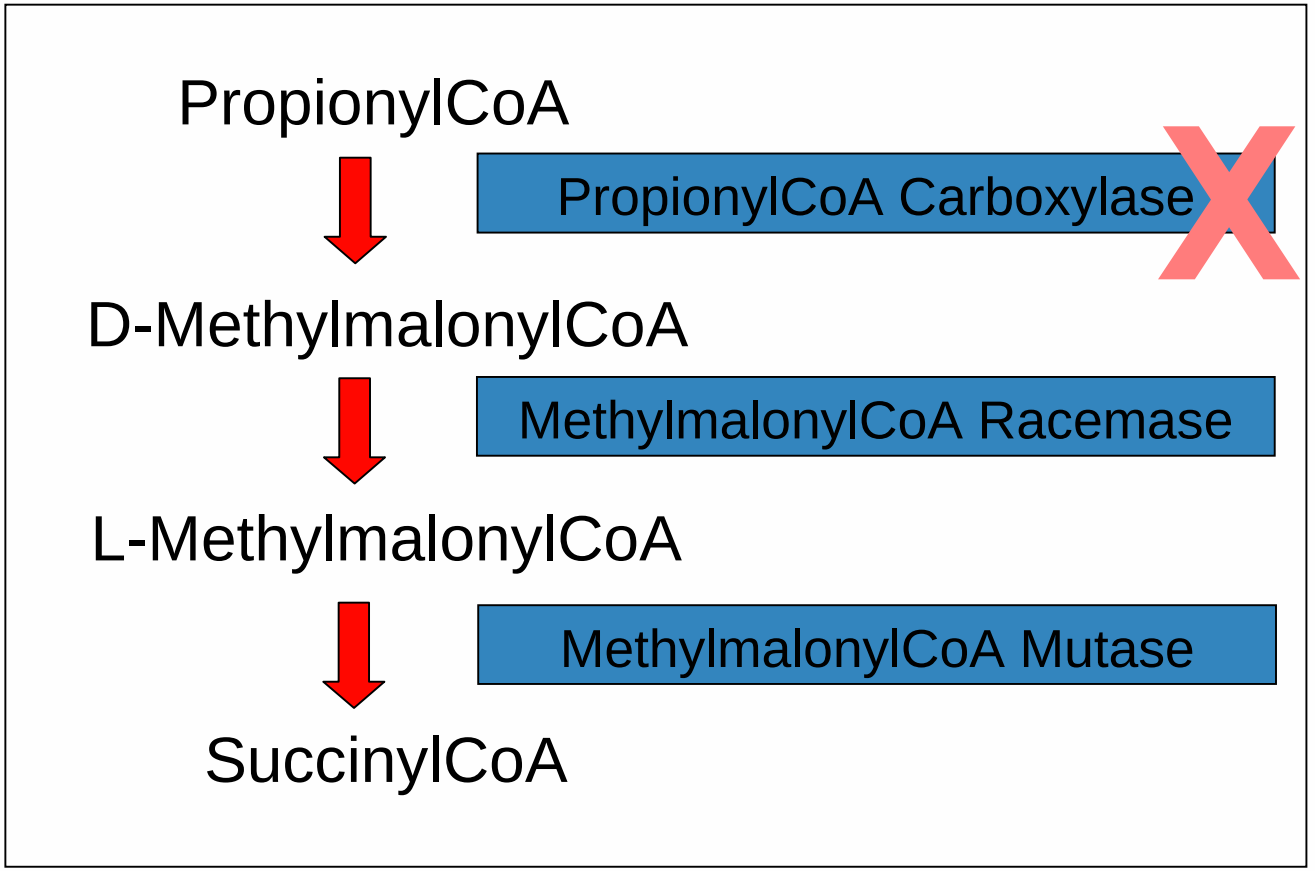
C3 propionyl carnitine: 14 µmol/L (Normal <3.6)
C3/C16 ratio: 14 (Normal <2.64)
C16 carnitine: 0.99 (Normal <5.3)

Elevated propionyl carnitine in absolute terms and relative to palmitoyl (C16) carnitine.

Propionic Acidaemia

Inborn error of metabolism due to a defect in propionyl CoA carboxylase; involved in the metabolism of valine, isoleucine, leucine, methionine, odd chain fatty acids and cholesterol.

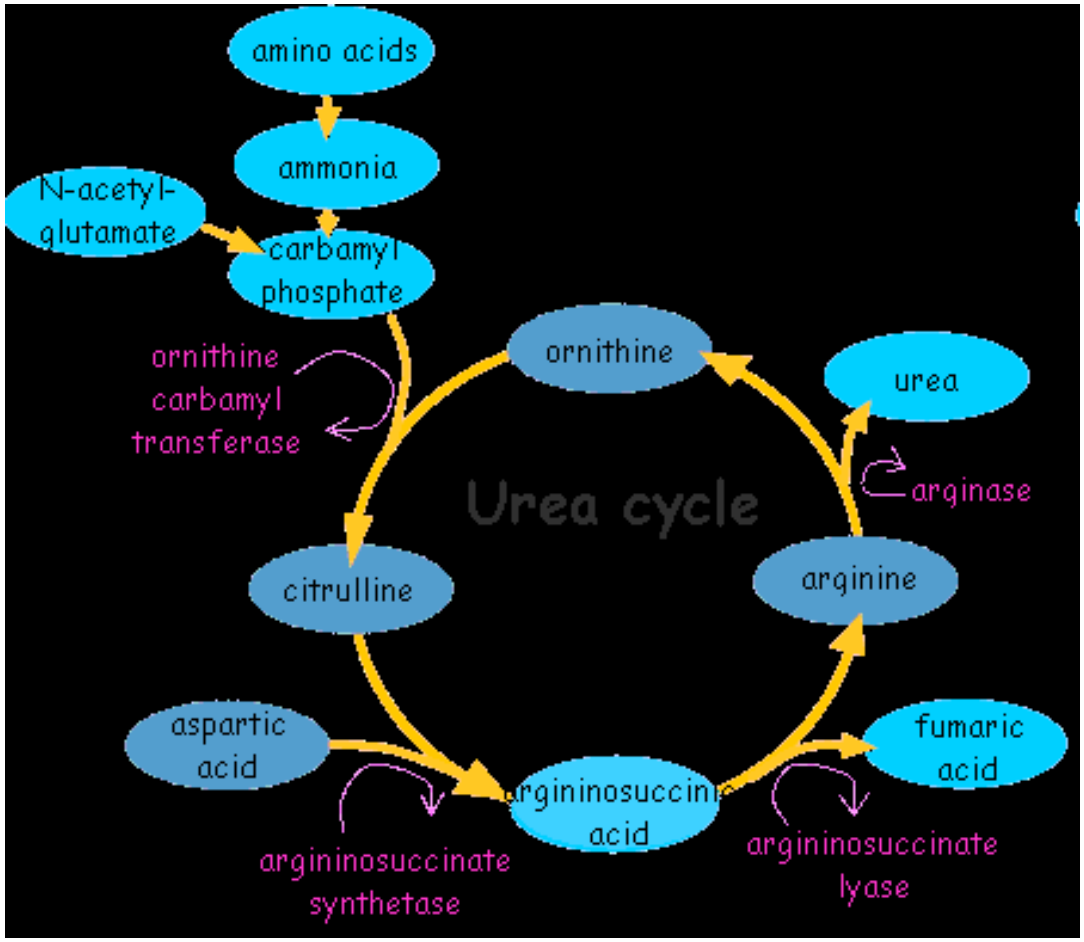
Incidence estimated at <1:100000, autosomal recessive (Two genes)



Propionic Acidaemia

• The cause of the hyperammonaemia is believed to be inhibition of ***N*** -acetylglutamate synthase (NAGS) by free propionic acid.

• ***N*** -acetylglutamate (NAG) is the allosteric activator of carbamoyl phosphate synthase.



• PropionylCoA probably also inhibits Krebs (TCA) cycle function resulting in high lactate.

Propionic Acidaemia

- Long term treatment is centred around a diet restricted in isoleucine, valine, threonine and methionine but with adequate calorific intake, vitamins & minerals.
- Carnitine and metronidazole are also routinely given.
- However despite treatment mental retardation, motor disorder, osteoporosis, pancreatitis and cardiomyopathy may develop.
- Liver transplant may be an option.

Current Condition

- Developing well but has had multiple admissions (~10) with hyperammonaemia.
- 1 month after diagnosis was admitted to PICU with NH_3 of 545 umol/L and required haemofiltration.
- Recently had a procedure to fit a permanent cannula for easy access.