Hyperammonaemia

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Metbionet guidelines

- causes of hyperammonaemia
  - pre-analytical factors
  - acquired hyperammonaemia
  - urea cycle defects
  - organic acidurias and other IMD

Interpretation

Plasma Ammonia (µmol/L)	Interpretation
<100	• No clinical significance in the acutely unwell neonate • May be significant in the context of later presentations and other metabolic disorders in the infant/ child
100-300	Mild symptomatic hyperammonaemia develops at concentrations above 100 - lethargy, confusion, vomiting • Could reflect increase secondary to other metabolic disorders • Commonly observed in acquired hyperammonaemia
300- 500	Significant encephalopathic features develop at concentrations above 300 - increased likelihood of urea cycle defect
500-2000	Severe hyperammonaemia associated with coma and convulsions Neonatal onset urea cycle disorders/organic acid disorders likely

Ammonia 500-2000μmol/l

- normalisation of ammonia within 24-48h compatible with good neurological outcome
- diagnosis usually achievable within few hours

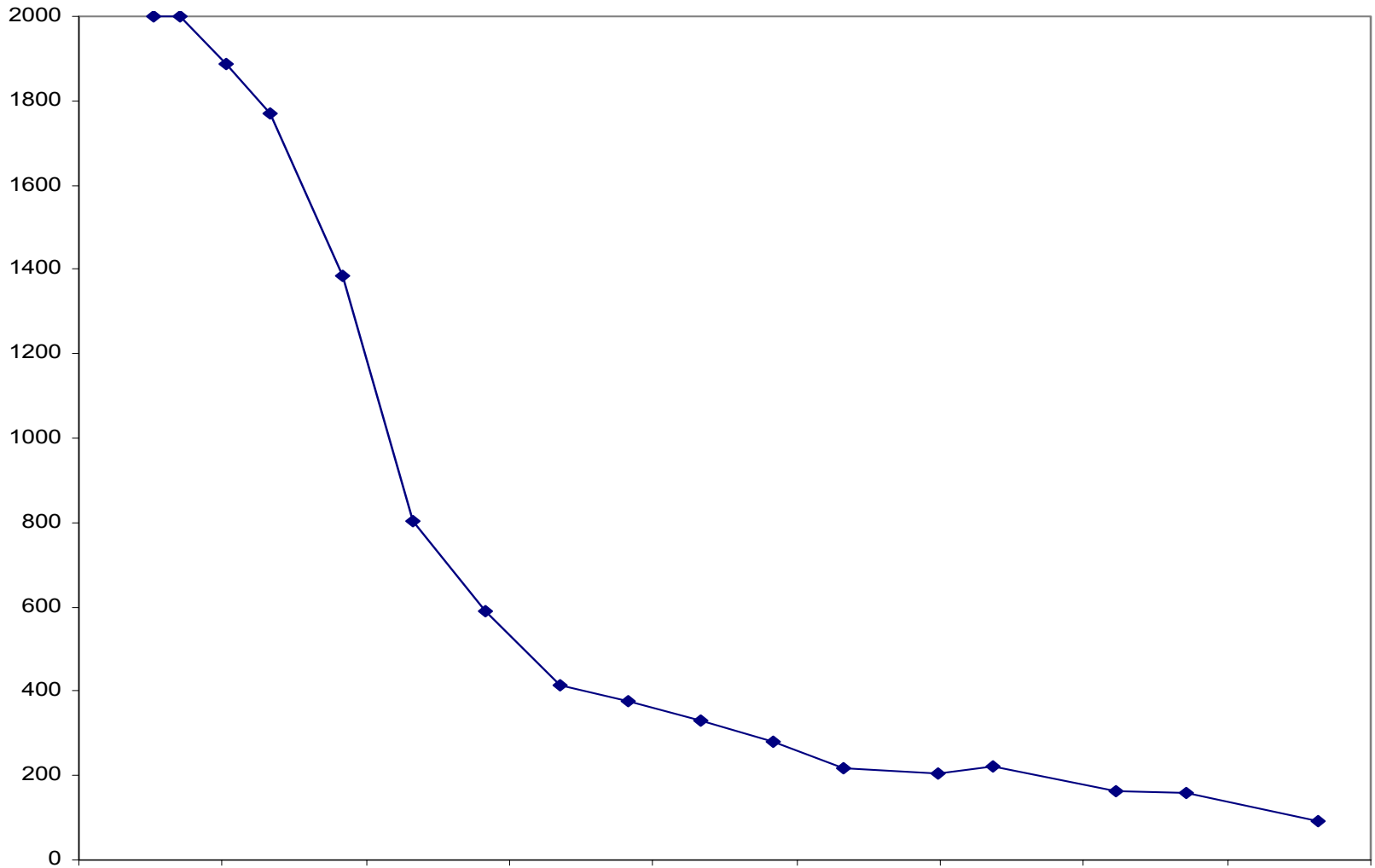
Investigation of hyperammonaemia

- first line investigations
  - urea
  - blood gases
  - liver function tests
  - electrolytes, calcium
  - glucose, lactate
  - urine ketones
- specialist investigations
  - plasma and urine amino acids
  - organic acids +/- orotic acid
  - acyl carnitines

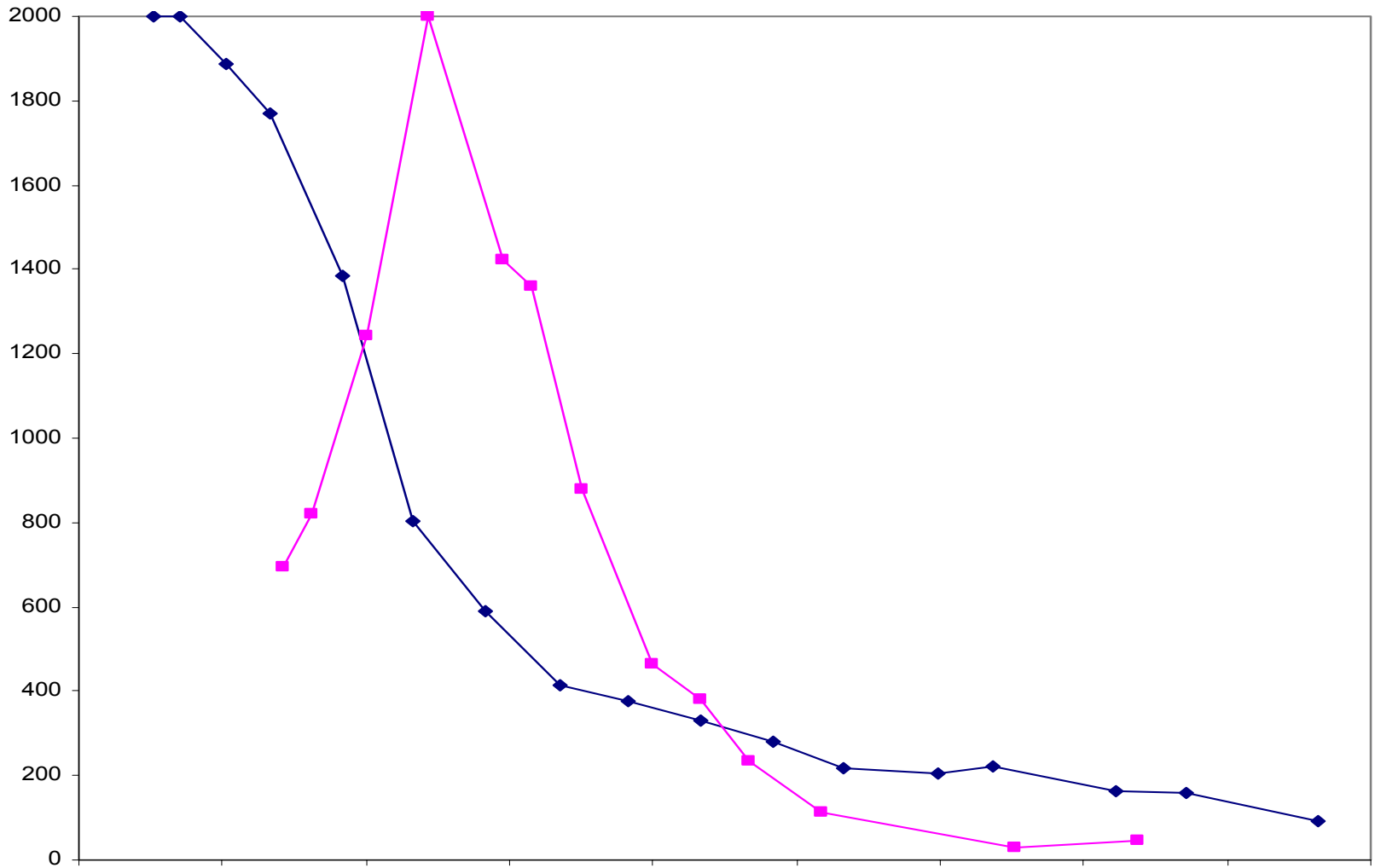
Treatment of hyperammonaemia

- stop protein
- arginine
- benzoate
- phenylbutyrate
- CVVH (continuous veno-veno haemofiltration) if NH_3 >350μM

CVVH and plasma ammonia (μM)



CVVH and plasma ammonia (μM)



Ammonia 100-300 μmol/l

- 4 cases
  - hyperinsulinaemia hyperammonaemia syndrome
  - N-acetylglutamate synthetase
  - 1 year old girl
  - 34 year old lady

Hyperinsulinism/hyperammonaemia syndrome

- 17m boy
  - 3rd afebrile seizure
  - 2 previous seizures
    - 3 months previously
    - 1 week previous
      - glucose 2.7 mmol/l
- PMH nil of note

Investigations

- Na, K, LFTs, acid base NAD
- NH_3 152 μmol/l
- Endocrine (glucose 2.7mmol/l)
  - cortisol 85 nmol/l
  - GH 7 mU/l
  - insulin 13 pmol/l
  - C-peptide 109 pmol/l

Further endocrine investigations

- Synacthen test

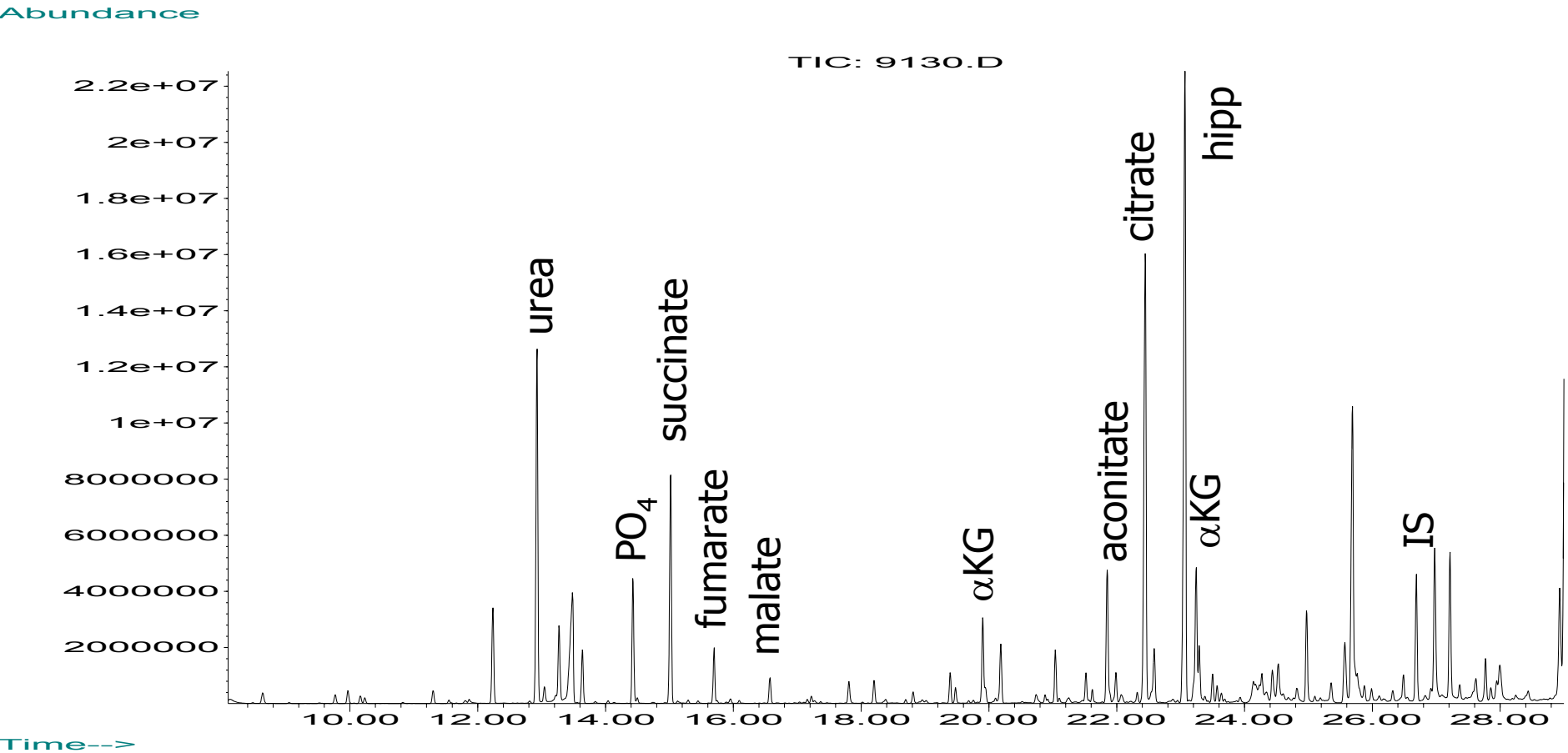
	cortisol
0 mins	320 nmol/l
30 mins	580 nmol/l
60 mins	623 nmol/l

- VLCFA — normal

- CT pancreas — normal

Metabolic investigations

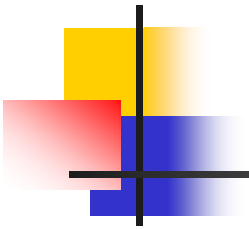
- urine amino acids — NAD
- urine organic acids — TCA intermediates
- acyl carnitines — NAD
- plasma quantitative amino acids
  - alanine — 147 μmol/l
  - valine — 135 μmol/l
  - isoleucine — 42 μmol/l
  - leucine — 74 μmol/l
- FFA — 838 μmol/l
- 3OH butyrate — 301 μmol/l


Abundance
TIC: 9130.D
2.2e+07
2e+07
1.8e+07
1.6e+07
1.4e+07
1.2e+07
1e+07
8000000
6000000
4000000
2000000
urea
PO4
succinate
fumarate
malate
αKG
aconitate
citrate
αKG
hipp
IS
10.00
12.00
14.00
16.00
18.00
20.00
22.00
24.00
26.00
28.00
Time-->

Progress

- asymptomatic pre-prandial hypoglycaemia

glucose mM	NH3 μM	insulin pM	C-peptide pM
2.8	152	13	109
1.8	152		
2.8	98		
2.6		28	192
1.7		241	1073
	67		



- probable hyperinsulinism/hyperammonaemia syndrome
- Rx
  - Diazoxide
  - Chlorthiazide
  - Hypostop
  - UCCS
  - protein restricted diet

Glutamate dehydrogenase (GLUD 1 gene)

- allosterically activated by leucine
  - glutamate $\rightarrow$ α-ketoglutarate + NH3
  - expressed in pancreas and liver
- heterozygous for missense gain-of-function mutation
  - ~70% of cases are *de novo* mutations
  - parents may have mild symptoms, previously overlooked
- persistent hyperammonaemia (3-5X ULN)

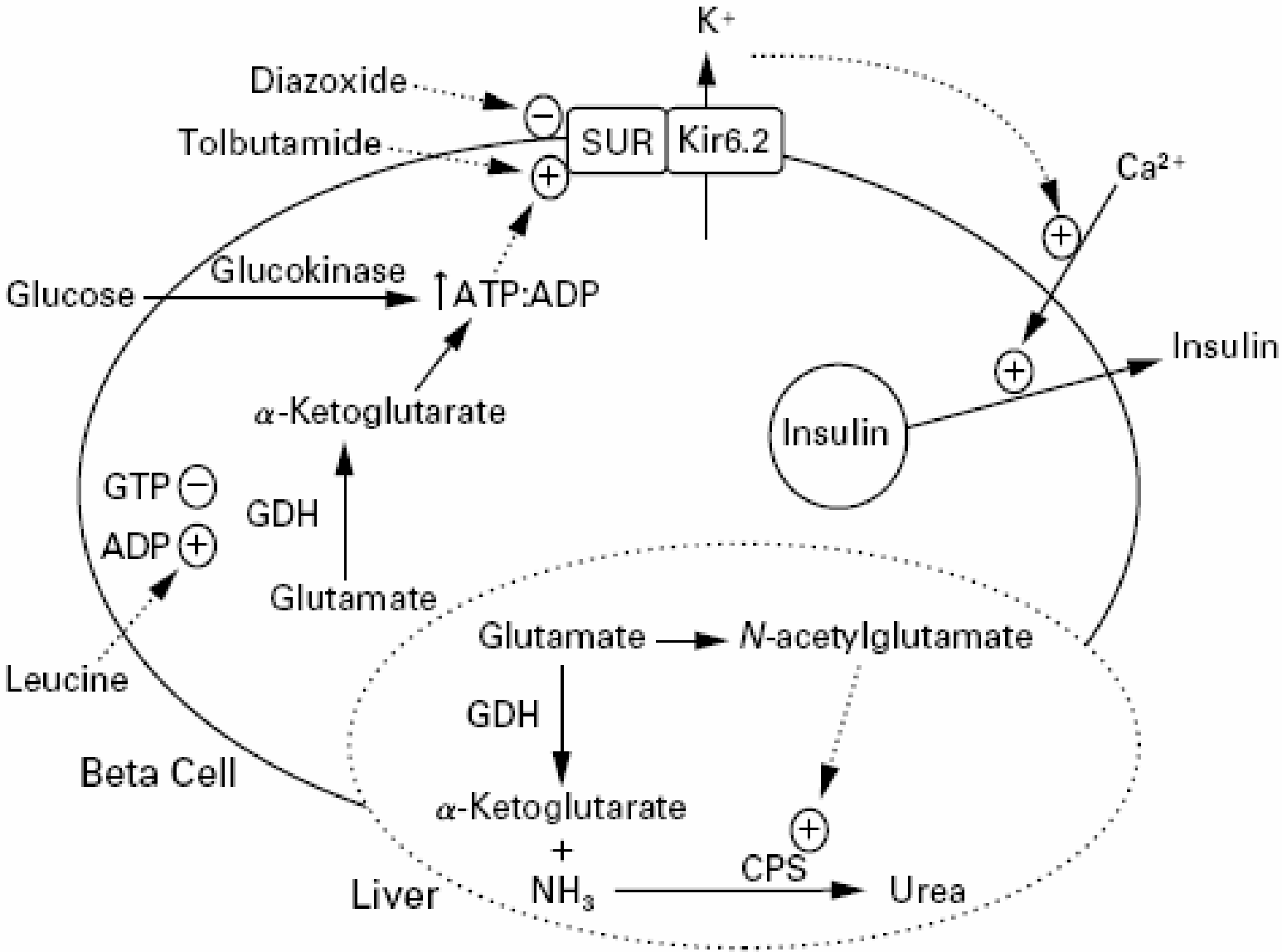


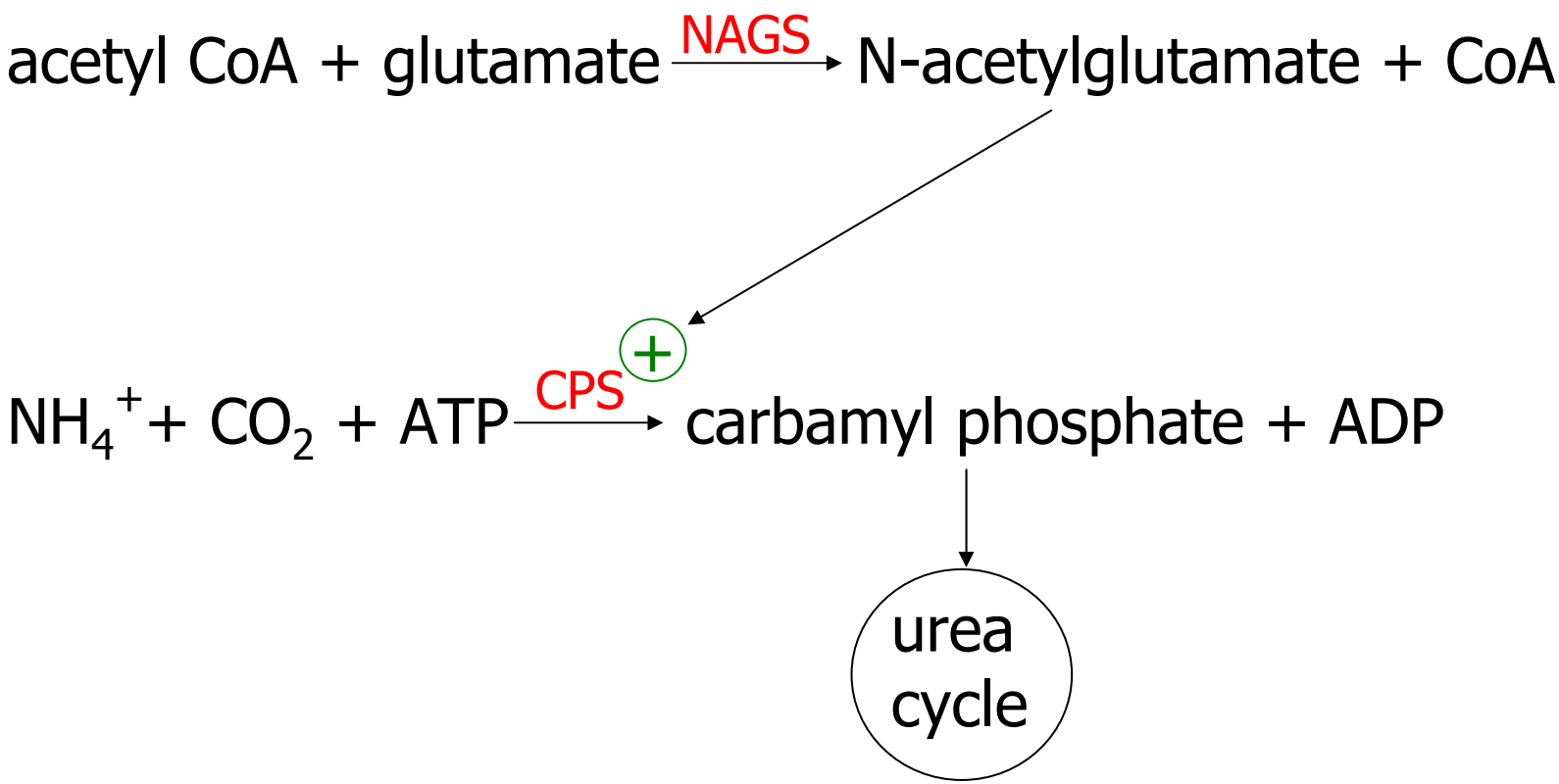
Figure 1. Glutamate Dehydrogenase (GDH) and the Regulation of Insulin Secretion and Hepatic Ureagenesis.

N Engl J Med 1998;338:1352-7

NAGS deficiency

- first reported 1981 – Bachmann et al
  - neonatal hyperammonaemia
  - responded to benzoate, carbamylglutamate, arginine
- subsequently
  - neonates and children described
- diagnosis
  - hyperammonaemia without orotic aciduria
  - large liver biopsy required
  - DNA now available

N-acetylglutamate synthetase



NAGS deficiency case

- 11y boy (1 of 7 children)
- h/o episodes of acute confusion
  - abdominal pain
  - headache
  - no response to paracetamol
  - dislikes protein since a young child
  - behind at school

Investigations

- ammonia 187 μmol/l
- urine organic acids
- urine orotic acid
- plasma and blood spot acyl carnitines
- plasma amino acids (previously normal)
  - glutamine 935 μmol/l
  - alanine 596 μmol/l
  - citrulline 25 μmol/l

Progress

- readmitted
  - commenced arginine and benzoate
- on discharge
  - ammonia 41 μmol/l
  - coherent
  - engaged in conversation
- in outpatients
  - dad begging for same treatment for 2 sibs

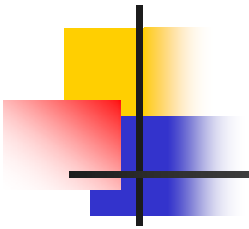
DNA for NAGS gene

- Johannes Haeberle, Muenster
  - homozygous mutation
  - ?pathogenic

Family studies

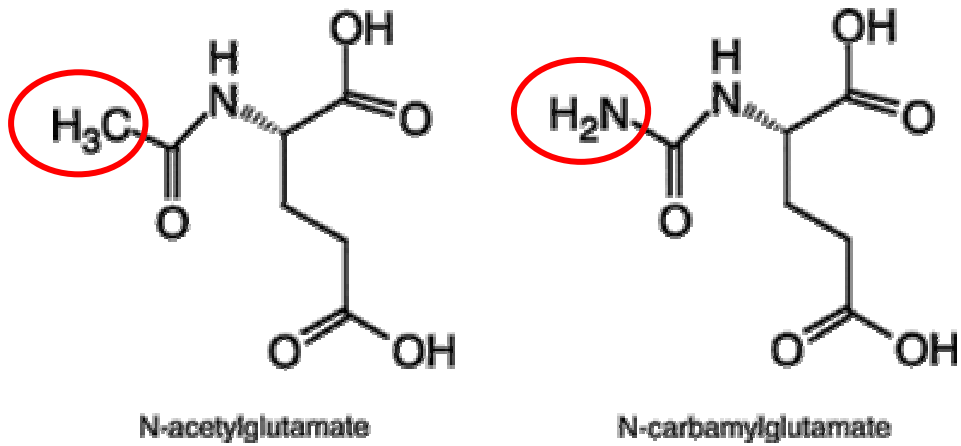
- 2 girls had protein aversion
- 3 sibs no symptoms
- 1 infant

- DNA analysed blind to clinical status
- 2 girls and infant also affected
- slight hyperammonaemia in 2 girls



- Somalian family
- 4 children affected with mild NAGS deficiency
- treated with benzoate and arginine
- carbaglu not necessary

Carbamylglutamate



carbamylglutamate test

200mg/kg and measure NH_3 2hourly for 6 hours

http://www.biochemj.org/bj/372/0279/bj3720279f06.gif

1 year old girl

- FTND
  - developing and growing normally
  - pulls to standing
  - fully immunised
  - no illnesses
- day 1 of illness (age 10m)
  - not herself, decreased feeding, drowsy
  - CT scan normal, CSF normal
  - EEG ? encephalitis
  - R_x acyclovir, cefotaxime
  - home day 10

- day 14
  - 24h h/o vomiting and increasing lethargy, signs of viral infection
  - LFTs abnormal
    - Alt 1377 IU/L
    - INR 4.3
    - ammonia 157 μmol/l
  - stop acyclovir, iv vitamin K
  - home day 24
- day 27
  - URTI and pyrexia, drowsiness
    - Alt 2895 IU/l
    - INR 2.4
    - R_x - acyclovir, amoxycillin, metronidazole, cefuroxime, vitamin K, parvolex, fluid restriction
  - transfer to liver unit day 28

Progress at BCH

- gradual improvement in LFTs
- due to be discharged

BUT

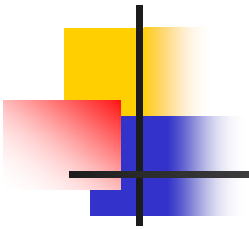
- further episode floppy and lethargic with vomiting

	ammonia uM		
01/04/2006 15:00	245	grizzly, vomited, GCS 12/15	
01/04/2006 19:50	125	no protein	
02/04/2006 10:00	79	no protein	
02/04/2006 16:00		recommenced half strength feeds	
02/04/2006 22:30	77		
03/04/2006 09:50	28	reintroduce full strength feeds	
04/04/2006 10:15	274	stop protein	commenced Rx
04/04/2006 15:30	64		
05/04/2006 02:30	40	1 g/kg/day protein	
05/04/2006 19:15	57	1.3 g/kg/day protein	
06/04/2006 09:50	34	1.5 g/kg/day protein	
07/04/2006 09:40	21		

IMD investigations

- glutamine 1281 μmol/l
- alanine 682 μmol/l
- proline 348 μmol/l
- citrulline 25 μmol/l

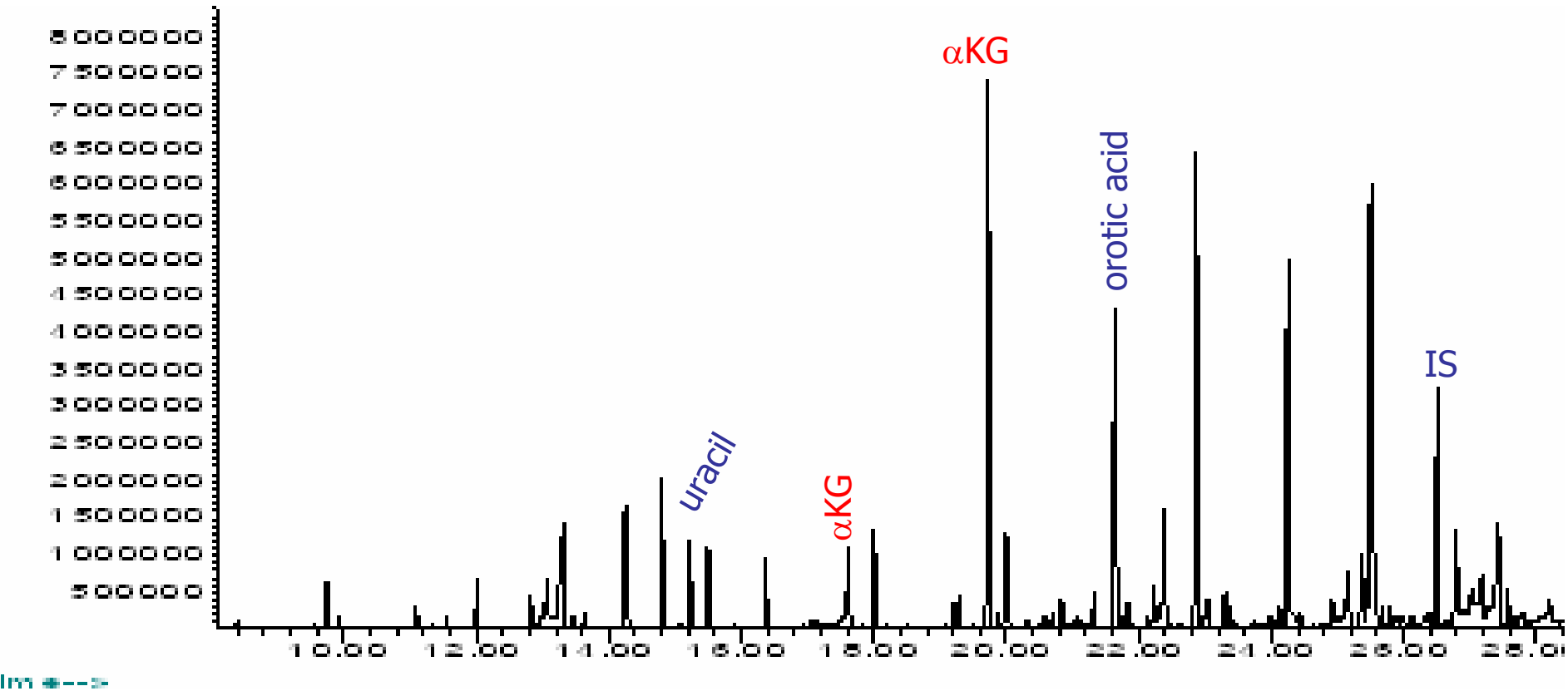
- lysine 613 μmol/l
- methionine 143 μmol/l



- acyl carnitines normal
- organic acids
  - increased orotic acid
- DNA
  - truncating mutation in OTC gene

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

OTC – organic acids

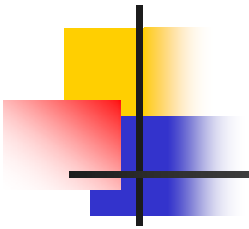


OTC case – discussion points

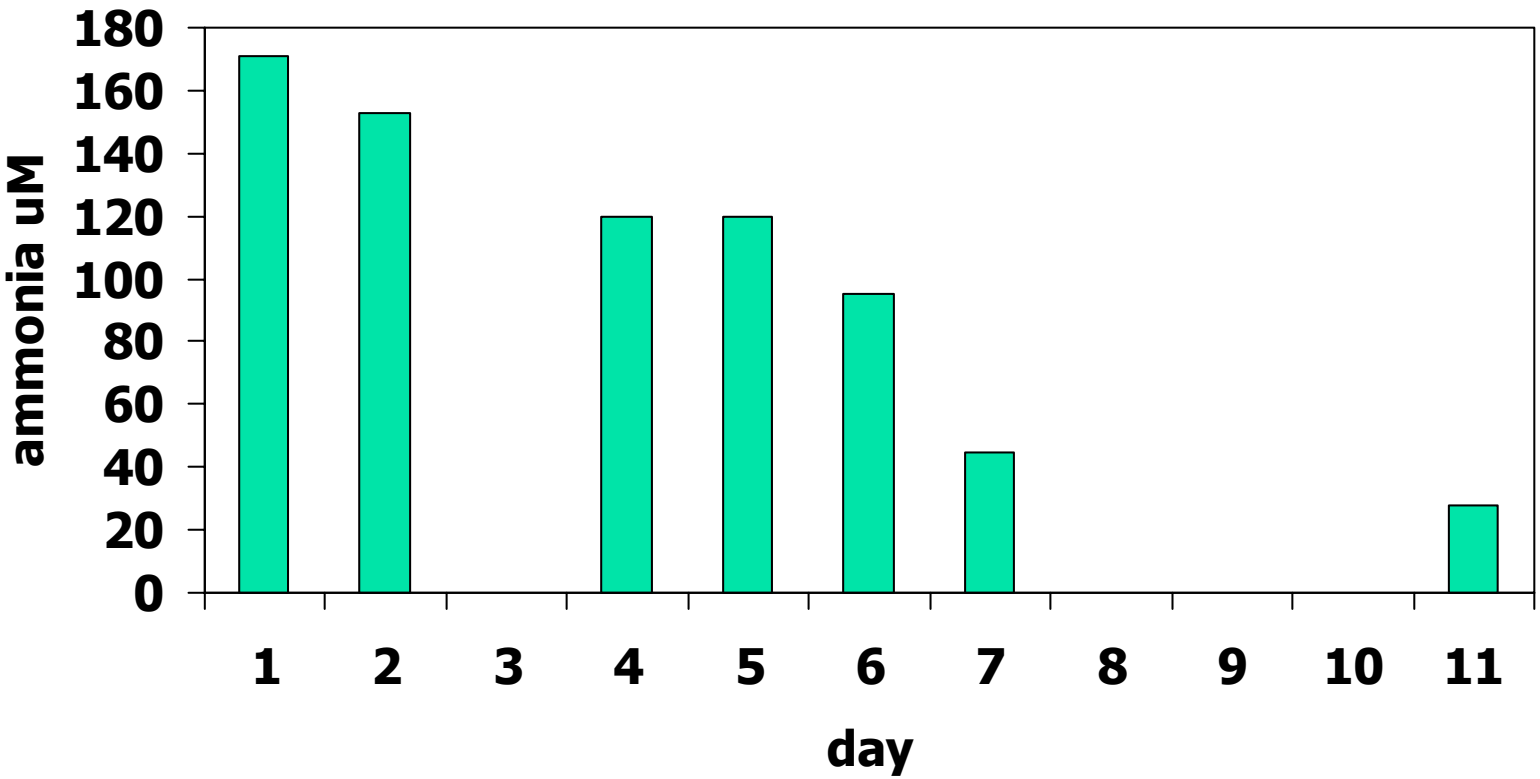
- significance of 2-oxoglutarate
- variability of ammonia concentrations
- plasma ammonia in liver dysfunction

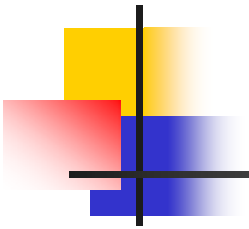
34 year old lady

- infertile
- IVF – miscarried
- ovarian hyperstimulation syndrome
  - ascites
  - intra-abdominal sepsis
  - 3X laparotomy for wash-outs
  - worsening LFTs and coagulopathy
  - reduced conscious level
  - acute renal failure
  - ITU

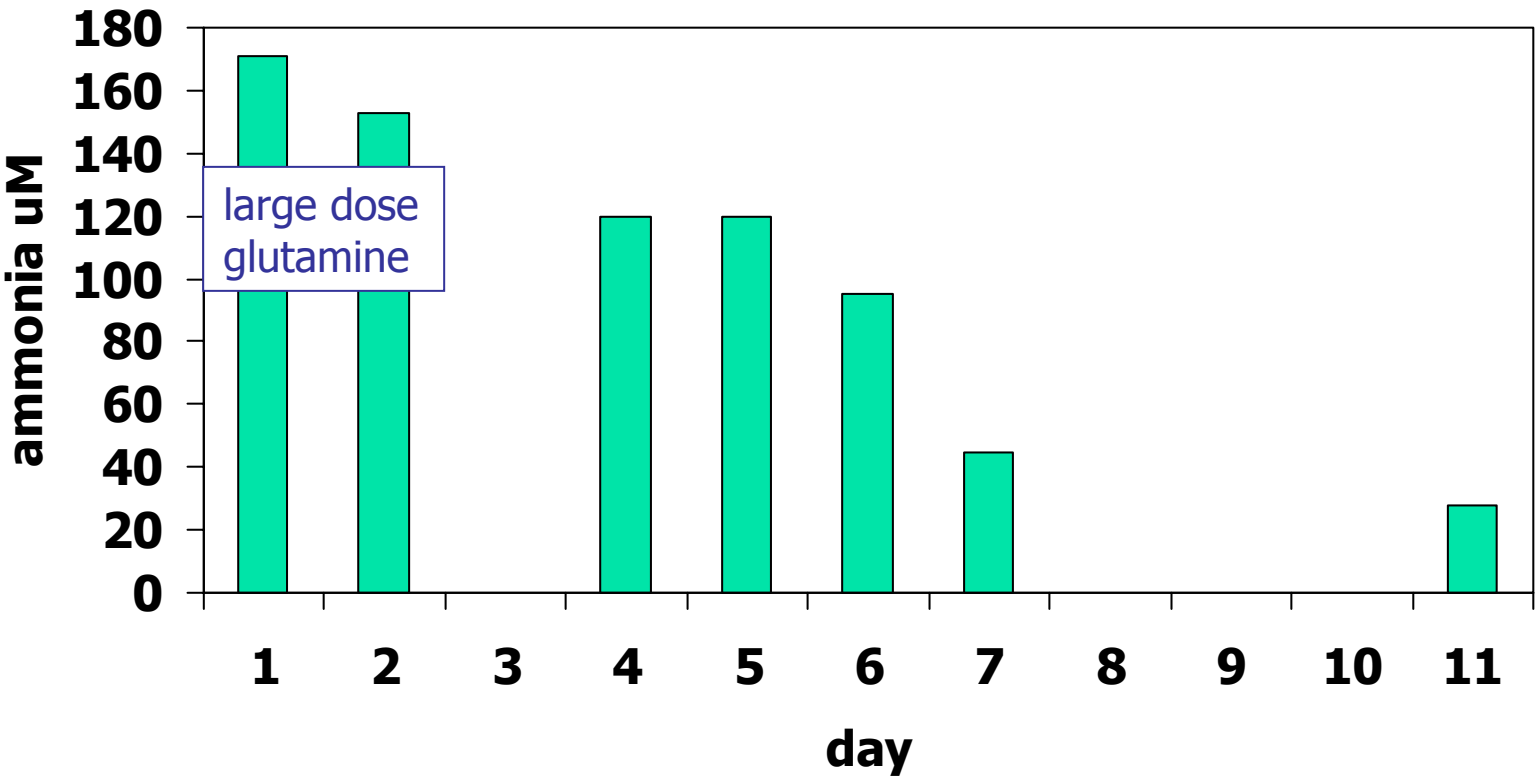


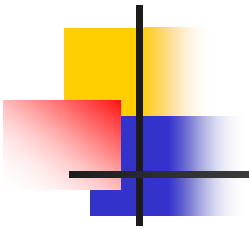
- prior to 3rd laparotomy
  - NH_3 171 μmol/l
  - 'coma was striking'
- post-op
  - NH_3 153 μmol/l
- treated with benzoate and arginine


ammonia uM
180
160
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
day



- Does she have a urea cycle defect?


ammonia uM
180
160
140
120
100
80
60
40
20
0
large dose
glutamine
1
2
3
4
5
6
7
8
9
10
11
day



- Does she have a urea cycle defect?

Pocketchem BA

- 20 μl whole blood
- 3 min 20 sec
- range 7-286 μmol/l
- Hi and Lo warning displays

- detachable printer

Conclusion

- ammonia >500 μmol/l
  - diagnosis usually straightforward
  - prompt recognition and treatment
- ammonia 100-300 μmol/l
  - pay attention to detail
    - relation to symptoms
    - relation to feeding
    - response to treatment
- ammonia still an under-requested test

The Management of a Child (aged 0 – 18 years) with a Decreased Conscious Level

An evidence-based guideline for health professionals based in the hospital setting

Review date January 2008

Nationally developed by
The Paediatric Accident and Emergency Research Group

Appraised by

Royal College of Paediatrics and Child Health

British Association for Emergency Medicine

Algorithm for the management of a child aged 0-18 years with a decreased conscious level

Patient entry criteria (see page 2)

GCS<15
V, P or U on AVPU scale

Assessment

AIRWAY
↓
BREATHING
↓
CIRCULATION
↓
DISABILITY

Give oxygen

Consider intubation if:
Airway obstructs if not supported
Airway compromised by vomiting
Resp rate inadequate for ventilation
O_2 sats <92% despite high flow O_2 / airway opening manoeuvres
Signs of shock despite 40ml/kg fluid
Exhaustion
GCS≤8 or deteriorating
Signs of raised ICP

See Problem list below

Monitoring

Heart rate *+
Resp rate *
O_2 sats *+
BP *
Temperature
ECG+

*recorded every hour
+monitored continuously

GCS assessment
If GCS <12 every 15mins
If GCS 12-14 every hour

Start urine collection

Core investigations (see page 9)

All children → **Capillary Glucose**

Perform the following in **all children** with reduced conscious level ***except*** those post trauma and those within one hour post convulsion (see pages 4&5)

Blood gas (capillary, venous, arterial)
Urinalysis (dipstick at bedside)
Laboratory glucose (even if capillary glucose normal)
Urea and electrolytes (Na, K, Cr)
Liver function tests
Plasma ammonia
Full blood count
Blood culture
1-2ml plasma } to be separated, frozen and saved
1-2ml plain serum }
10ml urine to be frozen and saved

History features to ask about

Vomiting
Headache
Fever
Convulsions
Alternating periods of consciousness
Trauma
Ingestion of drugs
Presence of any drugs at home
Any previous infant deaths in family
Length of symptoms

Examine the child

Problem list

Identify all the problems considered below (see pages 4 and 5)

Shock
Sepsis
Trauma
Metabolic illness
Intracranial infections
Raised ICP
Hypertension
Prolonged convulsions
Post-convulsive state
Cause unknown e.g. drug ingestion

Management

Manage **concurrently** all the problems identified from the Problem list (see pages 6, 7 and 8)

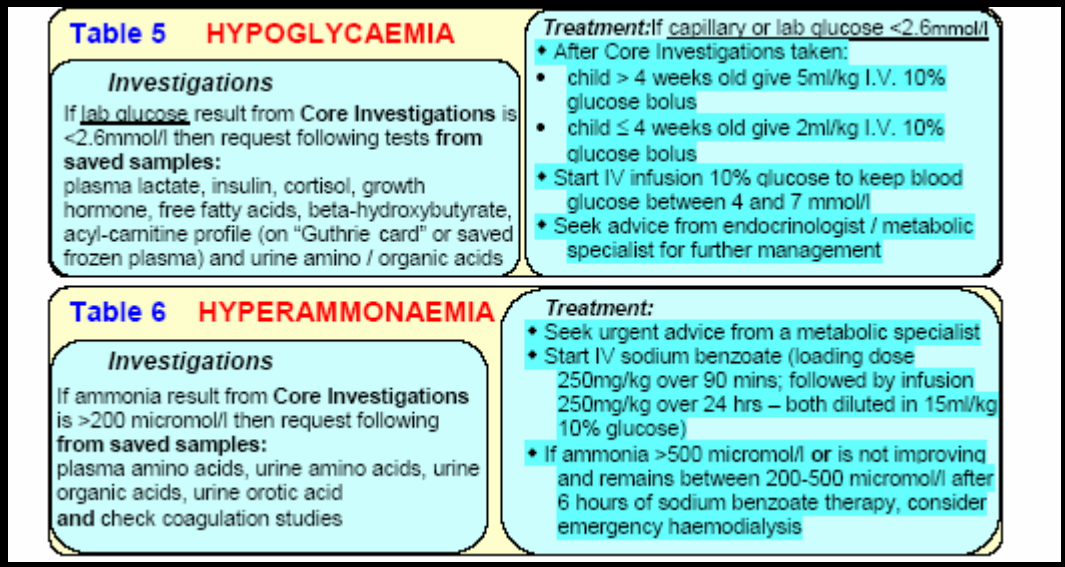


Table 5 HYPOGLYCAEMIA

Investigations

If lab glucose result from **Core Investigations** is <2.6mmol/l then request following tests **from saved samples:**
plasma lactate, insulin, cortisol, growth hormone, free fatty acids, beta-hydroxybutyrate, acyl-carnitine profile (on "Guthrie card" or saved frozen plasma) and urine amino / organic acids

Treatment: If capillary or lab glucose <2.6mmol/l

- After Core Investigations taken:
  - child > 4 weeks old give 5ml/kg I.V. 10% glucose bolus
  - child ≤ 4 weeks old give 2ml/kg I.V. 10% glucose bolus
- Start IV infusion 10% glucose to keep blood glucose between 4 and 7 mmol/l
- Seek advice from endocrinologist / metabolic specialist for further management

Table 6 HYPERAMMONAEMIA

Investigations

If ammonia result from **Core Investigations** is >200 micromol/l then request following **from saved samples:**
plasma amino acids, urine amino acids, urine organic acids, urine orotic acid
and check coagulation studies

Treatment:

- Seek urgent advice from a metabolic specialist
- Start IV sodium benzoate (loading dose 250mg/kg over 90 mins; followed by infusion 250mg/kg over 24 hrs – both diluted in 15ml/kg 10% glucose)
- If ammonia >500 micromol/l **or** is not improving and remains between 200-500 micromol/l after 6 hours of sodium benzoate therapy, consider emergency haemodialysis

www.nottingham.ac.uk/paediatric-guideline