Paediatric Emergencies

Euro Medlab ACB Training Day 13/5/05
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Deaths in childhood

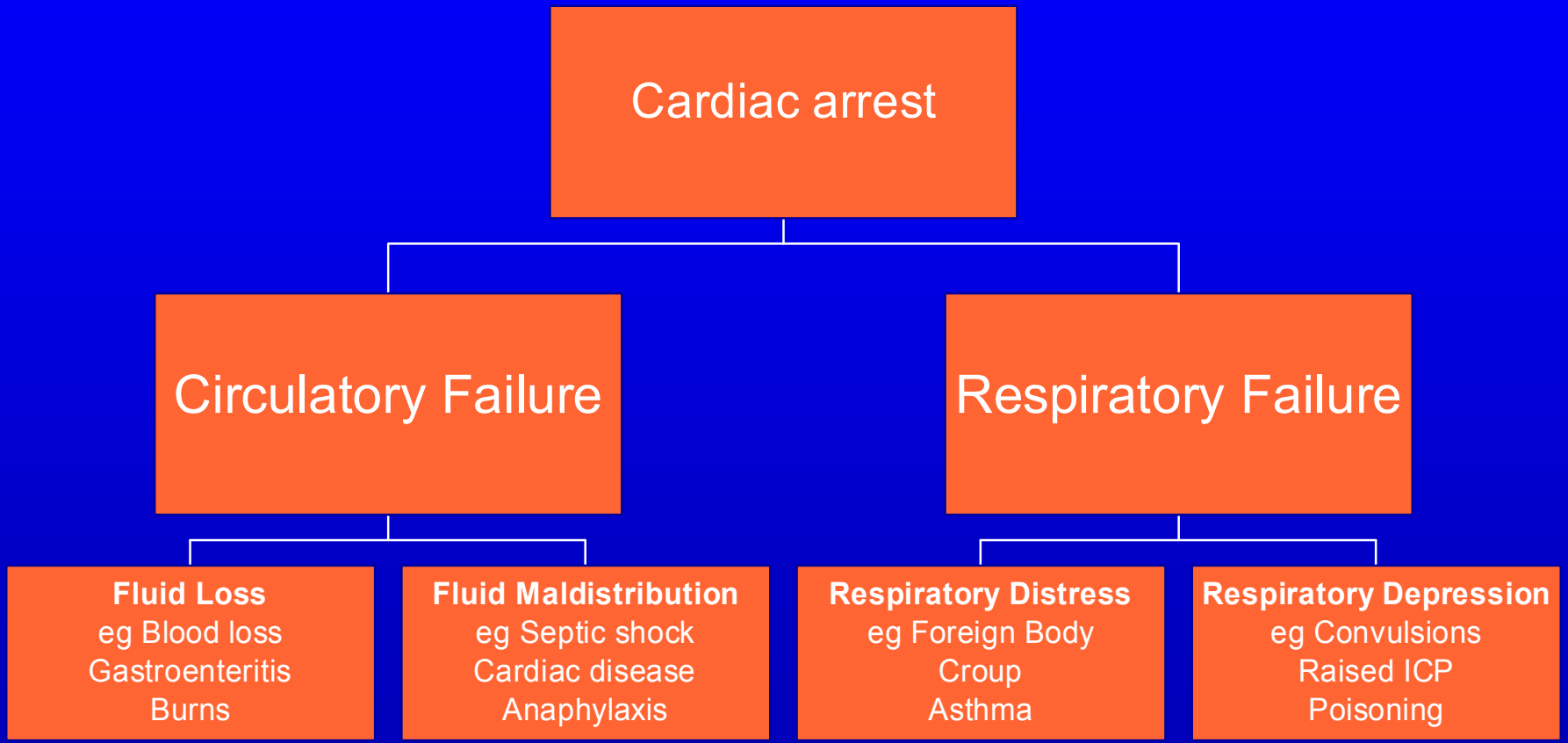
1998 (England & Wales office of national statistics)

Age group	Rate/1000 population
0-28 days	3.8
4-52 weeks	1.9
1-4 years	0.28
5-14 years	0.13

Number of deaths due to common causes by age group. (E & W 1998)

Cause	4-52 weeks	1-4 years	5-14 years
Cot death (SUDI)	239	0	0
Congenital abnormality	285	102	66
Infection	228	69	35
Trauma	53	143	219
Neoplasms	22	94	232

Patients admitted to PICU



Advanced Paediatric Life Support: the practical approach
Eds: Machway Jones K, Molyneaux E, Phillips B.
London BMJ books 2001

A/E attenders (NSD Scotland 3 day survey Apr 04)

	Children's Hospital Edinburgh (150 beds)	Adult Hospital Edinburgh (~800 beds)
All A/E	361	737
Resus %	1.4	1.9
Trolley %	15	32
Walking wounded %	83	66

Infants and children develop extremely abnormal biochemistry – extremely rapidly

Examples to be covered:

1. Acid base
2. Electrolytes
3. Glucose
4. Hyperbilirubinaemia (in neonates)
5. Ammonia
6. Toxicological

1. Acid Base – commonest abnormality seen

Metabolic acidosis:

- Diabetic ketoacidosis
- Loss of bicarbonate in fluid
- Lactic Acidosis
- Starvation ketoacidosis

- Poisonings
- Renal tubular acidosis
- Inborn Errors

eg Paediatric ICU retrieval
23 month old boy

In A/E pH 6.9, glucose 1.3mmol/L, urine ketones +++

On arrival in PICU

pH	7.052 (hydrogen ion 88.7)
pCO2	1.89
pO2	11.51
Standard bicarb	6.6
Base excess	-24.6

Final diagnosis in this case was an organic aciduria. Ketone bodies were the greatest contributor to the acidosis.

Discharged well & without sequelae 4 days later

2. Electrolytes: Hypernatraemia

Hypernatraemic Dehydration

- inadequate intake
- excessive loss
  - GI tract
  - urine

diabetes insipidus
(cranial or nephrogenic)

Sodium overload

- iatrogenic
- poisoning

Breast feeding hypernatraemic dehydration

40 cases reviewed in literature

Uneventful gestation, delivery & perinatal history

Diminished milk secretion (increased sodium concentration may or may not be a contributory factor)

Predominantly breast fed with little or no supplementation

Present >5days & < 6weeks of age

Loss of 10% or greater of birthweight

Clinical signs of dehydration

Mother often unaware infant is seriously ill

Sleepy, quiet "good" baby

No underlying organic disease

Hypernatraemic dehydration in a child with complex medical history

9year old boy admitted to PICU

Chromosome 6 deletion syndrome
Epilepsy
Cerebral palsy
Nephropathy, rickets
Pneumonia & respiratory failure

Admission Urea = 8.1, Na 173, K 6.1, Cl >120mmol/L
Plasma Osmo 368 Urine osmo 640 mmol/kg

Correction of hypernatraemia

Brain is dehydrated

Neurons produce osmoprotective molecules

Aim of correction is to restore volume, while reducing sodium very slowly

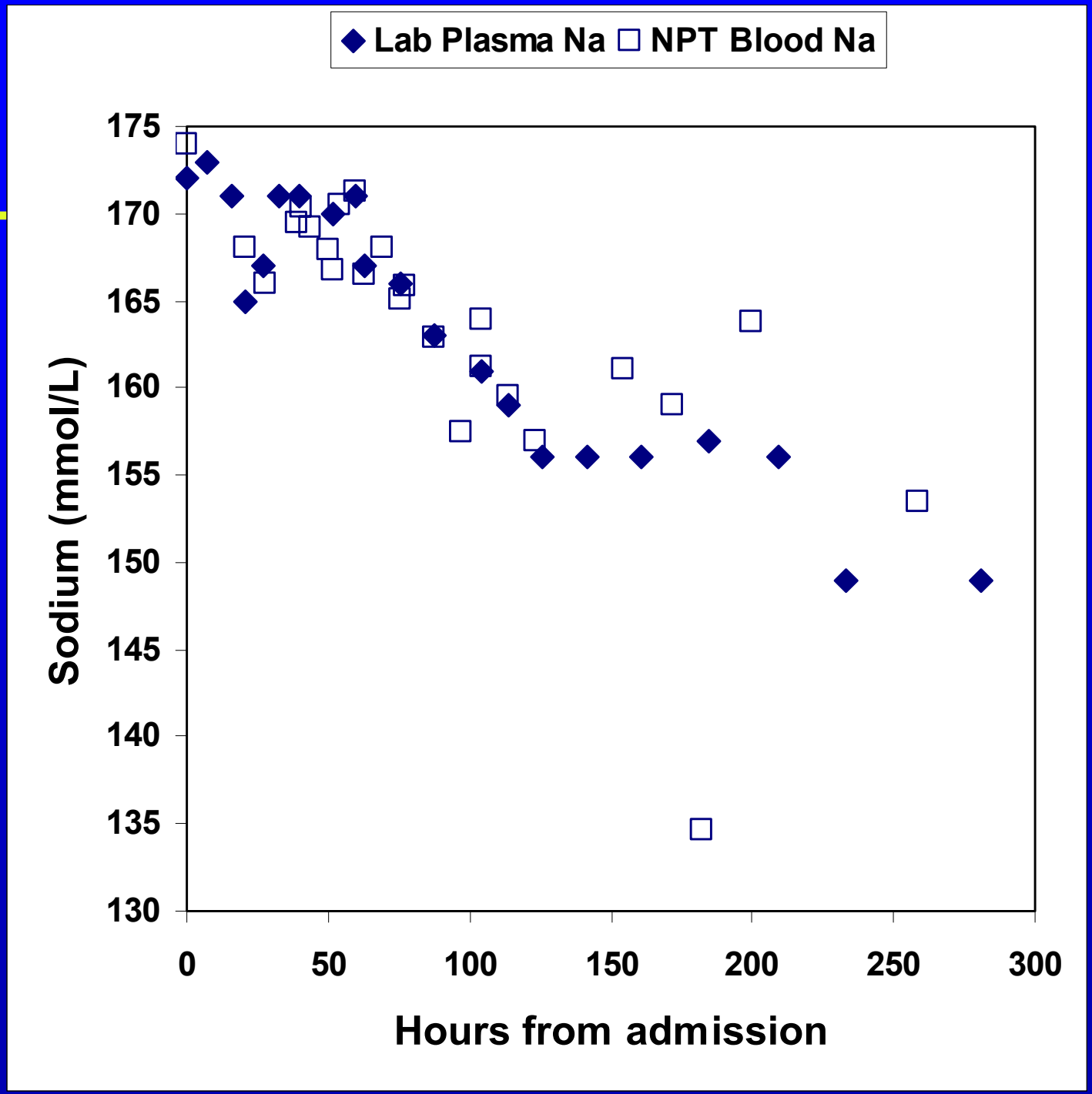
Rapid reduction in sodium leads to an osmotic gradient across the blood brain barrier

Water crosses & results in cerebral oedema

Close monitoring of rehydration phase is needed.

How? NPT or lab sodium

12 days in ITU



Hyponatraemia (commoner)

Water overload

- rehydration with sodium poor fluids
- Renal or cardiac failure
- SIADH

Sodium loss
- GI tract
- urine – recovery phase of acute renal failure
  - osmotic diuresis
  - adrenal insufficiency (CAH, Addisons, pseudohypoaldosteronism)

Collapsed patients with Hyponatraemia

9 yo boy.
A/E

Urea	13.8 mmol/L
Na	115mmol/L
K	6.5mmol/L
Glucose	1.1mmol/L

Cortisol	<50nmol/L
ACTH	59mU/L

Calcified large mass R adrenal. ? Old TB ?tumour

12 day old boy
A/E

Urea	8.8mmol/L
Na	106mmol/L
K	6.6mmol/L
Glucose	2.7mmol/L

17aOH progesterone 6000nmol/L

Urine steroid profile – consistent with CAH

3. Glucose : Hypoglycaemia

Brain is an obligate glucose user.

Only ketones can substitute.

Hypoglycaemia results in energy failure and neuronal damage.

Definition: blood glucose <2.2mmol/l

Neuroglycopenia

Symptoms of hypoglycaemia due to cerebral dysfunction

Acute: Panic, palpitations, sweating, unsteady gait.

Subacute: Reduction in spontaneous activity, somnolence. Hypothermia, fits.

Variable, non specific. May be present without hypoglycaemia, or absent in hypoglycaemia.

Neonates

May not show symptoms of neuroglycopenia.

Perception that neonates could tolerate lower blood glucose levels than older children.

Studies demonstrated this was not so.

Sensory evoked potentials in newborns and older children.

Demonstrated changes at minimum blood glucose levels of 0.7-2.5mmol/l.

Multicentre feeding study of pre term infants.
Lancet 1989 Leader p882

Hypoglycaemia prevalence 4-31%

Small for dates and low birth weight babies especially at risk.

Moderate hypoglycaemia of 0.6-2.6mmol/l much commoner than severe <0.6mmol/l.

Hypoglycaemia tended to recur.

Symptoms were not reliably associated with hypoglycaemia.

Analysis of neurodevelopmental outcome concluded minimum safe plasma glucose 2.5mmol/l.

Sample/Methodology

Whole blood glucose < plasma glucose

Difference approx 10-15% - wide variation in different studies.

Haematocrit - Variable effects depending on method.

Strip test methods:

Erythrocyte barrier may slow entry of glucose into measuring system.

- Overall effect is to increase false positives for hypoglycaemia.
- Errs on side of safety.

Normal adaptation to falling glucose levels during fasting:

Insulin level falls: limits glucose entry to non cerebral tissue.

Hepatic gluconeogenesis stimulated.

Glycogen breakdown activated.

Fatty acid oxidation activated.

Cortisol and growth hormone release stimulated

….provided that:

- Sufficient substrate is present - glycogen, fatty acid stores
- Enzymes for pathway present and active
- Pathway activated (hormonal control)

Differential diagnosis of hypoglycaemia 1

- Increased demand
  - sepsis, pyrexia, large tumour
- Reduced supply
  - substrate exhausted (eg glycogen post prolonged fast)
- Single enzyme defects
  - Glycogenolysis
  - Fatty acid oxidation
  - Gluconeogenesis

Differential diagnosis of hypoglycaemia 2

- Multiple effects
  - severe hepatic damage
  - eg Reyes syndrome, galactosaemia, tyrosinaemia, HFI
- Pathway not activated
  - hyperinsulinism
  - adrenal insufficiency
  - pituitary insufficiency

Hyperinsulinism

Transient neonatal
- infants of diabetic mothers
- intrapartum maternal glucose infusion
- preterm asphyxiated babies
- erythroblastosis fetalis

Nesidioblastosis
Administration of insulin, hypoglycaemic drugs, quinine
Insulinoma
Beckwith Wiedemann syndrome

SURF defects – persistent, coupled with hyperammonaemia

Neonatal hypoglycaemia
Hypoglycaemia protocol samples collected when:

Recurrent hypoglycaemia

- Term infant after 1st 48 hrs
- Severe and/or recurrent after 1st 48 hrs
- Symptomatic
- High glucose requirement

Associated with

- Prolonged jaundice
- micropenis
- Hypo or hypernatraemia
- Midline defect (cleft palate, absent corpus callosum)

Infants and children - all hypoglycaemia requires investigation

Sample collection during hypoglycaemia

A metabolic snapshot during hypoglycaemia may be diagnostic.

Avoids potentially dangerous provocation tests. (eg prolonged fast, insulin tolerance test)

Subdivide samples and cascade analyses to make maximal use of limited blood volumes.

Glucose, lactate, 3-HOB, FFA

Insulin, cortisol, growth hormone, acylcarnitine profile

C-peptide, ACTH, testosterone, TFTs, amino acids

Urinary organic acids

Hypoglycaemia Case 1. Girl aged 2.5 years

Vomiting for 3 days. Now refusing all drinks.

Referred by GP to Casualty.

Dehydrated, listless.

Normal conscious level.

BM 1.0 mmol/l, confirmed by lab glucose

Ketotic hypoglycaemia

Appropriate physiological responses to falling glucose –

- ↑ cortisol 2070nmol/L
- ↑ ketones (therefore insulin is low and need not be measured)
- no evidence of impaired fatty acid oxidation on organic acid profile – (FFAs need not be done)

Slim child – little reserve

Poor diet – cucumber & low cal drinks for a long period

Then period of fasting/vomiting/pyrexia – increased requirement

Hypoglycaemia Case 2: Boy aged 10 years

Longstanding seizure disorder

History of episodes of drowsiness past few weeks

5pm Sunday - Admitted in coma.

BM undetectable, lab glucose <0.5mmol/L

Insulin Administration

↑↑ insulin 3780mU/L, inappropriate to low glucose

↓3HOB <0.06mmol/L

↑Cortisol 1260 nmol/L

Frozen sample analysed for C-peptide – undetectable

Demonstrated that insulin was of exogenous origin

Insulin syringes found to be missing from mother's workplace

(spot the biochemical error on the press report next slide!)

Scotsman 13/12/95

Probation for nurse who gave son potentially lethal dose

High Court: *Insulin was put into ten-year-old boy's drip as he lay ill*

A NURSE who gave her ten-year-old son a potentially fatal dose of insulin was put on probation for three years at the High Court in Glasgow yesterday.

Lord Johnston told the woman, who sat emotionless in the dock, that it was "an unusual and tragic case".

The woman pleaded guilty last month at the High Court in Edinburgh to two charges of assaulting the boy in the family home in Fife and in the Royal Hospital for Sick Children, Edinburgh, by administering insulin to him to his severe injury and the danger of his life.

She also admitted stealing insulin and syringes from a Fife hospital where she worked.

The woman was originally charged with attempted murder, but her plea of not guilty was accepted by the Crown.

The court heard earlier how she had put insulin into her son's drip as he lay ill in the Edinburgh hospital. She told police that her epileptic son had begged her to "give him a bit of peace" and let him join his grandfather, who had died years before. But Lord Johnston heard that, when the boy recovered, he denied this.

The court heard that the boy had suffered an injury at birth which led to epilepsy at the age of five and that he suffered migraines and would fly into cataclysmic rage reactions. In one of these rages he threw boiling water at his mother's face.

The advocate depute, James Campbell, told the court that the mother had given hospital colleagues the impression that her son's case was terminal and had asked whether insulin could be detected at a post-mortem examination.

The boy complained of headaches and she gave him painkillers in March this year. He was taken to hospital in Edinburgh where doctors found he had a remarkably high insulin level and they feared it was being produced by a tumour.

Later, medical staff at the mother's hospital contacted the Edinburgh hospital to say they had seen her with the keys for the drug refrigerator and with syringes and ampoules of adrenaline. A doctor checked the boy's condition in hospital and found he had a particularly high blood sugar level. The doctor concluded that it was "fairly possible" that insulin had been administered to the child in hospital. Police found an empty box of insulin at her home.

Mr Campbell said that, when the boy was admitted to hospital, his condition was "life-threatening" and, had he not received the treatment he did, the matter would have proved fatal or would have left him with substantial brain damage.

Gordon Jackson, QC, for the defence, said the family was doing its best to cope with the boy. He said: "I think it is difficult for any of us to understand the pressure built up within this family and put on this woman.

"The stress was such that it seems clear she simply became mentally ill and had a breakdown. There is no rational explanation for what she did. It appears it was a cry for help and she told police she loved her son more than anything else in the world and hated to see him suffer."

Lord Johnston told her yesterday that he was heartened by the background and medical reports submitted to the court. He placed her on probation with the condition that she continue to receive medical help.

Hypoglycaemia Case 3: Boy aged 11 months

Several days D &V, not eating

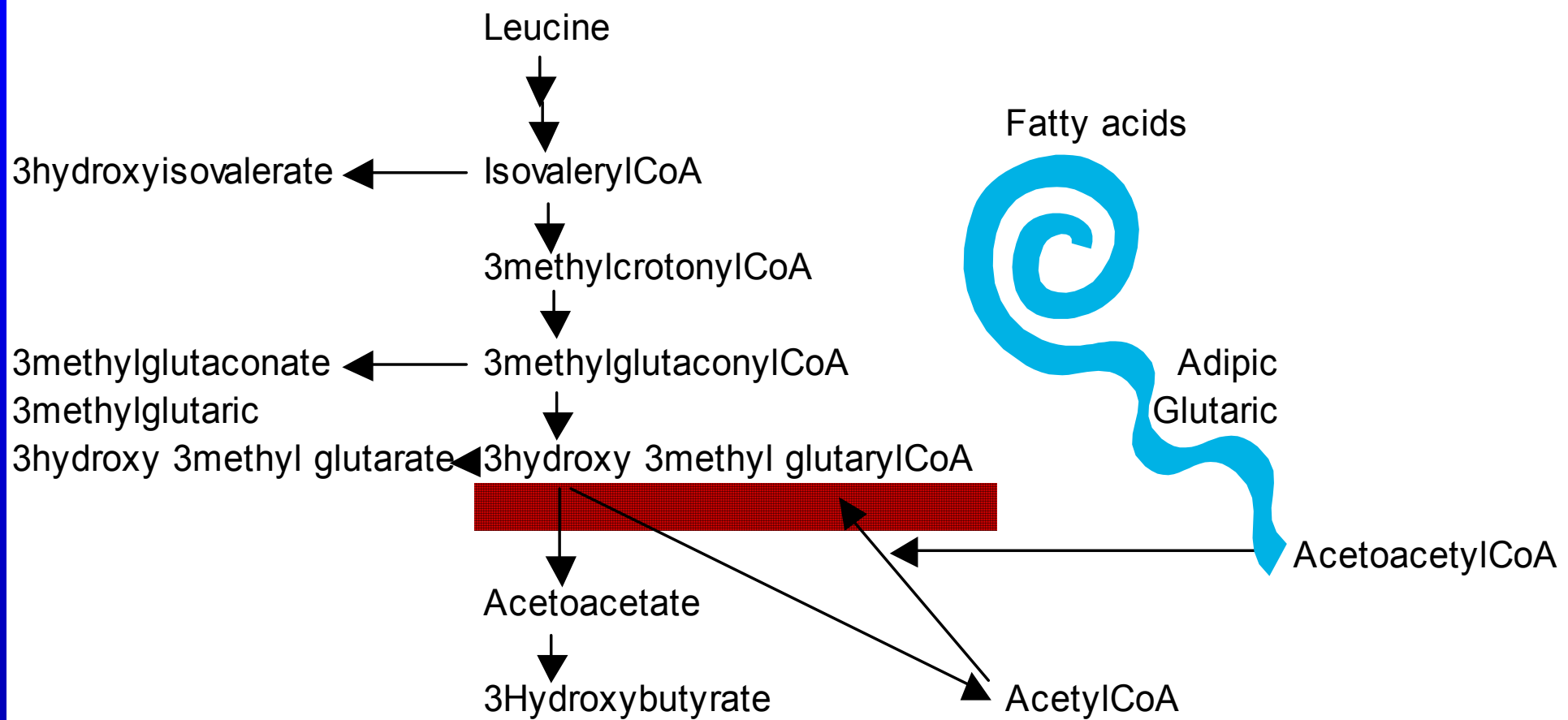
Found cold, clammy and unresponsive

Had two convulsions in ambulance to local hospital

BM stix on admission undetectable, lab glucose 0.8mmol/L

Blood gases showed metabolic acidosis

Urinary organic acid pattern was diagnostic



Deficiency of HMG CoA Lyase leads to defective ketone body production

4. Hyperbilirubinaemia in neonates. Unconjugated [Total] Neonatal Bilirubin

Marker of vulnerability to kernicterus:

yellow staining of subcortical nucleii and neuronal damage

Depends on:

- Plasma unconjugated bilirubin
- Albumin
- Acidosis
- Blood brain barrier status
- Competitive binders:

  frusemide, benzoate, FFAs, haemolysis products

Plasma bilirubin & brain damage

link systematically established in early 50s:

30 – 50 % untreated babies with severe haemolytic disease developed kernicterus

- usually Rhesus, sometimes ABO
- often asphyxiated, sick, delivered prematurely to avoid stillbirth
- Premature babies higher risk (cause or result?)

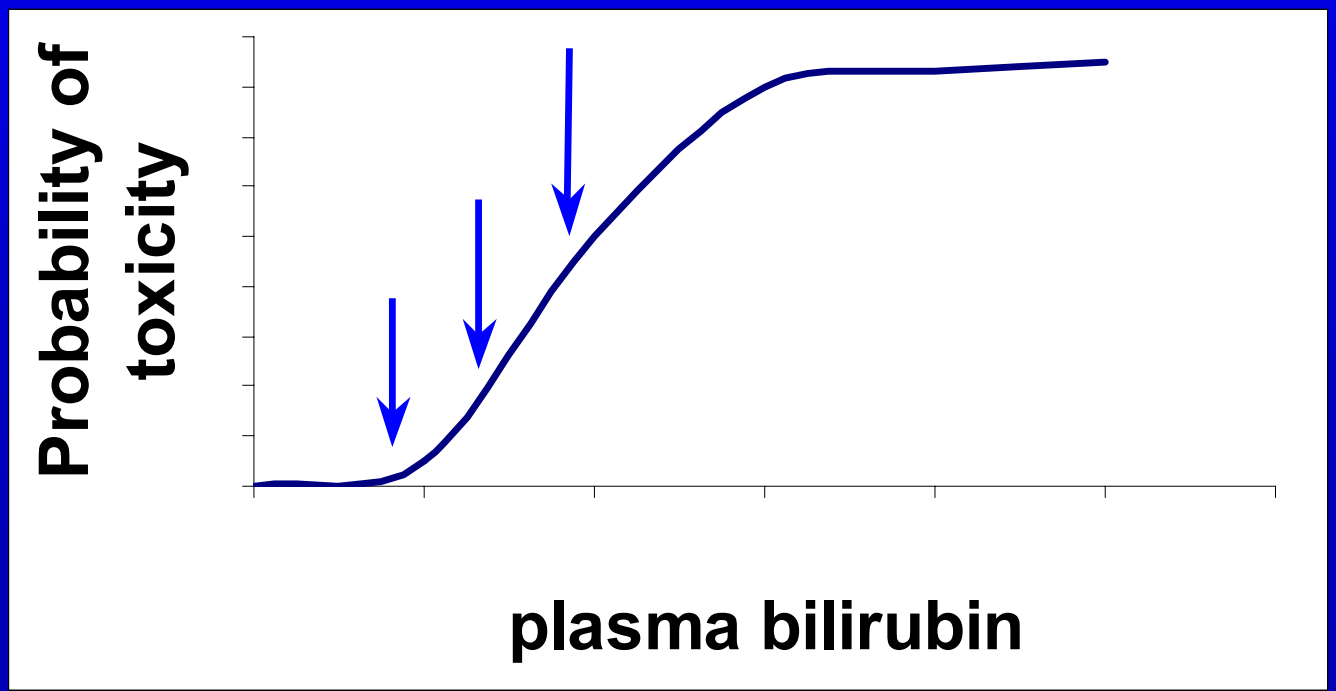
Risk ↑ dramatically with bilirubin

Non haemolysing jaundiced babies had lower kernicterus risk – overlap of bilirubin levels

Threshold and sigmoid curve

Outcome improved by exchange transfusion :

342umol/L became standard intervention level based on methodology at that time



Phototherapy: changed risk- benefit assessment

USA 1977-78: Collaborative Perinatal Project

Moderate elevations of bilirubin correlated to:

- Lower developmental score
- Lower IQ
- Increased risk of neurological abnormalities at bilirubin concentrations previously considered safe – spectrum of bilirubin toxicity with kernicterus at the extreme

Up to 25 % of well term jaundiced babies received phototherapy.

During 1980s marked reduction in autopsy proven classical kernicterus

1990s Re-evaluation

Were the statistics flawed by including premature & sick infants?

Controversial recommendations for well & sick, haemolysing and non haemolysing term infants

8 experts agreed to cautious and varying extents

intervention standard agreed before largest studies complete

case reports of kernicterus – numerators without denominators

early discharge in USA limits follow up data on natural course of physiological jaundice

British Version

Postal questionnaire: 60 UK paediatricians

Intervention limits already similar to US proposals

Half used Hillingdon chart or local related phototherapy action limits to postnatal & gestational age

Edinburgh Neonatal Unit Guidelines for initiating phototherapy.

	1st 24 hours	24 - 48 hours	> 48 hours
< 28 weeks	85	100	100
28 - 31 weeks	85	110	140
32 - 35 weeks	85	170	210
> 35 weeks	85	250	350

Intermittent phototherapy commoner

Interrupting breast feeding less common.

60% felt current policies could safely be liberalised

Laboratory Requirement:

Reliable measurement of total bilirubin over a wide concentration span.

Reliable measurement in haemolysing infants.

Which infants develop hyperbilirubinaemia?

ABO-incompatible neonates

+/- UDP-glucuronosyl transferase gene promoter polymorphism (Gilberts syndrome)

Incidence of neonatal jaundice was commoner only in those infants who were homozygous for the Gilberts polymorphism.

Similar reports for infants with other genetic predisposition eg G6PD deficiency

Hyperbilirubinaemia in neonates
Conjugated [Direct] Bilirubin

Diagnostic Tool: Urgent treatment needed on diagnosis

Neonatal hepatitis

Biliary atresia/hypoplasia

Hypothyroidism

Hypopituitarism

Galactosaemia

Tyrosinaemia

α1 antitrypsin deficiency

Cystic fibrosis

Dubin Johnson/Rotor syndromes

Rarities

? Earlier diagnosis/treatment of biliary atresia

Recommendation all infants with jaundice prolonged to 14 days should have total and direct/conjugated bilirubin estimated. Well baby review at 4 rather than 6 weeks.

(not supported by questionnaire response)

Laboratory Requirement

To identify significant conjugated hyperbilirubinaemia.

What is detection limit of "direct" bilirubin?

What is cross reactivity with total bilirubin?

Need information relevant to current methodology

Prolonged jaundice – Case 1

4 week old boy
Referred by Health visitor/GP to A/E
Breast fed, thriving

Total bilirubin 147umol/L, direct <20umol/L
Liver function tests: ALT 25, gGT 80, ALP 299, alb 35
fT4 25pmol/L TSH 3.0mU/L
Urine reducing substances negative

Diagnosis of exclusion – breast milk jaundice

Prolonged jaundice – Case 2

4 week old boy
Jaundiced day 1 – tBili 344, dbili 261umol/L
Peak bilirubin day 4 tbili 463. Abnormal LFTs
Hepatosplenomegaly from birth

Referred to GI team at 4 weeks
tbili 88, dbili 88umol/L,ALT 155, gGT 393, ALP 438 alb 32
Leucoerythroblastic blood film. Hb 8.9

Metabolic investigations (organic & amino acids, sugar chromatography – NSA
Liver biopsy – macrophages ++ with evidence of storage
Gaucher disease diagnosed by leucocyte enzyme analysis

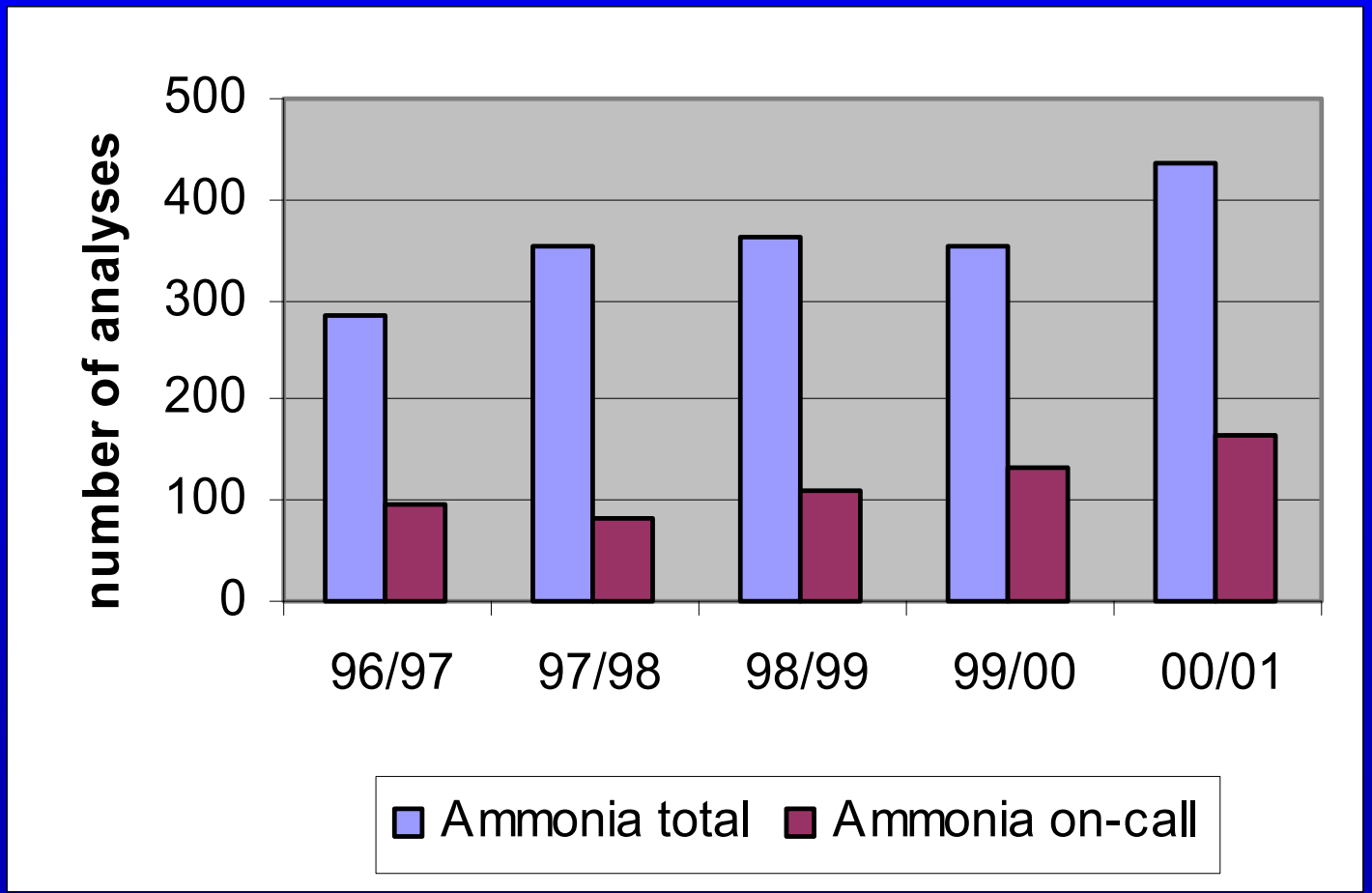
5. Ammonia: Effects of hyperammonaemia

Encephalopathy

Astrocyte swelling
Increased permeability of blood brain barrier
Mitochondrial changes
Cerebral oedema

Hyperammonaemia – Identification

300-400 requests per annum - approximately 1/3 of these on call



Hyperammonaemia - Identification

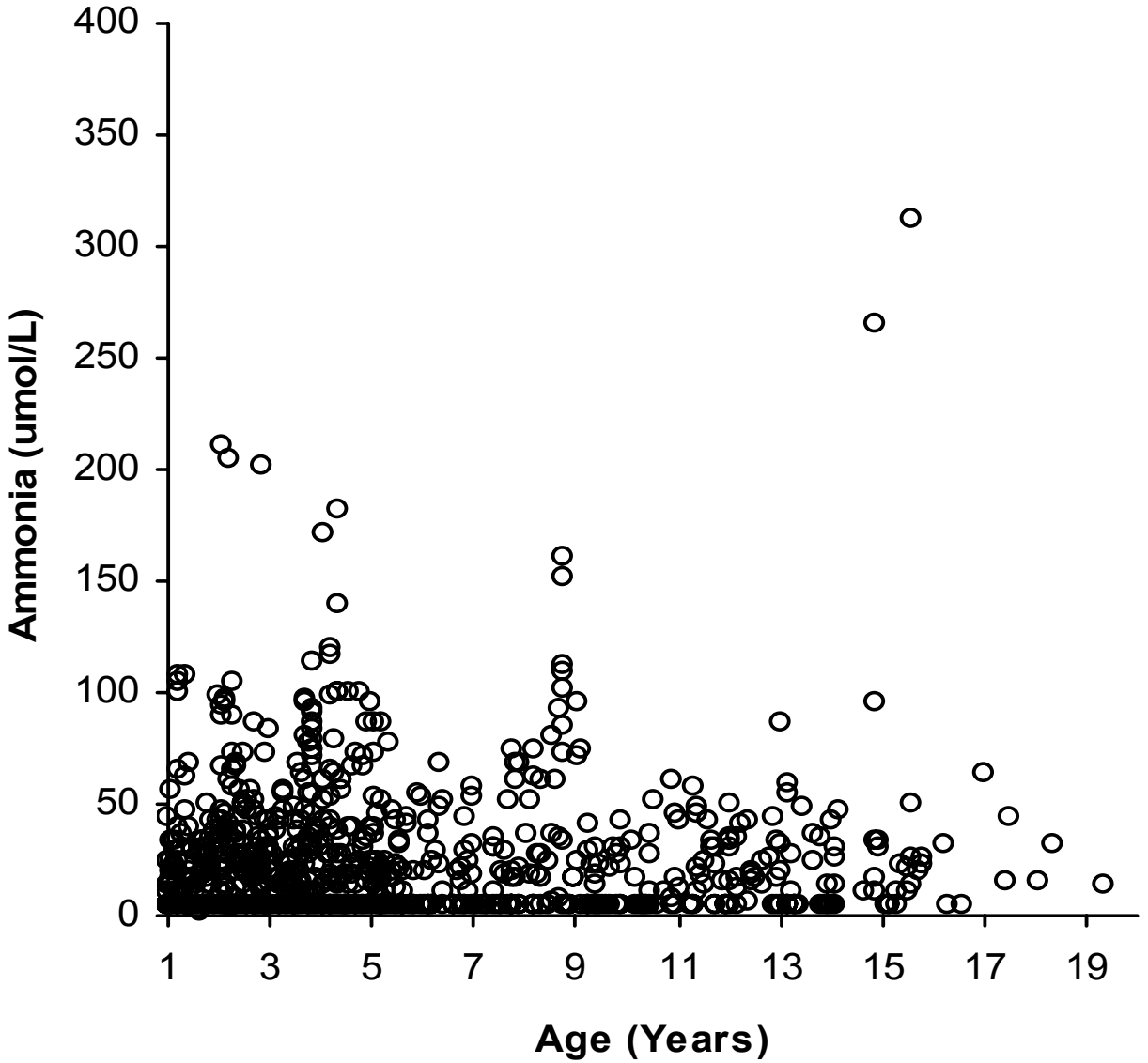
- Rapid rise in ammonia after sampling
  - Release of ammonia from amides (glutamine & protein)
  - Clotting process releases ammonia from platelets
- Collect lithium heparin sample
  - Avoid contamination
  - Immediately cool on ice
  - Send to lab by vacuum tube or other rapid transit
  - Centrifuge at 4'C and separate plasma from cells immediately on receipt
  - Analyse or freeze immediately

Reference Ranges

Green. Neonatology & Clinical Biochemistry.	Birmingham Children's Hospital	post neonatal	<100
		neonates	<200
Soldin. Pediatric Ref Ranges. 2nd edn.	Childrens National Medical Center.	all ages	9 - 33
	Toronto Sick Children's Hospital	child & adult	<35
		neonate	<50
RHSC Edinburgh (in –house data)		infants and children	<70
		neonates	< 115

n = 1188 patients >7 days old.

RHSC Ed Data collected 1996-2000

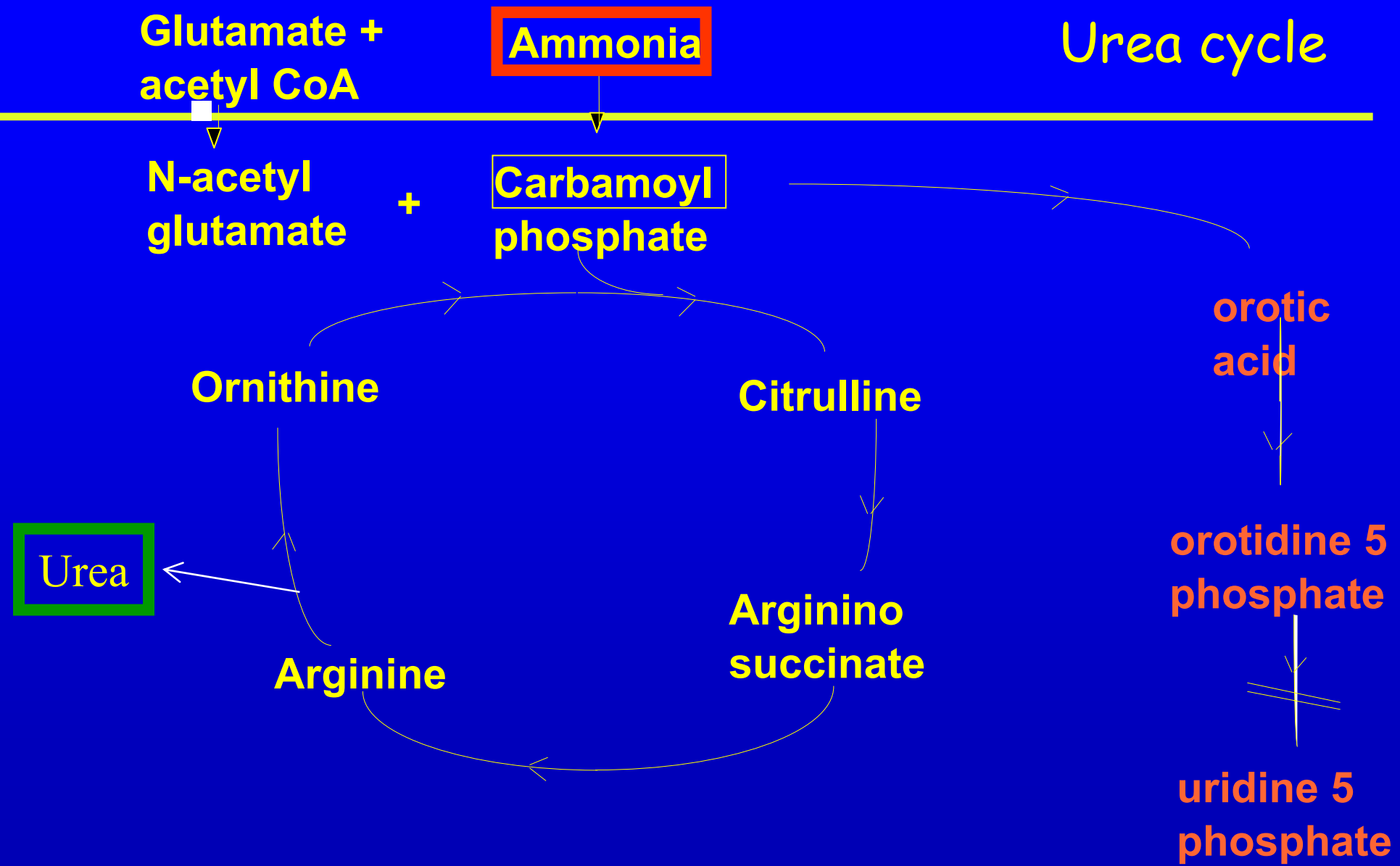


Differential Diagnosis

- Impaired urea cycle metabolism
  - Primary defects of urea cycle
  - Organic acidurias eg Propionic, methylmalonic aciduria
  - Mitochondrial damage due to
    - Hepatic failure
    - Toxins. "Reyes syndrome"
    - Malignant disease
- Increased production
  - Urea splitting organisms, particularly in alkaline environment

$$NH_4^+ \Leftrightarrow NH_3 + H^+$$

Urea cycle


Glutamate +
acetyl CoA
Ammonia
N-acetyl
glutamate
+
Carbamoyl
phosphate
orotic
acid
Ornithine
Citrulline
Urea
orotidine 5
phosphate
Arginino
succinate
Arginine
uridine 5
phosphate

Investigations

Plasma and urine amino acid profiles
Urine organic acid profile
Liver biopsy for urea cycle enzyme studies
DNA mutation studies

Liver function tests
Microbiology

Treatment to remove ammonia (whatever its cause)

Reduce production

- stop protein feeding,
- drain infected fluid collections

Remove by conjugation with:

- benzoate + NH_3 ⇔ hippurate
- Phenylbutyrate ⇔ phenylacetate + $2NH_3$ ⇔ phenylacetylglutamine

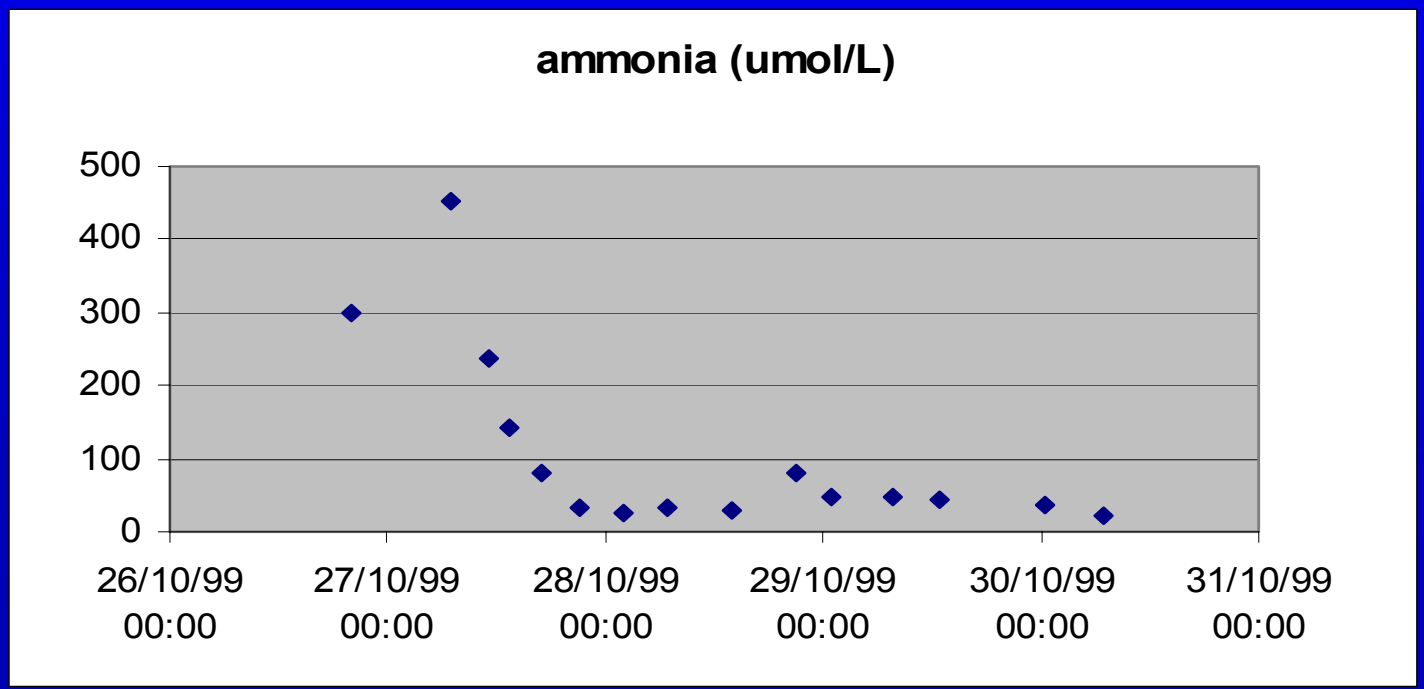
Use functioning part of urea cycle

- Arginine ⇒ citrulline or argininosuccinic

Remove by dialysis

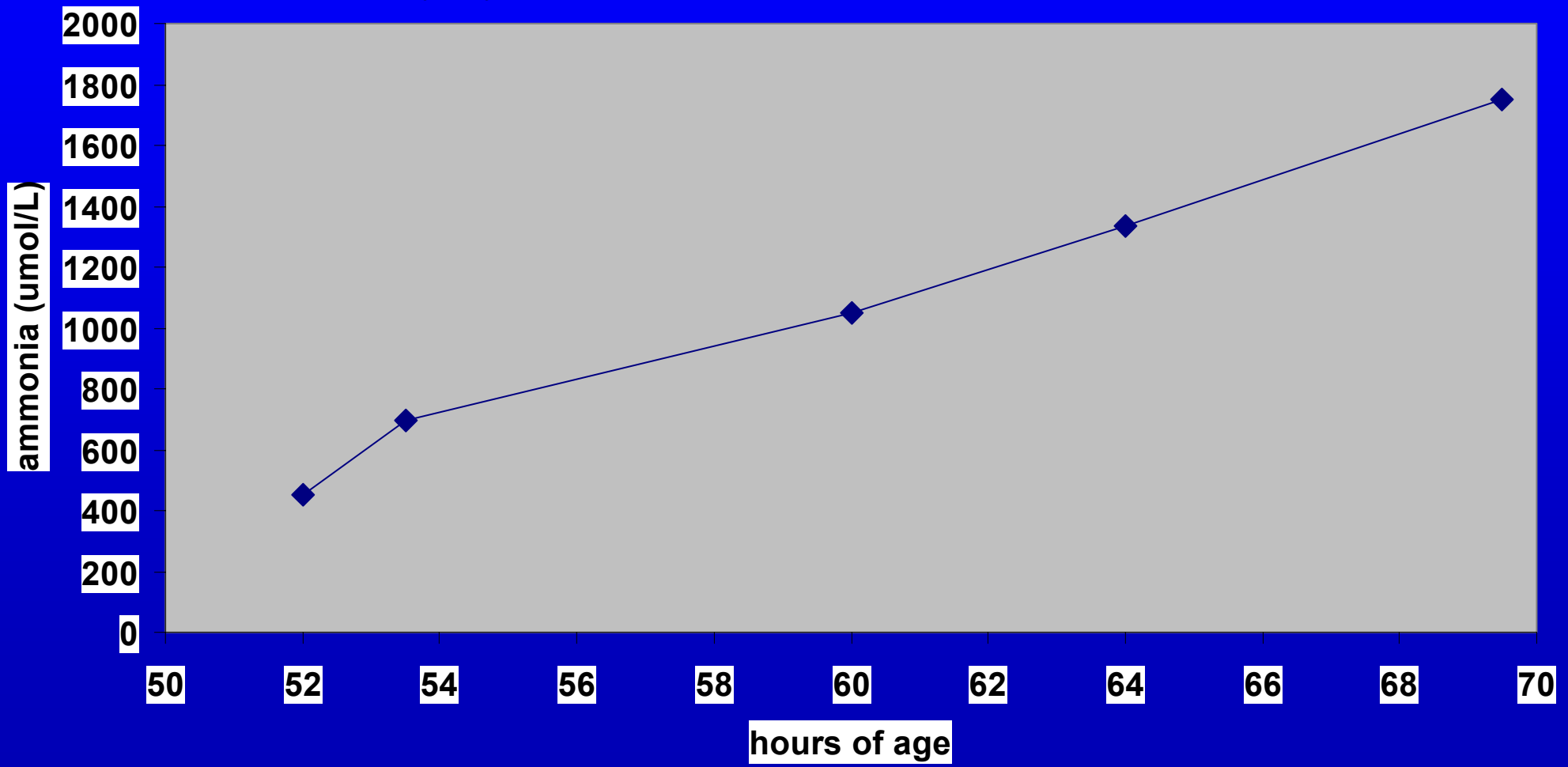
Treatment of patient with Proteus infection (urease splitting organism)

- On benzoate ammonia rose from 299 to 453umol/L
- sodium benzoate, sodium phenylbutyrate, arginine
- percutaneous nephrostomy

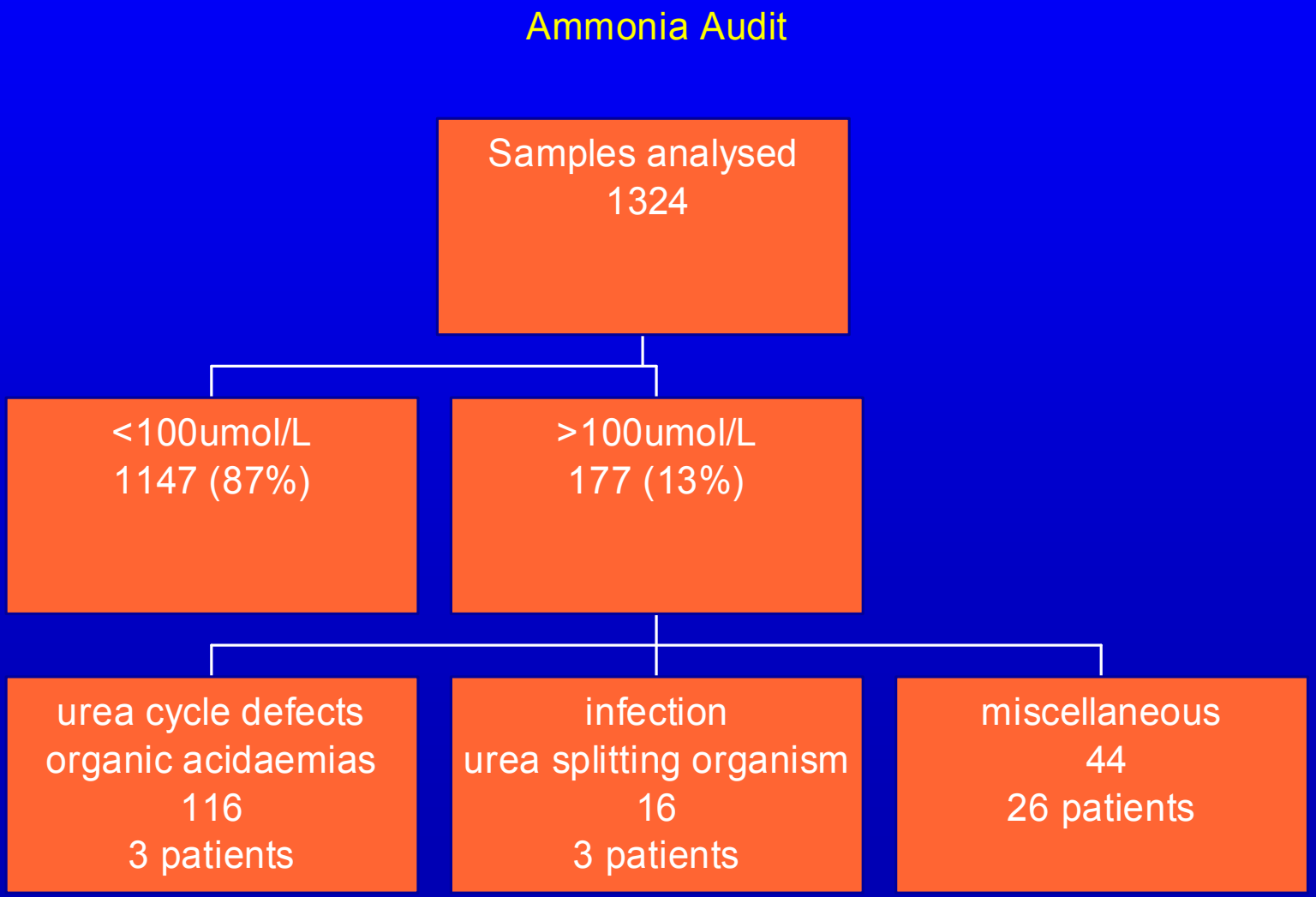


Male neonate with OTC deficiency

Treated with sodium phenylbutyrate and sodium benzoate. With this treatment increase of 70umol/L/hour



Ammonia in practice



Miscellaneous

Neonates	7
Cardiac arrest/failure	4
Hepatic failure/cirrhosis	12
Hepatic haemangioma	8
Valproate toxicity	3
Sample problem	1
Ischamic exercise test	2
No final diagnosis	7

6. Toxicology: accidental childhood poisonings and potential poisonings

Peak in toddler age group

20% of children <5 years old can open child resistant containers.

Child brought to A/E with history of being found with "tablets"

-specific analyses urgently

-Paracetamol, salicylate, iron

Child presents to A/E with symptoms/parental behaviour suggestive of ingestion of street drugs

Toxicology screen, ethanol

Deliberate & non accidental childhood poisonings and potential poisonings

Deliberate: usually older child

- Ethanol
- Street drugs – toxicology screen
- Paracetamol
- Salicylate

Non accidental – poisoning of child by family member

- A/E frequent attenders register
- Bizarre results, multiple diagnoses

Iron poisoning

Tablets commonly available in home

Highly toxic – vomiting, haematemesis, gastric ulceration, shock, convulsions, hepatic failure

Commonest cause of death as a result of childhood poisoning

Urgent measurement of plasma iron

Chelation treatment with desferrioxamine NB. In patients treated with desferrioxamine, the drug-bound iron does not react resulting in falsely lowered results.

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