

**THE EARLY DIAGNOSIS AND MANAGEMENT
OF
INBORN ERRORS OF METABOLISM
PRESENTING AROUND THE TIME OF BIRTH**

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**Diagnosis and early management of
inborn errors of metabolism presenting
around the time of birth.**

Acta Paediatr. 2006 Jan;95(1):6-14.

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

ARE RARE
(except in some genetic isolates)

BUT THERE ARE MANY OF THEM !

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

= a difficult problem!

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

AIM

To develop a strategy that identifies those at high risk

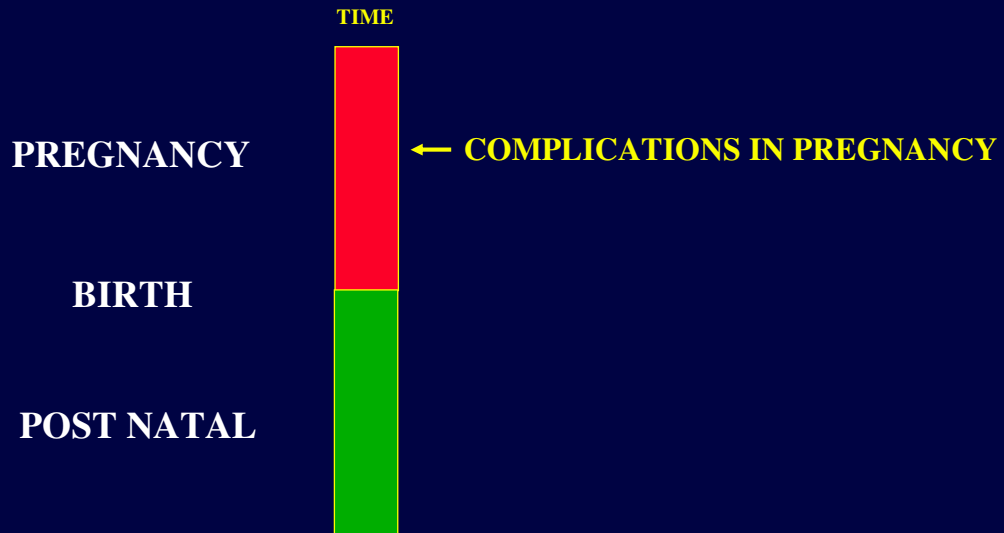
FOR specialist and general paediatricians

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

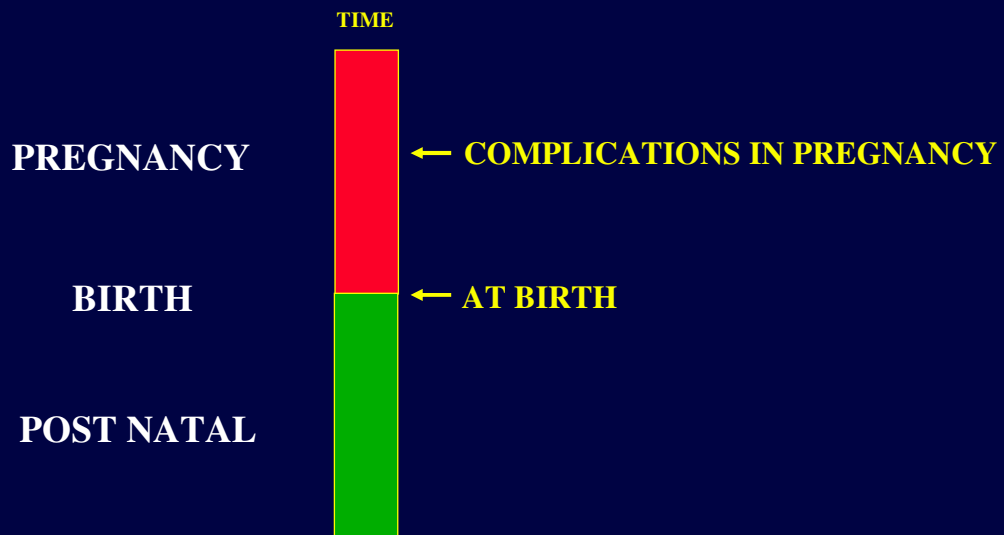
FAMILY HISTORY

- **Consanguinity (recessive)**
- **Unexplained death of sibling**
- **Unexplained similar illness in sibling
(male relative - X-linked disorder)**

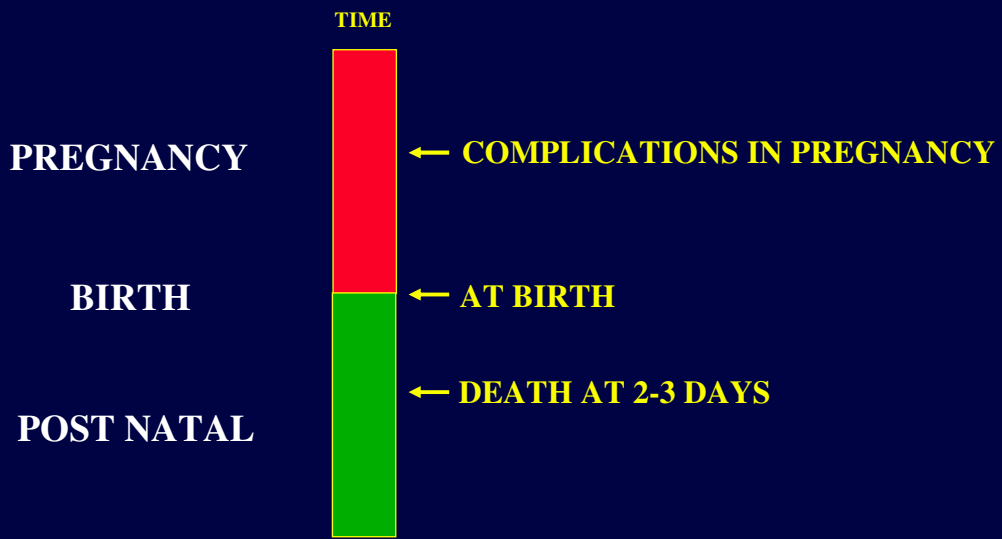
TIMING OF PRESENTATION OF INBORN ERRORS



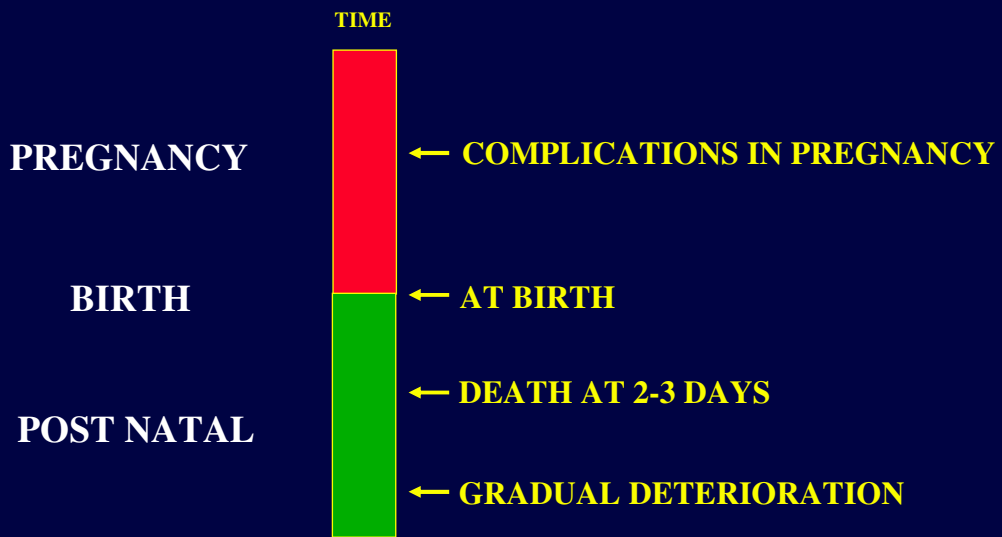
TIMING OF PRESENTATION OF INBORN ERRORS



TIMING OF PRESENTATION OF INBORN ERRORS



TIMING OF PRESENTATION OF INBORN ERRORS



INBORN ERRORS PRESENTING DURING PREGNANCY

1. Complications

HELLP syndrome
Fatty liver of pregnancy
Severe hyperemesis

- **LCHAD deficiency and others**

2. Abnormal fetal movements

Fits / hic-coughs
Paucity of movements

- **Early onset fits, etc**

METABOLIC DISEASE AT BIRTH

Most babies with metabolic disease are born:

- **at full term**
- **with a normal birth weight**
- **well**

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

PROBLEMS PRESENTING AT BIRTH

- **FITS / APNOEA**
- **HYPOTONIA (Severe)**
- **HYDROPS / ASCITES**
- **DYSMORPHIC**

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

PROBLEMS PRESENTING AT BIRTH

- **FITS / APNOEA**
 - Non - ketotic hyperglycinaemia**
 - Pyridoxine dependent fits and related disorders**
 - Molybdenum cofactor deficiency**
(xanthine and sulphite oxidase deficiency)
 - Peroxisomal disorders**
 - Congenital lactic acidoses**

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

PROBLEMS PRESENTING AT BIRTH

• **HYPOTONIA**

Non ketotic hyperglycinaemia

Congenital lactic acidoses

Peroxisomal disorders

Carbohydrate deficient glycoprotein syndromes

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

PROBLEMS PRESENTING AT BIRTH

• **HYDROPS / ASCITES (NON IMMUNE)**

Lysosomal storage disease

And many others

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

PROBLEMS PRESENTING AT BIRTH

• HYDROPS / ASCITES (NON IMMUNE)

Lysosomal storage disease

Erythrocyte enzymopathies

Respiratory chain disease and Pearson syndrome

Neonatal haemochromatosis

Carbohydrate deficient glycoprotein syndrome

Niemann Pick type C

Glycogen storage disease type IV

Primary carnitine deficiency

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

PROBLEMS PRESENTING AT BIRTH

• DYSMORPHIC

Peroxisomal Disorders

Zellwegers syndrome,etc

Cholesterol synthesis disorders

Smith - Lemli - Opitz syndrome

Conradi-Hunermann (X-linked)

And many others

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

PROBLEMS PRESENTING AT BIRTH

- **DYSMORPHIC**

Peroxisomal Disorders

Zellwegers syndrome, etc

Lysosomal storage disorders

GM1 gangliosidosis, I - cell disease, etc

Cholesterol synthesis disorders

Smith - Lemli - Opitz syndrome

Conradi-Hunermann (X-linked)

Carbohydrate deficient glycoprotein syndromes

Glutaric aciduria type II

Congenital Lactic Acidoses

Mevalonic aciduria

Metabolic disease in the newborn

Sudden (Unexpected) Death

- **Long and medium chain disorders of fatty acid oxidation**
- **? Respiratory chain disorders**

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

Initially appear normal

then

deteriorate - after a variable period

= ? Sepsis

INITIAL INVESTIGATIONS

(with septic screen)

Blood **pH and gases**
urea, electrolytes and anion gap
liver function tests
glucose
ammonia
Guthrie card for acyl carnitines,
aminoacids, DNA, etc

Urine **sugars**
ketones

INITIAL INVESTIGATIONS

(with septic screen)

| | |
|--------------|--|
| Blood | pH and gases urea, electrolytes and anion gap liver function tests glucose ammonia Guthrie card for acyl carnitines, aminoacids, DNA, etc |
| Urine | sugars ketones |

PLASMA AMMONIA CONCENTRATIONS

Neonates

| | |
|---------------------------|---|
| Full term | < 50 $\mu\text{mol/l}$ |
| Preterm | |
| Small for Dates | < 65 $\mu\text{mol/l}$ |
| Any illness | <180 $\mu\text{mol/l}$ |
| Metabolic disorder | >200 $\mu\text{mol/l}$ |

METABOLIC DISEASE IN THE NEWBORN

HIGH RISK GROUPS

- 1. Acute liver disease**
- 2. Acid-base disorders**
- 3. Cardiac disorders**
- 4. Neurological deterioration**
- 5. Unexplained hypoglycaemia**

METABOLIC DISEASE IN THE NEWBORN

ACUTE LIVER DISEASE

- Symptoms and signs**
- anorexia**
 - vomiting**
 - jaundice**
 - bleeding diathesis**
 - sepsis**
 - hepatomegaly**

METABOLIC DISEASE IN THE NEWBORN

ACUTE LIVER DISEASE

Differential diagnosis - galactosaemia (? cataracts)
- fructosaemia
- tyrosinaemia
- neonatal haemochromatosis
- congenital lactic acidoses
(can also have cataracts)

METABOLIC DISEASE IN THE NEWBORN

Practice point

IEM may predispose to sepsis

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

ACUTE METABOLIC LIVER DISEASE

Investigations

Blood

Full blood count
Liver function tests
Clotting studies
Aminoacids
Ferritin
RBC uridyl transferase

Urine

Sugars
Aminoacids

METABOLIC DISEASE IN THE NEWBORN

ACUTE LIVER DISEASE

Practice point

If galactose is present in the urine
and possibility of galactosaemia

STOP GALACTOSE

HIGH RISK CATEGORY No 2

ACID-BASE DISORDERS

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

ACID - BASE DISORDERS

Symptoms

Tachypnoea and grunting
Not shocked (initially)
Apnoea

Findings

Normal ECG and CXR

* **Metabolic acidosis**

Organic acidaemia
Congenital lactic acidosis
Fructose-1,6-bisphosphatase def
Defects of ketolysis

* **Respiratory alkalosis**

Hyperammonaemia

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

ACID-BASE DISORDERS

Urea cycle disorders may present with metabolic acidosis

Organic acidaemias may present with respiratory alkalosis

HIGH RISK CATEGORY No 3

CARDIAC DISORDERS

METABOLIC DISEASE IN THE NEWBORN

CARDIOMYOPATHY and ARRHYTHMIAS

Disorders of fatty acid oxidation

long chain fatty acid oxidation disorders

multiple acyl CoA dehydrogenase deficiency

And others

METABOLIC DISEASE IN THE NEWBORN

CARDIOMYOPATHY

1. Disorders of fatty acid oxidation

long chain fatty acid oxidation disorders

multiple acyl CoA dehydrogenase deficiency

2. Respiratory chain disorders

(3. Hyperinsulinaemic hypoglycaemia)

(4. Carbohydrate deficient glycoprotein syndromes)

Pompe disease (acid maltase deficiency)

? other lysosomal storage disorders)

Cardiac phosphorylase b kinase deficiency

Glycogen storage disease type IV

METABOLIC DISEASE IN THE NEWBORN

CARDIAC ARRHYTHMIAS

Disorders of fatty acid oxidation

long chain fatty acid oxidation disorders
multiple acyl CoA dehydrogenase deficiency

? Other metabolic disorders

HIGH RISK CATEGORY No 4

NEUROLOGICAL DETERIORATION

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

NEUROLOGICAL DETERIORATION

Initially well then:

**Often initially
labelled as
“birth asphyxia”**



**lethargy
poor feeding
irritability
changes in tone
hypotonia
hypertonia
fisting & cycling
convulsions
loss of reflexes
apnoea
full fontanelle**

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

NEUROLOGICAL DETERIORATION

Differential diagnosis

**Organic acidaemias and MSUD
Hyperammonaemia
Non-ketotic hyperglycinaemia
Pyridoxine dependent disorders, etc
Congenital lactic acidoses
Disorders of fatty acid oxidation
Peroxisomal disorders
Molybdenum co-factor deficiency
Remethylation defects**

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

NEUROLOGICAL DETERIORATION

Investigations

Plasma ammonia

Plasma aminoacids (+ CSF)

Blood lactate

Blood spot acyl carnitines

Plasma urate

Plasma VLCFA and others

Urine sulphite

Urine organic acids

CSF Neurotransmitters ,etc

HIGH RISK CATEGORY No 5

HYPOGLYCAEMIA

NEONATAL HYPOGLYCAEMIA

Common causes

Small for dates and Preterm

Perinatal asphyxia

Infant of diabetic mother

Rhesus disease

NEONATAL HYPOGLYCAEMIA

No obvious cause

- particularly in a full term baby

Endocrine

Metabolic disorders

NEONATAL HYPOGLYCAEMIA

Immediate investigations

- blood glucose (in laboratory)
- save 1-2 ml plasma in deep freeze (separate quickly)

NEONATAL HYPOGLYCAEMIA

TREATMENT

Asymptomatic

- Give oral feed
- Repeat blood glucose

Symptomatic

- Give intravenous glucose 200mg/kg
- Repeat blood glucose
- Continue glucose as infusion
at 5 - 8 mg/kg/min

NEONATAL HYPOGLYCAEMIA

Continuing course

- Severe recurrent hypoglycaemia
glucose infusion rate >10 mg/kg/min = hyperinsulinism
- Metabolic acidosis (not shocked) = organic acidaemia
- Obstructive jaundice = cortisol deficiency

NEONATAL HYPOGLYCAEMIA

Differential diagnosis

- Metabolic disorders
- Endocrine disorders

NEONATAL HYPOGLYCAEMIA

Differential diagnosis

Metabolic disorders

glycogen storage disease
fructose-1,6-bisphosphatase deficiency
organic acidaemias
disorders of Fatty acid oxidation
tyrosinaemia type 1
respiratory chain disorders
(hereditary fructose intolerance)

NEONATAL HYPOGLYCAEMIA

Differential diagnosis - Endocrine disorders

| | |
|--------------------------------|--|
| Hyperinsulinaemia | Persistent hyperinsulinaemia of infancy Glutamate dehydrogenase deficiency Glucokinase deficiency Transient disorders |
| Adrenal failure | Congenital adrenal hyperplasia Adrenal hypoplasia |
| Hypopituitarism | Midline defects |
| Glucagon deficiency (?) | |

INVESTIGATION OF ACUTE HYPOGLYCAEMIA

Blood/plasma

metabolites

glucose
free fatty acids
ketones
lactate (and pyruvate)
acyl carnitines

hormones

insulin and C-peptide
cortisol
growth hormone

Urine

organic acids

TREATMENT

Usually before the diagnosis is known

METABOLIC DISEASE IN THE NEWBORN PERIOD

TREATMENT

- 1. Stop any suspected 'toxic' nutrient** protein/galactose/etc
- 2. Give high energy intake** oral / intravenous
- 3. General neonatal care** **correct:**
 - dehydration
 - infection
 - hypothermia
 - acidosis

METABOLIC DISEASE IN THE NEWBORN PERIOD

TREATMENT

Metabolic acidosis

pH < 7.1 (or > 7.1 but deteriorating)

Sodium bicarbonate starting with half correction
(base deficit x weight (kg) x 0.3) / 2

- Administer slowly**
- Review frequently**
- Monitor potassium**
- Consider THAM if fluid or sodium overload**

pH > 7.1 **Correct tissue perfusion, dehydration, etc**
Keep under review

METABOLIC DISEASE IN THE NEWBORN PERIOD

TREATMENT

1. Stop any 'toxic' nutrient
2. Give high energy intake
3. General neonatal care **correct:**
 - dehydration
 - infection
 - hypothermia
 - acidosis
4. Dialysis
 - haemofiltration / haemodialysis / haemodiafiltration (peritoneal) ~~exchange transfusion~~
5. Insulin infusion (~0.05u/kg/h and increase as necessary)
6. Vitamins and specific therapy

METABOLIC DISEASE IN THE NEWBORN PERIOD

Co-factor responsive disorders

| | |
|--|--|
| Methylmalonic acidaemia | Hydroxocobalamin (Vitamin B ₁₂) |
| Holocarboxylase synthetase deficiency | Biotin |
| Biotinidase deficiency | Biotin |
| Early Onset fits | Pyridoxine and pyridoxal phosphate |

METABOLIC DISEASE IN THE NEWBORN PERIOD

SPECIFIC TREATMENT

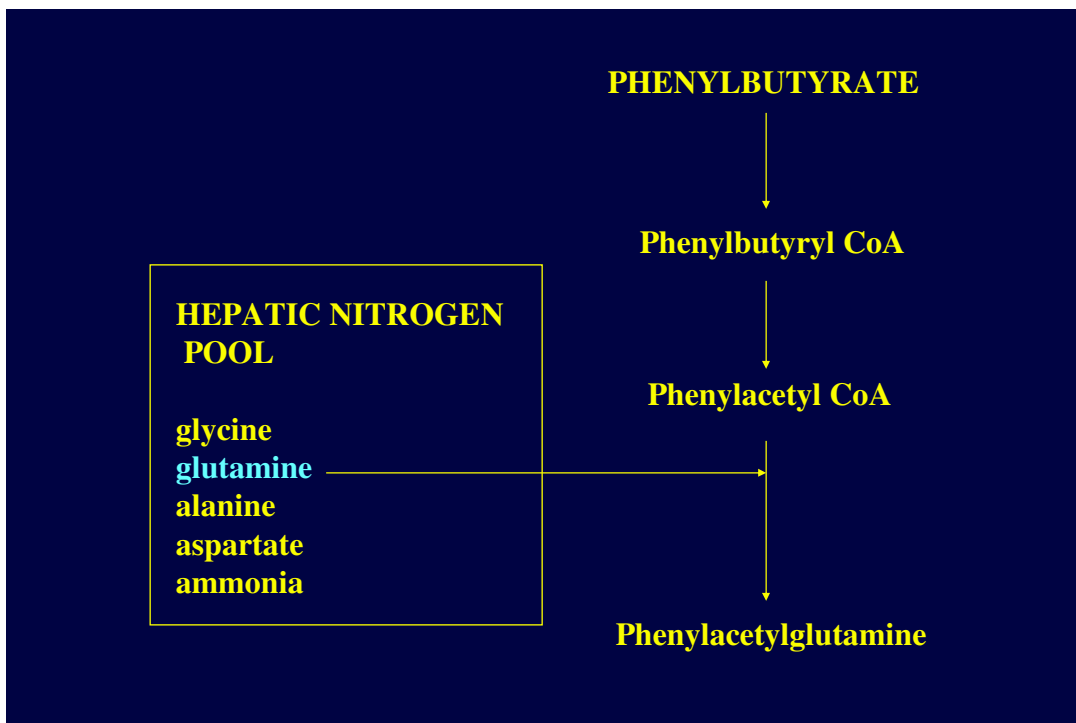
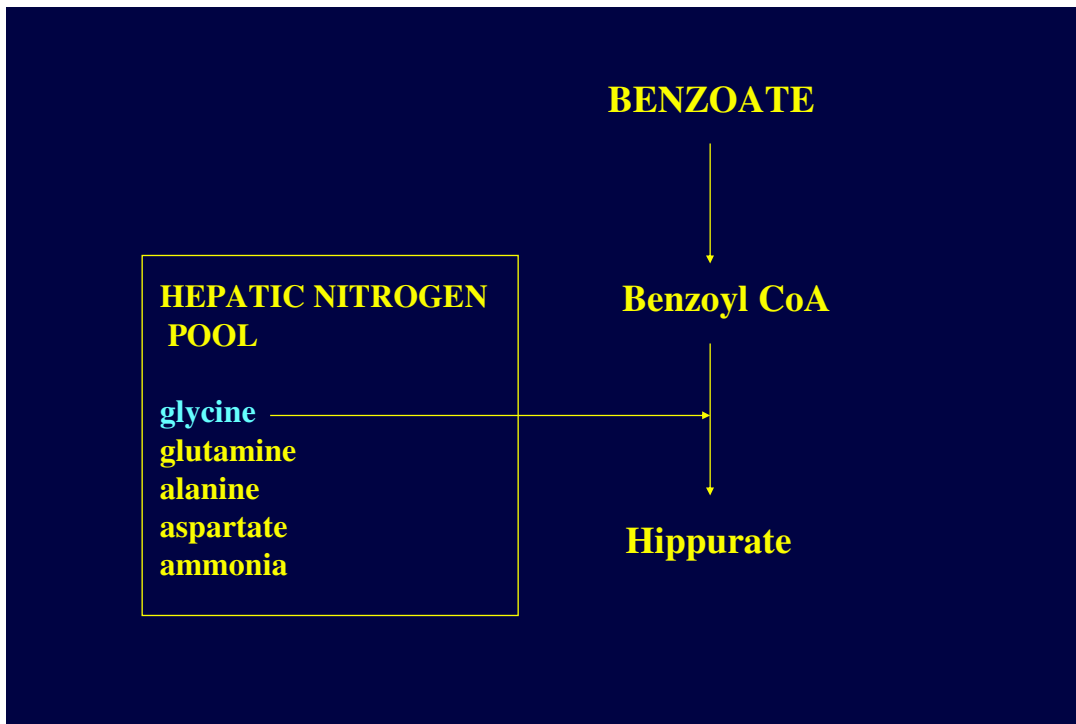
| | |
|--------------------------|---|
| Nitisinone (NTBC) | Tyrosinaemia type 1 |
| Carnitine | Organic acidaemias Carnitine transporter deficiency (other disorders of fatty acid oxidation) |
| Glycine | Isovaleric acidaemia |

METABOLIC DISEASE IN THE NEWBORN

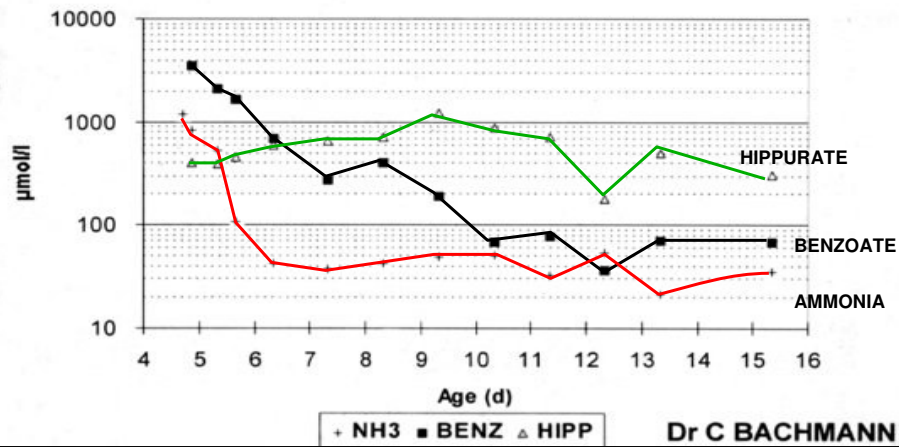
Treatment of Acute Hyperammonaemia

VERY URGENT!

- 1. DIET** stop protein
- 2. ENERGY INTAKE** give glucose oral / intravenous ± lipid
- 3. NEONATAL CARE** ? hypothermia
- 4. DIALYSIS** haemodialysis/haemofiltration (peritoneal)
- 5. SODIUM BENZOATE and SODIUM PHENYLBUTYRATE**



**Benzoate, Hippurate and Ammonia in Plasma in a Patient with neonatal ASA-uria
(tt: 300 mg NaBenzoate/kg bw. per day)**



NEONATAL HYPERAMMONAEMIA

Sodium benzoate in pregnancy

Good control of hyperammonaemia in babies at risk of a urea cycle disorder.

Das AM, et al Prenatal Benzoate Treatment in Urea Cycle Defects. Arch Dis Child Fetal Neonatal Ed. 2008 (epub)

METABOLIC DISEASE IN THE NEWBORN

Treatment of Acute Hyperammonaemia

- 1. DIET** stop protein
- 2. ENERGY INTAKE** give glucose oral / intravenous ± lipid
- 3. NEONATAL CARE** ? hypothermia
- 4. DIALYSIS** haemodialysis/haemofiltration (peritoneal)
- 5. SODIUM BENZOATE and SODIUM PHENYLBUTYRATE**
- 6. ARGININE**
- 7. INSULIN INFUSION**

METABOLIC DISEASE IN THE NEWBORN

Early Onset Fits

- 1. Diagnosis**
- 2. Treatment** with EEG and resuscitation facilities
 - **Pyridoxine** 50 – 100mg oral
 - **Pyridoxal-5-phosphate** 30 mg/kg oral
 - **Folinic acid** 5 - 30 mg oral

OUTCOME

MAPLE SYRUP URINE DISEASE

Outcome of classical disease

| | | IQ mean (SD) | Sib IQ |
|-----------------------------|---------------|-----------------|-----------|
| All patients | (n=13) | 78 (24) | 92 |
| Symptomatic | (n=10) | 74 (26) | 92 |
| Prospective | (n=3) | 91 (5) | 96 |
| Diagnosis <5 days | (n=5) | 97 (13) | 91 |
| >6 days | (n=8) | 65 (20) | 94 |

Kaplan et al 1991

MAPLE SYRUP URINE DISEASE

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Kaplan et al 1991

NEONATAL HYPERAMMONAEMIA

Outcome of OCT deficiency presenting in neonatal period

Symptomatic IQ 53 ± 6
related to duration and severity of
hyperammonaemia

Prospective IQ 97
range 57 - 133

Brusilow 1989

INBORN ERRORS PRESENTING IN THE NEWBORN PERIOD

CONCLUSIONS

- **High index of suspicion**
- **Early intervention**

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EMERGENCY PROTOCOLS

BIMDG website www.bimdg.org.uk

Emergency protocols - standard and A&E versions

Management of neonates at risk of UCDs, Organic acidaemia etc,

Management of those with inborn errors requiring surgery

Undiagnosed hyperammonaemia, cyclical vomiting, hypoglycaemia

And general information such UCD medicines dose calculator