METABOLIC & ENDOCRINE DISTURBANCES

Treatment of metabolic acidosis

in a haemodynamically stable baby:

where the base deficit ECF is >10 in a baby in whom there are no signs of hypovolaemia (such as increasing toe core gap, poor capillary refill) and no signs of hypotension;

where there is a base excess ECF of >10 the amount of bicarbonate which is given is a half correction which is calculated as folows:

0.3 x base excess x baby's weight ÷ 2

This is equivalent to the number of ml and half the number of millimoles of sodium bicarbonate that is required if 4.2% sodium bicarbonate is used (there is 0.5 mmol/ml of Hco_3 in 4.2%). This should be infused slowly at a rate of 1-2 ml/hr and no boluses of bicarbonate should be given over a period of <30 mins.

In small pre-term infants a figure of 0.4 is used because of the higher water content of the body (increased proportion of extra-cellular fluid).

1. Treatment of metabolic acidosis in a haemodynamically unstable baby:

   Differential diagnosis of metabolic acidosis in the pre-term include:

   a) hypoxaemia or ischaemia secondary to perinatal asphyxia

   b) severe lung disease

   c) volume depletion

   d) myocardial dysfunction caused by immaturity, sepsis or asphyxia

   e) severe acidosis caused by neonatal metabolic disorder is rare but must be considered.

   The most common causes in the haemodynamically unstable baby include hypovolaemia and hypotension.

   If there are signs of hypovalaemia - such as increasing toe core gap, worsening metabolic acidosis, poor capillary refill - the baby will need to be corrected with the appropriate fluid volume, blood if there is any anaemia (see transfusion protocol), or significant natural or iatrogenic blood loss, and possibly fresh frozen plasma if there is a coagulation defect and in very rare cases either albumin or normal saline solutions. If there is hypotension and there is no sign of hypovalaemia, it is possible that you may need to use ionotropes to counteract metabolic acidosis and hypotension (see hypotension protocol).

Inherited Metabolic Disorder

SAMPLES TO COLLECT WHEN AN INHERITED METABOLIC DISORDER IS SUSPECTED IN AN ACUTELY ILL BABY/CHILD

The most useful samples are those taken at the time of admission, when acutely ill, and this opportunity should not be missed. If a non-metabolic diagnosis is made subsequently, samples for the special biochemical tests can always be discarded.

1) Samples for essential preliminary tests

Haematology: Full blood count, differential and platelets
Clotting studies if suspect liver damage (bleeding, jaundice, hepatomegaly)

Biochemistry:

BLOOD Arterial blood gases and acid-base status; biochemical profile, including electrolytes and liver function tests, plasma glucose and plasma amino acids.

URINE Must be saved for organic acids and amino acids. The best sample is the first urine passed at the time of acute admission. Diagnostic abnormalities often disappear quickly following intravenous glucose or other resuscitation. A urine bag should be applied at one and, if possible, at least 5 ml of urine collected. This should be placed in a sterile urine bottle. Smell it! Test it (on the ward) with a Multistix, or similar (note especially, pH, ketones, glucose) and with a Clinitest. Then send it straight to the laboratory or, if out-of-hours, freeze it (ice cream compartment of ward specimen fridge). The next sample of urine passed should be saved as well.

Other tests at the time of presentation may be indicated by the clinical features, e.g. plasma ammonium (unexplained intractable fitting; Reye's syndrome-like illness); plasma insulin, growth hormone, cortisol (hypoglycaemia).

2) Hypoglycaemia without obvious cause
- acute samples

(These do not apply to the majority of babies with 'common' neonatal hypoglycaemia!)

Blood for: glucose, insulin, growth hormone, cortisol, amino acids (with alanine quantification), 3-hydroxybutyrate, free fatty acids, liver function tests, lactate (if hepatomegaly). If possible, take 2 ml of 'spare' blood into a lithium heparin tube, which can be separated and stored for special tests (e.g. carnitine).

* The first urine passed must always be tested for ketones and stored for organic acid and amino acid analysis.

Urea and electrolytes and, perhaps, blood gas and acid-base status will be needed for management.

Plasma ammonium should be measured in cases with a Reye's syndrome-like illness. (Note: when the child has recovered from the acute episode, it may be very difficult to establish a diagnosis without recourse to a fasting test, with the associated risks.)

3) Children with suspected hyperammonaemia

Ammonium is measured usually when a urea cycle defect is a possible diagnosis. Ammonium should be measured in any newborn with unexplained lethargy, neurological disturbance, fits, vomiting or hyperventilation, especially if the baby was well initially, in the first 24-72 hours of life. (Significant values generally exceed 150 μmol/L).

Later, measurement is indicated in any child with a Reye's syndrome-like illness or unexplained coma, or with epijsodes of ataxia, vomiting, drowsiness, disorientation or bizarre behaviour, or severe epilepsy. (Significant values generally exceed 80 μmol/L).

* Samples should also be collected for the 'essential preliminary tests' (page 1).

4) Encephalopathic child with Reye's syndrome-like illness
Samples to collect

Features, typically:	effortless vomiting; increasing lethargy; irritability; drowsiness progressing rapidly to delirium and coma, sometimes with fits.
At presentation:	liver is usually enlarted; hypoglycaemia. A metabolic defect must always be considered: especially fat oxidation defects (e.g. MCAD deficiency); urea cycle defects; organic acid disorders.
Blood for:	ammonium
	glucose
	biochemical profile
*	3-hydroxybutyrate and free fatty acids
	salicylate
*	carnitine
	lactate
	clotting studies
Urine for:	ketones
	organic acids
	amino acids
*	orotic acid

* Analyses may be unnecessary after preliminary results available.

5) Acutely ill child who is dying
in whom an inborn error is a strong possibility
Samples to collect

1. Samples listed for essential preliminary tests (page 1). * Essential to collect

and freeze urine.

2. Consider need for plasma lactate: ammonium.

3. Take 2 or 3 ml of 'spare' plasma to be frozen, in case of need.

4. Also take 5 ml blood into an EDTA tube, to be saved for future DNA analysis. The whole blood (not to be centrifuged!) may be stored at 4^0 C and sent as soon as possible to the local tissue culture laboratory. If forewarned, they will advise about, or supply, appropriate medium.

   In an emergency, skin biopsies may be kept overnight at 4^0 C in a dry sterile container (tissue culture laboratories vary in their preference). **DO NOT FREEZE!**

   Sterility is of paramount importance in collecting biopsies, particularly post-mortem. Skin should be cleansed thoroughly with, e.g., Hibitane and then dried with an alcoholic swab.

   From a living baby - use local anaesthetic. The inner side of the forearm or the back of the arm, just above the elbow, are suitable sites.

   After death - collect two biopsies from different sites and place into separate bottle of media.

5. If non-ketotic hyperglycinaemia is a possibility, 0.5-1 ml of CSF should be frozen (plain tube). If a congenital lactic acidosis, 0.5-1 ml CSF into a fluoride tube.

6. In rare circumstances in which deficiency of a liver enzyme which is not expressed in fibroblasts is a strong possibility (e.g. some urea cycle defect; von Gierke's disease) liver biopsy should be collected. If to be collected immediately post-mortem, it is kinder to obtain parental consent before death.

Two or three needle biopsies of tissue should be taken, wrapped in aluminium foil, and snap frozen in liquid nitrogen or solid carbon dioxide. Samples should be stored frozen, as cold as possible (-70^0C, or in liquid nitrogen preferably).

If histology, electron microscopy, or cytochemistry are required, additional tissue should be placed immediately into appropriate preservatives.

6) Special biochemistry tests
Samples to collect

* Plasma ammonium:	2 ml (minimum) blood into EDTA tube Must reach the laboratory within 10 mins of collection
* Plasma lactate:	2 ml (minimum) blood into fluoride tube (i.e. glucose tube) Must be taken straight to laboratory
Plasma amino acids:	1 ml blood into lithium heparin tube
Plasma free fatty acids:	1 ml into fluoride tube

Plasma for carnitine: 1 ml (minimum) into lithium heparin tube

CSF for glycine: 0.5-1ml into plasma tube

*CSF for lactate: 0.5-1ml into fluoride tube

Urine for organic and amino acids - at least 3 ml into a plain (MSSU) bottle. Send straight to laboratory during working hours. Freeze overnight if out-of-hours.
- if a dying child and very little urine, send whatever you can, however little!

Tissue culture fluid for skin biopsies - during working hours can be obtained from Histopathology, Level E, South Block.
- out-of-hours, put skin biopsies into a sterile (MSSU) bottle and keep at 4^0C (**do not freeze**). Next day, contact the Cytogenetics laboratory at Guy's Hospital.

* These must only be sent after discussion with the laboratory, since they need imediate analysis.

Problems With The External Genitalia & Genital Ambuguity

Any baby suspected of an intersex problem needs to be considered a medical and psycho-social emergency. Intersex problems should be identified and diagnosed early in the neonatal period in order to (1) diagnose congenital adrenal hypoplasia before the occurrence of adrenal crisis; (2) designate the correct sex of rearing; (3) correct problems early so that the patient may go through infancy and childhood with a normal body image and gender identity; (4) provide genetic counselling; (5) identify those at increased risk of developing a gonadal tumour.

In the Delivery Suite

Every baby must have a careful genital examination to verify the correctness of sex assignment and attempt to identify any problems early.

A normal genital examination in the newborn:

Female - vaginal opening fully visible (3 to 4 mm slit or still at orifice with heaped up mucosa) i.e. no posterior labial fusion. Clitoris width 2 to 6 mm, absence of gonads in labia majora in inguinal region.

Male - urethra at tip of glands (which may be inferred by a fully developed foreskin). Penis of normal stretched length (2.5 to 5 cms) and diameter (0.9 to 1.3 cms). Bilateral testes of normal size (8 to 14 mms) in the scrotal sacks.

If a baby is found to have overtly ambiguous genitalia the parents should be told something along the following lines: "the genitalia are unfinished in their development and we will need a few days to perform some studies to determine which sex your baby was intended to be".

The midwife or SHO or ANNP who identifies the problem should contact the Registrar and Consultant as soon as possible to come and counsel the family. Both parents should be present if possible, and as part of the discussion the infant's genitalia should be examined with the parents. The Consultant should outline what will happen (procedures - including imaging, consultations with surgical consultants)

and the time frame for results becoming available. Parents should be discouraged from the use of names which do not clearly identify gender (Alex, Lee, Pat etc). The family should be assured that when the data from the tests are available the correct sex will be known.

The parents should be advised that the baby should not be registered until the sex of the baby is known. The parents have up to six weeks to register the birth.

Referral for counselling and support to social worker or counsellor (Julia Wallace) may be helpful. Do not guess the sex of the baby. Bonding to the infant by parents may be seriously impaired if the professionals change their mind about the sex.

Characteristics of ambiguous genitalia:

Abnormality of any two of the following:
Phallus - size*,†
Urethral meatus - location
Labioscrotal folds - fusion
Gonad(s) - location or size‡

Presence of any of the following abnormalities
With male-appearing genitalia:

Micropenis*	Growth hormone or LH deficiency Testosterone deficiency (in second, third trimester) Partial androgen insensitivity Syndrome; idiopathic
Hypospadias (more severe, penoscrotal and perineal)	True hermaphroditism Mixed gonadal dysgenesis, dysgenetic testes XX male Male or femal pseudohermaphroditism Syndrome; idiopathic
Impalpable gonads	Anorchia Persistent mullerian duct syndrome XX with 21- or 11β-hydroxylase deficiency Cryptorchidism
Small gonads‡	XXY, XX male, dysgenetic or rudimentary testes
Inguinal mass (uterus or tube)	Persistent mullarian duct syndrome, dysgenetic testes

With female-appearing genitalia:

Clitoromegaly†	XX with 21- or 11β-hydroxylase or 3β-HSD deficiency Other female pseudohermaphroditism True hermaphroditism Gonadal dysgenesis, dysgenetic testes Male pseudohermaphroditism Tumor infiltration of clitoris Idiopathic
Posterior labial fusion	As for clitoromegaly

Palpable gonad(s)	True hermaphroditism Mixed gonadal dysgenesis, dysgenetic testes Male pseudohermaphroditism
Inguinal hernia or mass	As for palpable gonad(s)

*Length of penis is determined using maximally stretched penis, with ruler depressing suprapubic fat above pubic symphysis and measurement made from base of penis to tip of glans, ignoring excess foreskin. Width of stretched penis is measured at midshaft. Micropenis is defined by a stretched length or width below -2.5 SD of mean for age.
†Clitoris is abnormally enlarged if its width is more than 6 mm in neonate. The examiner should gently to firmly press the shaft of the clitoris between the thumb and forefinger to exclude excess skin from the measurement.
‡Gonad is abnormally small if longest diameter is less than 0.8 cm.

Diagnostic Evaluation of Intersex Problems in Newborn Babies

1. History: maternal androgens, drugs, teratogens; affected relatives; siblings who died in infancy; consanguinity
2. Examination: genitalia, gonads, rectal, hyperpigmentation, Turner stigmata, dysmorphic features
3. Investigations: a) chromosomes - rapid test (FISH) for X and Y chromosomes, karyotype. Send urgently to Guy's Hospital;

b) biochemistry - start a 24 hr urine collection (or timed spot >10 ml) in a plain bottle for steroid metabolites. Send the sample to Dr Norman Taylor at King's College Hospital. Send the sample via the Biochemistry Lab at RSCH, marked urgent, on a yellow form;

c) 17-OHP - take the blood sample after the first 48 hours as it may be elevated normally in the first 48 hours (1 ml red top without gel sent to Biochemistry Lab on a yellow form marked urgent, to be forwarded to a National Centre);

d) in babies where there is a concern about congenital adrenal hypoplasia, take blood for daily electrolytes and glucose until the result of 17-OHP is known. Watch for an early increase in the potassium.

Further investigations may be planned after discussion with neonatologist, surgeon, radiologist and endocrinologist.

4. Imaging: endoscopy, retrograde genitogram; ultrasound
5. Biochemical:

<u>If patient is</u>:	<u>Obtain serum levels at appropriate ages for</u>*:
XX with mullerian ducts	17OHP, CpdS, $17OHP_e$,T
XX without mullerian ducts	T, E_2, LH, FSH
XY with mullerian ducts	T, E_2, LH, FSH
XY without mullerian ducts	T, DHT, LH, FSH, and: If T/DHT is increased, determine urine etiocholanolone/ androsterone ratio, or if T is normal to low, obtain A,

DHEA, 17OHP, P, and $17OHP_e$

Basal hormone studies, if done at:

0 to 36 hours -	testes are active because of prior in utero hCG stimulation; T and DHT levels are increased
0.5 to 4 months -	pituitary-testicular axis is physiologically active; LH, FSH, T, and DHT are increased (peak levels occur at 1 to 2 months in term infant, later in premature infant)
Any age -	adrenal steroids are abnormal in untreated congenital adrenal hyperplasia

Hormone stimulation tests:
hCG (500 to 1,500 units intramuscularly or subcutaneously every 2 to 4 days over 1 to 2 weeks) - useful to assess for presence or adequacy of testicular (Leydig cell) tissue or to diagnose a testosterone biosynthetic defect after basal testing is done

ACTH - may be useful to dianose 17,20-desmolase deficiency
6. Gonadal biopsy: generally deferred until genital surgery is done at older age and limited to certain diagnoses, e.g. true hermaphroditism, gonadal dysgenesis with a Y chromosome, dysgenetic testes, rudimentary testes, XX male, persistent mullerian duct syndrome, and Leydig cell hypoplasia.

*A, androstenedione; CpdS, compound S or 11-deoxycortisol; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; E_2, estradiol; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; 17OHP, 17-hydroxyprogesterone; 17OHPe, 17-hydroxypregnenolone; P, progesterone; T, testosterone.

TANDEM-Mass-spectroscopy

Get blood on Guthrie-card

Send to
Peter Barnfield
Paediatric Biochemistry
Metablic Lab
Level IV
Guy's Tower
Guy's Hospital
London
Short cut phone: 8229 ext

Neonatal Thyroid Disorders

Neonatal hyperthyroidism is usually caused by transplacental passage of thyroid stimulating immunogobulins (TSIs) for mothers with Graves Disease or Hashimoto Thyroiditis. The preverence of Graves Disease in pregnant women is approximately 0.2% and it is likely that less than 10% of their babies will have overt hyperthyroidism. One case of overt neonatal thyrotoxicosis may present for every 4000 to 5000 deliveries with a further 3% of babies of mother's with Graves disease having biochemical thyrotoxicosis in the absence of symptoms. The incidence of hypothyroidism in babies of mothers who require treatment with anti-thyroid drugs to

term may be as high as 22%. Mortality has been reported to be 12-20%, usually from heart failure, but other complications include tracheal compression, infections and thrombocytopenia.

TSI's may continue to be produced even after ablation of the thyroid gland in the mother with surgery or radioiodine. Neonatal thyrotoxicosis secondary to TSI is a transient disorder limited by the clearance of maternal antibody from the baby's circulation. There is a rarer form of persistent hypothyroidism, usually, dominantly inherited which can occur in the absence of maternal autoimmunity because of activating mutations in the TSH receptor and activating mutations of the stimulatory G protein in McCune-Albright Syndrome. These conditions should be suspected if there are more than two generations affected by thyrotoxicosis or there are other 1st degree relatives with thyrotoxicosis.

Clinical features:

Complications are increased in mothers who remain hyperthyroid in the second half of pregnancy. The fetus is often growth retarded both from a direct affect of hyperthyroidism and associated pre-eclampsia. Tachycardia is common. Non-immune hydrops may occur. Goitre may be apparent on ultrasound scanning. In the baby, signs and symptoms of thyrotoxicosis may be obvious at birth or delayed for several days because of the effect of maternal anti-thyroid drugs or the effect of co-existent blocking antibodies. Symptoms are usually apparent by 10 days of life. Most infants have goitre. Symptoms include irritability, jitteriness, and restlessness. Eye signs may be present in the absence of maternal eye signs. Tachycardia and arrhythmia may progress to cardiac failure. Systemic and pulmonary hypertension may be present.

Transient neonatal hypothyroidism may occur in babies of mothers with a current or past history of Graves disease. This may be due to transplacental passage of the thionamides or due to the blocking nature of some thyrotrophin binding inhibitory immunoglobulins.
Investigation of babies of mothers with thyroid disease
Maternal hypothyroidism

This is usually secondary to Hashimoto's thyroiditis and the mother may be producing thyroid inhibiting or rarely thyroid stimulating antibodies so the baby may develop transient hypothyroidism or, very rarely, hyperthyroidism. These babies should be reviewed at 10 days to 2 weeks and thyroid function taken (TSH and fT4).

If the maternal hypothyroidism is secondary to congenital aplasia or hypoplasia of the thyroid gland, there is only a slightly increased risk to the baby of hypothyroidism and Guthrie should suffice.

If the hypothyroidism is secondary to treatment (surgery or radioiodine) for Graves disease, the baby is at risk of neonatal thyrotoxicosis and will need to be managed as below.

Maternal Thyrotoxicosis
Babies at risk for congenital hyperthyroidism
(Maternal Graves disease, family history of activating mutations in THS receptor)

↓

Cord Blood
For fT4, TSH, TSI (if available) concentration + examination

↓

If high risk (see table below) repeat fT4, TSH + examination
Age 2-7 days:

↓

In all babies: review in Reg Clinic, repeat fT4, TSH and examination
Age 10-14 days

↓

Results of thyroid function from any of the above:

Normal	Hypothyroid	Hyperthyroid
No treatment No clinic f/up Phone results to parents	Repeat fT4 and TSH Treat with thyroxine if confirmed	Consider treatment PTU/carbimazole +/- iodide +/- propranolol

Babies at high risk of neonatal thyrotoxicosis

Mother
Raised thyroid binding immunoglobulin levels in pregnancy
Thyroid binding immunoglobulin level not assessed
Clinical thyrotoxicosis in thrid trimester
Thionamide required in third trimester
Family history of TSH receptor mutation

Baby
Evidence of fetal thyrotoxicosis

*NB At least 1 ml of blood in lithium heparin bottle is required for fT_4 and TSH

[1] Ogilvie-Stewart A et al. Neonatal Thyroid Disorders. *Arch Dis Child Fetal Neonatal Ed 2002; 87:F165-F171*

(Updated July 2004, review July 2006)

Marfan Syndrome

Guidelines For Approaching A Baby With A Family History Of Marfan Syndrome

Variable expression in Marfan is the rule, but complete not-penetrance arise as new mutations (25%). A paternal age effect is present, on average, in sporadic cases.

You need to do the following:

FAMILY HISTORY

Who is affected. Ask about family history of Marfan Syndrome. Draw a family pedigree.

Look for any clinical evidence of Marfan in the family by asking if there is any family history of

Lens dislocation and myopia
Tall stature
Stillbirth
Cardiac manifestations e.g. ruptured aortic aneurysm
Skeletal manifestations

Ask if any chromosomal analysis was carried out before on any family members particularly parents and ask about result.

Baby Details

Full clinical examination of the baby looking for neonatal manifestations of Marfan's syndrome e.g. subluxation, long limbs, arachnodactly.
Arrange with

Sonalee Laboratory for Marfan Syndrome and Related Disorders
Department of Cardiological Sciences
St George's Hospital Medical School
Direct Line: 020 8725 5248

Currently (2001) there is an 80% chance of detecting a mutation in affected children.

For the baby to have a mutation screen (a minimum of 5ml of blood). You need to send a letter along with your sample detailing family history and full clinical details of the baby. * The result can take six months *.
There may be a charge for the investigation. If so, then please make sure you have clarified this with the consultant concerned.

<u>Plan:</u>

If the screen comes back positive, the baby will need referral to the general paediatric service for long term follow-up.