Guideline for the Investigation of Neonatal Conjugated Jaundice

Liver Steering Group, BSPGHAN **Revised December 2016**

Introduction

This guideline aims to advise clinicians on the initial investigations necessary when an infant with conjugated jaundice is identified. It is aimed at General Paediatricians, Neonatologists and Paediatric Gastroenterologists, who are the clinicians most likely to encounter infants with jaundice, and who should initiate investigations and then discuss with a Specialist Liver Centre. It is important that all infants with conjugated jaundice who are ill or who have pale stools are discussed with the Specialist Centre urgently, even while awaiting the results of the suggested investigations. In some instances, it may be appropriate for infants with conjugated jaundice to be referred directly to the Specialist Service without prior referral to the Regional Centre, depending on local expertise.

1. Definition of neonatal conjugated jaundice:

All infants who remain jaundiced at two weeks of age (or three weeks if born pre-term defined as less than 37 weeks gestation) should have a blood sample obtained for serum bilirubin, with both total and conjugated bilirubin values being assayed. If conjugated bilirubin is > 25 micromoles/litre, then this is the NICE definition of significant conjugated jaundice ("neonatal cholestasis") that warrants further investigation. It is also helpful to consider the percentage of the total bilirubin that is conjugated, with > 25% likely to be significant. If conjugated bilirubin level is > 25 micromoles/litre and / or > 25% of the total bilirubin, then the infant should be investigated promptly for possible underlying liver disease.

2. Clinical picture of liver disease in the newborn infant may be varied, and includes:

- An ill infant with liver failure, with a coagulopathy unresponsive to intravenous vitamin K
- An infant with jaundice without obviously pale stools, who may also have elevated liver enzymes ("neonatal hepatitis syndrome")
- An infant with jaundice and pale stools suggestive of biliary obstruction or a neonatal cholangiopathy.

However, there may be considerable overlap, and the differential diagnosis is wide. Early discussion with a Specialist Liver Service is necessary, particularly in those infants with liver failure or biliary obstruction. Please be aware that stool colour can be notoriously varied: there is a helpful stool colour chart on the CLDF web page (http://yellowalert.org/Baby-Jaundice). Do not delay in discussing infants while awaiting investigations if there is any concern.

3. Diagnoses that are amenable to specific treatment include:

- Bacterial sepsis
- Metabolic disease including galactosaemia and tyrosinaemia
- Endocrine disorders including hypopituitaritism and hypothyroidism
- Biliary obstruction due to biliary atresia or choledochal anomaly
- Gestational alloimmune liver disease GALD (previously termed neonatal haemochromatosis)

4. It is important to PREVENT significant complications of neonatal cholestasis including:

- Intracranial bleeding due to vitamin K malabsorption, by administering intravenous vitamin K to an infant with prolonged coagulation
- Hypoglycaemia: by monitoring glucose and ensuring adequate feed or fluid

5. Contact details for National Specialist Centres for Paediatric Hepatology and Transplantation

BIRMINGHAM
The Liver Unit, Birmingham Children's Hospital
Consultant Paediatric Hepatologist: switchboard 0121 333 9999
Registrar: via switchboard 0121 333 9999 and request registrar phone or bleep 55200
Nursing team: Liver Direct 0121 333 8989 or email Liver.Direct@bch.nhs.uk
Ward: Liver Unit Ward 8: 0121 333 9066
Office Fax: 0121 333 8251

LONDON
Paediatric Liver, Gastroenterology and Nutrition Centre, King's College Hospital, London
Phone 020 3299 9000
Fax 0202 3299 4228
Bleep 426 weekdays 9am-5pm
Phone 07866792368 (5pm-9am)

LEEDS
Children's Liver Unit, Leeds Children's Hospital.
Consultant Paediatric Hepatologist: switchboard 0113 2432799
Registrar: via switchboard or ward and request paediatric hepatology registrar (9am-5pm weekdays) OR Paediatric Specialty Registrar On Call (5pm-9am weekdays and weekends).
Clinical Nurse Specialist Team: 0113 3926151 / 3926138
Ward 50: tel 0113 3927450
Fax 0113 3925129 (Admin Office) or 0113 3923110 (Ward Doctors Office)

6. First and Second Stage Investigations which may be appropriate are summarised below. The results summary sheet should be updated and should accompany any referral document.

First Stage Investigations

These should be performed on infants with prolonged conjugated jaundice who are clinically stable.

History
Birth weight, type of milk feed, maternal illness, family illness, exposure to infection, previous affected children, obstetric history, early neonatal history (prematurity, parenteral nutrition, sepsis, congenital heart disease).

Clinical examination
Particular attention should be made to document dysmorphic features, skin rash, head circumference, cataracts, hepatosplenomegaly, heart murmurs and stool colour.

Haematology

- Full blood count and reticulocyte count
- Blood group and Coombs test
- INR and prothrombin time:
  If prolonged, give a dose of intravenous vitamin K 300 microgrammes/kg. Repeat the coagulation profile four hours later. If still abnormal, contact a liver centre urgently.
- APTT and fibrinogen

Biochemistry

- Blood Sugar and/or BMs pre-feed in first 24 hours of admission
- Na, K, urea, creatinine, serum lactate and bicarbonate
- Calcium, phosphate
- Bilirubin (total and conjugated)
- ALT+/-AST, Alkaline phosphatase, GGT
- Albumin
- Cholesterol and triglycerides

Metabolic investigations

- Galactose-1-phosphate uridyl transferase
- Alpha-1-antitrypsin level and phenotype
- Plasma and urine amino acids
- Urine organic acids (including succinyl acetone)
- Ward test urine for protein

Endocrine investigations

- Thyroid function
- Cortisol (ideally after four hour fast)
  If low: perform short synacthen test

Microbiology

- Blood and urine culture
- Urine for CMV
- Serology: TORCH, Hepatitis A,B,C and E
- Blood for HSV PCR, stool for enterovirus

Imaging
Ultrasound scan of abdomen should be performed in the fasting state: a four hour fast is usually adequate. Assessment should be made of liver size, texture and morphology, biliary tree, presence or absence of gall bladder, spleen size, presence of ascites and hepatic vessel patency.

Second Stage Investigations

These should be performed as appropriate, after considering the history, examination and first line investigation results. Discussion with a specialist centre is advisable.

Hepatobiliary scintigraphy / isotope excretion scan (eg HIDA)
Pretreatment with phenobarbitone 5mg/kg once daily (at night) should be completed for at least three days. Imaging should continue until 24 hours post isotope injection if there is no excretion seen at 4 hours

Liver Biopsy: This is seldom indicated, as other investigations may provide adequate information, and histology may be non-specific. Need for liver biopsy should be discussed with specialist centre, and only performed locally if there is sufficient expertise.

Molecular and extended virology: Syphilis serology and PCR for viruses on blood, stool or NPA may be indicated according to history

Ophthalmology assessment: To assess for evidence of Alagille syndrome (posterior embryotoxon), congenital infection (chorioretinitis), endocrine disorders (septo-optic dysplasia) or metabolic disorders (cataracts, retinal signs),

Spine X-Ray: For evidence of Alagille syndrome (butterfly vertebrae)

Cardiology assessment and CXR: If heart murmur present, or if other signs of Alagille syndrome.

Other investigations for rare disorders:

Blood:
Lactate, ammonia, pyruvate, uric acid, carnitine and acyl carnitine
Very long chain fatty acids or white cell enzymes (glycogen or lysosomal storage disorders)
Bile acids (quantitative and qualitative): *ideally when OFF ursodeoxycholic acid. If taking urso, specify on request form*
Alpha fetoprotein
Transferrin iso-electric focussing
Ferritin and transferrin saturation
Blood spot for LALD

Urine
Qualitative bile acids: *ideally when NOT taking urso. If on urso, specify on request form*
Tubular resorption of phosphate

CSF: Protein and lactate: *only after normalisation of coagulation*

Tissue
Muscle biopsy for mitochondrial cytopathy
Bone marrow aspirate / trephine for storage disorders
Skin biopsy for fibroblast culture

Imaging: MRI brain

Genetic testing: DNA for cholestasis gene panel, mitochondrial DNA mutations and mtDNA depletion syndrome and/or perforin expression.

Conjugated jaundice: Summary of Investigations
Revised December 2016

	Test	Date	Result
Stool Colour			
Haematology	Fbc		
	Reticulocytes		
	Group and Coombs		
	INR / PT		
	APTT / fibrinogen		
Biochemistry	Blood sugar / BM		
	U and E albumin bicarb		
	Bone profile		Ca PO4 ALP
	Bilirubin		Total conjugated
	Liver enzymes		ALT AST GGT
	Lipid profile		Cholesterol triglycerides
Metabolic	Galactosaemia		
	Alpha-1-antitrypsin		
	Plasma amino acids		
	Urine amino acids		
	Urine organic acids		
	Ward test protein		
Endocrine	Thyroid function		
	Cortisol		
	Short Synacthen test*		
Microbiology	Blood culture		
	Urine culture		
	TORCH serology		
	Hepatitis serology		
	Urine CMV		
Imaging	Fasting US scan		Liver
			Spleen
			Ascites
			Gall bladder
			Biliary tree
	Isotope scan*		
	CXR / spine X ray*		
Ophthalmology*			
Other*			

* Second line as appropriate