

## Paediatric Acute Liver Failure Protocol

For BSPGHAN website

Acute liver failure (ALF) is a potentially life-threatening condition that necessitates early recognition and optimal management and transfer to a Liver Transplant Centre for further management that might include liver transplantation.

### DEFINITION:

*A non-correcting coagulopathy with an INR > 2.0 due to liver dysfunction of less than 8 weeks duration without encephalopathy or >1.5 with encephalopathy*

High alanine transaminase (ALT) reflects hepatocyte loss and not function. ALT levels are variable and often greater than x5 times upper limit of normal (ULN) but it is *not* a criteria for diagnosis

Encephalopathy is often a late sign in ALF. A high level of vigilance should be observed especially as mild encephalopathy is hard to assess in children with ALF.

Some metabolic conditions mimic ALF and patients can become markedly encephalopathic. The differential diagnosis of ALF must therefore include metabolic diseases.

ALF can develop on a background of previously unrecognised chronic liver disease. This is termed 'acute on chronic liver failure'.

ALF may be classified as hyperacute, acute, or subacute, depending on the interval from the onset of jaundice to the development of encephalopathy.

	Hyperacute	Acute	Subacute
Time from jaundice to encephalopathy	0-1 week	1-4 weeks	4-12 weeks
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Degree of intracranial hypertension	++	++	+/-
Survival rate without emergency liver transplant	Good	Moderate	Poor
Typical cause	Paracetamol, Hep A, E	Hep B	Non-paracetamol drug induced liver injury

**All cases should be discussed *early* with a Paediatric Liver Centre**

### Aetiologies - Table 1

	NEONATES	PAEDIATRIC
--	----------	------------

GENETIC	Rapid whole genome sequencing (R14)	
<b>INFECTIVE</b>	Septicaemia e.g. Group B Strep  Congenital infection e.g. Herpes simplex virus (1 & 2), Cytomegalovirus (CMV), Syphilis  Hepatitis B, Parvovirus  Enterovirus	Hepatitis viruses A - E  HSV, CMV, EBV, Adenovirus, HHV-6 Enterovirus, Parvovirus B19, Varicella Measles, Influenza Sepsis (blood culture) <i>Leptospirosis, Q fever, Mycoplasma,</i> <i>Legionella, Brucellosis, Malaria</i> <i>Entamoeba histolytica</i>
<b>METABOLIC</b>	Galactosaemia Tyrosinemia Urea cycle defects (UCD) Organic acidaemias (OA) Congenital disorder of glycosylation (CDG)  Transaldolase deficiency  Mitochondrial disorders	Wilson disease  Fatty acid oxidation defects (FAO) e.g. Medium chain acyl-coA dehydrogenase deficiency (MCADD) Hereditary fructose intolerance Reye-like syndrome (rule out UCD, OA and FAO defects)  Mitochondrial disorders
<b>INFILTRATIVE</b>	Gestational alloimmune liver disease (GALD)  Congenital/Familial Haemophagocytic lymphohistiocytosis (HLH)  Leukaemia or other malignancy	Macrophage activation syndrome / secondary HLH  Leukaemia / other malignancy  X-linked lymphoproliferative (XLP) syndrome
<b>DRUG/TOXINS</b>	Anticonvulsants e.g. <i>Phenytoin</i>  Antibiotics	Paracetamol Anticonvulsants e.g. <i>Valproate,</i> Antituberculous e.g. <i>Isoniazid, Rifampicin</i> Chemotherapy e.g. <i>Methotrexate</i>  Others:- Antibiotics, NSAIDS Recreational drugs (cocaine, ecstasy) Herbal medications Irradiation, Carbon tetrachloride Halothane, <i>Amanita phalloides</i> (Toxic mushroom)  Check-point inhibitors e.g. anti-PD1, CTLA-4, LAG3
<b>ISCHAEMIC</b>	Hypoxic ischaemic injury e.g. antepartum haemorrhage? hypoxic ischaemic encephalopathy (HIE)?	Congenital heart disease Cardiac surgery (cross clamp time?)  Severe asphyxia Status epilepticus Major trauma Budd Chiari syndrome Venous-occlusive disease (VOD)

## EVALUATION

A full clinical history and examination to be performed with the following emphases:

### History (in context):

- Any prodromal symptoms / illnesses e.g. gastroenteritis, flu-like illnesses, febrile episodes.
- Any unwell contacts, history of foreign travel, camping, visit to rural areas, contact with farm animals / wildlife or open water swimming (lakes & rivers).
- Any history of foraging (mushroom ingestion), drinking from streams.
- Timing of onset of jaundice in relation to prodromal illness and presentation to hospital.
- Full drug history including use of analgesics/antipyretics during any illness.
- Any use of over-the-counter medicines, homemade / herbal remedies.
- Any family history of liver disease (or other significant illness) autoimmune disease, consanguinity.
- Any early/unexpected deaths in siblings or relatives
- Recreational drug use, alcohol, sexual activity, needlestick injuries
- Any Deterioration in schoolwork or clarity of speech
- Pregnancy history (jaundice in pregnancy, previous miscarriages, HELLP syndrome)
- If travel abroad – any exposure to blood products.

### Examination:

- Mental state – assess for the presence of encephalopathy (see table 2)
- Cardio-respiratory / hydration status
- Peripheral stigmata of chronic liver disease (clubbing, palmar erythema, spider naevi)
- Any evidence of spontaneous bruising or bleeding
- Presence of rash, lymphadenopathy, hepatomegaly, splenomegaly, ascites

### **Clinical stages of hepatic encephalopathy – Table 2**

<b>Stage</b>	<b>Asterixis</b>	<b>EEG changes</b>	<b>Clinical manifestations</b>
<b>I (prodrome)</b>	Slight	Minimal	Mild intellectual impairment, irritable, lethargy/mildly obtunded, disturbed sleep-awake cycle
<b>II (impending coma)</b>	Easily elicited	Generalized slowing of rhythm	Drowsiness, confusion, inappropriate/odd behaviour, disorientation/not recognizing parents, mood swings, photophobia
<b>III (stupor)</b>	Present if patient co-operative	Grossly abnormal slowing	Unresponsive to verbal commands, markedly confused, aggressive, delirious, hyperreflexia, positive Babinski sign
<b>IV (coma)</b>	Usually absent	Delta waves, decreased amplitudes	Unconscious, initial response to pain present, later decerebrate or decorticate response to pain present or absent, areflexia

### **Investigations:**

### Primary Investigations – Table 3

<b>Haematology</b>	Full blood count Blood film Coagulation screen (PT,INR, fibrinogen)
<b>Biochemistry</b>	Blood gas (inc. lactate), glucose Urea & electrolytes Liver function tests including GGT Ammonia Creatine Kinase Alphafoetoprotein Paracetamol level & 1st urine collect for toxicology
<b>Microbiology</b>	Blood culture Urine culture
<b>Virology</b>	Hepatitis A, B, C, E serology EBV & CMV serology (IgM & IgG), adenovirus, parvovirus, enterovirus Stool virology Nasopharyngeal aspirate (respiratory viruses)
<b>Immunology</b>	Alpha 1 antitrypsin level and phenotype Serum Immunoglobulins (total) Autoantibodies anti- ANA / SMA / LKM / SLA / LC1 Complement C3, C4 Caeruloplasmin (over 3 yrs of age)
<b>Metabolic</b>	Plasma amino acids Acyl carnitines Urine organic acids White cell enzymes
<b>Radiology</b>	Abdominal ultrasound (including dopplers of liver vessels) Chest X-ray, Echocardiogram (if history suggestive)

## MANAGEMENT

### Principles

- Maintenance of hydration and normoglycaemia
- Regular neuro-observations for the development of encephalopathy
- Neuroprotection
- Close monitoring of observations including acid-base status
- Close monitoring of fluid balance and urine output
- 1<sup>st</sup> line investigations to be sent at earliest opportunity (table 3).
- Avoid sedation - will complicate assessment of encephalopathy.
- Avoid blood products unless procedures/transfer are about to be undertaken (central line insertion, intubation etc)
- Avoid nephrotoxic drugs.

### Overview of Management

<b>Nursing</b>	
----------------	--

Head elevated at 30 degrees, no neck flexion, minimal handling	To decrease ICP and minimise cerebral irritability
No sedation	Masks encephalopathy, may precipitate respiratory failure
Maintain oxygenation with facial oxygen unless agitation is increased	
<b>Monitoring</b> Heart & Respiratory rate, ECG monitor Cutaneous oximetry, core temperature. Neuro-observations	4-hourly minimum – as clinically indicated
Urine output (catheterised if possible)	Aiming for >0.5mls/kg/hr
Blood glucose	Maintaining > 4mmol/L
Blood gases - including lactate	8-hourly minimum
Electrolytes including Ca, Mg & Phos	Twice daily
Liver Function Tests	Twice daily
Coagulation Screen	8-hourly
Urinary electrolytes, urea creatinine and osmolarity	Daily
<b>Fluids</b> 50-80% maintenance dextrose containing IV fluids.  Increase concentration as necessary to maintain blood glucose >4mmol/L.  Central access if >12.5% dextrose required.	
<b>Medications*</b> Broad spectrum antibiotics	Piptazobactam
Antifungals	Fluconazole or Ambisome
Antivirals - Neonates or if history suggestive	Aciclovir
IV omeprazole	daily
<b>Coagulation Support</b> IV vitamin K	Daily
Blood products (FFP, cryoprecipitate)	Only following discussion with Hepatologist
<b>Nutrition</b> Nil by mouth	Clinical suspicion of metabolic disorder – galactosaemia, urea cycle defect, fatty acid oxidation disorder
Restrict protein if sudden onset of encephalopathy in acute period	
* refer to BNFC for doses of all medications	

### **Paracetamol Overdose Treatment Protocol**

If paracetamol overdose is suspected or known, the child must be treated immediately with N-acetylcysteine, at the local hospital whatever the time between the alleged overdose and the visit to the hospital. N-acetylcysteine should be continued until the INR is normal (<1.2).

Refer to the Children's BNF, Toxbase or the UK National Poisons Information Service for reference ranges of serum paracetamol levels and indication for treatment with N-acetylcysteine and dosing regimens.

#### **Investigations & Management:**

LFTs, paracetamol level, INR, blood glucose, U&Es and blood gases including lactate. Blood glucose must be closely monitored.

Urine toxicology screen should be performed as soon as possible.

INR, blood sugar, renal function and blood gases must be repeated *at least twice a day* and, if abnormal, three times a day.

Start broad spectrum antibiotics and prophylactic antifungals if INR abnormal and in the presence of abnormal renal function.

Hypoglycaemia should be avoided, and the child maintained on 10% dextrose - higher concentrations of dextrose may be needed.

The most important prognostic parameter is acidosis on day 2. If, despite N-acetylcysteine treatment and good rehydration, the child becomes acidotic, the prognosis is poor.

Acidosis is the best prognostic factor independent from all other factors. Even in the presence of a very prolonged INR, a patient who is not acidotic will have 80% chance of surviving. If the pH is < 7.25, there is a 95% mortality. Therefore the child should be emergency listed for transplantation.

Other factors predicting a poor outcome are the development of grade 3 hepatic encephalopathy with oliguric renal failure (usually occurring 3-4 days following ingestion) and/or a prothrombin time of >100 seconds, and a raised plasma lactate.

**TRANSFER TO LIVER UNIT**

Transfer of children in ALF to a liver unit should be discussed with your local Intensive Care Transport / Retrieval service who will facilitate discussion between the receiving Liver Centre Hepatologist on call and Intensive Care Unit.

Early referral to Paediatric Critical Care is preferable before uncontrolled bleeding and encephalopathy occurs. *Any* Grade of encephalopathy and 1 more system failure (renal, respiratory, cardiovascular) should prompt immediate PICU referral.

Deterioration in level of consciousness can be triggered by any of the following events:

- Sepsis
- Gastro-intestinal bleed
- Hypovolaemia/dehydration/hypotension
- Disturbances of electrolytes or acid-base balance
- Hypoglycaemia
- Sedation
- Seizures
- Intracranial bleed
- Cerebral oedema

Poor prognostic factors for acute liver failure include:

- INR > 4
- Under 5 years of age
- Bilirubin >235 micromol/L
- Grade 3 or 4 encephalopathy in paracetamol overdose
- WBC >9 x 10<sup>9</sup>/l
- Elevated lactate

**Liver Centre Contact Details:**

<p>All Units have 24/7 Hepatology Consultant cover (Contact directly through switchboard)</p>
<p><b>Leeds General Infirmary</b> <b>Switchboard: 0113 243 2799</b> <b>08:30 - 16:30 Liver SpR on Bleep 1910</b> 16:30 - 08:30 Specialty SpR on Bleep 1904</p>
<p><b>Birmingham Children's Hospital</b> Switchboard: 0121 333 9999 Ask for 'outlier' liver registrar: 08:30 – 21:30 Will be put through to Liver SpR 21:30 – 08:30 Will be put through to the RMO on call for the hospital</p>
<p><b>Kings College Hospital</b> <b>Switchboard: 0203 299 9000</b> <b>09:00 - 17:00 Liver SpR on call: Bleep 426</b> 17:00 - 09:00 Liver SpR on call via mobile 07528 977446</p>