NEONATAL ACUTE LIVER FAILURE (Patient not known)

1 DEFINITION AND SYMPTOMS

NALF is defined by INR > 1.5 (PT ≥ 15 s; PT or factors < 50%) in the presence of encephalopathy, or INR > 2 (PT ≥ 20 s; PT or factors < 30%) in the absence of encephalopathy in a neonate < 28 days old. Hepatic encephalopathy is often absent in neonates. Neurological signs, when present, are often related to haemodynamic distress or the cause of liver failure. At this age, causes vary, but the most common include neonatal anoxia, gestational alloimmune liver disease (GALD), herpes virus infections, and hereditary metabolic diseases.

Differential diagnoses: hypovitaminosis K, congenital coagulation deficiencies

The clinical signs of neonatal acute liver failure can be misleading in an otherwise healthy-appearing baby. They may be present from birth or develop after a free interval of a few days or weeks: hypoglycaemia, neonatal distress, refusal to breastfeed or poor feeding, hypotonia, jaundice with conjugated bilirubin, which may be absent.

2 EMERGENCY TREATMENTS

- **Always transfer to a neonatal intensive care unit or neonatal resuscitation and call the hepatologist.**
- **Stop feeding** for at least 24–48 hours until initial aetiological results are available. This should be reassessed rapidly with specialist medical advice. Stop all intake of galactose (standard formula milks) and fructose (sucrose) until galactosaemia and hereditary fructose intolerance have been ruled out.
- **Polyionic infusion 10% glucose** (10 mg/kg/min, i.e. 6 mL/kg/h) with standard electrolytes. No IV protein or lipids during initial management.
- Inject 10 mg of **vitamin K** as a direct intravenous injection, repeat as needed.
- Start **IV aciclovir** while awaiting virological results.
- **Investigate and treat neonatal bacterial infections** (particularly *E. coli* in galactosaemia).
- NALF may be complicated by haemorrhagic or thrombotic syndromes. In the event of bleeding or if a major surgical procedure is planned, administer FFP (*always discuss this for neonates, due the risk of intracranial haemorrhage*).

- Specific treatment, if needed:
  - **If neonatal haemochromatosis** due to alloimmunisation is suspected (liver failure with jaundice and no free interval): Consider emergency exchange transfusion (equivalent to two blood volumes) and injection of pooled IV immunoglobulin (1 g/kg).
  - **In cases of hyperammonaemia > 100 µmol/L:** Continuous **IV sodium benzoate.** Start with a loading dose of 250 mg/kg over 2 hours, then 250–500 mg/kg/24 hours. Check ammonia levels at the end of the loading dose
  - **Carnitine if fatty acid oxidation disorder is suspected** (hypoglycaemia, rhabdomyolysis, cardiac involvement): Levocarnil 50 mg/kg/day by continuous IV infusion or divided into four doses, PO or IV.
  - **Orfadin if tyrosinaemia is suspected** (free interval of several weeks, elevated LAP, tubulopathy, elevated AFP, nodular liver): NTBC 1 mg/kg/day in two doses.

3 MONITORING

- Management: in the NICU, by a specialist team.
- ECG/SaO_2/respiratory rate/BP monitoring; neurological assessment and close monitoring of diuresis.
- Maintain normothermia
- Laboratory monitoring every 4–6 hours: at minimum, ABG, serum electrolytes, complete hepatic and haemostasis work-up
- Correct any electrolyte disturbances, maintain normoglycaemia, avoid salt overload (risk of oedema). Fluid intake must ensure normovolaemia. Energy intake must be maintained to prevent malnutrition and adjusted to the patient's neurological condition (risk of cerebral oedema) and aetiological diagnosis.

4 AETIOLOGICAL INVESTIGATION

- The aetiological investigation must be exhaustive and guided by initial clinical and laboratory data.
- It is essential to collect family and obstetric history, determine whether there was a free interval after birth, identify the presence of neurological signs or splenomegaly, and measure transaminase and conjugated bilirubin (CB) levels.
- The list of possible aetiologies for neonatal acute liver failure is long and heterogeneous, and includes a range of rare diseases. Rapid consultation with an expert centre is always required. The investigation should initially focus on treatable diseases, followed by untreatable conditions that may contraindicate liver transplantation.
- The main aetiologies (including treatable diseases) are listed in the table below (non-exhaustive list)
- In over 30% of cases, the cause remains unidentified. Ensure that the aetiological work-up is exhaustive and that DNA samples are stored.

5 AETIOLOGICAL WORK-UP TO BE CARRIED OUT

Basic work-up to be performed as an emergency in all cases of neonatal liver failure:
(tests in italics are not systematic and are only performed following specialist advice)
Blood tests:

- ABG, glycaemia, ammonaemia, lactataemia
- Serum electrolytes, calcium, albumin. Liver function tests (AST, ALT, GGT, LAP, total and conjugated bilirubin),
- PT, factors V, II, VII, X, fibrinogen, INR, D-dimers
- CBC, platelets, reticulocytes, Coombs test
- CPK, ferritin, alpha-fetoprotein, triglycerides, total serum bile acids
- PCR for herpes virus and enterovirus in blood
- Plasma amino acid chromatography. Plasma acylcarnitine profile.
- Spot test for galactosaemia before transfusion (if not possible, retrieve Guthrie test from newborn screening) Gal-1P
- Heparin tube for plasma (centrifuge and freeze). Dried blood spot (Guthrie card) before transfusion
- DNA sample (EDTA tube) to be conserved
- *Transferrin isoelectric focusing*
- *Plasma bile acid chromatography*
- *Plasma oxysterol and lysosphingomyelin*
- *Redox ratio, free fatty acids, plasma ketone bodies (β-OH butyrate, acetoacetate)*

Urine and stool:

- Urine dipstick test and electrolytes
- PCR for HSV and enterovirus in urine and stool
- Urinary organic acid chromatography
- Freeze the urine
- *Urinary succinylacetone, urinary pentose analysis, urinary orotic acid, urinary polyols Urinary bile acid chromatography*

Imaging and additional tests:

- Liver Doppler ultrasound
- *Echocardiography; brain MRI (+ spectroscopy), abdominal MRI with measurement of extrahepatic iron content*
- *Ophthalmological examination*
- *Accessory salivary gland biopsy (Perls' stain)*

In case of death: - 5 ml of blood in EDTA at ambient T° for gene panels. Skin biopsy for fibroblast culture (conserved in culture medium or sterile physiological serum at ambient T°). Muscle biopsy for histology and Western blot (fresh muscle specimen wrapped in a saline-soaked gauze at room temperature) and frozen muscle (liquid nitrogen) Seek opinion during working hours on dispatching the samples.

➔ If liver failure occurs within the first 24 hours of life, consider the following first:
- Neonatal haemochromatosis
- Infectious hepatitis, especially HSV hepatitis
- Mitochondrial diseases

➔ If liver failure presents in an infant after a free interval, consider toxic disorders:
- Galactosaemia
- Hereditary fructose intolerance (“fructosaemia”)
-Tyrosinaemia
- And also bile acid synthesis disorders (BASDs)

➔ In the absence of clear aetiological indications from the tests performed, specific genetic causes should be investigated, such as the NBAS gene and other related genes.

6 LIST OF AETIOLOGIES TO BE CONSIDERED

Aetiologies	Biology				Liver ultrasound	History, other organ involvement	Specific lab tests	Treatment
	AST/ ALT	CB	AFP	Ferritin				
No free interval								
Hypoxic liver injury	↑↑↑	↑		variable	Non-specific	Perinatal factors Other organ failure	--	--
Neonatal haemochromatosis	N or ↑	↑↑	↑↑	↑↑	Heterogeneous liver Cirrhosis	IUGR/anasarca/oligohydramnios/polyhydramnios Renal anomalies Previous pregnancy history Hypoalbuminaemia	--	Exchange transfusion IVIg
Transaldolase deficiency	↑ or ↑↑	↑↑	↑	N	Heterogeneous liver Splenomegaly Cirrhosis	IUGR/anasarca/oligohydramnios/ polyhydramnios Cardiomyopathy. Cutis laxa. dysmorphia	Polyols in urine	--
With or without free interval								
Infectious hepatitis	↑↑↑	↑↑		↑↑↑	--	Possible neuro involvement	PCR for HSV, enterovirus, HHV6 syphilis	IV aciclovir if HSV
Fatty acid oxidation deficiency	↑	N		N	+/- hepatomegaly (cardiac)	Hypoglycaemia without ketosis, cardiac involvement, rhabdomyolysis	Plasma acylcarnitines	Fat-free die Carnitine Riboflavin
Mitochondrial diseases	↑	↑	↑↑	↑↑	Heterogeneous liver +/- Cirrhosis	IUGR, other organ involvement, neuro involvement	Markers of oxidative stress in blood and CSF, brain MRI	--
Heart failure	↑↑↑	↑ (secondary)		variable	--	Heart failure	--	Possible secondary cholangiopathy
Familial lymphohistiocytosis	↑↑	↑↑		↑↑↑	Hepatomegaly Splenomegaly	Macrophage Activation Syndrome	--	Specialist haematological opinion (emergency treatment)
Bile acid synthesis disorders		↑↑ GGT ↓				0	Bile acid in plasma Bile acid chromatography	Cholic acid
With free interval								
Galactosaemia	↑	↑↑ LAP ↑		variable	Homogeneous hyperechoic liver	Galactose intake Tubulopathy Cataract *E. coli* infection	Spot test (before transfusion)GAL-1P Galactitol U	Galactose-free diet
Tyrosinaemia	↑	N or ↑ LAP ↑	↑↑	variable	Hyperechoic liver nodules	Tubulopathy	Urine succinylacetone or urine organic acid chromatography	NTBC Low-protein diet
Fructosaemia	↑	N or ↑		variable	Hyperechoic liver	Fructose/sucrose intake Tubulopathy	--	Fructose/sucrose-free diet
Urea cycle disorder	↑	N		N		0	CAAPs Orotic acid in urine	Low-protein diet Chelation therapy