VIEWPOINT

Approach to a Sick Neonate with Cholestasis in India

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INTRODUCTION

Sick neonate presenting with cholestasis is a common problem in tertiary referral centers with considerable dilemmas in the management. There are limitations at multiple steps with poor clarity in some areas. The aim of this review is to provide a step by step simplified approach to a sick neonate with cholestasis. We will focus only on the common etiologies and those that are treatable presently in India. Uncommon etiologies and their discussions are beyond the scope of the authors. The approach is based on authors' personal experiences.

What is neonatal cholestasis?

Presence of direct bilirubin >1 mg/dL confirms presence of cholestasis[1]. For practical purposes, any infant (irrespective of referral age) with onset of cholestasis starting in the neonatal period is neonatal cholestasis (NC).

How to identify a sick neonate with cholestasis at presentation?

In the authors opinion, sick NC is any cholestasis with one or more of the following urgencies: a) poor feeding or lethargy, b) hypoglycemia, c) seizure, d) uncorrectable coagulopathy or mucocutaneous bleeding, e) ascites, f) anemia, g) respiratory distress, h) shock, i) family h/o recurrent sibling death, abortions or stillbirths, j) preterm or low birth weight, g) features of sepsis[2].

What are the setbacks or issues in India?

Poor referral systems, low resource settings, unreliability of labs, cost-prohibitive genetic analysis and unavailability of various life saving drugs and feeding formulas are major limitations in the diagnosis and therapy of various etiologies. TORCH infection titres (especially cytomegalovirus which is an innocuous bystander) are often positive in any NC setting. When these are unnecessarily prioritised for therapy, the underlying disease is often missed or delayed.

What are the common etiologies pertinent to Indian settings?

By and large, biliary atresia (BA) forms 30–50% of all NC referrals and approximately 90% of all extrahepatic causes (authors' experience). Most are referred in a stable state. However advanced cases or those with concomitant cardiac anomalies are predisposed to community-acquired infections and become sick. Of all the extrahepatic causes, choledochal cyst (CC) is an etiology in <5%. Neonatal CC can develop cholangitis due to an obstructed system. In a given case with cyst at porta on sonology, absent or rudimentary gall bladder and presence of triangular cord sign reliably distinguishes BA from CC. Sick NC with intrahepatic causes are usually due to genetic-metabolic causes and rarely infections. In the authors experience, of all sick NC, biliary atresia with superimposed infections and galactosemia are the predominant etiologies. Table 1 shows the common etiologies of sick NC in India.

FAOD and respiratory chain defects are collectively termed as mitochondrial hepatopathies since the abberation is at the level of mitochondria. Features of these two disease considerably overlap as there is significant energy depletion. Among the FAOD, long chain, very long chain the carnitine pathyway

TABLE 1. Common Causes of sick neonatal cholestasis

Extrahepatic	*Intrahepatic*
• Biliary atresia with superimposed infections • Choledochal cyst with cholangitis	• Galactosemia • Tyrosinemia • Gestational alloimmune disorder (GALD) • Mitochondrial hepatopathies (MH) • Herpes simplex virus infection (HSV) • Hemophagocytic lymphohistiocytosis (HLH) • Hereditary fructose intolerance (HFI) • Niemann–Pick disease (type C) • Progressive familial intrahepatic cholestasis (especially types 2 and 5 • Bile acid synthetic defects

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defects are known to cause NC. POLG1, DGUOK, MPV-17 and TWINKLE are mutations that cause mitochondrial DNA depletion and often associated with liver failure[3,4].

Contrary to the popular belief that TORCH is a major cause of neonatal cholestasis, it is now clear that positive TORCH titers are a *red herring* in the workup of a neonate with cholestasis. Except for acquired HSV infection which has rapid deterioration, the rest of the TORCH infections rarely cause jaundice. Acquired cytomegalovirus (CMV) causing neonatal hepatitis is rare and most often self-resolving. CMV titres in blood or urine or antibodies to CMV are not sufficient criteria for therapy. It is mandatory to demonstrate CMV DNA by the polymerase chain reaction (PCR) or culture in liver tissue or document histological changes (inclusion bodies in vascular endothelium of the liver). Congenital CMV hepatitis should be treated only if the infection is proven in a setting of deteriorating liver functions or coagulopathy where no other alternative cause is found[5].

Other causes of sick NC that have been reported as isolated case reports or series are congenital disease of glycosylation (CDG) type 1, Coombs positive hemolytic anemia with giant cell hepatitis, congenital portosystemic shunts, Zellweger syndrome, Wolman disease, transaldolase deficiency, citrin deficiency, arthrogryposis renal dysfunction cholestasis (ARC) syndrome, urea cycle disorder (ornithine transcarbamylase deficiency), congenital leukemia, large hepatic hemangioma, metastatic neuroblastoma, panhypopituitarism (septo-optic dysplasia), neonatal lupus and congential cardiomyopathies[6,7].

What are the common presentations?

Presence of pigmented stools makes biliary atresia unlikely and mostly suggests intrahepatic causes. Acholic stools could be consistent with both intrahepatic (with significant cholestasis) and extrahepatic causes. Sick intrahepatic NC can present as neonatal liver failure (NLF), congenital ascites or hydrops (explained below). Significant family history is pertinent in genetic-metabolic causes and absent in biliary atresia. Hypoglycemia may suggest consequences of liver failure or glycopenia due to blocks in metabolic pathway (galactosemia, fatty acid oxidation defects, HFI). Seizures suggest hypoglycemia (due to above reasons), dyselectrolytemia, intracranial bleed (coagulopathy), infection (Herpes simplex virus encephalitis) or intoxication (mitochondrial diseases). Sites of bleeding can be oral, pulmonary, gastrointestinal intracranial, from umbilical stump and musculocutaneous. They are often spontaneous or secondarily due to intramuscular injections. Most often bleeding is due to coagulopathy. In rare cases, it may be compounded by thrombocytopenia (sepsis, HLH, transaldolase deficiency). Significant anemia may be secondary to bleeding, intravascular hemolysis, aplasia (parvovirus infection), hemolysis (Coombs negative in galactosemia, transaldolase deficiency and Coombs positive in associated giant cell hepatitis) or marrow infiltration (HLH). Clinical clues are shown in table 2.

What is neonatal liver failure?

The proposed definition of NLF is a sick baby with neonatal cholestasis (up to 2 months age) with international normalized ratio (INR) >3.0. The definition does not include encephalopathy as it is difficult to assess in newborns. INR up to 2.0 may be normal in premature newborns[8]. The common causes are gestational alloimmune liver disease (GALD), herpes simplex virus (HSV) infection, metabolic diseases (galactosemia, fatty acid oxidation defect, tyrosinemia type 1, and Niemann-Pick disease), hemophagocytosis lymphohistiocytosis (HLH), PFIC-2 and PFIC-5 and bile acid synthetic defects (BASD) [9,10,11]. Rarely HFI (infants on formula feeds), UCD, leucine-tRNA synthetase (LARS), transaldolase deficiency, glycogen storage disease type 4 and enterovirus infection (from mother) have been reported[12,13]. Fulminant Hepatitis B in an infant has also been reported in mothers who have Hepatitis B (pre-core mutant, e-antigen negative, e-antibody positive and DNA negative). This occurs due to an exaggeration in cytotoxic T-cell response[14]. GALD should be strongly suspected in a case of NLF with significant ascites but absence of splenomegaly. In this condition, the ductus venosus remains patent and prevents the development of splenomegaly[15]. The main differentiating features of some of the conditions are given in **Table 3**.

What is the significance of ascites?

Presence of ascites early in the neonatal or infancy period indicates that cirrhosis or liver failure has set in. In the presence of early onset (<4 months age) ascites, metabolic causes of NC must be considered, top most priority being galactosemia. Since biliary cirrhosis causes have delayed decompensation, the ascites in biliary atresia occurs after 3–6 months of age. Diagnostic tap is required to detect ascitic fluid infection (absolute neutrophil count >250/mm^3 and/or fluid culture positivity). Presence of coagulopathy and thrombocytopenia are not contraindications for an ultrasound guided diagnostic tap. Congenital ascites indicates that the cirrhosis has already started in utero and is classically seen in GALD. This condition is usually associated with shrunken liver. Hydrops is an even more severe form where the neonate is born with anasarca. Of the many mechanisms and diverse etiologies of hydrops, one of the mechanisms is liver failure and organ infiltration where the disease has started in the intrauterine period. Niemann Pick disease Type C (NPD-C), transaldolase deficiency and various other rare lysosomal storage disorders can be associated with hydrops. Hydrops has a universally poor outcome. Placental tissue analysis in the proband is recommended for subsequent pregnancies[16,17].

How to interpret LFT in a sick NC?

LFT per say is not discriminatory for any particular NC. However some assumptions can be made based on the LFT profile. Disproportionate derangement of INR as compared to total bilirubin and liver enzymes is usually found in tyrosinemia and GALD. These conditions also have mildly deranged enzymes as compared to other causes. ALP is usually raised tyrosinemia due to hypophosphatemic rickets and in NPD-C due to infiltration. Gamma glutamyl transpeptidase (GGT) is low in all PFIC (except PFIC-3) and BASD. CDG type 1 has hypoproteinemia due to protein losing enteropathy. HSV induced liver failure causes transaminases to be in thousands (U/L). Rising bilirubin, progressively worsening international normalised ratio (INR) and fall in albumin indicate that the trend of the patient is towards worsening of the disease and is a possible indication for liver transplantation LT referral. Though worsening INR has poor prognostic value, an improving INR is a good indicator of recovery. Even during recovery, albumin may take 3–4 weeks to normalise due to its half-life of 21 days.

TABLE 2. Clinical Evaluation of Intrahepatic Causes of Neonatal Cholestasis

Onset of jaundice	• At birth or soon after (days): GALD, HSV • Few weeks after birth: PFIC, galactosemia • Delayed-onset (after 1 month): Tyrosinemia, PFIC • Any point of time: MH, HLH
Affected sib or sib death	• Galactosemia, tyrosinemia, MH, HLH, PFIC, GALD
Seizures	• Hypoglycemia: Galactosemia, MH, HFI, panhypopituitarism • Intracranial bleed: All conditions • CNS infection: HSV • Intoxication: MH, CPSS, UCD
Maternal clues	• Genital vesicles: HSV • Oligoamnios, megaplacenta: GALD • Antenatal pruritus (3rd trimester) with similar history in maternal sisters or grandmother: PFIC • Pruritus on oral contraceptives: PFIC • Acute fatty liver of pregnancy: FAOD (long and very long chain disease) • Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: FAOD (long chain disease) • Recent diarrheal or respiratory illness: Enterovirus
Early-onset ascites	• Galactosemia, tyrosinemia, GALD, MH, HLH
Shrunken liver	• GALD (not in all but in a subset that presents as congenital ascites)
Splenohepatomegaly	• HLH, Niemann–Pick disease type C
Peripheral findings	• Scalp vesicles: HSV • Cataract: galactosemia • Cabbage odor urine: tyrosinemia • Rickets (craniotabes): tyrosinemia • Hypotonia: MH, Niemann–Pick disease type C • Hypertonia: CPSS, UCD • Chubby cheeks: Citrin deficiency • Micropenis: Panhypopituitarism • Vision fixation issues: Septo-optic dysplasia • Nystagmus, gaze palsy: NPD-C, Gauchers • Dysmorphism: Zellweger syndrome, transaldolase deficiency • Hirsutism, hypertrichosis and cutis laxa: transaldolase deficiency
Ultrasound-Doppler finding	• Gall stone: PFIC-2 • Anomalous vascular anatomy: Abernathy malformations (CPSS) • Nephromegaly: Tyrosinemia, HFI • Adrenal calcifications: Wolman disease • SOL in liver, adrenals: hemangiomas, metastatic neuroblastoma

PFIC: Progressive familial intrahepatic cholestasis; GALD: gestational alloimmune disease; HSV: Herpes simplex virus; MH: Mitochondrial hepatopathies; HLH: Hemophagocytic lymphohistiocytosis; FAOD: Fatty acid oxidation defects, CPSS: congenital portosystemic shunting, UCD: urea cycle defect, HFI: hereditary fructose intolerance, SOL: space occupying lesions, GB: gall bladder, NPC-D: Niemann-Pick disease type C

What is the role of tissue biopsy in a sick NC?

The role of liver biopsy is gradually being limited due to the increasing availability of genetic confirmation in many conditions. In the authors' opinion, if the workup is favouring the diagnosis of biliary atresia, then a liver biopsy is necessary for confirmation. However, many a times due to delayed referral, there is inadequate window between recovery of the infection and a timely surgery (<90 days of life). In such dire situations, the child may be taken up for POC without the liver biopsy. In GALD, a definitive diagnosis is obtained from documenting iron staining from salivary glands. For this a lip biopsy is necessary which may often be daunting in a child with profound coagulopathy. Diagnosis of HLH is made with a set of criteria which fulfil the same. In the absence of genetic confirmation, a bone marrow examination is required to document hemophagocytosis. Similarly in the absence of enzyme or genetic analysis, Niemann-Pick disease type C can be diagnosed by typical foamy histiocytes on bone marrow or liver. However the yield for the same is 40–60%[18]. Progressive liver disease due to CMV is extremely rare. Definitive diagnosis of CMV hepatitis is by documenting inclusion bodies in liver parenchyma. In the presence of genetic analysis, electron microscopy of liver and muscle have become near obsolete in MH. Immunohistochemistry of the liver is an optional but recommended workup in PFIC[4,9]. Other genetic-metabolic conditions do not require liver biopsy.

What is the role of genetic testing in a sick NC?

Clinical or whole exome sequencing, recently available in India has changed the understanding of neonatal cholestasis where etiologies were previously unascertained. The turnaround

TABLE 3. Differentiating features of neonatal liver failure

	Neonatal hemochromatosis	*HSV infection*	*Hemophagocytic lymphohistiocytosis (HLH)*	*Mitochondrial hepatopathy*	*Galactosemia type 1*	*Tyrosinemia type 1*
Age at presentation	Usually at birth	5–14 days of life	variable	Variable	Usually from second week of life onwards	Variable
Premature birth/IUGR	70–90%	Rare	Rare	Rare	No	No
Sibling death	Common	None	Possible	25%	Common	Common
Amniotic fluid	Oligoamnios	Normal	Normal	Polyamnios	Normal	Normal
Ascites at birth	Common	Rare	Rare	Rare	No. Occurs later	No. Occurs later
Liver	Shrunken (in-utero cirrhosis)	Enlarged	Enlarged	Enlarged	Enlarged	Enlarged
Extrahepatic involvement	Renal tubular dysplasia Patent ductus venosus	Meningitis Scalp vesicles	Bone marrow depression	Multisystemic commonly cardiomyopathy, Skeletal myopathy (hypotonia)	Cataract in 50–60% Renal tubular acidosis Hemolysis in 25% Gram negative sepsis	Rickets Nephromegaly Hypophosphatemia
Acidosis at presentation	None	None	None	++	No	Yes (renal tubular)
Coagulopathy	Profound (+++)	+	+	+	+	Profound (+++)
Alanine transminase (U/L)	Low normal (<100)	High (>1000)	High (>1000)	Moderate (100–500)	Moderate (100–500)	Low normal (<100)
Ferritin (ng/mL)	800–7000	>20,000	>20,000	Variable	normal	normal
Alpha fetoprotein (ng/mL)	80,000–300,000	<80,000	<80,000	Variable	normal	Variable but usually in thousands to lakhs
Definitive test	Lip biopsy MRI pancreas Complement C5b–9 complex	HSV-PCR	Perforin levels Genetics	Urine GCMS, Blood TMS Genetics	GAL-1-PUT enzyme assay Genetics	Urine or blood succinyl acetone Genetics

HSV: herpes simplex virus, PCR: polymerase chain reaction, GCMS: gas chromatography and mass spectroscopy; TMS: tandem mass spectroscopy; GAL-1-PUT: galactose-1-phosphate uridyl transferase; MRI: magnetic resonance imaging; IUGR: intrauterine growth retardation

time is approximately 4–6 weeks and must be sent with discretion of cost and time. "Variants of unknown significance" must be interpreted with caution in any clinical setting[19,20]. Based on clinical suspicion, empirical management must be instituted while awaiting genetic results. Genetic studies are useful in the following scenarios of sick NC:

- Presentation of babies with pruritus or steatorrhea (PFIC, bile acid synthetic defects)
- Low GGT cholestasis (PFIC, bile acid synthetic defects)
- Suspected galactosemia where enzyme assay is fallacious due to hemolysis or blood transfusion
- Suspected tyrosinemia where urinary succinyl acetone cannot be done and the suspicion is strong
- Neonatal liver failure where infectious causes have been ruled out
- Predominant extrahepatic manifestations (PFIC-1, bile acid synthetic defects, mitochondrial hepatopathy)
- Strong family or sibling history
- Significant clues on mass spectroscopy or gas chromatography

Genetic analysis has no role in diagnosis in GALD. Hence the absence of genetic yield during the workup of a proband with NLF should alert physician for subsequent pregnancies.

What are the special precautions during testing or caveats in interpretation?

- Urine NGRS, though a non-specific test, should be done while the child is on the incriminating feed. It is recommended to perform at least 3 samples. Patients on soy formulations and sucrose-free formula will have negative reports in galactosemia and HFI[11].
- GAL-1-PUT level assessment should be deferred in the presence of hemolysis or recent (<12 weeks) blood transfusion as the levels will be erroneously normal[11].
- Urine or blood succinyl acetone is a volatile compound and hence best collected at the lab or transported within 30 minutes.
- Urine or blood ketones should be documented at the time of hypoglycemia. Once resuscitated into a euglycemic state, the ketones are negative.
- Ursodeoxycholic acid should be stopped for 7 days prior to assessment of bile acid levels
- Ferritin may be high as acute phase reactant in an overtly sick child. Repeating values after stabilisation may be required.

Table 4: Investigations and therapy in the common etiologies of sick NC

Disease	Tier 1 investigations (screening or definitive)	Tier 2 investigations (confirmatory or invasive)	Specific therapy
Galactosemia	GAL-1-PUT levels (low)	Genetics (if hemolysis, blood transfusion or ambiguity in GAL-1-PUT levels)	Lactose-free diet
Tyrosinemia	Alphafetoprotein (high) Urine for succinyl acetone (Ur. SA) (positive)	Genetics (if Ur. SA is not available)	Tyr/Phe free diet Nitisinone (not marketed in India)
Mitochondrial hepatopathies and urea cycle defects	CPK (high), ABG (acidosis), lactate (high), ketones (positive), blood sugar (low) Urine GCMS/ Blood TMS (for abnormal metabolites)	Genetics	None except: Carnitine in carnitine deficiency Anti-ammonia measures in Urea cycle defects
HLH	Ferritin (high), triglycerides (high), fibrinogen (low) NK cell activity (low/absent) Perforin levels (low)	Bone marrow examination Genetics	HLH protocol therapy
GALD	Ferritin (high) Alphafetoprotein (high)	Lip biopsy MRI pancreas Liver biopsy for C5b–9 complex staining	IVIG DVET
PFIC	GGT (low) Bile acid levels (high)	Liver biopsy with IHC Genetics	None
BASD	GGT (low) Bile acid levels (low) Stool fat (steatorrhea)	Genetics	Cholic acid and chenodeoxycholic acid (not marketed presently in India)
Niemann-Pick disease Type C	Chitotridase (high) Acid sphingomyelinase (normal)	Bone marrow examination Genetics	None
HSV	HSV PCR (body fluids)	-	Acyclovir

GAL-1-PUT: galactose-1-uridyl phosphatase enzyme; GALD: gestational alloimmune disease; Ur SA: urinary succinyl acetone; Tyr/Phe: tyrosine/phenylalanine; GGT: gamma glutamyl transpeptidase; HLH: Hemophagocytic lymphohistiocytosis; MH: mitochondrial hepatopathies; CPK: creatinine phosphokinase; ABG: arterial blood gas; NK: natural killer; IVIG: intravenous immunoglobulin; DVET: double volume exchange transfusion; NGRS: non-glucose reducing substances; SBP: spontaneous bacterial peritonitis; USG: ultrasonography PFIC: Progressive familial intrahepatic cholestasis; BASD: bile acid synthetic defects; PCR: polymerase chain reaction; HSV: Herpes simplex virus; MRI: magnetic resonance imaging

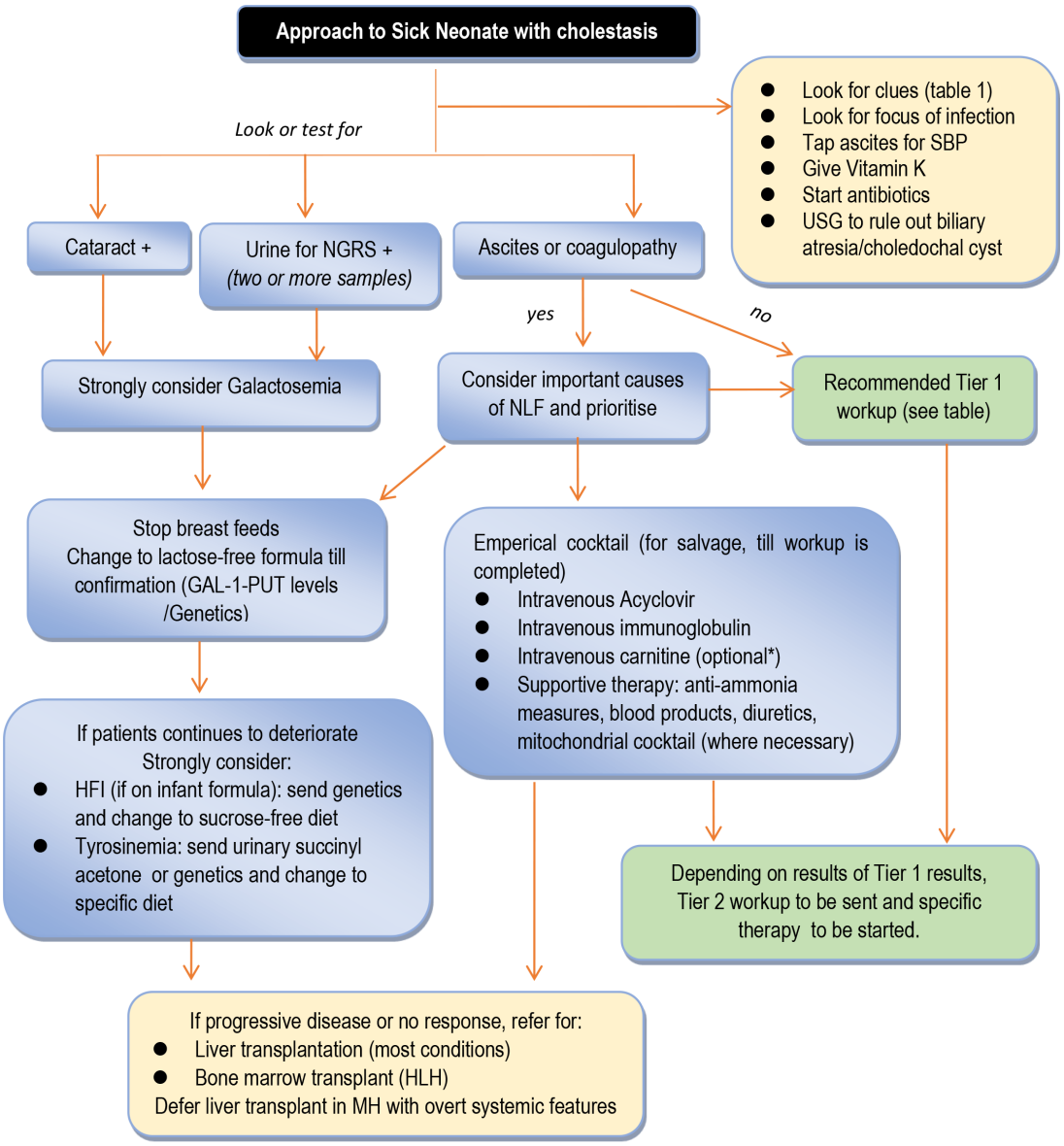
- Urine for gas chromatography and blood for tandem mass spectroscopy yield better in a decompensated state than in a resuscitated state.
- If a genetic-metabolic cause is suspected, it is suggested to store a blood sample of the proband a part of future genetic counselling.
- Non-contractile gall bladder on ultrasonography may not necessarily be due to biliary atresia. A sick NC with sepsis may transiently have an adynamic gall bladder. Repeat scans are recommended before proceeding for liver biopsy.
- Before MRI is performed in GALD, it should be carefully discussed with the radiologist for usage of appropriate software to detect iron overload in the extrahepatic tissue.

What diseases are treatable in India?

Galactosemia has an excellent liver outcome on lactose-free diet. In tyrosinemia, though the specific dietary formulations are available, the drug, nitisinone is not presently marketed in India. MH (espc. long and very long chain FAOD) are difficult to salvage with supportive therapy. LT is contraindicated if there are overt systemic features. GALD may survive with intravenous immunoglobulin therapy (IVIG) and double volume exchange transfusion (DVET) but most will require LT. Primary HLH should be given a trial of the HLH protocol before referring for bone marrow transplant. HSV is curable with acyclovir. Pleconaril is used on compassionate grounds for enterovirus infections in the West but unavailable in India. Enterovirus infections are not routinely tested for in India. Cholic acid (in pharmaceutical form) and chenodeoxycholic acid are not yet marketed in India and are possibly in the pipeline. CMV may be treated with ganciclovir in desperate measures.

What are the difficulties with diet in NLF?

Etiologies presenting as NLF often have overlapping features and not clearly distinguishable at presentation. Yet an empirical diet need to be prescribed that can encompass all the possible diseases. The challenge is the choice of the same. The is no consensus over this aspect and it is individualised as per the physician's experience. Since galactosemia is a major etiology and empirical dietary restrictions are required, many physicians choose soy formulations on compassionate grounds due to financial constraints. It is to be noted that soy formulations contain high amounts of tyrosine and phenylalanine that may make tyrosinemia worsen. Since some soy formulations also contain sucrose, HFI may worsen. Fatty acid oxidation defects (FAOD) ideally need a ketogenic diet. All NC need high medium chain triglycerides (MCT) in their diet. In the authors' opinion, an initiation with amino acid formula enriched with MCT is possibly safest bet in India. The diet may be modified as the etiology becomes clearer.



HFI: hereditary fructose intolerance; HLH: Hemophagocytic lymphohistiocytosis; MH: mitochondrial hepatopathies; NLF: neonatal liver failure; GAL-1-PUT: galactose-1-uridyl phosphatase enzyme; NGRS: non-glucose reducing substances; SBP: spontaneous bacterial peritonitis; USG: ultrasonography

** under cardiac monitoring for detection of arrythmias*

Figure 1: Approach to a sick NC without extrahepatic cause

Algorithm of management of sick NC

Sick NC is a dire emergency. Despite supportive management, the underlying metabolic or infectious processes quickly decompensate and progress rapidly. If not intervened on time, they are universally lethal. Hence swift and empirical management is required while simultaneously working them up for the underlying etiology. In this regard, a brief bed side algorithm of management of sick NC without an extrahepatic cause is suggested in Fig 1 with an accompanying table (table 4). Individual etiologies will need further reading.

CONCLUSIONS:

Sick children presenting as neonatal cholestasis have diverse etiologies with overlapping presentations. If an extrahepatic cause has been ruled out, galactosemia workup should be prioritised in India as this a rewarding disease to treat. Every effort should be made to salvage the rest of the metabolic disorders though setbacks in management are likely in India. The initial part of the management is largely presumptive and emperical for salvage. The algorithm of management is largely on the clinical wisdom of the physician. Genetic testing of the proband provides closure for the physician and enables genetic counselling for the family.

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