Approach to a Neonate with Cholestasis

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Introduction:

- Jaundice is the newborn fairly common and found in 2.4-15% neonates.
- However, this is predominantly unconjugated hyperbilirubinemia which resolves within 14 days after birth. Jaundice persistent beyond 14 days is not physiological and could represent serious hepatocellular or metabolic disease, especially if this is conjugated hyperbilirubinemia.
- Neonatal Cholestasis which is synonymous with conjugated hyperbilirubinemia, occurs because of a defect or abnormality in the bile synthesis, transport or excretion.
- Conjugated hyperbilirubinemiaisnevernormalanditstimelydiagnosisandtreatmentcouldpreventsevere liver damage andmortality.

Definition:

- ***Conjugated hyperbilirubinemia in a neonate is defined*** as a serum direct/conjugated bilirubin concentrationgreaterthan1.0mg/dLifthetotalserumbilirubin(TSB)is<5.0mg/dLorgreater than20percentofTSBiftheTSBis>5.0mg/dL.
- Theseinfantshavehighcolouredordark yellowcolouredurinewhichcharacteristicallystainthediapersalongwithpaleorlightyellow coloured stools.
- Neonates or young infants with liver failure i.e. those with ascites or uncorrected coagulopathy are extremely sick with high risk of mortality and need to be investigated and treated at the earliest at an appropriatecentre.

Approach to a case of neonatal cholestasis has been summarised in flowing tables and figures.

Table1.Causesof NeonatalCholestasis

<table>
<tr><th colspan="3">PREDISPOSINGFACTORSTOCHOLESTASISINNEONATES</th></tr>
<tr><td>• Prematurity</td><td>• Prolongedfasting</td><td>• Neonatalsepsis</td></tr>
<tr><td>• Lowbirthweight</td><td>• Totalparenteralnutrition</td><td>• Prolongedantibiotics</td></tr>
<tr><td>• Birth Asphyxia</td><td>• Necrotisingenterocolitis</td><td>• Circulatoryshock</td></tr>
<tr><td>• Exchangetransfusion</td><td>• Intestinalresection/surgery</td><td>• Congenitalheartfailure</td></tr>
<tr><th>Infections</th><th>Structural/Obstructive</th><th>GeneticCholestatic</th></tr>
<tr><td>Bacterial:
• Neonatalsepsis
• Urinarytractinfection
• Tuberculosis
• Listeriosis

Viral:
• TORCHgroup
• Echovirus
• Reovirus</td><td>• BiliaryAtresia
• CholedochalCyst
• Bile duct stenosis /tumour /mass
• Inspissated bilesyndrome
• Neonatalsclerosing cholangitis
• Spontaneousperforation ofbile duct
• CaroliDisease</td><td>• Progressive familialintrahepaticcholestasis
• Bileacidsyntheticdisorders
• Paucity of bile ducts – Syndromic / Nonsyndromic</td></tr>
<tr><th colspan="2">Metabolic</th><th>Immunological</th></tr>
<tr><td colspan="2" rowspan="2">• Disorders of Carbohydrate metabolism: Galactosemia,HereditaryFructoseIntolerance
• Disordersof aminoacidmetabolism:Tyrosinemia
• MitochondrialHepatopathies
• FattyAcidOxidationdefects
• UreaCycleDefects
• Storagedisorders: GlycogenstoragedisordersType4
Lipid storage disorders (Wolman Disease, GaucherDisease,CholesterolEsterstoragedisorder,NiemannPickDisease)
• Others: Cystic Fibrosis, Alpha1 antitrypsin deficiency,Citrindeficiency</td><td>• HemophagocyticLymph-histiocytosis
• Gestational AlloimmuneLiver Disease / NeonatalHemochromatosis</td></tr>
<tr><th>Others</th></tr>
<tr><td colspan="2"></td><td>• Endocrinopathies: Hypopituitarism, Hypo/Hyperthyroidism
• Drugs / Toxins:Ceftriaxone,Aluminium
• Chromosomalabnormalities:Trisomy21,Turner Syndrome
• Idiopathicneonatal hepatitis</td></tr>
</table>

Table2.HistoryandExaminationfindingsinacaseofNeonatalCholestasis

History&Examination	DifferentialDiagnosis
Prematurity, birth asphyxia, low birthweight, neonatal sepsis, urinary tractinfection, total parenteral nutrition,delayedenteralfeeding,NEC etc	Predisposetoneonatalcholestasis
Stoolcolour	Pale–Structuralcauses(BA,CDC) Pigmented–Metabolic,GeneticCholestatic,etc
Delayedpassageofmeconium	Cysticfibrosis,Intestinalobstruction
Hypoglycaemic symptoms /Hypoglycaemia	Galactosemia,Tyrosinemia,GSD,FAOD, Mitochondrialhepatopathy
Failuretothrive	PFIC,MLD
Developmentaldelay	Associatedchromosomalanomalies,Lipidst oragedisorders
Neonatal/Infantileliverfailure(Ascites,C oagulopathy,Encephalopathy)	Galactosemia,Tyrosinemia,GALD,UCD, Mitochondrialhepatopathy, FAOD
Characteristicurineandsweatodours	Tyrosinemia
Specific food aversions i.e. vomiting,altered sensorium, abdominal distension,diarrhoeaafter specificfoods	Fruits juices, Sweets: HFIHighprotein diet: UCD
FamilyHistory	**DifferentialDiagnosis**
Repeatedfoetalloss	GestationalAlloimmuneliverdisease
Consanguinity	AutosomalRecessivedisorders
Siblingwithsimilarhistoryofcholestaticdis ease/ end stageliverdisease	Genetic causes of cholestasis – PFIC, AlagilleSyndrome,Bile acidsynthetic defects
MaternalHistory	**DifferentialDiagnosis**
Pruritus during pregnancy i.e.Intrahepaticcholestasisofpregnancyo rhistoryofpruritusprecipitatedbydrugs	PFIC
Hyperemesis gravidarum, Acute fattyliverofpregnancy,HELLPsyndro me	Fattyacidoxidationdefects(Longchain)
Examination	**DifferentialDiagnosis**
Cataract	Galactosemia,HFI,TORCHinfections
DysmorphicFacies	AlagilleSyndrome,DownSyndrome,GSD
Midlineanomalies	Septo-opticdysplasia,Hypopituitarism
Cardiacdefects/Heartmurmur	AlagilleSyndrome,Downs Syndrome
Grosshepatomegaly	Storagedisorders
Multisystemicdisease	Mitochondrialhepatopathy
Renalinvolvement	Tyrosinemia,Galactosemia,HFI,Mitochondrialh epatopathy,Caroli Disease

BA: Biliary Atresia, CDC: Choledochal cyst, FAOD: Fatty Acid Oxidation Defect, GALD:Gestational Alloimmune Liver Disease, GSD: Glycogen Storage Disorder, HFI: HereditaryFructose Intolerance, MLD: Metabolic Liver Disease, NEC: Necrotising Enterocolitis, PFIC:ProgressiveFamilial IntrahepaticCholestasis, UCD:UreaCycle Defect

Table3.Investigationsin acaseof NeonatalCholestasis

USGFindings	Disease
Triangular cord sign, absent common bileduct, atretic / non contractile gall bladder,increasehepaticarterydiameter,increasedhepaticsubcapsular flow,polysplenia.	BiliaryAtresia
DilatedCBD withoutany sludge	Choledochalcyst
Biliarysludgewith/withoutdilated CBD	Inspissatedbileduct
SpecificBiochemicalInvestigations	**Disease**
GGT	High:BiliaryAtresia,CDC,CF,PFICType3,CMV, NSC Low/Normal:PFIC,BASD,MLD
ElevatedPT/INR(correctedbyVitK)	Neonatalliverfailure
Serumbileacids	LowinBileacid syntheticdisorders
Thyroidfunctiontests,Cortisollevels	Hypothyroidism,Panhypopituitarism
Hypoglycaemia	Nonketotic:FAOD Ketotic:Galactosemia,GSD,LiverfailureGalactosemia,HFI
Elevatedarterialbloodammonia	Liverfailure,UCD
ElevatedLactate:Pyruvateratio	Liverfailure,Mitochondrialhepatopathy
Abnormallipidprofile	GSD,AlagilleSyndrome,CESD,PFIC
ElevatedUricacid	GSD
UrineNonGlucoseReducingSugars(NGRS) i.e.Benedict'stestpositive,UrineDipstickne gative:	Galactosemia,HFI
LiverBiopsy	**Disease**
• Ductularproliferation,Portalexpansion,Ductularbileplugs	• BiliaryAtresia
• "Bland"cholestasis	• PFICType1
• Ductularproliferation,cholestasis	• PFICType3
• Cholestasis with predominantinflammation,Giantcelltransformation,ballooningdegeneration	• OthertypesofPFIC
• Paucityofbileduct,cholestasis	• AlagilleSyndrome,CMV,CF,DownsSyndrome
• Steatosis	• Metabolicliverdisease

CDC: Choledochal cyst, CESD: Cholesterol Ester Storage Disorder, CF: Cystic fibrosis,CMV:Cytomegalovirus,FAOD:FattyAcidOxidationDefects,GGT:Gamma-glutamylTransferase, GSD: Glycogen Storage Disorders, HFI: Hereditary Fructose Intolerance, INR:International Normalised Ratio, MLD: Metabolic Liver Disease, PFIC: Progressive FamilialIntrahepaticCholestasis, PT: Prothrombin Time, UCD:UreaCycleDefects

Table4.GeneralmanagementofNeonatalCholestasis

Nameof drug	Dose&Regimen
Dietarymanagement	
Modeoffeeding	Oral / Nasogastric tube feeding – bolus /continuousdrip feeding
TotalCalories/day	1.5-2times theRDA/150-200 kcal/kg/day
TotalProtein intake/day	2.5-3gm/day,ifHepaticEncephalopathythen0.5-1gm/kg/day
Lipids	MCTsupplementation
Fatsolublevitamins	2-10times theRDA
• VitaminA	3000-10000units/day
• VitaminD	800-5000units/ day
• Vitamin E	15-25units/kg/day(TPGS)
• VitaminK	2.5-5mgIM/IVper week
• Calcium	50-100mg/kg/day
• Phosphorus	25-50mg/kg/day
Drugsusedtotreatpruritus	
• Ursodeoxycholicacid	10-30mg/kg/day
• Cholestyramine	250-500mg/kg/day
• Diphenhydramine	10 mg/kg/day
• Rifampicin	5-10mg/kg/day
• Ondansetron	0.2 mg/kg/day
• Naltrexone	1 mg/kg/day
Drugs used in Mitochondrialhepatopathies	
• Carnitine	50-100mg/kg/day
• CoenzymeQ	3-5mg/kg/day
• Vitamin B1	50-200mg/day
• Vitamin B2	50-400mg/day
• Vitamin E	15-25units/kg/day(TPGS)
• Vitamin C	5mg/kgdaily

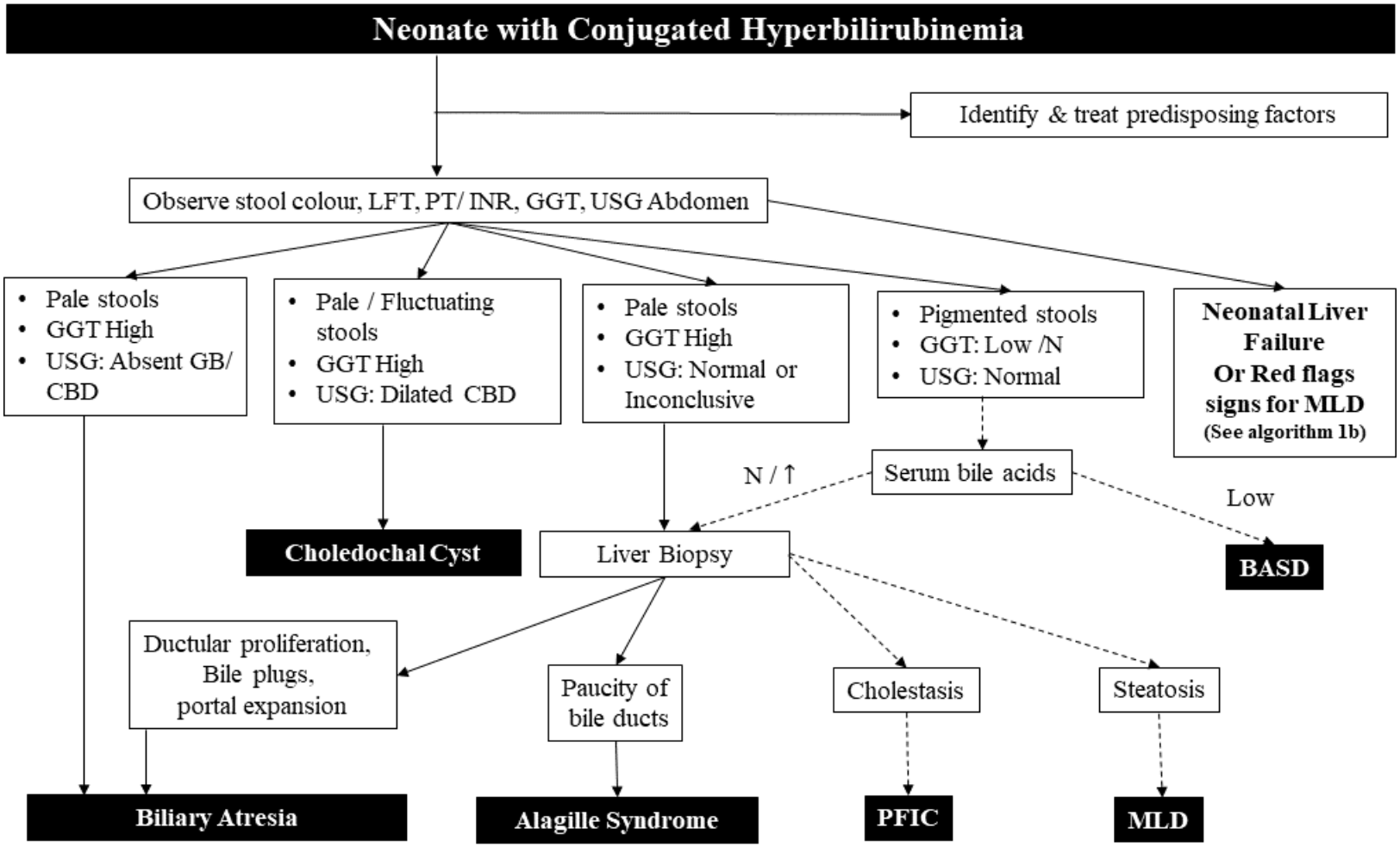
MCT: Medium Chain Triglycerides, RDA: Recommended Daily Allowance, TPGS:TocopherolPolyethyleneGlycol Succinate

Table5.Specifictreatmentoptionsin neonatalcholestasis.

Disease	Treatmentoptions
Perinatalfactorswhichpredisposetocholestasis	Supportive care, early initiation of enteralfeeding, aggressive treatment of sepsis, avoidprolongdurationofparenteralnutrition,correctconcentration of lipids in TPN preparations,UDCA,VitaminA,D, E, Ksupplementation,
BiliaryAtresia	KasaiPortoenterostomy
CholedochalCyst	Cyst excision with Roux-en-YHepaticojejunostomy
Progressivefamilialintrahepaticcholestasis	UDCA,supplements,Biliarydiversion
Bileacidsyntheticdisorders	CholicacidorUDCA
Gestational Alloimmune LiverDisease	IVIg+ExchangeTransfusion/Plasmapharesis
HerpesSimplex	IVAciclovir
Hypothyroidism/Panhypopituitarism	Hormonereplacementtherapy
Galactosemia	Lactosefreediet
Hereditaryfructoseintolerance	Fructose +Sucrosefreediet
Tyrosinemia	Tyrosinefreediet +Nitisinone
Glycogenstoragedisorder	Uncookedcornstarchdiet
Fattyacidoxidationdefects	Avoidanceofprolongfastingorcatabolicstress,Lowfat MCT based diet,Carnitinesupplementation
Mitochondrialhepatopathy	Highfat,lowcarbohydratediet
Ureacycledefects	Lowproteindiet
Lysosomalstoragedisorders	Enzymereplacementtherapy
Cysticfibrosis	Pancreaticenzymereplacementtherapy +UDCA

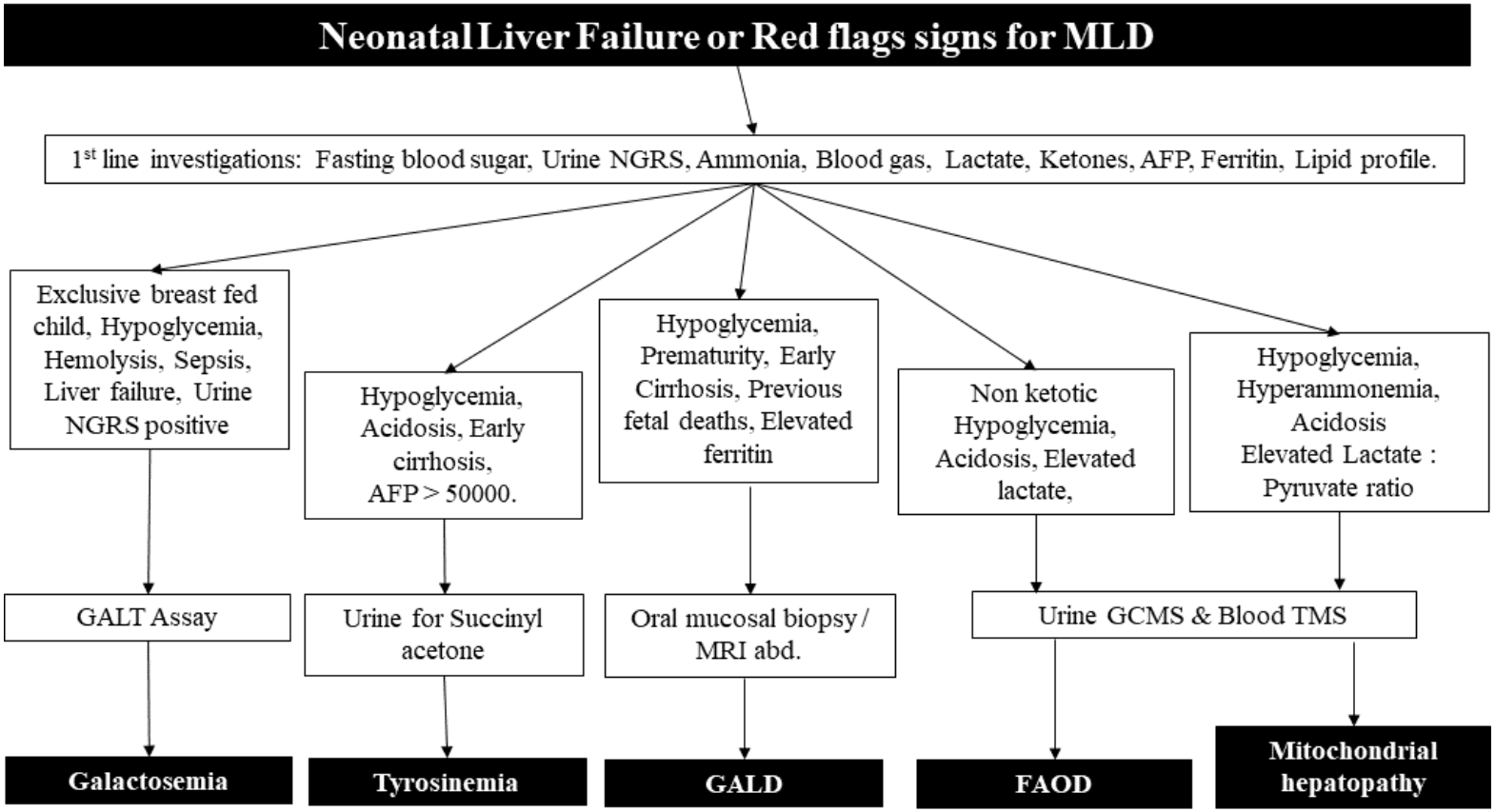
TPN:TotalParenteralNutrition,UDCA:Ursodeoxycholicacid,

Fig. 1A: Algorithm to approach a case of Neonatal Cholestasis



BASD: Bile acid synthetic disorders, MLD: Metabolic Liver Disease, PFIC: Progressive Familial Intrahepatic Cholestasis

Fig. 1B: Algorithm to approach a case of Neonatal Liver Failure



AFP: Alpha fetoprotein, GALD: Gestational Alloimmune Liver Disease, GALT: Galactose 1-Phosphate Uridyl Transferase, GCMS: Gas Chromatography Mass Spectroscopy, FAOD: Fatty Acid Oxidation Defects, MLD: Metabolic Liver Disease, NGRS: Non glucose reducing sugars, PFIC: Progressive Familial Intrahepatic Cholestasis, TMS: Tandem Mass Spectroscopy

Suggested readings:

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