Neonatal Cholestasis

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- Conflict of Interest: None

- Disclosures: None

Introduction

- Neonatal/Infantile Cholestasis:
  - **Conjugated Hyperbilirubinemia-**
    - Direct Bilirubin > 1.0 mg/dL if total bilirubin < 5.0; or
    - > 20 % of Total Bilirubin if Total Bilirubin >5.0 mg/dL

Conjugated (direct) hyperbilirubinemia **(>1.0 mg/dL)** is pathological and warrants diagnostic evaluation

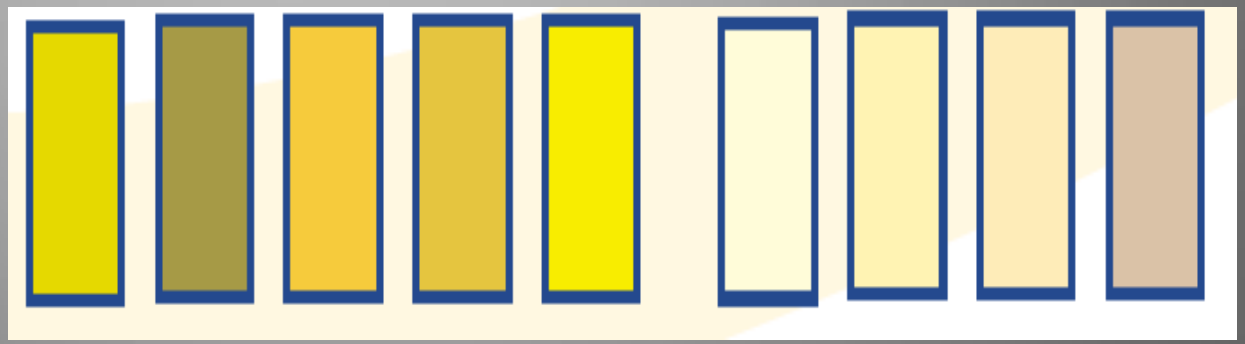
JPGN 2017;64: 154–168

BEFORE WE PROCEED……

Conjugated vs Unconjugated Jaundice

- Color of the urine
  - Staining of the diapers

- Stool Colour



Jaundice Protocol: Yellow Alert - Early identification and referral of liver disease in infants. *Children's Liver Disease Foundation*

Causes of Neonatal Cholestasis

Top 10
Biliary Atresia
Biliary Atresia
Biliary Atresia

Biliary Atresia + Unknown: 2 out of every 3 NCS Case

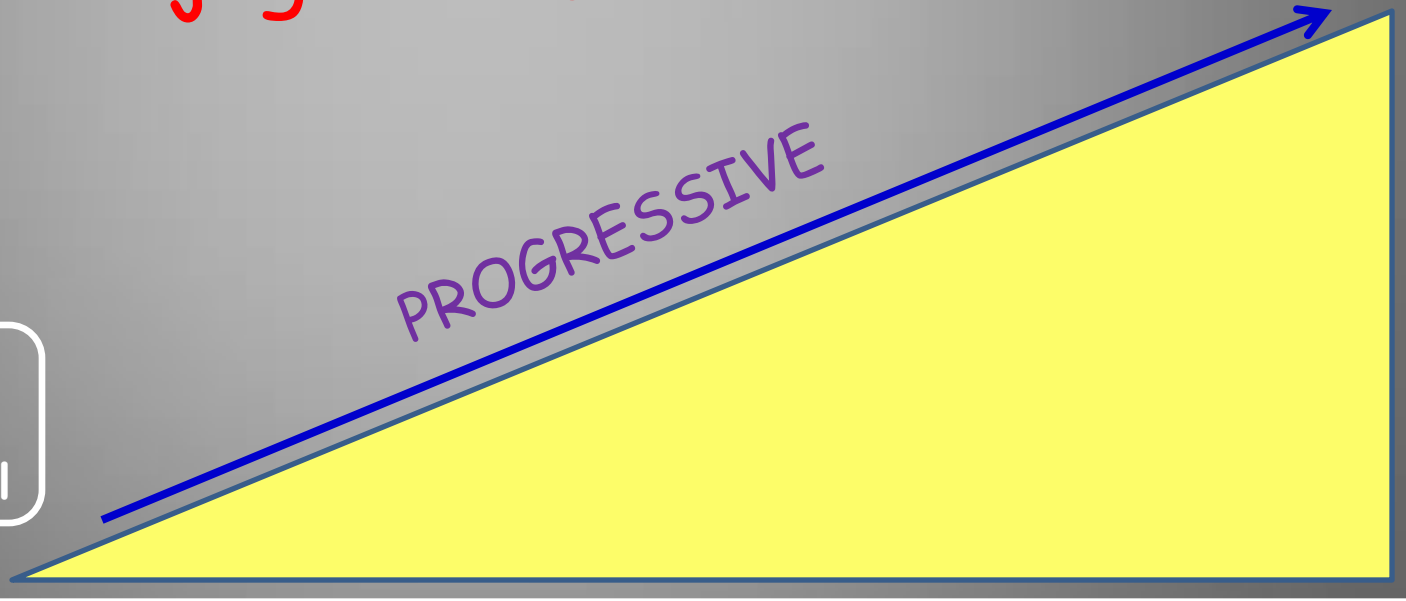
- Genetic/Metabolic Causes-
  - Galactosemia, Familial Cholestasis Syndromes (PFIC) etc
- Infections: Systemic Infections (UTI etc), Rarely Congenital
- Hypothyroidism etc
- Unknown Cause: 1/3rd to 1/4th Cases

CASE SCENARIO 1

3 month/Male

Yellow Eyes →Jaundice,
Yellow/Dark urine, Diaper staining, Whitish Stools

'Conjugated Jaundice'

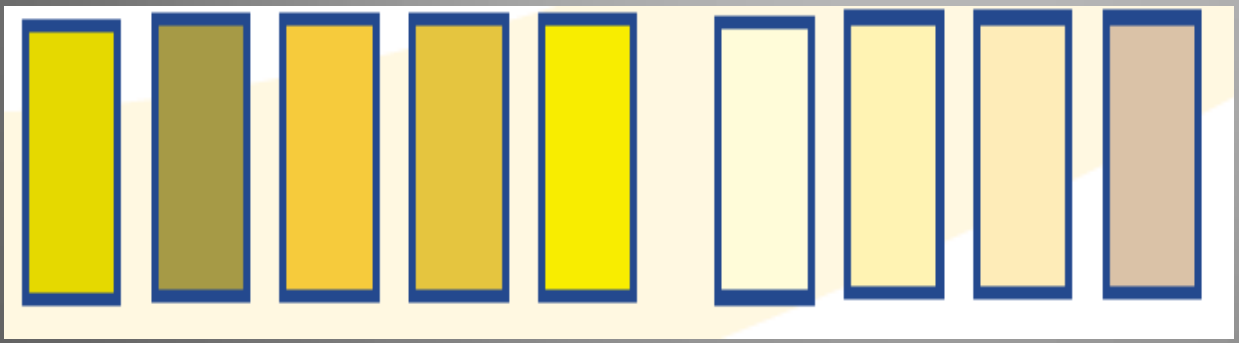


Term, NVD
B.Wt 3 kg
F. History: Normal

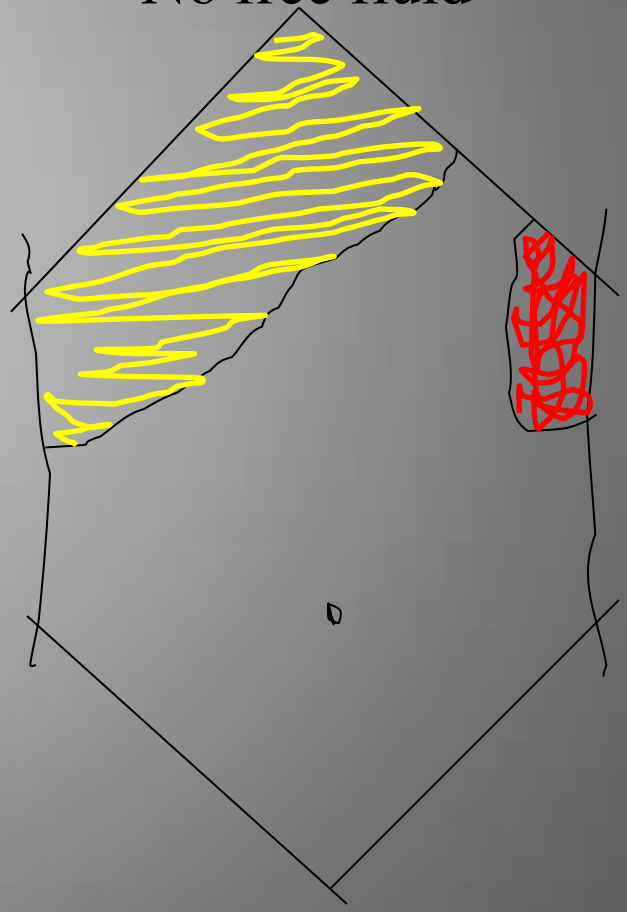
Birth | 14 days | 3 months

Examination

- Weight, Length Z scores 0 to -1
- Icterus +++
- Stools – Acholic **(Confirmed on 3 days)**

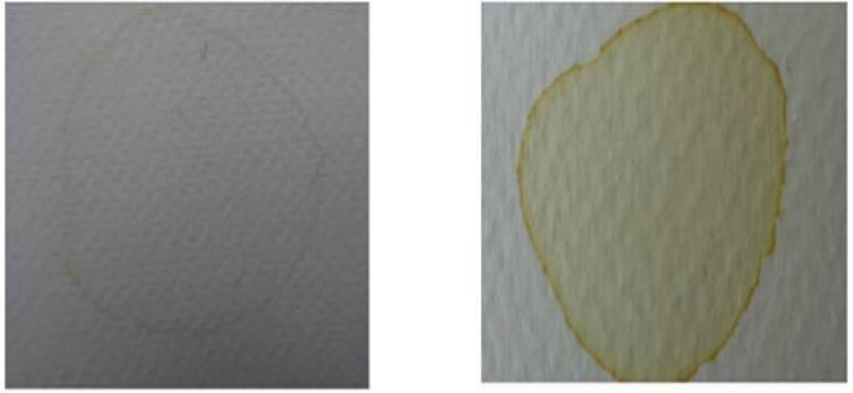


Liver 4 cm BCM, firm
Spleen 3 cm BCM
No free fluid



Jaundice Protocol: Yellow Alert - Early identification and referral of liver disease in infants. *Children's Liver Disease Foundation*

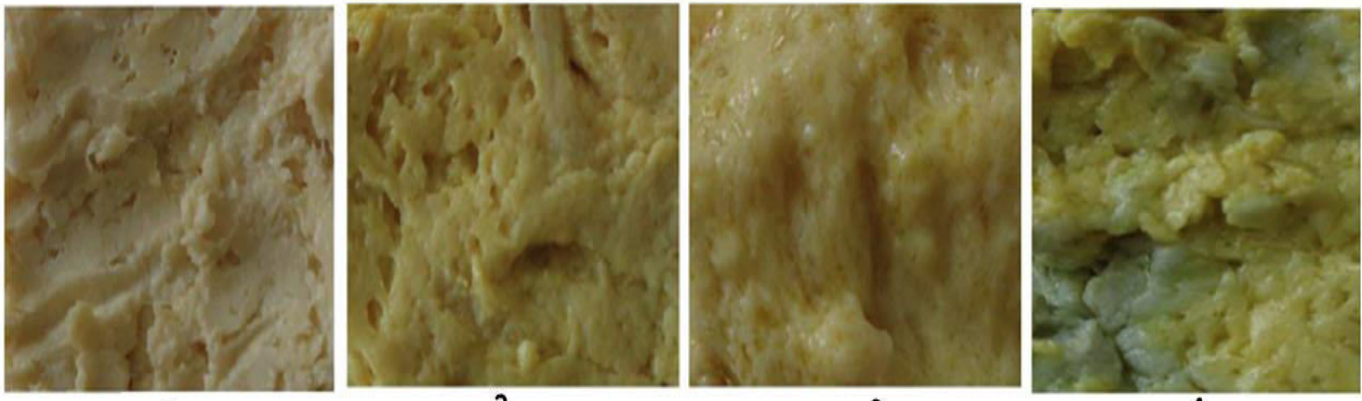
Panel 1: Urine color
1: normal
2: dark yellow



1 2

Panel 2: Stool color

1-4: pale



1 2 3 4

Panel 3: Stool color

5-7: pigmented

5 6 7

Investigations Needed

Tests to be done
LFT, PT-INR
Ultrasound of Abdomen
TORCH Profile
Metabolic Testing- TMS, GCMS
HIDA Scan
Thyroid Profile
HbsAg/Anti HCV
Ceruloplasmin
ANA, ASMA

LFT, PT-INR
Ultrasound Abdomen

Investigations

	Day 8	Day 40	Day 86
INR		5.7	7 → 1.2
Bilirubin (T/D)	7/1.0	9.5/4.5	13/9.7
AST/ALT			179/66
SAP/GGT			1129/342
Prot/Alb			6.2 / 3.6

Post Vit.-K

Vit. K Responsive Coagulopathy – Conjugated Jaundice – High Cholestatic Enzymes

Role of Imaging

Ultrasound:

- Liver 7.4 cm, Normal echotexture
- CBD not visualized
- Spleen 7.6 cm
- GB not visualised (fasting)
- No Ascites

Biliary Atresia:

Non-visualized Gall Bladder

- Small GB (< 15 mm), or absent
- No/poor contraction

Triangular cord sign

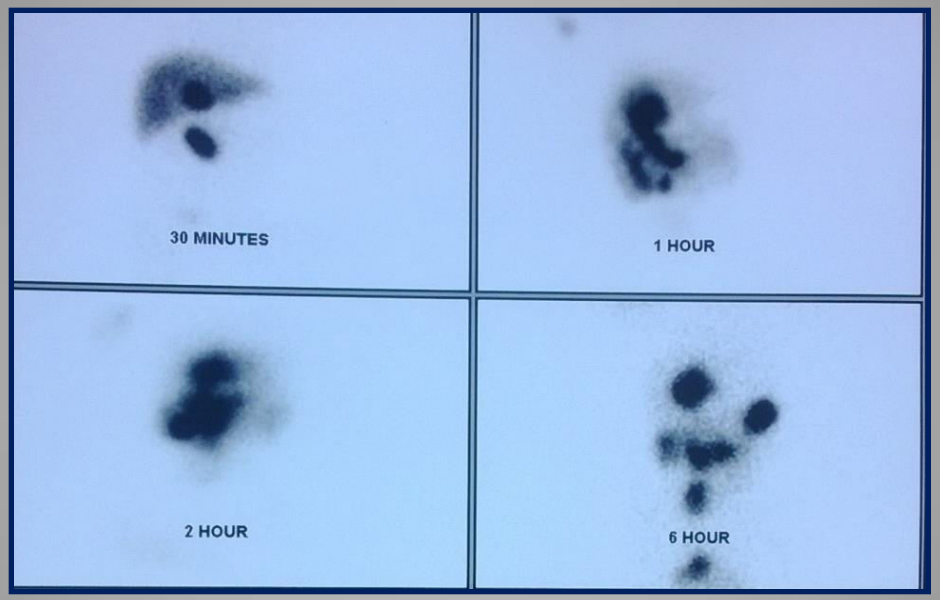
Choledochal Cyst:

Dilated CBD

- >1.5 mm in Newborns
- > 3 mm in Infants

Is HIDA needed?

Should we waste time in doing HIDA?



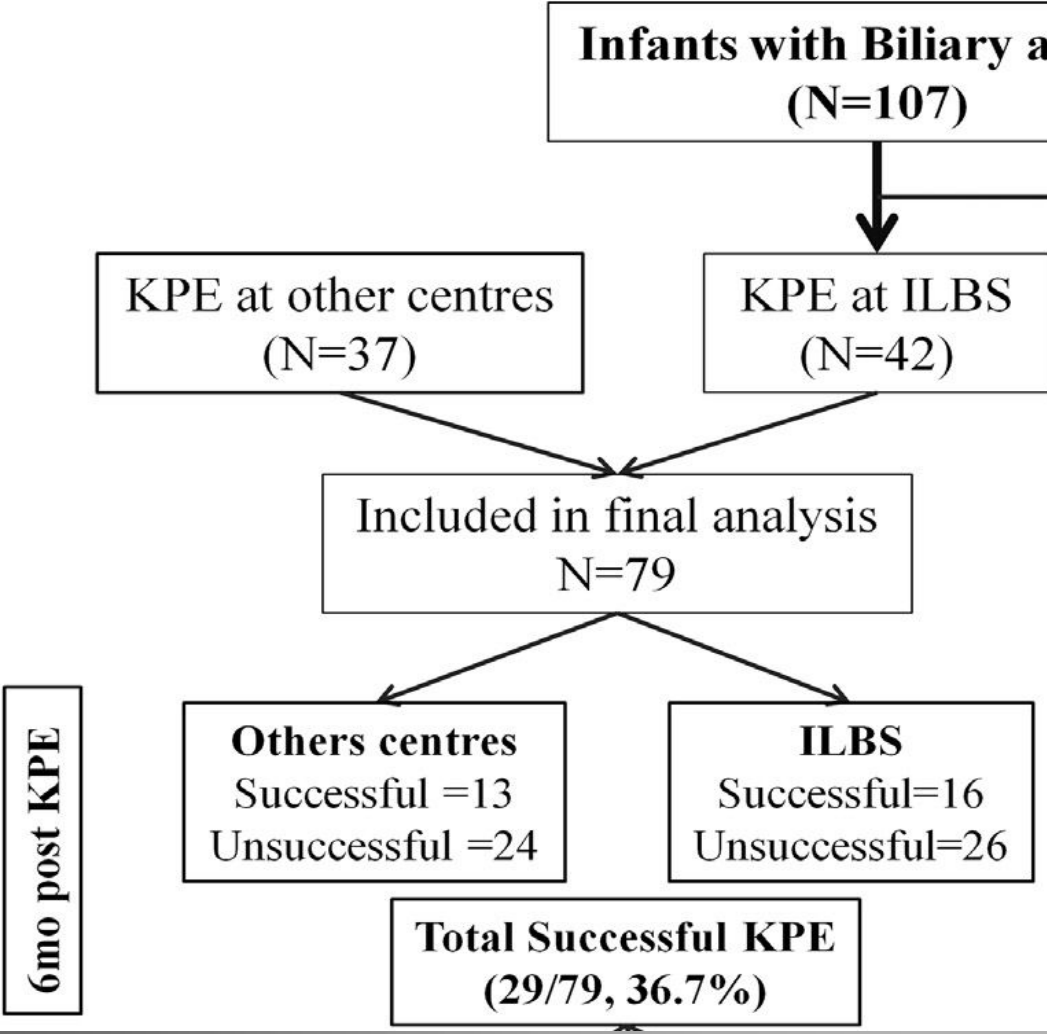
Acholic stools are equally informative as non-excretory HIDA

Only indicated when stool colour is fluctuating: **to exclude BA**

Average Delay of 7-15 days

When to do TORCH Profile ?

- Microcephaly
- Preterm/LBW/SGA
- Chorioretinitis
- Skin rash
- Intracranial Calcification



- 11 % operated < 60 days
- 51 % between 60-90 days
- 25 % between 90–120 days
- 13 % beyond 120 days of life

Youngest child operated at 49 DOL

J Clin Exp Hepatol 2019;9:453–459

Historical Data

- Onset to Presentation:
  - 120 days (SGPGI 1996)
  - 81 days (PGI 2009)
- Mean age of presentation: 2.8–3.9 mo (vs 1-1.5 mo)
- Age of KPE: 2.7 (1.5–4.2) mo (PGI 2009)

Indian Pediatr. 1996;33:729–34.Acta Paediatr. 2009;98:1260-4.

Role of Liver biopsy

- **> 90% accuracy for Biliary Atresia**

Bile ductular proliferation

Portal expansion

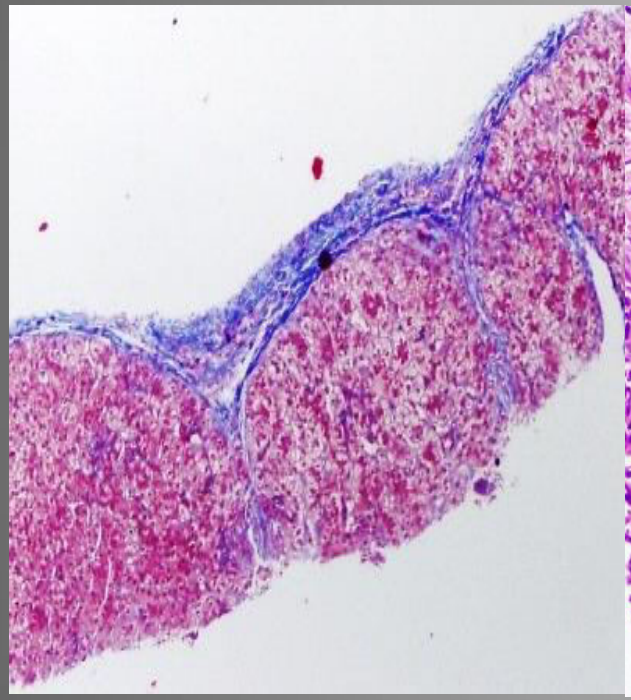
Portal & periportal fibrosis

Bile plugs

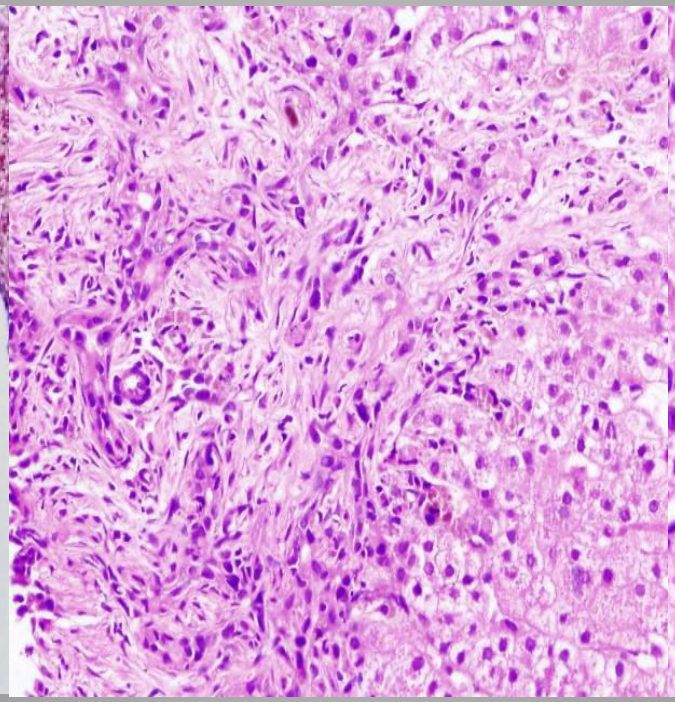
→ **Biliary Atresia**

Clin Gastroenterol Hepatol 2011;9:357–62e2.

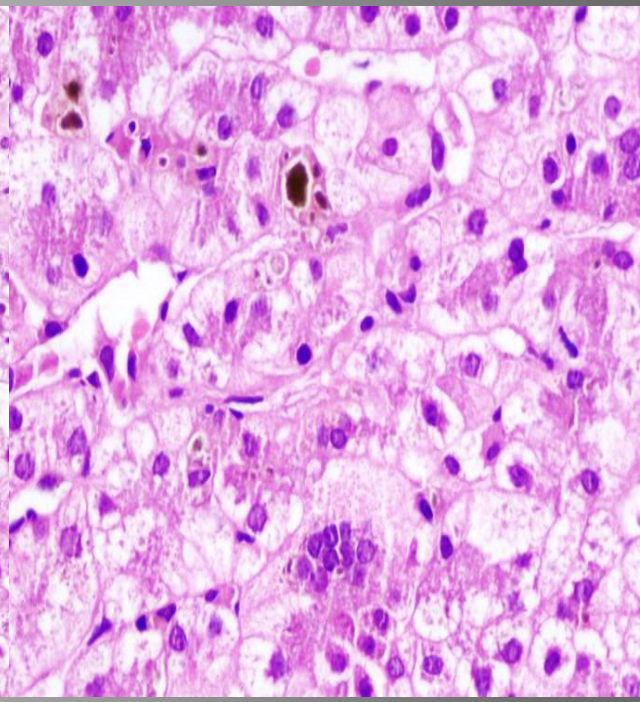
Liver biopsy



Distorted acinar architecture
Bridging fibrosis



Expanded Portal tracts,
Ductular Proliferation



Canalicular bile plugs,
Hepatocellular choelstasis

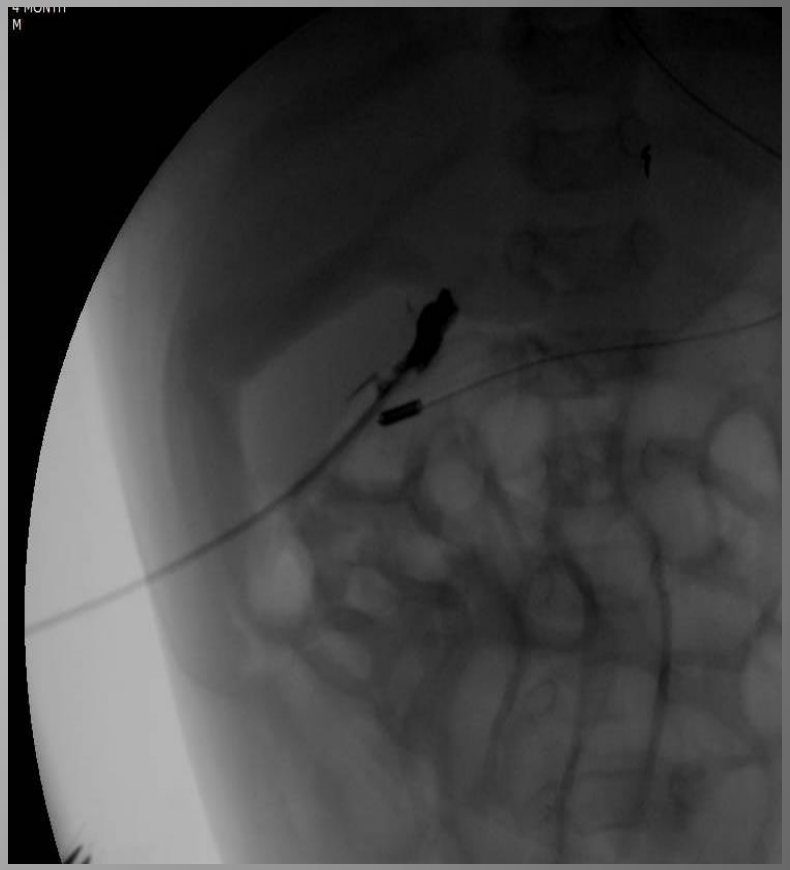
Gold Standard for Biliary Atresia

Pediatric Surgeon

Only for confirming and not for diagnosing Biliary Atresia

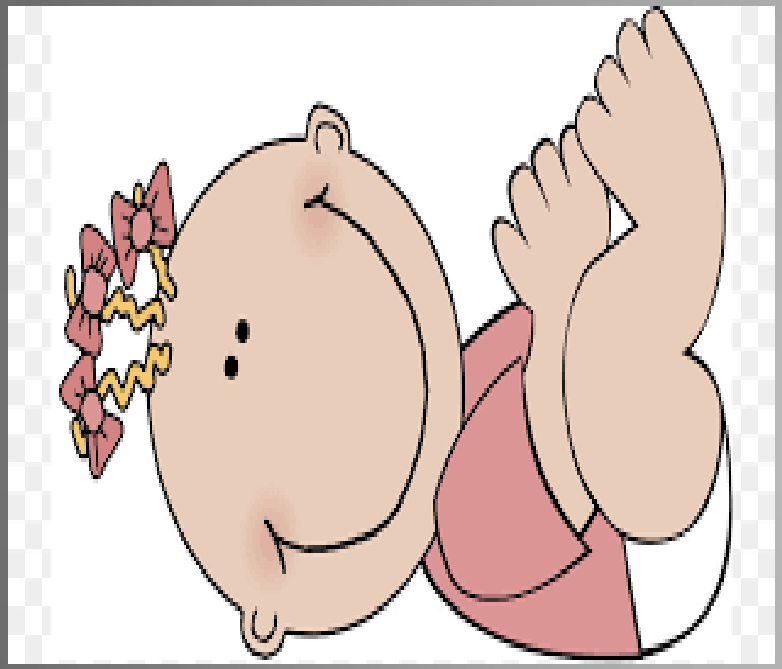
Final Diagnosis: Biliary Atresia

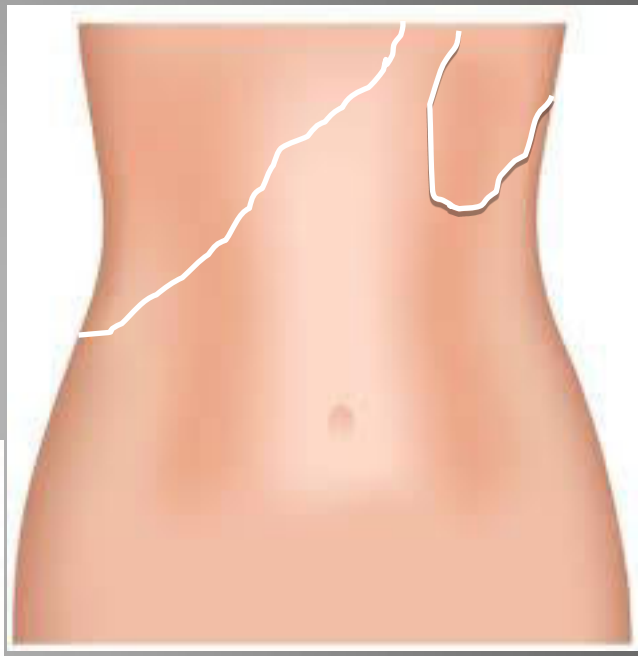
Intra operative Cholangiogram



- Kasai Porto-enterostomy:
  - Gall Bladder:
    - Partially distended
    - No bile
  - Biliary tree: Cord like

Biliary Atresia- Summary





Happy Growing Child, Progressively Jaundice + White Stools

High GGTP Levels

Hepatosplenomegaly

Neonatal Cholestasis

Give injection Vitamin-K

LFT + **Check colour of 3 consecutive stools**

Acholic / fluctuating stool colour

USG (Fasting)

Small or abnormal GB

Biliary atresia

Early Referral

Choledochal cyst

Pigmented stools

Well child

Prematurity
TPN usage
PFIC
Niemann-Pick C

Sick child

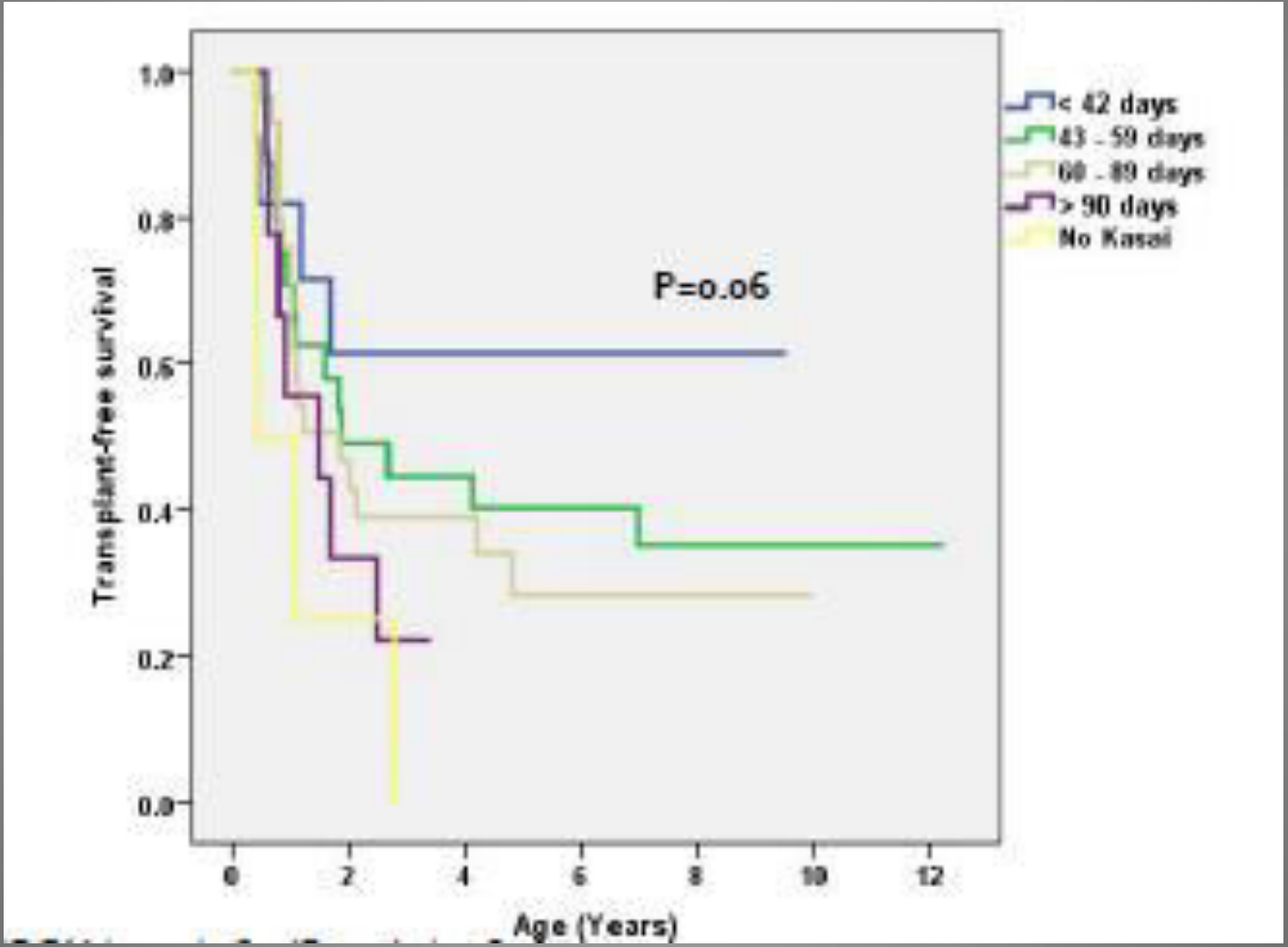
Infections
Sepsis, UTI

Synthetic failure
Metabolic Liver ds
Galactosemia
Tyrosinemia

Specific scenarios: Do CMV, HSV, Ferritin, AFP, Urine succinylacetone

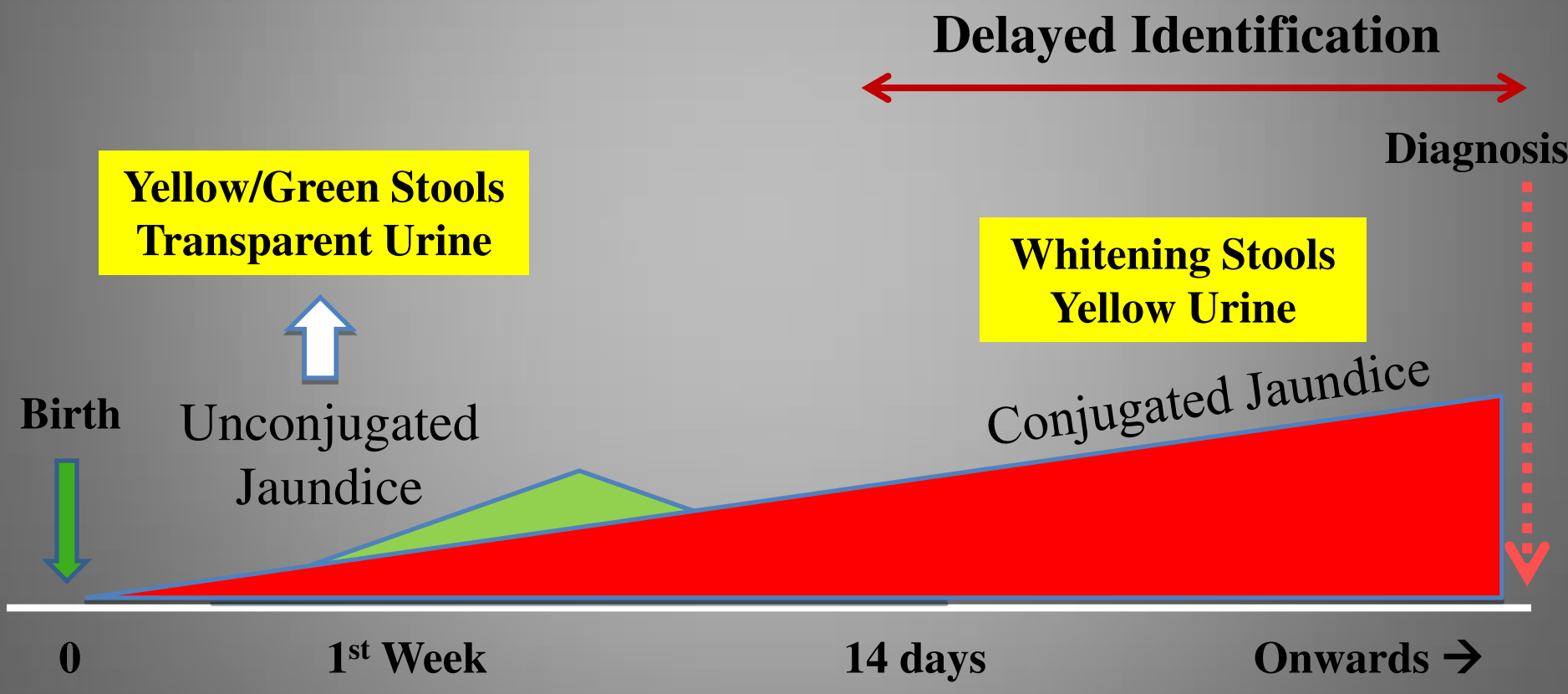
Bhatia V et al. Indian Pediatr 2014;51

Why is Biliary Atresia an Emergency ?



JPGN (2015): 60 (Suppl 1);183; *Pediatrics 2009;123;1280*

Diagnosing Biliary Atresia Early



LIFE STARTS AT BIRTH……

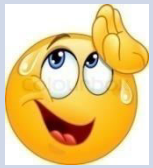
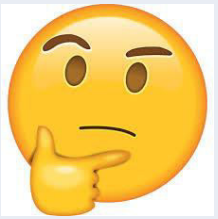
Newborn Screening

Direct Bilirubin* (Normal 0 to 0.3 mg/dl)	Neonates with BA	Controls
< 24 hours of life	0.98 ± 0.17 mg/dL	0.11 ± 0.05
24-48 hours of life	1.4 ± 0.43 mg/dL	0.19 ± 0.075 mg/dL

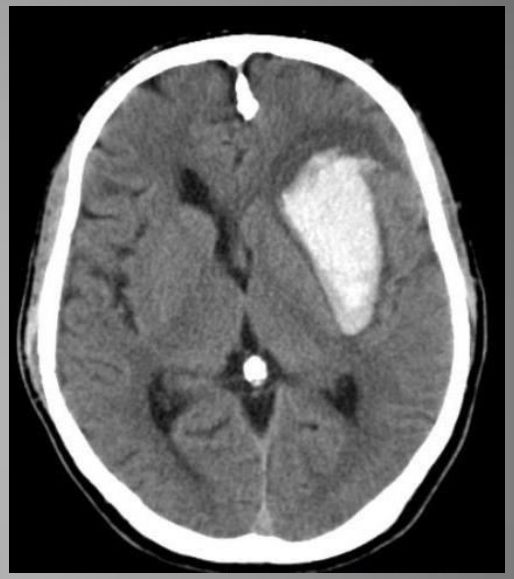
***Total Bilirubin levels below Phototherapy Cut offs**

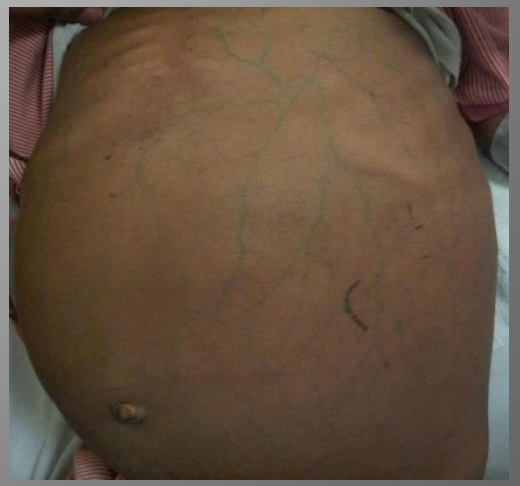
Pediatrics. 2011 Dec;128(6):e1428-33
J Pediatr Gastroenterol Nutr. 2016 Jun;62(6):799-803.

Closer Look at the Direct Bilirubin

Day of Life	Total Bilirubin	Direct Bilirubin	Interpretation
Day 5	8 mg/dl	[redacted]	
Day 5	13 mg/dl		
Day 7	23 mg/dl		

Initial Intervention → Outcomes





What should we know…

- **Neonate with Conjugated Jaundice → Look for Biliary Atresia first**
  - **CAN DIAGNOSE BA EVEN IN IST WEEK OF LIFE**
- **Never do Total Bilirubin alone**
  - **Do not ignore mildly elevated D. Bilirubin → Repeat**
- **Always ask for stool and urine colour**
- **Do not advise sunlight exposure without detailed history**

CASE SCENARIO 2

3 months/Male

Failure to thrive

2.7 Kg

3.1 Kg

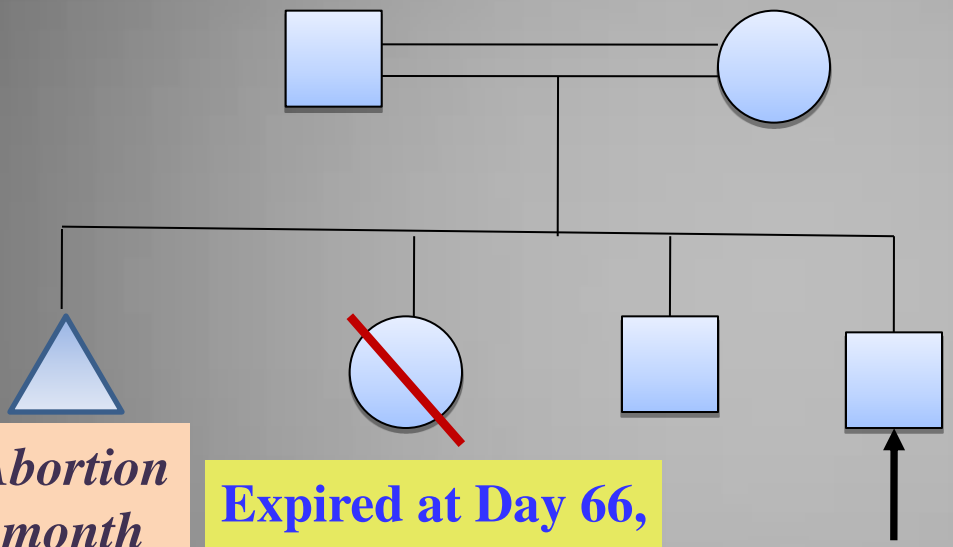
Abdominal Distension, Edema

Jaundice, Dark Urine, Yellow Stools

Term/NVD
B wt 2.7kg

Birth | 10 days | 1.5 months | 3 months

Family History



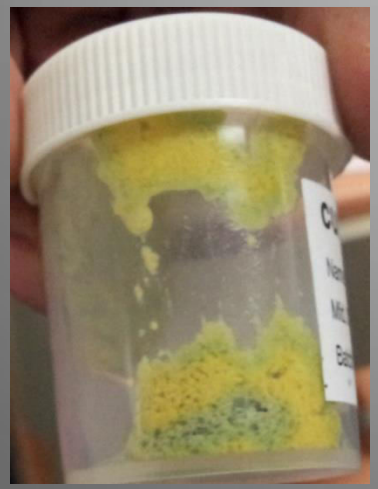
1 Abortion
6 month

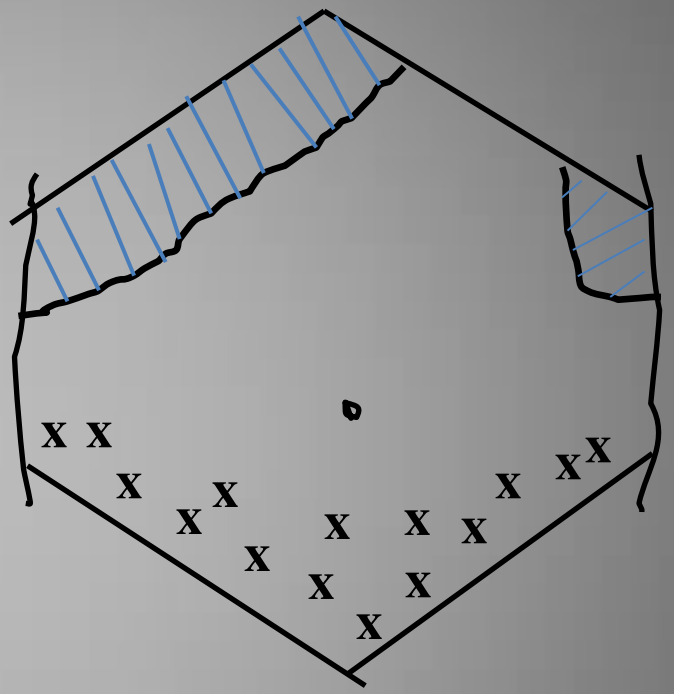
Expired at Day 66, Jaundice +

3^0 Consanguinity

Examination

- Lethargic
- Icterus ++, Edema +
- **Bilateral Cataract +**
- Failure to thrive





Liver- 3cm BCM, sharp margins

Spleen- 2cm BCM

Ascites ++

Investigations

INR	2.2
Bilirubin (Total/Direct)	6.2/3.4
AST/ALT	179/66
SAP/GGT	364/61
Protein/Albumin	3.2/1.8

Unresponsive Coagulopathy – Low Albumin– Normal Cholestatic Enzymes

Pointers to an MLD

- Consanguinity, recurrent abortions, neonatal deaths (Family History)
- Recurrence of symptoms
- Failure to thrive, Diarrhea, Vomitings (GIT)
- Seizures, Irritability, Lethargy (CNS)
- Developmental delay, Hypotonia, Cataract (CNS)
- Rickets, Renal Tubular Acidosis (Renal)
- Hypoglycemia, Lactic acidosis, High Ammonia

Work up

Suspected MLD	Tests to Do
Galactosemia	•Urine for Reducing Substances (+ Urine Routine) •Plasma GALT Assay
Tyrosinemia	•Serum AFP •If High → Urine for Succinyl Acetone

Present Case

- Urine Tests:
  - Urine Routine- No Sugar
  - Urine for reducing substances- Positive (++, ++, +++)
- GALT Assay:
  - 5 U/gram of Hb (Normal > 15)
- Management:
  - Lactose Free Feeds
  - 4 month follow up- Jaundice Resolved, Normal Growth, Cataract still present

Neonatal Cholestasis

Give injection Vitamin-K

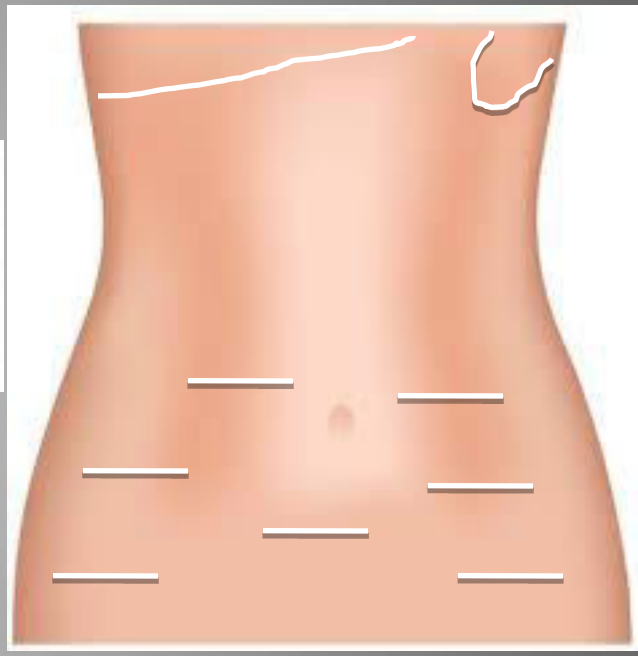
LFT + Check colour of 3 consecutive stools

- Acholic / fluctuating stool colour
  - USG (Fasting)
    - Small or abnormal GB
      - **Biliary atresia**
        - Early Referral
    - **Choledochal cyst**
- Pigmented stools
  - Well child
    - **Prematurity**
      TPN usage
      PFIC
      Niemann-Pick C
  - **Sick child**
    - **Infections**
      Sepsis, UTI
    - **Synthetic failure**
      Metabolic Liver ds
      Galactosemia
      Tyrosinemia
      Neonatal ALF

Specific scenarios: Do CMV, HSV, Ferritin, AFP, Urine succinylacetone

Bhatia V et al. Indian Pediatr 2014;51.

Metabolic Liver Disease- Summary



Poorly Growing Child, Jaundice +/- White Stools

Vomiting/Loose Stools/Irritability/Ascites

Common Treatable Causes

Etiology	Test
Biliary Atresia	GGTP levels, USG Abdomen, Liver Biopsy
Choledochal Cyst	USG Abdomen
Galactosemia	Urine Routine + Urine for reducing substances Serum GALT assay
Tyrosinemia	Serum AFP, Urine Succinylacetone
Sepsis	Sepsis Screen (including Urine Routine)
Endocrine	FT4/TSH levels, Fasting Blood Sugar, Serum Cortisol

Take Home Messages

- **Jaundice in Neonate/Infant:**
  - Look for stool/urine color, staining of diaper
  - Check Direct Bilirubin
  - Give Inj. Vitamin-K
  - **Early Referral to a higher centre**

Look For Biliary Atresia

Thanks