Neonatal Cholestasis Syndrome (NCS)

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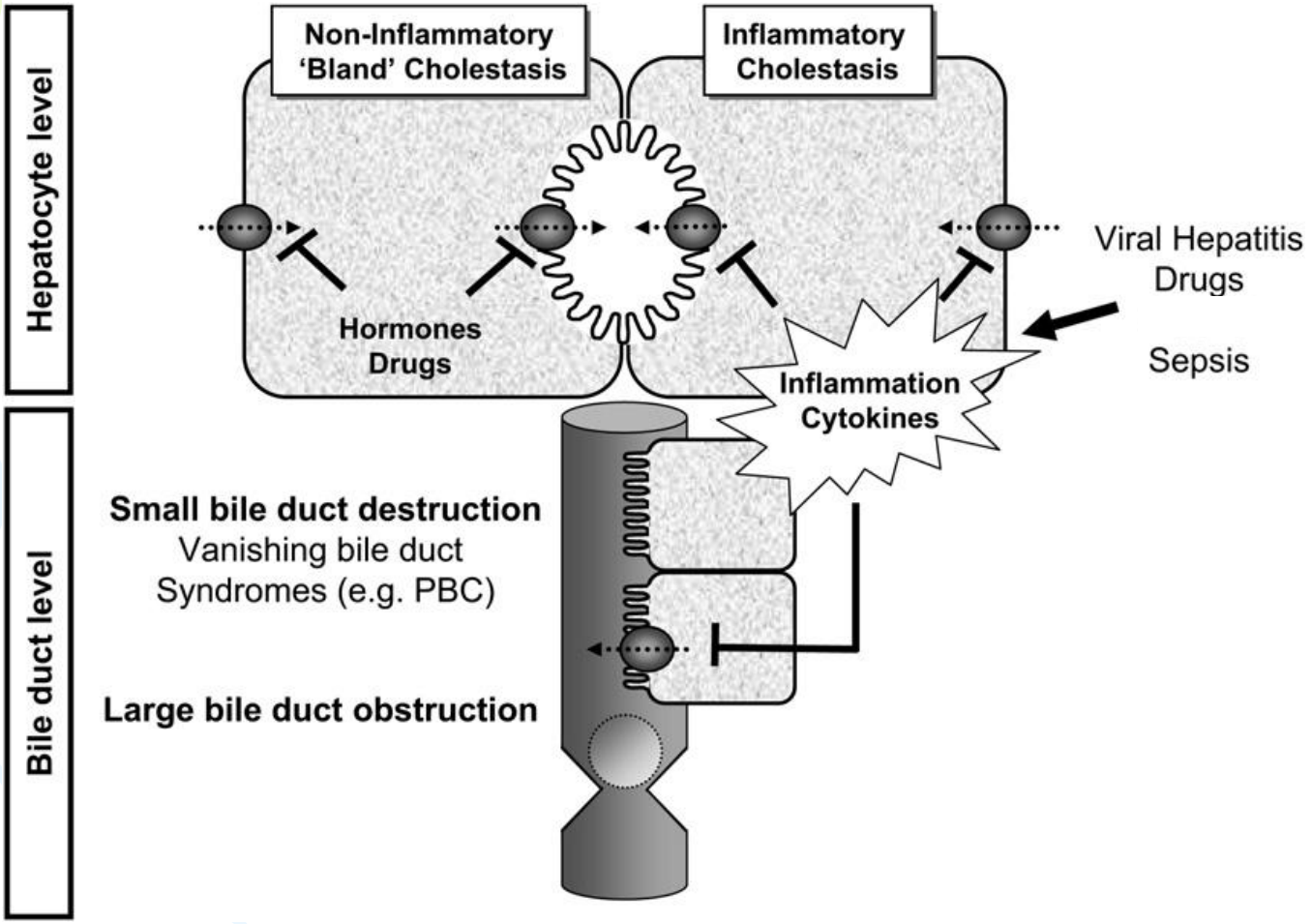
Overview

- Introduction
- Incidence
- Pathophysiology
- Clinical features
- Evaluation
- Management
- Cholestasis in VLBW
- Cholestasis –TPN

Neonatal Cholestasis Syndrome (NCS)

- Neonatal Cholestasis: conjugated hyperbil in a newborn, as a consequence of diminished bile flow
- Conjugated bilirubin level
  - > 1 mg/dl, if TSB <5
  - >20%, if TSB >5
- Diazo method overestimate direct bilirubin

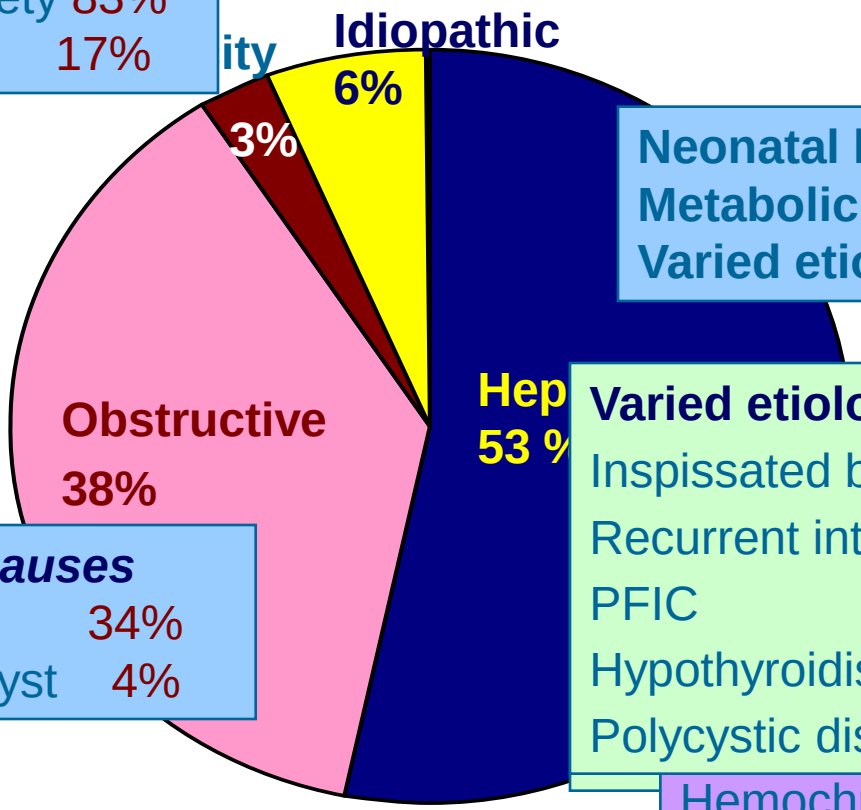
Pathophysiology NCS



Gernot Zollner et al , Mechanism of cholestasis: clinics in liver disease 12 (2008):1-26

Causes of neonatal cholestasis
(n=1080)

Ductal paucity
Non-syndromic variety 83%
Syndromic variety 17%



Neonatal hepatitis 47%
Metabolic 4%
Varied etiology 2%

Obstructive causes
Biliary atresia 34%
Choledochal cyst 4%

Varied etiology:
Inspissated bile plug syndrome
Recurrent intrahepatic cholestasis
PFIC
Hypothyroidism
Polycystic disease
Hemochromatosis 2%

Clinical presentation

- Dark urine and/or pale stool
- Pale stool for BA
  - Sensitivity 89.7%
  - Specificity 99.9%
  - PPV 28.6%
- Mean age of Px
  - Biliary atresia: 3-12 days
  - Heapatocellular causes: 16-24 days
- BA: well baby with normal growth & development
- Stool colour card

Sequalae of cholestasis

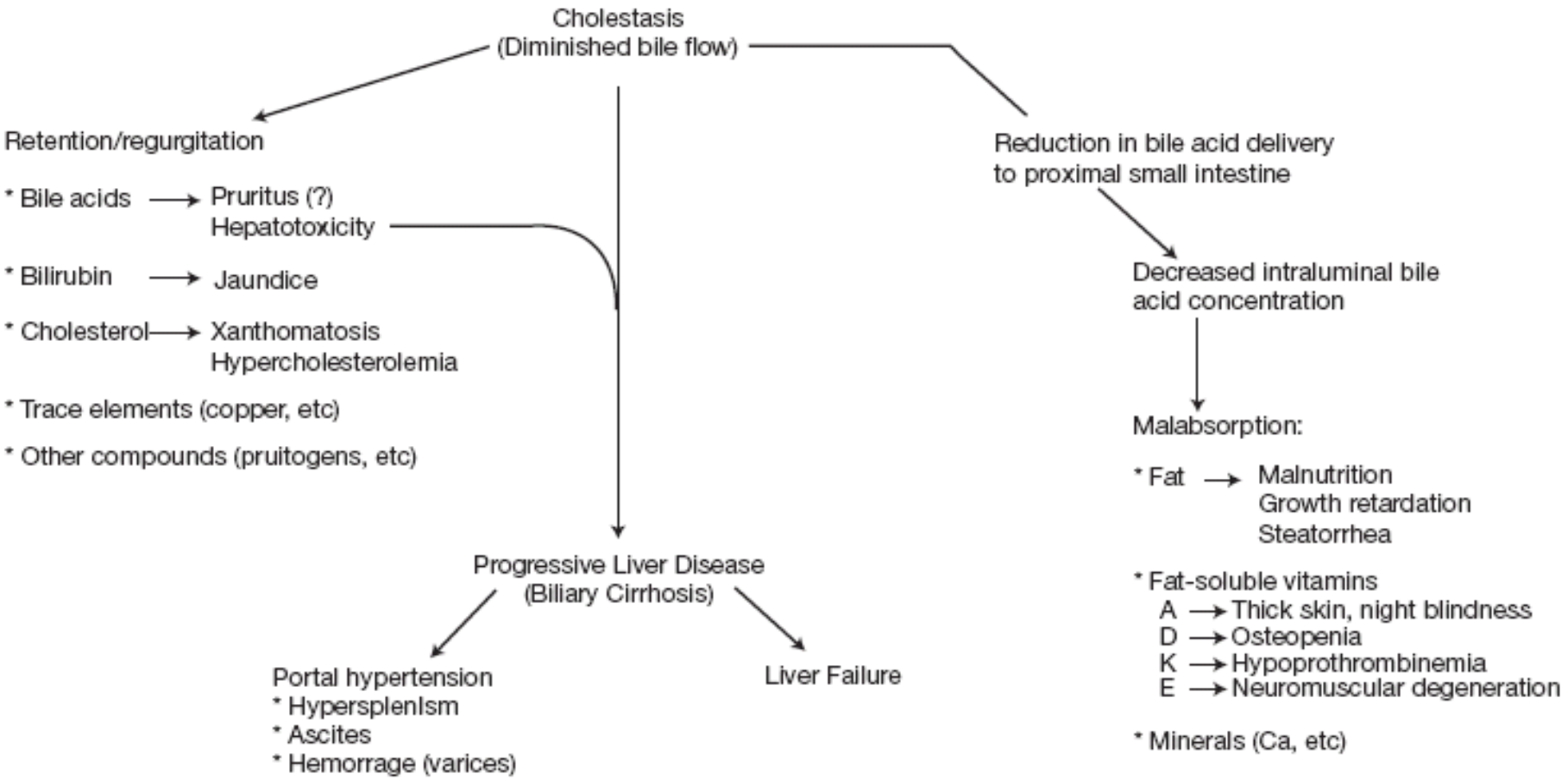


FIGURE 49-3 Clinical sequelae of chronic cholestasis. Numerous consequences of cholestasis become clinically manifest and result from retention of substances excreted in bile, reduction of intestinal bile acids, and progressive damage to the liver. See text for relationship between bile acids and pruritus.

Evaluation of NCS

- Sick or well
- Liver function test
- Thyroid function test
- Sepsis screen

Figure 1

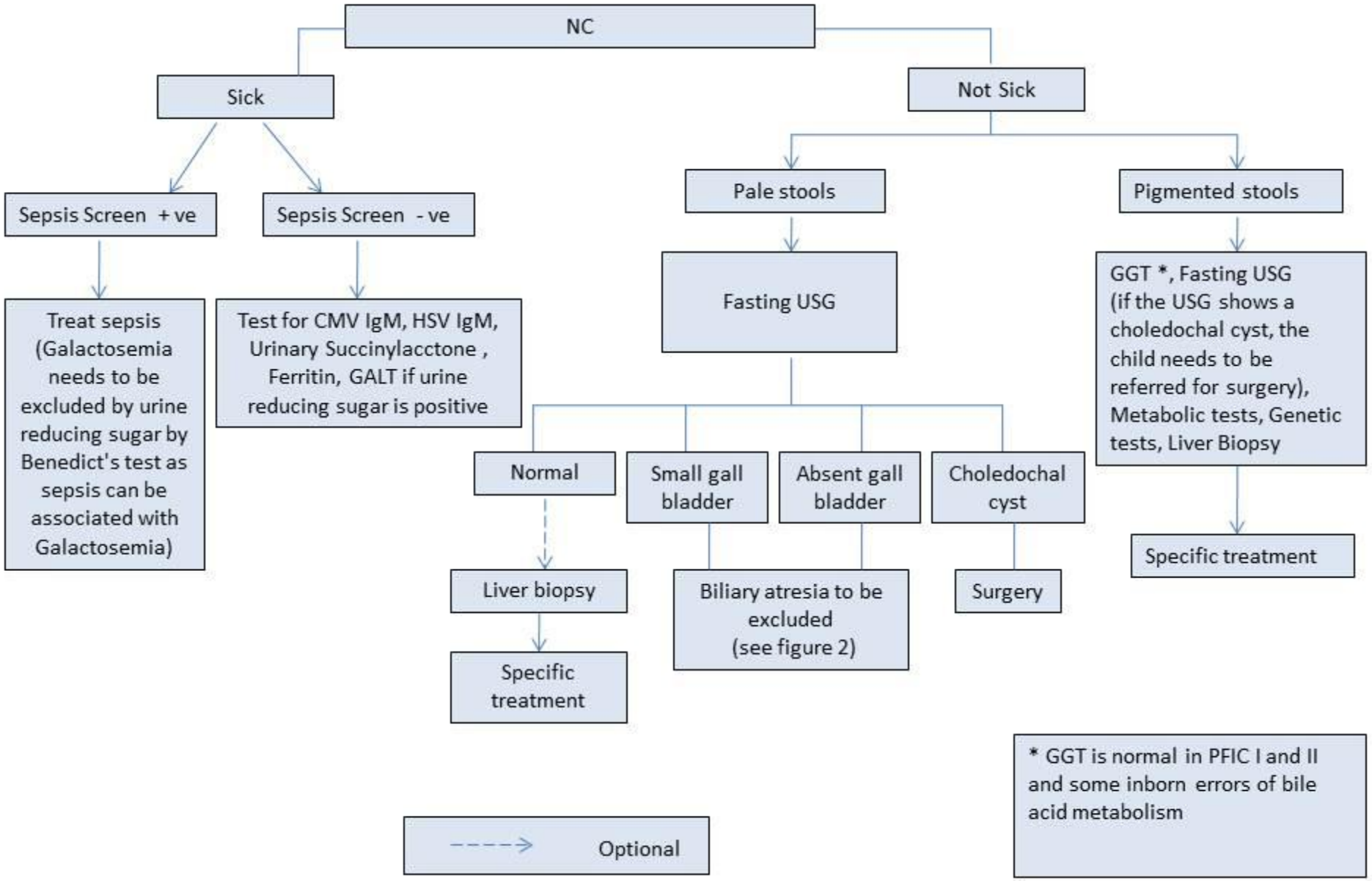
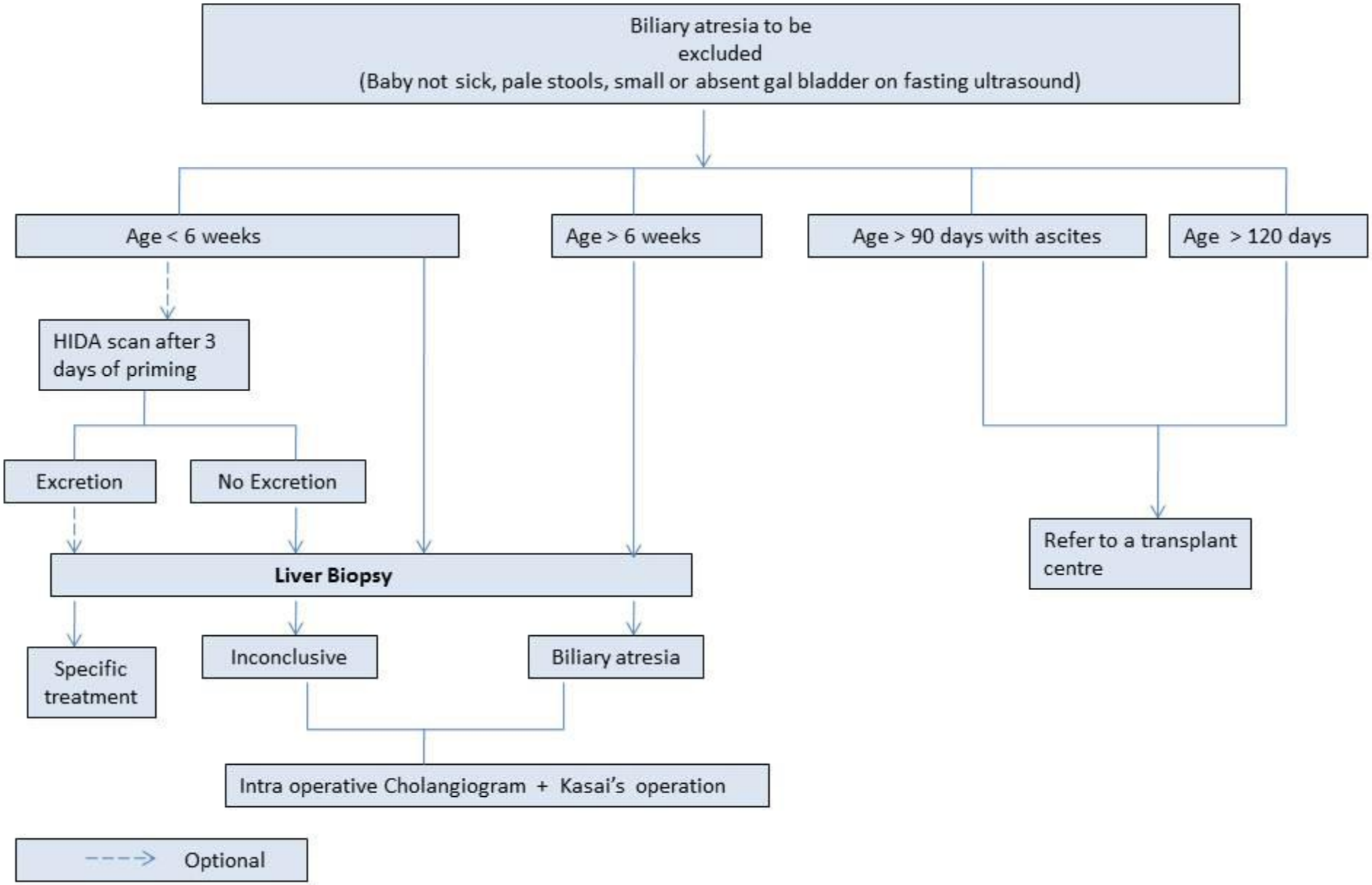

NC
Sick
Not Sick
Sepsis Screen + ve
Sepsis Screen - ve
Pale stools
Pigmented stools
Treat sepsis (Galactosemia needs to be excluded by urine reducing sugar by Benedict's test as sepsis can be associated with Galactosemia)
Test for CMV IgM, HSV IgM, Urinary Succinylacctone , Ferritin, GALT if urine reducing sugar is positive
Fasting USG
GGT *, Fasting USG (if the USG shows a choledochal cyst, the child needs to be referred for surgery), Metabolic tests, Genetic tests, Liver Biopsy
Normal
Small gall bladder
Absent gall bladder
Choledochal cyst
Liver biopsy
Biliary atresia to be excluded (see figure 2)
Surgery
Specific treatment
Specific treatment
* GGT is normal in PFIC I and II and some inborn errors of bile acid metabolism
Optional

Figure 2


Biliary atresia to be excluded
(Baby not sick, pale stools, small or absent gal bladder on fasting ultrasound)
Age < 6 weeks
Age > 6 weeks
Age > 90 days with ascites
Age > 120 days
HIDA scan after 3 days of priming
Excretion
No Excretion
Liver Biopsy
Refer to a transplant centre
Specific treatment
Inconclusive
Biliary atresia
Intra operative Cholangiogram + Kasai's operation
Optional

Evaluation of NCS

Conditions that require immediate treatment

1. Metabolic conditions
    1. Galactosemia: urinalysis, urine reducing substance, GALT assay
    2. urine organic acids, urine & serum AA
    3. Tyrosenemia: urine succinylacetone
    4. Neonatal hemochromatosis: S. iron & ferritin
2. Viral serology

Evaluation of NCS

Establish other specific diagnoses :

1. @1 Anti trypsin def: Serum A1AT levels & phenotype
2. Sweat chloride for cystic fibrosis
3. Genetic testing for Alagille syndrome & PFIC
4. X-ray skull & long bones,eye exam for chorioretinitis
5. Bone marrow examination & skin fibroblast culture for storage disorders

USG abdomen

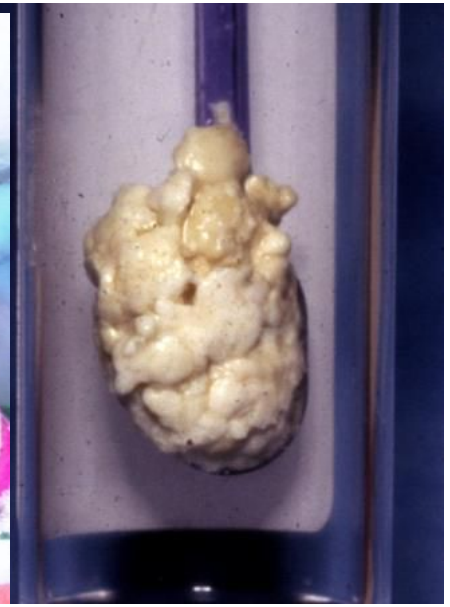
- Suggest BA and confirm other surgical conditions
- BA: 4 hrs fasting
  - Triangular cord sign
  - Abnormal GB morphology
  - No contraction of GB post feed
  - Non visualisation of CBD

HIDA Scan

- Limited role if documented pale or pigmented stool
- Priming time is limitation
- Optional test
- Uncommon diagnosis: CBD perforation

HIDA Scan: fallacies

- 8 weeks, male
- Pale stools since birth
- GGT 1339
- USG – contracted GB



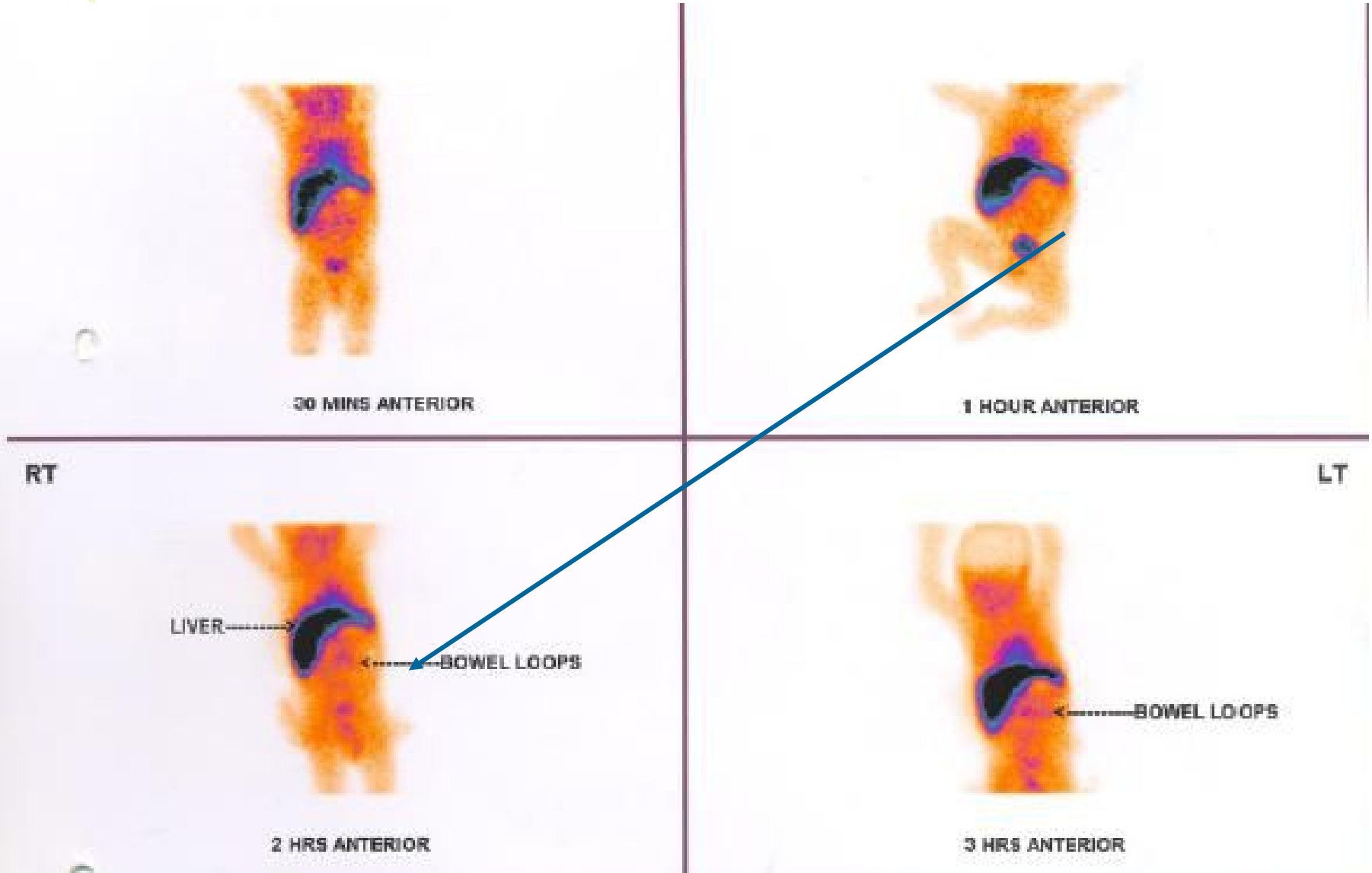
HIDA images


30 MINS ANTERIOR
1 HOUR ANTERIOR
RT
LT
LIVER
BOWEL LOOPS
2 HRS ANTERIOR
BOWEL LOOPS
3 HRS ANTERIOR

Results…

- HIDA: intestinal activity at 2 hours
- Rules out biliary atresia – a big relief !
- Metabolic and infective work up negative
- LFT continued to deteriorate, stools remain acholic
- Biopsy reviewed – Pathologist very sure of biliary atresia
- HIDA scan reviewed at 10 weeks

HIDA images


30 MINS ANTERIOR
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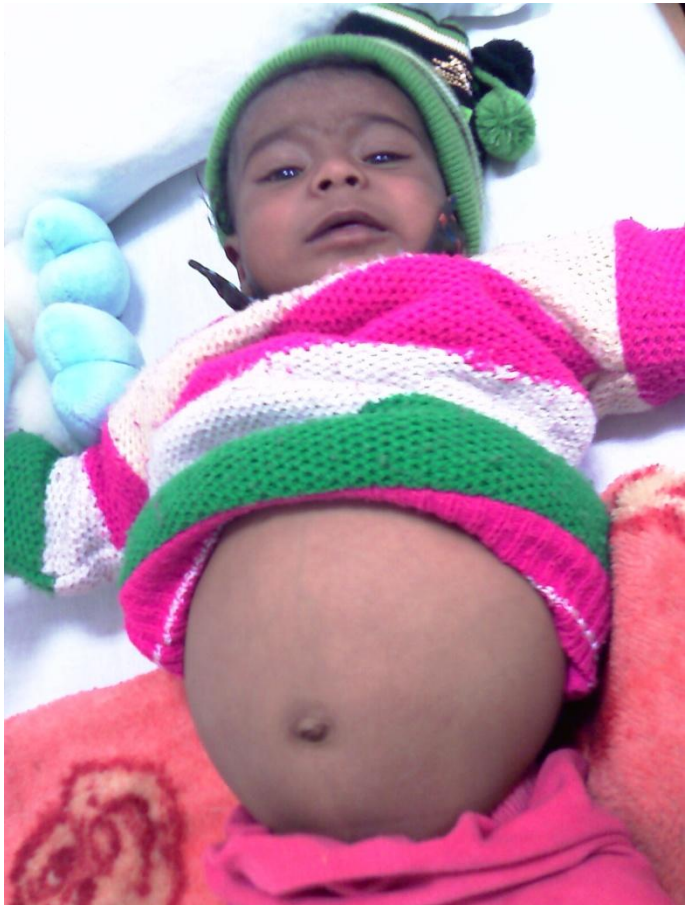
Outcome…

- Family could not be convinced for POC and opted to leave to GOD
- At 6 months – ascites

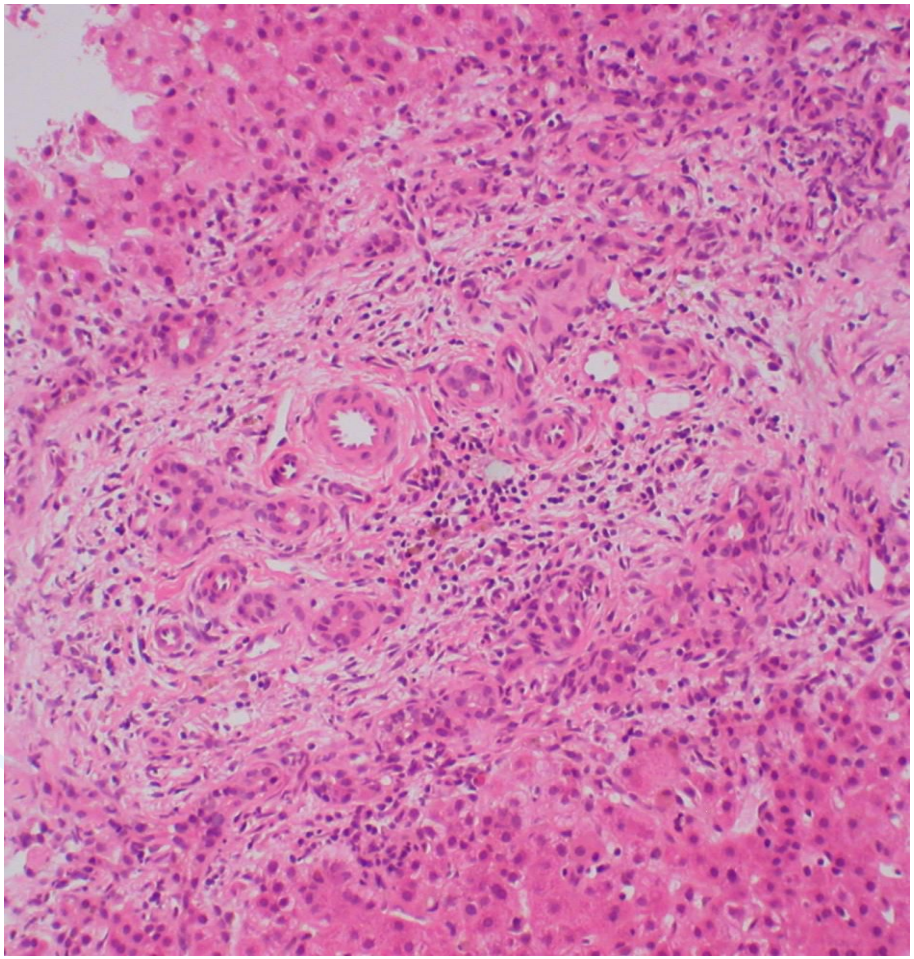


died

Liver biopsy

- Bile duct proliferation
- Bile plug in ducts
- Fibrosis
- Lymphocytic proliferation in portal tract

Liver Biopsy



Management of cholestasis

- Nutritional
- Pruritus
- Infection
- Associated problems
- Specific diseases

Nutrition

- Breast feeding to continue
- Supplement medium chain triglycerides
- Caloric intake :125% RDA (200 kcal/kg/day)
- Proteins 1-2 gm/kg/day
- 2-3% calories from EFA
- Nasogastric feeding – if not feeding well

Nutrition

- Vit A 50,000 IU IM at diagnosis & 10,000 IU monthly
- Vitamin D 30,000 IU IM at diagnosis & then monthly till cholestasis resolves/1000 IU daily
- Oral Vitamin E supplementation (50- 200 mg)
- Vitamin K 2.5 mg /day IM x 3days & then2.5 mg weekly. PT - monthly

Injectable Vitamin E and water soluble formulations of vitamins A, D and K are not yet marketed in India.
In the West these are available and are used.
The vitamin recommendations are based on current availability in India.

Pruritus

- Decreasing levels of bile acids in blood improves symptoms
- Ursodeoxycholic acid 10-20 mg/kg/day
- Phenobarbital 3-10 mg /kg/d
- Cholestyramine 0.25-0.5 g/kg/d

Infection

- Presence of ascites & end stage liver disease – predispose
- Ascitic fluid culture for appropriate antibiotic therapy.
- Cefotaxim and amikacin

Transplantation

- Liver transplantation –

  Only option for infants with EHBA with decompensated liver disease (ascites and/or encephalo-pathy) or failed portoenterostomy.

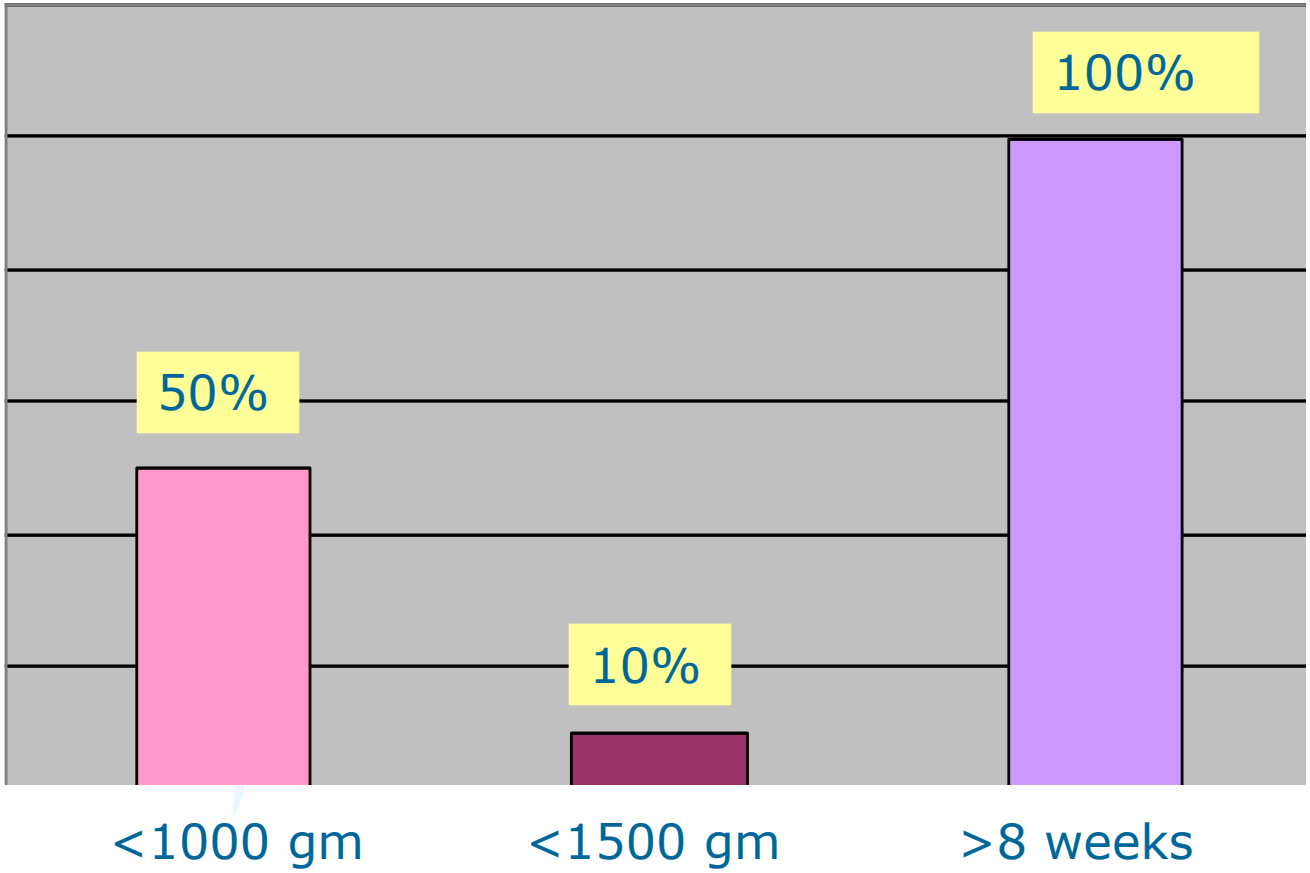
Cholestasis in VLBW: etiology

- Immaturity of biliary excretory system
- Diminished immune response to sepsis
- Increased incidence of NEC & short bowel syndrome
- Increased exposure to parenteral nutrition (PN)
- NPO, sepsis & translocation of endotoxin or bacteria

Cholestasis in VLBW: management

- HIDA & liver biopsy - delayed until CGA is at term & weight is > 2kg.
- ***Liver biopsy***: ***Indication***
- Acholic stools
- Cholestasis persisting beyond CGA 2 months
- Nonexcreting hepatobiliary scan

Parenteral nutrition associated cholestasis



Sepsis adds 30% more to both the categories

TPN associated cholestasis

- Onset after 2 weeks of receiving TPN.
- Multifactorial pathogenesis.
  - IV AA & lipid emulsions and their phytosterol content.
  - Critically ill newborns: oxidative liver injury bacterial endotoxin, lipid emulsions, specific amino acids and degradation products

Underlying disease requiring TPN

- Gastrointestinal problems
- Short bowel syndrome
- Medical illness
- Sepsis
- NEC

Loss of physiological enteral intake

- Lack of enteral stimulation by intraluminal nutrients during TPN

Lack of cholecystokinin release

↓

Decreased emptying of the gall bladder

↓

Bile stasis

Lack of oral intake

↓

Decreased release of GI hormones and growth factors

↓

Enterocyte hypoplasia

Composition of amino acids

- AA required by the premature baby are cysteine and taurine for conjugation.
- breast milk contains taurine
- TPN lacks taurine: conjugation is with glycine.
- glycine conjugates are hepatotoxic

TPN associated cholestasis

- Can lead to progressive liver disease & cirrhosis.
- Initiate enteral feedings as early as possible
  - Stimulus for bile flow, gallbladder contraction, and intestinal motility
- Cholestasis may take month to resolve completely
- Chances of residual hepatic fibrosis or even cirrhosis.

Treatment

1. Feeding: even small amounts

2. Modifications of TPN :
    - Energy: only the required energy
    - Amino acids : 2gm/kg/day
    - Lipids : restrict to 1 gm/kg/day

3. Role of drugs: not established

NCS – carry home message

- Always ask urine and stool color in any jaundiced newborn
- Fractionated bil for jaundice >2 wks of age
- Pale stool more alarming than jaundice:Educate mother
- Always rule out Biliary atresia in every case of NCS with pale stools.
- Let HIDA or TORCH never delay a diagnosis of Biliary atresia
- Institute vitamins early in all NCS