

Standard Operating Procedure (SOP): Evaluation and Initial Management of Neonatal Cholestatic Disease

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1. Purpose

Neonatal cholestasis is **pathological** and mandates **urgent, structured evaluation**. The central objective is **early identification or confident exclusion of biliary atresia (BA)**, because outcomes depend on timely intervention.

In parallel, treatable genetic and metabolic disorders must be identified early to prevent irreversible liver injury.

2. Definition

Neonatal cholestasis is present when:

- Age >14 days, and
- Direct (conjugated) bilirubin:
 - ≥ 1 mg/dL if total bilirubin <5 mg/dL, or
 - $\geq 20\%$ of total bilirubin if total bilirubin ≥ 5 mg/dL.

Principle: Prolonged jaundice beyond 2 weeks is not physiological until conjugated bilirubin is measured.

3. Rationale for Urgency

- BA is the most common surgically correctable cause of neonatal cholestasis.
- Kasai portoenterostomy is most effective when performed **before 45-60 days of life**.
- Delays reduce bile drainage, increase fibrosis, and worsen native liver survival.
- Several metabolic causes are **rapidly reversible** if treated early.

Operational rule: Investigations must be **parallel**, not sequential. Observation without evaluation is inappropriate once cholestasis is confirmed.

4. Entry Criteria (Day 0)

Initiate this SOP immediately if any of the following are present:

- Jaundice persisting beyond 14 days
 - Pale, grey, or clay-colored stools
 - Dark urine
 - Hepatomegaly or firm liver
 - Poor weight gain with jaundice
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5. Step 1 - Immediate Confirmation (Day 0-1)

A. Confirm conjugated hyperbilirubinemia

Order:

- Total bilirubin
- Direct (conjugated) bilirubin

B. Stool color assessment

Document stool color carefully.

Pale or acholic stools are a **major red flag for BA** and mandate expedited evaluation.

Use Royal care Stool card.

6. Step 2 - Baseline Laboratory Evaluation (Day 0-1)

A. Liver injury and cholestasis panel

Order:

- AST
- ALT
- ALP
- **GGT**
- Total bilirubin
- Direct bilirubin

Interpretation

- High GGT: obstructive or biliary pattern (BA likely)
 - Low/normal GGT: consider metabolic/genetic cholestasis (PFIC, bile acid synthesis defects)
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B. Liver synthetic function

Order:

- INR / PT
- Serum albumin
- Blood glucose

Interpretation

- Prolonged INR: impaired hepatic synthesis or vitamin K deficiency
 - Hypoglycemia: severe liver dysfunction, urgent attention required
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C. Systemic assessment

Order:

- CBC
 - CRP
 - Blood culture (if clinically unwell)
 - Urine culture (if febrile or ill)
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D. Additional baseline tests

- Serum ammonia
 - Serum bile acids
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7. Step 3 - Infection Evaluation

Order:

- Urine CMV PCR
- TORCH IgM (as per institutional policy)

Interpretation

- CMV infection may contribute to cholestasis but **does not exclude BA**.
 - Infectious etiologies often coexist and should not delay BA evaluation.
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8. Step 4 - Genetic and Metabolic Evaluation (Parallel Testing)

This block of tests must be ordered **concurrently with imaging**.

A. Galactosemia

Tests

- RBC galactose-1-phosphate uridyltransferase (GALT) activity
- Galactose-1-phosphate level (RBC)

Interpretation

- Absent or markedly reduced GALT activity: classic galactosemia

Clinical implication

- Medical emergency
- Immediate lactose/galactose-free diet
- Liver dysfunction can reverse rapidly if treated early

B. Tyrosinemia Type 1

Tests

- Plasma or urine **succinylacetone** (mandatory)
- Plasma amino acids (supportive)

Interpretation

- Detectable succinylacetone: diagnostic
- Tyrosine level alone is unreliable

Clinical implication

- High risk of acute liver failure and hepatocellular carcinoma
- Initiate nitisnone promptly
- Early transplant evaluation if response is inadequate

C. Bile Acid Synthesis Defects

(Suspect particularly with low/normal GGT cholestasis)

Tests

- Serum bile acids
- Urinary bile acid profile by LC-MS/MS or FAB-MS

Interpretation

- Low or inappropriately normal serum bile acids despite cholestasis
- Abnormal bile acid intermediates in urine: diagnostic

Clinical implication

- Treatable with primary bile acid replacement (cholic acid)
- Avoid unnecessary surgery
- Excellent outcomes with early diagnosis

9. Step 5 - Imaging Evaluation

A. Abdominal ultrasound (Day 1-3)

Requirements:

- Fasting (4-6 hours)
- Performed by experienced pediatric radiology team

Assess:

- Gallbladder presence, size, and contractility
- Triangular cord sign
- Liver echotexture
- Splenic anomalies (polysplenia/asplenia)
- Portal vein anatomy

Interpretation

- Absent or abnormal gallbladder with triangular cord sign: strong suspicion of BA
- Normal ultrasound **does not exclude BA**

B. Hepatobiliary scintigraphy (HIDA scan)

- Optional and selective
- Phenobarbitone priming if time permits

Interpretation

- Absence of bowel excretion supports obstruction
- Limited specificity and sensitivity

Principle

- HIDA scan must **never delay surgical exploration** if BA is suspected.

10. Step 6 - Supportive Medical Management

A. Fat-soluble vitamin supplementation

Initiate immediately once cholestasis is confirmed:

- Vitamin A: 5,000 IU orally once daily
- Vitamin D: 800-1,000 IU orally once daily
- Vitamin E: water-soluble TPGS 15-25 IU/kg/day orally
- Vitamin K: 2.5 mg orally twice weekly
 - If INR prolonged: 1-2 mg IV or IM, then oral maintenance

Monitor INR and vitamin levels during prolonged cholestasis.

B. Nutrition

- High-calorie intake: 120-140 kcal/kg/day
- Medium-chain triglyceride (MCT)-enriched feeds
- Regular weight monitoring to ensure growth

11. Step 7 - Decision Gate: Exclusion of Biliary Atresia

Features increasing likelihood of BA

- Pale or acholic stools
- High GGT cholestasis
- Absent or abnormal gallbladder on ultrasound
- Onset of jaundice in early neonatal period

If BA **cannot be confidently excluded**:

- Proceed urgently to liver biopsy and/or operative cholangiogram.
- Perform Kasai portoenterostomy if BA is confirmed.

Target timeline

- Diagnostic completion and surgery by **≤45-60 days of life**.

12. Documentation and Communication

- Stool color, feeding adequacy, growth, and laboratory trends must be clearly documented.
 - Caregivers should be informed early about the time-sensitive nature of decisions.
 - Multidisciplinary coordination (hepatology, surgery, radiology, genetics) is essential.
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13. Indications for Early Transplant Evaluation

- Failed Kasai portoenterostomy
 - Progressive synthetic dysfunction
 - Recurrent cholangitis
 - Metabolic liver disease with inadequate response to medical therapy
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Key References

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