Laboratory testing for evaluating a neonate or young infant with suspected cholestatic liver disease

Finding	Implications
Initial tests for all infants	
▪ Comprehensive metabolic panel	
• Total and conjugated bilirubin	To evaluate for conjugated hyperbilirubinemia (cholestasis) versus unconjugated hyperbilirubinemia.
• ALT and AST	To assess for hepatocyte injury.
• Alkaline phosphatase and GGTP	To assess for biliary injury. Furthermore, several genetic/metabolic disorders can be divided into high- and low-GGTP categories*.
• Total protein and albumin	To assess hepatocyte function. Low albumin suggests poor nutrition, renal losses, or poor hepatic synthetic function.
• Electrolytes, bicarbonate, glucose	To assess for metabolic disease. Abnormalities in these results are often seen in infants with metabolic disease.
▪ CBC with differential	To assess for infection and/or splenic sequestration. Elevated WBC is suggestive of infection. Low WBC and platelet count could indicate portal hypertension (with splenic sequestration).
▪ PT/INR and PTT	To assess hepatocyte function and/or vitamin K deficiency. Abnormal results indicate impaired liver synthetic function and/or vitamin K deficiency.
Additional tests to evaluate for systemic illness of specific liver diseases¶	
▪ Urinalysis and urine culture	Appropriate for most infants with cholestasis to exclude urinary tract infection and to evaluate possible renal involvement.
▪ Blood culture	If clinical presentation suggests sepsis.
▪ Urine-reducing substances	Screen for galactosemia (in infants ingesting lactose)Δ.
▪ Serum bile acids	Elevations are diagnostic of cholestasis. Serum bile acids will be low in infants with bile acid synthetic disorders.
▪ Alpha-1 antitrypsin concentration	Low levels suggest alpha-1 antitrypsin deficiency. Normal levels do not exclude alpha-1 antitrypsin deficiency, because this is an acute phase reactant.
• Protease inhibitor phenotype (PI type)	The primary alleles associated with liver disease are PI*ZZ homozygosity or PI*SZ heterozygosity.
▪ TSH, T4	Screen for congenital hypothyroidism (primary or central).
▪ Urine bile acid analysis by	Screen for inborn errors of bile acid metabolism (BASD), which may present

FAB-MS	with low-GGT cholestasis◊.
▪ Metabolic testing	If a metabolic disorder is suspected, initial screening includes plasma amino acids, urine organic acids, acylcarnitine profile, ammonia, lactate:pyruvate ratio.
▪ Genetic testing	Genetic testing is rapidly evolving with the availability of new technologies§.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGTP: gamma-glutamyl transpeptidase; CBC: complete blood count; WBC: white blood cell count; PT: prothrombin time; INR: international normalized ratio; PTT: partial thromboplastin time; TSH: thyroid-stimulating hormone (thyrotropin); T4: thyroxine; FAB-MS: fast atom bombardment mass spectrometry; GGT: gamma-glutamyl transferase.

* GGTP is disproportionately elevated (compared with AST and ALT) in the most common types of neonatal cholestasis, including biliary atresia and Alagille syndrome, while a normal or low GGTP is seen in most forms of progressive familial intrahepatic cholestasis, BASD, and arthrogryposis-renal dysfunction-cholestasis syndrome.

¶ These tests are selected based upon the clinical presentation and results of initial tests.

Δ Urine-reducing substances is only valid as a screen for galactosemia if the infant is fed breast milk or a cow's milk-based formula (which contains lactose, then hydrolyzed to galactose).

◊ Infants must be off of ursodeoxycholic acid for at least 5 days prior to urine collection for bile acid analysis because the FAB-MS signature of the drug overlaps with some of the abnormal bile acid metabolites seen in BASD.

§ Individual gene sequencing can be done if the clinical presentation suggests a specific diagnosis, such as Alagille syndrome. For screening of multiple genes associated with inherited cholestasis, next-generation sequencing panels are available. Each panel interrogates approximately 20 to 50 genes. Current information is available at GeneTests.org.

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