of BA. Documentation of cases such as the one presented here by Harpavat et al., and additional studies addressing sensitivity and cost issues, will help to shift the focus to screening all children rather than the current standard of care of screening only those children having persistent jaundice beyond 2 weeks of life. Such a shift could have a dramatic positive impact on the care and outcome of BA, which remains a formidable cause of morbidity in children.

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Reference

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Commentary

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Not all neonatal jaundice is created equal. Unconjugated hyperbilirubinemia and its associated risk of kernicterus get lots of publicity but conjugated hyperbilirubinemia presents a formidable diagnostic challenge. In addition to BA, the differential diagnosis includes infection, Alagille syndrome, hypothyroidism, galactosemia, bile acid metabolic defects, cystic fibrosis, α_1-antitrypsin deficiency, and genetic syndromes like PFIC (progressive familial intrahepatic cholestasis). In the case of BA, early recognition and treatment is essential to spare liver function.

The first clues to cholestasis are often biochemical because affected infants remain asymptomatic or only mildly symptomatic for many days or weeks after birth. The laboratory tools at our disposal, however, are not designed to detect small increases of conjugated bilirubin. The conjugated bilirubin assay relies on the intrinsic absorptivity of conjugated bilirubin between 420–430 nm and may be compromised by chromophores that absorb in the same region. Direct diazo methods compare poorly across platforms and are variably sensitive to the often substantial amounts of unconjugated bilirubin in neonatal blood. Neither measure of bilirubin glucuronides provides exceptional precision near the upper limit of the reference interval. Given truncation of direct or conjugated bilirubin to the nearest 0.1 mg/dL (1.7 μmol/L), the smallest detectable change at 0.2 mg/dL (3.4 μmol/L) is 50%. Better tools are clearly needed.

Finally, this case illustrates the importance of clinical context when applying reference intervals. When analyte values in unaffected and affected patients overlap, a clinical cutoff must account for the downside of missing disease as well as the consequences of overdiagnosis. In the case of pediatric cholestasis, optimizing sensitivity spares livers at the potential cost of a repeat bilirubin measurement. Optimizing specificity may lead to irreversible hepatic failure and liver transplant, or death. As the authors of this case point out, optimizing sensitivity in this context is preferable.

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