Indian Academy of Pediatrics (IAP)

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Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Role of direct bilirubin in predicting biliary atresia: Can Watson equal Sherlock Holmes?

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BASED ON ARTICLE

Liao FM, Chang KC, Wu JF, Chen HL, Ni YH, Chang MH. Direct bilirubin and Risk of Biliary Atresia. Pediatrics. 2022; 149:e2021053073. doi: 10.1542/peds.2021-053073. PMID: 35506333.

SUMMARY

Liao et al conducted a retrospective, cross-sectional study in a tertiary medical center in Taiwan. Infants indicated for total bilirubin and direct bilirubin (D-bil) measurements before age 60 days were included. The first bilirubin assessment was considered the test point. 4468 cholestatic infants were enrolled, including 38 with biliary atresia (BA). Cholestasis was defined as D-bil >1.0 mg/dL or direct/total bilirubin (D/T) ratio >20% in the infant group (D3-60) and D-bil >0.5 mg/dL the neonatal group (< D3), Among infants, a sensitivity of 100% (95% confidence interval, 90.3-100.0) was found for D-bil ≥1.0 mg/dL and either D-bil ≥1.0 mg/dL or D/T ratio ≥20%. However, D-bil ≥1.0 mg/dL had higher specificity (77.3% [76.0-78.5] vs 68.3% [66.8-69.7], respectively). In neonates, D-bil ≥0.5 mg/dL was considered a positive result, with a sensitivity of 50%. D-bil >0.45 mg/dL was a better cutoff point in receiver operating characteristic analysis, with a sensitivity and specificity of 100% (95% CI: 15.8-100) and 15.4% (95% CI, 11.8-19.7), respectively. The authors observed their BA cohort over a span of 8 years after portoenterostomy. Success was seen in approximately 50%, survival rates at 2 and 5 years were above 90% and overall survival with native livers was seen in half of the cohort [1].

COMMENTARY

Missing biliary atresia (BA) in the setting of neonatal cholestasis (NC) is a nightmare that haunts the repute of a paediatrician, gastroenterologist and surgeon. Except for patients with pigmented stools and neonatal liver failure, the rest of the NC have significant overlap and confounding effect with BA. The workup of NC is a step by step process, a “science of deduction”, much like the concept of Sherlock Holmes. To prove BA, the per-operative cholangiogram (POC) is the gold standard, the “Sherlock Holmes” of NC that puts the mystery to rest. The rest of the screening and ancillary investigations (stool card, sonography, biliary scintigraphy, liver histology etc.) lay the ground work like “Watson” despite their fallacies. Both are mutually co-dependent. But can the suspicion of BA be easier, faster and more efficient? Can Watson come up with something more ingenious? In 1995, Mowat and his colleagues suggested that D-bil fraction shortly after birth may have some predictive value. This

simple yet dawning concept took a backseat as researchers were rather exploring sonography, scintigraphy and cholangiography in those days. Competitive successes and failures were subsequently reported, however none achieved the gold standard benchmark. Mass screening with stool cards in Japan and Taiwan were exemplary and made the headlines. From 2011, Harpavat et al, resurfaced the concept of D-bil in BA prediction and gained steady grounds in screening of this condition in newborns [2, 3].

Taiwan is a compact country with effective screening programs and referral systems that are in place. The paper from Liao et al adds volume and further clarity on the concept of D-bil and BA. They screened two sets of patients, neonates <3 days and infants 3-60 days of life. They explored the various permutation-combination of the direct and total bilirubin fractions in predicting BA and non-atretic conditions. Should we use absolute D-bil value or a D/T ratio or a combination? Due to adequate numbers in the infant group, the authors concluded that the D-bil value >1mg/dL was far better than using D/T ratio or any other combination. Sensitivity reported was 100% with D-bil alone. In the newborn group, D-bil >0.45 mg/dL could be used as a cut-off but numbers in this study were not adequate to make this as a definitive conclusion. BA has a limited incidence of 1:8000 to 15000 live births in any country [1]. Hence there is not much scope to improvise on these values unless pooled multinational or global studies are conducted.

What is the utility of this paper in India? For screening, step one would be to use the **integrated neonatal cholestasis card** [4] which has been recently devised to suit our population. It uses an additional 7th stool colour and also high coloured urine chart as a guide [4]. This has an immense potential to be implemented at the grass root level. However we understand that not all patients will be detected by this method. Enter Watson to the rescue! Here comes the application of this paper by Liao et al. In India, healthy newborns are often discharged from hospitals by or after 72 hours. **D3 D-bil** should be keenly noted at this time point or in those undergoing workup for jaundice. Where a doubt is raised, then the second step of detailed investigation should begin consisting of the usual sonography, histology etc. In the third and final step, a POC should be performed if the index of doubt is strong for BA. With a sensitivity of 100% reported, we hope that D-bil cut-off >1mg/dL should not miss any BA. Hence Watson has the potential to equal Holmes.

The referral patterns of BA continues be dismal in India. Back in 2005, only 28% BA were referred by D60, with an average referral delay of 107 days to tertiary care centers [5]. Personal experience in last 15 years has shown some improvement in the referral pattern but still far from optimal. Here is a fresh chance to pick up this disease as early as D3. Hence let us commit and pledge to the same!

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