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Case Study

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Moving Beyond Direct Bilirubin in Neonatal Jaundice: Insights from a Systematic Review on Conjugated and Delta Bilirubin

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Abstract

Introduction: Investigating neonatal jaundice are basically by plasma total bilirubin, indirect and direct bilirubin (DB). However, DB is not equivalent to conjugated bilirubin (Bc) but includes delta bilirubin (ΔB). It overestimates the degree of conjugated hyperbilirubinemia. The prolonged DB elevation is also evident during cholestasis recovery phase. Fractionated bilirubin measurements can distinguish resolving jaundice from genuine conjugated hyperbilirubinemia. This study aims to illustrate the significance of fractionated bilirubin assays in the clinical management of neonatal jaundice.

Methods: The clinical and biochemical data of 89 patients aged below six months old with plasma total bilirubin level outside the age-specific reference intervals and fractionated and DB results were analysed and compared. Five cases were presented in detail to illustrate the importance of clinical use of Bc.

Results: Among the 89 patients with hyperbilirubinemia, 56% were due to breastmilk feeding, 13% total parenteral nutrition-related, 10% no specific causes detected, 9% congenital heart diseases, 8% infection-related, 3% blood transfusion-related or ABO incompatibility and 1% biliary atresia. After comparing the DB and Bc levels and their respective percentage over total bilirubin, Bc was shown to be more specific than DB. Elevated DB has led to unnecessary investigations.

Conclusion: Bc is more specific for the diagnosis of neonatal cholestasis than DB and we recommend its routine use for every case of neonatal jaundice. Bc also drops earlier than DB in the recovery phase of resolving neonatal jaundice. The use of Bc over DB in clinical settings avoids unnecessary investigations.

Keywords: Biliary atresia; Conjugated bilirubin; Delta bilirubin; Direct bilirubin; Neonatal cholestasis; Prolonged neonatal jaundice

Introduction

Neonatal jaundice (NNJ) is a common paediatric problem with incidence of 1 in 2,500 to 5,000 live births [1]. NNJ is conventionally classified into unconjugated and conjugated hyperbilirubinemia [2]. The latter is considered to be pathological until proven otherwise. The common causes are biliary atresia, neonatal hepatitis and viral infection [3,4]. According to National Institute for Health and Care Excellence (NICE) guideline, prolonged NNJ is "jaundice lasting more than 14 days in term babies and more than 21 days in preterm babies" [5]. Prompt investigations including liver function test,

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ultrasonography (USG), hepatobiliary scintigraphy (EHIDA scan), and/or liver biopsy should be considered to identify the causes of prolonged NNJ and type of hyperbilirubinemia [6].

To differentiate unconjugated or conjugated hyperbilirubinemias, the essential investigations are plasma total bilirubin (TB), indirect and direct bilirubin (DB) tests. However, DB includes both conjugated bilirubin (Bc) and albumin-bound bilirubin (delta bilirubin, ΔB). It is not uncommon for DB to overestimate the degree of conjugated hyperbilirubinemia, leading to mis-interpretation and unnecessary investigations.

The "classic" wet chemistry bilirubin measurement involves the reaction between bilirubin and diazotized salts of sulfanilic acid, with or without the addition of accelerator [7]. Both Bc and ΔB can "directly" react with diazo compound without accelerator, named as "direct" bilirubin. With the 21-day half-life of albumin, ΔB remains in plasma with a much slower clearance even after free bilirubin has been eliminated [8]. It is particularly evident in the recovery phase of jaundice, causing an apparently prolonged "direct hyperbilirubinemia".

In fractionated bilirubin measurements, a dry chemistry assay is used employing a multi-layered dry slide as the reacting platform (Vitros clinical chemistry analyser, Johnson and Johnson, USA) [9]. It has a spreading layer which filters ΔB, leaving only the Bc and unconjugated bilirubin (Bu) for subsequent measurement by binding to cationic mordant, which produces signals at two different wavelengths (400 nm and 460 nm) measurable by reflectometry. ΔB fraction can thus be calculated by subtracting Bc and Bu from TB. However, this instrument is not widely available in most clinical settings. As a result, TB and DB are commonly used as surrogates.

Many guidelines have interchangeable use of Bc and DB, which in fact may cause diagnostic pitfall [10-12]. Davis et al. [13] conducted a retrospective study on 271,186 term newborns correlating their DB and Bc with ICD-9 diagnosis. He found the 99th percentile of DB among the cohort subjects was 36 μmol/L and that of Bc was 8.6 μmol/L only. Given the discrepancy, the two measurements actually measure different bilirubin fractions and should not be interpreted interchangeably.

In this study, we performed a retrospective review on 89 patients with NNJ and examined the significance of using fractionated bilirubin assays in their management.

Methods

Patients younger than six-month-old whose plasma TB exceeded the age-specific reference interval (RI) from January to March 2020 in Queen Mary Hospital were included in this study (N=89). Their clinical and biochemical data were reviewed. Results after treatment were excluded from analysis. Neonatal conjugated hyperbilirubinemia is defined as Bc greater than 17 μmol/L when TB is less than 86 μmol/L, or Bc greater than 20% of TB [14]. DB is calculated by the formula: DB = Bc + ΔB, if only fractionated bilirubin assay was done for that patient. Percentages of DB and Bc over TB (%DB/TB and %Bc/TB respectively) of all patients were compared. Descriptive statistics by Microsoft Excel and receiver operating characteristic (ROC) curve analysis by IBM® SPSS® Statistics version 27 were performed to find out the sensitivity and specificity of DB and Bc at various cut-offs in the diagnosis of NNJ. Two cases of the cohort were presented with details. In addition, three other cases were discussed together to illustrate the clinical utility of Bc over DB.

This study was approved by the local research ethics committee (reference numbers: UW 22-159, the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and PAED-2022-023, the Hospital Authority Central Institutional Review Board).

Results

Among the 89 patients, there were 56 males and 33 females, aged from 1 to 5.4 months (mean age 1.6 months). All subjects were managed in a hospital with both diazo method and fractionated bilirubin assays available. All patients had at least one Bc measurement taken and 19 (21%) of them had it measured more than once. Concentrations of TB, Bc and DB ranged as 24–527 μmol/L (mean 128, SD 103), 0–389 μmol/L (mean 31, SD 66) and 0.9–481 μmol/L (mean 60, SD 83) respectively. Bc greater than 163 μmol/L was 2SD above the mean. There were 71 (80%) with undetectable Bc. In contrast, taking the RI for DB as <5 μmol/L, only 13 (15%) had normal DB readings.

Among the final diagnoses, 50 (56%) were due to breastmilk feeding, 11 (13%) were total parenteral nutrition (TPN)-related, 9 (10%) were due to unidentified causes, 8(9%) were congenital heart diseases, 7 (8%) were infection-related, 3 (3%) were blood transfusion-related or ABO incompatibility and 1 (1%) was biliary atresia. Bc and DB of seven diagnostic groups were analysed in terms of their RIs and respective percentage over TB (Table 1).

Case Presentation

Case 1

A 40-day-old girl presented with prolonged NNJ. Investigations showed conjugated hyperbilirubinaemia, with Bc 76 μmol/L, Bu 30 μmol/L and ΔB 46 μmol/L. EHIDA scan showed markedly impaired hepatic excretion: biliary atresia (BA) could not be excluded. Kasai operation was done consistent with BA.

After Kasai operation, Bc peaked on Day 6 post-operation

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to 154 µmol/L, then decreased gradually. Bc and %Bc/TB declined (from 154 µmol/L on Day 6 to 11 µmol/L on Day 28; from 61% to 16%), indicating resolving obstructive jaundice, while DB dropped from 217 to 55 µmol/L on Day 28. %DB/TB remained >75% four weeks post-operation. Due to the presence of ΔB, DB and %DB/TB remained elevated which gave a false impression of stagnant cholestasis. Several studies reported the same observation in patients with BA during the first month after Kasai operation, where ΔB apparently meddled with the DB measurement [15-17]. Bc is a more accurate marker for diagnosing cholestasis and treatment monitoring.

Case 2

A boy presented with NNJ at 21 hours of age. Investigations showed unconjugated hyperbilirubinaemia, with Bu 186 µmol/L and Bc 4 µmol/L with elevated GGT. Direct Coomb's test was positive. He was diagnosed with NNJ due to ABO incompatibility. After phototherapy, his Bu decreased while Bc increased gradually. On Day 6 post-admission, his Bu was 140 µmol/L and Bc 82 µmol/L. USG liver and EHIDA scan excluded BA. His liver function normalized subsequently.

In this patient we observe increasing Bc and decreasing Bu during the resolution of unconjugated bilirubinaemia. In fact, due to maturation of his liver function, more Bu underwent conjugation to Bc physiologically. The rise in Bc should not be interpreted as cholestasis. Any further investigations done would be unnecessary. The bilirubin profile taken on Day 48 days showed decreasing %Bc/TB, while %DB/TB remained high due to ΔB. Hence, Bc and B instead of DB can better represent the resolving hyperbilirubinemia and reduce parental anxiety caused by apparently abnormal results.

Cases 3 to 5 will be discussed together:

Case 3

A 1-month-old girl presented with abdominal distension and prolonged NNJ. She was referred for conjugated bilirubinaemia with TB 138 µmol/L and DB 89 µmol/L. On the same day, fractionated bilirubin assay showed Bu 61 µmol/L, Bc 29 µmol/L and B 36 µmol/L. The elevated DB due to high ΔB gave a false impression of cholestasis, while the fractionated bilirubin assay showed it was mixed hyperbilirubinemia. TB and Bc improved afterwards. She was later diagnosed with hepatitis due to post-natal CMV infection. USG was performed showing no evidence of BA.

Case 4

A 1-month-old boy presented with prolonged NNJ, deranged liver function and failure to thrive. Initial investigation showed TB 86 µmol/L and DB 68 µmol/L. His ALP level was persistently high. Fractionated bilirubin assay was done a day later with Bu 29 µmol/L, Bc 15 µmol/L and ΔB 38 µmol/L. USG showed no evidence of BA. Laparoscopic cholangiogram showed bilateral patent biliary drainage. Liver biopsy showed paucity of intrahepatic ducts and marked steatosis. Subsequent workups showed elevated serum citrulline and positive urine galactose. Genetic analysis confirmed the diagnosis of neonatal-onset citrullinemia type

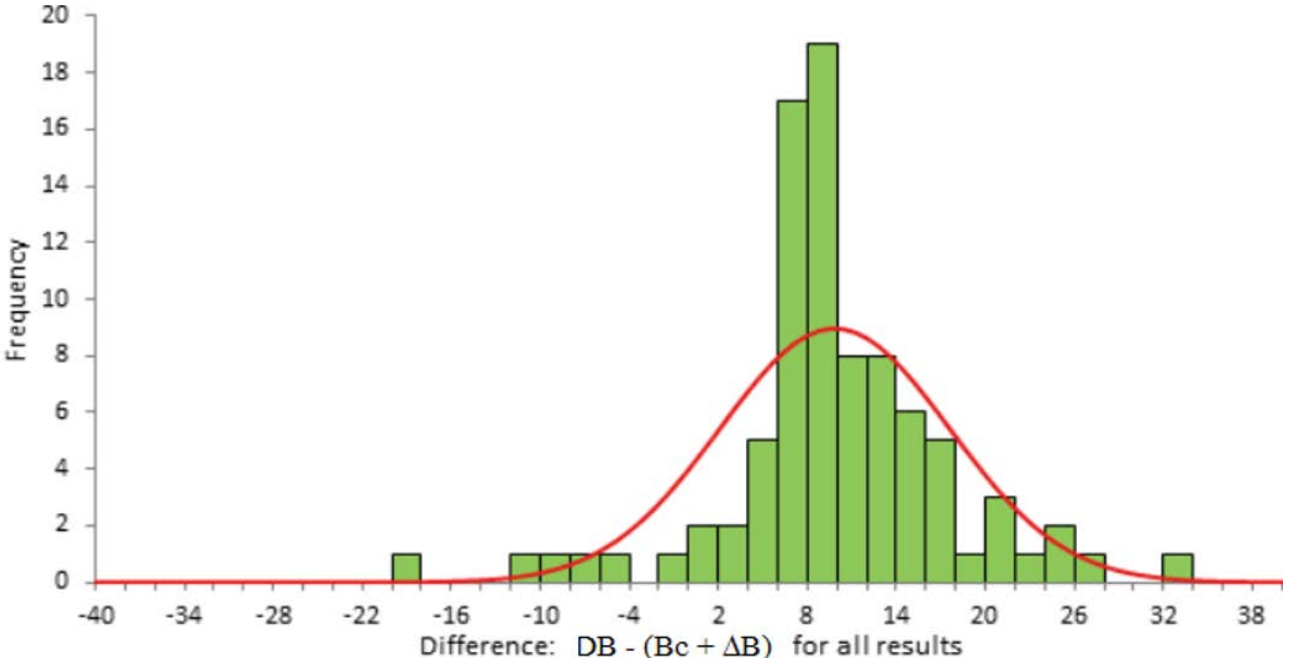

Figure 1: In-house data analysis showing 86 paired results (Bc and delta bilirubin measured by fractionated bilirubin assay and DB measured by diazo method) taken during the period from January 2021 to June 2021 were compared. The differences (DB- (Bc + delta bilirubin)) were plotted as a histogram.

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II. Ursodeoxycholic acid was given and TB normalized after 1.5 months.

Case 5

A 26-week preterm girl presented with ileus. She was put on TPN for two months and was later found to have elevated TB 257 µmol/L and DB 171 µmol/L. TPN-related cholestasis was diagnosed. She was started on ursodeoxycholic acid and omegavan. TB dropped to 120 µmol/L and DB to 89 µmol/L. USG and EHIDA scan were unremarkable. Fractionated bilirubin assay showed Bu 19 µmol/L, Bc 6 µmol/L and ΔB 44 µmol/L, which suggested resolved cholestasis.

Cases 3 to 5 showed conjugated hyperbilirubinemia with different diagnoses. There are three implications after reviewing these cases.

Firstly, increased DB may not directly imply diseases of the liver or biliary system. In case 3, the girl was found to have %DB/TB of 64%. However, fractionated bilirubin assay showed that %Bc/TB was only about 23%. In case 4, the boy's %DB/TB was about 65% while %Bc/TB was found to be about 18%. Similarly, in case 5 the %Bc/TB was only around 9% while %DB/TB were >70%. These discrepancies can be attributed to the elevated ΔB. Since Bc plays a major role in hepatobiliary diseases, interpreting DB alone is insufficient to make a judgement on whether patients have the disease. It might sometimes give false positive results due to elevated ΔB. A fractionated bilirubin assay for Bc is recommended if DB is high.

Secondly, fractionated bilirubin assay can prevent unnecessary investigations and reduce parental anxiety due to "false positive" DB measurement. In case 3, as Bc normalized over one month, EHIDA scan, liver biopsy and intraoperative cholangiogram were unnecessary for further investigation. However, in case 5, as fractionated bilirubin assay was unavailable at presentation, EHIDA scan was done to exclude BA while Bc level was found to be low later in hospital with the test. If fractionated bilirubin assay could be done initially, unnecessary investigations and parental anxiety could be spared.

Thirdly, the measurement of DB does not equate Bc plus ΔB analytically although theoretically they are expected to be equal. In case 3, DB was measured as 89 µmol/L, while the sum of Bc and ΔB measured was 29+36=65 µmol/L. The difference was 24 µmol/L. The positive bias can be attributed to the direct reaction between diazo reagent and Bu when TB is high (unpublished data). We analysed 86 blood samples from January 2021 to June 2021 testing both DB and sum of Bc+ΔB by fractionated assays. The result shows a mean bias of 9.8 µmol/L (ranged from -18.4 µmol/L to +32.7 µmol/L) for the value of DB compared to the sum of Bc and ΔB (Figure 1). The details of the biochemical results of these five cases were given in the Supplementary Table.

Discussion

We analysed 89 patients with NNJ and characterized the superior clinical utility of fractionated bilirubin assays (Bu, Bc and ΔB) over DB measurement.

For unconjugated hyperbilirubinemia, almost all patients (60/62 patients) had undetectable Bc (0 µmol/L), except one patient with breastmilk feeding (1 µmol/L) and one patient with ABO incompatibility (17 µmol/L). In contrast, 53 patients (85%) had DB greater than the RI (< 5 µmol/L). When using %DB/TB, five patients (8%) were >/= 20% and two patients received abdominal USG. Their Bc and %Bc/TB were normal. Therefore, %DB/TB is more specific than DB alone in unconjugated hyperbilirubinemia, whereas false positives can be avoided by measuring Bc and %Bc/TB. Newman et al. [18] reported that among 2877 jaundiced term new-borns, 149 had DB higher than RI. Among them, 52% remained unexplained with spontaneous recovery; 23% with associated conditions in which DB did not contribute to the diagnosis (isoimmunisation, sepsis, congestive heart failure, pyloric stenosis, extremely small for gestation age, hypothyroidism, and choledochal cyst). The author commented DB was seldom helpful in evaluating jaundice in term new-borns, where elevations only contributed to the diagnoses in a minority.

Regarding the patient with BA, DB and Bc ranged from 90 to 217 µmol/L and 29 to 154 µmol/L respectively, %DB/TB from 55.7% to 86.5%, % Bc/TB from 25.2% to 61.4%. Both Bc and DB could pick up BA at presentation. However, DB remained high after Kasai operation while Bc normalized during recovery. Fujio et al. [16] reported a BA patient underwent the operation at 60 days of age and jaundice resolved 41 days post-operation. His Bc decreased four weeks post-operation (%Bc/TB from around 50 to < 20) while ΔB increased and remained elevated after the first month (%delta bilirubin/TB around 60% to 80%). This study and our case show that Bc is a superior marker to DB in post-operative monitoring as it is more sensitive to the resolution of cholestasis.

For the remaining groups with TPN, infection and congenital heart diseases (26 patients), which presented as mixed unconjugated and conjugated hyperbilirubinemia, 13 (50%) had Bc greater than RI while 23 (88%) had DB greater than RI. Eleven patients (42%) had %Bc/TB >/= 20 whereas 22 patients (85%) had %DB/TB >/= 20. Arvan et al. [19] reported 13 patients recovering from different hepatobiliary diseases including pancreatic masses, cholelithiasis and alcoholic hepatitis. During the first day of decreasing hyperbilirubinemia, Bc decreased to an average of 51% while DB decreased to only 68%. By the end of the first week, average Bc was less than 20% of its pre-relief value, while DB and TB were still greater than 20% of their pre-

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relief values at the end of the second week. Hence, Bc is more sensitive to the improvement of biliary excretion than DB.

Regarding the sensitivity and specificity of screening tests for BA, Harpavat et al. [23] had conducted three two-stage screening studies with DB or Bc measurement, showing sensitivity of 100% (in all three studies), specificity of 98.2% to 99.9%, positive predictive value of 5.9% to 18.2% and negative predictive value of 100% [20-22]. He also demonstrated the use of %DB/TB < 15 as the cut-off shows an improvement of the specificity (99.3%) besides using DB alone [21]. This is compatible with our results. Although both DB and Bc give a high sensitivity, the higher specificity of using Bc or %DB/TB compared with DB alone is evident. Thus, the use of fractionated bilirubin assay for patients with abnormal DB values can potentially reduce the false positive rate.

The terminologies used in describing bilirubin measurements were found to be confusing in literature, which had been mentioned in a case report from Harpavat et al. [23] that the result was reported as "DB" while fractionated bilirubin assay was done. The lack of uniformity in the terminology of different bilirubin entities can be misleading since it is unclear if the value was measured by the diazo method, fractionated bilirubin assay, or by calculation. The terminologies should be accurate enough to distinguish different methods. This is important for making clinical decisions.

There are three of the major clinical guidelines for the evaluation of NNJ, including American Academy of Paediatrics (AAP) in 2022 [10], NICE in 2016 [11], Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in 2015/2016 [12]. AAP guideline applied both cut-off values of DB (> 17 µmol/L) and Bc (>/= 5 µmol/L), indicating that there is analytical bias due to the measuring method and presence of ΔB, but they may be interchangeable if the two confounding factors are constant. If ΔB is high (e.g., resolving jaundice), DB would no longer be equivalent to Bc. It is worth noting that, the specificity of DB is still inferior to Bc, even in the case of low ΔB, due to overestimation of DB in a background of elevated TB. NICE guideline provided different bilirubin threshold levels according to baby's postnatal age in hours. Although it said to "follow expert advice about care for babies with a Bc level greater than 25 µmol/L because this may indicate serious liver disease". Still, the use of DB and Bc are apparently mixed in the guideline. ESPGHAN guideline only indicated the cut-off value of DB (> 17 µmol/L) without stating that of Bc. It mentioned serum bilirubin measurement should always be fractionated. Although Bc is put together with DB in the context, it is explained that DB includes Bc and ΔB, while the specific measurement of Bc might be unavailable.

The interchangeable usage of DB and Bc has been long-standing, although many studies show that the two are not equivalent. Given the superior specificity of Bc in terms of diagnosing cholestasis, and the higher sensitivity to detect resolving neonatal jaundice, we recommend a clear differentiation between these two terms, to clarify the method of measurement for better clinical decision-making.

Conclusion

As DB measures both Bc and ΔB, it can lead to over-diagnosis of neonatal cholestasis with unnecessary investigations and parental anxiety. For resolving neonatal jaundice, Bc is also shown to be more sensitive than DB. Healthcare professionals should be aware of the limitations of DB in clinical decision-making of NNJ management. We recommend the use of Bc over DB, and all elevated DB should be confirmed with Bc.

References

1. Suchy FJ. Neonatal cholestasis. Pediatr Rev 25 (2004): 388-96.
2. Singh A, Koritala T, Jialal I. Unconjugated Hyperbilirubinemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing (2023).
3. McKiernan PJ. Neonatal cholestasis. Semin Neonatol 7 (2002): 153-165.
4. Tripathi N, Jialal I. Conjugated Hyperbilirubinemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing (2023).
5. Rennie J, Burman-Roy S, Murphy MS. Guideline Development Group. Neonatal jaundice: summary of NICE guidance. BMJ 340 (2010): c2409.
6. De Bruyne R, Van Biervliet S, Vande Velde S, et al. Clinical practice: neonatal cholestasis. Eur J Pediatr 70 (2011): 279-284.
7. Kirk JM. Neonatal jaundice: a critical review of the role and practice of bilirubin analysis. Ann Clin Biochem 45 (2008): 452-462.
8. Pitt HA, Nakeeb A, Espat NJ. Bile secretion and pathophysiology of biliary tract obstruction. In: Blumgart's Surgery of the Liver, Pancreas and Biliary Tract (Fifth Edition). Elsevier (2012): 113-122.
9. Thomas M, Greaves RF, Tingay DG, et al. Current and emerging technologies for the timely screening and diagnosis of neonatal jaundice. Crit Rev Clin Lab Sci 59 (2022): 332-352.

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DOI:10.26502/jppch.74050204

10. Kemper AR, Newman TB, Slaughter JL, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics. 150 (2022): e2022058859.

11. Amos RC, Jacob H, Leith W. Jaundice in newborn babies under 28 days: NICE guideline 2016 (CG98). Arch Dis Child Educ Pract Ed. 102 (2017): 207-209.

12. Fawaz R, Baumann U, Ekong U, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 64 (2017): 154-168.

13. Davis AR, Rosenthal P, Escobar GJ, et al. Interpreting conjugated bilirubin levels in newborns. J Pediatr 158 (2011): 562-565.e1.

14. Hyperbilirubinemia, Direct (Conjugated Hyperbilirubinemia). In: Gomella T, Cunningham M, Eyal FG, Tuttle DJ. eds. Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs, 7e. McGraw-Hill Education (2013).

15. Ye W, Rosenthal P, Magee JC, et al. Childhood Liver Disease Research and Education Network. Factors Determining δ-Bilirubin Levels in Infants with Biliary Atresia. J Pediatr Gastroenterol Nutr 60 (2015): 659-663.

16. Ito F, Ando H, Watanabe Y, et al. Serum bilirubin fractions in cholestatic pediatric patients: determination with Micronex high-performance liquid chromatography. J Pediatr Surg 30 (1995): 596-599.

17. Kozaki N, Shimizu S, Higashijima H, et al. Significance of serum delta-bilirubin in patients with obstructive jaundice. J Surg Res 79 (1998): 61-65.

18. Newman TB, Hope S, Stevenson DK. Direct bilirubin measurements in jaundiced term newborns. A reevaluation. Am J Dis Child 145 (1991): 1305-1309.

19. Arvan D, Shirey TL. Conjugated bilirubin: a better indicator of impaired hepatobiliary excretion than direct bilirubin. Ann Clin Lab Sci 15 (1985): 252-259.

20. Harpavat S, Garcia-Prats JA, Shneider BL. Newborn Bilirubin Screening for Biliary Atresia. N Engl J Med 375 (2016): 605-606.

21. Harpavat S, Ramraj R, Finegold MJ, et al. Newborn Direct or Conjugated Bilirubin Measurements As a Potential Screen for Biliary Atresia. J Pediatr Gastroenterol Nutr 62 (2016): 799-803.

22. Harpavat S, Garcia-Prats JA, Anaya C, et al. Diagnostic Yield of Newborn Screening for Biliary Atresia Using Direct or Conjugated Bilirubin Measurements. JAMA 323 (2020): 1141-1150.

23. Harpavat S, Devaraj S, Finegold MJ. An infant with persistent jaundice and a normal newborn direct bilirubin measurement. Clin Chem 61 (2015): 330-333.

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Bilirubin Results of Five Cases

Case 1	Day 0	Day 7	Day 15	Day 22	Day 24*	Day 25	Day 25	Day 26	Day 27	Day 29	Day 34	Day 37	Day 44	Day 47	Day 51	Day 58	Day 65
TB (μmol/L)	167	151	181	152	147	113	113	143	156	251	190	156	146	115	70	42	32
Bu (μmol/L)	74	59	45	30	22	23	21	28	29	34	30	25	22	20	15	9.3	7
DB (μmol/L)	93	92	136	122	125	90	91	115	127	217	160	131	115	95	55	33	25
Bc (μmol/L)	50	52	91	76	79	54	59	71	88	154	77	63	40	29	11	1.2	0
ΔB (μmol/L)	43	40	45	46	45	32	36	44	39	63	83	68	75	66	44	32	25
% Bc/TB	29.9	34.4	50.3	50.1	54.1	47.8	52.4	50	56.4	61.4	40.7	40.4	29.4	25.2	15.7	2.9	0
% DB/TB	55.7	60.9	75.1	80.4	84.8	79.6	81.0	80.3	81.4	86.5	84.2	84.0	84.1	82.6	78.6	77.9	78.1

* Kasai operation was done on Day 24
Days: counted from the first result of bilirubin available.

Case 2	Day 0	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 13	Day 27	Day 48	Day 58	Day 73	Day 102
TB (μmol/L)	-	-	-	-	-	-	-	-	-	-	106	121	76	17
Bu (μmol/L)	186	208	232	253	216	195	188	140	76	41	30	29	18	8
DB (μmol/L)											76	92	58	9
Bc (μmol/L)	4	22	56	78	100	95	84	82	54	35	40	45	17	0
ΔB (μmol/L)	-	-	-	-	-	-	-	-	-	-	36	47	41	9
% Bc/TB	-	-	-	-	-	-	-	-	-	-	38	37	22	0
% DB/TB	-	-	-	-	-	-	-	-	-	-	72	76	76	53

Case 3	Day 0	Day 0	Day 6	Day 10	Day 38
TB (μmol/L)	138	126	97	69	20
Bu (μmol/L)	49#	61	40	23	8
DB (μmol/L)	89	65	57	46	12
Bc (μmol/L)	-	29	19	13	<2
ΔB (μmol/L)	-	36	38	34	12
% Bc/TB	-	23	20	19	<10
% DB/TB	64	52	59	67	60

#: level of indirect bilirubin

Case 4	Day 0	Day 1	Day 4	Day 6	Day 12	Day 20	Day 41	Day 49
TB (μmol/L)	86	82	107	54	52	38	27	17
Bu (μmol/L)	18#	29	39	7#	8#	10	-	-
DB (μmol/L)	68	-	-	47	44	-	-	-
Bc (μmol/L)	-	15	27	-	-	<2	-	-
ΔB (μmol/L)	-	38	42	-	-	27	-	-
% Bc/TB	-	18	25	-	-	-	-	-
% DB/TB	79	-	-	87	85	<5	-	-

#: level of indirect bilirubin

Case 5	Day 0	Day 6	Day 13	Day 19	Day 25	Day 31	Day 38	Day 45	Day 59	Day 68
TB (μmol/L)	257	216	152	170	147	120	69	72	46	53
Bu (μmol/L)	86#	63#	39#	47#	40#	31#	19	24#	19#	29#
DB (μmol/L)	171	153	113	123	107	89	-	48	27	24
Bc (μmol/L)	-	-	-	-	-	-	6	-	-	-
ΔB (μmol/L)	-	-	-	-	-	-	44	-	-	-
% Bc/TB	-	-	-	-	-	-	9	-	-	-
% DB/TB	67	71	74	72	73	74	-	67	59	45

#: level of indirect bilirubin

Citation: Chloe Miu MAK, Jimmy Chi Lap WONG, Gary Ka Chung WONG, Ka Chai CHEUNG, Jacky Kwan Ho LEE, Toby Chun Hei CHAN, Koon Yuen YUET, Eric LAW, Ching Wan LAM. Moving Beyond Direct Bilirubin in Neonatal Jaundice: Insights from a Systematic Review on Conjugated and Delta Bilirubin. Journal of Pediatrics, Perinatology and Child Health. 8 (2024): 217-223.