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ORIGINAL ARTICLE

Relationship between infectious screening and early unconjugated hyperbilirubinemia in well-appearing neonates

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Abstract

Background: Neonatal hyperbilirubinemia (NH) may be the initial and solitary sign of infectious condition in neonates. This retrospective cohort study aims to evaluate the risk of sepsis or urinary tract infection in well-appearing infants with NH below 7 days old.

Methods: All neonates (n = 8779) born in Taipei Veterans General Hospital from 2013 to 2017 were evaluated retrospectively. A total of 2523 initially well-appearing babies were admitted because of NH. After being hospitalized, patients were categorized into two groups according to the initial transcutaneous bilirubin (TCB) level. Infectious screening results, which include C-reactive protein (CRP), differential count, blood culture, urinalysis, and urine culture, were analyzed.

Results: Regarding CRP, 2.7% (18/667) of neonates with NH had elevated CRP (≥1 mg/dL). Among 547 blood cultures, eight were positive, with 0.4% (2/547) non–coagulase-negative staphylococcus (CoNS) bacteremia and 1.1% (6/547) CoNS bacteremia. In urinalysis, 16.6% (182/1094) of NH neonates had pyuria, and 6.7% (25/372) had positive urine cultures. NH with a higher initial TCB level was related to an increased chance of elevated CRP (4.7% vs. 1.5%, odds ratio: 3.29, $p = 0.024$) and pyuria (20.6% vs. 12.6%, odds ratio: 1.79, $p < 0.001$). The rate of positive urine culture between the higher and lower TCB groups had no significant difference (6.6% vs. 6.9%, $p > 0.99$). Significant bacteriuria was more common in NH neonates admitted at later age (>2 days) (4.9% vs. 11.5%, $p = 0.035$).

Conclusion: In well-appearing neonates below 7 days old, NH with a higher initial TCB is associated with an increased rate in pyuria and abnormal CRP. No difference was found in the rate of positive urine culture between higher and lower TCB levels. Significant bacteriuria was more common in older NH neonates. Septicemia is rare among well-appearing neonates with NH.

Keywords: Hyperbilirubinemia; Neonatal; Infectious diseases; Screening; Sepsis; Urinary tract infections

1. INTRODUCTION

Neonatal hyperbilirubinemia (NH) is a common condition that accounts for most of admissions in neonates. Most of NH neonates can be managed conservatively by undergoing phototherapy and ensuring adequate intake.[1–4] However, NH may be the initial and solitary sign of infectious condition in neonates, such as urinary tract infections (UTIs)[5–16] and sepsis.[17,18]

As recommended, NH neonates should undergo laboratory evaluation for sepsis if indicated by history and physical examination.[4] Septicemia was found in patients with early neonatal jaundice before any clinical suspicion had emerged.[17] Another condition that may be related to sepsis is rebound hyperbilirubinemia after phototherapy.[18] Recent data assessing on the association between sepsis and asymptomatic jaundice are unavailable.

The association between UTI and prolonged jaundice was previously studied.[5–10] Testing for UTI is recommended for infants with the onset of jaundice after 8 days of age. In addition to prolonged jaundice, UTI could occur and should be investigated in neonates with hyperbilirubinemia of unknown cause in the first 1 to 2 weeks of life.[11,12] High UTI prevalence (16.7%) among newborns with idiopathic neonatal jaundice onset younger than 10 days old was reported.[13] Urine culture was suggested to be included in the diagnostic evaluation of neonates older than 3 days with idiopathic jaundice.[14] Meanwhile, some studies have conflicting results wherein children with prolonged jaundice do not have an increased risk of UTI.[15] Although many studies agreed on the increased risk of UTI in neonates with prolonged jaundice, few has discussed about the risk of UTI in early (onset within 7 days after birth) asymptomatic jaundice.

In our hospital, infectious disease screening, which includes blood culture, serum C-reactive protein (CRP), urinalysis, and urinary culture, is frequently performed in NH neonates to rule out associated infectious disease. However, this practice lacks recent data supporting its necessity and efficacy in well-appearing babies at <7 days old. Hence, this study aims

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to evaluate the risk of sepsis or UTI in well-appearing babies with NH <7 days old.

2. METHODS

We retrospectively evaluated all neonates (n = 8779) born in Taipei Veterans General Hospital from 2013 to 2017, and 6613 (75.3%) initially well-appearing infants were brought to nursery after delivery. Among these infants in nursery, 3018 were admitted before 7 days old, and 2523 of them were admitted due to NH. The NH neonates were categorized into two groups according to the transcutaneous bilirubin (TCB) level upon admission (Table 1). Consequently, 963 neonates comprised the NH group with higher TCB levels, whereas 1560 neonates constituted the NH group with lower TCB levels (Figure). The rationale for categorizing the NH neonates into higher or lower TCB groups is based on the assumption that neonates with higher TCB levels have more significant hyperbilirubinemia than those with lower TCB levels; thus, the difference in infectious screening results between the two groups may indicate the impact of hyperbilirubinemia severity on sepsis risk evaluation. The cutoff values for TCB levels with respect to age were modified according to the thresholds for phototherapy for infants at medium risk as provided by American Academy Pediatrics.[4] Because only the dates but not the exact times of TCB measurements were available in our database, we used simplified cutoff values that included one cutoff value for each specific age by day. In addition, comparison was made between NH neonates admitted at earlier (≤2 days) and later (>2 days) ages to have more understanding on the characteristics of enrolled patients.

Results of infectious screening, which includes CRP, band-form, blood culture, urinalysis, and urine culture, were analyzed. As used in most studies, we used 1 mg/dL (or 10 mg/L) as the cutoff value for abnormal CRP.[19] For urinalysis, white blood cell (WBC) count of ≥5 per high-power field indicated pyuria. Furthermore, urine culture specimens were acquired by bladder catheterization. Urine culture data with bacteriuria <10 000 colony-forming units (CFU) or contaminated specimens were regarded as clinically irrelevant and excluded, modified as per the guideline published by American Academy of Pediatrics.[20]

Data analysis and statistical calculation were performed using the R language 3.5.0 (The R Foundation for Statistical Computing). Continuous variables are presented as mean with SD and nominal variables as frequencies with associated percentages. Welch's two sample *t* test was used for two-group comparisons, and Fisher's exact test was used to determine significant difference in proportion. In addition, $p < 0.05$ was considered significant, and all the tests were two-tailed.

The study is approved by the institutional review board (IRB) of Taipei Veterans General Hospital (IRB 2019-02-002CC).

3. RESULTS

Among 6613 initially well-appearing neonates in the nursery, 2523(38.2%) were admitted due to NH. No significant difference was found in birth body weight or male-to-female ratio between those who were admitted for NH and non-NH causes (Table 2).

Table 1

Categorizing of NH into higher or lower TCB subgroup by TCB levels upon admission

	TCB level measured by day(s) after birth, mg/dL			
Category	**1 d**	**2 d**	**3 d**	**4 d or later**
Higher TCB group	≥9	≥13	≥16	≥19
Lower TCB group	<9	<13	<16	<19

NH = Neonatal hyperbilirubinemia; TCB = transcutaneous bilirubin.

Table 3 lists the results of infectious screening tests in well-appearing neonates with NH. Among 2523 NH neonates, 667 (26.4%) underwent CRP test, and 18 (2.7%) of them yielded abnormal CRP results. Nevertheless, no significant difference was found in the proportion of CRP test recipients between the higher and lower TCB groups (26.7% vs. 26.3%, $p = 0.853$). Conversely, the rate of abnormal CRP levels between these TCB groups was significantly different. Abnormal CRP levels were more common in the higher TCB group than in the lower TCB group (4.7% vs. 1.5%, odds ratio: 3.29, $p = 0.024$).

Differential count of WBC was measured in 2342 (92.8%) neonates. Elevated band-form proportion (≥5%) was found in 9 (0.3%) NH neonates, but no significant difference was observed between the higher and lower TCB groups.

Moreover, blood cultures were performed in 547 (21.6%) NH neonates, more commonly in the higher TCB group than in the lower TCB group (30.6% vs. 16.2%, $p < 0.001$). *Bacillus* species (n = 1), *Micrococcus* species (n = 1), and coagulase-negative staphylococci (CoNS; *Staphylococcus capitis*, n = 1; *Staphylococcus epidermidis*, n = 5) were cultured. The results may not have clinical significance because no specific septic signs, such as fever, decrease in feeding amount, cardiopulmonary distress, and/or ill appearance, were recorded.

Urinalysis was performed in 1094 (43.3%) NH neonates, and 182 (16.6%) of them had pyuria. The higher TCB group was more likely to receive urinalysis (56.9% vs. 35.0%, $p < 0.001$). In addition, the higher TCB group obtained a significantly increased proportion of pyuria (20.6% vs. 12.6%, odds ratio: 1.79, $p < 0.001$).

Meanwhile, urine culture was performed in 372 (14.7%) NH neonates, more frequently in the higher TCB group than in the lower TCB group (23.69% vs. 9.3%, $p < 0.001$). Among these NH neonates, 25 (6.7%) had significant bacteriuria, but the rate of significant bacteriuria between the higher and lower TCB groups had no difference (6.6% vs. 6.9%, $p > 0.99$).

Table 4 shows the comparison between NH neonates admitted at earlier (≤2 days) and later (>2 days) ages. Abnormal CRP levels (4.8% vs. 0.6%, $p < 0.001$) and pyuria (23.0% vs. 10.5%, $p < 0.001$) were more common in NH neonates admitted at earlier age. Nevertheless, significant bacteriuria was more common in NH neonates admitted at later age (4.9% vs. 11.5%, $p = 0.035$).

4. DISCUSSION

This study demonstrated that higher TCB levels were associated with higher rates of pyuria and abnormal CRP in well-appearing neonates with early NH. Despite the increased rates of pyuria and abnormal CRP, the increased rate of positive urinary culture was not evident in the higher TCB group. Furthermore, the risk of significant (non-CoNS) bacteremia in well-appearing neonates with NH was low (2/547, 0.4%).

According to the American Academy Pediatrics guideline published in 2004, urinalysis, urine culture, and sepsis are evaluated if the patient had elevated direct bilirubin level and if indicated by history and physical examination.[4] In a prospective study, three out of 93 infants with NH developed septicemia before any clinical suspicion had emerged.[17] In a retrospective study of 306 infants with NH, none of them had bacteremia or incipient sepsis.[21] Moreover, the risk of sepsis in well-appearing babies with NH has not been recently studied.

The correlation between initial TCB level and abnormal CRP rate is first examined by this study. Our study showed that NH in the higher TCB group was more likely to have abnormal CRP,

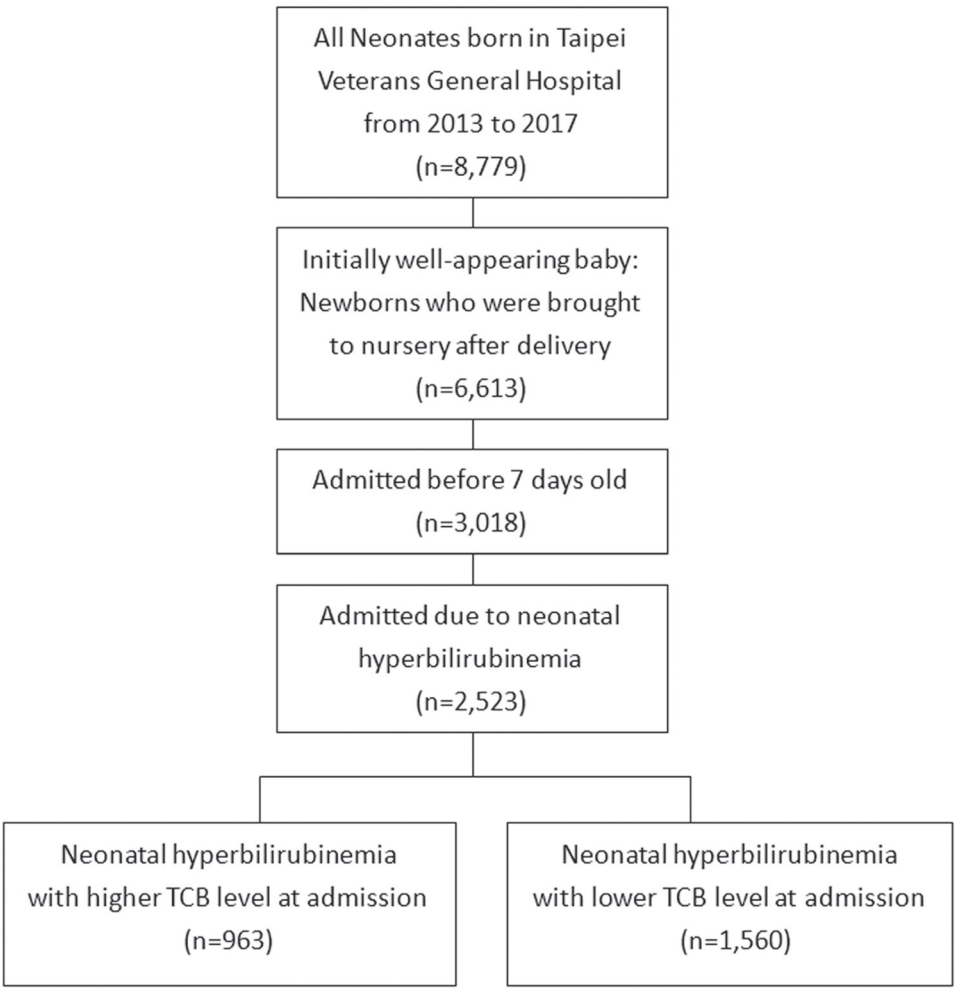

Figure Case enrollment and categorizing: all neonates (n = 8779) born in Taipei Veterans General Hospital from 2013 to 2017 was evaluated. Here, 2523 out of 6613 well-appearing neonates admitted due to neonatal hyperbilirubinemia were enrolled and categorized into subgroups according to their individual initial transcutaneous bilirubin levels.

Table 2

Characteristics of newborns in the nursery

Characteristic	All neonates in the nursery (n = 6613)	Admitted for NH (n = 2523)	Admitted for non-NH (n = 431)
Percentage	...	38.2	6.5
Birth bodyweight (SD)	3127 (349)	3120 (358)[a]	3069 (379)[a]
Male-to-female ratio	1.10	1.08[b]	1.29[b]

NH = neonatal hyperbilirubinemia.

[a]No significant difference by Welch's two sample *t* test, $p = 0.742$.

[b]No significant difference by Fisher's exact test, $p = 0.106$.

but the risk of significant (non-CoNS) bacteremia remained low (0.4%, two out of 547 neonates with NH). Considering that the specificity of single CRP test for sepsis is undetermined in otherwise asymptomatic newborns,[19] the insight into whether the risk of sepsis increased in the group with higher initial TCB levels cannot be concluded.

The correlation between UTI and NH has been discussed in previous studies.[5–16] Most authors suggested that NH, especially prolonged jaundice, is a sign of UTI in infants;[5–12,14] however, some opposed to this assumption.[15,16] Only one study focused on the relationship between early NH and UTI,[13] and it showed increased total serum bilirubin levels in early NH neonates with positive urine culture.

Our study is the first to assess the risk of UTI in well-appearing neonates at <7 days old with NH. In our data, pyuria was found in 16.6% of early NH neonates who received urinalysis, and those with higher TCB levels had increased rates of pyuria (20.6% vs. 12.6% in the lower TCB group). Moreover, bacteriuria was found in 6.7% of patients who underwent urine culture examination. The rate of positive urine culture between the higher and lower TCB groups had no difference. Thus, a higher TCB may be associated with noninfectious pyuria in neonates with NH. In our opinion, increased rate of noninfectious pyuria and increased CRP levels without other initial presentation of sepsis may suggest there is a link between early NH and noninfectious inflammatory response; however, this assumption needs further evidence.

We tried to explore whether performing infectious disease screening test in well-appearing NH infant younger than 7 days is safe. The information obtained could also be utilized to evaluate the efficacy of conducting infectious disease screening test in well-appearing neonates with early NH. According to the results, in well-appearing neonates with early NH, screening for UTI including urine analysis and urine culture is reasonable because the rate for abnormal findings was relatively high, especially in neonates with higher TCB levels or older than 2 days.

Table 3

Infectious screening test in well-appearing babies with NH grouped by initial TCB levels

Screening item (n; %)	NH (2523)	TCB		p^a
		Higher (963; 38.2)	Lower (1560; 61.8)	
CRP tested, %	667 (26.4)	257 (26.7)	410 (26.3)	0.853
CRP ≥1(% of tested)	18 (2.7)	12 (4.7)	6 (1.5)	0.024
Differential count tested, %	2342 (92.8)	908 (94.3)	1434 (91.9)	0.026
Band-form ≥5% (% of tested)	9 (0.4)	3 (0.3)	6 (0.4)	>0.99
Blood culture performed, %	547 (21.7)	295 (30.6)	252 (16.2)	<0.001
Blood culture (+) (% of performed)[b]	2 (0.4)	1 (0.3)	1 (0.4)	N/A
Urinalysis performed, %	1094 (43.4)	548 (56.9)	546 (35.0)	<0.001
Pyuria (% of performed)	182 (16.6)	113 (20.6)	69 (12.6)	<0.001
Urine culture performed, %	372 (14.7)	227 (23.6)	145 (9.3)	<0.001
Urine culture (+) (% of performed)[c]	25 (6.7)	15 (6.6)	10 (6.9)	>0.99

N/A = not available; NH = neonatal hyperbilirubinemia; TCB = transcutaneous bilirubin.

[a] *p* values were calculated using Fisher's exact test to show statistic difference between the higher and lower TCB groups.

[b] *Bacillus* species (n = 1) and *Micrococcus* species (n = 1) were included, coagulase-negative staphylococci (n = 6) was excluded.

[c] Urine culture <10 000 colony-forming units (CFU) or contaminated specimen was excluded.

Table 4

Infectious screening test in well-appearing babies with NH grouped by age of admission

Screening item (n; %)	NH (2523)	Age of admission, d		p^a
		≤2 (924; 36.6)	>2 (1599; 63.4)	
CRP tested, %	667 (26.4)	332 (35.9)	335 (21.0)	<0.001
CRP ≥ 1 (% of tested)	18 (2.7)	16 (4.8)	2 (0.6)	<0.001
Differential count tested, %	2342 (92.8)	923 (99.9)	1591 (99.5)	0.168
Band-form ≥5% (% of tested)	9 (0.4)	2 (0.2)	7 (0.4)	0.500
Blood culture performed, %	547 (21.7)	349 (37.8)	198 (12.4)	<0.001
Blood culture (+) (% of performed)[b]	2 (0.4)	1 (0.3)	1 (0.5)	N/A
Urinalysis performed, %	1094 (43.4)	534 (57.8)	560 (35.0)	<0.001
Pyuria (% of performed)	182 (16.6)	123 (23.0)	59 (10.5)	<0.001
Urine culture performed, %	372 (14.7)	268 (29.0)	104 (6.5)	<0.001
Urine culture (+) (% of performed)[c]	25 (6.7)	13(4.9)	12 (11.5)	0.035

N/A = not available; NH = neonatal hyperbilirubinemia; TCB = transcutaneous bilirubin.

[a] *p* values were calculated using Fisher's exact test to show statistic difference between groups with age of admission ≤2 and >2 d.

[b] *Bacillus* species (n = 1) and *Micrococcus* species (n = 1) were included, coagulase-negative staphylococci (n = 6) was excluded.

[c] Urine culture <10 000 colony-forming units (CFU) or contaminated specimen was excluded.

Meanwhile, CRP test or blood culture may have low efficacy in well-appearing neonates with early NH, given that none of the 2523 well-appearing neonates with NH had developed clinically relevant sepsis.

The strengths of this study are having relatively large data, which were collected from a tertiary medical center, and a long duration of patient enrollment, providing a good representation of the cohort.

In contrast, its limitation is that the comparison between neonates with and without NH is unavailable because infectious disease screening was limited only to hospitalized patients. However, we made an effort to provide useful information by comparing the results of infectious disease screening between the higher and lower TCB groups.

In conclusion, in well-appearing babies younger than 7 days old, NH with higher initial TCB levels was associated with increased rates of pyuria and abnormal CRP. No difference was observed in the rate of positive urine culture between the higher and lower TCB groups. Significant bacteriuria was more common in older NH neonates. Septicemia is rare among well-appearing neonates with NH. This study may help in establishing rationale for the evaluation strategy in NH.

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