Association between Hyperbilirubinemia and Hearing Screen Failure in the Neonatal Intensive Care Unit in Infants Born Preterm

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Objective To characterize the association between hyperbilirubinemia and a failed newborn hearing screen in infants born at 22-32 weeks of gestation.

Study design We included infants with gestational ages of 22-32 weeks who were discharged from neonatal intensive care units in the US from 2002 to 2017 with available newborn hearing screen results obtained after 34 weeks postmenstrual age. We excluded infants with severe birth asphyxia or craniofacial abnormalities. We identified 95 672 infants from 313 neonatal intensive care units. We used multivariable logistic regression to examine the association between maximum total bilirubin at <21 days postnatal age with failed hearing screen, adjusting for important demographic and clinical risk factors.

Results The median gestational age and birth weight were 30 weeks (IQR, 28-32 weeks) and 1330 g (IQR, 1010-1630 g), respectively. The median maximum total bilirubin was 8.3 mg/dL (IQR, 6.7-10.0 mg/dL), and 5275 infants (6%) failed their newborn hearing screen. On adjusted analysis, each 1 mg/dL increase in maximum total bilirubin was associated with a small, but significant, increase in odds of a failed hearing screen (OR, 1.03; 95% CI, 1.02-1.04).

Conclusions An increased maximum total bilirubin level was independently associated with hearing screen failure. Further prospective studies are needed to understand whether this increased risk of hearing screen failure translates to increased risk of hearing loss. *(J Pediatr 2021;231:68-73)*.

Neonatal jaundice is a common condition, developing in approximately 60% of full-term and 80% of premature newborns.[1,2] Most episodes of neonatal jaundice are benign; however, significantly elevated bilirubin levels can lead to central nervous system toxicity and kernicterus.[3,4] Auditory pathways are particularly susceptible to the toxic effects of neonatal hyperbilirubinemia. Neonatal hyperbilirubinemia is a common cause of early acquired sensorineural hearing loss, especially in infants with prematurity, because unconjugated unbound bilirubin can cross the blood-brain barrier and affect brainstem auditory nuclei and the cochlear nerve, as well as central auditory pathways.[5,6]

There is growing evidence for increased vulnerability of infants born premature and low birth weight to even moderate levels of serum bilirubin. Infants hospitalized in the neonatal intensive care unit (NICU) are known to be at higher risk of sensorineural hearing loss and auditory neuropathy.[4,7] Several studies have found evidence of kernicterus or other neurodevelopmental problems in infants with low birth weights with peak serum bilirubin levels well below the treatment threshold in infants born at full term.[8-10] Although the American Academy of Pediatrics has published guidelines for hyperbilirubinemia treatment in infants born at full term or near full term, no such evidence-based guidance has been endorsed for infants with prematurity.[4,11,12]

Prior studies have identified risk factors for hearing loss in infants hospitalized in the NICU, including hyperbilirubinemia.[13-15] However, to our knowledge, no studies have assessed the risk of a failed newborn hearing screen with moderate levels of hyperbilirubinemia. This knowledge could be valuable in determining treatment thresholds of hyperbilirubinemia in infants born prematurely. The aim of this study was to quantify the association between moderate hyperbilirubinemia and a failed newborn hearing screen in the NICU.

Methods

We identified infants born at 22-32 weeks of gestation who were discharged from NICUs managed by the Pediatrix Medical Group in the US from 2002 to 2017 who had available newborn hearing screen results obtained after 34 weeks postmenstrual age.[16] Deidentified data are collected by the Pediatrix Medical Group

CMV	Cytomegalovirus
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit

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using software that captures medical documentation, including admission, progress, and discharge notes. Data on various facets of patient care are available, including demographics, medications, laboratory results, culture results, diagnoses, and maternal history. This dataset is generated from a diverse group of NICUs ranging in size from small community NICUs to large academic ones, representing approximately 20% of NICU admissions in the US.[16] We excluded infants with severe birth asphyxia or craniofacial abnormalities that predispose children to failed hearing screening (**Appendix**; available at www.jpeds.com). The primary end point was failure of final newborn hearing screen before discharge. The hearing screen was performed as dictated by individual NICU protocols. As a result, both automated auditory brainstem response and otoacoustic emissions were used as screening methods.

We collected demographic information including birth weight, gestational age, sex, and infant race. Infant race was assigned by clinical providers according to local practices. We also collected information on the type of hearing screen performed. In addition, we collected clinical risk factors for failed hearing screen including the Apgar score at 5 minutes, birth weight small or large for gestational age, congenital and postnatal infections, duration of exposure to aminoglycosides, duration of mechanical ventilation, duration of vasopressor support, sepsis, and presence of a known risk factor for hyperbilirubinemia or grade 3 or 4 intraventricular hemorrhage (IVH). We considered known risk factors for hyperbilirubinemia including ABO isoimmunization, Rh isoimmunization, and glucose-6-phosphate dehydrogenase deficiency. We defined birth weight small or large for gestational age using the Olsen growth curves.[17] We considered congenital infections to include diagnoses of toxoplasmosis, rubella, syphilis, and herpes simplex virus. Cytomegalovirus (CMV) infections were included if either a congenital CMV infection or a postnatal infection.[18] Prior works have shown aminoglycosides such as gentamicin or amikacin are likely ototoxic to infants, whereas medications such as furosemide and vancomycin are less definitely ototoxic.[19-22] As a result, we considered only exposure to aminoglycosides as a covariate in this study. Duration of exposure to aminoglycosides was categorized as no exposure, less than 7 days of exposure, 7-29 days of exposure, and 30 or more days of exposure.[19] We defined sepsis as a positive blood or cerebrospinal fluid culture for an organism not generally considered a contaminant. We included episodes of coagulase-negative *Staphylococcus* if they were probable or definite.[23]

We report summary statistics (n and % for categorical variables, median and IQR for continuous variables) for all infants, and divided these into those who passed and failed their newborn hearing screen. We performed unadjusted comparisons of the 2 groups using chi square test (categorical variables) or the Wilcoxon rank-sum test (continuous variables), with a significance level of 0.05. We described demographics and predictor variables, as defined elsewhere in this article, and compared them in the 2 populations. We repeated these unadjusted analyses after stratification by birth weight, gestational age, risk factors for hyperbilirubinemia, size for gestational age status, congenital infection, duration of exposure to aminoglycosides, duration of mechanical ventilation, and duration of vasopressor support. Finally, we used multivariable logistic regression to evaluate association between hearing screen failure and maximum total bilirubin level before postnatal day 21 using all variables from the univariable analyses. As a sensitivity analysis, we repeated the regression excluding infants who received an otoacoustic emissions hearing screen or an unknown type of hearing screen. Analyses were performed using Stata version 16.1 (StataCorp).

Results

We identified 95 672 infants from 313 NICUs who met the inclusion and exclusion criteria and were included in the analysis. The median gestational age and birth weight were 30 weeks (IQR, 28-32 weeks) and 1330 g (IQR, 1010-1630 g), respectively (**Table I**). A total of 50 349 (53%) infants were male. Median 5-minute Apgar score was 8 (IQR, 7-9) (**Table I**). Most infants—90 713 (95%)—were discharged home, 4734 (5%) were transferred to another facility, and 42 (0.04%) died before discharge. The median maximum total bilirubin was 8.3 mg/dL (IQR, 6.7-10.0 mg/dL), and 5275 infants (6%) failed their newborn hearing screen (**Table I**). Hearing for 72 126 (75%) infants was screened by automated auditory brainstem response, 4062 (4%) were screened using otoacoustic emissions, and 19 484 (20%) did not have the type of screening reported within the database. The median duration of hospitalization was 46 days (IQR, 32-69 days) for infants who passed the hearing screen and 65 days (IQR, 42-90 days) for those who failed the infant hearing screen ($P < .001$).

Vasopressor support was given to 10 908 infants (11%), with a median duration of vasopressor support of 4 days (IQR, 2-7 days). Six percent of infants (n = 5421) who passed the hearing screen were large for gestational age, compared with 6% (n = 305) of infants who failed their newborn hearing screen ($P = .54$). Infants who failed their newborn hearing screens had a lower median peak bilirubin level (7.7 mg/dL; IQR, 6.1-9.5 mg/dL) compared with those who passed their newborn hearing screens (8.4 mg/dL; IQR, 6.8-10.0). However, a higher percentage of infants with earlier gestational ages failed their hearing screens ($P < .001$; **Table II**). Peak serum bilirubin levels within the first 21 postnatal days increased as gestational age at birth increased, nearly doubling between 22 and 32 weeks ($P < .001$; **Table II**). The median peak serum bilirubin occurred on postnatal day 3 (IQR, 2-7 days) for those who passed their newborn hearing screen, and day 4 (IQR, 2-8 days) for infants who failed their newborn hearing screen ($P = .42$). On multivariable logistic regression analysis, an increased maximum total bilirubin was associated with increased odds of failing the newborn hearing screen (OR, 1.03; 95% CI, 1.02-1.04; **Table III**).

Table I. Demographics and risk factors for infants with and without elevated bilirubin levels

Factors	Infants who passed newborn hearing screen (n = 90 397)	Infants who failed newborn hearing screen (n = 5275)	*P* value
5-minute Apgar score	8 (7-9)	8 (7-9)	<.001
Birth weight (g)			<.001
≤500	553 (0.6)	113 (2)	
501-1000	20 484 (23)	2392 (45)	
1001-1500	36 519 (40)	1812 (34)	
1501-2000	28 201 (31)	837 (16)	
>2000	4635 (5)	121 (2)	
Gestational age (weeks)			<.001
<24	801 (0.9)	164 (3)	
24-26	11 201 (12)	1506 (29)	
27-29	23 933 (26)	1741 (33)	
30-32	54 462 (60)	1864 (35)	
Male	47 347 (52)	3002 (57)	<.001
Race/ethnicity			<.001
White	42 956 (50)	1877 (37)	
Black	20 701 (24)	1969 (39)	
Hispanic	17 857 (21)	1003 (20)	
Other	5222* (6)	231† (5)	
Risk factor for hyperbilirubinemia			
ABO incompatibility	1057 (1)	44 (1)	.03
Rh incompatibility	148 (0.2)	8 (0.2)	.83
G6PD deficiency	104 (0.1)	9 (0.2)	.25
Small for gestational age	11 781 (13)	988 (19)	<.001
Congenital infection			
CMV	347 (0.4)	74 (1.4)	<.001
Toxoplasmosis	4 (<0.01)	0 (0)	.63
Rubella	0 (0)	0 (0)	-
Syphilis	41 (0.05)	5 (0.09)	.11
Herpes simplex virus	91 (0.1)	11 (0.2)	.02
Duration of aminoglycoside exposure, days			<.001
0	17 571 (19)	608 (12)	
1-6	45 215 (50)	2181 (41)	
7-29	25 776 (29)	2186 (41)	
>30	1835 (2)	300 (6)	
Days of intubation and mechanical ventilation	0 (0-3)	2 (0-20)	<.001
Received vasopressors	9646 (11)	1262 (24)	<.001
Days of vasopressor support if received vasopressors	4 (2-6)	4 (3-9)	<.001
IVH, grade 3 or 4	2910 (3)	389 (7)	<.001
Sepsis	6604 (7)	816 (15)	<.001
Peak total serum bilirubin postnatal age <21 days, mg/dL	8.4 (6.8-10.0)	7.7 (6.1-9.5)	<.001

G6PD, glucose-6-phosphate dehydrogenase.
Values are n (%) for categorical variables and median (IQR) for continuous variables.
*These 5222 infants include the following race/ethnicity categories: 2932 Asian, 637 Native American/Alaskan, 199 Pacific Islander, and 1454 with race as other – not otherwise specified.
†These 231 infants include the following race/ethnicity categories: 110 Asian, 38 Native American/Alaskan, 16 Pacific Islander, and 67 with race as other – not otherwise specified.

For each 1 mg/dL increase in peak total serum bilirubin levels, there was a 3% increased odds of failing a newborn hearing screen. Other statistically significant risk factors included male sex, Black or Hispanic race, lower gestational age, small for gestational age status, presence of a congenital infection, sepsis, total number of ventilator days, total number of pressor days, duration of aminoglycosides, and grade 3 or 4 IVH (Table III). After only considering infants with hearing screening by automated auditory brainstem response (n = 72 126), an increased maximum total bilirubin remained associated with increased odds of failing the newborn hearing screen (OR 1.04; 95% CI, 1.02-1.05).

Discussion

High levels of bilirubin are associated with neurologic dysfunction such as hearing loss in infants born late preterm or full term.[24-26] Unconjugated unbound bilirubin crosses the blood-brain barrier, and inhibits *N*-methyl-d-aspartate–receptor ion channels and the uptake of tyrosine.[4] As a result, bilirubin inhibits excitatory neural signaling. Several studies have shown that infants with prematurity may be at increased risk of neurodevelopmental problems at lower peak bilirubin levels than infants born at term.[8-10,27] One study found imaging evidence of kernicterus in 5 infants born at 25-29 weeks gestational age with peak bilirubin levels of 8.7-11.9 mg/dL, which is below the treatment threshold for full-term infants.[8] Other studies have also found evidence of kernicterus or other neurologic problems in infants with low birth weight and bilirubin levels of less than 10 mg/dL.[9,10]

The effect of hyperbilirubinemia can be compounded with other risk factors for hearing loss, such as exposure to ototoxic medications, hypoxia, low birth weight, and mechanical ventilation.[14,28] Unfortunately, many infants with preterm birth are critically ill, posing a problem for the analysis of independent risk factors. This study used a multivariable logistic regression analysis to control for and study the effects of multiple variables, including gestational age, birth weight, sex, Apgar scores, congenital infections, exposure to aminoglycosides, mechanical ventilation, vasopressor support, sepsis, and grade 3 or 4 IVH. Official guidance does not exist for treatment thresholds to prevent complications of hyperbilirubinemia, such as hearing loss in infants born preterm, likely in large part owing to the lack of data. This study shows that, for each 1 mg/dL increase in peak total serum bilirubin levels, there is a modest, but statistically significant, increased odds of failing a newborn hearing screen at 1.03 (95% CI, 1.02-1.04), when accounting for common confounding variables.

The modest effect of hyperbilirubinemia may be partially attributed to the lower median peak bilirubin levels in infants who failed their newborn hearing screen compared with those who passed (Table I). On unadjusted analysis, an elevated peak bilirubin level was protective against a failed hearing screen. However, an elevated bilirubin increased the odds of a failed hearing screen on multivariable regression (Table II). This finding could be due to Simpson's paradox, a statistical phenomenon in which opposite trends occur based on whether data are combined or separated by another variable.[29] In this case, the effect of elevated bilirubin levels reverses depending on whether the data are aggregated or split by gestational age. Gestational age has been a confounder in prior literature, as we believe

Table II. Failure of hearing screen and peak bilirubin levels as a function of gestational age

Gestational ages (weeks)	Failed hearing screen, No. (%)	Peak total serum bilirubin, mg/dL, median (IQR)
22 (n = 48)	11 (23)	5.1 (4.0-6.6)
23 (n = 917)	153 (17)	5.7 (4.5-7.0)
24 (n = 2896)	443 (15)	5.9 (4.8-7.2)
25 (n = 4272)	521 (12)	6.2 (5.1-7.5)
26 (n = 5539)	542 (10)	6.6 (5.4-7.8)
27 (n = 6899)	573 (8)	6.9 (5.8-8.2)
28 (n = 8849)	623 (7)	7.4 (6.2-8.7)
29 (n = 9926)	545 (5)	8.0 (6.7-9.3)
30 (n = 12 836)	556 (4)	8.5 (7.2-10.0)
31 (n = 16 648)	584 (4)	9.1 (7.7-10.5)
32 (n = 26 842)	724 (3)	9.6 (8.1-11.0)
Total (n = 95 672)	5275 (6)	8.3 (6.7-10.0)

Table III. Multivariable logistic regression analysis results for failed hearing screen

Variables	OR	95% CI	*P* value
Peak total bilirubin, mg/dL	1.03	1.02-1.04	<.001
5-Minute Apgar score 7-10 (comparison of score 4-6)	0.97	0.89-1.05	.47
Gestational age, weeks (comparison <24 weeks)			
24-26	0.89	0.74-1.09	.26
27-29	0.64	0.53-0.79	<.001
30-32	0.34	0.27-0.42	<.001
Male	1.20	1.13-1.27	<.001
Race/ethnicity (compared with White)			
Black	1.93	1.80-2.06	<.001
Hispanic	1.20	1.11-1.31	<.001
Other	0.97	0.84-1.12	.71
Known risk factor for hyperbilirubinemia	0.88	0.68-1.15	.36
Small for gestational age	1.53	1.41-1.65	<.001
Congenital infection	1.79	1.37-2.34	<.001
Aminoglycoside exposure, days (compared to no exposure)			
<7	1.16	1.05-1.28	.002
7-29	1.27	1.14-1.41	<.001
>30	1.18	0.98-1.41	.08
Days mechanically ventilated	1.01	1.005-1.009	<.001
Days of vasopressor support	1.02	1.01-1.03	<.001
Sepsis	1.21	1.10-1.33	<.001
Grade 3 or 4 IVH	1.20	1.06-1.35	.003

it is in this study.[30] This paradox could be because NICUs are more conservative in testing and treating hyperbilirubinemia in younger infants. Currently, each NICU establishes its own guidelines for testing and treatment in infants born preterm. Providers may have more concern for hyperbilirubinemia in infants with a lower gestational age. They may test earlier or more frequently, and initiate treatment at lower bilirubin levels. We could not determine treatment thresholds from our dataset, and thus we cannot report how treatment such as phototherapy or exchange transfusion affected the risk of hearing screen failure in our cohort. Prior work has established that the majority of infants born preterm receive treatment for hyperbilirubinemia despite the lack of official treatment guidelines.[11]

Investigators have proposed approaches to management of hyperbilirubinemia in infants born preterm. These include consensus-based guidelines in the US.[31] However, further work is needed to determine if these lower treatment thresholds result in a significant decrease in adverse outcomes.[10,32] A randomized controlled trial of 1974 infants showed that aggressive phototherapy was associated with a decreased risk of profound hearing loss, but also an increase risk in mortality in extremely low birth weight infants.[12] This finding highlights the need for official guidelines for monitoring and interventions to prevent both excessive and insufficient treatment in infants born preterm. Our results suggest that more aggressive treatment of lower peak bilirubin levels may decrease the risk of hearing screen failure, and by extension, may decrease the risk of hearing loss and associated language and communication delays. Early access to pediatric hearing and speech services including confirmatory diagnosis, hearing interventions including hearing aids and cochlear implants, and language enrichment services are needed to improve language outcomes.[33,34]

Our study considered demographics in the multivariable model such as sex and race. This study incidentally demonstrated a statistically significant increase in likelihood of failing the newborn hearing screen for males compared with females, which has been an area of controversy in the literature (**Table III**).[35,36] Our study also found race to have a significant association with failed newborn hearing screen. Black and Hispanic children had increased odds of hearing screen failure compared with White children at 1.93 (CI, 1.80-2.06; $P < .001$) and 1.20 (1.11-1.31, $P < .001$), respectively (**Table III**). This finding is at odds with a prior study on the effects of race where only Hispanic infants were at increased risk of hearing screen failure.[36] This difference could be due to dissimilar study populations and screening methods, because our study looked at NICU patients screened predominantly using automated auditory brainstem response testing, whereas the other report addressed healthy newborns screened using otoacoustic emissions testing.

There are several hypotheses for this higher risk of hearing screen failure among Black and Hispanic NICU infants. This could be due to higher rates of CMV infection. Prior work has shown that Black and Hispanic infants have a higher rate of congenital CMV infection.[37,38] Our study considered CMV infections as a covariate, but our known infection rate was below published values.[37,39] Because universal CMV screening is not mandated, all infections may not have been caught. Another possible explanation is that Black infants are at increased risk for hemolytic diseases such as glucose-6-phosphate dehydrogenase deficiency, which may cause adverse outcomes at lower bilirubin levels.[40] Yet another possibility is that Black and Hispanic children were treated for jaundice at a higher peak bilirubin level or older age. This previously unreported racial difference in hearing screening results among NICU patients points to an area of potential disparity in need of further research. Consistent with prior research, our study also found an increased risk

of failed hearing screening associated with sepsis, grade 3 or 4 IVH, days of vasopressor support and days of mechanical ventilation.[12-14,41,42]

This study does have several limitations. One is that the primary end point is a failed newborn hearing screen. In our study, 6% of newborns failed their final newborn hearing screen before discharge, similar to prior works.[35] However, infants with failed hearing screens need follow-up with thorough hearing evaluations. We did not have access to additional hearing testing after hospital discharge. Some infants who initially failed their newborn hearing screen may have had normal hearing on further testing. One study found that automated auditory brainstem responses overestimated sensorineural hearing loss by about 10% in NICU infants.[43] Additionally, prior work has shown that the effects of hyperbilirubinemia on hearing may be transient, which would be missed by this study.[44,45] Last, newborn hearing screens may not catch all congenital causes of hearing loss, especially if caused by auditory neuropathy, CMV, enlarged vestibular aqueduct, or a mild hearing loss.[46] Furthermore, auditory neuropathy is missed with otoacoustic emissions testing, which was the testing method for at least 4% of infants in this study. Auditory neuropathy is associated with hyperbilirubinemia more than other etiologies of hearing loss.[47,48] However, the exclusion of these infants did not change the association between hyperbilirubinemia and a failed hearing screen.

Another limitation is that this was a retrospective cohort study across many NICUs. As a result, it is possible that confounding was a factor, because gestational age seemed to be a confounder between peak total serum bilirubin and hearing screen failure. Yet another limitation is the distribution of gestational ages in this study. There were a relatively small number of infants born at 22-23 weeks of gestation, and a greater percentage born at gestational ages of 30-32 weeks. Although there was a high incidence of hearing screen failure in infants born extremely premature, this may be diluted owing to their small proportion of the overall study population. A further limitation is that we did not examine the effects of albumin levels on bilirubin toxicity because we did not have paired albumin and bilirubin measurements for many of the infants in our study cohort. Unconjugated unbound bilirubin in particular is associated with neurotoxicity and subsequent changes in the auditory brainstem response.[49,50] Another limitation is that severity of illness may affect a child's risk of hearing loss, and we were not able to fully account for this in our model, because the database does not capture all clinically relevant information such as vital signs.

The primary strength of this study was the sample size. This factor allowed us to detect small, but statistically significant, ORs. Additionally, this large sample size allowed us to consider the effects of rarer conditions, like congenital or postnatal infection with CMV, in the multivariable logistic regression.

Our findings suggest that even a small increase in peak total serum bilirubin levels is associated with a statistically significant increase in the risk of hearing screen failure. Further work is needed to determine whether this increase in risk is clinically significant, and at what cumulative increase in risk justifies treatment. However, these findings show the need for further research to inform official guidelines for treatment of hyperbilirubinemia in preterm and sick infants to prevent adverse outcomes like sensorineural hearing loss or kernicterus. ■

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