Risk of Sepsis in Newborns With Severe Hyperbilirubinemia

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ABSTRACT. Because bacterial infection is a potential cause of hyperbilirubinemia, some authors suggest that newborns with significant unexplained indirect hyperbilirubinemia should be evaluated for sepsis. We reviewed the charts of 306 newborns admitted to a pediatric ward within 21 days of birth with a diagnosis of indirect hyperbilirubinemia (peak serum bilirubin level 316 ± 48, range 217 to 498 μmol/L) (18.5 ± 2.8, 12.7 to 29.1 mg/dL). Ninety percent were fully or partially breast-fed. Sepsis was identified in 0 of 306 newborns (upper 95% confidence limit for the risk of sepsis = 1%). The overwhelming majority of newborns who require readmission to hospital for indirect hyperbilirubinemia are healthy, breast-fed newborns and do not need to be investigated for sepsis. If indirect hyperbilirubinemia is ever the only manifestation of bacteremia or incipient sepsis, it must be a rare event. ***Pediatrics* 1992;90:741–743;**
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Bacterial infection is a recognized cause of hyperbilirubinemia in the newborn, and some reports suggest that unexplained indirect hyperbilirubinemia may be the only manifestation of sepsis in otherwise healthy-appearing newborns.[1–3] Because it is now the prevailing practice (in the United States) to discharge most neonates from newborn nurseries before age 48 hours, readmission of a newborn to the hospital for hyperbilirubinemia in the first weeks after birth has become common. Should these newborns be subjected to lumbar puncture and blood and urine cultures even if they appear otherwise well? To evaluate this question, we reviewed our experience with jaundiced newborns readmitted to our pediatric service.

METHODS

We reviewed all admissions (n = 21 700) to our pediatric ward between January 1, 1985, and December 31, 1990, and identified 306 newborns (1.4%) admitted within 21 days of birth with the diagnosis of indirect hyperbilirubinemia. We excluded those admitted for evaluation of prolonged direct hyperbilirubinemia. Clinical and laboratory data were extracted from the charts, and discharge diagnoses were assigned after review of the chart. The majority (82%) of these newborns were cared for by private pediatricians. The diagnosis of possible ABO hemolytic disease was made if the mother was group O, the infant group A or B, and the direct Coombs' test was positive. At Beaumont Hospital, blood types and direct Coombs' test are obtained routinely on cord blood in all babies born to group O mothers. Newborn records were not available for babies born at surrounding hospitals and, in these newborns, Coombs' tests were obtained at the time of admission.

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RESULTS

The results are shown in Tables 1 through 4. Consistent with previous studies,[4–10] there was a striking preponderance of breast-feeding in these newborns—77% were fully breast-fed and 14% partially breast-fed. Only 9% were exclusively bottle-fed (compared with 47% of our nursery population). There was also an excess of boys (63%) and some degree of prematurity (mean gestation 38.1 ± 3.0 weeks). The average hospital stay was 1.9 ± 0.9 days (range 0-7 days). Two hundred eighty newborns (91.5%) were admitted in the first week, 24 (8%) between 8 and 14 days,

TABLE 1. Characteristics of 306 Neonates Admitted With Hyperbilirubinemia*

	n	%
Born at Beaumont Hospital	141	46.1
Male	192	62.7
White	284	92.8
Breast-fed	235	76.7
Breast- and bottle-fed	42	13.7
Bottle-fed	28	9.2

* Feeding information not available in one newborn.

TABLE 2. Clinical Data

	Mean	SD	Range
Age on admission, d	5.0	2.0	2–17
Length of stay, d	1.9	0.9	0–7
Birth weight, kg	3.3	0.54	2.1–4.6
Gestation, wk	38.1	2.8	33–42
Peak serum bilirubin			
μmol/L	315	4.8	217–498
mg/dL	18.5	2.8	12.7–29.1

TABLE 3. Laboratory Investigations Performed

Test	n	%
Blood type	286	93.5
Coombs' test	286	93.5
Complete blood cell count	282	92.2
Reticulocyte count	182	59.5
Blood culture	59	19.3
Urine culture	126	41.2
Spinal fluid culture	15	4.9

TABLE 4. Discharge Diagnosis

Test	n	%
Hyperbilirubinemia (cause unknown) or breast milk jaundice	290	94.8
Cephalhematoma or bruising	3	1.0
ABO hemolytic disease*	11	3.6
Anti-E hemolytic disease	1	0.3
Galactosemia	1	0.3
Sepsis	0	

* Mother O, infant A or B, direct Coombs' test positive.

and 2 after 14 days. Only 13 newborns received antibiotics during the hospital stay. Of these, 12 had blood and urine cultures performed and 8 had spinal fluid cultures as well. Average hospital stay for the newborns who received antibiotics was 3.1 days. Two were sick at the time of admission. One was an 11-day-old newborn whose bilirubin level at age 3 days was 311 μmol/L (18.2 mg/dL). He was brought to the hospital because of a cough and congestion, and physical examination revealed retractions. A chest radiograph showed a right middle lobe infiltrate. The bilirubin level at the time of admission was 344 μmol/L (20.1 mg/dL). Cultures were negative and the white blood cell count suggested a viral pneumonia. He received ampicillin and gentamicin during his 3-day hospitalization and oral amoxicillin after discharge. (This was the only newborn to receive antibiotics after discharge.) The second newborn was a 5-day-old boy who had vomited almost all feedings for 2 days prior to admission. Just before admission, the physician's office was notified by the state laboratory that his newborn screen was positive for galactosemia. At the time of admission the serum bilirubin level was 366 μmol/L (21.4 mg/dL) and the direct reacting bilirubin level was 29 μmol/L (1.7 mg/dL). The bilirubin level subsequently rose to a peak of 424 μmol/L (24.8 mg/dL) but then responded well to phototherapy. Regrettably, blood cultures were not obtained and antibiotics were not given. Nevertheless, he was well at the time of discharge, 4 days later, when the total bilirubin level was 111 μmol/L (6.5 mg/dL) and the direct bilirubin level was 46 μmol/L (2.7 mg/dL).

Most newborns (93%) had blood type determined and Coombs' test performed, and 92% had a complete blood cell count. Urine cultures were performed in 41%, blood cultures in 19%, and spinal fluid culture in 5%. All cultures were negative.

Sepsis was not identified in any newborn. The upper 95% confidence limit for the risk of sepsis, given a rate of 0 of 306, is 1%.[11]

DISCUSSION

Because we could not perform a Coombs' test until day 4 or 5 in neonates not born at Beaumont Hospital, false-negative tests were likely to occur, and it is possible that we underestimated the true incidence of ABO hemolytic disease in the outborn neonates. It is difficult to make a firm diagnosis of ABO hemolytic disease unless a Coombs'-positive neonate has a rapidly rising bilirubin level in the first few days after birth.[12] The presence of jaundice on day 4 or 5 in a breast-fed, Coombs'-positive, ABO-incompatible neonate, however, does not mean that we can conclude that the jaundice is due to ABO hemolytic disease.

An obvious limitation of this study is that only 19% of our neonates had a blood culture performed, and we cannot be certain that none of these neonates were bacteremic. Nevertheless, only 13 (4.2%) of 306 neonates admitted received antibiotics during their hospital stay; all cultures were negative and all neonates were well when discharged. Thus, we can be fairly confident that none of the neonates were septic. Three neonates were readmitted to the hospital within 2 weeks of discharge: one because of a serum bilirubin level of 350 μmol/L (28.0 mg/dL), which turned out to be a laboratory error. The subsequent bilirubin level was 243 μmol/L (14.2 mg/dL) and the child was sent home without treatment. Two other children were admitted on days 12 and 13, respectively—one because of apnea and the other with a diagnosis of "rule-out sepsis." In both cases a full evaluation for sepsis was negative.

Some investigators have reported that jaundice may be the first sign of bacterial sepsis in otherwise well-appearing neonates in the first few days after birth. Rooney et al[2] described a series of 22 newborns with documented bacterial infection and hyperbilirubinemia. In some of these newborns, serum bilirubin levels were exceptionally high (484 to 856 μmol/L, 28.3 to 50 mg/dL) and several had significant elevations of direct reacting bilirubin. Nine babies were said to be "active and well throughout, and jaundice was the only abnormal clinical finding." Linder et al[1] identified 93 jaundiced newborns out of 5805 newborns. These were all full-term neonates younger than 7 days old who had serum bilirubin levels exceeding 171 μmol/L (10 mg/dL) in the first 48 hours after birth or 257 μmol/L (15 mg/dL) thereafter. Three had positive blood cultures: the organisms identified were *Proteus mirabilis, Bacteroides* sp, and *Klebsiella pneumoniae.* All three had other signs indicating that something was amiss (increase in serum bilirubin level by 92 μmol/L [5.4 mg/dL] in 6 hours in a newborn receiving phototherapy; refusal to feed; vomiting). In a prospective study of 69 newborns with unexplained hyperbilirubinemia, Chavalitdhamrong et al[3] found bacterial infection in only 2, both of whom had asymptomatic Gram-negative urinary tract infections. We obtained urine cultures in 126 newborns (41.2%), but none were positive.

As any clinician and the published data will confirm,[4,13] in the majority of term, jaundiced newborns, no (pathologic) cause of the jaundice is ever identified. Jaundice is a very common entity, and the finding of a positive blood or urine culture in a newborn with indirect hyperbilirubinemia does not prove that the infection is the *cause* of the jaundice. Thus, this type of jaundice alone should not be a reason to initiate an investigation for sepsis. On the other hand, some newborns do deserve more careful screening and may merit an evaluation for sepsis—those who have late-onset jaundice (after physiologic icterus has resolved) or direct hyperbilirubinemia, or something in the history, physical examination, or laboratory investigations that is out of the ordinary. But the overwhelming majority of newborns who require readmission to hospital for hyperbilirubinemia are healthy, breast-fed newborns with "breast-feeding-associated jaundice" and do not need to be investigated for sepsis. In the United States, more than 300 000 newborns each year have a serum bilirubin level ≥222 μmol/L (13mg/dL).[13] If indirect hyperbilirubinemia is ever the *only* manifestation of bacteremia or incipient sepsis, it must be a rare event indeed.

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