

# Characteristics of Hyperbilirubinemic Neonates in Need of Exchange Transfusion and Their Mothers

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## ABSTRACT

**Background:** Severe hyperbilirubinemia is potentially neurotoxic and can lead to long-term complications in neonates. Exchange transfusion (ECT) is one of the most important treatments for hyperbilirubinemia. In this regard, the present study aimed to determine the characteristics of hyperbilirubinemic neonates who need ECT and their mothers.

**Methods:** This cross-sectional study was performed on 380 infants born after 35 weeks of gestation who were 2-14 days old. The studied neonates had bilirubin levels higher than 17 mg/dl and underwent ECT in Ghaem Hospital in Mashhad, Iran during 2010-20. Moreover, it should be noted that the participants were selected using the convenience sampling method and the required data were collected using a checklist. This checklist was designed based on the neonatal examination, maternal (maternal age, parity), and neonatal status (age, gender, and weight) and serial laboratory tests before and after ECT (total bilirubin, hematocrit, and platelet). Finally, these variables were compared based on the cause of hyperbilirubinemia.

**Results:** The mean levels of serum bilirubin were 28.5 mg/dl and 26.5 mg/dl in male and female infants ( $P=0.096$ ), respectively. Furthermore, the mean levels of serum bilirubin in neonates born by cesarean section and normal vaginal delivery were 29.5 and 28.1 mg/dl, respectively ( $P=0.458$ ). Based on the findings, 60% of the neonates suffered from weight loss and 22% had more than 3% daily weight loss. In the present study, the most prevalent risk factors among the studied neonates were RH incompatibility, ABO incompatibility, and G6PD deficiency, in that order.

**Conclusion:** Overall, these findings suggest that normal vaginal delivery, repeated breastfeeding, prevention of severe weight loss, early detection of RH and ABO incompatibility, and G6PD deficiency, as well as appropriate management of hyperbilirubinemia, can reduce the need for ECT and alleviate complications of neonatal hyperbilirubinemia.

**Keywords:** Cause, Etiology, Exchange transfusion, Hyperbilirubinemia, Jaundice, Mothers, Neonate, Risk factors

## Introduction

Hyperbilirubinemia is a common disorder during the first week of life and in most cases, it is mild and transient and disappears without any complications (1). However, its severe cases are potentially neurotoxic and can lead to complications, the most severe form of which is kernicterus. This will significantly harm parents and children and also impose a considerable financial burden on the national healthcare system of the country (2, 3). Based on the statistics, up to 19% of neonatal hospital readmissions are ascribed to jaundice (3).

The risk factors for jaundice include low

birth weight, prematurity, a previous sibling with jaundice, treatment with phototherapy and exchange transfusion, decreased breast milk intake, significant weight loss, nutritional problems, hypernatremic dehydration, jaundice in the first 24 h after birth, male gender, and early discharge. Moreover, the major causes of jaundice include unknown causes (64.44%), ABO incompatibility (13.63%), infection (10.35%), G6PD deficiency (9.70%), RH incompatibility (6.07%), polycythemia (3.85%), cephalohematoma (2.35%), minor blood group incompatibility (1.25%), skin ecchymosis (0.6%) and Crigler-Najjar syndrome (4). The goal

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of clinical management is to prevent neurotoxicity caused by indirect bilirubin and preclude unwanted damages to the neonate's brain.

Phototherapy, and if unsuccessful, exchange transfusion (ECT) is the primary treatment used to maintain maximal total bilirubin serum level below the pathological level. Phototherapy is the primary treatment for hyperbilirubinemia, which can significantly reduce the demand for ECT (5). However, if intensive phototherapy fails or if the risk of kernicterus is greater than that of ECT, double volume ECT is performed to reduce the level of serum bilirubin to a safe level (6).

To date, little is known about the factors that determine the need for ECT, such as the demographic characteristics (e.g., age), the severity of hyperbilirubinemia, the severity of lysis, neonatal gender, and type of delivery. Given the high prevalence of neonatal jaundice in Asian countries, including Iran, multiple risk factors of severe hyperbilirubinemia and its major complications (e.g., kernicterus), and the importance of identifying demographic characteristics of neonates with hyperbilirubinemia, ECT may be an efficient method for the recognition of its early causes and proper management. In this regard, the present study aimed to investigate the demographic characteristics of hyperbilirubinemic neonates in need of ECT.

## Methods

This cross-sectional study was performed on 380 infants born after 35 weeks of gestation who were 2-14 days old with bilirubin levels above 17 mg/dl and underwent ECT in Ghaem Hospital in Mashhad, Iran during 2010-20. In this study, the participants were selected using the nonprobability and purposive sampling methods to determine the characteristics of hyperbilirubinemic neonates in need of ECT. This research was approved by the Ethics Committee of Mashhad University of Medical Sciences (code: 990114) and obtained an ethics certificate (IR.MUMS.MEDICAL.REC.1399.177).

In the first step, the list of neonates who had undergone ECT during the past 10 years was extracted from the hospital archive. Subsequently, term and late preterm (over 35 weeks of gestation) neonates who were in need of ECT were selected using the convenience sampling method. Thereafter the checklist form was completed based on the neonatal examination, medical history, laboratory tests, and maternal (age, parity, type of delivery) and neonatal status (age, gender, and weight). The types of tests

requested by their physicians were also recorded by the researchers. Eventually, the characteristics of hyperbilirubinemic neonates were explored based on their medical history, examinations, and laboratory tests.

Based on the records, the patients were diagnosed with ABO incompatibility if the blood type of the mother was O positive and that of the infant was A or B, and at least two of the following conditions were observed: 1) jaundice on the first day after birth, 2) positive direct Coombs test, 3) microspherocytes in peripheral blood, and 4) positive indirect Coombs test. If no Rh or ABO incompatibilities were observed while the direct Coombs test was positive, the result was subgroup incompatibility. Moreover, if the maternal RH was negative, the neonatal RH was positive, and the direct Coombs test result was reported positive, the diagnosis was RH incompatibility. The G6PD activity was also evaluated by a semi-quantitative method using fluorescence dyes, and activity levels of lower than 30 were considered enzyme deficiency.

The diagnosis of sepsis was based on positive blood culture as well as clinical symptoms. Furthermore, neonates with a blood sodium level of more than 150 mg/dl and more than 3% daily weight loss were diagnosed with hypernatremic dehydration, provided that no other known causes were involved.

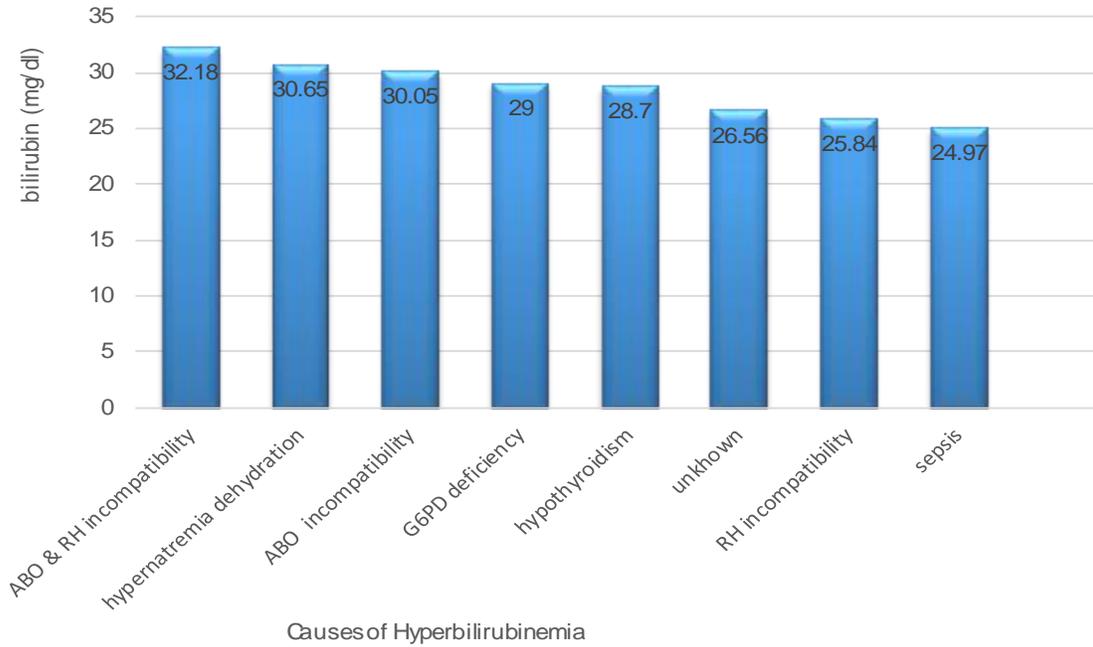
The collected data were analyzed in SPSS software (version 24) using descriptive statistics, including central tendency and dispersion. It should be noted that a p-value of less than 0.05 was considered significant for all tests.

## Results

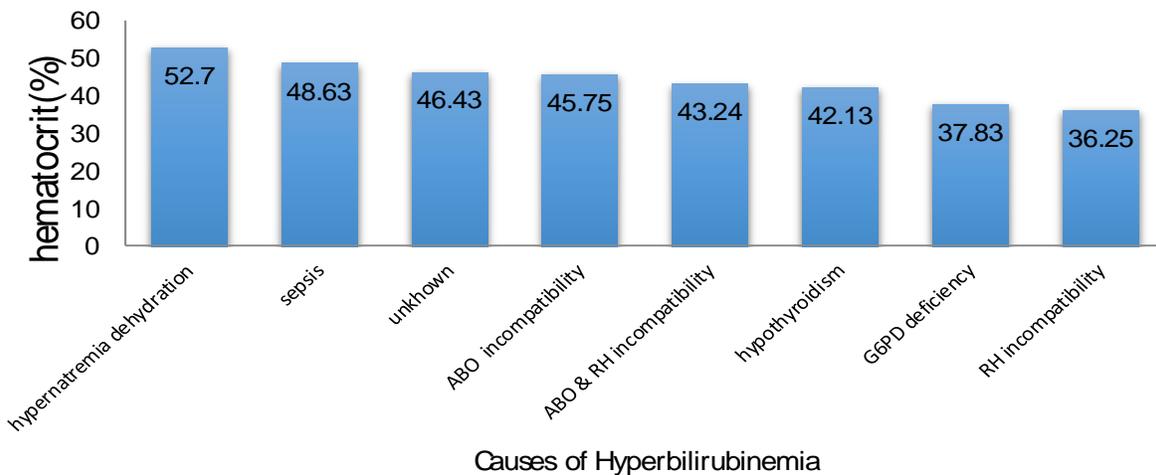
This study was carried out on 380 neonates who underwent ECT during the past 10 years. However, 18 and 3 subjects were excluded due to the gestational age of fewer than 35 weeks and ECT for reasons other than jaundice. The mean level of serum bilirubin was 28.5 and 26.5 mg/dl in males and females, respectively ( $P=0.096$ ). The demographic characteristics of the studied neonates are summarized in Table 1.

**Table 1.** Demographic characteristics of neonates

Variable	Mean $\pm$ SD
Maternal age (year)	26.5 $\pm$ 6.27
Number of deliveries	1.84 $\pm$ 1.01
Admission age (day)	5.4 $\pm$ 4.4
Birth weight (g)	2810 $\pm$ 670
Admission weight (g)	2720 $\pm$ 630
Apgar score	9.7 $\pm$ 0.30
Bilirubin (mg/dl)	27.5 $\pm$ 10.05
Hematocrit	44.92 $\pm$ 8.02



**Figure 1.** Mean level of serum bilirubin in neonates based on the causes of hyperbilirubinemia



**Figure 2.** Mean values of hematocrit based on the causes of hyperbilirubinemia

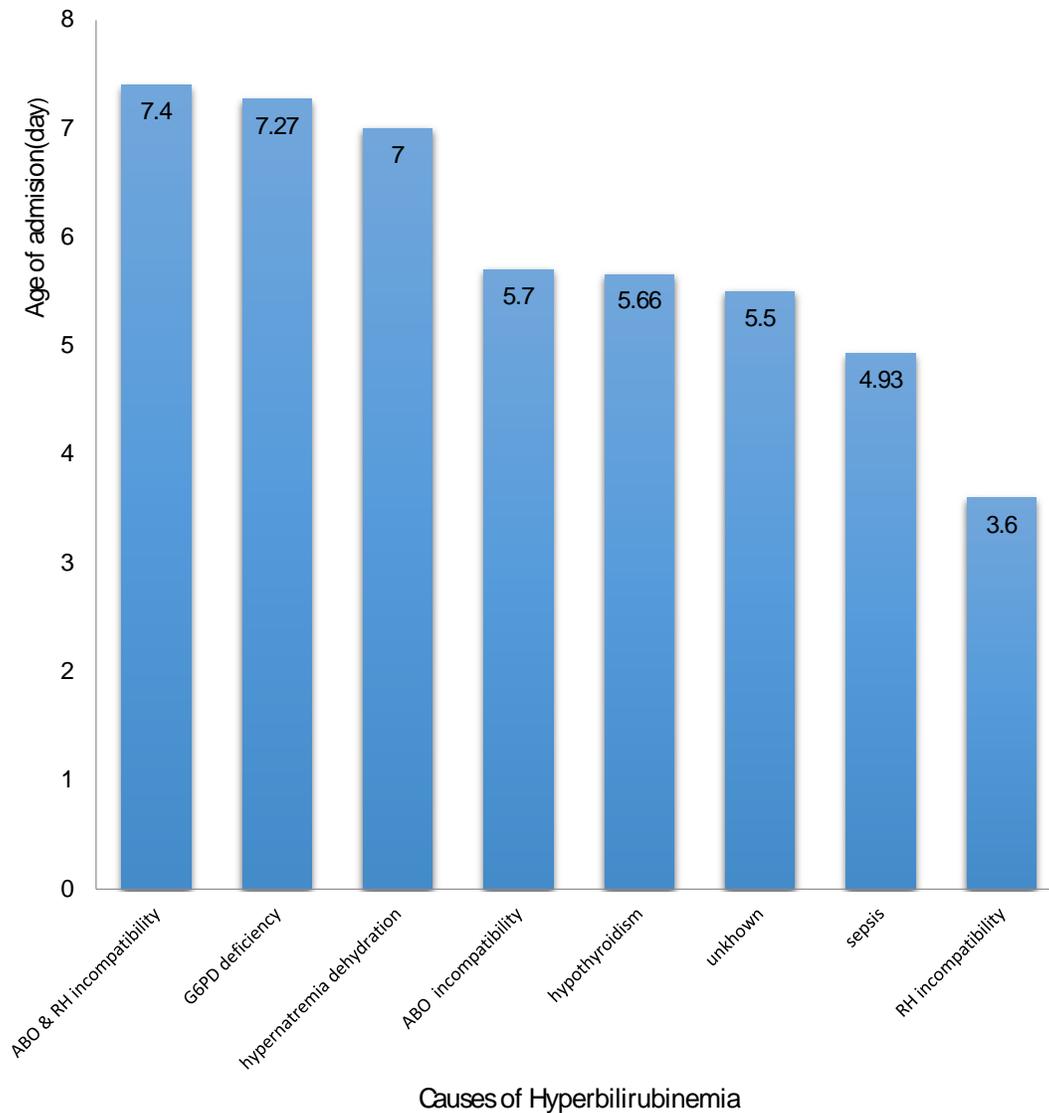
Mean levels of serum bilirubin were 29.5 and 28.1 mg/dl in neonates born by cesarean and normal vaginal delivery (NVD) ( $P=0.458$ ). Moreover, the mean level of serum bilirubin, hematocrit, and admission age of the neonates based on the causes of hyperbilirubinemia are shown in figures 1, 2, and 3.

## Discussion

Based on the results of the present study, the mean age of the mothers of hyperbilirubinemic neonates in need of ECT was about 26 years, which is similar to the findings of other studies

that found the mean age of mothers of such neonates to be 26.5 years (7-9). This result can be attributed to the fact that this age is within the range of women's reproductive years (10). According to the National Collaborating Centre for Women's and Children's Health, the maternal age over 25 years is associated with a 2.6-fold increase in the risk of neonatal hyperbilirubinemia (10).

According to the findings, two-thirds and one-third of the neonates who needed ECT were born by NVD and C-section, respectively. In other studies, about 50-70% and 23-40% of the



**Figure 3.** Mean admission age of neonates based on the causes of hyperbilirubinemia

neonates who had undergone ECT were born by NVD and C-section, respectively (10-12). In the present study, no relationship was found between the type of delivery and the severity of hyperbilirubinemia; however, the mean level of serum bilirubin in neonates born by NVD was lower than those born by C-section. This finding seems to be consistent with those of the other research which revealed no association between the type of delivery and the severity of hyperbilirubinemia or the need for ECT (13-15).

In total, 56% of the studied neonates in the present research were male while in other studies, 53-64% of neonates were reported to be male (7, 9, 11, 12). The severity of jaundice in male infants was approximately 2 mg/dl higher in comparison to the female neonates. A possible explanation for

this result is the higher prevalence of G6PD deficiency in males; however, the exact reason for the greater incidence of hyperbilirubinemia and ECT in males is still unclear. No other studies have found a relationship between gender and the severity of jaundice (9, 14).

According to the results, 60% of the neonates had weight loss while 22% of them had more than 3% daily weight loss. In other studies, a significant weight loss was reported in 12-27.5% of the neonates with hyperbilirubinemia (3, 16, 17). Given that weight loss in infants can exacerbate jaundice, breastfeeding can possibly prevent pathological weight loss and eventually the exacerbation of jaundice with unknown causes (16). Consequently, weight loss and exacerbation of jaundice can be expected in newborns with

nutritional problems (3). This result can be justified by the fact that inadequate neonate breastfeeding and consequently insufficient calorie intake reduce bowel movements and elevate the bilirubin levels, leading to an increase in the enterohepatic circulation and delay in maturation of hepatic bilirubin-conjugating enzymes. Eventually, these processes exacerbate the neonate's hyperbilirubinemia in the first week of life as the result of breastfeeding reduction (3).

The mean age at the time of hospital admission in this study was 5-6 days, while other studies have reported a mean age of 3-7 days (17, 18). Delayed neonatal admission aggravates jaundice and leads to further complications (19). The findings of the present research suggest that jaundice first appeared in infants with RH incompatibility, ABO incompatibility, and finally G6PD deficiency, in that order. However, based on the results of previous studies, jaundice appeared significantly earlier in neonates with hemolysis, compared to those with idiopathic jaundice.

The most common risk factors of hyperbilirubinemia in the studied neonates were Rh incompatibility, ABO incompatibility, and G6PD deficiency, in that order (20) since jaundice had the highest severity in neonates with Rh incompatibility. However, in our country, the delayed admission of neonates with G6PD deficiency could be due to the absence of routine screening for this enzyme during the first few days after birth, as well as the lack of screening for ABO and RH incompatibility and insufficient emphasis on follow-up. Hence, routine screening for this enzyme deficiency can help the early diagnosis and management of hyperbilirubinemia which can alleviate its complications.

In this study, the mean level of total serum bilirubin in neonates who underwent ECT was 27.5 mg/dl. This value has been reported to be 24-29 mg/dl in other studies (7, 17, 21). Moreover, in a study performed by Cheng et al., the mean levels of serum bilirubin in neonates with severe hyperbilirubinemia were  $23.3 \pm 3.2$  and  $26.1 \pm 3.2$  regarding ABO and Rh incompatibility risk factors, respectively (22). Moreover, in a study conducted by Boskabadi, the mean levels of serum bilirubin in neonates with severe hyperbilirubinemia were  $23.4 \pm 7.3$  and  $25.1 \pm 7.4$  regarding ABO and Rh incompatibility risk factors, respectively (23).

Based on the results, the mean level of total serum bilirubin in neonates with sepsis was  $24.97 \pm 4.87$  mg/dl which was lower, compared to neonates with other causes. This value was  $16.8 \pm 4.9$  mg/dl and  $23.6 \pm 2.8$  in the studies

carried out by Maamouri et al. (1) and Cheng et al. (22), respectively. Sepsis causes jaundice by the elevation of hemolysis and incomplete bilirubin conjugation (1). According to the results of this study, the lowest hematocrit was observed in neonates with RH incompatibility, G6PD deficiency, ABO and RH incompatibility, and finally ABO incompatibility, in that order. The highest level of hematocrit was observed in neonates with hypernatremic dehydration which was consistent with the results of the reviewed literature (22, 23).

## Conclusion

Based on the findings, the severity of jaundice and the need for ECT was higher in male infants and the neonates born by C-section; however, there was no significant relationship between the type of delivery, infant gender, severity of jaundice, and delay in neonatal referral. Moreover, about one-fifth of the studied neonates suffered from considerable weight loss. The studied neonates were admitted to the hospital mainly due to RH incompatibility, followed by ABO incompatibility and G6PD deficiency, in that order. The lowest hematocrit level was observed in neonates with RH incompatibility followed by G6PD deficiency, ABO and RH incompatibility, and ABO incompatibility, in that order. Given the high prevalence of jaundice in Asian countries, including Iran, its prevention before and during birth, change of discharge time, emphasis on the appropriate time and place of admission, and accurate diagnosis and management can help address some of the problems afflicting neonates with jaundice and their parents.

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## Conflicts of interest

There are no conflicts of interest.

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