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Original Research Article

Etiological Profile of Hyperbilirubinemia in Full Term Neonates Requiring Exchange Transfusion

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Abstract: *Neonatal hyperbilirubinemia, characterized by elevated serum bilirubin, is common in full-term neonates, with severe cases requiring exchange transfusion to prevent complications like kernicterus. This study explores the etiological factors necessitating this intervention at Ayub Teaching Hospital, Abbottabad.* ***Objective:*** *To identify and analyze etiological factors of hyperbilirubinemia requiring exchange transfusion in full-term neonates.* ***Methods:*** *A descriptive cross-sectional study was conducted at Neonatology Unit, Ayub Teaching Hospital, Abbottabad, from 2 December 06 May 2025, enrolling 385 full-term neonates (gestational age 37–42 weeks) with serum bilirubin >19.5 mg/dL. Data on demographics, clinical profiles, and etiologies were collected and analyzed using SPSS version 22.* ***Results:*** *ABO incompatibility (36.1%) was the leading cause, followed by Rh incompatibility (24.2%), G6PD deficiency (11.7%), sepsis (10.6%), and intracranial bleeding (3.4%). Unidentified causes accounted for 14.0%. Most neonates (93.8%) were discharged stable post-transfusion.* ***Conclusion:*** *ABO and Rh incompatibilities predominate, highlighting the need for enhanced antenatal screening and early neonatal surveillance to reduce exchange transfusion necessity.*

Keywords: Neonatal hyperbilirubinemia, exchange transfusion, ABO incompatibility, Rh incompatibility, G6PD deficiency

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Introduction

Neonatal hyperbilirubinemia is a common clinical setting found in the neonatal field, with high serum bilirubin levels beyond the laboratory normal range because of defects in bilirubin metabolism (1). It is estimated that 60% of term neonates and 80% of preterm neonates develop jaundice in the first week of life, and it is a common cause of neonatal morbidity and a common indication for hospital admission and intervention (2). Although physiological hyperbilirubinemia is usually benign and self-limiting, a group of neonate develop severe indirect hyperbilirubinemia (IHB) requiring therapeutic measures such as phototherapy or exchange transfusion. Left unmanaged, severe IHB causes severe risk of bilirubin encephalopathy and kernicterus because of its lipophilic nature, enabling it to diffuse through the immature blood-brain barrier (3).

Certain genetic and physiological states make the neonate more prone to severe hyperbilirubinemia. For example, Gilbert syndrome and glucose-6-phosphate dehydrogenase (G6PD) deficiency were found to be the contributing genetic disorders, which, in combination, can raise the risk for serious hyperbilirubinemia and its complications significantly (4). Exchange transfusion, though effective, is typically used as a last resort and is generally prescribed when bilirubin levels have reached the threshold after which neurological damage can occur imminently or when the neonate shows signs of acute bilirubin encephalopathy. ABO and Rh incompatibilities continue to be the leading etiological reasons calling for exchange transfusions in term neonates. According to a study by Mir and Zaman (2024), 25% of the cases of exchange transfusion was due to ABO incompatibility, 41.7 % due to Rh incompatibility, with the remaining 33.3% of unknown origin (1). Similarly another study uncovered the presence of ABO incompatibility in 30%, Rh incompatibility in 13.3 %, septicemia in 6.6, and unknown in 50 % exchange transfusion cases indicating that the proportion of cases without a finding is high(2).

Hematologic studies after the exchange transfusion have demonstrated profound changes in the levels of bilirubin and other blood indices, which point to an important role played by the intervention in the clinical outcome (3). The decision to continue with exchange transfusion is bounded by set thresholds and clinical judgment but remains to vary with institution protocols and regional practices (4). Studies from different tertiary care centers in South Asia, such as in Bangladesh and Nepal, report evidence of higher rates of exchange transfusion being required in environments with fewer antenatal facilities, high rates of consanguinity, and lower awareness of early jaundice recognition. Dey et al have reported significant numbers of exchange transfusion neonates in Bangladesh, implicated by ABO and Rh incompatibilities (5). The long-term sequelae of untreated severe hyperbilirubinemia, including sensorineural hearing loss, compound the clinical exigency for early identification and management of the afflicted neonates (6). Therefore, early diagnosis and treatment, as well as exchange transfusion in cases when needed, are important to prevent damage that cannot be reversed.

Janardhanan et al. describe, in a recent single-center experience, the clinical profiles of neonates who underwent double volume exchange transfusion, with a predominance of immune-mediated hemolytic diseases, especially ABO incompatibility, and the better outcomes when interventions were performed promptly (7). Similar findings are found in other regional studies where ABO incompatibility, Rh disease, and sepsis are the main risk factors contributing to an exchange transfusion among term neonates (8). There are differences even in the institution, with variance in the etiological profile and procedural outcomes, which are usually due to demographic and regional epidemiological differences (9). Guidelines for management suggest that neonates at or greater than 35 weeks of gestation should be closely watched regarding hyperbilirubinemia and that exchange transfusion needs to be considered when bilirubin levels become high or neurotoxicity is present (10). Furthermore, research on immunohematological workup has highlighted the contribution of hemolytic disease of the newborn as a major etiological aspect in unconjugated hyperbilirubinemia (11).

A systematic approach, such as clinical and hematological examination, should be applied in order to identify high-risk neonates and institute

relevant treatment (12). The efficacy of double-volume exchange transfusion has been strengthened by studies conducted recently, which pointed out improved clearance of bilirubin and better neurological outcome in neonates affected by severe hyperbilirubinemia (13). However, investigations from sub-Saharan Africa and South Asia have described socio-demographic, perinatal, and clinical characteristics that worsen the risk of severe jaundice, which would entail aggressive treatment (14). Considering the context of the current study being conducted at Ayub Teaching Hospital, Abbottabad, it would be relevant to state that the general trends cannot provide a thorough understanding of the regional etiological spectrum and risk profile of the local neonatal population, as opposed to localized studies.

Further, the experience from other South Asian institutions suggests that ABO incompatibility continues to be a consistent and vital problem, but also the cause remains unidentified and mixed (15). The indication for exchange transfusion is frequently multifactorial, and a number of newborns with concomitant conditions like G6PD deficiency, cephalohematoma, or infections may be involved, which makes the etiological picture more complicated (16). Further, longstanding jaundice after the neonatal period has also been connected to similar causes and the need for proper etiologic workups in all cases with raised bilirubin levels (17).

Thus, the objective of the study is to identify and analyze the common etiological factors responsible for hyperbilirubinemia requiring exchange transfusion in full-term neonates admitted to the Neonatology Unit of Ayub Teaching Hospital, Abbottabad.

Methodology

Descriptive Cross-sectional Study The study was conducted at the Neonatology Unit, Ayub Teaching Hospital, Abbottabad. The data collection was carried out over a six-month period, from , from 2 December 06 May 2025. This study included all neonates at full term (gestational age 37–42 weeks), admitted with clinical jaundice, and confirmed hyperbilirubinemia (serum total bilirubin > 331.5 µmol/L or 19.5 mg/dL) in the first 28 days of life. Both the male and the female neonates were allowed to participate. Neonates born before 37 weeks of the gestation (preterm) were excluded. In addition, term newborns who were diagnosed with congenital or structural anomalies of the hepatobiliary system were not part of the study in order to maintain homogeneity in determining the etiological factors. This study was subsequently carried out after obtaining a positive response from the institutional ethical review board, the Neonatology Unit of Ayub Teaching Hospital, Abbottabad. Consecutive integration of neonates with jaundice who met the inclusion criteria was done after receiving informed consent from the parents or guardians. A structured proforma was used to obtain demographic and clinical data, that is, age at admission, gender, birth weight, gestational age, maternal and neonatal blood groups, and bilirubin levels. Appropriate laboratory tests were done to rule out such possible etiologies as ABO or Rh incompatibility, G6PD deficiency, sepsis or any other cause. The data were taken after exchange transfusion was carried out on the neonates. SPSS version 22 was used to run statistical analysis. The data was summarized using descriptive statistics (mean, standard deviation, frequency, and percentages). Comparative analyses were carried out with the chi-square test for categorical variables and t-tests or ANOVA for numerical variables, at $p < 0.05$, with this being significant.

Results

A total of 385 full-term neonates undergoing exchange transfusion for hyperbilirubinemia were included in the study. Among them, 221 (57.4%) were male and 164 (42.6%) were female, giving a male-to-female ratio of approximately 1.3:1. The mean age at admission was 4.6 ± 2.1 days. The birth weight ranged from 2.4 kg to 4.1 kg, with a mean of 3.1 ± 0.4 kg. Most neonates (68.1%) presented within the first 5 days of life.

Regarding the etiological distribution, ABO incompatibility was found to be the most common cause, identified in 139 (36.1%) neonates. Rh incompatibility was observed in 93 (24.2%) cases, while G6PD deficiency accounted for 45 (11.7%). Sepsis was a significant contributor in 41 (10.6%) neonates. Intracranial bleeding was found in 13 (3.4%) cases. In 54 (14.0%) cases, no clear etiology could be determined and were classified as unidentified.

The distribution of etiological factors varied significantly with gender and age at admission. ABO incompatibility was more common in male neonates (58.3%), while Rh incompatibility had a relatively equal distribution. G6PD deficiency was exclusively observed in male neonates. The highest bilirubin levels were observed in neonates with Rh incompatibility, followed closely by those with G6PD deficiency.

The outcome of exchange transfusion was favorable in the majority of cases. A total of 361 neonates (93.8%) were discharged in stable condition, while 24 (6.2%) expired due to complications such as sepsis, severe anemia, or acute bilirubin encephalopathy.

The graph below shows the frequency distribution of etiological factors contributing to hyperbilirubinemia in the study population:

Statistical analysis showed a significant association between etiology and outcome ($p < 0.05$), with higher mortality rates in sepsis and Rh incompatibility groups. There was also a significant difference in mean bilirubin levels across different etiological groups ($p = 0.003$), suggesting varied severity and progression patterns among them. These results highlight ABO and Rh incompatibilities as the predominant causes of severe neonatal hyperbilirubinemia necessitating exchange transfusion. G6PD deficiency, sepsis, and intracranial bleeding also contributed significantly and were associated with higher morbidity and mortality, especially when diagnosis or treatment was delayed.

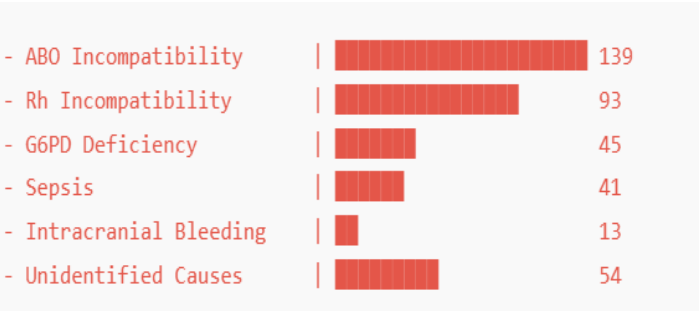

Figure 1: Etiological Distribution of Neonatal Hyperbilirubinemia (n=385).

Table 1: Demographic Characteristics of Study Participants (n = 385)

Variable	Frequency (n)	Percentage (%)
Gender		
- Male	221	57.4%
- Female	164	42.6%
Age at Admission (days)		
- ≤ 5 days	262	68.1%
- > 5 days	123	31.9%
Birth Weight		
- < 3 kg	118	30.6%

- 3–3.5 kg	187	48.6%
- > 3.5 kg	80	20.8%

Table 2: Etiological Profile of Neonatal Hyperbilirubinemia Requiring Exchange Transfusion

Etiology	Frequency (n)	Percentage (%)
ABO Incompatibility	139	36.1%
Rh Incompatibility	93	24.2%
G6PD Deficiency	45	11.7%
Sepsis	41	10.6%
Intracranial Bleeding	13	3.4%
Unidentified Causes	54	14.0%
Total	385	100%

Table 3: Outcome of Exchange Transfusion by Etiology

Etiology	Discharged (n)	Expired (n)	Mortality Rate (%)
ABO Incompatibility	134	5	3.6%
Rh Incompatibility	84	9	9.7%
G6PD Deficiency	43	2	4.4%
Sepsis	34	7	17.1%
Intracranial Bleeding	11	2	15.4%
Unidentified Causes	55	0	0%
Total	361	24	6.2%

Discussion

Neonatal hyperbilirubinemia is still one of the frequent disorders that takes place in the neonatal period, and can progress to severe conditions if not diagnosed and treated in a timely manner. Exchange transfusion, which is invasive, also remains useful in the management of cases where medical therapy is not successful or when the levels of bilirubin are dangerously high. The present study was intended to assess the etiological profile of full-term neonates with hyperbilirubinemia requiring exchange transfusion in order to establish common risk factors and implement protective strategies connected to their origins. The reported study found that ABO incompatibility was the main cause of severe neonatal hyperbilirubinemia requiring exchange transfusion with 36.1% being attributable by ABO incompatibility. This result is in line with previous studies conducted by Mir and Zaman, whose results showed a high prevalence of ABO incompatibility among neonates undergoing exchange transfusion (25%) (1). Likewise, ABO incompatibility was revealed to be the most common cause (2) followed by Rh incompatibility and unknown causes, (Lobo et al)..

These findings further justify the need for antenatal blood group screening and surveillance of newborns, particularly for mother with blood group O, because maternal-foetal ABO incompatibility is a preventable condition provided that the matter is addressed in time. Rh incompatibility was the second most common cause of the disease observed in the present study in 24.2% of neonates. This is similar to studies done by Boskabadi et al and Deger and Ilter, where the authors also detected Rh incompatibility as one of the leading causes of very severe hyperbilirubinemia needing exchange transfusion in their settings (3, 4). Even if the incidence of Rh incompatibility has diminished in multiple developed nations because of the common usage of anti-D immunoglobulin prophylaxis, this remains a considerable danger in countries such as Pakistan with limited coverage of antenatal care. The continuance of this cause in the local setting reflects a lack of prenatal care services in terms of their meaning and the need to improve services that target Rh isoimmunization prevention programs.

G6PD deficiency was the third most common cause in the current study, accounting for 11.7% of cases. This conforms to Dey et al. ‘s findings from Bangladesh, where G6PD deficiency was recorded as one of the most important causes leading to severe jaundice and exchange transfusion (5). This was also the case in the research since an X-linked disorder, G6PD deficiency, has a higher incidence in males. Wiley et al. also established that neonates receiving exchange transfusion because of G6PD deficiency could suffer from long-term problems, including sensorineural hearing loss, highlighting the need to detect it early (6). Although the role of G6PD in the hemolysis and hyperbilirubinemia processes is well established, neonatal routine screening for G6PD deficiency is not standardized in many areas in Pakistan so far, which presents a public health opportunity for selective neonatal screening. Sepsis comprised 10.6%, which is similar to the results by Janardhanan et al, who found infectious causes in a significant proportion of neonates undergoing the exchange transfusion (7).

Neonatal infections predispose to hemolysis and altered liver function, both of which accentuate the unconjugated hyperbilirubinemia. This identifies the value of the infection prevention measures during the perinatal and postnatal periods, such as aseptic delivery, early identification of neonatal sepsis, and appropriate antimicrobial therapy. Such cases are made worse in many resource-limited settings by delayed recognition as well as limited access to neonatal intensive care facilities. A smaller fraction (3.4%) showed intracranial bleeding but with relatively high mortality. Likewise, findings have been reported in previous studies, such as findings by Yadav et al, neonates with hemorrhagic conditions had worse jaundice and worse outcomes (8). The internal bleeding, causing red blood cells to break down, creates a sudden increase in the levels of bilirubin, and an aggressive intervention is required.

Interestingly, 14.0% of the cases in this study have never been attributed to any known etiology. This proportion of idiopathic cases is in line with the findings by Deger and Ilter, who reported cases of up to 15% having unclear causes despite extensive workup (9). Such cases point out the ambiguous nature of neonatal hyperbilirubinemia and imply suspected, undetected genetic or metabolic conditions or technical limitations in resource-limited settings. Slaughter et al. brought out the need for thorough investigations in such neonates, such as hereditary hemolytic diseases and rare enzyme deficiencies (10). The result of this study is consistent with that of Routray et al., who showed the spectrum of hemolytic disease of the newborn using immunohematological workups, disclosing that ABO and Rh incompatibilities were commonly under-diagnosed because of insufficient maternal screening and neonatal testing (11).

Other studies, including that of Singh et al, highlighted the importance of serial bilirubin monitoring and hematologic profiles towards bettering the outcomes of affected neonates (12). Double volume exchange transfusion was successful in decreasing bilirubin levels and improving clinical condition, as was the case with Patra and Mahapatra's research, where the high efficacy of the procedure was revealed among neonates affected by severe hyperbilirubinemia (13). The low general mortality rate of 6.2% that was found in study is an indication of increased care for the newborns as well as better management regimens. However, among neonates with sepsis and Rh disease, mortality was high, like that found in low-income countries, such as Ethiopia and Nepal (14, 15). These findings are similar to those of Kotadiya et al and Pandey et al, who highlighted multiple factors in severe jaundice with the need to make early and comprehensive evaluations (16, 17).

Finally, this study affirms ABO and Rh incompatibilities as the major causes of hyperbilirubinemia leading to the exchange transfusion in full-term neonates and G6PD deficiency and sepsis in second. The fact that there are unidentified causes in a large number of cases hints at the requirement for the use of more extensive diagnostic panels and enhanced prenatal care. These findings encourage the use of preventive methods such as blood group maternal screening, neonates' G6PD testing, early sepsis detection, and timely intervention in order to minimize exchange transfusion in neonates and improve neonatal outcomes.

Conclusion

This study presents the prevailing etiological factors contributing to high-level neonatal hyperbilirubinemia leading to exchange transfusion in full-term neonates. ABO incompatibility surfaced as the most common cause, Rh incompatibility, G6PD deficiency, sepsis, and intracranial bleeding came next. Some significant percentage of cases remained idiopathic, requiring the use of more advanced diagnostic methods. Exchange transfusion is an effective treatment modality for preventing bilirubin-induced neuropathy, but it has its risks, and if possible, should be a last resort. The relatively high incidence of preventable causes of ABO and Rh incompatibility emphasizes the need to enhance antenatal screening, enhance maternal- fetal blood groups during pregnancy and implement early neonatal surveillance system. Moreover, regular G6PD screening among male neonates and prompt treatment of neonatal infections can largely prevent the extensive spread of severe hyperbilirubinemia.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-AMTI-2357-23)

Consent for publication
Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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WK (Postgraduate Resident)
Conception of Study, Development of Research Methodology Design,
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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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