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Comparison of Phototherapy and Exchange Transfusion Thresholds According to the Turkish Neonatology Society and the 2022 American Academy of Pediatrics Guidelines in Neonates with Indirect Hyperbilirubinemia

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Comparison of Phototherapy and Exchange Transfusion Thresholds According to the Turkish Neonatology Society and the 2022 American Academy of Pediatrics Guidelines in Neonates with Indirect Hyperbilirubinemia

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Highlights

What are the main findings?

- Phototherapy and exchange transfusion thresholds were significantly higher when calculated according to the 2022 American Academy of Pediatrics guideline compared with the Turkish Neonatology Society guideline.
- A substantial proportion of neonates hospitalized for indirect hyperbilirubinemia met admission criteria according to the national guideline but not according to the 2022 American Academy of Pediatrics guideline.

What are the implications of the main findings?

- Differences between national and international guidelines may lead to considerable variation in hospitalization practices in neonatal intensive care units.
- Real-life comparative data may support future evaluations of guideline-based management strategies for neonatal hyperbilirubinemia.

Abstract

Background: Clinical management of neonatal indirect hyperbilirubinemia relies on guideline-based thresholds for phototherapy and exchange transfusion. In 2022, the American Academy of Pediatrics (AAP) updated its guideline, raising treatment thresholds for neonates born at ≥35 weeks of gestation. In Türkiye, clinical practice is guided by the Turkish Neonatology Society (TNS) guideline, which applies lower treatment thresholds. **Methods:** This single-center, retrospective cross-sectional study included neonates born at ≥35 weeks of gestation who were admitted to a neonatal intensive care unit solely due to indirect hyperbilirubinemia. Phototherapy and exchange transfusion thresholds were calculated according to both the TNS guideline and the 2022 AAP guideline. Guideline compliance and admission indications were compared. Statistical analyses were performed using appropriate non-parametric tests. **Results:** A total of 344 neonates were included in the analysis. Mean phototherapy and exchange transfusion thresholds were significantly higher according to the AAP 2022 guideline compared with the TNS guideline ($p < 0.001$ for both). While 89.2% of admissions were compliant with the TNS guideline, only 36.6% met the admission criteria based on the AAP 2022 guideline. Approximately 64.4% of hospitalized neonates did not have an admission indication according to the AAP 2022 recommendations. **Conclusions:** Substantial differences exist between national and international guidelines for the management of neonatal indirect hyperbilirubinemia. These differences significantly influence treatment thresholds and hospitalization practices. Real-life comparative data may contribute to future evaluations of guideline-based management strategies.

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1. Introduction

Neonatal jaundice remains one of the most common causes of hospital admission during the early postnatal period. Although the majority of cases are benign and self-limited, severe indirect hyperbilirubinemia may lead to bilirubin-induced neurological dysfunction (BIND) and kernicterus if not recognized and treated appropriately [1]. Therefore, timely identification and management of hyperbilirubinemia continue to be a critical component of neonatal care. Clinical decision-making in neonatal hyperbilirubinemia relies heavily on guideline-based treatment thresholds for phototherapy and exchange transfusion. These thresholds aim to balance the prevention of bilirubin neurotoxicity against the risks and burdens associated with overtreatment, including unnecessary hospital admissions, prolonged hospitalization, parental anxiety, and increased healthcare costs [1,2]. Consequently, updates to international guidelines have significant implications for daily clinical practice.

In 2022, the American Academy of Pediatrics (AAP) updated its clinical practice guideline for the management of hyperbilirubinemia in infants born at ≥35 weeks of gestation [3]. Compared with previous recommendations, the updated guideline raised both phototherapy and exchange transfusion thresholds, reflecting accumulating evidence that higher bilirubin levels may be tolerated safely in selected neonates without increasing the risk of neurotoxicity [3,4]. In addition, the AAP emphasized individualized risk assessment, incorporating gestational age and specific neurotoxicity risk factors into treatment decisions.

In Türkiye, neonatal hyperbilirubinemia is managed according to the national guideline published by the Turkish Neonatology Society (TNS) [5]. While this guideline has been widely adopted in clinical practice, it differs from the updated AAP recommendations, particularly regarding treatment thresholds for phototherapy and exchange transfusion. These differences may lead to variation in admission practices and treatment decisions, especially in neonatal intensive care units (NICUs).

To date, real-life comparative data evaluating the impact of these two guidelines on clinical practice are limited. In particular, there is a lack of studies assessing how differences in treatment thresholds translate into hospital admission rates among neonates with indirect hyperbilirubinemia [6].

The aim of this study was to compare phototherapy and exchange transfusion thresholds according to the TNS guideline and the 2022 AAP guideline in neonates born at ≥35 weeks of gestation who were admitted to a NICU with indirect hyperbilirubinemia. By evaluating guideline compliance and potential differences in admission indications, we sought to highlight the clinical implications of applying national versus updated international recommendations in routine neonatal care.

2. Materials and Methods

Study Design and Setting

This study was designed as a single-center, retrospective cross-sectional analysis. The study was conducted in the Neonatal Intensive Care Unit (NICU) of HSU İzmir Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital, a tertiary referral center. Medical records of neonates hospitalized with a diagnosis of indirect hyperbilirubinemia were reviewed.

Study Population

Neonates admitted to the NICU between the predefined study period were screened using relevant ICD-10 diagnostic codes. Infants born at ≥35 weeks of gestation who were hospitalized solely due to indirect hyperbilirubinemia were eligible for inclusion.

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Inclusion criteria were:

- Gestational age ≥35 weeks
- Admission to the NICU due to indirect hyperbilirubinemia
- Absence of major comorbid conditions
- Exclusion criteria included:
- Presence of additional systemic diseases
- Incomplete medical records
- Admission for reasons other than indirect hyperbilirubinemia

After applying inclusion and exclusion criteria, a total of 344 neonates were included in the final analysis.

Data Collection

Demographic, clinical, and laboratory data were obtained from electronic medical records and patient files. The following variables were recorded: gestational age, birth weight, sex, postnatal age at admission, feeding type, duration of hospitalization, and duration of phototherapy.

Laboratory parameters included total serum bilirubin (TSB) levels at admission, direct Coombs test results, blood group incompatibilities (ABO and Rh), reticulocyte count, C-reactive protein (CRP), thyroid function tests (TSH and free T4), glucose-6-phosphate dehydrogenase (G6PD) deficiency status, blood culture results, and presence of urinary tract infection.

Guideline-Based Assessment

For each patient, phototherapy and exchange transfusion thresholds were calculated according to both the Turkish Neonatology Society (TNS) guideline and the 2022 American Academy of Pediatrics (AAP) guideline, based on gestational age, postnatal age, and presence of neurotoxicity risk factors. Compliance with each guideline was evaluated by determining whether the measured TSB level at admission met the respective phototherapy or exchange transfusion thresholds. Guideline-based admission indication rates were compared between the two recommendations.

Outcomes

The primary outcome was the difference in phototherapy and exchange transfusion thresholds between the TNS and AAP 2022 guidelines. Secondary outcomes included guideline compliance rates and potential differences in admission indications according to gestational age.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normal distribution using the Shapiro–Wilk test. Data were presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were expressed as numbers and percentages. Paired comparisons of phototherapy and exchange transfusion threshold values between the two guidelines were conducted using the Wilcoxon signed-rank test. Comparisons of hospitalization and phototherapy durations across gestational age groups were performed using the Kruskal–Wallis test. A p-value <0.05 was considered statistically significant.

3. Results

A total of 510 neonates admitted to the neonatal intensive care unit during the study period were initially screened. Of these, 100 neonates were excluded due to unavailable medical records and 66 neonates did not meet the inclusion criteria. Consequently, a total of 344 neonates born at ≥35 weeks of gestation and hospitalized solely due to indirect hyperbilirubinemia were included in the final analysis.

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3.1. Baseline Characteristics

The baseline demographic and clinical characteristics of the study population are summarized in Table 1. The mean gestational age of the included neonates was 37.7 ± 1.43 weeks, and the mean birth weight was 3234.6 ± 1372.5 g. Of the infants, 54.4% were male. The median postnatal age at admission for jaundice was 5 days. The mean total serum bilirubin level at initiation of treatment was 17.88 ± 4.92 mg/dL. The mean duration of hospitalization was 4.46 ± 3.21 days, and the mean duration of phototherapy was 17.52 ± 10.87 hours (Table 1).

3.2. Clinical and Laboratory Findings

Categorical clinical and laboratory characteristics are presented in Table 2. ABO incompatibility was present in 21.5% of the neonates, while Rh incompatibility was observed in 6.1%. Direct Coombs test positivity was detected in 7.3% of cases. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was identified in 9.7% of the neonates. Blood culture positivity was detected in 2.6% of cases; however, these results were interpreted as contamination. Urinary tract infection was identified in 13.4% of the infants. Exchange transfusion was performed in 2.0% of the study population. The majority of neonates (89.0%) were exclusively breastfed (Table 2).

3.3. Comparison of Guideline Thresholds

Phototherapy and exchange transfusion threshold values according to the Turkish Neonatology Society (TNS) and the American Academy of Pediatrics (AAP) 2022 guidelines are shown in Table 3.The mean phototherapy threshold according to the TNS guideline was 15.83 ± 2.46 mg/dL, whereas the mean phototherapy threshold according to the AAP 2022 guideline was 19.61 ± 2.31 mg/dL. This difference was statistically significant ($p < 0.001$). Similarly, the mean exchange transfusion threshold was 20.43 ± 2.43 mg/dL according to the TNS guideline and 25.76 ± 1.57 mg/dL according to the AAP 2022 guideline, demonstrating a statistically significant difference ($p < 0.001$) (Table 3).

3.4. Guideline Compliance

Among the 344 neonates admitted due to indirect hyperbilirubinemia, 307 infants (89.2%) met the admission criteria according to the TNS guideline. In contrast, only 126 infants (36.6%) met the admission criteria based on the AAP 2022 guideline. When compliance with the two guidelines was evaluated according to gestational age, approximately 64.4% of the hospitalized neonates did not have an indication for admission according to the AAP 2022 guideline.

Table 1. The baseline demographic and clinical characteristics of the study population.

Variable	n	Mean	SD	25th percentile	Median	75th percentile
Gestational age (weeks)*	344	37.74	1.43	37.00	38.00	39.00
Birth weight (g)*	344	3234.6	1372.5	2826.3	3161.0	3468.8
Postnatal age at admission (days)*	344	6.30	5.08	3.00	5.00	7.00
TSH (mIU/L)*	321	4.99	4.29	2.26	3.75	6.37
Free T4 (ng/dL)*	324	1.62	0.43	1.31	1.56	1.91
CRP (mg/dL)*	344	0.16	0.34	0.02	0.06	0.13
Total serum bilirubin at treatment initiation (mg/dL)*	344	17.88	4.92	15.60	17.50	19.57
Length of hospital stay (days)*	344	4.46	3.21	2.00	3.00	5.00
Duration of phototherapy (hours)*	344	17.52	10.87	10.00	15.00	24.00
Reticulocyte count (%)*	342	2.80	2.40	1.13	2.00	3.79

* Continuous variables are presented as mean ± standard deviation and percentiles.

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Table 2. Categorical clinical and laboratory characteristics of the study population.

Variable	Category	n	%
Sex*	Male	187	54.4
	Female	157	45.6
ABO incompatibility*	Absent	270	78.5
	Present	74	21.5
Rh incompatibility*	Absent	323	93.9
	Present	21	6.1
Direct Coombs test*	Negative	319	92.7
	Positive	25	7.3
Blood culture positivity*	Absent	335	97.4
	Present	9	2.6
G6PD deficiency*	Absent	307	90.3
	Present	33	9.7
Urinary tract infection*	Absent	297	86.6
	Present	46	13.4
Exchange transfusion*	Not performed	337	98.0
	Performed	7	2.0
Breastfeeding*	No	38	11.0
	Yes	306	89.0
Formula feeding*	No	306	89.0
	Yes	38	11.0

* Categorical variables are presented as number (percentage).

Table 3. Comparison of phototherapy and exchange transfusion thresholds according to guidelines.

Variable	n	Mean	SD	25th percentile	Median	75th percentile	p-value*
TNS phototherapy threshold (mg/dL)*	344	15.83	2.46	15.00	15.70	18.00	<0.001
AAP 2022 phototherapy threshold (mg/dL)*	344	19.61	2.31	19.00	20.00	21.00	
TNS exchange transfusion threshold (mg/dL)*	344	20.43	2.43	19.00	21.00	22.50	<0.001
AAP 2022 exchange transfusion threshold (mg/dL)*	344	25.76	1.57	25.50	26.00	27.00	

* Paired comparisons between guideline thresholds were performed using the Wilcoxon signed-rank test.

4. Discussion

In this retrospective cross-sectional study, we compared phototherapy and exchange transfusion thresholds defined by the Turkish Neonatology Society (TNS) guideline and the updated 2022 American Academy of Pediatrics (AAP) guideline in neonates born at ≥35 weeks of gestation who were admitted to a neonatal intensive care unit due to indirect hyperbilirubinemia. The main finding of our study is the substantial difference between the two guidelines in terms of treatment thresholds and, consequently, admission indications. Our results demonstrate that both phototherapy and exchange transfusion thresholds were significantly higher when calculated according to the AAP 2022 guideline compared with the TNS guideline. This finding is consistent across the entire study population and reflects the more conservative approach of the national guideline in comparison with the updated international recommendations (1,2,7). One of the most striking observations in our study is the marked difference in guideline compliance rates. While the majority of neonates admitted with indirect hyperbilirubinemia met the admission criteria according to the TNS guideline, less than half of these admissions were compliant with the AAP 2022 guideline. Furthermore, when evaluated according to gestational age, approximately two-thirds of the hospitalized neonates did not meet the admission criteria based on the AAP 2022 recommendations. This discrepancy suggests that the use of different guidelines may significantly influence hospitalization practices in neonatal intensive care

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units (1,2,8). National guidelines for the management of neonatal hyperbilirubinemia have traditionally adopted a more conservative approach, largely driven by the desire to minimize the risk of bilirubin-induced neurological dysfunction and kernicterus (9). Given the potentially irreversible consequences of severe hyperbilirubinemia, earlier initiation of treatment and lower intervention thresholds may be favored to maximize patient safety (10). This cautious strategy, while prioritizing neuroprotection, may also lead to increased rates of phototherapy initiation and NICU admissions, particularly in settings where close outpatient follow-up may be challenging (11,12).

In contrast, the 2022 AAP guideline emphasizes an individualized, risk-based approach by incorporating gestational age and specific neurotoxicity risk factors into treatment decisions. The upward revision of treatment thresholds reflects growing evidence that higher bilirubin levels can be safely tolerated in selected neonates when appropriate monitoring and follow-up are ensured (13). Importantly, available data indicate that the implementation of higher thresholds has not been associated with an increased incidence of bilirubin-related neurological complications, supporting the safety of this approach. The observed differences between the two guidelines may also have implications for healthcare resource utilization. Admission to a neonatal intensive care unit is associated with increased healthcare costs, longer hospital stays, and separation of the newborn from the family (14,15). In this context, our finding that a substantial proportion of admitted neonates did not meet AAP 2022 admission criteria suggests that guideline selection may influence not only clinical management but also NICU workload and family-centered outcomes. Nevertheless, patient safety remains the primary concern, and any reduction in hospitalization should be accompanied by reliable systems for early detection, monitoring, and follow-up.

This study has several strengths, including a relatively large sample size and the use of real-life clinical data from a tertiary neonatal intensive care unit. However, certain limitations should be acknowledged. The retrospective and single-center design may limit the generalizability of the findings. In addition, long-term neurological outcomes were not assessed, which precludes direct evaluation of neurodevelopmental safety associated with different treatment thresholds.

5. Conclusions

In conclusion, our study demonstrates significant differences between national and international guidelines in the management of neonatal indirect hyperbilirubinemia. These differences have important implications for hospitalization practices and resource utilization in neonatal care. The findings may contribute to future discussions regarding guideline evaluations and support consideration of evolving international evidence in national clinical practice.

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