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A Clinico-Pathological Study Of Unconjugated Hyperbilirubinemia In Neonates And Its Outcome In A Tertiary-Care Hospital

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ABSTRACT

Background: Unconjugated hyperbilirubinemia (UHB) affects 60-80 % of term and pre-term neonates worldwide and remains a leading, yet preventable, cause of kernicterus and long-term neuro-developmental disability [1, 2]. Local data identifying modifiable risk factors are essential to optimise guideline-driven care.

Methods: We conducted a prospective, descriptive study of 100 consecutive neonates (day 1–28) admitted with clinically apparent jaundice to the NICU/SNCU of Malda Medical College, India, over 12 months. Detailed maternal–infant histories, physical examinations, and targeted laboratory/radiologic investigations were performed. Total serum bilirubin (TSB) trajectories were plotted against the 2004 AAP nomogram. Management, including phototherapy and exchange transfusion (ET), followed institutional protocols. Outcomes (discharge, neurologic status, mortality) were documented at discharge and at 3-month follow-up.

Results: Seventy-two per cent of infants were inborn; 57 % were male; 21 % were pre-term. ABO incompatibility (65 %) and Rh iso-immunisation (16 %) were the dominant aetiologies, followed by G6PD deficiency (8 %). Mean (±SD) admission TSB was 21.3 ± 3.8 mg/dL; mean peak TSB 23.5 ± 5.0 mg/dL. Twenty-six per cent required ET. Higher admission TSB correlated significantly with sepsis, positive DCT, hypocalcaemia and metabolic acidosis ($p < 0.05$). Moderate/severe BIND scores predicted abnormal oto-acoustic emissions, BERA and neuro-imaging, and poorer neuro-developmental outcome (χ^2, $p < 0.05$). Overall mortality was 3 %.

Conclusion: In our setting, haemolytic disease (especially ABO incompatibility) remains the principal driver of hazardous UHB, compounded by sepsis and metabolic derangements. Adherence to the AAP 2004 threshold chart enabled timely ET and limited kernicterus; nevertheless, one-quarter of survivors showed early auditory or neuro-imaging abnormalities. Universal bilirubin screening, strengthened Rh/ABO-matching programmes, and routine G6PD testing could further reduce the burden.

Keywords: *Neonatal jaundice; unconjugated hyperbilirubinemia; ABO incompatibility; exchange transfusion; kernicterus; neuro-developmental outcome.*

1. INTRODUCTION

Neonatal jaundice is ubiquitous, yet its progression to bilirubin-induced neurologic dysfunction (BIND) or kernicterus is largely preventable [1]. The unbound fraction of unconjugated bilirubin crosses the immature blood–brain barrier, depositing predominantly in the basal ganglia [2, 3]. Global modelling attributes ~114 000 neonatal deaths and >63 000 cases of moderate-to-severe disability each year to severe hyperbilirubinaemia, with South-Asia bearing a disproportionate share [4].

Risk stratification algorithms—exemplified by the American Academy of Pediatrics (AAP) nomogram (2004) and its 2022 update—combine pre-discharge TSB or transcutaneous bilirubin values with gestational age and risk factors to guide phototherapy and exchange transfusion [5, 6]. Nonetheless, guideline uptake is inconsistent in low- and middle-income countries (LMICs) where G6PD deficiency, sepsis, and limited access to phototherapy increase the likelihood of late presentation [4, 7].

Indian data are heterogeneous; reported ET rates range from 6 % in urban tertiary units to 20 % in resource-constrained settings [8]. Moreover, auditory pathway injury may occur at TSB levels below classic kernicteric thresholds [9]. Few Indian studies have correlated AAP-based management with short-term neurosensory outcomes using objective tools such as oto-acoustic emission (OAE), brain-stem evoked response audiometry (BERA) and MRI.

Against this background, we undertook a clinico-pathological assessment of neonates admitted with UHB to a tertiary-care hospital in eastern India, with three objectives: (i) to quantify the relative contribution of recognised aetiologies; (ii) to evaluate outcomes against the AAP 2004 chart; and (iii) to explore early-life neurologic sequelae. We hypothesised that haemolytic aetiologies would predominate and that elevated BIND scores on admission would predict adverse auditory/neuro-imaging findings at discharge.

2. MATERIALS AND METHODS

Study design and setting: Prospective, observational study conducted in the Level-III NICU and Level-II SNCU of Malda Medical College & Hospital, West Bengal, India, from January 1 to December 31, 2024, after Institutional Ethics Committee approval (Ref MMC/IEC/NEO-23/112).

Participants: All neonates (0–28 days) with clinically significant jaundice were screened. Inclusion criteria were TSB exceeding age-specific visual thresholds; both in-born and out-born infants were eligible. Exclusion criteria encompassed conjugated hyperbilirubinaemia (direct bilirubin > 2 mg/dL or > 20 % TSB), moribund neonates dying before evaluation, and parental refusal.

Sample size: A prevalence of neonatal jaundice of 50 %, $\alpha = 0.05$, margin-of-error 10 % yielded N = 96; we enrolled 100 patients for robustness.

Data collection: Standardised proformas captured demographics, perinatal history, breastfeeding status, maternal comorbidities, and family history. Physical assessment included BIND scoring. Investigations comprised complete blood count, reticulocyte count, blood group (mother and infant), direct Coombs' test (DCT), G6PD assay, serum electrolytes, liver function tests, arterial blood gas, sepsis screen, and TSB at admission, every 12 h during treatment, post-phototherapy, and pre-/post-ET. Radiologic work-up included cranial USG; MRI brain was reserved for BIND ≥ moderate. OAE and BERA were performed before discharge.

Management protocol: TSB values were plotted on the AAP 2004 nomogram to decide initiation/escalation of phototherapy and the need for ET. Double-surface LED phototherapy units were calibrated weekly; ET employed O-negative packed RBCs reconstituted with fresh frozen plasma. All infants received breastfeeding support and monitoring for hypocalcaemia, hypoglycaemia, and temperature instability.

Outcomes: Primary outcome—distribution of aetiologies of UHB. Secondary outcomes—requirement of ET, complications (e.g., hypocalcaemia, sepsis), in-hospital mortality, auditory/neuro-imaging abnormalities, and neuro-developmental status (good = normal tone and reflexes; poor = abnormal tone/reflexes, seizures, or feeding difficulty) at 3 months.

Statistical analysis: Data were analysed with SPSS v22. Categorical variables are expressed as numbers (%) and compared using χ^2 or Fisher's exact test. Continuous variables are presented as mean ± SD; Student's t-test/ANOVA assessed group differences. A p-value < 0.05 was considered significant.

3. RESULTS

Baseline characteristics

Of the 100 neonates, 72 % were inborn and 28 % referred. Male-to-female ratio was 1.33 : 1. Term infants constituted 74 %, pre-term 19 %, and post-term 7 %. Extreme-low-birth-weight (ELBW) prevalence was 27 % (Table 1). Exclusive breastfeeding (EBF) was practised in 74 %. Common maternal morbidities included pregnancy-induced hypertension (41 %) and gestational diabetes (35 %).

Aetiology and risk factors

ABO incompatibility (mother O, infant A/B) accounted for 65 % of UHB cases, whereas Rh-D iso-immunisation was implicated in 16 %. G6PD deficiency (enzyme activity < 4.6 U/g Hb) was confirmed in 8 % and a positive DCT in 11 % (Figure 1). Non-haemolytic risk factors—sepsis (24 %), hypo-albuminaemia (23 %), hypocalcaemia (24 %), metabolic acidosis (15 %) and anaemia (38 %)—frequently co-existed (Table 2).

Median age at peak TSB was 68 h. Mean admission TSB was 21.3 mg/dL, rising to a peak of 23.5 mg/dL despite phototherapy. Admission TSB was significantly higher in neonates with sepsis (+4.5 mg/dL) or metabolic acidosis (+4.8 mg/dL) ($p = 0.024$ & 0.017, respectively).

Therapeutic interventions and in-hospital outcomes

All infants received intensive phototherapy; 26 % required one exchange transfusion and 4 % required two. ET was strongly

associated with abnormal OAE/BERA and MRI findings (Table 3). Three neonates (3 %) succumbed—two to refractory septic shock and one to acute bilirubin encephalopathy.

Early neuro-developmental follow-up

At 3 months (n = 97 survivors), 24 % exhibited abnormal OAE, 26 % abnormal BERA, and 24 % pathological MRI changes (globus pallidus/subthalamic hyper-intensity or parieto-temporo-occipital dys-myelination). Overall, 28 % demonstrated poor neurologic status (Figure 2). Moderate/severe BIND score on admission predicted every adverse neurosensory outcome ($p < 0.05$, Table 4).

TABLES AND FIGURES

TABLE 1. DEMOGRAPHIC PROFILE OF STUDY NEONATES (N = 100)	
Male : Female	57 : 43
Gestation < 37 weeks	21 (21 %)
Birth weight < 2500 g	42 (42 %)
Mode of delivery—NVD / LSCS / Instrumental	83 / 14 / 3
Multiple gestation (twins)	6 (6 %)

TABLE 2. ASSOCIATION OF SELECTED RISK FACTORS WITH MEAN ADMISSION TSB

Risk factor	Mean TSB (mg/dL)	*p*
Sepsis	25.8	0.024
Hypocalcaemia	23.1	0.010
Metabolic acidosis	26.1	0.017
Positive DCT	25.3	0.019

TABLE 3. EXCHANGE TRANSFUSION VERSUS FOLLOW-UP NEUROSENSORY FINDINGS (N = 26)

Outcome	Abnormal	Normal
OAE	20	6
BERA	19	7
MRI brain	21	5
Neurologic status	22	4

TABLE 4. BIND SCORE AT ADMISSION AND COMPOSITE ADVERSE NEUROLOGIC OUTCOME

BIND category	Poor outcome n/N (%)	χ^2	*p*
Mild (n = 10)	0/10 (0)	62.8	0.019
Moderate (n = 69)	16/69 (23)		
Severe (n = 21)	12/21 (57)		

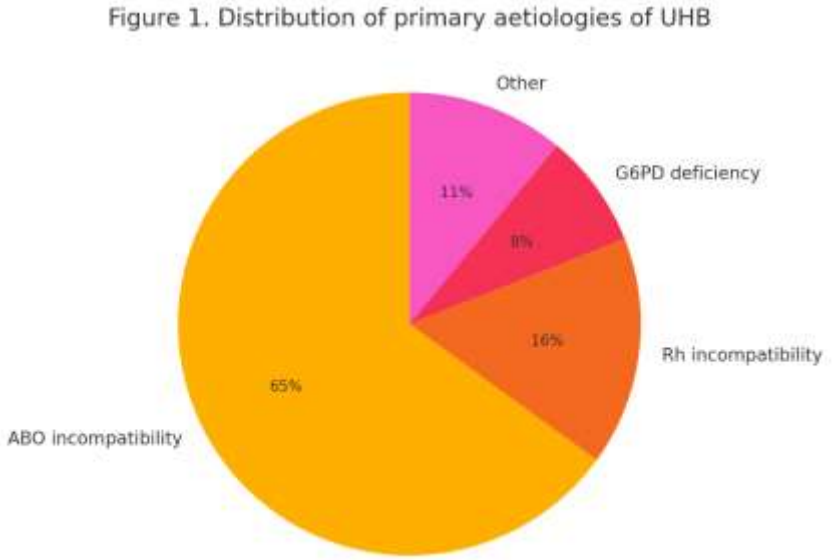

Figure 1. Distribution of primary aetiologies of UHB (ABO 65 %, Rh 16 %, G6PD 8 %, others 11 %).

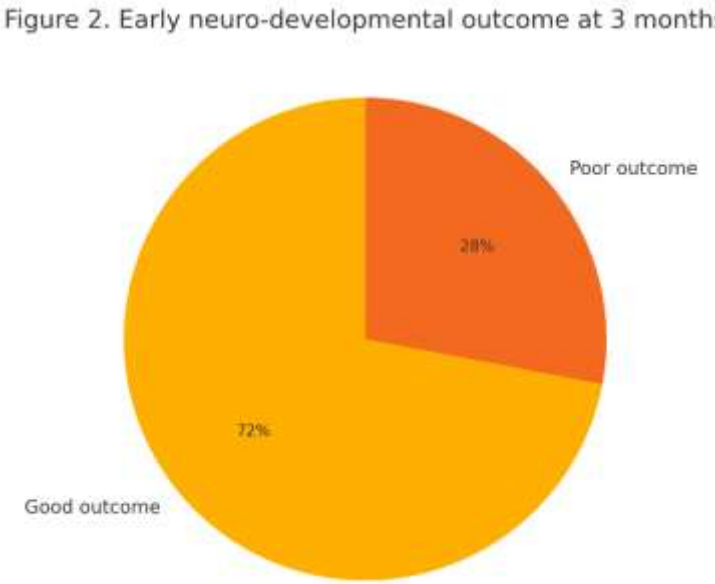

Figure 2. Early neuro-developmental outcome at 3 months (good 72 %, poor 28 %).

4. DISCUSSION

This study affirms that haemolytic disorders, particularly ABO incompatibility, remain the dominant precipitant of significant UHB in Indian tertiary neonatal units, consistent with recent multicentre data from South Asia [10]. The 65 % prevalence we observed exceeds the 40-50 % reported in developed settings [5, 11], underscoring the need for systematic maternal–infant blood-group screening and vigilant post-natal bilirubin surveillance.

Rh iso-immunisation, once the archetype of severe neonatal jaundice, accounted for 16 % of our cases—a decline attributable to improved antenatal anti-D prophylaxis yet still substantial compared with <5 % in high-income countries (HICs) [3, 12]. G6PD deficiency (8 %) mirrors regional allele frequencies and justifies routine newborn enzymatic screening advocated by the WHO [13].

Our mean admission TSB (21.3 mg/dL) and ET rate (26 %) parallel figures reported from resource-constrained African units [14] but surpass those from urban Indian cohorts (<15 %) [8]. Late referral (28 % out-born), sepsis, and metabolic acidosis contributed to higher bilirubin burdens. The observed TSB increment of ~4.5 mg/dL in septic neonates supports synergistic neuro-toxicity mediated by pro-inflammatory cytokines, as demonstrated in rodent models [15].

Importantly, we corroborate the predictive validity of the BIND score: moderate/severe categories were strongly associated with abnormal OAE/BERA, MRI changes and poor clinical outcome, echoing findings by Iskander et al. [16]. While universal auditory screening is mandated in many HICs, its integration into jaundice follow-up protocols in LMICs remains patchy; our 25 % abnormal OAE rate argues for routine implementation.

The AAP 2004 nomogram guided timely ET and likely averted more deaths—mortality was 3 %, below the 5-8 % pooled LMIC estimates [4]. However, one-quarter of survivors manifested early neurosensory deficits, signalling that current TSB thresholds, derived largely from HIC datasets, may underestimate risk when comorbidities are prevalent [17]. The 2022 AAP revision recommends lower treatment thresholds for late pre-terms; whether further adjustment is needed for sepsis-complicated jaundice merits prospective evaluation.

Strengths of our study include complete follow-up, objective auditory/neuro-imaging assessments, and replication of real-world management pathways. Limitations encompass single-centre design, relatively small sample, and lack of long-term neuro-developmental testing beyond three months. Nevertheless, our data furnish actionable insights for similar resource-limited settings.

Future research should explore cost-effective point-of-care bilirubinometry, phototherapy irradiance auditing, and adjunctive neuro-protective agents. Multicentre registries could refine population-specific treatment nomograms incorporating comorbidity weighting.

5. CONCLUSION

In this prospective Indian cohort, two-thirds of severe UHB derived from ABO incompatibility, and one-quarter of affected neonates required exchange transfusion despite intensive phototherapy. Sepsis and metabolic derangements exacerbated bilirubin toxicity, while the BIND score proved a robust bedside predictor of early neurosensory injury. Integration of universal bilirubin screening, targeted prevention of haemolysis, prompt sepsis management, and post-therapy auditory surveillance is imperative to minimise kernicterus. Tailoring AAP treatment thresholds to the LMIC risk milieu warrants further investigation.

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