

# Utility of Serum Bilirubin Screening during the First 24-Hours Following Birth of Pre-Term Neonates <35 Weeks' Gestation

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## Abstract

**Background:** Neonates with severe hyperbilirubinaemia are at increased risk for neurological morbidity. Risk factors for early onset hyperbilirubinaemia include prematurity, red cell haemolysis and birth trauma. As most neonates are asymptomatic and clinical evaluation in detecting early jaundice limited, clinical practice guidelines at the Royal Women's Hospital recommend a serum bilirubin (SBR) level in the first 24 hours following birth for neonates <35 weeks' gestation. Our audit aims to describe the utility of SBR screening in this population.

**Method:** Eligible neonates born between January and October 2015 were identified from the electronic database of the Royal Women's Hospital. Patient demographic data was collected and cross-referenced with the hospital's online pathology system.

**Results:** During the study period there were 432 eligible neonates. SBR samples were taken in 348 (80.7%) in the first 24 hours. These neonates had a median (range) gestation of 31.5 (24.1-34.6) weeks and birth weight 1503 (367-3686) grams. Samples were taken at a median (range) time of 12 (birth-24) hours. Phototherapy (PTx) was indicated in 29 (8.3%) and commenced in 19 (5.5%).

**Conclusions:** Routine SBR testing of neonates <35 weeks' gestation in the first 24-hours of age changes management in only 5% of neonates. Routine blood sampling appears unnecessary and the utility of alternative non-invasive means of measuring bilirubin in this high-risk population should be studied.

**Keywords:** Preterm; Serum bilirubin; Hyperbilirubinaemia; Phototherapy; Transcutaneous bilirubin

**List of Abbreviations:** SBR: Serum bilirubin; PTx: Phototherapy; DCT: Direct Coomb's test; GA: Gestational age; BW: Birth weight; TCB: Transcutaneous bilirubin

## Introduction

Preterm neonates less than 35 weeks' gestational age (GA) commonly have elevated serum bilirubin (SBR) levels. If severe and left untreated, unconjugated hyperbilirubinaemia progressively may result in acute bilirubin encephalopathy and kernicterus [1]. Kernicterus, an end stage manifestation describes permanent bilirubin-induced neurological dysfunction with a spectrum of resultant morbidity including cerebral palsy and neurosensory hearing loss [2]. Neurological injury is secondary to bilirubin binding to the basal ganglia, particularly the globus pallidus and the subthalamic nucleus followed by neuronal necrosis.

The principle pathophysiologic mechanism of hyperbilirubinaemia in neonates involves release of unconjugated bilirubin from increased erythrocytic breakdown and immature hepatobiliary clearance mechanisms. Preterm neonates are inherently at increased risk of hyperbilirubinaemia as they have increased red cell breakdown and decreased hepatic clearance as compared to term neonates [3].

Therapeutic interventions such as phototherapy (PTx) and red blood cell exchange transfusion are available to help reduce SBR levels. Indications for the utilisation of these modalities in neonates greater than 35 weeks' gestation are based on age-specific, percentile based nomograms created in the era of Rhesus isoimmunisation. These are used to aid in decisions regarding when to initiate therapy in order to prevent neurological sequelae. However, in neonates less than 35 weeks' GA, a group potentially at increased risk we have limited data and no randomised controlled trials and we are reliant on consensus guidelines [4,8].

The reasoning behind this lack of evidence-based guidelines is multi-fold. Uncertainty surrounding the variability of clinical manifestations, a lack of reliably predictive measures of bilirubin neurotoxicity and unclear risk-benefit profile of interventions available confounds the picture in this age group [5].

Clinical practice guidelines at The Royal Women's Hospital (RWH), an Australian tertiary newborn care facility, currently recommend that all pre-term neonates <35 weeks' GA have an SBR level taken within 24 hours following birth to determine the need for clinical intervention with PTx or exchange transfusion. Neonates that meet this age criteria have a routine SBR test performed via heel-prick testing within 24 hours of birth regardless of the presence or absence of other known risk factors or clinical findings.

We aimed to audit these guidelines in order to determine the clinical utility of routine SBR sampling in this age group.

## Methodology

Eligible neonates born between 01 January and 21 October 2015 were retrospectively identified from the electronic database of the RWH neonatal nursery. Patient demographic data was collected (GA, time of birth and BW) from this E-database and cross-referenced with the hospital's online pathology system (CLARA).

SBR results were then obtained from the hospital online pathology system. Parameters pertaining to timing of test and result were collected. The result of available Direct Coomb's Testing (DCT) from throughout admissions was also collected. Finally, evidence of significant birth trauma was noted from the discharge summary of each patient.

SBR results obtained were then manually plotted on RWH SBR nomograms, which are in turn referenced from consensus nomograms based on population studies. This was performed in order to determine whether or not intervention was objectively indicated. The E-database was then again referenced to determine whether or not intervention (either PTx or exchange transfusion) was actually implemented.

Sub-analysis was performed for GA-brackets less than 28 weeks' GA, between 28 to less than 32 weeks' and those aged between 32 to less than 35 weeks'. These gestational age brackets were selected as they form part of the hospital's SBR-intervention threshold nomograms, which are based on generally accepted definitions of extreme prematurity (<28 weeks), severe prematurity (28-32 weeks) and moderate prematurity (>32 weeks).

Results collected were analysed as percentage values rounded from two decimal places.

## Results

During the determined study period, there were 431 eligible neonates. Of these, SBR samples were collected from 348 (80.7%) within the first 24 hours of age as per hospital protocol.

Our population had a median (range) gestation of 31+5 (24+1 – 34+6) weeks and a birth weight (range) 1503 (367-3686) grams.

SBR samples were taken at a median (range) time of 12.3 (0-24) hours.

Characterises the 348 neonates in whom a SBR was performed within the first 24 hours of age as per protocol (Table 1).

	PTx not indicated (N=320)	PTx indicated (N=28)	Total DCT positive (N=10)	Total with signs of birth trauma (N=4)
PTx commenced	0	19	2	0
No PTx commenced	320	9	8	4

**Table 1:** Characterises the 348 neonates in whom a SBR was performed

Of the 348 neonates from whom an SBR was collected as per protocol, 29 neonates returned a result that indicated commencement of phototherapy. An analysis of this group is shown in (Table 2).

	PTx commenced (N = 19)	No PTx commenced (N = 10)
Median GA (weeks)	29.3 (25.3-34.6)	29.3 (27.1-32.3)
Median birth weight (grams)	943 (623-2052)	1196 (607-2639)
DCT Positive	2	0
Signs of birth trauma	0	0
Median No. of SBR tests during admission	9 (5-26)	8 (1-11)

**Table 2:** Phototherapy analysis of 29 Neonates

A sub-analysis of our results for gestational age brackets <28, 28<32 and 32<35 weeks was also performed (Table 3).

GA	Number indicated for PTx/Number that had SBR as per guideline (%)	No. actually commenced on PTx/Number that had SBR as per guideline (%)
<28	10/57 (17.5)	8/57 (14.0)
28 ≤ x < 32	14/149 (9.4)	7/149 (4.7)
32 ≤ x < 35	5/142 (3.5)	4/142 (2.8)

**Table 3:** A sub-analysis of gestational age

## Discussion

SBR testing, also known as total bilirubin (TB) testing, is the most frequent laboratory test utilised in the identification of hyperbilirubinaemia in preterm neonates. Algorithms for determining interventional thresholds have been developed based upon birth weight and gestation [5].

Our audit aimed to illustrate the portion of screening SBR tests which actually resulted in management changes as a parameter for determining clinical utility. Our results demonstrate that in the study population, only 29 neonates (8.3%) had intervention indicated as per SBR threshold-treatment nomograms. Furthermore, only 19 (5.5%) actually had management commenced. One is able to note that an exceedingly low proportion of screening tests in this population resulted in management change.

For the remaining 10 neonates who had SBR results indicating phototherapy but were not commenced, this was likely to be a result of individual clinician decision-making based on multiple factors. This cannot be confirmed however, as it did not constitute part of our auditing process.

When a sub-analysis is performed for gestational age brackets as previously described, the trend remains consistent. The most pronounced result was found in neonates aged between 32<35 weeks' GA, whereby only 4 of 143 routine SBR tests (2.8%) effected management changes.

Each SBR test costs the hospital a minimum of \$9.70 AUD, which does not take into account transportation, collection and other logistical costs involved with testing. From this study period, we estimated that a minimum \$3200.00 AUD was spent on routine screening tests that did not change management.

In addition to economic considerations, it is important to consider the effect on the neonatal population directly. For one, the process of heel-prick testing is inherently traumatic to neonates. Studies have demonstrated physiological parameters indicative of stress-response in preterm neonatal groups to heel prick testing including significant variability in heart rate, respiratory rate and transcutaneous gaseous tension [6]. Recall also that preterm neonates have an inherently low birth-weight and that haemoglobin is directly proportional to this. Volumes of blood required for accurate sampling may result in iatrogenic anaemia, which in turn prompts further investigation and management.

Furthermore, as with all investigations, SBR testing is affected by logistical error [12]. Mishaps such as insufficient volumes and labelling errors often necessitate repeat testing. This exacerbates both economic and patient-based negatives associated with testing described above.

Given the above, and a lack of consensus evidence for the predictive capacity of SBR testing, it becomes increasingly difficult to advocate for blanket screening in the pre-term age group despite our understanding that they are at an inherently increased risk of significant hyperbilirubinaemia. Based on our results we do not believe that routine testing should be done at less than 24 hours without a clinical indication. The majority of our neonates were tested at 12 hours because the blood test was collected at the same time as the CRP.

TCB measurement devices utilise spectral reflectance from skin surfaces in order to estimate serum bilirubin levels without requiring invasive blood sampling [7]. In addition, a single device may be used over multiple instances, an economically attractive alternative. Despite these eminent benefits however, further high quality research is required in order to elucidate the predictive capacity of TCB testing and thus help determine its utility in defining treatment thresholds. Our study did not look specifically into TCB measurement devices.

## Limitations of study

Our study was limited by a low representative number of neonates who had evidence of risk factors for significant hyperbilirubinaemia (DCT positivity and signs of birth trauma).

Hospital policy at the time of audit completion dictated that a Direct Coomb's test was completed when a neonate was known to require intervention for hyperbilirubinaemia; that is, after the fact. This may have resulted in a significant number of neonates who did not have SBR levels requiring intervention without documentation of a DCT status whether positive or negative. This may

explain the relatively low number of neonates who were documented as being DCT positive.

Further, our audit was retrospective and only able to establish status of birth trauma from clinical documentation, which may reflect clinical subjectivity and documentation only when birth trauma in excess of “normal”. This may explain the low number of neonates with signs of birth trauma in our population.

From our results we are unable to give strong screening recommendations in regards to preterm neonates with evidence of these risk factors.

## Conclusion

The results of our audit suggest that only a small proportion of SBR tests performed as routine screening in a preterm neonatal population within the first 24 hours of age indicated commencement of interventional measures. Further, due to individual clinician variability in practice, close to one third of these test results did not affect management change. These trends were consistently pronounced with increasing gestational age on sub-analysis.

As a result of our audit we have changed clinical practice to stop 12 hour SBR being done routinely in neonates 32 to <35 weeks and plan to evaluate why phototherapy was not started when it was indicated.

We suggest that it may be reasonable to not perform SBR screening in this population at less than 24 hours given the expense and low yield. Emerging technologies such as TCB measurement should be prospectively evaluated in this population. Further high quality evidence is required to guide management approaches in this preterm age bracket.

## Declarations

The authors declare that there is no conflict of interest.

## References

1. Johnson L, Bhutani VK (2011) The clinical syndrome of bilirubin-induced neurologic dysfunction. *Semin Perinatol* 35:101-13.
2. Wusthoff CJ, Loe IM (2015) Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes. *Semin Fetal Neonatal Med* 20:52-7.
3. Watchko JE, Maisels MJ (2003) Jaundice in low birthweight infants: pathobiology and outcome. *Arch Dis Child Fetal Neonatal Ed* 88: F455-8.
4. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (2004) Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 114: 297-316.
5. Oh W, Tyson JE, Fanaroff AA, Vohr BR, Perritt R, et al. (2003) Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. *Pediatrics* 112: 773-9.
6. McIntosh N, van Veen L, Brameyer H (1994) Alleviation of the pain of heel prick in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 70: F177-81.
7. Maisels MJ, Coffey MP, Kring E (2015) Transcutaneous bilirubin levels in newborns <35 weeks' gestation. *J Perinatol* 35: 739-44.
8. Maisels MJ, Watchko JE, Bhutani VK, Stevenson DK (2012) An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol* 32: 660-4.
9. Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, et al. (2004) Risk factors for severe hyperbilirubinemia in neonates. *Pediatr Res* 56: 682-9.
10. Johnson LH, Bhutani VK, Brown AK (2002) System-based approach to management of neonatal jaundice and prevention of kernicterus. *J Pediatr* 140: 396-403.
11. Kaplan M, Hammerman C, Vreman HJ, Wong RJ, Stevenson DK (2014) Direct antiglobulin titer strength and hyperbilirubinemia. *Pediatrics* 134: e1340-4.
12. Wennecke G (2004) Useful tips to avoid preanalytical errors in blood gas testing: neonates. Accessed on July 15, 2016.

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