Original Article

Identifying Risk of Neonatal Hyperbilirubinaemia and Early Discharge for Glucose-6-Phosphate Dehydrogenase Deficient Newborns in Singapore

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Abstract

Introduction: This study aims to compare and assess usefulness of day 3 and 4 (49 to 96 hours) pre-phototherapy total serum bilirubin (TSB) in predicting subsequent significant hyperbilirubinaemia (SHB) in glucose-6-phosphate dehydrogenase (G6PD) deficient neonates. Methods: This prospective study was on all the G6PD deficient newborns weighing >2500 g. Day 3 and 4 pre-phototherapy TSB and phototherapy requirements in their first 2 weeks of life were analysed for its value in predicting subsequent SHB. Results: The frequency of G6PD deficiency was 2.4%, 1 per 42 live births (1.3% in males and 1.1% in females). Phototherapy was required in 51% of G6PD deficient infants, all within the first week of life. In the absence of SHB in the first week, the probability of its development in the second week was zero (95% confidence interval, 0 to 0.051). The day 4 pre-phototherapy TSB of <160 umol/L predicted no measurable risk of subsequent SHB (sensitivity, 94%; 95% confidence interval, 83.5% to 97.9%; specificity 82.8%; 95% confidence interval, 71.1% to 90.4%). Conclusions: G6PD deficient newborns without SHB in their first week of life were at no measurable risk of its development in the second week. Day 4 pre-phototherapy has better sensitivity and specificity compared to day 3 pre-phototherapy TSB in predicting the risk of subsequent SHB. Low-risk infants, thus identified, may be eligible for discharge on or before day 7 of life. Infants with Day 4 TSB <160 can be even discharge on day 4 with follow-up appointment. Evidence-based early discharge can decrease the social, emotional and financial burden of G6PD deficiency in Singapore.

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Key words: Neonatal jaundice, Pre-phototherapy total serum bilirubin

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency was discovered half a century ago, at the end of World War II.[1] It is probably the most common sex-linked Mendelian disease and inherited enzyme defect recorded worldwide and is estimated to affect hundreds of millions of people.[2-4] G6PD deficiency is a major cause of severe neonatal hyperbilirubinaemia with the devastating potential of bilirubin encephalopathy or kernicterus.[2,3,5,6] In a report of Kernicterus Registry, 19 of 61 (31.5%) term and near-term neonates who were readmitted for kernicterus within 7 days of life had G6PD deficiency.[7]

The story of G6PD deficiency in Singapore stemmed from cases of Chinese and Malays who developed intravascular haemolysis following exposure to certain drugs. In contrast to Caucasian babies with kernicterus, where the commonest cause was Rh incompatibility, cases of kernicterus in Singapore did not stem from Rh-negative mothers because Rh negativity is rare among Chinese and Malays. Majority of kernicterus in Singapore was due to G6PD deficiency. This condition accounted for the commonest cause of mental retardation during that period in Singapore.[1]

G6PD deficiency occurs in 2.5% of Singapore's population, and affected newborns are at risk for severe neonatal hyperbilirubinaemia and kernicterus.[8] In the past 4 decades, neonatology units in local restructured hospitals have hospitalised all affected newborns for 14 to 21 days after birth because of this risk. This practice is unique to Singapore and originated from the Kernicterus Surveillance Programme.[1] Started in 1965, the programme also involved universal screening of newborns for G6PD deficiency and a nationwide campaign to educate the public on hyperbilirubinaemia and kernicterus prevention. Its success led to the virtual disappearance of kernicterus in Singapore for the last 4 decedes.[9]

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However, with escalating healthcare cost and easily accessible primary health services, local paediatricians have begun to question the necessity of this prolonged hospitalisation. Local reports suggest that 42.6% to 55% of G6PD deficient babies never had significant hyperbilirubinaemia (SHB) at all.[8,9] Tan et al[10] and Lim HH[8] reported that SHB usually occurs in the first week of life only. However, it was not clear which factors were predictive of low risk for SHB, or on which day these infants can be safely discharged. Some local paediatricians have begun discharging G6PD deficient babies earlier at various postnatal ages. However, indiscriminate early discharge of all patients may lead to a resurgence of kernicterus. This has been reported in America,[11-16] Denmark[17] and Africa,[18] especially after the American Academy of Pediatrics introduced a more liberal guideline for the management of neonatal jaundice in 1994.[19]

In the United States, age-specific total serum bilirubin (TSB) has been used for the prediction of hyperbilirubinaemia in healthy-term and near-term newborns.[20-22] Kaplan et al[23] similarly demonstrated the usefulness of hour-specific (44 to 72 hours) serum bilirubin values in delineating G6PD deficient Sephardic Jewish newborns at low risk of hyperbilirubinaemia. G6PD deficient newborns were found to be at low risk for SHB if their hour-specific TSB was <50th percentile for age. On the other hand, those G6PD deficient infants who had pre-phototherapy TSB levels above 50th percentile but below 75th percentile were at moderate risk of SHB (23%), while those above 75th percentile, 82% developed SHB.[23]

Universal pre-discharge TSB screening would undoubtedly complement visual recognition of SHB that might be hampered by skin pigmentation. However, there are no data available correlating pattern of rise of TSB in the first week, particularly comparing predictability of day 3 and day 4 pre-phototherapy TSB, which can complement successful prospective early discharge of all G6PD deficient babies, without increasing risk of kernicterus and the risk of hyperbilirubinaemia. Resurgence of kernicterus, a preventable condition, in recent years, concomitant with the era of early postnatal hospital discharge,[6] has made identification of infants at high-risk for this condition essential. Our prospective study aims to assess the predictive value of day 3 and 4 (49 to 96 hours) pre-phototherapy TSB for SHB, evaluate the feasibility of early discharge on or before day 7 of life, and henceforth propose an alternative discharge plan for G6PD deficient newborns.

Materials and Methods

Subjects

The study was conducted in Singapore General Hospital between 1 November 2001 and 30 December 2005. The population studied consisted of G6PD deficient neonates born in the hospital with birth weight >2500 g. Cord or quantitative analysis of G6PD enzyme level. A newborn was deemed deficient if the cord or venous enzyme activity was <12.6 IU/gHb or <6.0 IU/gHb, respectively.

Data Collection

All G6PD deficient newborns were hospitalised and monitored for jaundice till day 8 of life. During this period, they were observed visually for the development of jaundice and TSB was performed on all the G6PD deficient newborn on Day 3, 4, 5 when they were not on phototherapy and daily and when clinically indicated on all the babies who required phototherapy. However, only day 3, 4 pre-phototherapy (between 49 and 96 hours of life) TSB in newborns weighing >2500 g was used for prediction analysis. SHB was defined as neonatal jaundice that required phototherapy. In accordance with our department's guideline, phototherapy was initiated when TSB >200 umol/L for those >2500 g. Exchange transfusion was performed if TSB was persistently >300 umol/L, despite intensive phototherapy for at least 4 hours. Full blood count, reticulocyte counts, blood group typing and direct Coomb's Test were done if phototherapy was required. Breastfeeding was encouraged, although nursing mothers were warned to avoid food or drugs known to cause haemolysis in G6PD deficiency. The newborn was discharged on day 8 of life, if serum bilirubin was <180 umol/L, without significant upward trend of TSB (defined as increment of TSB <30 umol/L in 24 hours), are not on phototherapy on day of discharge and parents who had given written consent to be reviewed 48 hours following discharge in out-patient specialist clinic. In the event of discharge against medical advice before day 7, telephone interviews were conducted to obtain the history of phototherapy requirement and outpatient TSB measurements between discharge and day 14. Those newborns that were not fit for discharge on day 8, because they were still on phototherapy or due to other medical reasons, were discharged on or after day 14 in line with routine departmental and national guidelines. Letters detailing precautions and drug to be avoided will be given to parents. If follow-up post-discharge was inadequate and phototherapy requirement could not be clearly determined, the case was considered a defaulter and excluded from analysis.

Demographic and clinical risk factors for hyperbilirubinaemia were recorded. Demographic factors included gender, gestation, birth weight, race, type of deficiency, family history of G6PD deficiency and type of feeding. Maternal factors included mode of delivery, preterm labour, maternal fever, preeclamsia, prolonged rupture of membrane, anaemia, gestational diabetes, maternal drug history, and multiple births.

Laboratory Analysis

G6PD screening was performed using a fluorescent visualisation method (Roche diagnostics G6PD deficiency screening test) in the hospital's biochemistry laboratory. If the result was suggestive of G6PD deficiency, a blood sample was sent to the Department of Pathology in Singapore General Hospital for G6PD quantitative analysis using spectrophotometry (Roche Diagnostics MPR 1 G6PDH). TSB was measured by direct spectrophotometry (Creichert-Jung Unistat Bilirubinometer, Model 10310C/ 10311, Leica) in the hospital's laboratory. Only heel-prick capillary samples were used, with precautions taken to avoid exposure of sample to phototherapy light during collection and transport. For day 3, 5 and 7 TSB, only measurements performed in the hospital laboratory were used for data analysis. Blood group determination and direct Coombs' test and full blood counts were performed by routine laboratory techniques in our hospital.

Data Analysis

The incidence of SHB and its 95% confidence interval (CI) were determined using the formula by Agnesti and Coull.[24] Predictive characteristics of day 3 and 4 pre-phototerapy TSB were assessed based on the frequency of SHB. The outcome was binary, i.e. SHB was either "present" or "absent". The quartiles and 50th percentile of day 3 and 4 TSB were calculated. Predictive characteristics (sensitivity, specificity, positive and negative predictive values) of day 3 and 4 TSB in relation to these percentiles were computed and the receiver operating characteristic curves presented. The 95% CIs of significant predictive characteristics were derived using the Confidence Interval Analysis Program.[25] Categorical variables were compared using chi-square (2) analysis, and Student's *t*-test for continuous variables. Statistical significance was defined as $P < 0.05$. Analysis was done using SPSS for Windows (version 10.0.1), unless otherwise specified.

Results

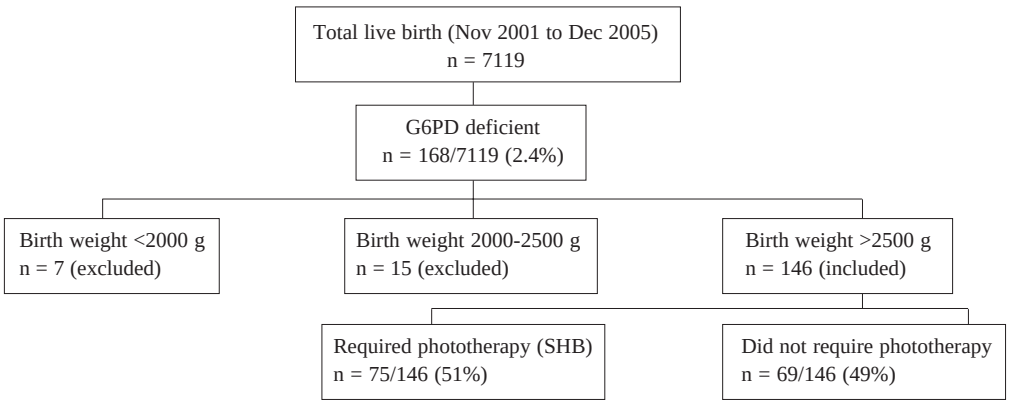
In this study, the incidence of G6PD deficiency was (168/7119) 2.4%, 24 per 1000 live births. Twenty-two (13%) patients were excluded because their birth weight was <2500 g. Only 146 (87%) who weighed >2500 g at birth were included in the study, were used for prediction of SHB analysis (Fig. 1). Fifty-four per cent of enrolled subjects were male and 46% were female. They were racially diverse (49% Chinese, 41% Malays, 2% Indians, 8% Other/mixed). The mean birth weight was 3189 g (range, 2510 to 4480) and the mean gestation was 38.4 weeks (range, 34 to 42) (Table 1).

Seventy-five (51%) G6PD deficient newborns of the total 146 subjects developed SHB and all received their first session of phototherapy within the first week of life. Three of the 75 patients (7%) were started on phototherapy <48 hours of life. Majority of them [33/75 (44%) babies] were stated on phototherapy on day 4. By day 5, 68/75 (91%) of all subjects with SHB were already on phototherapy (Table 2).

In contrast, 75 (41%) G6PD deficient newborn did not have SHB at all in both the first and second weeks of life. Therefore, with absence of SHB in the first week of life, the probability of its development in the second week was zero (95% CI, 0 to 0.057).

Comparing the demographics and clinical risk factors between groups, there was a statistically significant increase in the proportion of male subjects ($P = 0.007$), and previous sibling with G6PD deficiency ($P = 0.019$) among newborn with SHB. No significant differences were found in terms of birth weight, presence of ABO and Rh incompatibility, delivery mode, maternal use of medications, multiple birth, maternal diabetes, thyroid disease, infections and supplementation with breast milk (Table 1).

Of the 146 subjects who were >2500 g at birth, 128 subjects had valid day 3 and 118 subject had valid day 4 pre-



SHB: significant hyperbilirubinaemia

Fig. 1. Assembly of study sample.

Table 1. Relation of Infant, Maternal and Pregnancy/Delivery Characteristics of Cases Who Did and Who Did Not Develop Significant Hyperbilirubinaemia (SHB)

Variable	Overall n = 146	Cases with SHB n = 75 (%)	Cases without SHB n = 71 (%)	*P* value
Gestation size				0.562
SGA	4 (2.7)	2 (2.7)	2 (2.8)	
AGA	138 (95)	72 (96)	66 (93)	
LGA	4 (2.7)	1 (1.3)	3 (4.2)	
Soft tissue trauma	16 (11)	9 (12)	7 (10)	0.679
Gender (M:F)	79:67 (1.1:1)	48:27 (1.7:1)	31:40 (0.7:1)	0.007*
Birth weight (g)	3189 ± 384	3155 ± 371	3225 ± 396	0.753
Gestational age (weeks)	38.4 ± 1.4	38.2 ± 1.4	38.7 ± 1.3	0.336
Race				0.020*
Chinese	72 (49)	45 (60)	27 (38)	
Malay	60 (41)	22 (29)	38 (54)	
Indian	3 (2)	1 (1)	3 (3)	
Other	11 (7.5)	7 (9)	4 (6)	
Maternal drugs	44 (30)	22 (28)	23 (32)	0.563
Parity	2.1 ± 1.3	2 ± 1.4	2.2 ± 1.2	0.934
Hypertension	6 (4)	3 (2)	3 (2)	0.744
Diabetes mellitus	11 (8)	8 (11)	3 (4)	0.388
Antepartum bleeding	2 (1)	1 (1)	1 (1)	0.969
Smoking/alcohol	3 (2)	1 (1)	2 (3)	0.528
Mode of delivery				0.824
Vaginal delivery	118 (81)	60 (80)	58 (82)	
Caesarian section	28 (19)	15 (20)	13 (18)	
Maternal pyrexia	3 (2)	2 (2)	1 (3)	0.890
PROM	5 (4)	2 (3)	3 (4)	0.812
Type of deficiency				0.033*
Deficiency	85 (58)	50 (67)	35 (49)	
Intermedia	61 (42)	25 (33)	36 (51)	
Previous baby G6PD	38 (26)	24 (32)	14 (16)	0.0194*
ABO incompatibility	11 (8)	8 (11)	3 (4)	0.141
Rh incompatibility	2 (1)	1 (1)	1 (1)	0.969
Direct coomb positive	2 (1)	0 (0)	1 (1)	0.143
Type of feeding				0.365
Breast feeding	6 (4)	2 (3)	4 (6)	
Formula	85 (58)	43 (57)	42 (59)	
Mixed	55 (38)	30 (40)	25 (35)	

AGA: appropriate for gestational age; LGA: large for gestational age; PROM stands for prolonged rupture of membrane; SGA: small for gestational age

Table 2. Distribution of Day Newborn was Started on Phototherapy

Day phototherapy started	n = 75 (%)	Cumulative (%)
Day 2	3 (4)	7
Day 3	21 (28)	32
Day 4	33 (44)	76
Day 5	11 (15)	91
Day 6	6 (8)	99
Day 8	1 (1)	100

phototherapy TSB for computation of the percentiles and prediction analysis. Three patients opted for discharge against medical advice before day 3 and 3 patients were already on phototherapy by day 2. Twelve subjects had no available day 3 TSB. A total of 128 day 3 and 118 day 4 pre-phototherapy TSB were available for prediction analysis. Three patients (2%) had phototherapy before day 3, and another 3 were discharged against medical advice, 12 had no TSB done on day 3. Day 3 TSB levels ranged from 32

to 245 umol/L (mean, 152). The 25th, 50th and 75th percentiles correspond to TSB of 121 umol/L, 145 umol/L and 181 umol/L, respectively. Day 4 TSB levels ranged from 19 to 236 umol/L (mean, 160). The 25th, 50th and 75th percentiles correspond to TSB of 141 umol/L, 160 umol/L and 197 umol/L respectively. The predictive characteristics of day 3 and 4 TSB levels for these percentiles are shown in Tables 3 and 4.

Day 4 TSB level <160 umol/L predicted no measurable risk of SHB, with a negative predictive value of 94.1% and sensitivity of 93.9% (95% CI, 83.5 to 97.9) and specificity 82.8%, (95% CI, 71.1 to 90.4). When compared, day 3 TSB of <145 had negative predictive value of 78.1%, sensitivity of only 79.4% (95% CI, 67.9 to 88.3) and specificity of 83.3%, (95% CI, 71.5 to 91.7) which is lower than predictive value of day 4 TSB. Conversely, day 4 TSB >160 umol/L predicted a high risk for SHB, with a specificity of 82.8% and positive predictive value 82.1% (95% CI, 70.2 to 90.4). There were significantly more non-Chinese among those with day 4 TSB <160 umol/L compared to those with day 4 TSB >160 umol/L (P = 0.006). There were also significantly more patients with a positive family history of SHB in those with day 4 TSB >160 umol/L compared to those with day 4 TSB <160 umol/L (P = 0.035). The other risk factors were not significantly different among the groups.

Discussion

The absence of SHB in the first week of life predicted that the baby would not require phototherapy subsequently. These babies may be eligible for discharge at day 7 of life. The use of day 4 TSB <160 umol/L had a high negative predictive value in predicting SHB compared to day 3 TSB. It was, therefore, highly unlikely that a newborn would require phototherapy if his/her serum bilirubin was <160 umol/L on day 4. This newborn may be eligible for earlier discharge, possibly at day 4 of life. On the contrary, day 4 TSB >160 umol/L had a high positive predictive value (82%) for SHB. This indicated that a newborn with day 4 TSB >160 umol/L was at high risk of developing SHB and should be closely monitored for hyperbilirubinaemia. Previous studies have indicated the usefulness of day 3TSB as a predictor for SHB.[21,23] But using day 4 TSB as a predictive factor also has several advantages over day 3 TSB. Firstly, TSB of most G6PD deficient babies peak on day 3 to 4 of life as shown in Table 3. Seventy-six per cent (65/86) of newborns were already on phototherapy by day 4 of life. In addition, if the newborn has significant rise of TSB >30 umol/L over 24 hours from day 3 to day 4, suggesting rapid rate of haemolysis, the newborn may be further observed and not discharge earlier than day 4. Sampling at this age would potentially give the best predictive values. For prediction analysis, only infants weighing >2500 g were chosen because they constituted the largest number of deficient newborns, who were otherwise well, with the potential for early discharge. They also had the same criteria for initiation of phototherapy, which was necessary for prediction analysis.

It has been our department's policy to initiate phototherapy for G6PD deficient newborns at TSB >200 umol/L or >187 umol/L, if they weighed >2500 g or between 2000 and 2499 g respectively. The definition of SHB has been controversial,[26,27] with levels at TSB >256 umol/L,[23,28-30] or TSB >95th percentile for age[14] being the more commonly used definitions. Using a stricter criterion for SHB, our study may underestimate the potential number of newborns who may be discharged at an earlier date. In our study, more male, Chinese premature babies and those with a positive family history of SHB were at a higher risk of developing SHB. This suggests the presence of additional genetic factor(s) that increase the risk of SHB. Kaplan et al[31,32] reported a synergistic effect between variant promoter gene for uridine 5'-diphosphate glucuronosyl-transferase 1 seen in Gilbert's syndrome with G6PD Mediterranean563T mutation. In the presence of both mutations, newborns were at higher risk of SHB compared to the presence of either factor alone. Similar genetic interactions may explain our observations. Future local research should, therefore, be directed at identifying the prevalence of mutations associated with increased risk of SHB, the genetic variants of G6PD deficiency and interactions between these genes.

Table 3. Predictive Characteristics of Pre-phototherapy Day 4 Total Serum Bilirubin

Day 4 TSB (umol/L)*	No.	SHB (Phototherapy)		Predictive characteristic (%)			
		Yes	No	PPV (%) (95% CI)	NPV (%) (95% CI)	Sensitivity(%) (95% CI)	Specificity**(%) (95% CI)
<141	26	0	26	59.6	98.1	99.0	44.2
>=141	82	49	33	(48.9-69.5)	(84.1-98.0)	(91.1-99.9)	(32.3-56.7)
<160	52	3	48	82.1	94.1	93.9	82.8
>=160	56	46	10	(70.2-90.0)	(84.1-98.0)	(83.5-97.9)	(71.1-90.4)
<197	79	20	59	98.3	74.4	59	99.2
>=197	29	29	0	(85.9-99.8)	(63.3-82.7)	(45.2-71.9)	(92.5-99.9)

* 25th percentile = 141 umol/L; 50th percentile = 160 umol/L; 75th percentile = 197umol/L
** Predictive characteristic PPV: positive predictive value; NPV: negative predictive value
95% CI: 95% confidence interval; SHB: significant hyperbilirubinaemia; TSB: total serum bilirubin

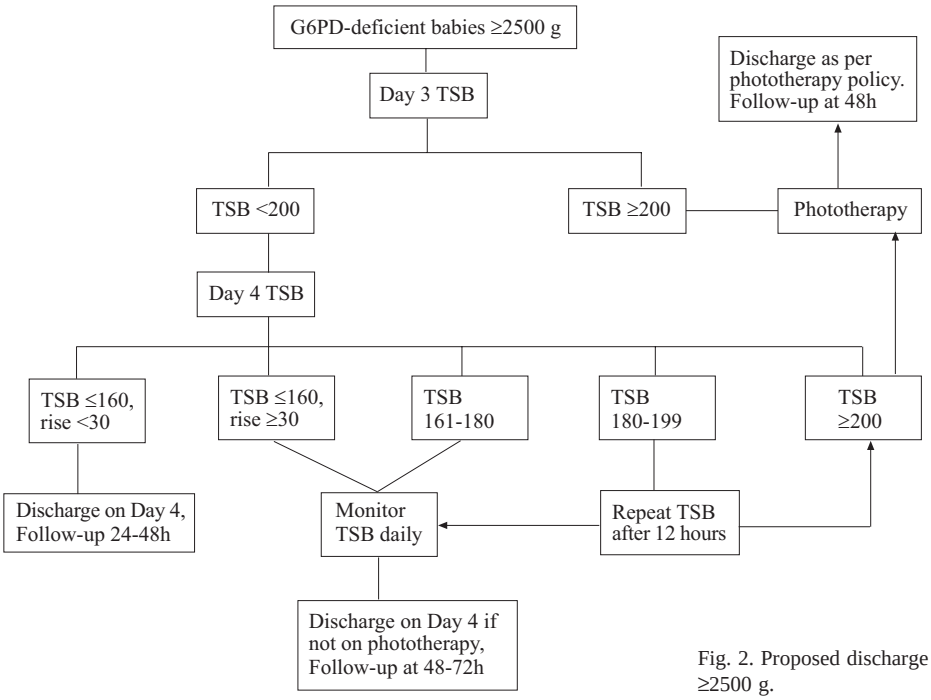


Fig. 2. Proposed discharge plan for G6PD deficient baby with birth weight ≥2500 g.

On the other hand, contrary to logical deduction, concurrent ABO and Rhesus incompatibility did not increase the risk of SHB. This was also reported in another study.[30] However, further studies with larger sample sizes may be required to examine the effect of this risk factor independently using logistic regression.

Our results have demonstrated that early discharge of low-risk G6PD-deficient newborns in Singapore may be possible. We have provided important predictive factors to help us formulate a new discharge plan for these babies. A possible alternative discharge plan based on current data is illustrated in Figure 2.

Using the day 4 TSB of <160 umol/L, in the absence of significant rise, an estimated 43% of G6PD-deficient infant can be discharged by day 4 of life. Another 23% at day 7, and the remaining (36%) by day 9 of life of G6PD deficient newborns may be eligible for discharge. This translates to potential savings of up to S$19,000 per year in hospital ward charges alone for this cohort of newborn. From the perspective of a healthcare organisation, our study results will enable administrators to better allocate healthcare expenditure and resources.

The current 14-day hospitalisation policy for these infants discourages mothers from breast-feeding their newborns. In our study, none of the subjects were fully breastfed, and only 50% received partial breast-feeding or breast milk supplementation. This contrasts with a general figure of 11% total breast-feeding, and 79% partial breast-feeding or breast milk supplementation rate in babies born in our hospital during the same period of time. Early discharge will certainly decrease interruption of breast-feeding and promote maternal-infant bonding.

Our results though promising are limited by the small sample size. Further study targeting at larger population size is essential to validate our experience.

Meanwhile, we propose alternative discharge plan for G6PD deficient newborn (Fig. 2).

Our study involved newborns in a segregated environment devoid of any

Table 4. Predictive Characteristics of Pre-phototherapy Day 3 Total Serum Bilirubin

Day 3 TSB (umol/L)*	No.	SHB (Phototherapy)		Predictive characteristic (%)			
		Yes	No	PPV (%) (95% CI)	NPV (%) (95% CI)	Sensitivity(%) (95% CI)	Specificity**(%) (95% CI)
<121	30	4	26	65.3	86.7	94.0	43.3
>=121	98	34	64	(55.0-74.6)	(69.3-96.2)	(85.6-98.3)	(30.6-56.8)
<145	64	14	50	84.4	78.1	79.4	83.3
>=145	64	54	10	(70.2-90.0)	(66.0-87.5)	(67.9-88.3)	(71.5-91.7)
<181	96	36	60	100	62.5	47.1	100
>=181	32	32	0	(89.1-100)	(52.0-72.2)	(45.2-71.9)	(94.0-100)

* 25th percentile = 121 umol/L; 50th percentile = 145 umol/L; 75th percentile = 181 umol/L
** Predictive characteristic PPV: positive predictive value; NPV: negative predictive value
95% CI: 95% confidence interval; SHB: significant hyperbilirubinaemia; TSB: total serum bilirubin

triggering factors for haemolysis and aggravating postnatal factors for hyperbilirubinaemia, e.g., dehydration. Therefore, care must be taken to educate parents to avoid potential triggers in the home environment, avoiding unknown herbal medicine and all the known drugs contraindicated with G6PD deficient infants in the event of early discharge. The public education, in particular parents and families of G6PD deficient newborns on condition of G6PD deficiency, triggers and its implications, as well as accessibility of medical services for the newborns are essential elements that determines the success of early discharge of G6PD deficient newborn.

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