UNIVERSITY OF THE WITWATERSRAND

SCHOOL OF CLINICAL MEDICINE

DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

REVIEW OF EXCHANGE TRANSFUSION FOR NEONATAL HYPERBILIRUBINEMIA AT CMJAH FROM 2006 TO 2011

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DECLARATION

I, RUGAMBA GILBERT, declare that this research report is my own original work. It is being submitted for the degree of Master of Medicine in paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any University.

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The 30th of September 2013 Place: Johannesburg

ABSTRACT

Background: Improvement in neonatal care has changed the features of severe hyperbilirubinemia and reduced the number of babies who need exchange transfusion (ET) to avoid bilirubin-induced neurological dysfunction. We conducted this study to determine the demographic and clinical characteristics of the exchanged babies, in order to identify their risk factors, and to determine the adverse effects and outcomes associated with ET.

Methodology: This was a retrospective descriptive study, reviewing folders of infants who required ET at CMJAH from June 2006 to December 2011.

Results: There were 63 patients who underwent 66 exchange transfusions. Patients exchanged in the neonatal unit accounted for 60.3%, with the rest of the patients (39.7%) being exchanged in the general ward. Preterm babies accounted for 45.7%, and the majority were inborn (44%). The majority were male (58.7%), term (54.3%), and the mean birth weight was 2.29 Kg (±0.89). The median age at exchange was 5 days (mean 4.5 days ±2.1 SD). The cause of jaundice was undetermined in most patients (84.1%), while ABO incompatibility and Rhesus disease accounted for 7.9% and 6.3%, respectively. Seven babies (11.1%) had an abnormal neurological examination before exchange and five (7.9%) were labelled as kernicterus.

The mean bilirubin before exchange was 325 mmol/l ±118. The complications of ET were seen in 22.2% of patients. These were Necrotising Enterocolitis (NEC) (1.58%); seizure (1.58%); apnoea (4.76%); bleeding (3.1%); renal failure (3.1%); hypoglycaemia (4.76%); thrombocytopenia (67.6%); and hypercalcemia (85%).

We had three deaths, of which two were due to neonatal sepsis acquired prior to exchange, with one case of perforated NEC in an infant with other comorbidities. Hence, the mortality associated with ET in our study was 1.5 percent. At discharge, three infants remained with signs of kernicterus (4.7%).

Conclusion:

Kernicterus remains a cause of concern in our settings, and mechanisms ought to be put in place to detect severe jaundice in discharged term babies who may benefit from early phototherapy (PTT) and ET; as this is shown to be a relatively safe procedure in our settings, especially in infants without other severe comorbidities.

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ABBREVIATIONS

ABO- Blood group ABO

AGA -Appropriate for gestational age

BIND-Bilirubin induced neurological dysfunction

C/S-Caesarean section

CMJAH-Charlotte Maxeke Johannesburg Academic Hospital

CRP- C-reactive protein

ELBW- Extremely low birth weight

ET- Exchange transfusion

FBC- Full blood count

GA -Gestational age

Hb -Haemoglobin

HMD- Hyaline membrane disease

ICU- Intensive care unit

IQR -interquartile range

LBW -Low birth weight

M -Median

NEC- Necrotising enterocolitis

NICU- neonatal intensive care unit

PTT- phototherapy

SD -Standard deviation

SGA- Small for gestational age

TB- total bilirubin

TcB- transcutaneous bilirubin

U/E- Urea and electrolyte

VLBW -Very low birth weight

CHAPTER 1 : LITERATURE REVIEW

Background

Neonatal jaundice is the most common neonatal condition dealt with by paediatric health workers, and is the first cause of readmission in the newborn period (1). Jaundice refers to the yellowish discoloration of the skin and/or sclera caused by bilirubin deposition (2) . Almost all newborns develop hyperbilirubinemia as a normal transition in physiology; the average full-term newborn infant has a peak serum bilirubin concentration (TB) of 5 to 6 mg per decilitre (86 to 103 µmol per litre). Values above this threshold (7 to 17 mg per decilitre, or 104 to 291 µmol per litre) are not considered physiologic and a level of TB greater than 95 percentile for hours of age on the Bilirubin chart, proposed by Bhutani (2);(3), requires careful attention and management in order to prevent bilirubin-induced neurological dysfunction (BIND) or kernicterus.

The association between jaundice and encephalopathy was first proposed by Hervieux in 1847, but the term kernicterus was used for the first time by Schmol in 1905 to describe the yellow staining of basal ganglia by bilirubin (4). The terms 'bilirubin-induced neurological dysfunction' (BIND) and 'kernicterus' are used interchangeably to characterise the same condition, even if some authors consider the term BIND as referring to clinical manifestations, and kernicterus as referring to an anatomical diagnosis (5). In this review, we will use the term kernicterus both to describe the neuropathology of bilirubin-induced brain injury, and its clinical findings, whether subtle or marked (6).

The true incidence of neonatal jaundice is unknown, because for infants to be tested, it will depend on an observer's attention and on visual inspection, which has been found to be unreliable (7, 8). The reported incidence also depends on the infant's ethnicity, mode of feeding and presence of haemolysis (2). The incidence ranges from 6% in USA, to 39% in Japan. There is also wide variability in the incidence of neonatal jaundice within the same country; for example, a multicentre study showed that the incidence varies from 4.3% to 16% in USA (9) and from 8% to 21% in Israel (9). Severe hyperbilirubinemia above exchange level also varies greatly. In one study done in California of 18,000 infants between 2005 and 2007 (9), 22 (0.1%) had a TB level more than exchange level, where only one was exchanged.

However in Japan, Funako (10) in his 15 year review of infants admitted for neonatal jaundice, found 7% with severe hyperbilirubinemia. In South Africa, the incidence of severe hyperbilirubinemia in a Durban-based study from 1981 revealed a rate of 13.5% and a rate of ET of 5 percent (11). In Sub-Saharan countries, severe hyperbilirubinemia is still very common, and is associated with high morbidity and mortality. This is best illustrated in the study done by Ibekwe (12), which showed that 16.5% of all infants admitted for jaundice had ET; with a high mortality of 17.5 percent.

Clinical presentation

The clinical presentation of babies with severe neonatal jaundice has changed throughout the years, from frank kernicterus to subtle neurological signs. Severe cases are commonly only seen in readmitted babies, where the majority of babies born in hospitals are currently discharged within the first two days. Thus, babies readmitted with severe jaundice are usually term or near term, with a mean age at presentation of four days (2). Among them, abnormal neurological examination is found in 12% to 21% (13).

Clinically, Kernicterus progresses in 3 stages: the first stage is characterised by subtle signs like mild to moderate hypotonia, irritability, high pitched cry; while hypertonia, lethargy, jitteriness, retrocollis and opisthotonus characterise the second stage. Without intervention, the child progress to the third stage, where apnoea, seizures, coma and death become common. Death occurs due to seizures or as a result of a coma (5, 6).

In a Canada based study of 258 infants with severe hyperbilirubinemia (424mmol/l), 12.4 % showed evidence of kernicterus, while 20 infants presented with equivocal neurological signs that may have been due to kernicterus. Infants with signs of kernicterus had a higher level of bilirubin when compared to those without, and were admitted after 48 hours (14). In another observational study of 249 neonates with hyperbilirubinemia conducted in Egypt, 18% were

diagnosed with mild kernicterus, while 22% had moderate kernicterus, with the rest being any neurological signs. Their level of hyperbilirubinemia was higher in mild and moderate kernicterus, compared to those without kernicterus, and analysis found sepsis to increase the risk of kernicterus (15).

Risk factors and screening

There are well recognised factors associated with severe unconjugated hyperbilirubinemia, such as haemolysis, breastfeeding, hematoma, polycythaemia, the infant being born to a diabetic mother, hypothyroidism (2) and a family history of severe jaundice. Infants with those risk factors should undergo careful follow up and have their level of bilirubin plotted on the Bhutani normogram for greater accuracy. A level greater than the 95th percentile on the hour specific and weight bilirubin level normogram must be urgently managed in order to prevent kernicterus (16). In an analysis of infants with kernicterus, Johnson and Bhutani (17) found that there were identifiable risk factors that could have prevented the disease. These identified risk factors include discharge before 48 hours after birth, failure to measure the TB concentration in an infant with jaundice, lack of concern regarding the presence of jaundice, lethargy, or poor feeding, and delayed initiation of phototherapy in infants with elevated TB (15).

Two screening approaches are used to identify babies with a risk of severe hyperbilirubinemia: first, a systemic approach is used to test all infants before discharge; and then a selective approach is used in which the need for bilirubin testing is determined by the presence of clinical risk factors for severe hyperbilirubinemia. If resources are available, most guidelines

recommend a systemic approach, as visual inspection is not reliable and not all infants discharged early receive follow up (18). The current situation in CMJAH is not different from that of other public hospitals: mothers and babies are discharged 6 hours after a normal, uncomplicated delivery. Despite the national recommendation that post-natal visits should be part of routine delivery, only 29.9% of babies are reviewed within 6 days of delivery (20). This puts babies at risk of developing severe hyperbilirubinemia. For this reason, a routine systematic approach to testing all infants before discharge would be appropriate in our setting.

Bilirubin measurement

Bilirubin testing is undertaken by means of two methods. Chemical analysers which directly measures the TB concentration in a blood sample or spectrophotometric testing which estimates the TB value by measuring the multi wavelength of bilirubin (21). The photometric methods include devices that uses minimal blood samples, such as a blood gas machine, or a transcutaneous device; which is applied on the skin and measures its bilirubin content by spectroreflectance. Many studies showed a close correlation between transcutaneous bilirubin (TcB) and TB across racially and ethnically diverse populations. For levels above 257 mmol/l , TcB was found to underestimate the level of TB (21), and some authors still dispute the accuracy of TcB in dark-skinned infants (22) .

The use of TcB in discharged patients showed a reduction in the number of blood tests when compared to visual screening, without compromising the detection of severe jaundice. However, some experts recommend more studies may serve to evaluate of use of the TcB

device by non-hospital health workers in case of discharge (23). TcB is invaluable for screening, but if high levels are detected – or when TcB exceeds the 75th percentile – a blood sample must be done for TB (21).

The causes of severe jaundice

The causes of jaundice may help in determining the natural progression of TB. Jaundice – due to haemolytic disease – is severe, and requires careful monitoring due to the fact that TB can rise very fast and without warning. Studies have shown that causes of severe hyperbilirubinemia vary. In a Canadian paediatric surveillance review from 2002 to 2004, looking at 258 term and near term infants, causes of severe hyperbilirubinemia were identified in only 93 cases. The majority had ABO incompatibility (n=48), glucose-6-phosphate dehydrogenase deficiency (n=20) and hereditary spherocytosis (n=7). In this study 57 (22.1%) had ET (14).

In the USA, Patra and colleagues(24) found Rhesus disease to be the most frequent cause of ET in 34%, followed by ABO incompatibility in 20%, with the causes of jaundice not able to be identified in 44 percent. In most of the studies (Iran, India and Nigeria), more than the half of the cases of severe hyperbilirubinemia who had ET , no causes were identified. ABO incompatibility was present between 20% and 40%, Rhesus disease 5% to 34%, red blood cells enzymes defects or membranopathy between 0% and 19.1 percent (12, 25, 26). In South Africa, Vos GH showed that ABO incompatibility was responsible for 44.4 % of newborn infants who had ET (27).

Investigations

Investigations in severe hyperbilirubinemia aim to find its cause and associated comorbidities. Depending on the clinical picture, the following tests may be requested in infants with severe hyperbilirubinemia (2): TB; conjugated bilirubin; Blood type and Coombs tests for the infant and the mother; blood culture; CRP; urine analysis; complete blood count and smear; reticulocyte count; urea and electrolytes; calcium magnesium and phosphate. To perform a lumbar puncture for all infants remains controversial, however LP is recommended in severe hyperbilirubinemia if the baby presents with neurologic signs, or if sepsis is suspected on history or clinical grounds, in order to exclude associated meningitis (15). Certain tests, such as end-tidal carbon oxide measurement (ETCO) and bilirubin albumin ratio, are not available in our settings.

Imaging modalities are not required in the acute management of infants with severe hyperbilirubinemia. Theoretically, MRIs can detect increased signal in posteromedial aspect of the globus pallidus, and abnormal grey matter, but its clinical use has been unsatisfying in the early stages of kernicterus (6). Brainstem auditory-evoked responses (BAER) may be of value in detecting neurologic damage of hyperbilirubinemia. Hyperbilirubinemia causes auditory neuropathy by increasing brainstem conduction, which may resolve if TB is lowered (6). These tests still have experimental value in early clinical management, and are not used currently in CMJAH.

Pathophysiology

Unconjugated hyperbilirubinemia results from increased production of bilirubin, combined with impaired conjugation and elimination of bilirubin. Newborns are prone to hyperbilirubinemia. Reasons include an increased red blood cell mass; decreased red cell life span of 90 days as compared to 120 days in older patient; impaired conjugation due to immaturity of the liver conjugation; and increased enterohepatic circulation, seen in the newborn period due to failure to establish adequate breastfeeding or immaturity of intestinal flora (2). The metabolism of heme and bilirubin is shown in figure 1.

The enzyme UGT1A1 that conjugates lipid soluble bilirubin into water soluble product is deficient in the early days of life. UGT activity for infants at 7 days of age occurs in approximately 1% of the adult liver, and does not reach adult levels until the infant is 14 weeks of age. In normal term babies, the level of unconjugated bilirubin rises progressively from birth, and reaches a plateau around the fourth day, before clearing around the seventh day, while the preterm babies reach their peak bilirubin level nearer the seventh day, and may only lower at the end of the second week (2).

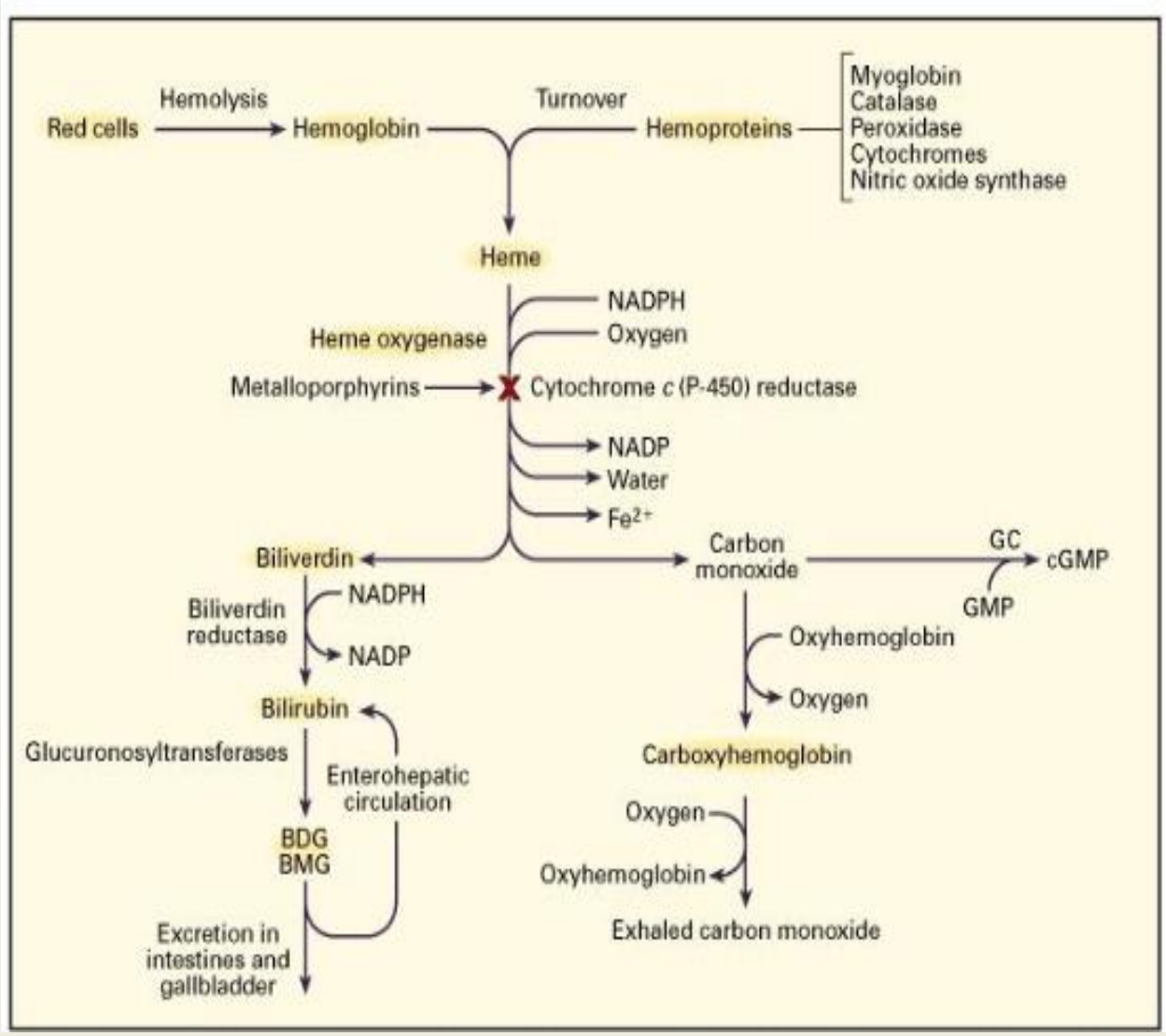


Figure 1: Metabolism of heme and bilirubin (2)

Heme derived from haemoglobin or from other hemoproteins is degraded by the enzyme heme oxygenase, with the involvement of NADPH and oxygen, producing iron, carbon monoxide and biliverdin. The enzyme biliverdin reductase catabolises biliverdin into bilirubin, which is also degraded by the enzymes glucuronosyltransferase and uridine diphosphate into bilirubin

monoglucuronide and bilirubin diglucuronide. The latter products are either excreted in intestine, or reabsorbed into the circulation after being deconjugated by bacteria. Carbon monoxide generated in this reaction is used in the formation of cyclic guanosin monophosphate, or it combines with oxyhemoglobin and is exhaled (2).

Treatment modalities

Since its first use in early 1940, phototherapy remains the standard of care for the treatment of hyperbilirubinemia in infants. It rapidly reduces the serum bilirubin concentration by transforming bilirubin into its isomers, such as lumirubin, which are water soluble and easily excreted by the kidney (28). ET is considered as the most effective as well as the fastest method for lowering the bilirubin level in infants at high risk of kernicterus (29). It reduces TB by approximately 50 percent. Unconjugated bilirubin is fat soluble, so post ET, the TB may rebound to three-quarter of the original value (30). A second exchange may be necessary for some infants in order to lower total bilirubin to less harmful values. ET is indicated when infants have TB greater than the exchange threshold level, despite intensive phototherapy, when a jaundiced infants presents with signs of kernicterus, irrespective of TB level. ET is particularly useful when there is an excessive haemolysis (18). The principle of ET is to remove not only bilirubin from the circulation, but also antibodies that destroy the red blood cells. The infant's circulating blood volume is approximately 80 to 90 ml/kg. A double-volume ET (160 to 180 ml/kg) replaces approximately 85% of the infant's circulating red blood cells, with appropriately cross-matched fresh whole blood in less than 72 hours (if not available, blood less than seven

days can be used). Heparin and calcium gluconate are added to each unit of blood to be transfused. An umbilical vein catheter is inserted, and blood is removed and replaced in aliquots that are approximately 10% or less of the infant's blood volume, (usually 5 ml to 10 ml aliquots).

During the procedure, serum electrolytes, serum glucose and bilirubin are measured periodically and heart rate, respiration, colour and oxygen saturation are monitored continuously during the procedure, and closely in the first 6 hours after the procedure (20).

The development of safe bilirubin normogram

It took six decades of research to reach a consensus on the threshold of bilirubin, as well as on which phototherapy or ET should be performed in a safe, cost effective manner. In 1952, Hsia and colleagues (31) made the observation that kernicterus was common and that it could be prevented, by keeping the bilirubin level less than 340 mmol/l, and thereby fixing the obligatory exchange level at that value. From that year to late 1970s physicians were aggressively treating neonatal jaundice, despite the high rate of complications associated with exchange transfusion.

In late 1960, the decline in family size and the use of immunoglobin D to prevent Rhesus disease, combined with the zealous use of phototherapy and ET, made kernicterus a rare disease (32). In 1979, Cockington devised different thresholds of phototherapy according to birth weight and age in hours, but kept the exchange level at 340 mmol/l for all babies (33) (See appendix 2a and 2b). The trend reversed in 1980 and 1990, when a series of studies suggested

that kernicterus was rare, and that too many patients were subjected to a relatively dangerous procedure unnecessarily (34).

In 1999, Bhutani published a more accurate hour-specific TSB normogram that can predict which newborn is at high, intermediate or low risk for developing significant hyperbilirubinemia (3). In 2003, the review of studies by Watchko and Maisels comparing the presentation of kernicterus and bilirubin levels, suggested that higher threshold for ET could be used, as very many big healthy-term babies did not develop kernicterus at a level above 340 mmol/l; and the authors proposed the adoption of the Bhutani normogram (35). Ironically, this change in the management of jaundice coincided with a trend towards discharge of newborn babies, and many cases of severe hyperbilirubinemia were thus overlooked. This caused the incidence of kernicterus to increase once again (36). In 2006, South African neonatal academic hospital consensus adopted a new normogram based on that of Bhutani (36). Appendix 3 shows the current chart used for ET in our hospital.

Complications of exchange transfusion

There are many complications associated with ET, which include transfusion reaction, infections (including blood borne or nosocomial sepsis), graft versus host disease, metabolic instability, electrolyte disturbances, vessel perforation by umbilical catheterisation, hypotension, necrotising enterocolitis, hematologic abnormalities, seizures, and death (37). The mortality associated with exchanged transfusion varies from 0.3 to 3.5% in tertiary centres to 17.5% in

level 1 or 2 unit (12). The most common events are thrombocytopenia, calcium abnormalities, and metabolic acidosis (13).

In a retrospective study done in Washington looking at the outcome of ET from 1981 to 1995 in healthy versus ill babies, there was no death, but one patient developed necrotizing enterocolitis (38). In a 21 year review studies of 141 newborns who had exchange transfusion, there was also no deaths related to the technique, but five patients died of unrelated causes (39). In another series of 55 infants between 1992 and 2002, a high rate of complications was seen, most of them laboratory abnormalities. There was one death, and many complications, including thrombocytopenia (44%), hypocalcaemia (29%), and metabolic acidosis (24%) in a retrospective study of 55 infants undergoing ET between 1992 and 2002 (13).

Studies in Third World countries showed a similar rate of complications. In a three year retrospective chart review of 68 babies who had an ET in Iran (25), one patient died (1.5%) while in a records of 92 newborns who underwent an ET in India, two (2.1%) infants died (26); however, the rate of complications is very high in sub-Saharan countries. This is best shown in a prospective study of 40 infants over a period of two years done in Nigeria, where 7 (17.5%) patients died after exchange transfusion (12). As the frequency of exchange transfusions decline, so the complication rate in level 1 and 2 settings may increase as health workers are no longer experienced in this procedure.

In conclusion, despite advances in neonatal care and evidence-based principles of prevention and management, severe neonatal hyperbilirubinemia requiring ET continues to be a problem

worldwide, and kernicterus remains a preventable tragic reality. Most of the studies showed that the majority of infants who had ET were readmitted, and identifiable factors could have prevented the disease and its ET complications. It was also noted that this procedure remains a dangerous one, not only in level 1 or 2 units, but in tertiary centres as well.

Aim

Our retrospective review aims to describe the clinical and laboratory features of severe hyperbilirubinemia requiring ET, and its outcome at Charlotte Maxeke Academic Johannesburg Hospital (CMJAH), and to formulate recommendations based on our findings for better clinical practice.

CHAPTER 2 : METHODS

Study design

This study was a retrospective record study, reviewing files of infants who required ET at CMJAH from June 2006 to December 2011. All newborns that underwent an exchange transfusion at CMJAH between June 2006 and December 2011 were included in the study. Babies readmitted to the general wards were identified from a review of hospital admission registers. Patient files were then obtained and reviewed. Babies exchanged while in the neonatal unit were identified from the computer database.

Study site organisation

At CMJAH, preterm/LBW babies less than 1.75 kg are routinely admitted to the neonatal unit after birth. Term and near-term babies who have neonatal complications are also admitted at birth to the neonatal unit. Babies in good health more than 1.75 kg are discharged to their mothers. Babies found to be jaundiced in the postnatal wards are admitted to the neonatal unit for exchange transfusion if required. Any baby who has been home is readmitted to the general paediatric wards. The decision to perform an ET as well as complementary investigations was at discretion of the attending physician, based on the bilirubin normogram charts (see Appendix 3).

Exclusion criteria

Patients undergoing ET whose files were missing and without other sources of information, were excluded.

Data collection

Variables were extracted from the neonatal database or patients files and entered into an Excel spread sheet as per the data collection sheet (Appendix 1).

Each file was given a code according to the order of admission, and this code was used to link the data entered into the Excel sheet, and identifying details were removed so that the data remained anonymous and confidential.

Ethics

Ethics approval was obtained from the Human Ethics Research Committee of the University of the Witwatersrand, which issued certificate number (see Appendix 4). Institutional approval was obtained from the Chief Executive Officer of CMJAH.

Data analysis

Participants' information was captured into an MS-Excel spread sheet. Data cleaning was done to check for missing values, any inconsistencies, and to identify any extreme values. After data cleaning, the MS-Excel spreadsheet was then imported to statistical software (Stata Version 12) for descriptive analysis purposes. Standard statistical methods were used. Categorical data was described using frequencies and percentages. The distribution of continuous variables was determined. These were then described using measures of central tendency: mean ± standard deviation for normally distributed data; and median and interquartile range for skewed data. Morbidity and outcome between premature infants and term babies readmitted was compared. Fisher's exact test was used to compare categorical values and a paired t-test was used to compare laboratory values before and after exchange transfusion as data was normally distributed.

CHAPTER 3: RESULTS

From June 2006 to December 2011, records of 69 babies who had been exchanged were retrieved. Six patients did not have records and were excluded from the study. There were therefore 63 babies included in this observational study.

Demographics characteristics

The main characteristics of infants included are described below: see Table 1

Table 1 : General characteristics of the study population

Characteristics	Frequency	Mean± SD	Median (IQR)
Gender: male	37 (58.7%)	-	-
Inborn	38 (60.3%)	-	-
Neonatal ward	38 (61%)	-	-
Age at exchange (days)	-		5 (3-6)
Gestational age (weeks)	-	35.4±4.4	37 (33-39)
Birth weight (kilograms)	-	2.29±0.9	2.45 (1.3-3.0)
NVD	34 (53.5%)	-	-
APGAR at 5, less than 7	4 (8.5%)	-	-
Breastfeeding	18 (43.9%)		
HIV exposed	8 (16.3%)	-	-

The majority of our sample were male infants (58.7%). All the babies were of African descent, except two patients of mixed-race origin. The majority of babies were inborn 38(61 %), of which 27 were admitted to the neonatal ward, and 11 were discharged and readmitted to the general ward. Twenty-five babies were referral from other hospital or clinics. Ten (15%) babies were transferred from surrounding clinics, while 13(20.6 %) were transferred from regional hospitals. There was missing information on the origin of two referred babies. In total, neonatal ward had 38(60.3%) neonates exchanged and general ward had 25 (39.6%) babies who underwent ET. For babies who were readmitted, the mean age of readmission to CMJAH paediatric care was 4.3 days ±2.4 days.

Vaginal delivery including 2 breech presentations accounted for 34 (62.9%) of all deliveries. Of those delivered by caesarean section, emergency accounted for the largest part at 17 (31.4%), compared to an elective 3(5.5%). However, information about mode of delivery was not recoverable for 9 (14.2%) patients included in the study.

Gestational age

Most babies were term 31(54.3%), while 9(15.7%) were less than 32 weeks (see table 2). Six infants had missing information about gestation age. The infants' gestational ages ranged between 26 and 43 weeks, with a mean of 35.4 weeks ± 4.4SD. The mean gestational age for those in the neonatal ward was 34.8 weeks ±4.8SD, while the mean gestational age was 37.3 weeks ±2.1SD in general ward.

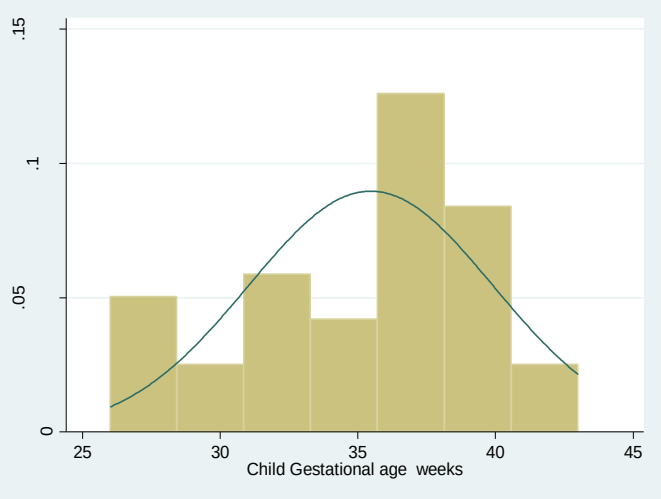


Figure 1: Distribution gestational age

Table 2 : General characteristics of the study population according to the G.A

Variables	Gestational age				
Gestation age	Less than 32 weeks n=9(15.7%)	Between 32-36 weeks n=17(29.8%)	More than 36 weeks n=31 (54.3%)	Missing data on GA n=6	Total n=63
Age at exchange(days)	M= 4.5: IQR:3-6	M= 4.5: IQR:2.5-6	M= 4.5: IQR:3-5	M= 6.5: IQR:4.5-6	M= 5: IQR:3-6
Inborn (versus referral)	8(88%)	10 (58%)	16(56%)	4(66%)	38(44 %)
Mode of delivery (NVD)	4 (missing data = 2)	10 (missing data = 2)	20 (missing data = 5)	-	34(62.9%)
Gender(M)	3(33%)	12(70.5%)	19(61%)	3(50%)	37(58.7%)
Apgar at 5 min (less than 7)	1 (missing data = 2)	1 missing data = 5)	1 (missing data = 6)	1 (missing data = 5)	4(8.5%)
Feeding mode (formula)	6 (missing data = 3)	8 (missing data = 3)	6 (missing data = 12)	2 (missing data = 4)	22(53%)
Birth weight(KG)	1.09±0.17	1.7 ±0.58	2.9±0.47	1.615±0.21	2.29 ±0.9
RVD status of the mother (Positive)	2 (missing data = 3)	2 (missing data = 4)	1 (missing data = 4)	3 (missing data = 3)	8(16.3%)
Neonatal ward (versus general ward)	9(100%)	12/5(70%)	15/16(48.3%)	2/4(33%)	38(61%)

M: Median

Birth weight

The mean birth weight was 2.29 ±0.9, with a minimum of 0.894 kg, and a maximum of 4.0 kg.

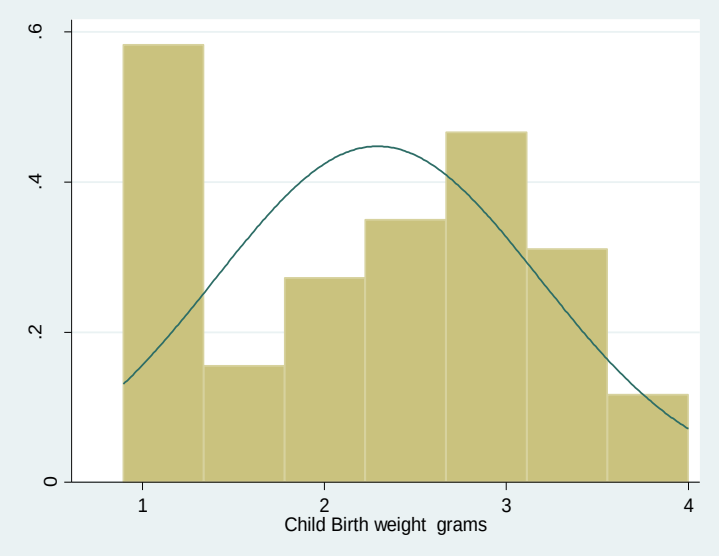


Figure 2: Birth weight

The majority 28(47.4%) were of normal birth weight, while the LBW, VLBW, ELBW accounted for 23.7%, 20.3% and 8,47%, respectively. There were no records of birth weight for 4 patients.

Of the 41 patients whose the type of feeding was described, 22 (53.6%) were formula fed, 18(43.9%) were breastfed, and one was mixed-fed at time of exchange. Complete antenatal care blood results were available in only 65% of the participants. Eight (16.3%) were HIV-exposed. Missing HIV status, or unknown, and refusal of testing altogether accounted for 13 infants (20.6%).The majority of mothers (52%) were RPR negative, and no positive RPR patient

was found. Missing information was excessively high on RPR result (48%). Most mothers were rhesus positive at 44 (69.8%).

The apgar score at one minute was less than 7 in 12 (19%) babies, and at five minutes it was less than seven in 4 (8.5%) babies, with one baby diagnosed as having severe birth asphyxia.

Details of exchange transfusion

The median age at first ET was 5 days, with the minimum of 2 days and maximum age of 11 days, while interquartile range was between three and six days (See Figure 3). One third of the babies 19(30.1%) was exchanged within 72 hours of life.

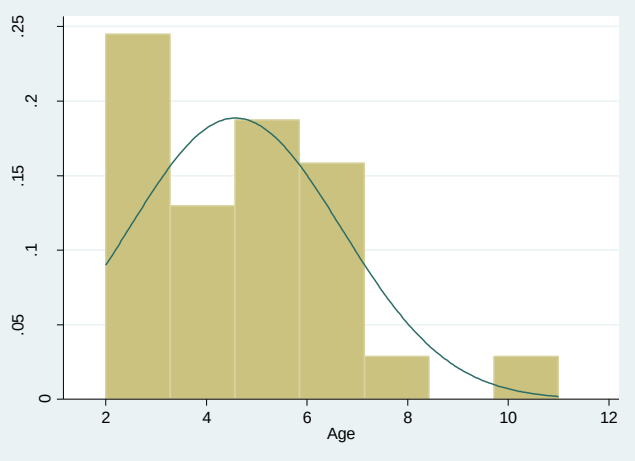


Figure 3: Age at exchange

The cause of jaundice was undetermined in 53 (84.1%) cases, five (7.9%) were diagnosed with ABO incompatibility, rhesus incompatibility was suspected in 4(6.3%) patients, and one was labelled as red cell membranopathy.

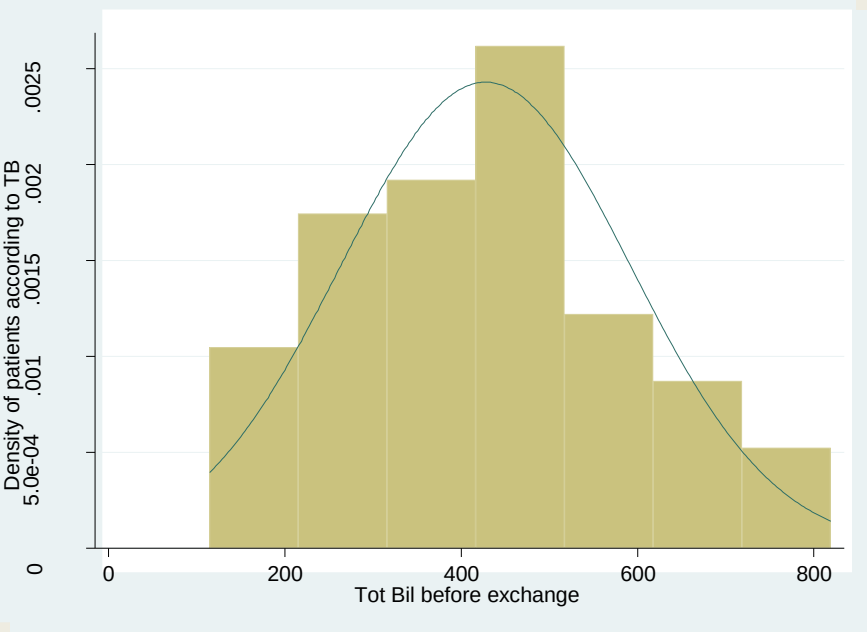


Figure 4: Distribution bilirubin level before exchange

The mean bilirubin level before exchange was 427mmol/l ± 164SD, with a minimum of 115 mmol/l and a maximum of 819 mmol/l (See Figure 4).

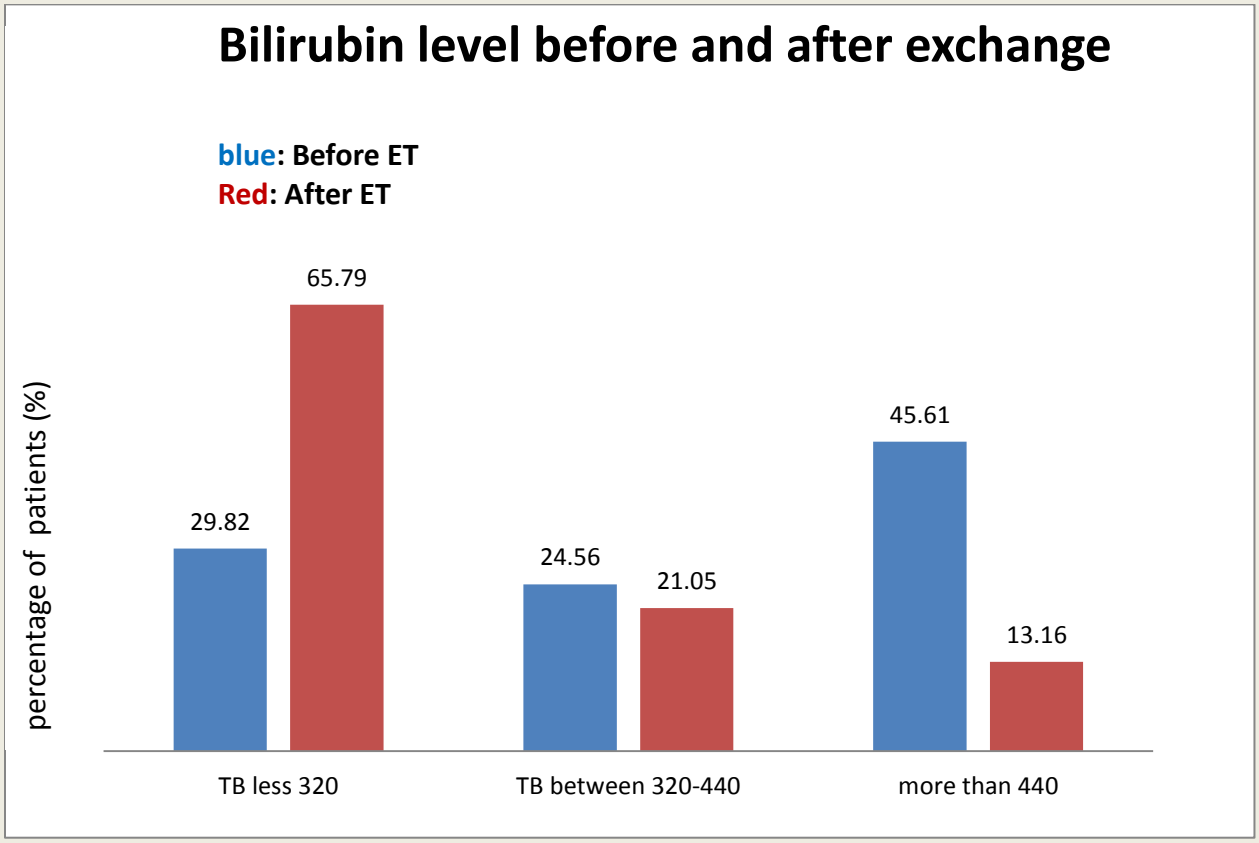


Figure 5: Bilirubin comparison after exchange

After the first exchange transfusion, the overall TB mean was 262 ±128 mmol/l, with a minimum of 25 and a maximum of 515 mmol/l. Three infants required a second exchange transfusion.

According to the bilirubin threshold for exchange, the biggest group (45, 6%) was exchanged at a bilirubin level greater than 440 mmol/l, while those exchanged between 320 and 440 mmol/l were 24.5%, and at less than 320 mmol/l, were 29.8 percent (See Figure 5).

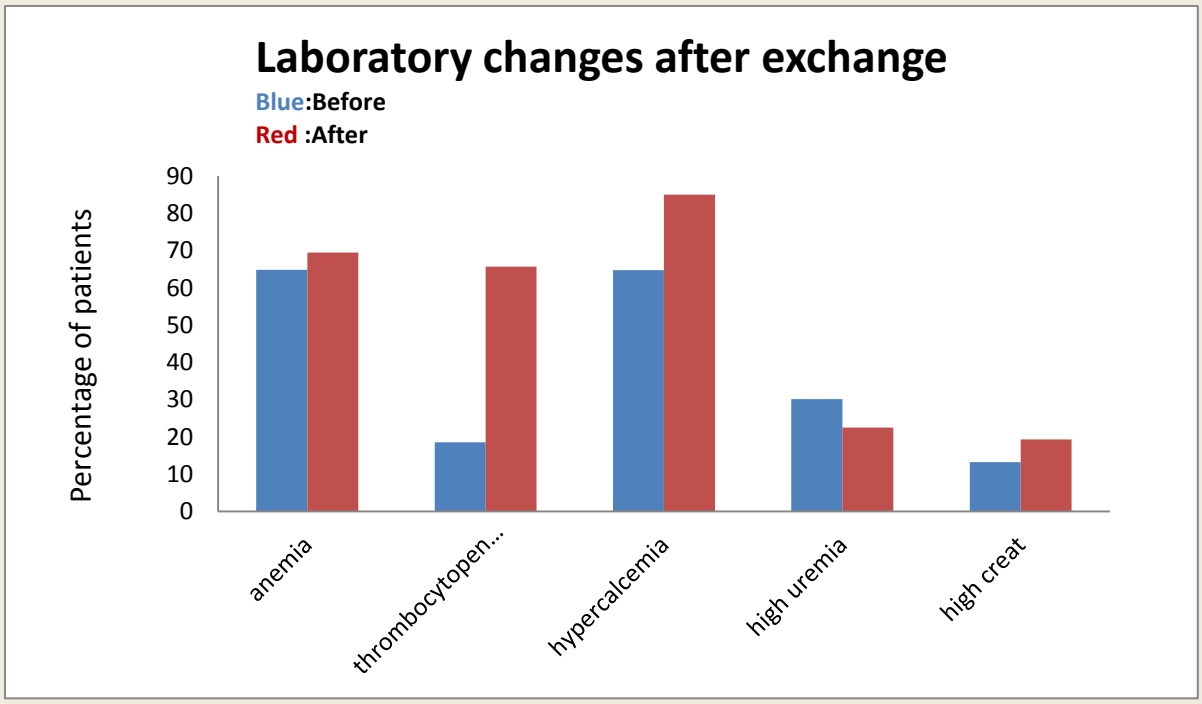


Figure 6: laboratory results changes after exchange

As the majority of our patients were exchanged between three and seven days, and were term or near-term, we defined normal haematological values as Hb within the range of 17.9±2.5 g/dl; WCC within the range of 5 and 21 x 109/l; and platelets within the range of 150-450 x 103

/µl(40); and we considered normal electrolytes within the following range: sodium (135-147 mmol/l), potassium (3.5-6.0mmol/l); urea(1.4-6.1 mmol /l); creatinine less than 104 for preterms, and 81 for term babies. Calcium, magnesium and phosphate were considered normal within the following ranges 2.1-2.64mmol/l, 0.65-0.91mmol/l, 1.4-2.5 mmol/l ((20),(40)).

Table 3 : FBC changes after exchange

FBC before exchange				**FBC after exchange**				
Tests	Mean	Min	Max	tests	Mean	min	max	T test
WCC(x 10^9/l)	12.2±7.1	3.1	40.1	WCC	10.0±7.9	1.64	34	(p=0.26)
HB(g/dl)	13.6±2.7	8.1	22	HB	14.1 ±1.8	10.4	18.4	(p=0.12)
Plat(x10_3 /µl)	267±131	90	720	Platelets	137.1±118	14	520	(p=0.00)

Before exchange, the mean white cell count, haemoglobin, platelets were 12.2 x 10^9±7.1, 13.6 g/dl±25, and 267x 10^3/µl±131, respectively (See Table 4). The normal WCC were seen in 83.3%; leukopenia in 9.2%; leucocytosis in 7.41%; anaemia in 64.8%; and thrombocytopenia in 18.5% of the patients. The FBC after exchange showed leukopenia in 30%; anaemia in 69.4%; and thrombocytopenia was seen in 67.6% of the patients, while marked thrombocytopenia (less than 100 x 10^3/µl) was seen in 51.4% of those tested. Nine patients were transfused packed red cells, 2 patients received fresh frozen plasma, and 1 received platelet transfusion.

There was a significant statistical difference for reduction in platelets (p value=0.000).

Before exchange, CRP mean was 8.1 mg/l ±12.2, and an increase was noted (more than 10mg /l) in 19.6% of the infants. Of those with high CRP, 4 (33%) had a positive blood culture, while 3(25%) had abnormal white cell counts.

The admission blood culture was positive in 14 infants (25.9%). The following micro-organisms were isolated: escherichia coli (n=1); streptococcus pneumonia (n=1); coagulase negative staphylococcus (n=7); streptococcus viridans (n=2); acinetobacter baumani (n=1); pseudomonas (n=1); and micrococcus (n=1). A septic work up was repeated within a week in 29 (46%) patients, and only nine (31%) had a positive blood culture. The observed organisms in repeated blood culture were CONS (n=6), e-coli (n=2) and acinetobacter baumani (n=1).

Table 4: Electrolytes and renal function tests after exchange transfusion

Tests	Mean (mmol/l)	SD	Minimum	Maximum
Na	140.2	±7.6	114	151
K	4.5	±0.89	3.4	6.8
urea	10.6	±24.38	1	105
creat	61.4	±43.0	1.3	231
Ca	3.0	±53	1.93	4.15
Mg	0.91	±0.22	0.68	1.96
PO4	1.9	±0.53	0.79	4.71

There was a significant statistical difference for calcium and phosphate changes (p=0.00)

High urea and creatinine were found in 30.1% and 13.2% of the patients, respectively. After exchange, abnormal urea and creatinine were found in 22.5% and 19.3% of patients, respectively (see Figure 6).

Electrolytes imbalances were found in 24.4% (Sodium), 18.8% (potassium) before exchange. Approximately, 5.6% had hyponatremia and 18.8% had hypernatremia, while hyperkalemia was seen in seven (13.2%) infants and hypokalemia in three infants (5.6%). After exchange, full urea and electrolytes were measured in 31 (49%), hypernatremia was found in four (12.9%), hyponatremia in six (19.6%), hyperkalemia in five (16.1%) (See Table 4).

After exchange, there was no patient with hypocalcemia. In contrast, hypercalcemia was found in the vast majority, at 85% of the tested patients, with a mean of 3.0 mmol/l ± 0.53; and hyperphosphatemia was found in 52.9%; with hypophophatemia in 8.8% of infants.

There was a significant statistical difference for calcium and phosphate changes before and after exchange (p=0.00).

Morbidity and Mortality

Out of all patients, 34 (53.9%) infants were admitted with a diagnosis other than neonatal jaundice. The majority of these infants were admitted in neonatal unit (n=30) (see Table 6).

The most frequent diagnosis was suspected sepsis in 30 (78.9%) patients, and proven in five (16.6% of the suspected), with one case of confirmed meningitis. Sepsis was the cause of death for the three babies. Respiratory disease was found in 25 (65.7%) of the babies in the neonatal ward. HMD accounted for the majority (13 or 52%), with congenital pneumonia (5 or 20%), transient tachypnoea of the newborn (eight or 32%) and one case of meconium aspiration syndrome. Three babies were suspected to have necrotising enterocolitis, and this was confirmed in one case.

No baby admitted in neonatal unit was reported to have BIND. One was diagnosed with severe birth asphyxia, and six (15.7%) had an abnormal cranial ultrasound (two had intraventricular haemorrhage), one had agenesis of corpus callosum, and two had periventricular leucomalacia.

In the general ward, the most frequent diagnosis was suspected sepsis in 19 (76%), proven in 9(36%). Among them, two had meningitis. Seven (11.1%) infants were noted to have abnormal neurological examination before ET. Signs described included hypotonia in one infant, hypertonia in three infants, seizures in three infants and high pitched cry in one infant and opisthotonus in three infants. Of those who had abnormal neurological findings, five were diagnosed with kernicterus before exchange, and three were discharged with abnormal neurology (signs described were hypotonia in one patient, and increased reflexes in two patients).

Table 5 : Recapitulation of details of exchange transfusion according to gestational age

Variables	Gestational age				
Gestational age	Less than 32 weeks n=9	32- 36 weeks n = 17	More than 36 weeks n=31	Missing data on GA n=6	Total n=63
Total bilirubin (mmol/l)	242±76	375±130	519±149 SD	404±61	427±164.1
Diagnosis other than Neonatal jaundice	9 (100%)	12 (70.5%)	10 (32.2%)	3 (50%)	34 (53.9%)
Patient with Complication during and after exchange	3 (30%)	2 (5.8%)	9 (29%)	-	14 (22.2%)
Patients with neurological manifestations	-	-	6 (19.3%)	1 (16.6)	7 (11.1%)
TB after exchange (mmol/l)	177± 121	255 ± 151	279±116	322±63	262±128
Patients with thrombocytopenia after exchange	2 (50%) Tested: 4	7 (70%) Tested: 10	12 (%) Tested: 16	2 (50%) Tested: 4	23 (67.6% of the tested)
Patients with hypercalcemia (mmol/l)	2 (20%) Tested: 5	11 (100%) Tested:11	17 (75%) Tested :20	4 (100%) Tested:4	34 (85%)
Hospital stay after exchange (days)	M=18.5 (IQR11.5-28.5)	M=12 (IQR6-21)	M=6 (IQR5-8)	M=14.5 (IQR3-26)	M=8 (IQR=3-18)
Death	1	1	1		3 (4.76%)

Complications

There were 10 patients who developed complications after ET in neonatal ward, with hypoglycaemia in two patients; hyperglycaemia in one patient; bleeding in two patients; renal failure in two patients; two apnoeas that required ventilation; one patient with NEC. The most frequent laboratories abnormalities in this ward were thrombocytopenia in more than 57% and hypercalcemia in 52.9 percent.

Table 4: Comparison between admission ward and neonatal ward

Criteria	Neonatal ward (n=38)	General ward (n=25)
Age at exchange	M=4:IQR3-6	M=5:IQR:(2-6)
Gestational age	34.8±4.8	37.3±2.1
Birth weight	2.05±0.93	2.7 ±0.58
TB before ET	351+143	531+132
TB after exchange	242±159	289±59
Patients with Neurological Manifestations before exchange	-	7 (28% of ward admission)
Complications during exchange	10(26.3%)	4(16%)
Thrombocytopenia	12 (57% of the tested)	11 (78% of the tested)
hypercalcemia	18 (52.9% of the tested)	16 (88.8% of the tested)
Discharge time after exchange	M=9 (IQR5.5-20)	M=6(IQR:5-9)
Death	3(4.7%)	-

M=Median

There were four complications reported in general ward: apnoea requiring ventilation (n=1); seizure (n=1); hypoglycaemia (n=1); and bleeding (n=1). In the general ward for babies, hypercalcemia was seen in 88.8% and thrombocytopenia in 78% of infants.

Out of all the patients studied, three infants died (4.7%), although no baby seemed to have died as a direct result of ET. Sepsis was suspected in two cases of death, in infants that died at six days and 10 days of age, repsectively. The sepsis was suspected even before ET, as evidenced by clinical features, high CRP, thrombocytopenia, but negative blood culture were found in both cases. The first one was a male baby born before arrival at 29 weeks, with a birth weight of 1.32 kg, who was admitted into the neonatal unit. The second death concerned a 2.8 kg baby girl, referred to CMJAH and admitted into the neonatal unit for sepsis, whose exchange transfusion procedure was complicated by apnoea, and who was ventilated until she died 4 days after exchange transfusion.

Sepsis was proven in the third case of death, where e.coli has been isolated in a clinically septic baby, born at 32 weeks of gestation age in CMJAH with a birth weight of 1.3 kg; who had components of perinatal asphyxia as shown by APGAR less than 5/10 at five minutes, and who developed perforated NEC and demised at seven days of age (three days after exchange).

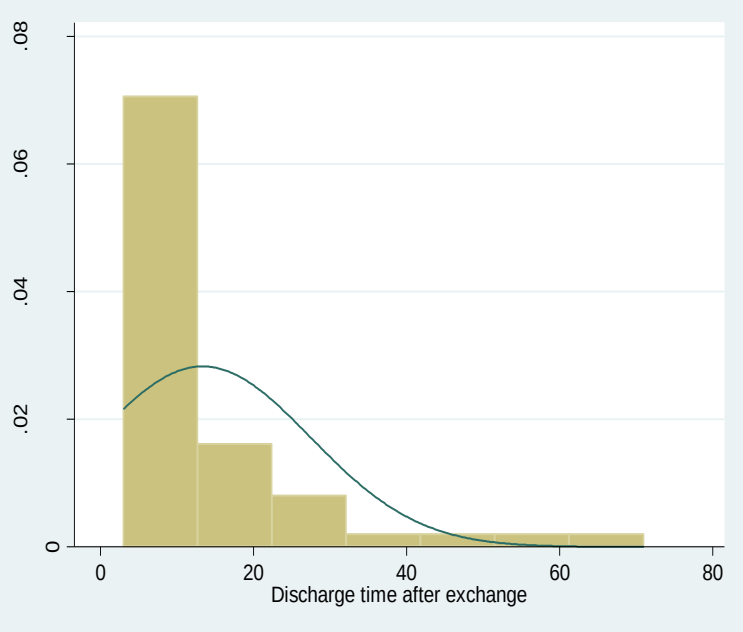


Figure 7: Discharge time after exchange

The median discharge time after exchange was eight days, with IQR of five days and a maximum of 18 days.

CHAPTER 4: DISCUSSION

Despite the decline in number of severe neonatal hyperbilirubinemia due to the widespread use of phototherapy, declining family size and anti D immunoglobulin (35), there are still many cases of severe hyperbilirubinemia. Many studies, including the present one, have been done on severe hyperbilirubinemia in order to identify the risk factors of the adverse effects of ET when compared to the risk of Bilirubin-induced neurological dysfunction. Our results have shown that most of our exchanged patients had no previously identifiable risk factors, as the majority were term babies, and formula fed. A significant number presented very late, with abnormal neurological examination (11.1%), and advanced sepsis; of which three infants died.

The majority of exchanged babies are term babies (54.3%). This is an agreement with other studies such as that by Badiee (25), who found a predominance of term babies in exchanged transfusion population with the mean gestation age of 38.8 weeks ±1.8 weeks. This may be explained by the fact that preterm babies are specifically observed in hospitals and managed early, compared to term babies, who are discharged sooner after their birth.

It was noted in the present study, that the patients with signs of kernicterus were all term, and were readmitted. This can be partly explained by the fact that clinical features of kernicterus are less obvious in preterm infants, and 15% have no obvious neurologic symptoms, despite very high levels of bilirubin (2).

The historical findings that male babies are more susceptible to disease is confirmed in our study, as the majority of our patients were males (58.7%). It was interesting to note that the

majority of our exchanged babies had no obvious risk factors, apart from suspected sepsis: only 43.9% were breastfed; only two had significant haematomas and there were no evidence of haemolysis in most of the patients. This may still be explained by the fact that the patients with identifiable risks receive more attention and benefit from intensive phototherapy and other management modalities early, thus avoiding exchange transfusion. It is thus recommended to increase awareness and early intervention in term babies without risk factors of severe hyperbilirubinemia.

Antenatal care was suboptimal in our patients, as only 65% of the mothers had antenatal blood recorded. Birth asphyxia was comparable to an international standard (41), as only four (8.5%) patients had APGARS, less than seven at five minutes, and only one was diagnosed as having severe birth asphyxia, due to a difficult breech delivery.

The majority of our babies (53.9%) had associated diagnoses other than jaundice, results which prove similar to other studies such us that of Patra(13), which showed comorbidities and abnormal neurological examination neurological examination in 62% and 12.5% of the patients studied, respectively .

Blood cultures were positive in seven patients, and gram-negative sepsis was confirmed in only two patients. This is not in keeping with other studies, which have shown the predominance of gram-negative sepsis in babies presenting with jaundice (2).

The age at ET in the present study was similar to that of some other series (25);(42), whereas others report the majority of exchange to be between 48 and 72 hours (25);(13);(43). In our case, only 31.4% were exchanged before 72 hours. This could be explained by the late detection of jaundice in our study, or non-pathological causes of jaundice in contrast to the findings of other studies, where pathological jaundice was found to be the most frequent (see Table 7). Our rate of 7.9% of ABO incompatibility is extremely low when compared to the previous studies done in black South African (Durban), which showed ABO incompatibility set up in 58% of infants, resulting in exchange in 44.4% in 1981 (11). Our results compare to a study in Canada, which found a rate of ABO incompatibility of 12.7%, with a very high rate of undetermined causes (42). Our low rate could be explained by a high number of missing records on blood groups and coombs variables, as well as failure to record causes of jaundice in most of the summaries; or it could mean a difference in ABO set up of the studied population (Durban) when compared to ours, which is a less likely hypothesis. Our effort to consult laboratory and blood bank databases could not clarify this matter.

Table 5: Jaundice causes in different studies

Series ,country ((number of participants)	RH disease	ABO incompatibility	G6PD /Red cell defects ed cells defects	Idiopathic and others *
Bedie ,Iran (68)	11.7%	22%	19.1%	49.2%
Bhat, India (92)	21.3%	25%	0	54.6%
Patra, USA (55)	34%	22%	N=2	44%
Masood, Pakis (50)	8%	40%	N=2	36%
Ibekwe, Nigeria (40)	5%	20%	5%	50%
Our study (63)	6.3%	7.9%	N=1	84.1%

* = sepsis, low birth weight, prematurity, hematoma,

Our total mean bilirubin before the first exchange was low compared to that reported in Patra review (19mg/dl±8=324mmol/l±136), but similar to other series where the mean maximum bilirubin were found to be 24.9 mg/dl ±3.8 (423.4mmol/l ±64.6), in Bhat's study and 29.3 (498mmol/l ±103.7) in Behjati's study. In our study, only three patients (4.7%) required a second ET. This rate of multiple exchange is close to that seen in Bhat's study (6.5%), but well

below the rate found in other studies (12.3% by Patra, 32% by Jackson) (24);(38). This difference can be explained by the population differences, and different causes of jaundice. The procedure was without complications in the majority of the patients, but there were few serious complications that can be related to the procedure.

Of concern were three patients with apnoea, requiring ventilation post exchange. The rate of complications is comparable to the one found in other studies (see Table 8: Complications of ET). The majority of laboratory abnormalities were thrombocytopenia and hypercalcemia however, in other studies, thrombocytopenia and hypocalcaemia are the common findings after ET. Hypercalcemia could be explained by the routine presupplementation of blood with calcium gluconate, as recommended in our ET guidelines. Therefore, we conclude that the supplementation of blood with calcium gluconate is not necessary, which is in agreement with the findings of other authors (24);(25).

Table 6: Complications of ET in different studies

Complications	**Our study (n=63)**	**Patra (USA) (n=55)**	**Bhat (India) (n=92)**	**Ibekwe (Nigeria) (n=40)**
Death	1 (1.58%)	1 (2%)	2 (2.1%)	7 (17.5%)
Apnoea	3 (4.7%)	-	1 (1%)	1 (2.5%)
Seizure	1 (1.58%)	1 (2%)	1 (1%)	-
Hypoglycaemia	3 (4.7%)	2 (4%)	4 (4.3%)	-
Hyperglycaemia	1 (1.5%)	-	-	-
NEC=1	1 (1.58%)	-	1 (1%)	1 (2.5%)
Bleeding=B/DIC=D	B=3 (4.7%)	-	D=1 (1%)	D=1 (2.5%)
Thrombocytopenia	67.6%	29 (44%)	6 (6.5%)	-
Hypocalcaemia	-	19 (29%)	1 (1%)	-
Hypercalcaemia	85%	-	-	-
Acute renal failure	2	1	-	

Within one week of ET, sepsis was still suspected in 46%, but only 20.6% had a positive blood culture, with the majority of organisms being Coagulase negative staphylococcus. This maybe a skin contaminant, but it is also known to be the most frequent cause of nosocomial sepsis (42).

Sepsis was the cause of deaths in the 3 observed cases. None of the deaths appeared to be as a direct result of hyperbilirubinemia or ET, as all the babies who died were assessed as critically sick before ET. One patient died as a result of perforated NEC, which is a well recognised complication of ET, but this infant had other risk factors of NEC (was born prematurely, by breech, with some components of perinatal asphyxia, as evidenced by Apgar less than 5 at 5 minutes, and proven sepsis by e-coli isolated in the initial blood culture).

This makes the overall mortality in this study to be 4.7%, with only one death (1.5%) due to NEC seems to be associated with ET, which is comparable to other studies, where the mortality associated with ET is evaluated to be between 0.66% and 3.5% (24).

The time of discharge after exchange varied greatly, from three to 71 days, and no patients had permanent sequelae attributable to ET. However, among five patients admitted with diagnosis of kernicterus, and others with abnormal neurological findings, three were discharged with findings attributable to kernicterus. The causes of jaundice in these two infants were ABO incompatibility, and one had been exchanged twice.

This shows that kernicterus remains a serious cause of concern in our setting, contrary to the conclusion reached by Watchko, that kernicterus is a rare disease, with too many infants undergoing ET unnecessarily (43).

Conclusion

Though most of the infants presenting with severe hyperbilirubinemia respond to intensive phototherapy, a good number still need ET to prevent kernicterus. The majority of exchanged babies are term, readmitted, and most of them are exchanged after 72 hours. Kernicterus is an avoidable disease, but we had three cases with non-resolved neurological dysfunction due to kernicterus. In this study, ET is shown to be a relatively safe procedure, but one has to be aware of many adverse effects, even though most of them are minor and asymptomatic laboratory abnormalities. Only one death due to NEC could be linked directly to ET, although this baby was critically sick even before the procedure, thus considering our mortality related to ET to be 1.5 percent.

Recommendations

Kernicterus can be prevented by carefully following babies with jaundice. Guidelines recommend screening of bilirubin at 48 hours after discharge, or to measure serum bilirubin if an infant looks jaundice prior to discharge. With regards to this, we recommend transcutaneous bilirubin of all infants prior to discharge, without weight consideration, as it has been shown in this study that term and appropriate for the gestational age are those detected late and present with signs of kernicterus requiring ET. ET was relatively safe, however cardio-respiratory monitoring and resuscitation equipment should be kept ready during exchange transfusion and in the hours following exchange transfusion. The majority of patients' complications are laboratory abnormalities after exchange transfusion; thus we suggest close

laboratory follow up during the 72 hours after exchange for platelets, electrolytes and renal function. Effort should be made to use fresh, whole blood less for than 72 hours for the purposes of exchange transfusion, to avoid thrombocytopenia. Supplementing blood with calcium gluconate is not necessary, as hypercalcemia was a common complication.

Sepsis was suspected in the majority of the patients, and was a contributive factor in all cases of mortality, therefore all patients with neonatal jaundice, especially preterm patients, should be scrutinised for infection and promptly managed if there is any suspicion of such.

Only 65% of the mothers had all antenatal blood documented, so we recommend the staff in referral hospitals, surroundings clinics and hospitals to increase their efforts in performing those tests, as well as in documenting the results – especially the rhesus result which showed significance in our study.

As an important number of readmitted babies presented for the first time with abnormal neurogical examination, newborn infants, who are discharged early, should go to the clinic at 48 hours for a jaundice check.

Though the ET procedure had a few serious complications, cardio respiratory monitoring is important, and equipment should be made ready to deal with any emergency.

Babies who had been exchanged need close follow up in the first 72 hours of exchange for apnoea, sepsis, bleeding, electrolytes and renal dysfunction.

As missing data was very common in file and summaries, doctors should put more effort into documentation and the record of every important point and should be filled into the discharge summaries thoroughly.

Furthermore, all the medical stuff, nurses, filing systems and ward clerks should make sure that no file is lost and that identification and main diagnosis are written clearly.

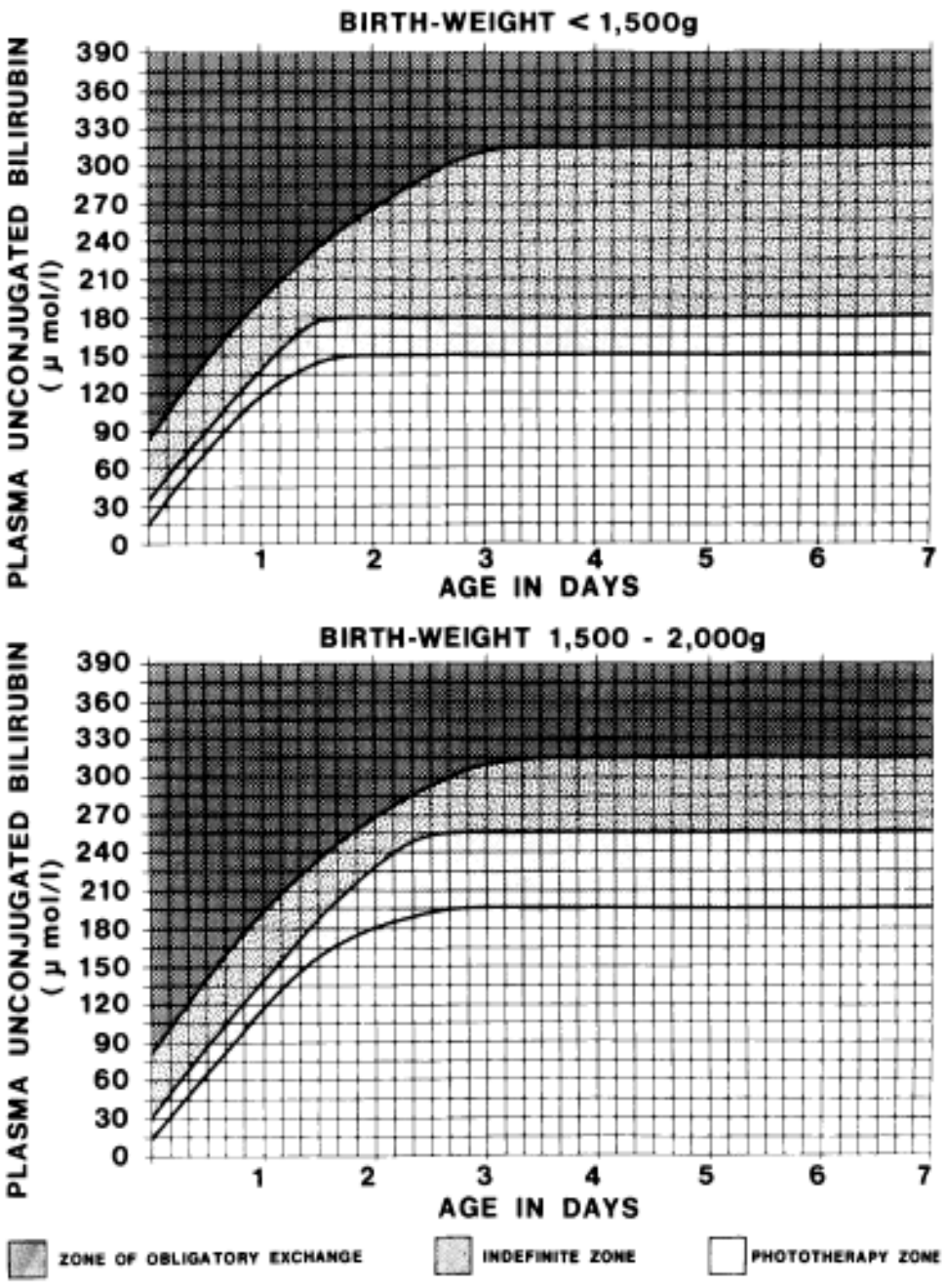
Appendix 1: Data Collection Form

	1	2
1. Study Number		
2. Ward: 1) Paediatric ward **2)** Neonatal ward		
3. DOB		
4. Place of birth		
Gender		
5. Birth weight (g)		
6. Birth head circumference (cm)		
7. Birth length (cm)		
8. APGAR 1) APGAR Score at 1 minute 2) APGAR Score at 5 minutes 3) APGAR Score at 10 minutes		
9. Gestational Age (weeks)		
10. Feeding mode 1) Breastfeeding 2) Formula 3) Mixed		
11. BLOOD GROUP 1) BABY 2) MOTHER 3) BABY COOMBS		

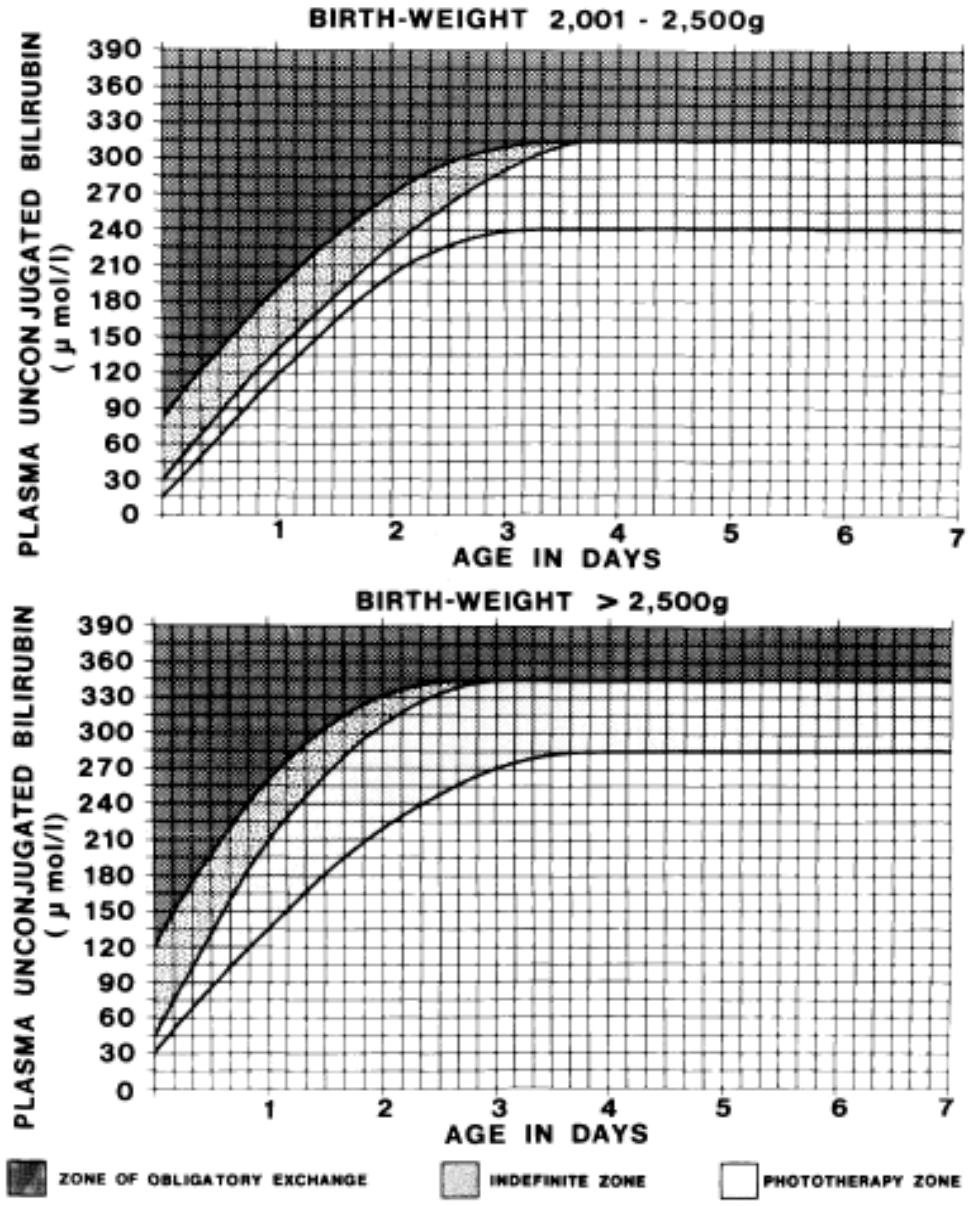
4) MOTHER COOMBS		
12. CRP		
13. BC		
14. Lab results before exchange and after exchange (per exchange) 1) WCC 2) HB 3) PLAT 4) Ca 5) Mg 6) Phosphate 7) Na 8) K 9) Urea 10) Creat		
15. Complications during exchange (per exchange) 1) Cardio-pulmonary arrest 2) Hypothermia 3) Hypotension 4) Hypoglycaemia 5) Seizures 6) Apnoea 7) other		
16. Hyperbilirubinemia complications 1) Hypotonia 2) hypertonia 3) Poor feeding 4) Seizures 5) Irritability 6) Bulging fontanel 7) Others:		

17. Discharge 1. Date of death 2. Date of discharge		

Appendix 2 a : (33)



Appendix 2 b (33)



Appendix 3(36)

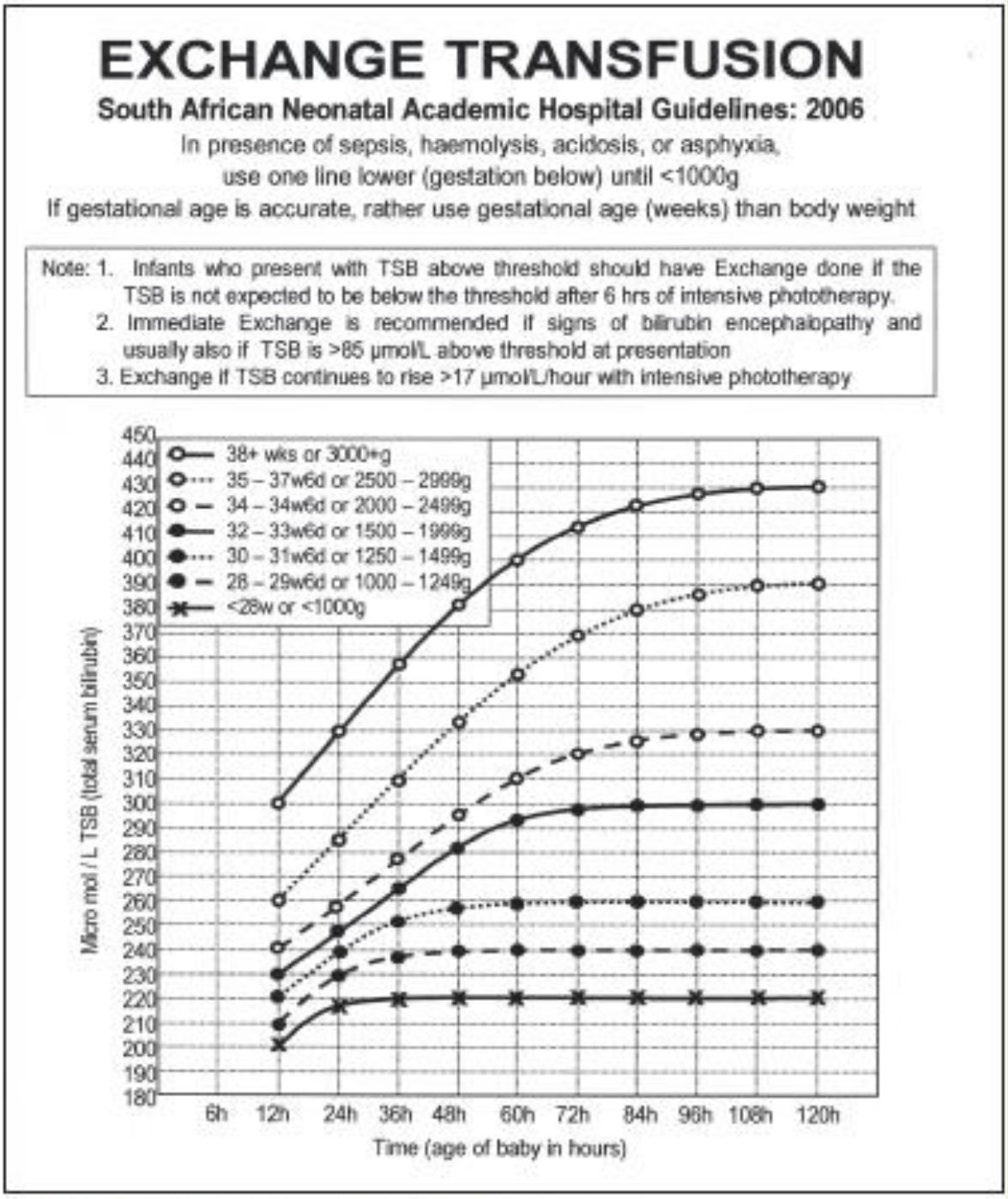


Fig. 5. Exchange transfusion guidelines for all gestational ages.

Appendix 4 Ethic clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Rugamba Gilbert

CLEARANCE CERTIFICATE	M120439
PROJECT	Review of Exchange Transfusion for Neonatal Hyperbilirubinemia at CMJAH from 2006-2011
INVESTIGATORS	Dr Rugamba Gilbert.
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	04/05/2012
+DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04/05/2012 CHAIRPERSON .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Professor D Ballot

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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