RETROSPECTIVE ASSESSMENT AND MANAGEMENT OF NEONETAL JAUNDICE CASES IN GOVERNMENT HOSPITAL TIRUPUR

Dissertation Submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

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In partial fulfilment for the award of the degree of

MASTER OF PHARMACY

IN

(PHARMACY PRACTICE)

Submitted by

ANEES RAHMAN.T

REGISTER NO: 261640402

Under the guidance of

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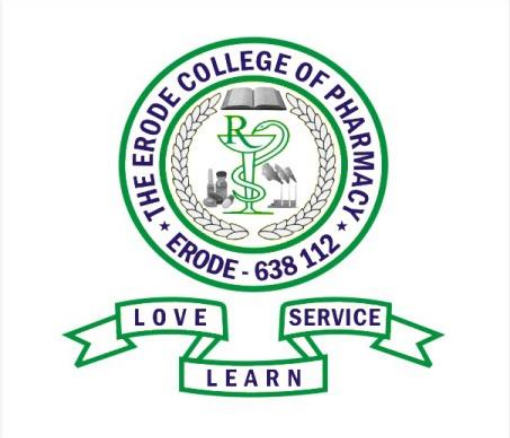

APRIL - 2018

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CERTIFICATE

This is to certify that the dissertation work entitled **"Retrospective assessment and management of neonatal jaundice cases in government hospital tirupur"** submitted by **Register No: 261640402** to The Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment for the degree of **Master of Pharmacy in Pharmacy Practice** is the bonafide work carried out under the guidance and direct supervision of **Prof. Dr.R.SENTHIL SELVI, M.Pharm., Ph.D.,** Head, Department of Pharmacy Practice, The Erode College of Pharmacy and Research Institute, Erode- 638112, during the academic year 2017-2018.

Prof. Dr. R. SENTHIL SELVI, M.Pharm., Ph.D.,
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EVALUATION CERTIFICATE

This is to certify that dissertation work entitled **"Retrospective assessment and management of neonatal jaundice cases in government hospital tirupur**", submitted by **Register no: 261640402** to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment for the degree of **Master of Pharmacy** is a bonafide thesis work carried out by the candidates at the Department of Pharmacy Practice, the **Erode College Of Pharmacy and Research Institute, Erode-638112** and was evaluated by us during the academic year **2017-2018.**

1. INTERNAL EXAMINERS **2.EXTERNAL EXAMINERS**

3. CONVENER OF EXAMINATION

Examination Centre: The Erode College Of Pharmacy and Research Institute.

Date:

DECLARATION

The research work embodied in this dissertation work entitled **"Retrospective assessment and management of neonatal jaundice cases in government hospital tirupur "** was carried out by myself in the Department of Pharmacy Practice, The Erode College of Pharmacy and Research Institute, Erode, under the guidance and direct supervision of **Prof. Dr. R.senthil selvi, M.Pharm., Ph.D.,** Head, Department of Pharmacy Practice, The dissertation is submitted to **The Tamil Nadu Dr. M.G.R Medical University, Chennai,** as a partial fulfilment for the award of degree of **Master of Pharmacy in Pharmacy Practice** during the academic year 2017-2018.

This work is original and has not been submitted in part or full for the award of any other Degree or Diploma of this or any other university.

Place: Erode **Register No: 261640402**

Date:

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Register No: 261640402

TABLES

FIGURES

ABBREVIATIONS

UDGT	URIDINE DPHOSPHATE GLUCURONOSYL TRANSFERASE
QBP	QUALITY BASED PROCEDURE
DAT	DIRECT ANTIGLOBULINE TEST
IAT	INDIRECT ANTIBODY TEST
PTx	PHOTOTHERAPY
LED	LIGHT EMITTING DIODES
TSB	TOTAL SERUM BILIRUBIN
IVIG	INTRA VENOUS IMMUNO GLOBULINS
DVET	DOUBLE VOLUME EXCHANGE TRANSFUSION
PJ	PROLONGED JAUNDICE
BMJ	BREAST MILD JAUNDICE
NVD	NORMEL VAGINEL DELIVERY
LSCS	LOWER SEGMENT CAESSOREAN SEGMENT
LBW	LOW BIRTH WEIGHT
ADR	ADVERSE DRUG REACTION
AAP	AMERICAN ACADEMI OF PEDIATRICS
ABE	ACCUTE BILURUBIN ENCEPHALOPATHY
BIND	BILURUBIN INDUCED NEUROLOGICAL DYSFUNCTION
DVET	DOUBLE VOLUME EXCHANGE TRANSFUSION

INDEX

PROFORMA

PATIENT DETAILS

NAME :

IP NO :

SEX :

AGE: days

DOB:

GESTATIONAL AGE:

BIRTH WEIGHT:

CHIEF COMPLAINTS:

DIAGNOSIS:

OUTCOME OF HOSPITALIZATION: Survived [ ], Died [ ], Unknown [ ]

MOTHER'S DETAILS

NAME :

AGE :

BLOOD TYPE:

TYPE OF DELIVERY:

PAST MEDICATION HISTORY :

PREVIOUS COMPLICATIONS OF PREGNANCY:

PARA: GRAVIDA:

PRESENCE OF ANY OF THE FOLLOWING : **Y/N**

- Prematurity < 38 weeks [ ]
- Low birth weight [ ]
- History of hyperbilirubinemia [ ]
- ABO/ Rh incompatibility [ ]
- Non optimal feeding [ ]
- Central hematocrit more than 65% [ ]
- Presence of signs of underlying illness like

  Vomiting/lethargy/poor feeding/temperature instability/apnea. [ ]
- Jaundice visible on the first day of life [ ]
- Newborn's trunk is distinctly yellow stained

  with yellow tinge of palms and soles. [ ]
- Geographic prevalence of G-6PD deficiency [ ]
- Primipara mother [ ]
- Reduced sucking [ ]
- Fever [ ]
- Other infections eg septicemia, UTI [ ]
- Diarrhoea [ ]

DAY 1

General physical examination:

Wt: Icterus:

Color: Abdomen:

Vital signs:

Temp: HR:

RR:

Laboratory investigations:

Hb : TWC:

Platelet count: CRP:

Blood culture:

Serum Bilurubin :

Total :

Direct:

Treatment:

DAY 7

General physical examination:

Wt: Icterus:

Color: Abdomen:

Vital signs:

Temp: HR:

RR:

Laboratory investigations:

Hb : TWC:

Platelet count: CRP:

Blood culture:

Serum Bilurubin :

Total :

Direct:

Treatment :

DAY 14

General physical examination:

Wt: Icterus:

Color: Abdomen:

Vital signs:

Temp: HR:

RR:

Laboratory investigations:

Hb : TWC:

Platelet count: CRP:

Blood culture:

Serum Bilurubin :

Total :

Direct:

Treatment :

OTHER INFORMATION:

INFORMED CONSENT

Participant written informed consent

I understand that my participation is voluntary and that I may withdraw from this study at any time without giving any reason or to decline to answer any particular question in the study. I consent the members of the study to have access to my response and to publish the result, provided my identity is not revealed. I voluntarily agree to participate in the study.

Participant signature with date

INTRODUCTION

RETROSPECTIVE STUDIES

Retrospective studies are conceived after some people have already developed the outcomes. The investigations find the subjects and begin collect information about them after outcomes have already occurred. These studies are very efficient for studying rare or unusual exposure, but there are many potential problems. Sometimes exposure status is not clear when its not necessary to go back, in time and use whatever data is available, especially because the data being used was not designed to answer a health question.

A cohort is identified and classified as to exposure to the risk factor at some date in the past and followed up to the present to determine incidence rate. This is called a retrospective cohort studies/ historical prospective study prospective study of past data.

Retrospective study is an epidemiological study in which participating individuals are classified as either having some outcomes (cases) or lacking (control); the outcome may be a specific disease, and the person histories are examined for specific factors that might be associated with the outcomes. Cases and controls are often matched with respect to certain demographic or other variables but need not be.[1]

ADVANTAGES

Retrospective cohort studies exhibit the benefits of cohort studies and have distinct advantages relative to prospective ones:

- They are conducted on a smaller scale.
- They typically require less time to complete.
- They are generally less expensive, because resources are mainly devoted to collecting data.
- They are better for analyzing multiple outcomes.
- In a medical context, they can potentially address rare diseases, which would necessitate extremely large cohorts in prospective studies.

Retrospective studies are especially helpful in addressing diseases of low incidence, since affected people have already been identified so. The fact that retrospective studies are generally less expensive than prospective studies may be another key benefit. [2]

DISADVANTAGES

Certain important statistics cannot be measured. Large bias may be introduced both in the selection of control and in recalls of past exposure to risk factors.

DRUG UTILIZATION STUDY

Drug utilization study can be targeted towards any of the following links in the drug use chain:

- The systems and structures are surrounding drug use

  E.g: How drugs are ordered, delivered and administrated in a hospital or health care facility.

- The processes of drug use

  E.g: What drugs are used and how they are used and doses, their use comply with the relevant criteria, guidelines or restriction.

- The outcomes of drug use.

  E.g: Efficacy, Adverse drug reactions and the use of resources such as drugs, lab tests, Hospital beds, or procedures.[3]

CROSS-SECTIONAL STUDIES

Cross sectional data provide a snap shot of drug use at a particular time (e.g – over a year a month or a day). Used for making comparison with similar data collected over the same period in a different country, health facility or ward and could be drug, problem, indication, prescriber or patient based. It can be carried out before and after an educational or other intervention. Studies can measure drug use, or can be criteria based to assess drug use in relation to guidelines or restrictions.

LONGITUDINAL STUDIES

It's about the trend in drug use. Drug based longitudinal data can be on total drug use as obtained through a claims data base or the data may be based on a statistically valid sample of pharmacies or medical practitioners. It can be obtained by repeated cross sectional studies. Data collection is continuous, but the practitioner surveyed therefore the patients are continually changing. It gives information about over all trends, but not about prescribing trends for individual practitioners or practices.

CONTINUOUS LONGITUDINAL STUDIES

Here, data at the individual practitioners and patient level can be obtained. Claim data base are often able to follow individuals patients unique identifier. Data provide information about concordance with treatment based on the period between prescriptions co-prescribing, duration of treatment etc.. These data bases are very powerful and can address a range of issue including reasons changes in therapy, ADR and health outcomes.

NEONATAL JAUNDICE

Neonatal jaundice is a yellowish discoloration of the white part of the eyes and skin in a newborn baby due to high bilirubin levels. Other symptoms may include excess sleepiness or poor feeding. Complications may include seizures, cerebral palsy, or kernicterus.[4]

In many cases there is no specific underlying disorder (physiologic). In other cases it results from red blood cell breakdown, liver disease, infection, hypothyroidism, or metabolic disorders (pathologic). A bilirubin level more than 34 μmol/l (2 mg/dL) may be visible. Concerns, in otherwise healthy babies, occur when levels are greater than 308 μmol/L (18 mg/dL), jaundice is noticed in the first day of life, there is a rapid rise in levels, jaundice lasts more than two weeks, or the baby appears unwell. In those with concerning findings further investigations to determine the underlying cause are recommended.

The need for treatment depends on bilirubin levels, the age of the child, and the underlying cause. Treatments may include more frequent feeding, phototherapy, or transfusions. In those who are born early more aggressive treatment tends to be required. Physiologic jaundice generally lasts less than seven days. The condition affecting over half of babies in the first week of life Of babies that are born early about 80% are affected.[2]

TYPES

1. Physiological jaundice [5]

- Appears after 24 houres.
- Maximum intensity by $4^{th} – 5^{th}$ day interm and 7^{th} day in preterm.
- TSB level within normal centiles for age in hours
- Clinically not detectable after 14 days.
- Disappear without any treatment.

2. Pathological jaundice[6]

- Apeares within 24 houres of age.
- Increase of bilirubin >5mg / dl/day or at a rate of >0.2 mg / dl /hr.
- Serum bilirubin >95 percentile for age in hrs based on normogram.
- Jaundice persisting after 14 days in full term babies.
- Stool clay, white colored and urine staining clothes yellow.
- Direct bilirubin >2mg / dl or > 20 % of TSB.

EPIDIMIOLOGY

United States data

An estimated 50% of term and 80% of preterm infants develop jaundice, typically 2-4 days afer birth [9]. Neonatal hyperbilirubinemia is extremely common because almost every newborn develops an unconjugated serum bilirubin level of more than 30 µmol/L (1.8 mg/dL) during the first week of life. Incidence figures are difficult to compare because authors of different studies do not use the same definitions for significant neonatal hyperbilirubinemia or jaundice. In addition, identification of infants to be tested depends on visual recognition of jaundice by health care providers, which varies widely and depends both on observer attention and on infant characteristics such as race and gestational age [10].

With the above caveats, epidemiologic studies provide a frame of reference for estimated incidence. In 1986, Maisels and Gifford reported 6.1% of infants with serum bilirubin levels of more than 220 µmol/L (12.9 mg/dL)[11]. In a 2003 study in the United States, 4.3% of 47,801 infants had total serum bilirubin levels in a range in which phototherapy was recommended by the 1994 American Academy of Pediatrics (AAP) guidelines, and 2.9% had values in a range in which the 1994 AAP guidelines suggest considering phototherapy[12]. In some LMICs, the incidence of severe neonatal jaundice may be as much as 100 times higher than in higher-income countries [13].

International data

Incidence varies with ethnicity and geography. Incidence is higher in East Asians and American Indians and lower in Africans. Greeks living in Greece have a higher incidence than those of Greek descent living outside of Greece.

Incidence is higher in populations living at high altitudes. In 1984, Moore et al reported 32.7% of infants with serum bilirubin levels of more than 205 µmol/L (12 mg/dL) at 3100 m of altitude [14].

A study from Turkey reported significant jaundice in 10.5% of term infants and in 25.3% of near-term infants [15]. Significant jaundice was defined according to gestational and postnatal age and leveled off at 14 mg/dL (240 µmol/L) at 4 days in preterm infants and 17 mg/dL (290 µmol/L) in the term infants. Severe neonatal jaundice is 100-fold more frequent in Nigeria than in industrialized countries [13]. In Denmark, 24 in 100.000 infants met exchange transfusion criteria, while 9 in 100.000 developed acute bilirubin encephalopathy [16].

Studies seem to suggest that some of the ethnic variability in the incidence and severity of neonatal jaundice may be related to differences in the distribution of the genetic variants in bilirubin metabolism discussed above [17,18].

Race-related demographics

The incidence of neonatal jaundice is increased in infants of East Asian, American Indian, and Greek descent, although the latter appears to apply only to infants born in Greece and thus may be environmental rather than ethnic in origin. African infants are affected less often than non-African infants. For this reason, significant jaundice in an African infant merits a closer evaluation of possible causes, including G-6-PD deficiency. In 1985, Linn et

al reported on a series in which 49% of East Asian, 20% of white, and 12% of black infants had serum bilirubin levels of more than 170 µmol/L (10 mg/dL)[19].

The possible impact of genetic polymorphisms on ethnic variation in incidence and severity should be recognized. Thus, in a study of Taiwanese infants, Huang et al reported that neonates who carry the 211 and 388 variants in the *UGT1A1* and *OATP2* genes and who are breastfed are at particularly high risk for severe hyperbilirubinemia[17].

Sex- and age-related demographics

Risk of developing significant neonatal jaundice is higher in male infants. This does not appear to be related to bilirubin production rates, which are similar to those in female infants.

The risk of significant neonatal jaundice is inversely proportional to gestational age.

prognosis

Prognosis is excellent if the patient receives treatment according to accepted guidelines. Brain damage due to kernicterus remains a true risk, and the apparent increased incidence of kernicterus in recent years may be due to the misconception that jaundice in the healthy full-term infant is not dangerous and can be disregarded.

Mortality/morbidity

Kernicterus is a complication of neonatal jaundice. The incidence of kernicterus in North America and Europe ranges from 0.4-2.7 cases per 100,000 births[20]. Death from physiologic neonatal jaundice per se should not occur. Death from kernicterus may occur, particularly in countries with less developed medical care systems. In one small study from rural Nigeria, 31% of infants with clinical jaundice tested had G-6-PD deficiency, and 36% of the infants with G-6-PD deficiency died with presumed kernicterus compared with only 3% of the infants with a normal G-6-PD screening test result[21].

ETIOLOGY

Physiologic jaundice is caused by a combination of increased bilirubin production secondary to accelerated destruction of erythrocytes, decreased excretory capacity secondary to low levels of ligandin in hepatocytes, and low activity of the bilirubin-conjugating enzyme uridine diphosphoglucuronyltransferase (UDPGT).

Pathologic neonatal jaundice occurs when additional factors accompany the basic mechanisms described above. Examples include immune or nonimmune hemolytic anemia, polycythemia, and the presence of bruising or other extravasation of blood.

Decreased clearance of bilirubin may play a role in breast feeding jaundice, breast milk jaundice, and in several metabolic and endocrine disorders.

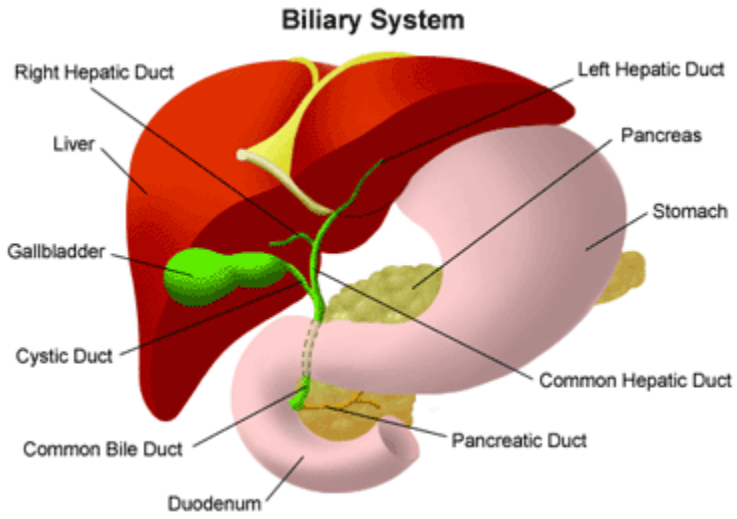
Risk factors include the following:

- Race: Incidence is higher in East Asians and American Indians and is lower in Africans/African Americans.
- Geography: Incidence is higher in populations living at high altitudes. Greeks living in Greece appear to have a higher incidence than those living outside of Greece.
- Genetics and familial risk: Incidence is higher in infants with siblings who had significant neonatal jaundice and particularly in infants whose older siblings were treated for neonatal jaundice. Incidence is also higher in infants with mutations/polymorphisms in the genes that code for enzymes and proteins involved in bilirubin metabolism, and in infants with homozygous or heterozygous glucose-6-phosphatase dehydrogenase (G-6-PD) deficiency and other hereditary hemolytic anemias. Combinations of such genetic variants appear to exacerbate neonatal jaundice[17,22,23,24].
- Nutrition: Incidence is higher in infants who are breastfed or who receive inadequate nutrition. The mechanism for this phenomenon may not be fully understood. However, when inadequate feeding volume is involved, increased enterohepatic circulation of bilirubin probably contributes to prolonged jaundice. Recent data have shown that breast milk jaundice correlates with higher levels of epidermal growth factor, both in breast milk and in infants' serum[25].Data suggest that the difference between breastfed and formula-fed infants may be less pronounced with some modern formulas. However, formulas containing protein hydrolysates have been shown to promote bilirubin excretion.
- Maternal factors: Infants of mothers with diabetes have higher incidence. Use of some drugs may increase the incidence, whereas others decrease the incidence. Some herbal remedies taken by the lactating mother may apparently exacerbate jaundice in the infant.
- Birthweight and gestational age: Incidence is higher in premature infants and in infants with low birthweight.
- Congenital infection

PATHOPHYSIOLOGY

Bile formation

Bile is a bitter yellow, blue and green fluid produced by hepatocytes in the liver, draining through the many bile ducts that penetrate the liver.During this process, the epithelial cells add a watery solution that is rich in bicarbonates and that dilutes and increases alkalinity of the solution. Bile then flows into the common hepatic duct, which joins with the cystic duct from the gall bladder to form the common bile duct. The common bile duct in turn joins with the pancreatic duct to empty into the duodenum



Constituents of bile:

Bile has various components, some of which are produced by hepatocytes in the liver. The main components include

- Water.
- Cholesterol.
- Bile pigments.
- Bile acids (glycocholic and taurocholic acid).
- Phospholipids (mainly lecithin).
- Bicarbonate and acids.

Bilirubin Production

Bilirubin is a product of the breakdown of the heme portion of hemoglobin that occurs when red blood cells are destroyed. Normally, bilirubin is excreted through the body after passing through the liver,spleen, kidneys and the gastrointestinal tract.

TYPES OF BILIRUBIN

There are two types of bilirubin circulating in the blood stream, unconjugated and conjugated.

1.Unconjugated bilirubin (or **indirect bilirubin**) can be found in circulating blood either Bound to albumin or not. It is fat-soluble and therefore more potentially toxic since it can bind to the tissues. Most of the unconjugated bilirubin is bound to albumin and transported to the liver. There, it is converted to glucuronic acid aided by uridine diphosphate glucuronosyl transferase (UDGT) to produce conjugated bilirubin. Once it becomes conjugated, it is sent to the gut for excretion via the biliary system. The unbound, unconjugated bilirubin is most likely to cross the blood-brain barrier and settle in the tissues where it can cause temporary or permanent neurological damage. Once it settles in the brain, it is there forever. The unbound bilirubin is difficult to measure but it is thought that it is directly related to the amount of unconjugated bilirubin.

2.Conjugated bilirubin (or **direct bilirubin**) is water-soluble and therefore is a more stable and non-toxic form. This allows it to be easily excreted from the body in urine and stool. Elevated levels of conjugated bilirubin may indicate evidence of liver disease.

FACTORS AFFECTING BILIRUBIN METABOLISM

Increased Production

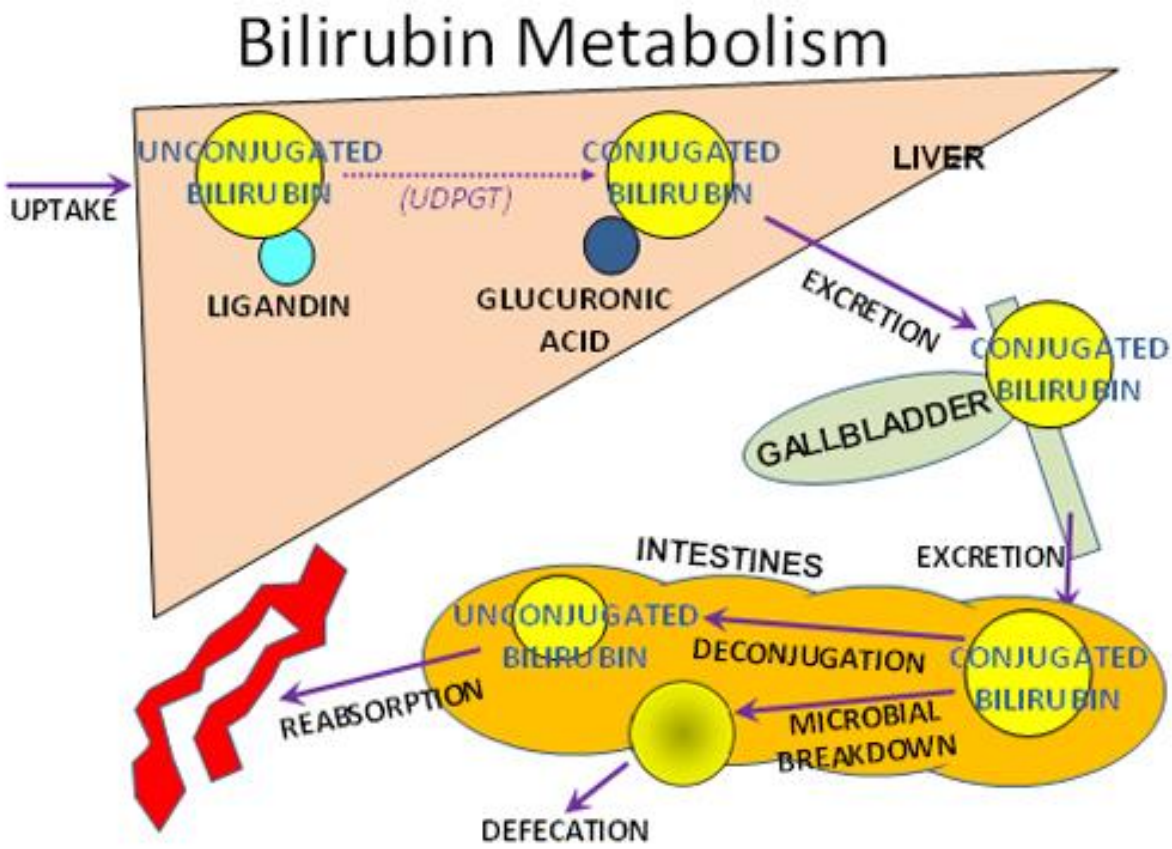
Any disorder which causes an increase in the number of red blood cells such as polycythemia, will lead to an increase in the amount of bilirubin produced as these cells breakdown. If there is a decreased amount of albumin available, there will be decreased binding capacity and conversion of indirect to direct bilirubin in the liver resulting in more indirect bilirubin that could potentially cross the blood-brain barrier or settle in the tissues. Bruising will also increase the breakdown of RBCs and increase bilirubin levels.

Decreased Conjugation

Conditions such as acidosis and hypoxia can also affect the bilirubin/albumin ratio for binding. The presence of any type of liver disease, metabolic or enzyme disorder will also

affect the ability of the body to convert bilirubin to the direct form to allow for excretion.

Because bilirubin is changed in the gut to urobilinogen with the assistance of the normal intestinal flora, anything that affects normal gut function can affect the excretion of bilirubin from the body. We know that at birth, the infant's gut is not fully developed so that prematurity and/or any disorder of the bowel, as well as antibiotic therapy, can slow the excretion of bilirubin.



Neonatal physiologic jaundice results from simultaneous occurrence of the following two phenomena[17] :

- Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates[26,9].
- Hepatic excretory capacity is low both because of low concentrations of the binding protein ligand in in the hepatocytes and because of low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).

Bilurubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes. In the first oxidation step, biliverdin is formed from heme through the action of heme oxygenase, the rate-limiting step in the process, releasing iron and carbon monoxide. The iron is conserved for reuse, whereas carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production.

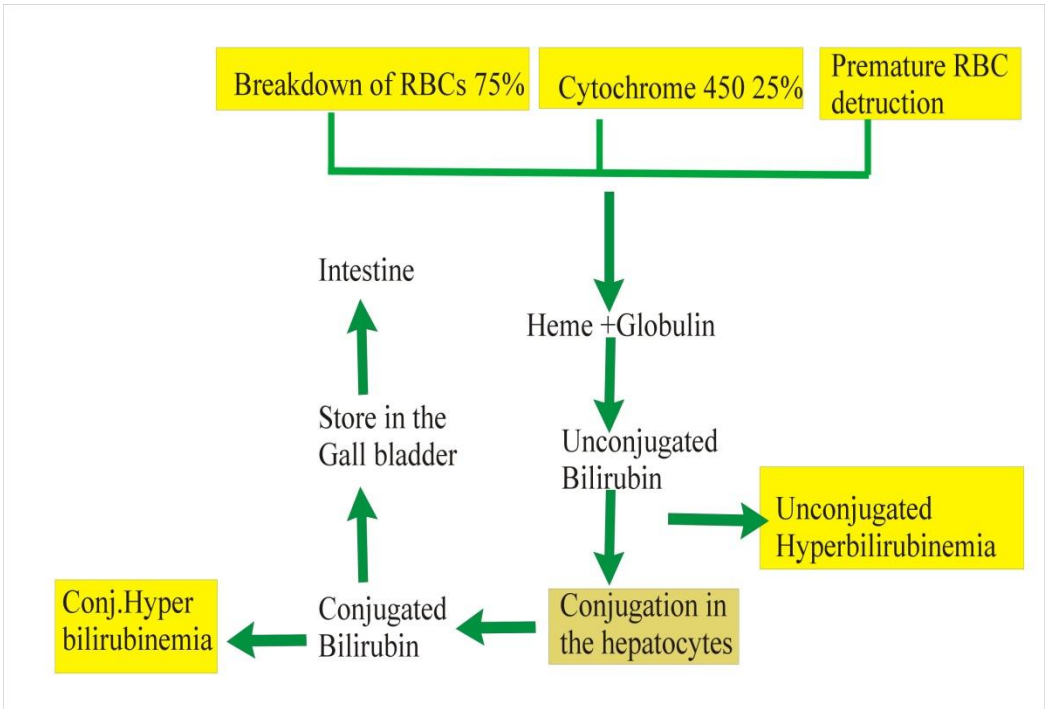
Next, water-soluble biliverdin is reduced to bilirubin, which, because of the intra-molecular hydrogen bonds, is almost insoluble in water in its most common isomeric form (bilirubin IXα Z,Z). Because of its hydrophobic nature, un conjugated bilirubin is transported in the plasma tightly bound to albumin. Binding to other proteins and erythrocytes also occurs, but the physiologic role is probably limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill.

The presence of endogenous and exogenous binding competitors, such as certain drugs, also decreases the binding affinity of albumin for bilirubin. A minute fraction of unconjugated bilirubin in serum is not bound to albumin. This free bilirubin is able to cross lipid-containing membranes, including the blood-brain barrier, leading to neurotoxicity. In fetal life, free bilirubin crosses the placenta, possibly by a carrier-mediated process, [27] and excretion of bilirubin from the fetus occurs primarily through the maternal organism.

When it reaches the liver, bilirubin is transported into liver cells, where it binds to ligandin. Uptake of bilirubin into hepatocytes increases with increasing ligandin concentrations. Ligandin concentrations are low at birth but rapidly increase over the first few weeks of life. Ligandin concentrations may be increased by the administration of pharmacologic agents such as phenobarbital.

Bilirubin is bound to glucuronic acid (conjugated) in the hepatocyte endoplasmic reticulum in a reaction catalyzed by uridine di phospho-glucuronyl transferase (UDPGT). Mono conjugates are formed first and predominate in the newborn. Dic-onjugates appear to be formed at the cell membrane and may require the presence of the UDPGT tetramer.

Bilirubin conjugation is biologically critical because it transforms a water-insoluble bilirubin molecule into a water-soluble molecule. Water-solubility allows conjugated bilirubin to be excreted into bile. UDPGT activity is low at birth but increases to adult values by age 4-8 weeks. In addition, certain drugs (phenobarbital, dexa-methasone, clofibrate) can be administered to increase UDPGT activity.



Infants who have Gilbert syndrome or who are compound hetero-zygotes for the Gilbert promoter and structural mutations of the *UDPGT1A1* coding region are at an increased risk of significant hyperbilirubinemia. Interactions between the Gilbert genotype and hemolytic anemia's such as glucose-6-phosphatase dehydrogenase (G-6-PD) deficiency, hereditary spherocytosis, or ABO hemolytic disease also appear to increase the risk of severe neonatal jaundice.

Further, the observation of jaundice in some infants with hypertrophic pyloric stenosis may also be related to a Gilbert-type variant. Genetic polymorphism for the organic anion transporter protein OATP-2 correlates with a 3-fold increased risk for developing marked neonatal jaundice. Combination of the *OATP-2* gene polymorphism with a variant *UDPGT1A1* gene further increases this risk to 22-fold. Studies also suggest that polymorphisms in the gene for glutathione-S-transferase (ligandin) may contribute to higher levels of total serum bilirubin.

Thus, some inter individual variations in the course and severity of neonatal jaundice may be explained genetically [28]. As the impact of these genetic variants is more fully understood, development of a genetic test panel for risk of severe and/or prolonged neonatal jaundice may become feasible [29].

Once excreted into bile and transferred to the intestines, bilirubin is eventually reduced to colorless tetrapyrroles by microbes in the colon. However, some deconjugation occurs in the proximal small intestine through the action of B-glucuronidases located in the

brush border. This unconjugated bilirubin can be reabsorbed into the circulation, increasing the total plasma bilirubin pool. This cycle of uptake, conjugation, excretion, deconjugation, and reabsorption is termed 'enterohepatic circulation'. The process may be extensive in the neonate, partly because nutrient intake is limited in the first days of life, prolonging the intestinal transit time.

In mother-infant dyads who are experiencing difficulties with the establishment of breast feeding, inadequate fluid and nutrient intake often leads to significant postnatal weight loss in the infant. Such infants have an increased risk of developing jaundice through increased enterohepatic circulation, as described above. This phenomenon is often referred to as breastfeeding jaundice and is different from the breast milk jaundice described below.

Certain factors present in the breast milk of some mothers may also contribute to increased enterohepatic circulation of bilirubin (breast milk jaundice). B-glucuronidase may play a role by uncoupling bilirubin from its binding to glucuronic acid, thus making it available for reabsorption. Data suggest that the risk of breast milk jaundice is significantly increased in infants who have genetic polymorphisms in the coding sequences of the *UDPGT1A1*[30] or *OATP2* genes. Although the mechanism that causes this phenomenon is not yet agreed on, evidence suggests that supplementation with certain breast milk substitutes may reduce the degree of breast milk jaundice.

Neonatal jaundice, although a normal transitional phenomenon in most infants, can occasionally become more pronounced. Blood group incompatibilities (eg, Rh, ABO) may increase bilirubin production through increased hemolysis. Historically, Rh iso-immunization was an important cause of severe jaundice, often resulting in the development of kernicterus. Although this condition has become relatively rare in industrialized countries following the use of Rh prophylaxis in Rh-negative women, Rh isoimmunization remains common in low- and middle-income countries (LMICs).

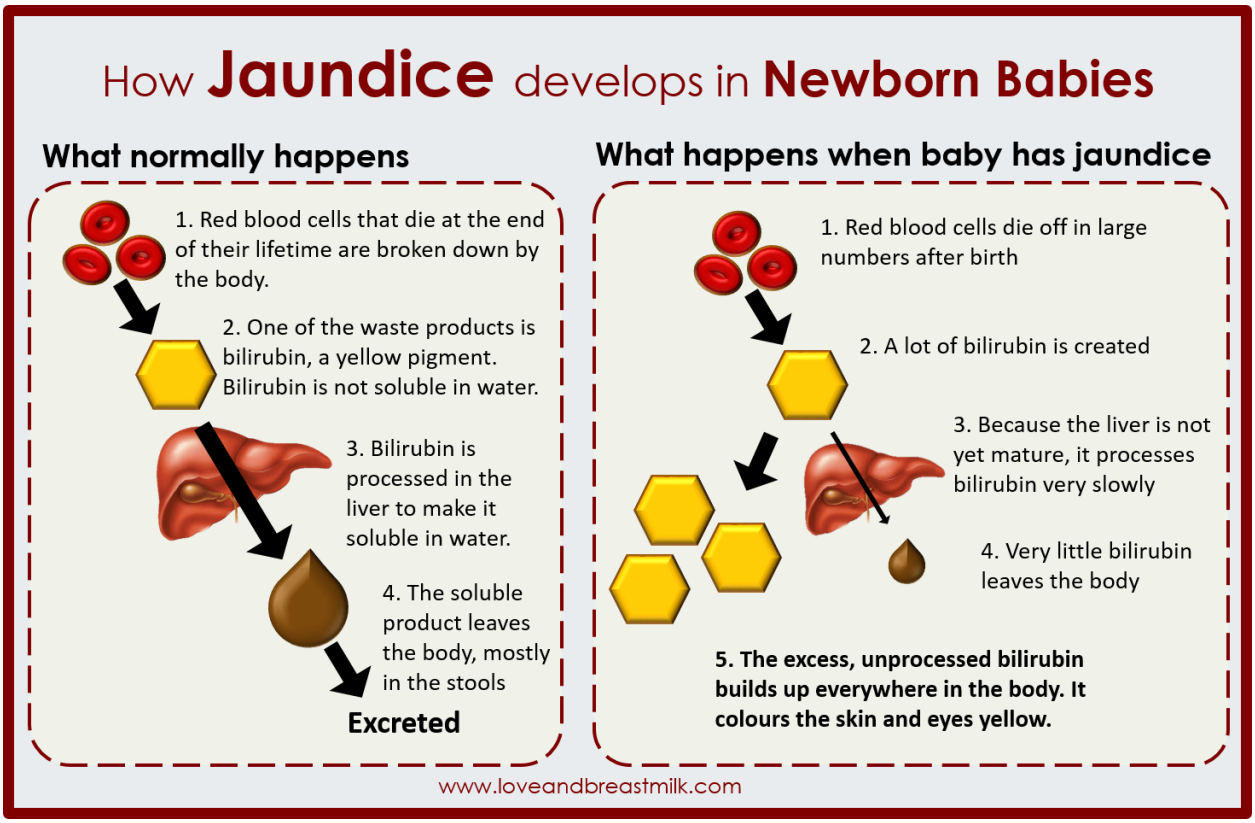
Non immune hemolytic disorders (spherocytosis, G-6-PD deficiency) may also cause increased jaundice, and increased hemolysis appears to have been present in some of the infants reported to have developed kernicterus in the United States in the past 15-20 years. The possible interaction between such conditions and genetic variants of the Gilbert and *UDPGT1A1* genes, as well as genetic variants of several other proteins and enzymes involved in bilirubin metabolism, is discussed above. More recently, 3 novel mutations in genes encoding either alpha or beta spectrin (SPTA1 or SPTB) were found in 3 unrelated neonates with non-immune hemolytic jaundice [31].

These discoveries also highlight the challenges involved in the common use of the terms physiologic jaundice and pathologic jaundice. Although physiologic jaundice is a helpful concept from a didactic perspective, applying it to an actual neonate with jaundice is more difficult.

Consider the following metaphor: Think of total serum bilirubin in neonatal jaundice as a mountain covered by a glacier. If a measurement of the height of the mountain is taken when standing on the summit, the amount of rock and the amount of ice that comprise this measurement is unclear. The same is true for many total serum bilirubin values obtained in neonatal jaundice. An underpinning of physiologic processes and pathological process (eg, Rhesus incompatibility) may clearly contribute to the measurement. However, how much of the measured total value comes from each of these components is unclear. Also, because genetic variants in bilirubin metabolism are only exceptionally pursued in the diagnostic work-up of infants with jaundice, their possible contribution to the measured total serum bilirubin is usually unknown.

CAUSES

In newborns, jaundice tends to develop because of two factors—the breakdown of fetal hemoglobin as it is replaced with adult hemoglobin and the relatively immature metabolic pathways of the liver, which are unable to conjugate and so excrete bilirubin as quickly as an adult.



This causes an accumulation of bilirubin in the blood (hyperbilirubinemia), leading to the symptoms of jaundice. If the neonatal jaundice does not clear up with simple phototherapy, other causes such as biliary atresia, Progressive familial intra-hepatic cholestasis, bile duct paucity, Alagille syndrome, alpha 1-antitrypsin deficiency, and other pediatric liver diseases should be considered. The evaluation for these will include blood work and a variety of diagnostic tests. Prolonged neonatal jaundice is serious and should be followed up promptly. Severe neonatal jaundice may indicate the presence of other conditions contributing to the elevated bilirubin levels, of which there are a large variety of possibilities (see below). These should be detected or excluded as part of the differential diagnosis to prevent the development of complications.

SIGNS AND SYMPTOMS

The primary symptom is yellowish discoloration of the white part of the eyes and skin in a newborn baby. Other symptoms may include excess sleepiness or poor feeding.[7] A bilirubin level more than 34 μmol/l (2 mg/dL) may be visible. For the feet to be affected level generally must be over 255 μmol/l (15 mg/dL).[7]

BILIRUBIN ENCEPHALOPATHY (BILIRUBIN TOXICITY)

Normally, hyperbilirubinemia resolves on its own as the infant processes the bilirubin and excretes it. However, in some infants, it can become harmful and will need treatment. If not detected or left untreated and levels rise too high, some of the bilirubin may cross the blood brain barrier and settle into brain tissue where it can cause acute bilirubin encephalopathy (ABE). This encephalopathy, if not detected early and treated, can develop into kernicterus. Kernicterus is a potentially fatal disease and results in permanent injury to specific parts of the brain [32].

To help quantify the degree of ABE, the Bilirubin-Induced Neurological Dysfunction (BIND) score was developed. It describes three phases of worsening encephalopathy and the clinical signs in each phase:

Initial phase:

- lethargy, decrease in tone or activity

Intermediate phase:

- moderate stupor, irritability and variable activity
- increased tone, some retrocollis/opisthotonus
- minimal feeding, high-pitched cry

Advanced phase:

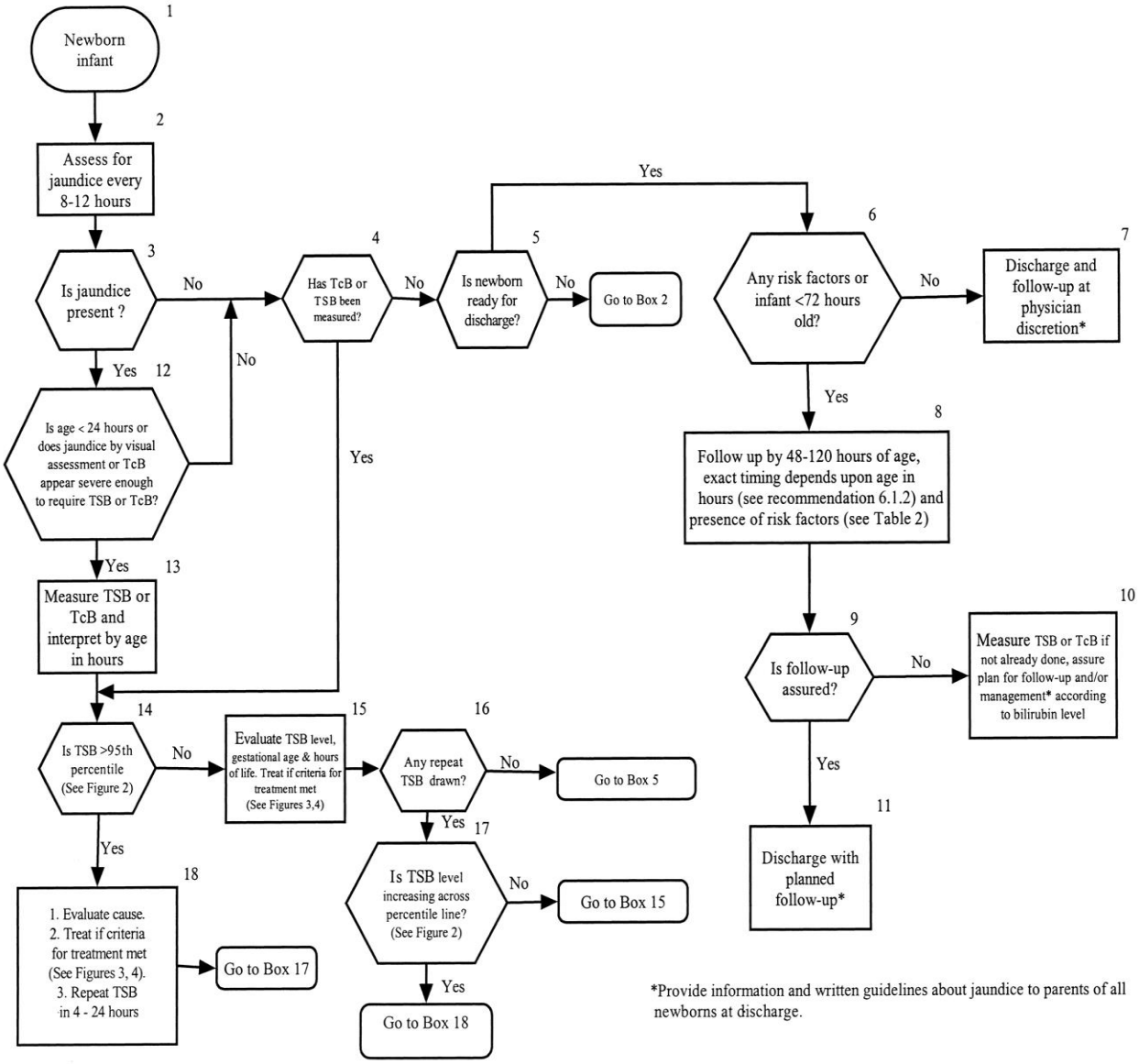
- deep stupor to coma, hyper-tonicity
- retrocollis/opisthotonus
- no feeding, shrill cry, seizures, death

SCREENING STEPS

The content of this section is based on the Ontario Ministry of Health and Long-Term Care (MOHTLC) Quality-Based Procedure (QBP) titled Hyperbilirubinemia in Term and Late Pre-Term Infants (≥ 35 weeks) (2013). The key objectives of the QBP for Hyperbilirubinemia are to:

- ensure all newborns receive bilirubin screening between 24-72 hours of life (if not clinically indicated and performed earlier)
- ensure infants receive systematic bilirubin monitoring as per the treatment graph and risk nomograms recommended by evidence-based guidelines

- utilize health care resources responsibly through avoidance of unnecessary/excessive testing, timely discharge, appropriate outpatient follow-up and minimization of preventable readmission
- reduce the incidence of severe hyperbilirubinemia and acute bilirubin encephalopathy[33].



ASSESSMENT OF JAUNDICE

1. Physical Assessment

• **Visual assessment**: Jaundice moves from head to toe, with the eyes affected last.

Serum bilirubin (approx.)

= 85 micromols/L - When yellow tinge first becomes visible

= 150 micromols/L - Yellow tinge appears on trunk

= 200 micromols/L - Yellow tinge appears on legs

= 250 micromols/L - Eyes (sclera) are affected

• Although visual assessment alone cannot determine the degree of jaundice, a general Assessment of the extent of jaundice can be done under bright light. It is important to:

- Blanch skin to determine underlying colour.
- Press over a bony prominence for best results (nose, forehead).
- Check sclera.

NOTE: For dark skinned infants, the colour of the sclera, conjunctiva and oral mucosa is most reliable indicator of level of jaundice[34].

NOTE: Petechiae may indicate underlying sepsis or haemolytic disease.

• **Level of activity:**

- Increasing levels of unconjugated bilirubin in the brain can lead to decreased levels of Consciousness or alertness. Infants may become lethargic and less responsive[39].

• **Level of hydration**:

- Monitor intake and output.
- Adequate hydration is necessary to help maintain enough fluid to help with the absorption and excretion of conjugated bilirubin once it passes through the liver.

• **Stools:**

- Monitor frequency, type and colour of stools (meconium versus transitional).
- Unconjugated bilirubin can accumulate in stool and thus has the potential to be Reabsorbed[38].
- Conjugated bilirubin can also become unconjugated in the gut and become reabsorbed into the blood stream.

2. Laboratory Assessment

- Obtain serum bilirubin levels as per algorithm .

- NOTE: When bloodwork is being drawn, phototherapy should be stopped to prevent the sample
- from being affected by the lights. The total bilirubin should be interpreted according to the
- infant's age in hours to determine the treatment plan and timing of reassessment.
- Other blood work that may be ordered[40].
- Serum albumin - to help determine how much albumin is available for binding
- CBC and differential – can help determine level of red blood cell destruction, haemolytic anemia, sepsis or polycythemia[42]
- Direct Antiglobulin Test (DAT) - to look for presence of maternal antibodies in infant's serum. NOTE: Indirect Antibody Test (IAT) is done on maternal serum antenatally
- G6PD (glucose-6-phosphate dehydrogenase) – helps maintain RBC wall integrity; a deficiency indicates enzyme deficiency and a possible metabolic reason for jaundice.

THERAPEUTIC OPTIONS

1. Phototherapy

Phototherapy (PTx) remains the mainstay of treating hyperbilirubinemia in neonates. PTx is highly effective and carries an excellent safety track record of over 50 years. It acts by converting insoluble bilirubin (unconjugated) into soluble isomers that can be excreted in urine and feces. Many review articles have provided detailed discussion on phototherapy related issues. The bilirubin molecule isomerizes to harmless forms under blue-green light (460 to 490 nm); and the light sources having high irradiance in this particular wavelength range are more effective than the others[42].

Types of phototherapy lights

The phototherapy units available in the market have a variety of light sources that include florescent lamps of different colors (cool white, blue, green, blue-green or turquoise) and shapes (straight or U-shaped commonly referred as compact florescent lamps ie CFL), halogen bulbs, high intensity light emitting diodes (LED) and fibro-optic light sources. With the easy availability and low cost in India, CFL phototherapy is being most commonly used device. Often, CFL devices have four blue and two white (for examination purpose) CFLs but this combination can be replaced with 6 blue CFLs in order to increase the irradiance output. In last couple of years, blue LED is making inroads in neonatal practice and has been found to at least equally effective. LED has advantage of long life (up to 50,000 hrs) and is capable of delivering higher irradiance than CFL lamps. Fiber-optic units can be used to provide undersurface phototherapy in conjugation with overhead CFL/LED unit to enhance the efficacy of PTx but as a standalone source, fiber-optic unit is lesser effective than CFL/LED unit. It is important that a plastic cover or shield be placed before phototherapy lamps to avoid accidental injury to the baby in case a lamp breaks.

Maximizing the efficacy of phototherapy

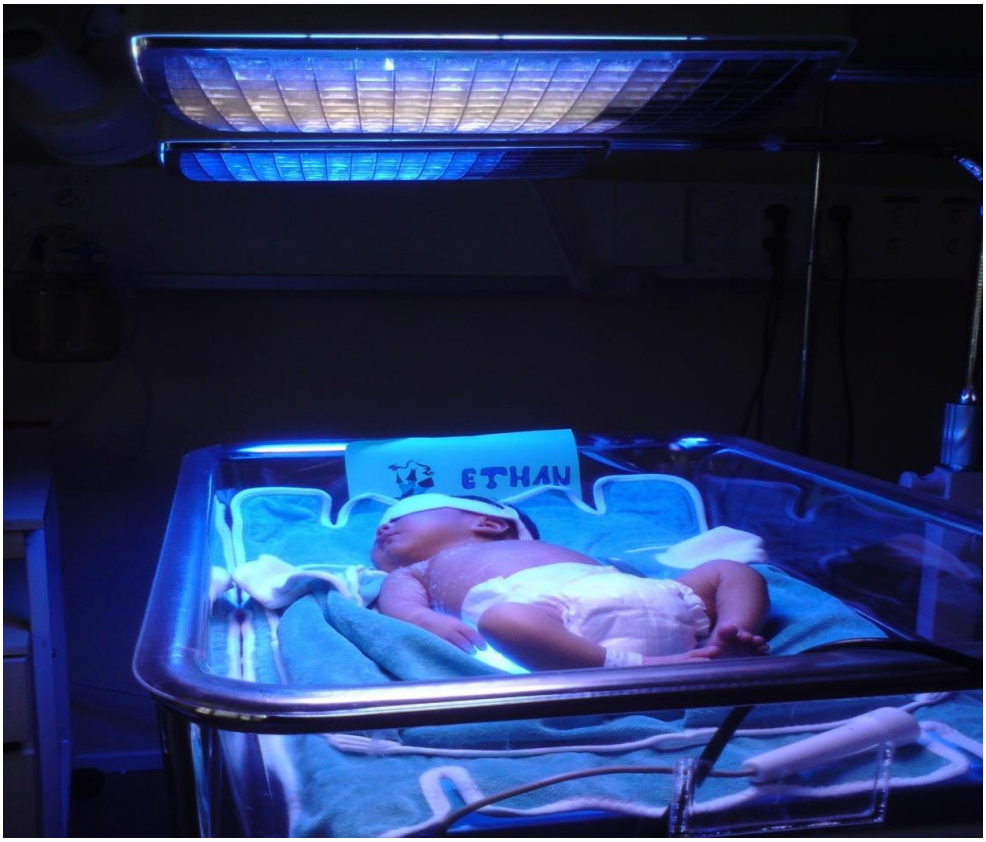
The irradiance of PTx lights should be periodically measured, and a minimum level of 30 μW/cm2 /nm in the wavelength range of 460 to 490 nm must be ensured. As the irradiance varies at different points on the footprint of a unit, it should be measured at several points. The lamps should be changed if the lamps are flickering or ends are blackened, if irradiance falls below the specified level or as per the recommendation of manufacturers. Expose maximal surface area of the baby[34,42]. Avoid blocking the lights by any equipment (say radiant warmer), a large diaper or eye patch, a cap or hat, tape, dressing or electrode etc. ensure good hydration and nutrition of the baby. Make sure that light falls on the baby perpendicularly if the baby is in incubator. Minimize interruption of Ptx during feeding sessions or procedures.

Administering phototherapy

Make sure that ambient room temperature is optimum (250 to 280) to prevent hypothermia or hyperthermia in the baby. Remove all clothes of the baby except the diaper. Cover the baby's eyes with patches, ensuring that the patches do not block the baby's

nostrils. Place the naked baby under the lights in a cot or bassinet if weight is more than 2 kg or in an incubator or radiant warmer if the baby is small (›2kg)

Keep the distance between baby and light 30 to 45 cm (or as per manufacturer recommendation). Ensure optimum breastfeeding. Baby can be taken out for breastfeeding sessions and the eye patch can be removed for better mother-infant interaction. However, minimize interruption to enhance effectiveness of phototherapy. There is no need to supplement or replace breast milk with any other types of feed or fluid (e.g. breast-milk substitute, water, sugar water, etc.)



Monitoring & stopping phototherapy

Monitor temperature of the baby every 2 to 4 hr. Measure TSB level every 12 to 24 hours. Discontinue PTx once two TSB values 12 hr apart fall below current age specific cut offs. The infant should be monitored clinically for rebound bilirubin rise within 24 hours after stopping phototherapy for babies with hemolytic disorders.

Role of sunlight

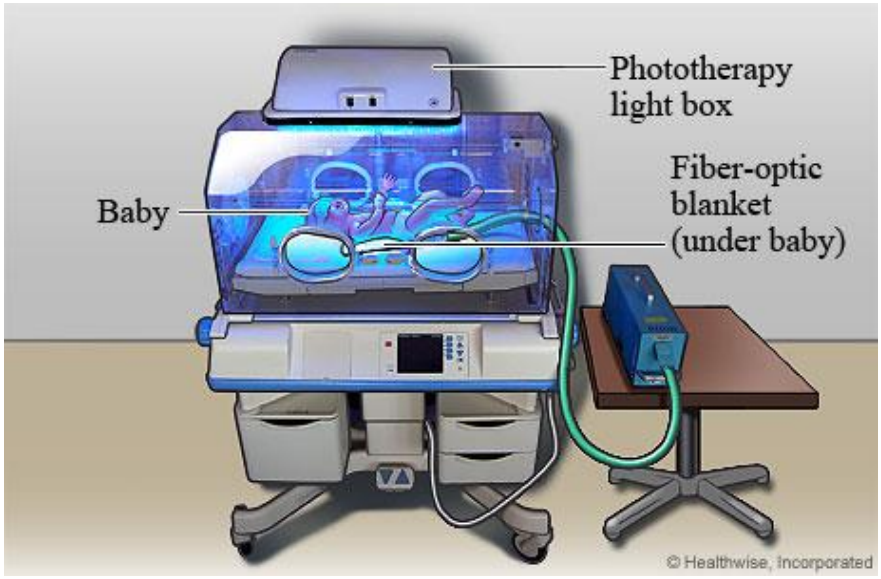
Exposing the baby to sunlight does not help in treatment of jaundice and is associated with risk of sunburn and therefore should be avoided.

PHOTOTHERAPY PRINCIPLES

Phototherapy acts on unconjugated bilirubin to a depth of 2 to 3 mm. Through photoisomerization, fat soluble molecules are reconfigured to water soluble molecules and are excreted by the liver without actual conjugation[42].

Effectiveness of phototherapy =

Area of skin exposed + Radiant energy + Wavelength of light used



- The most effective light sources for degrading bilirubin are those that emit blue-green light in a relatively narrow wavelength range (425 – 490 nanometers).
- When phototherapy is used, the decrease in bilirubin level is proportionately greater in the skin than in the serum. The infant should have as much skin as possible exposed to the lights.
- It is possible to increase the efficacy of treatment by using multiple sources of phototherapy to optimize the amount of skin exposed.
- According to standards of care phototherapy is ordered as either intensive (high) or standard (low) intensity and expressed in nanometers of light.

PHOTOTHERAPY EQUIPMENT

There are a variety of methods of delivering phototherapy. The method used depends on the equipment availability in each institution[38,44]. The following are the current recommended methods:

- **Phototherapy Lights:** Deliver light in the narrow spectrum most effective for reducing bilirubin. Their effectiveness depends on the distance from the baby as measured by a specific light meter.
- **Bili Bassinet:** Self-contained unit that combines a mattress area and three phototherapy light units to provide phototherapy and may be used as an adjunct therapy to phototherapy lights, but should not be used as the sole source of therapy.
- **Bili Blanket:** A small fiber optic pad is placed under the infant. It can be used as an adjunct to overhead phototherapy lights but not as the only source of phototherapy. The advantage of a bili blanket is that it can remain in place for breastfeeding, providing continuity of therapy.

POTENTIAL SIDE EFFECTS OF PHOTOTHERAPY [39]

Altered Activity

• Lethargy or irritability

• Decreased eagerness to feed

Altered Fluid Status

• Increased peripheral blood flow

• Increased insensible water loss with open bed or warmer

Altered GI Function

• Increased number and frequency of watery, greenish-brown stools

• Decreased time for intestinal transit

• Decreased absorption, retention of nitrogen, water, electrolytes

Hematological Function

• Increased rate of platelet turnover

• Damage to circulating red blood cells with decreased potassium and increased ATP (energy) activity

Ocular Effects

• Lack of sensory input and stimulation

• Use of eye patches for prolonged period

Skin Changes

• Tanning

• Rashes

• Burns

• Bronze Baby Syndrome

Altered Thermal /Metabolic Function

• Increased environmental and body temperature changes

• Increased O_2 consumption

• Increased respiratory rate

• Increased skin blood flow

NURSING CARE

Nursing care of the infant with hyperbilirubinemia is focused on assessment and management of the signs and symptoms of the disease. The main goals of treatment are to reverse the haemolytic process and prevent the development of bilirubin-induced encephalopathy. Most infants with hyperbilirubinemia will require the use of phototherapy to help reduce the amount of unconjugated (indirect) bilirubin. The guidelines included here refer to newborns receiving phototherapy[36,37].

Feeding and Nutrition

- Fluid intake is crucial to treatment success so this is an important factor to consider in caring for an infant with jaundice. Dehydration may be associated with increased serum bilirubin concentrations and intravenous (IV) therapy may be necessary to ensure adequate hydration.
- Breastfeeding should always be strongly encouraged and supported, even when the infant is receiving phototherapy. Although more frequent breastfeeding may be beneficial, it is important to minimize the time that intensive phototherapy is interrupted to 20 minutes within a 3-hour. period If possible, provide a referral to a Lactation Consultant for a more specific assessment of breastfeeding[44].
- Accurate recording of intake and output, including stool pattern, is necessary. If the infant is receiving IV therapy, usual standards of care should be followed.

Skin Care and Thermoregulation

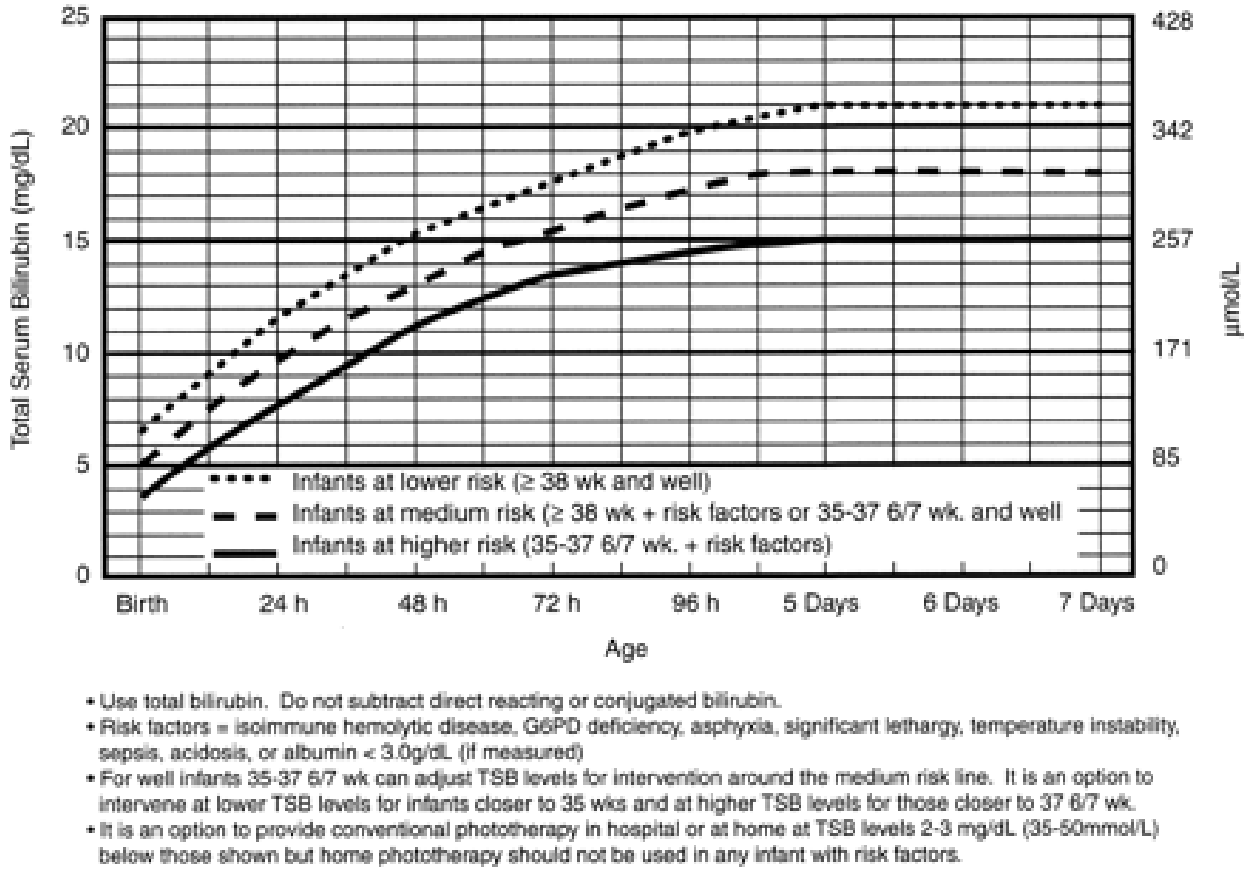
- Skin plays an important role in the regulation of body temperature and serves as a route of water excretion.
- Skin care includes observing colour, rashes and excoriation; cleaning the skin with warm water, especially the perineal area after stooling; changing position every 2 hours. NOTE: Prompt cleansing of perianal area after stooling is important as photo-oxidation of bilirubin results in loose green caustic stools and can result in excoriation.
- Phototherapy is most effective when the exposed skin area is maximized, so infants in isolettes should be exposed as much as possible; otherwise, diapers to catch urine and stool should be used.
- The infant's temperature must be monitored at least every 4 hours to maintain a safe environment.

Eye Care

- The infant's eyes must be protected from the phototherapy lights to prevent retinal damage. Place the pads correctly over the eyes:
  - Use the appropriate size of the eye pad or prefabricated eye protection.
  - Make sure the eyes are closed first to help prevent corneal abrasion, irritation and/or infection
  - Check frequently to make sure the eye pads remain in place and are not obstructing the nares[39,43].
- Eye protection should be removed every 2 to 4 hours and eyes cleansed with normal saline to reduce irritation and promote eye contact, socialization and attachment.

NOTE: Eye patches are not necessary if only the Bili Blanket is being used since the infant's eyes are not directly exposed to the blue lights.

GUIDELINES FOR INTENSIVE PHOTOTHERAPY FOR INFANTS ≥ 35 WEEKS



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation. Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy which should be used when the TSB exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin,45–47 the blood-brain barrier,48 and the susceptibility of the brain cells to damage by bilirubin.48"Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 µW/cm2 per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system, If total serum bilirubin levels approach or exceed the exchange transfusion line, the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material. This will increase the surface area of the infant exposed and

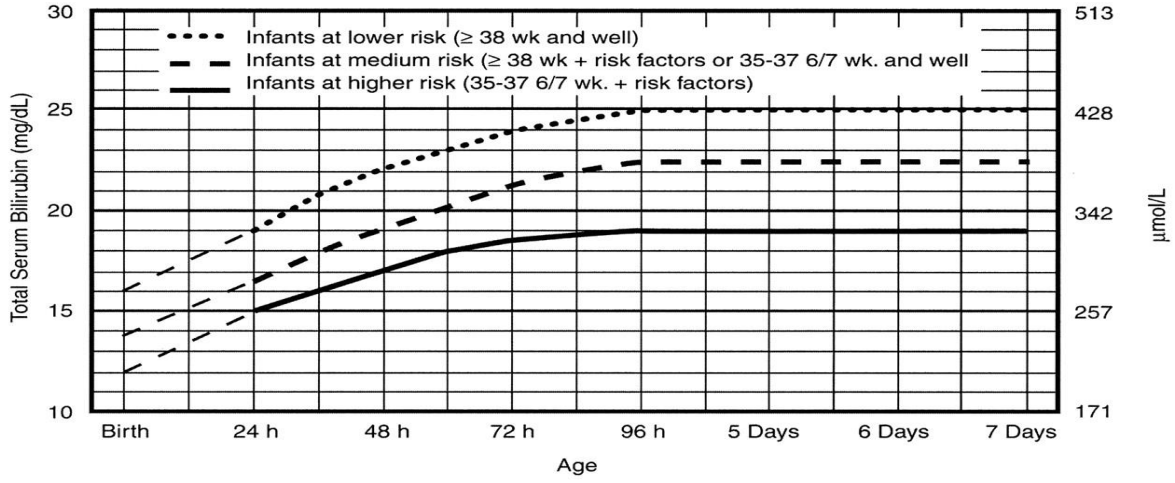
increase the efficacy of phototherapy.51 If the total serum bilirubin does not decrease or continues to rise in an infant who is receiving intensive phototherapy, this strongly suggests the presence of hemolysis. Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome.

2. Exchange transfusion Double volume exchange transfusion (DVET) should be performed if the TSB levels reach to age specific cut-off for exchange transfusion or the infant shows signs of bilirubin encephalopathy irrespective of TSB levels. Indications for DVET at birth in infants with Rh isoimmunization include[45]:

1. Cord bilirubin is 5 mg/dL or more
2. Cord Hb is 10 g/dL or less

At birth, if a baby shows signs of hydrops or cardiac decompensation in presence of low PCV (<35%), partial exchange transfusion with 50 mL/kg of packed cells should be done to quickly restore oxygen carrying capacity of blood. The ET should be performed by pull and push technique using umbilical venous route. Umbilical catheter should be inserted just enough to get free flow of blood [46].

GUIDELINES FOR EXCHANGE TRANSFUSION FOR INFANTS ≥35 WEEKS



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Guidelines for exchange transfusion in infants 35 or more weeks' gestation. Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. for risks and complications of exchange transfusion. During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours.The following B/A ratios can be used together with but in not in lieu of the TSB level as an additional factor in determining the need for exchange transfusion52: If the TSB is at or approaching the exchange level, send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red cells and plasma) crosshatched against the mother and compatible with the infant

3. Intravenous immunoglobulin's (IVIG)

IVIG reduces hemolysis and production of jaundice in isoimmune hemolytic anemia (Rh isoimmunisation and ABO incompatibility) and thereby reduces the need for phototherapy and exchange transfusion. We give IVIG (0.5 to 1 gm/kg) in all cases of Rh isoimmunisation and selected case of ABO incompatibility with severe hemolysis. IVIG administration can cause intestinal injury and necrotizing enter colitis.

4. IV hydration

Infants with severe hyperbilirubinemia and evidence of dehydration (e.g. excessive weight loss) should be given IV hydration. An extra fluid of 50 mL/kg of N/3 saline over 8 hr decreases the need for exchange transfusion[47].

5. Other agents

There is no proven evidence of benefit of drugs like phenobarbitone, clofibrate, or steroids to prevent or treat hyerbilirubinemia in neonates and therefore these agents should not be employed in treatment of jaundiced infants.

PROLONGED JAUNDICE

There is no good definition of prolonged jaundice (PJ). Generally, persistence of significant jaundice for more than 2 wk in term and more than 3 weeks in preterm babies is taken as PJ. Though, it is not uncommon to see persistence of mild jaundice in many infants for 4 to 6 weeks of age. Most of these babies do well without any specific intervention or investigation. The first and foremost step to manage an infant with PJ is to rule out

cholestasis (Figure 2). Yellow colored urine is a reasonable marker for cholestasis; however the urine color could be normal during initial phase of cholestasis. For the practical purpose, an infant with PJ with normal colored urine can be considered to have unconjugated hyperbilirubinemia. If the infant has dark colored urine, the infant should be managed as per cholestasis guidelines[48]. Infants with true PJ (unconjugated hyperbilirubinemia) should be assessed clinically for severity and possible cause of prolongation of jaundice. If the clinical assessment of jaundice suggests TSB levels below phototherapy cut offs for age (say <15 to 18 mg/dl interm infant), the infant may not be subjected to any unnecessary investigations. As many of these infants have PJ as a result of inadequate feeding, appropriate measures are taken to optimize breastfeeding. Thyroid screen can be considered in such infants at this stage if routine metabolic screen for hypothyroidism has not been carried out at birth.

If baby appears significant jaundice at this stage, TSB level should be performed and possible underlying cause should be looked for. In such infants, G6PD level, thyroid screen, ABO of infant & mother if not done earlier should performed to delineate possible cause. Infants having TSB in phototherapy range should be started on phototherapy[49]. The adequacy of breastfeeding should be assessed by history, observation of breastfeeding session, and degree of weight loss. Many of the mothers, even at this stage, have persisting breastfeeding problems such as poor attachment, sore nipple etc.

Breast mild jaundice (BMJ) is relatively a common cause of jaundice, but, inadequacy of breastfeeding being more common than it should be carefully ruled out. BMJ being an innocuous entity, cessation of breastfeeding is not required in practically any case. Infants with BMJ should be treated with phototherapy, if required. For a rare infant with TSB hovering in exchange range, a brief trial of interruption of breastfeeding can be considered. We haven't stopped breastfeeding even for once for treatment of BMJ in last 15 years!

In an infant failing to respond to these measures, a diagnosis of CNS should be entertained. A trial of phenobarbitone can be considered to establish the diagnosis[50].

PATIENT EDUCATION

Parents should be educated about neonatal jaundice and receive written information prior to discharge from the birth hospital. The parent information leaflet should preferably be available in several languages.

A novel 2-color icterometer (Bilistrip) appears to have the potential to facilitate early maternal detection of clinically significant jaundice and help them in decision making to seek

medical treatment. In a study that trained mothers in a maternity hospital to use the icterometer on the blanched skin of their infant's nose to determine absence (light yellow) or presence (dark yellow) of significant jaundice, there was a 95.8% sensitivity and 95.8% negative predictive value for detecting infants requiring phototherapy.

A smart phone application (BiliCam) has also been developed to assess neonatal jaundice. It shows promise for effectively screening newborns in a diverse sample of newborns (age <7 days), including black, Hispanic, and Asian infants. In a study comprising 530 newborns whose estimated bilirubin levels were calculated and compared with total serum bilirubin levels, the use of 2 decision rules resulted in the application providing accurate estimates of total serum bilirubin levels.

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RIVIEW OF LITERATURE

Ronald S. Cohen et al., conducted a study about the neonatal jaundice in infants.it can be best understood as a balance between the production and elimination of bilirubin, with a multitude of factors and conditions affecting each of these processes. When an imbalance results because of an increase in circulating bilirubin (or the bilirubin load) to significantly high levels (severe hyperbilirubinemia), it may cause permanent neurologic sequelae (kernicterus). In most infants, an increase in bilirubin production (e.g., due to hemolysis) is the primary cause of severe hyperbilirubinemia, and thus reducing bilirubin production is a rational approach for its management. The situation can become critical in infants with an associated impaired bilirubin elimination mechanism as a result of a genetic deficiency and/or polymorphism. Combining information about bilirubin production and genetic information about bilirubin elimination with the tracking of bilirubin levels means that a relative assessment of jaundice risk might be feasible. Information on the level of bilirubin production and its rate of elimination may help to guide the clinical management of neonatal jaundice[51].

Blackburn S et al.,conducted a study to find out Jaundice is a common physiologic problem seen in both term and preterm infants. Normal transitional changes in bilirubin metabolism lead to physiological jaundice in many infants. In some infants these normal changes at birth may be exaggerated, such as occurs with immaturity, or may interact with health alterations (pathologic jaundice), result ing in the accumulation of excess bilirubin and development of hyperbilirubinemia. Caregivers must appreciate the processes and the basis for physiologic jaundice and hyperbilirubinemia and recognize infants at risk for these disorders. This article reviews neonatal bilirubin metabolism as a basis for understanding the causes and treatment of physiologic jaundice and hyperbilirubinemia arising from either physiologic or pathologic causes. Patterns of bilirubin in breast fed infants are discussed along with other issues related to breast feeding and jaundice. Treatment of hyperbilirubinemia and implications for nursing assessment and management of infants under phototherapy are also described[52].

McKiernan P et al., conducted a study to find out the Neonatal jaundice lasting greater than 2 weeks should be investigated. Pale stools and dark or yellow urine are evidence of liver disease, which should be urgently investigated. The neonatal hepatitis syndrome has many causes, and a structured approach to investigation is mandatory. It should be possible to confirm or exclude biliary atresia within one week, so that definitive surgery is not delayed unnecessarily. Babies with the neonatal hepatitis syndrome should have vigorous fat-soluble vitamin supplementation, including parenteral vitamin K if coagulation is abnormal. The prognosis for infants with idiopathic neonatal hepatitis and multifactorial cholestasis is excellent[53].

Ronald J. Wong et al., conducted a study about the Cleavage of the alpha-methene bridge of heme by membrane-bound heme oxygenase yields equimolar amounts of biliverdin, carbon monoxide, and reduced iron. Biliverdin is catalyzed by biliverdin reductase to bilirubin. The process occurs in all nucleated cells except mature anucleated red blood cells. Neonates in whom bilirubin production is increased tend to have higher bilirubin concentrations, and excessive bilirubin production or impairment of elimination causes dramatic deviations from the hour-specific nomogram that can be seen as “jumping” percentile tracks early in the postnatal period or later in the first week after birth. After formation, bilirubin diffuses into the circulation. In the absence of conjugates, the total bilirubin concentration in plasma is the sum of bilirubin bound to albumin plus a minimal amount of free bilirubin. Bilirubin is excreted more slowly in newborns than in adults. Although no clinical tests can measure bilirubin uptake and conjugation by the liver, an elevated hour-specific total bilirubin value when bilirubin production is normal or decreasing is a sign of impaired or abnormally delayed bilirubin excretion. The accuracy and precision of clinical laboratory total bilirubin measurements are a concern, and studies are underway to assess whether measurements of free bilirubin, the bilirubin-binding constant, the bilirubin:albumin ratio, or albumin binding capacity might improve the ability to identify infants at greater risk for bilirubin-induced neuroinjury rather than simply those at greater risk for having a higher bilirubin concentration[54].

V K Bhutani, R J Vilms et al.,conducted a study to find out the severity of jaundice. To reduce the incidence of severe neonatal hyperbilirubinemia affecting newborns with jaundice in the United States and to prevent kernicterus, there is a need to implement proven prevention strategies for severe neonatal hyperbilirubinemia as recommended in the 2004 American Academy of Pediatrics Guidelines for newborns >35 weeks gestational age. The purpose of universal predischarge bilirubin screening is to identify infants with bilirubin levels >75th percentile for age in hours and track those with rapid rates of bilirubin rise (>0.2 mg per 100 ml per h). Early identification has been reported to predict severe hyperbilirubinemia and allow for evidence-based targeted interventions. A systems approach is likely to reduce the preventable causes of acute bilirubin encephalopathy. To do so, highest priority should be given to (i) designating extreme hyperbilirubinemia (total serum bilirubin >427 μmol l^{-1} or >25 mg per 100 ml) as a reportable condition by laboratories and health-care providers through public health mandates; (ii) implementation of Joint Commission's Sentinel Report for kernicterus; (iii) nursing outreach to communities for education of prospective parents; (iv) development of clinical pathways to monitor, evaluate and track infants with extreme hyperbilirubinemia; and (v) societal awareness. These efforts should be monitored by a state and national surveillance system in order to critically improve the timeliness and completeness of notifications and to allow evaluation and interventions at the policy and individual family level[55].

Jon F Watchko et al.,conducted a study and Advances in the clinical assessment strategies used to identify neonates at risk for the development of severe hyperbilirubinemia and bilirubin neurotoxicity, as well as the treatment measures to control hyperbilirubinemia in newborns, continue to be made. They include, among others, universal predischarge birth hospitalization bilirubin screening, the confirmation that hemolysis is an important risk factor for bilirubin neurotoxicity, the use of a numeric scoring system to help stage the severity of acute bilirubin encephalopathy, the potential advantages of turquoise-light phototherapy, and the potential role of heme-oxygenase inhibitors in preventing the need for exchange transfusions, all of which are reviewed here[56].

Jean M Kirk et al., conducted a study about the biliurubin concentration in neonates.Neonatal jaundice is common, and usually harmless, because of physiological jaundice or breast-feeding. In some neonates unconjugated bilirubin concentration, coupled with other risk factors, is sufficient to allow free bilirubin to cross the blood-brain barrier and cause kernicterus. Another subgroup of infants is jaundiced because of elevated conjugated bilirubin; a marker for a number of pathological conditions. Bilirubin measurement must identify those infants at risk. Transcutaneous bilirubin measurement is increasingly used in healthy infants, especially before early discharge or at home, to assess the need for laboratory bilirubin measurement. Transcutaneous measurements are not covered by laboratory quality assessment schemes. Guidelines on management of neonatal jaundice utilize age in hours and other risk factors to define bilirubin action thresholds, which may be as low as 100 μmol/L for sick premature infants, whereas early discharged babies may only present after bilirubin concentrations are extremely high. Hence, there is a requirement for accurate total bilirubin measurement from <100 to >500 μmol/L, with sufficient precision to assess the rate of bilirubin change with time. Babies presenting with late jaundice always require conjugated bilirubin measurement. It is of concern that many total and direct bilirubin automated kit methods suffer from haemolysis interference, while use of in-house methods or modification of commercial methods has virtually disappeared. External quality assessment has a vital role in providing data on different methods' performance, including accuracy, precision and susceptibility to interference. Laboratories should consider whether their adult bilirubin methods are suitable for neonates[57].

Janki Deshmukh et al., Conducted a study about the Neonatal jaundice requiring phototherapy is associated with significant socioeconomic burden including hospital readmission, prolonged hospital stay, and separation of the baby from mother. To assess the efficacy and safety of probiotics in reducing the need for phototherapy and its duration in neonatal hyperbilirubinemia.the methods are used A systematic review of randomized controlled trials (RCTs) of probiotic supplementation for prevention or treatment of jaundice in neonates (any gestation or weight) using the Cochrane methodology. Primary outcome was the duration of phototherapy. Secondary outcomes included incidence of jaundice, total serum bilirubin (TSB) level at 24, 48, 72, 96 h, and day 7, duration of hospital stay, and adverse effects (e.g. probiotic sepsis). Results were summarized as per GRADE guidelines. It resultes Nine RCTs (prophylactic: six trials, $N = 1761$; therapeutic: three trials, $N = 279$) with low to high risk of bias were included. Meta-analysis (random-effects model) showed

probiotic supplementation reduced duration of phototherapy [$N = 415$, mean difference (MD): −11.80 (−17.47, −6.13); $p < .0001$; level of evidence (LOE): low]. TSB was significantly reduced at 96 h [MD: −1.74 (−2.92, −0.57); $p = .004$] and 7 d [MD: −1.71 (−2.25, −1.17); $p < .00001$; LOE: low] after probiotic treatment. Prophylactic probiotics did not reduce the incidence of jaundice significantly [$N = 1582$, relative risk (RR): 0.56 (0.25, 1.27); $p = .16$; LOE: low]. There were no probiotic-related adverse effects. and the experiment was found the Limited low-quality evidence indicates that probiotic supplementation may reduce the duration of phototherapy in neonates with jaundice. Routine use of probiotics to prevent or treat neonatal jaundice cannot be recommended. Large well-designed trials are essential to confirm these findings[58].

Olayinka O Goodman et al., (2016) conducted a community-based survey was conducted amongst mothers aged 15–49 years living in Mosan-Okunola, Lagos, Nigeria to determine the knowledge of, attitudes to, preventive and treatment practices towards neonatal jaundice (NNJ).The mothers were selected using a multi-stage sampling technique. A pre-tested interviewer-administered structured questionnaire was used to obtain data. The knowledge of the mothers was scored and scores lower than 50% were graded as poor, 50–74% as fair and ≥75% as good. The practice was also categorised as appropriate if one correct option was identified and was categorised as inappropriate where an incorrect option(s) was identified singly or in combination with a correct option.the results is Three hundred and fifty-eight mothers were recruited. The mean age was 34.8 ± 9.05 years. Two hundred and seventy (75.4%) mothers had ever heard about the condition. Two hundred and forty-seven (91.4%) mothers correctly identified the condition and infection was the only most common known cause (47%). Only 34% of the mothers knew that NNJ could cause brain damage, and 40% identified refusal of feeds as a danger sign. Up to 64% of the mothers believed attending antenatal care could prevent the condition, and 58% were of the opinion that exposing babies to sunlight could prevent the condition. Sixty-eight percent (68.9%) of the mothers had a poor level of knowledge. Age and educational qualification did not show any statistically significant relationship with knowledge about NNJ ($P < 0.05$) but increasing maternal age had a significant association with an appropriate treatment practice ($P < 0.05$), the association was negative ($r = −0.32$). this experiment is helps to Knowledge about NNJ was low in this community and ineffective preventive practices were utilised. Efforts should be made to increase it, and health workers should play a leading role[59].

Roya Raeisi et al., (2017) conduted a systemtic review of neonatal jaundice. Neonatal jaundice is one of the most common diseases among neonates that may cause irreparable complications such as kernicterus. This systematic review article was conducted to report and introduce medicinal plants that are used to treat neonatal jaundice in Iranian traditional medicine. To conduct this systematic review, the terms jaundice and icterus combined with the terms ethnobotanical, ethno-medicinal plants, ethnopharmacology, phytotherapy, and Iran were used to search for potentially relevant publications in Google Scholar, and Scientific databases ISI, PubMed, and Scopus. According to ethnobotanical evidence, six plant species from five families consisting of Cotoneaster discolour, *Ziziphus jujube* Miller, *Hordeum vulgare* L., *Alhagi graecorum* Boiss, *Fumaria parviflora*, and *Chicorium intybus* have been more frequently reported to be used to treat neonatal jaundice in Iran on which a number of studies have been conducted. However, a combination of two or more number of these plants has been reported to be used for treating neonatal jaundice. Although the plants and their compounds cause reduction in neonatal jaundice through different mechanisms of action, they cannot be considered an independent treatment in most cases. Therefore, it is recommended to use plants and their compounds as a complementary treatment to reduce bilirubin[60].

Nasrin Khalesi et al., (2008) to conduct a cross sectionel study A cross-sectional study, was done on 400 mothers, who delivered at Ali-Ebne Abitaleb hospital in Zahedan-Iran during April and May 2006.To determine knowledge, attitude, and behaviour of mothers about neonatal jaundice In this cross-sectional study, 400 cases who delivered at Ali-Ebne Abitaleb Hospital in Zahedan-Iran during April and May 2006 were interviewed to complete 21-point questionnaires. The first data was analyzed descriptively then analytically by c2, Pearson correlation, and independent t-test using SPSS 11 software.The mean age of mothers was 26.8±6.5 years. The mean of knowledge score was 7.25±2.1 out of 13.5. Although knowledge of mothers about diagnostic methods was acceptable, it was not sufficient about causes, complications, harmful symptoms and prevention of the disease. The mean of attitude score was 18.5±3.7 out of 25. The mean of behaviour score was 6.8±2.3 out of 10.5. Knowledge had a significant association with history of neonatal jaundice (P=0.033), mother's age (P<0.001), and child's birth rank (P=0.001). There was also a significant association between mother's attitude and their educational level (P<0.001). Results showed a direct correlation between knowledge, attitude and behaviour (P<0.001). Increasing mothers'

knowledge about jaundice of neonates can be the first step to enhance healthy behaviours; through education programmes during pregnancy (JPMA 58:671; 2008)[61].

Sahoo M et al., (2016) to conduct a prospective study at ASRAM Medical College and Hospital, a tertiary care centre, Eluru, West Godavari District, Andhra Pradesh Some of the most common causes of neonatal jaundice include physiological jaundice, breast feeding or non feeding jaundice, breast milk jaundice, prematurity and ABO incompatibility. Aims and objectives of study IS To study the incidence, various risk factors in newborns with clinical jaundice progressing to jaundice needing treatment and to assess no of neonates requiring phototherapy & exchange transfusion in ASRAM hospital, during May 2013 to July 2014. Method: The present study was a prospective hospital based study involving all neonates who were born at ASRAM Medical College and Hospital, a tertiary care centre, Eluru, West Godavari District, Andhra Pradesh. Observation: Out of 560 newborns, 273 (48.8%) newborns developed clinical jaundice. Out of 273 newborns with clinical jaundice, 166 (61%) newborns developed physiological jaundice and 107 (39%) newborns developed non physiological jaundice requiring therepeutic intervention in the form of phototherapy or exchange transfusion. Conclusion: Present study concludes that the leading cause of pathological jaundice is breastfeeding jaundice, ABO incompatibility and prematurity[62].

Daynia E. Ballot and Gilbert Rugamba et al., conducted a study . Exchange Transfusion for Neonatal Hyperbilirubinemia in Johannesburg, South Africa, from 2006 to 2011 Severe hyperbilirubinaemia requiring exchange transfusion has become less common in recent years; however, kernicterus still occurs. The aim of this study was to review babies undergoing exchange transfusion for severe hyperbilirubinaemia in a Johannesburg hospital. This was a retrospective review of babies who required exchange transfusion in both the neonatal and the paediatric wards from June 1, 2006, to December 31, 2011. Results. There were 64 patients who underwent 67 exchange transfusions. Isoimmune haemolysis (both Rh and ABO incompatibility) was the cause of jaundice in 9/64 (14%). Most babies who underwent exchange transfusion were sick or preterm and were admitted in hospital after birth (38/64; 59.5%); three of these babies died, but not during the exchange transfusion (3/38; 7.9%); all three had signs suggestive of neonatal sepsis. The remaining 26 babies (40.6%) were readmitted to the paediatric wards for exchange transfusion. Six of these babies (6/26; 23.0%) had signs of kernicterus. The most significant complication of exchange transfusion was apnoea requiring mechanical ventilation in three patients (3/64; 4.6%). The

conclusion of this study is. Despite a relatively low number of babies undergoing exchange transfusion, kernicterus still occurs and must be prevented. Proper protocols for screening and management of severe hyperbilirubinaemia need to be enforced[63].

Heier HE, et al.,The present prospective study indicates that children of mothers with blood group O run a double risk of hyperbilirubinemia requiring treatment as compared to children of mothers of blood group A, and 5-10 times increased risk of needing exchange transfusion. The most frequent cause of need for exchange transfusion was ABO-incompatibility between mother and child. A positive direct ant globulin reaction in an ABO-incompatible child in need of treatment doubles the risk of exchange transfusion being required. Blood group O in the mother should be considered to be an independent risk factor for the child, and O-pregnant women should be ABO-grouped for this reason[64].

Lucas GN.,A prospective study was carried out on 101 neonates with jaundice due to ABO incompatibility. The direct Coomb's test was weakly positive in 4 cases. The indirect Coomb's test using the eluate was positive in 8 cases. In the maternal blood either IgG anti-A or anti-B haemolysin was present in high titer in every case. Phototherapy was given when the indirect serum bilirubin level exceeded 9 mg/dl. Exchange transfusion was done-in 39 cases, 9 babies requiring multiple exchanges. There were 2 deaths[65].

Beazley JM, et al., studied of 1353 labours and the relevant newborn failed to reveal any significant difference between the incidence of neonatal hyperbilirubinemia (defined as a level of 12 mg. or more per 100 ml.) following spontaneous labour, and after labour induced or accelerated by oxytocin. The incidence of unexplained neonatal hyperbilirubinemia after spontaneous labour was 6-3 per cent. Following induced labour however there was a highly significant (P less than 0-001) association between the mean total dose of oxytocin used for induction and the incidence of neonatal hyperbilirubinemia. The proportion of babies who developed hyperbilirubinemia increased in direct relation to the total dose of oxytocin used for the induction. In this series the incidence of hyperbilirubinemia increased sharply when the total dose of oxytocin exceeded 20 units as it did hyperbilirubinemia and birth weight, or duration of spontaneous labour. When labour was induced, however, the proportion on newborn babies with hyperbilirubinemia increased with the duration of labour. The significance of these findings is discussed[66].

Corchia–et al studied idiopathic hyperbilirubinemia (in Sardinian infants) in the first 4 days of life among 431 healthy full term infants with birth weight >2,500 gms. All infants

were free from malformations or any disease, requiring treatment other than jaundice. They were ABO and Rh incompatible with their mothers and were not G6PD deficient. The regression analysis indicated that high alpha-fetoprotein concentrations in cord blood. History of neonatal jaundice in previous full term siblings, delayed first meconium passage and weight loss were associated with jaundice. These results suggest the high rate of constitutional and possible hereditary factors[67].

Rosenthal–et al.– assessed liver function and hyperbilirubinemia in the newborn. "Liver Function" is assessed, by either measuring the concentration of substances produced by the hepatocyte, measuring the serum content of substances that are changed by hepatocyte damage. Evaluating the serum concentrations of substances released from the cells as a result of injury, assessing the ability of the liver to perform a metabolic task such as conjugation or detoxification, or by measuring enzyme activity and substitute content of the cell and its organisms. After birth with cessation of placental functions, the neonatal liver must assume many different tasks. Distinct developmental sequences rapidly progress for numerous hepatic functions as the newborn adapts to its environment. Lastly they concluded that the manuscript is an attempt to provide guidelines for the evaluation and management of the newborn infant by assessing live function and hyperbilirubinemia[68].

Gartner LM et al., studied Optimal management of breastfeeding does not eliminate neonatal jaundice and elevated serum bilirubin concentrations. Rather, it leads to a pattern of hyperbilirubinemia that is normal and, possibly, beneficial to infants. Excessive frequency of exaggerated jaundice in a hospital or community population of breastfed infants may be a warning that breastfeeding policies and support are not ideal for the establishment of good breastfeeding practices. The challenge to clinicians is to differentiate normal patterns of jaundice and hyperbilirubinemia from those that indicate an abnormality or place an infant at risk[69].

B Wood, P Culley, et al., conducted a study Plasma bilirubin was estimated on 690 term infants on about the 6th day of life. Perinatal factors were recorded and the results analysed. Hyperbilirubinemia was defined as a level greater than 205 micromol/1 (12 mg/100 ml) and this was present in 20% of cases. Three factors-- epidural analgesia, breast feeding,

and poor weight recovery--showed highly significant associations with jaundice. The relative importance of these is discussed and compared with recent reports. Induction of labour, for reasons other than postmaturity, and a gestational age less than 39 weeks showed a slightly increased incidence of jaundice. There was no correlation with other factors tested including oxytocin drug administration. Despite the high incidence (20%) of hyperbilirubinemia, only 2.5% infants needed treatment and none required exchange transfusion. Radical changes in obstetric management or infant feeding are not indicated[70].

Ablfors – et al. performed a study on the criteria for exchange transfusion in jaundiced newborns, which lowers critical bilirubin concentrations when the serum albumin falls to <2.5 g/dl. This study investigates using the biirubin / albumin ration instead of the single albumin concentration eliminate this potential ambiguity in the criteria. They concluded that the bilirubin / albumin ration is a simple, non-ambiguous way of incorporating the serum albumin concentration in to exchange transfusion criteria. The bilirubin / albumin ratio was defined as a reliable indicator of bilirubin / albumin binding of the frequency curves of specific unbound bilirubin concentrations are normally distributed functions of the ratio. Therefore, the bilirubin / albumin ratios at which the unbound bilirubin reached the 10, 15 and 20 nmon/1 were determined by the peroxides method in 35 well full term, 10 ill full term and 19 ill pre term neonates. The frequency curves for each unbound bilirubin concentration was plotted against the bilirubin / albumin ratio were tested for normality. Furthermore, the mean ratio at which each unbound bilirubin occurred did not differ significantly among the groups of neonates. The author concluded that the bilirubin / albumin ratio is a simple, non-ambiguous way of incorporating the serum albumin concentration into exchange transmission criteria[71].

Rubaltelli – et al. Carried out a study on management of neonatal hyperbilirubinemia and prevention of kernicterus. Hyperbilirubinemia remains as one of the most common and more important pathological conditions in the newborn. Current methodologies for suppressing severe neonatal jaundice include; (a) attempts to stimulate liver conjugating enzymes using drugs such as Phenobarbital; (b) attempts to degrade bilirubin with phototherapy; and (c) exchange transfusion. It is too soon to consider tin-protoporphyrin as a drug for the prevention and treatment of neonatal hyperbilirubinemia. However, if it can be shown that tin-protoporphyrin can serve as a safe and less costly alternate treatment, a considerable improvement in the management of neonatal jaundice can be achieved[72].

Tan - et al. studied the efficacy of "high-intensity" blue-light and "standard" daylight phototherapy for non hemolytic hyperbillirubinemia. They stated that, nursing of infants under high-intensity blue light was more difficult and inconvenient as was clinical monitoring. The light also cause more stress to the nursing and medical personnel. However, the infants tolerated both types of phototherapy equally well. High-intensity blue-light phototherapy would seem to be the treatment of choice for infants with rapidly increasing or very high bilirubin levels, as well as, in those not responding adequately to daylight phototherapy. And carried out a study on phototherapy and the brain-stem auditory evoked response in neonatal hyperbilirubinemia, The brain-stem auditory evoked response of infants with hyperbilirubinemia were significantly greater before phototherapy than after phototherapy. Theses values of the brain stem auditory-evoked response improved significantly during phototherapy and correlated significantly with the declining bilirubin levels. Improvement continued after phototherapy, despite a rebound of serum bilirubin concentrations[73].

Altha Roberts Edgren - Full-term infants rarely require an exchange transfusion if intense phototherapy is initiated in a timely manner. It should be considered if the total serum bilirubin level is approaching 20 mg/dL and continues to rise despite intense in-hospital phototherapy. Exchange transfusion corrects anemia associated with the destruction of red blood cells and is effective in removing sensitized red blood cells before they are destroyed. It also removes about 60 percent of bilirubin from the plasma, resulting in a clearance of about 30 percent to 40 percent of the total bilirubin. If a transfusion is not performed and bilirubin levels get higher, the infant progresses through three phases. In the first two to three days the infant is lethargic, has muscle weakness, and sucks weakly. Progression is marked by a tensing of the muscles, arching, fever, seizures, and high-pitched crying. In the final phase, the patient is hypotonic for several years[74].

Newman – et al. examined the association between neonatal bilirubin levels and subsequent neuro developmental outcome. He carried out a study on 41, 24 singleton white or black infants with birth weight > 2.500 gms, who had neonatal bilirubin measurement recorded and survived at least 1 year. Lastly, he concluded neonatal bilirubin levels seem to have little effect on IQ, definite neurological abnormalities or hearing loss. Higher bilirubin levels are associated with minor motor abnormalities[75].

Bysshe studied deafness in childhood. In his study, he stated the risk factors for

deafness are low birth weight, neonatal jaundice, family history of deafness etc.

De-Caceres – et Al. evaluated behavioral differences in healthy newborns in relationship to bilirubin serum levels within the normal physiological range. They concluded that physiological bilirubin levels cause significant neurological disturbances; these results suggest that newborns with higher physiological bilirubin levels have some difficulties interacting with their caretakers[76].

Ozmert – et al. carried out a retrospective follow up study to evaluate the suitability of the recently reported exchange transfusion limits (serum indirect bilirubin level of 428-496 mumol/1, 25-29 mg/dl) for Turkey. Children were grouped according to their maximum serum bilirubin levels and direct Coomb's test results. Physical and neurological examinations, visual and brainstem auditory evoked potentials and the Wechsler Intelligence Scale for children were performed. They concluded that children whose direct Coomb's tests were positive, had significantly lower IQ scores and more prominent neurological abnormalities ($P<0.05$)[77].

NEED FOR THE STUDY

The role of developmental assessment is to see that the child is progressing as per norms set by a large majority of children of the same age. It is by no means a predictor of future intelligent quotient and any deviation from the normal is brought to the notice of the parents, only in reassuring ways. The cause and effect relation between developmental deficits and risk factors can be much more complicated than we imagine. We cannot presume that neonatal jaundice will lead to mental retardation, fine and gross motor abnormalities, hearing loss and vision problems. But most of the children have developmental disabilities after neonatal jaundice.

Hence it is ideal to have some sort of developmental evaluation for all babies like measuring length, Head Circumference, Chest Circumference, Midarm Circumference, weighing weight & reflexes of the neonates. The Preliminary analysis and statistics from many child developmental centers and out-patient departments in hospitals have showed that babies with neonatal hyperbilirubinemia have higher incidence of delayed developmental milestones and other associated problems.

Hence the investigators were prompted to follow the children who suffered from neonatal jaundice in order to identify the complications very early and promote optimum growth & development of the children.

AIM AND OBJECTIVE

AIM

The aim of this study is provides recommendations aimed to improve management of neonatal hyperbilirubinemia in infants.

0BJECTIVE

- To study the treatment used in the management of neonatal jaundice.
- To study the sign , symptoms and duration of the diseases.
- Collect information on the diagnosis, and treatments.
- To assess the diagnosing methods.
- Observe the entire treatment methods.
- to establish the most effective treatment methods for neonatal jaundice

PLAN OF WORK

- Initial study to identify the scope of work
- Literature survey
- Preparation of study of protocol
- Obtaining consent from the hospital authority
- Collection of data format from case sheets
- Data analysis
- Evaluations of data
- Results and Discussion
- Summary & Conclusion

METHODOLOGY

Study site: The study is conducted in Government district headquarters hospital, Thirupur district, Tamil Nadu.

Study period: November 2017 - June 2018

Study type: Retrospective study

Sample size: 80 patients

Study population: babies attended in neonatal intensive care unit, case sheets from medical record department.

Inclusion criteria:

- New birth babies diagnosed with neonatal jaundice
- Patients those willing to give their consent.

Exclusion criteria

- Patient above 6 month years old.
- addult.

Study procedure

The present study was conducted at Government district headquarters hospital, Thirupur for the retrospective assessment of neonatal jaundice cases The study involves mainly 3 steps.

1-**Collection of the prescriptions**

The prescription were collected from the neonetal intensive care unit, medical record department of Government district headquarters hospital, Thirupur. For a period of 6 months that is from Sep 17 to feb 2018.The study was conducted in retrospective manner, The data was collected from the respective departments of the hospital on proforma.

2-**Analysing the prescription**

The Collected data from the prescription were entered in to proforma were analysed. The phototherpy , its duration and other important parameters are noted.

3-Statistical analysis

The datas were collected according to the proforma and was entered in separate excel sheets in respective of their proformas or the parameters and they were analysed for the outcomes of the individual parameters like gender, age groups, others by making a table first and then followed by a graphical representation of the data.

The study was designed in a Retrospective manner. It was conducted in babies neonatal Intensive care unit of Government district headquarters hospital, Thirupur district (Tamilnadu) from sep 2017-feb 2018.

A study population of 80 patients (new babies and diagnosed with neonatal jundice) was selected. The study population consisted of both sex.

Prescriptions were collected from the respective departments of the hospital. Collected Data were recorded using a predesigned proforma and entered in to Microsoft Excel worksheets. Appropriate tests were applied for analysis.
Prevalence of neonatal joundice risk factors and , phototherapy frequency were noted.

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GENDER WISE DISTRIBUTION OF NEONALAL JAUNDICE

Table -1

	NO OF PATIENTS	PERCENTAGE %
MALE	44	55 %
FEMALE	36	45 %
TOTAL	80	100 %

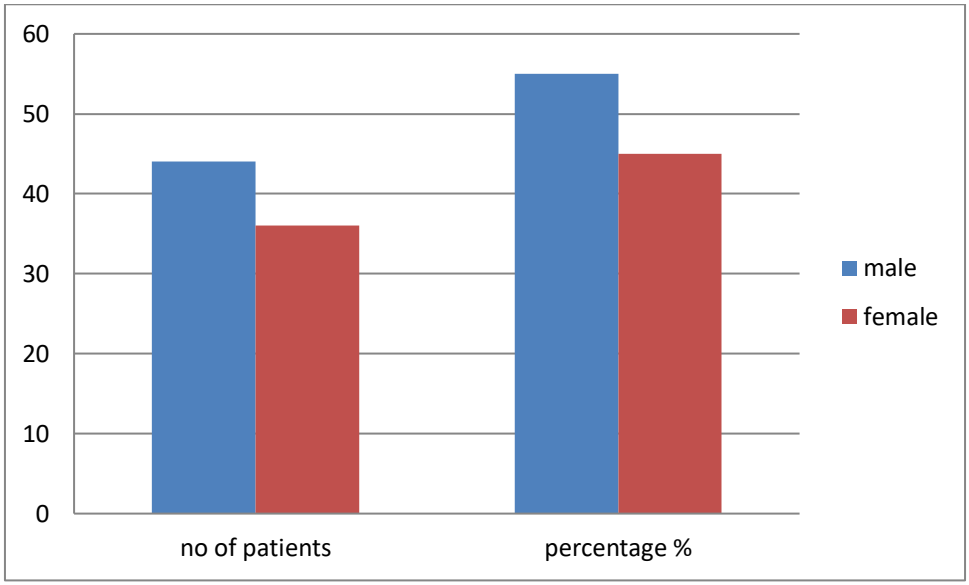

Figure-1

BODY WEIGHT DESTRIBUTION OF NEONATAL JAUNDICE CASES

Table -2

BODY WEIGHT	FREQUENCY (n = 80)	PERCENTAGE %
NORMAL BODY WEIGHT	48	60 %
LOW BODY WEIGHT	28	35 %
VERY LOW BODY WEIGHT	4	5 %

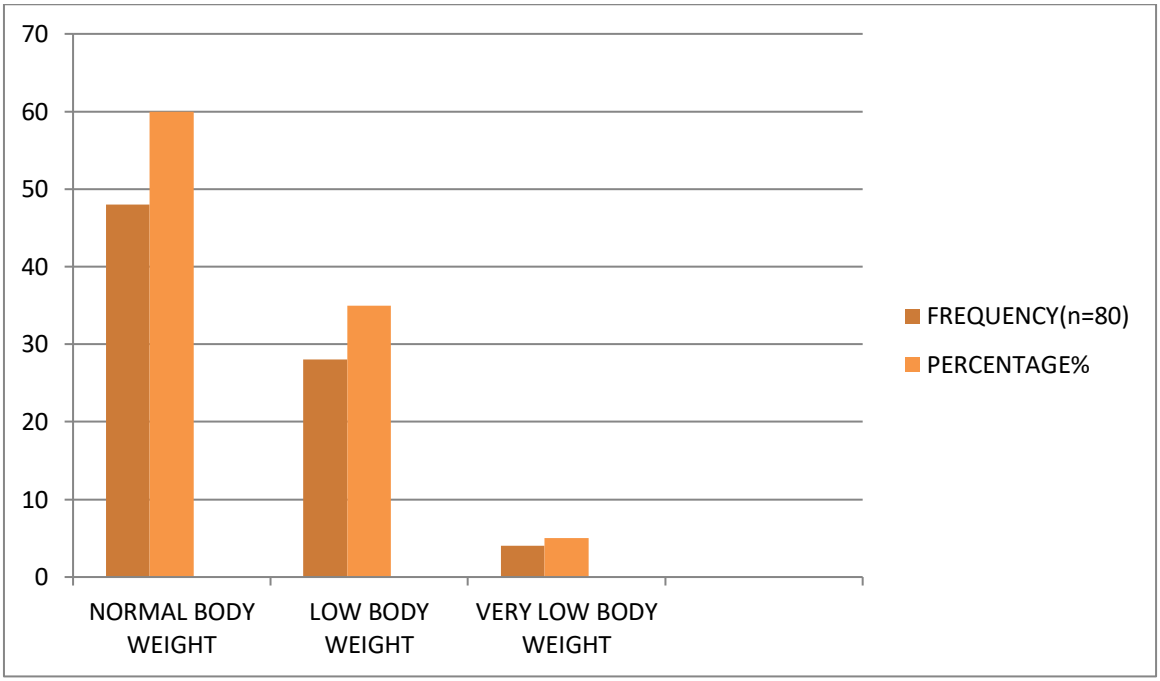

Figure -2

DISTRIBUTION OF GESTATIONAL AGE OF NEONATAL JAUNDICE

Table-3

GESTATIONEL AGE	FREQUENCY (n = 80)	PERCENTAGE %
TERM(> 35 WEEKS)	62	77.5 %
NEAR TERM(35-37 WEEKS)	10	12.5 %
PRE TERM(<35 WEEKS)	8	10 %

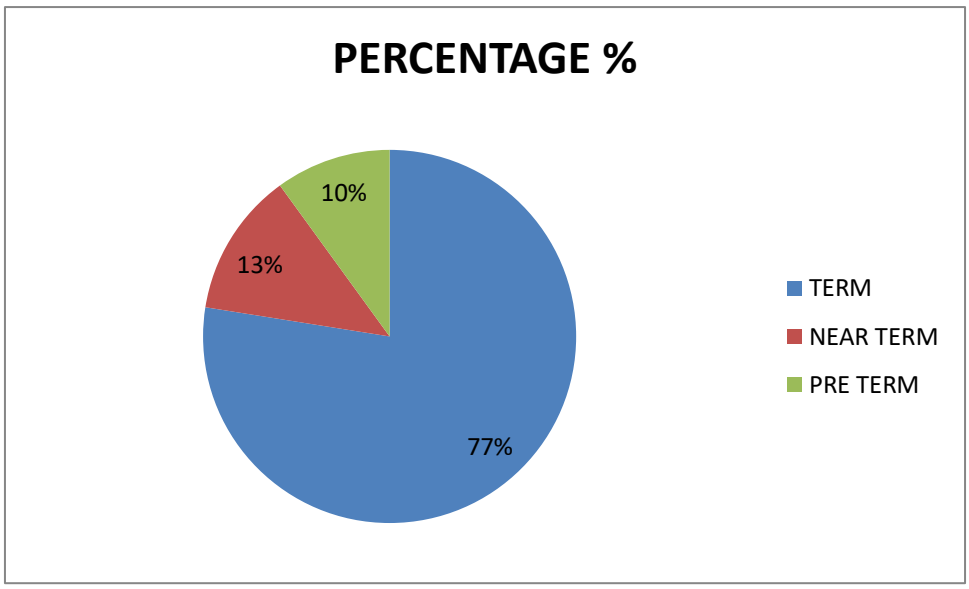

Figure-3

TYPES OF MOTHER

Table-4

TYPE OF MOTHER	FREQUENCY (n = 80)	PERCENTAGE %
NORMAL	57	71.2 %
PRIMI MOTHER	23	28.8 %

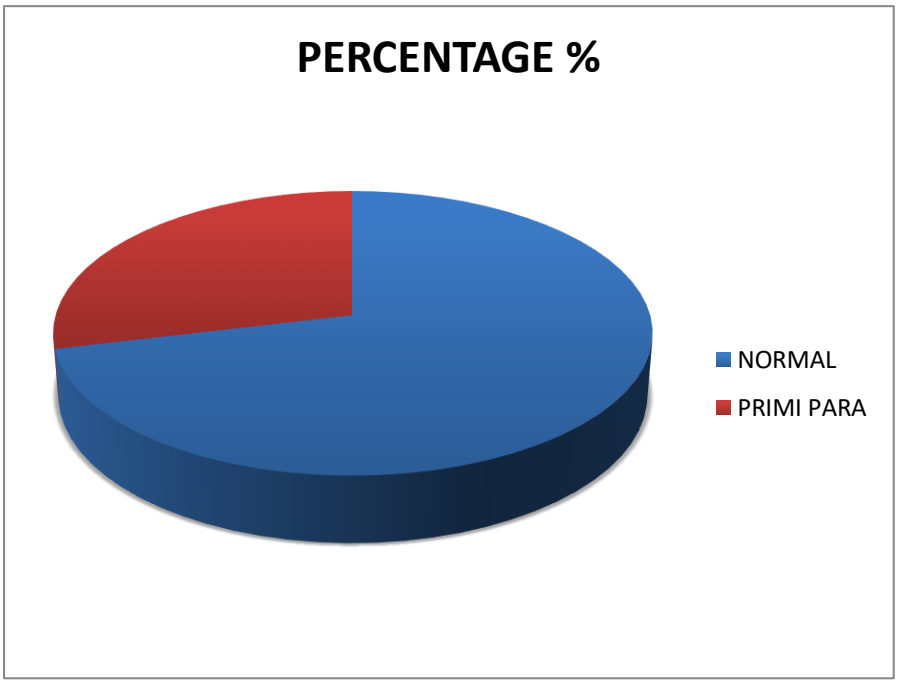

Figure-4

TYPE OF DELIVERY

Table-5

TYPE OF DELIVERY	FREQUENCY(N=80)	PERCENTAGE %
NVD	31	38.7%
LSCS	49	61.3%

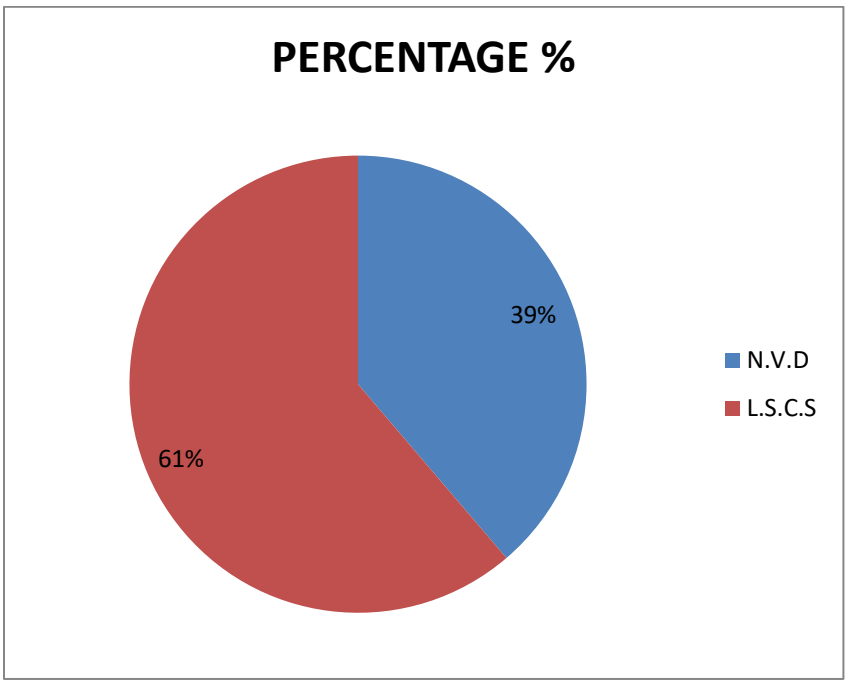

Figure-5

NO.OF RISK FACTERS IN PATIENTS

Table-6

RISK FACTER	NO.OF NEONETES	PERCENTAGE %
LOW BIRTH WEIGHT	32	40%
SEPSIS	28	35%
FEVER	18	22.5%
POOR FEEDING	38	47.5%
PRIMI MOTHER	23	28.8%

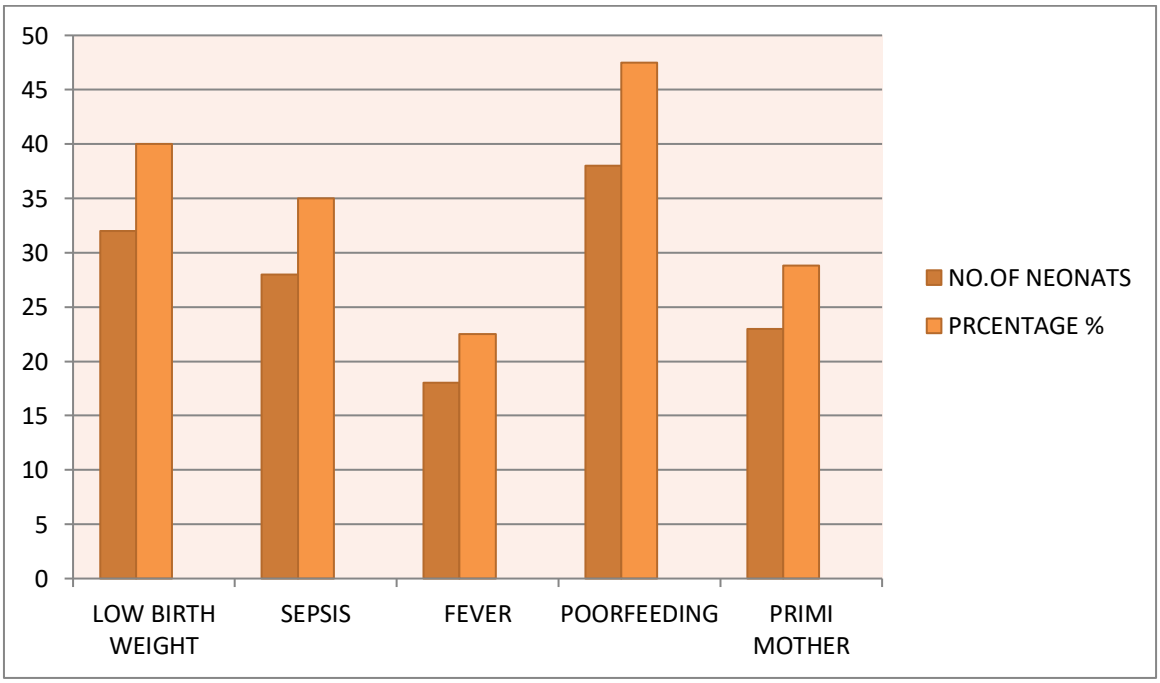

Figure-6

PHOTOTHERAPY DURATION

Table-7

DURATION (DAY)	NO.OF PATIENTS	PERCENTAGE
2 DAYS	33	41.5%
3 DAYS	21	26%
4 DAYS	22	27.5%
5+ DAYS	4	5%

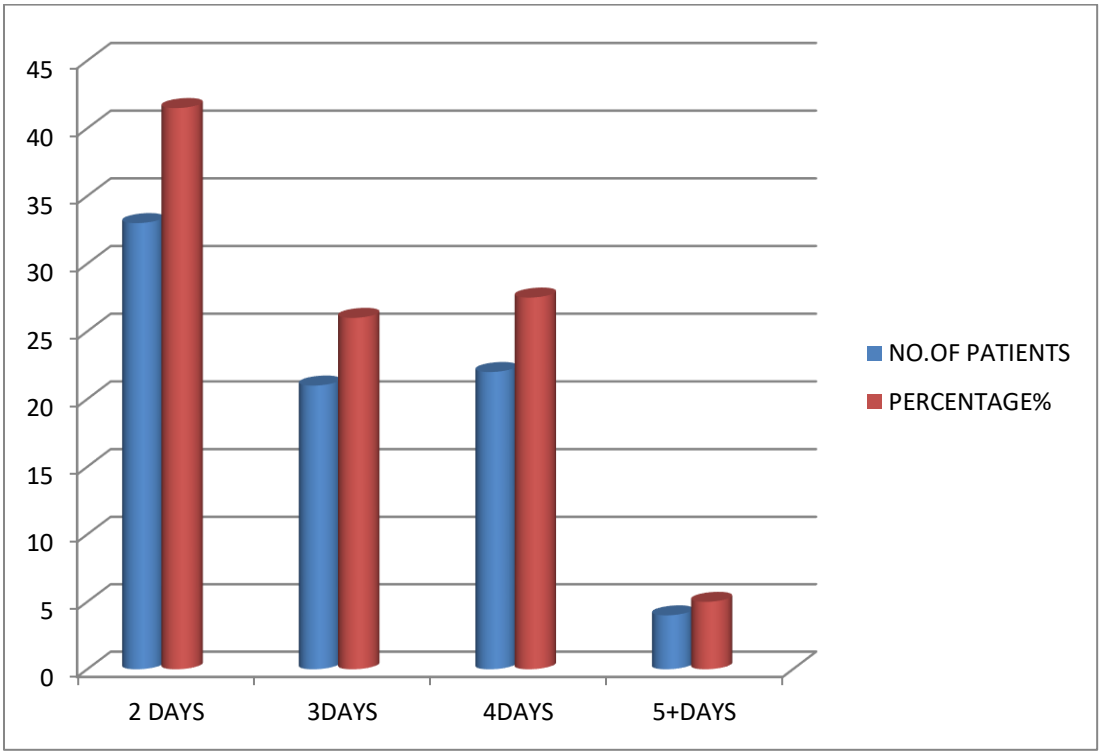

Figure-7

DISTRIBUTION OF BILURUBIN CONCENTRATION

Table-8

T.S.B CONCENTRATION (mg/dl)	NO.OF PATIENTS (n=80)	PERCENTAGE %
5-10	22	27.5%
10-15	52	65%
15 above	6	7.5%

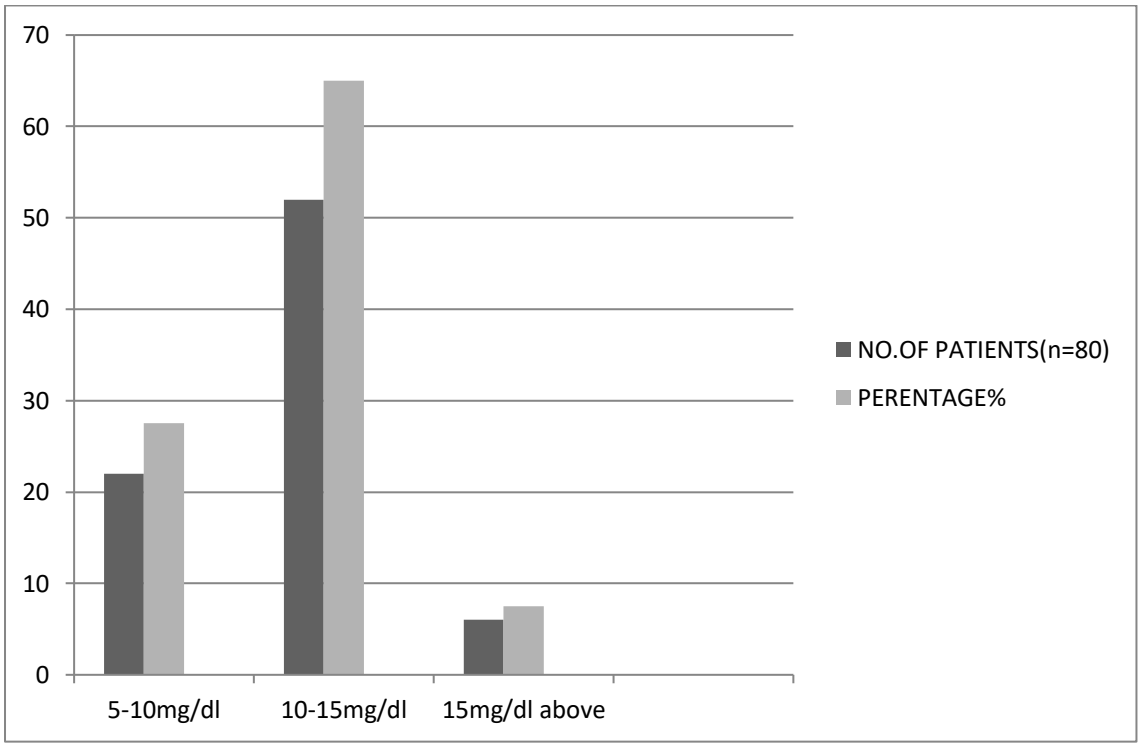

Figure-8

DRUG PATTERN IN TREATMENT OF JAUNDICE ALONG WITH SEPSIS

Table-9

MEDICATION	NO OF PATIENTS	PERCENTAGE %
Ampicillin	22	80
Gentamycin	23	82.5
Cefotaxime	18	65
Piperacillin	3	10
Amikacin	17	60

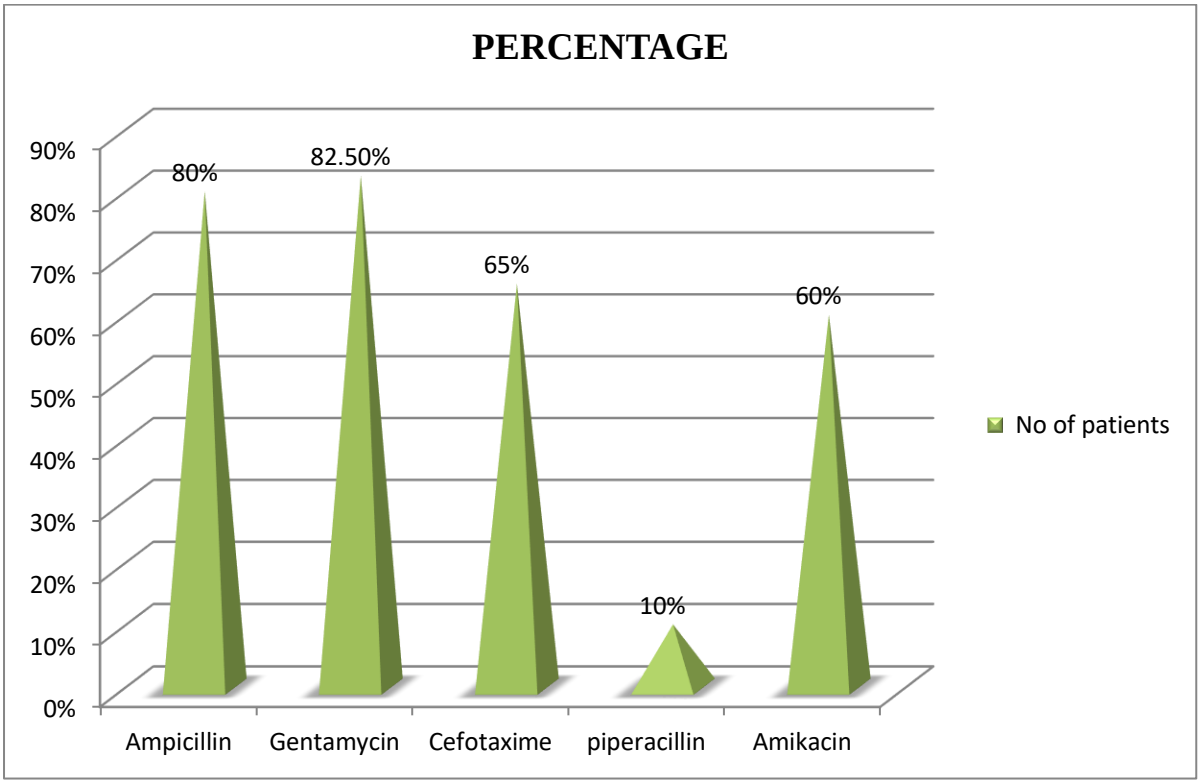

Figure-9

DISCUSSION

80 patients were selected for the retrospective study. The study population consisted of 44 male infants (55%) and 36 female infants (27%) Figure.1

Neonates selected for the study had different body weight. It includes. Study population include normal body weight neonates (60%), low body weight neonates (35%) and very low birth weight neonates (5%). Infants with normal bodyweight found to be more susceptible to neonatal jaundice. And the low birth weight neonates are risk factor of neonatal jaundice.Figure.2

The total infants are categorised on the basis of gestational weeks such as term(77.5%), near term (12.5%) and pre term (10%). The neonatal jaundice is mostly effected category is normal infants.Figure.3

The primi para mother is the one of the risk factor of neonatal jaundice. The primi para mother have totaly 23 present the total case. that is the 30 % neonatal jaundice effected in the case of primi para mother.Figure.4

61.3% of study population contain caesarean type delivery(LSCS).and 38.7% of mother in normal delivery (NVD).the caesarean infants are mostly effected neonatal jaundice than normal delivery infants .LSCS is also a risk factor of neonatal jaundice.Figure.5

Among the study population ,the most prevalent risk factor was found to be poor feeding (47.5%) followed by low birth weight (40%) and effect of sepsis (35%). 28% of mothers are primi para type. 22.5% of infants effected in fever. Figure. 6

Phototherapy treatment is the commonly used treatment of neonatal jaundice mainly the duration is mostly preferred to two days (41.5%) normally followed by four days (27.5%) and three days (26%).The duration depend up on the severity of jaundice. Only 5% is preferred to more than four days.Figure.7

The bilurubin concentration is the main diagnostic tool of neonatal jaundice .The 27.5%of the neonates contain bilurubin range is 5-10mg/dl most of the neonates (65%) contain the range of 10-15 mg/dl .Only 7% neonates is the higher bilurubin concentration level. That is mostly the bilurubin level is medium concentration.Figure.8

28 infants are effected jaundice along with sepsis and the drug pattern are used mainly antibiotics. Ampicillin and Gentamycin were the most commonly used antibiotic medication. Gentamycin was used in 23 patients (82.5) and Ampicillin was used in 22 patients (80%).Cefotaxime was used in 18 patients (65%) and Amikacin was used in 17 patients (60%) and Piperacillin was used in 3 patients (10%) out of 28 patients.Figure.9

CONCLUSION

- Neonatal jaundice was found to be more prevalent in male infants compared to females. This reflects male gender is an important risk factor for neonatal jaundice.
- The primipara mother is one of the most risk factor of neonatal jaundice. Near 50 % of infants found to be poor feeding. That is the main symptom of neonatal jaundice.
- Sepsis effected to 35 % of the neonates. That is it's also one of the most risk factor of neonatal jaundice.
- Most of the infants about 65% of neonates effected to medium level of neonatal jaundice the range of bilirubin concentration is shown in to 10-15 mg/dl.
- Birth weight of infants are affected .low birth weight of infants are also one of the risk factor. And gestational age of infants is effected rarely only 10% of pre term neonates are effected neonatal jaundice.
- Bilirubin concentration is a highly sensitive parameter in detection of cases of neonatal jaundice.
- Recommendation for the duration of photo therapy can be decided based on the results of visual assessment and total serum bilirubin concentration.
- The phototherapy is the main treatment method of neonatal jaundice. It is an effective treatment method normally.drugs is not ordinarily used.

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PROFORMA

PATIENT DETAILS

NAME :

IP NO :

SEX :

AGE: days

DOB:

GESTATIONAL AGE:

BIRTH WEIGHT:

CHIEF COMPLAINTS:

DIAGNOSIS:

OUTCOME OF HOSPITALIZATION: Survived [ ], Died [ ], Unknown [ ]

MOTHER'S DETAILS

NAME :

AGE :

BLOOD TYPE:

TYPE OF DELIVERY:

PAST MEDICATION HISTORY :

PREVIOUS COMPLICATIONS OF PREGNANCY:

PARA: GRAVIDA:

PRESENCE OF ANY OF THE FOLLOWING :	**Y/N**
• Prematurity < 38 weeks	[ ]
• Low birth weight	[ ]
• History of hyperbilirubinemia	[ ]
• ABO/ Rh incompatibility	[ ]
• Non optimal feeding	[ ]
• Central hematocrit more than 65%	[ ]
• Presence of signs of underlying illness like Vomiting/lethargy/poor feeding/temperature instability/apnea.	[ ]
• Jaundice visible on the first day of life	[ ]
• Newborn's trunk is distinctly yellow stained with yellow tinge of palms and soles.	[ ]
• Geographic prevalence of G-6PD deficiency	[ ]
• Primipara mother	[ ]
• Reduced sucking	[ ]
• Fever	[ ]
• Other infections eg septicemia, UTI	[ ]
• Diarrhoea	[ ]

DAY 1

General physical examination:

Wt: Icterus:

Color: Abdomen:

Vital signs:

Temp: HR:

RR:

Laboratory investigations:

Hb : TWC:

Platelet count: CRP:

Blood culture:

Serum Bilurubin :

Total :

Direct:

Treatment:

DAY 7

General physical examination:

Wt: Icterus:

Color: Abdomen:

Vital signs:

Temp: HR:

RR:

Laboratory investigations:

Hb : TWC:

Platelet count: CRP:

Blood culture:

Serum Bilurubin :

Total :

Direct:

Treatment :

DAY 14

General physical examination:

Wt: Icterus:

Color: Abdomen:

Vital signs:

Temp: HR:

RR:

Laboratory investigations:

Hb : TWC:

Platelet count: CRP:

Blood culture:

Serum Bilurubin :

Total :

Direct:

Treatment :

OTHER INFORMATION:

INFORMED CONSENT

Participant written informed consent

I understand that my participation is voluntary and that I may withdraw from this study at any time without giving any reason or to decline to answer any particular question in the study. I consent the members of the study to have access to my response and to publish the result, provided my identity is not revealed. I voluntarily agree to participate in the study.

Participant signature with date