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health technology assessment

MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA

HEALTH TECHNOLOGY ASSESSMENT UNIT
MEDICAL DEVELOPMENT DIVISION
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EXECUTIVE SUMMARY

Jaundice in the newborn or neonatal hyperbilirubinemia, is a common problem. It encompasses neonates with physiological jaundice, breast milk jaundice and non-physiological jaundice. In the United States, for example, 65% of all newborn infants appear jaundiced during the first week of life. A survey of government hospitals and health centres under the Ministry of Health Malaysia in 1998, found that about 75% of newborns were jaundiced in the first week of life.

Increased levels of serum bilirubin will cause unconjugated bilirubin to enter nerve cells and kill these cells, leading to brain damage, this being termed as kernicterus. Severe kernicterus has a high mortality. Even survivors usually suffer sequelae including athetoid cerebral palsy, high frequency hearing loss, paralysis of upward gaze and dental dysplasia

In the management of neonatal hyperbilirubinemia, the major issues are to establish the level of serum bilirubin at which there should be intervention, and also the serum levels for the various treatment options. Intervention is either by phototherapy, drug treatment or by exchange transfusion.

The objective of this study is to assess the safety, efficacy and effectiveness, and cost implications of management of neonatal hyperbilirubinemia

Based on the evidence obtained it is recommended for laboratory diagnosis, the laboratory should select the appropriate method based on needs and availability of technical resources. Quality control programmes and other measures need to be instituted to increase the accuracy of results. Transcutaneous bilirubinometry should be carried out on a selective basis. Periodic instrument calibration and generation of individualised correlation curves (institutional or regional) between transcutaneous bilirubinometer indices and serum bilirubin levels should be instituted. Local data on the reliability of transcutaneous bilirubinometry in a multi-ethnic population with varying intensities of skin pigmentation, as well as its cost effectiveness is needed. More data is also needed with respect to laboratory diagnosis like the indications for use of the non-invasive end tidal carbon monoxide excretion (ETCOc) technique and the best method of bilirubin determination for identifying the infant at risk for kernicterus.

In the treatment of hyperbilirubinemia, phototherapy should be considered at serum bilirubin levels of 222-260μmol/l taking into account other clinical factors. White light phototherapy is recommended, using intensive or blue light phototherapy only if serum bilirubin levels are high and it does not respond to conventional phototherapy.

In using exchange transfusions, serum bilirubin levels, bilirubin/albumin ratio and other clinical factors should be taken into consideration. All necessary precautions should be taken to limit morbidity and mortality.

Drug treatment is not recommended at present, until more evidence on efficacy is available.

CONTENTS

1. INTRODUCTION

Jaundice in the newborn or neonatal hyperbilirubinemia, is a common problem. Neonatal hyperbilirubinemia encompasses neonates with physiological jaundice, breast milk jaundice and non-physiological jaundice.

Jaundice is apparent clinically when the level of bilirubin in the serum rises above 5mg/dL. In the United States, for example, 65% of all newborn infants appear jaundiced during the first week of life (Maisels, 1988). A survey of government hospitals and health centres under the Ministry of Health Malaysia in 1998, found that about 75% of newborns were jaundiced in the first week of life. The majority of these were mild jaundice, although the levels of jaundice were however, not mentioned (Ministry of Health Malaysia, 1998).

Increased levels of serum bilirubin will cause unconjugated bilirubin to enter nerve cells and kill these cells, leading to brain damage, this being termed as kernicterus. Severe kernicterus has a high mortality. Even survivors usually suffer sequelae including athetoid cerebral palsy, high frequency hearing loss, paralysis of upward gaze and dental dysplasia (Hathaway, 1990). When this potential for neonatal hyperbilirubinemia to produce brain damage became apparent, there were concerns raised about the need for diagnostic and therapeutic procedures to prevent such outcome. Since it was discovered that dermal icterus progresses in direct relation to serum bilirubin, for several years, the only reliable available method of assessing neonatal jaundice was through serum bilirubin determinations. This technique, besides being invasive, is also limited by accessibility to testing facilities and the costs involved. Direct visual estimate of jaundice, on the other hand, has been found to be unreliable, and thus, carries the risk of underestimating significant neonatal jaundice.

In the late 1970s, direct relationship was established between dermal spectral reflectance (between the wavelengths 400 to 750 nm) and the degree of dermal icterus (Hannemann 1978; Peevy 1978). Consequently, a hand-held prototype that could non-invasively estimate serum bilirubin through transcutaneous spectrophotometry was developed in 1979 (Yamanouchi, 1980). Efforts have been subsequently underway to ascertain the reliability of this technique as a screening tool for neonatal jaundice.

In the management of neonatal hyperbilirubinemia, the major issues are to establish the level of serum bilirubin at which there should be intervention, and the serum levels for the various treatment options. Intervention is either by phototherapy, drug treatment or by exchange transfusion. At lower serum levels, phototherapy is the treatment of choice, while exchange transfusion is carried out when high serum bilirubin levels are attained.

In 1958, Cremer et al published their report on the successful use of phototherapy to bleach jaundiced infants. A decade later after the studies by Lucy et al in 1968 and Behrman and Hsia (1969), there was an explosion in the use of phototherapy. Since then various forms of phototherapy, lights had been used. The aim of phototherapy is to

prevent potentially dangerous bilirubin levels and to decrease the need for exchange transfusion

Drugs that have been used in the past to treat neonatal hyperbilirubinemia include phenobarbitone, cholestyramine, agar that prevents the reabsorption of unconjugated bilirubin from the intestines into the blood, and vitamin E. The newer drugs are the metalloporphyrins like tin porphyrin.

Exchange transfusion refers to the procedure where the baby's blood is replaced with other compatible blood. Some of the criteria for exchange transfusions that had been widely accepted in the past, such as the 20mg/dL total serum bilirubin concentration for the initiation of exchange transfusion in full-term infants, have been seriously questioned recently and new recommendations published (La Rosa, 1986; Kalpoyiaannis, 1982). Furthermore, with recent insights into bilirubin binding or "free" bilirubin theory, the findings of auditory brainstem evoked response, and the behaviour of jaundiced infants indicate that asymptomatic and even symptomatic neurotoxicity caused by bilirubin may occur relatively frequently at relatively low serum bilirubin concentration (Guaran, 1992).

2. TECHNICAL FEATURES

2.1 Pathophysiology of Neonatal Jaundice

Jaundice can be divided into three major groups – physiological jaundice, breast milk jaundice, and non-physiological jaundice.

2.1.1 Physiological jaundice

Under normal circumstances, 99.9% of unconjugated bilirubin in plasma is bound to albumin. Free bilirubin is only present in very small amounts (Robertson, 1986). The serum bilirubin level is a reflection of the bilirubin load to the liver, the rate of hepatic excretion and the ability of the serum binding protein to retain the bilirubin within the plasma space (Robertson, 1992). In-utero, unconjugated bilirubin is cleared by the placenta resulting in a cord serum bilirubin level of usually 35μ mol/l (2mg%) or less. The great variation in individual response to a bilirubin load, precludes establishing a precise definition of the level of normal serum bilirubin level or physiological jaundice; a level beyond which therapy has been shown to do more good than harm (Maisels, 1988). However, in general, any neonate with elevated serum bilirubin concentration, but which is less than 210 μ mol/l (12mg%) by the 3rd day of life, should be considered to have physiological jaundice. The pattern of physiological jaundice varies with prematurity, ethnic origin, and other factors. For instance, premature infants have a higher maximum bilirubin peak on the fifth to sixth day of life, and prolonged jaundice, sometimes lasting for weeks. On the other hand, normal Chinese infants tend to have higher maximum bilirubin levels that reach their peak after 4-5 days of life (Valae, 1976).

2.1.2 Breast milk jaundice

Breast-feeding is highly related to the development of early onset jaundice. This appears to be the most common type of jaundice requiring phototherapy in breast fed infants in whom no cause for the jaundice could be determined (Adams, 1985). Breast fed infants also have been found to have significantly higher serum bilirubin levels compared to formula fed infants (Saigal, 1982; Kuhr, 1982; Hall, 1983). It may not be necessary to investigate a healthy breast fed infant unless the serum bilirubin exceeds 15mg/dl Maisels, 1988).

Classical kernicterus in full term breast fed infants, although rare, has been described to occur in apparently healthy full term breast fed infants with no hemolytic disease or any other discernable cause for their jaundice. Less frequent breast feeding and stooling, and excessive infant weight loss seem to be the best predictors of severe hyperbilirubinemia (Tudehope, 1991).

Breast milk jaundice can be divided into early and late onset jaundice. Early onset breast milk jaundice is associated factors related to feeding, such as how often a mother feeds, how well the baby suckles, how often and how much supplementary or complementary feeds of water, glucose or infant formula is given. Late onset breast milk jaundice, on the other hand, is related to the milk received rather than the manner of feeding (Auerbach, 1987).

2.1.3 Non physiological jaundice

When neonates have serum bilirubin levels exceeding 12 mg/dL, the current practice is to carry out diagnostic tests to rule out non-physiological or "pathological" jaundice, due to haemolytic disease or sepsis. The American Association of Paediatrics in 1994 recommended the following factors and clinical signs be considered when assessing a jaundiced infant:

Factors suggesting the possibility of hemolytic disease

- family history of significant hemolytic disease
- onset of jaundice before 24hrs
- increasing bilirubin level of more than 0.5mg/dl/h
- pallor, hepatomegaly
- rapid increase in the total serum bilirubin after 24-48 hours (glucose 6-phosphate dehyrogenase [G6PD] deficiency may need to be considered)
- ethnicity suggestive of inherited disease(G6PD deficiency etc.)
- failure of phototherapy to lower the total serum bilirubin level

Clinical signs suggesting the possibility of other disease such as sepsis - vomiting, lethargy, poor feeding, hepatosplenomegaly, excessive weight loss, apnoea, temperature instability, tachypnea

2.2 Pathophysiology of Kernicterus

Kernicterus results from free bilirubin acid combining with lipids in the cell wall of neurones in the basal ganglia, brain stem and cerebellum thereby causing cell death. In ill babies with sepsis, hypoxia and asphyxia may disrupt the blood brain barrier. With jaundice, bilirubin bound to albumin can leak into the brain's extracellular fluid. Free bilirubin acid can also form and bind to cell membranes (Robertson, 1986). Although the association between elevated serum bilirubin levels and kernicterus has been established, most studies have failed to substantiate a specific level of total serum bilirubin during non-hemolytic hyperbilirubinemia in term babies and subsequent intelligence or serious neurologic impairment. The factors influencing bilirubin toxicity in the brain cells of newborn infants are complex and incompletely understood. These include serum albumin concentration, binding of albumen to bilirubin, the penetration of bilirubin into the brain, and the vulnerability of brain cells to the toxic effects of bilirubin. However, kernicterus is an uncommon event even in premature infants, even when levels of serum bilirubin are allowed to rise more than those previously thought to place the premature infant at risk.

2.3 Diagnosis of Hyperbilirubinemia

2.3.1 Laboratory diagnosis

Bilirubin is insoluble in water, unstable, susceptible to interferences, and exists in multiple species. For decades, the determination of serum bilirubin has been a frequent laboratory test in pediatrics because of its usefulness in diagnosis and therapeutic monitoring. Pediatricians have sought to use bilirubin values in the differential diagnosis of hepatic dysfunction or haemolysis. Knowledge of bilirubin levels is thought necessary to avoid neurologic disease. Although the reasons for measuring serum bilirubin have not changed, the thinking about bilirubin measurements and their significance has.

The laboratory diagnosis of bilirubin can be conventionally carried out by spectrophotometric, diazo and enzymatic methods, as well as by newer methods like breath carbon dioxide measurement. Bilirubin is yellow in colour by virtue of its absorbance at about 450nm, and its concentration can be measured by *spectrophotometric* methods. The use of the caffeine reagent in *direct spectrophotometry* of bilirubin was introduced in 1924. It is also very photo labile and specimens must be protected from light prior to the assay. Two absorbance's are measured, one nearing the bilirubin peak, and the other at a higher wavelength as a blank against possible interfering compounds.

A chemical coupling reaction between *diazotized* sulphanilic acid and bilirubin was first described by Erlich, then applied for use in serum by van den Bergh in 1913, and subsequently, Jendrassik and Grof published major modifications of this method. The

reaction is very pH dependent and a number of accelerating agents like caffeine, dyphylline, and surfactants can be used to increase the rate of reaction.

The diazo methods for bilirubin assay have been automated including the use of dry films. Interference in diazo methods may arise from turbidity (usually from lipaemia), haemoglobin, metal ions, and certain drugs. Hence, a 'standard method' has been proposed based upon that of Jendrassik and Grof.

Enzymatic methods for measurement of serum bilirubin depend upon *bilirubin oxidase* which catalyses the oxygen-dependent conversion of bilirubin to biliverdin. Like the spectrophotometric and diazo methods, this method also gives lower values in the presence of haemoglobin. Newer methods include breath *carbon monoxide* levels as an index of rate of formation of unconjugated bilirubin from heme.

Methods for the measurement of *bilirubin species* involve the application of *high performance liquid chromatography* (HPLC). With this technique, unconjugated, monoconjugated, and diconjugated bilirubins, as well as another species, delta bilirubin can be identified. Spectrophotometric and enzymatic methods as well as direct assays have also been tried to measure the bilirubin species.

The preparation of suitable materials for the *standardization of bilirubin assays* is compounded by the variability and instability of bilirubin preparations, the nature and concentration of the different species present in serum, and their different behaviour in virtually all the methods. The method of Jendrassik and Grof is more robust in this respect and standards in either human or bovine albumin can be used satisfactorily. Several commercial materials are available, but may not be suitable for use with all methods. There is also the danger of potential infectious agents in the preparation of standards with pooled serum.

2.3.2 Transcutaneous bilirubinometers

All transcutaneous bilirubinometers are spectrophotometric instruments that operate in the following manner:

Step One: A pressure-sensitive probe is activated when pressed on the infant's skin. This illuminates a light-generating tube (Xenon in the Minolta Air-Shields instrument) to produce a bright strobe light.

Step Two: This bright light travels for a short distance through the skin (where the pressure-probe is applied) and Tran illuminates the underlying subcutaneous tissue.

Step Three: The resultant scatter of light is then channeled through fiber optic filaments to a spectrophotometric module.

Step Four: In the spectrophotometric module, a dichromic mirror splits the reflected light into two component spectra that pass respectively through green (with maximum absorption at wavelength 550nm) and blue (with maximum absorption at wavelength 460nm) light filters. The difference between the optical densities of the beams traversing through the two filters indirectly indicates the intensity of yellow colour of the reflected beam and therefore, of the dermis of the infant.

Step Five: The instrument translates this yellow colour intensity to an arbitrary displayed number; the higher the number, the higher the intensity of yellow colour. The instrument is calibrated to read white light as zero. During regular use, the instrument is calibrated against glass standards (with specific colour intensities) and the coefficient of variation for successive readings in a particular subject should not exceed 5% (manufacturers' recommendations).

At least eight brands of hand-held transcutaneous bilirubinometers are available worldwide, although in Malaysia, only two such brands, Minolta-Air Shields Jaundice Meter and the BiliCheck are available (Appendix B). Studies examining the various available transcutaneous bilirubinometry instruments showed little inter-instrument variability (with respect to correlation characteristics with serum bilirubin) (Yamauchi, 1989; Brown, 1990; Bilgen, 1998).

2.4 Treatment of Hyperbilirubinemia

2.4.1 Phototherapy

The native bilirubin is insoluble in water. Phototherapy works by using the light energy to change bilirubin into a more soluble form to be excreted in the bile or urine. When native bilirubin absorbs light, there is a photochemical reaction called isomerisation. There is also an irreversible conversion into another chemical isomer known as lumirubin that is rapidly cleared from the plasma into bile. This is the major degradation photoproduct of bilirubin in humans. A small component of the unconjugated plasma bilirubin is converted into dipyrrole compounds by light. This is excreted in the urine. Photo isomers of bilirubin are more polar than the native compound and can be excreted directly into the bile. Only photo oxidation products are excreted in the urine.

(a) Types of Phototherapy

Conventional phototherapy - provide light in the 425-475 nm wavelength band corresponding to the peak absorption of light by bilirubin. The usual light intensity is 6-12 μwatt/cm^2 per nm. There have been many modifications of the traditional phototherapy over the last 3 decades - the number and configurations of phototherapy bulbs, the source of light (fluorescent vs. halogen bulb) and the colour of bulbs (white, blue, or green). All, however, have involved the delivery of light from a source at a distance from the baby, usually 35-50 cm above the baby. The number of the bulbs used range from six to eight, comprised of blue (F20T12/B), special blue light (F20T12/BB) or Daylight fluorescent tubes. Special blue light has the disadvantage of making the infant look blue, although in **healthy newborns this is generally not a concern. To mitigate this effect, four special blue light tubes may be used in the central portion of a standard phototherapy** unit and two daylight fluorescent tubes may be used on either side of the unit. Other units use tungsten-halogen lamps in different configurations.

Fibre Optic Phototherapy (FOPT) - uses a fibreoptic cable, containing about 2000 – 2400 individual acrylic fibres, to deliver light from a tungsten halogen lamp to a light pad where the fibres are woven together. The pad, which remains cool, is inserted into a disposable paper jacket to avoid soiling of the pad and allowing it to be held securely to the infant's back. The baby can be dressed and wrapped normally thus enhancing his postural and autonomic stability, and can be nursed by the mother without interruption of phototherapy during breast-feeding. It is unnecessary to cover the eyes of babies nursed with the FOPT. The light delivered is in the 400-500 nm broad wavelength band and is of high intensity (35$\mu w/cm^2$ per nm ± 20% on the higher setting), compared to up to 16 (usually 6-12) $\mu w/cm^2$ per nm in the 380-480 nm range for conventional phototherapy, but the area of exposure is smaller. Much of the spectral emission of the FOPT device is in the green region that is less effective than blue light.

Because the fibre optic mat used in the FOPT system is relatively small, the area of exposure is smaller as compared to the conventional setup. With increasing body weight, the fraction of body surface exposed to fibre optic light will become less.

The first generation FOPT unit was the 'Wallaby' system, but studies on its effectiveness were disappointing. The Biliblanket (Ohmeda, Columbia, M D, USA) is a more sophisticated system containing a greater number of fibres with more points of light and a greater intensity of 35 $\mu w/cm^2/nm$.

Intensified Phototherapy (IP) - is a system that provides an increased irradiance of 26 - 40 $\mu w/cm^2/nm$, as compared to the irradiance of 7-16 $\mu w/cm^2/nm$ in conventional phototherapy. There are 3 methods available for providing IP:

i. using seven daylight fluorescent tubes placed close under the floor of the crib with the sides and top of the crib covered with a reflecting film
ii. using high intensity blue lights with seven overhead lamps and four lamps placed below the infant..
iii. high intensity double surface phototherapy on a fluid bed - this gave an irradiance of 26 to 30 $\mu w/cm^2/nm$ using a standard phototherapy unit close to the floor of the bassinet and conventional phototherapy given from above. The fluid bed acts as a thermal reservoir smoothing out temperature fluctuations.

(b) Factors Affecting the Efficacy of Phototherapy

The efficacy of phototherapy depends on the intensity of irradiance, spectral emission curve and the exposed area of the baby. There is a dose response relationship to bilirubin degradation until the saturation dose is reached. This can be achieved by exposing the maximum skin surface to an irradiance of 40 $\mu w/cm^2$ per nm of appropriate light. Beyond the saturation point, further increase in intensity will have no added effect. The efficacy of phototherapy also depends on the intensity of light emitted, a dose between 6-12 nm being necessary.

The efficacy of phototherapy increases with increasing bilirubin concentration. It is ineffective in reducing the bilirubin concentration at levels below 100μmol/l. A 50%

decline can be achieved within 24 hrs with bilirubin concentrations above 255 μmol/l using blue light i.e. light of the same spectral emission as the absorption spectrum of bilirubin.

Other factors that influence the efficacy of phototherapy are postnatal age of the infant, gestational age, birth weight and the etiology of jaundice. It is most effective in very small pre-term infants and least effective in very small (severely growth retarded) full term infants with elevated haematocrits.

Factors that reduce the efficacy of phototherapy are inadequate skin exposure, a light source too far from the infant (irradiance decreases inversely with the square of the distance), overheating of the fluorescent lamps causing rapid decay of the phosphor, and incorrect emission spectrum of the lamps.

2.4.2 Exchange transfusion

An exchange transfusion can be carried out by the automated method or the classical push-pull technique. It can be carried out via the umbilical or peripheral vessels, and takes about 1.5 to 2 hours. The major items required for the procedure are disposable blood exchange sets, two disposable intravenous drip sets and disposable needles and blades. A pint of fresh blood is required, and hemoglobin levels are monitored during the transfusion.

2.4.3 Drug treatment

Drugs that have been used in the past to treat neonatal hyperbilirubinemia include phenobarbitone, cholestyramine, agar and vitamin E.

Phenobarbitone enhances conjugation and excretion of bilirubin. However, it is not routinely recommended for treatment of jaundice in neonates, as its effect on bilirubin metabolism is not manifested until after several days of administration. In addition, it is less effective than phototherapy in reducing serum bilirubin (Nelson, 1996). Cholestyramine is a quartenary ammonium ion exchange compound with a strong affinity for bile salts. Its side effects include long-term steatorrhoea, deficiency of fat-soluble vitamins and folic acid, flatulence and constipation and even intestinal obstruction (Nicolopoulus, 1978).

Agar is a dried hydrophilic colloidal substance obtained from various species of algae. It protects bilirubin from the action of intestinal bacteria, and prevents the reabsorption of unconjugated bilirubin from the intestines into the blood (Harold, 1973). Vitamin E deficiency increases red cell hemolysis.

More recently tin potoporphyrin and tin mesoporphyrin have been used. These competitively inhibit the activity of heme oxygenase, the rate-limiting enzyme in heme catabolism. This reduces the production of bilirubin and thereby, substantially

diminishes plasma level of the bile pigment. This is unlike other strategies like phototherapy and exchange transfusion that acts by accelerating removal of bilirubin. However, although bilirubin levels may decline, the effect is similar to phototherapy. The baby can develop transient erythema if concomitant phototherapy is also administered (Nelson, 1996).

3. OBJECTIVE

To assess the safety, efficacy and effectiveness, and cost implications of management of neonatal hyperbilirubinemia

4. METHODOLOGY

4.1 Laboratory diagnosis

Database: Medline, Evidence-Based Medicine, Embase, Bandolier, Health Technology Assessment.
Keywords: *Laboratory diagnosis, bilirubin, neonatal hyperbilirubinemia, neonatal jaundice, calibration, standards, interlaboratory variability, cord blood, quality control.*
Year: 1982 – 1999 (before 974, abstracts generally not available)
Language: English
Electronic search: 1430 titles
Relevant titles: 165
Abstracts reviewed: 36
Full texts: 14

4.2 Diagnosis, Drug Therapy

The database used was MEDLINE using the Internet. The keywords used were *hyperbilirubinemia, definition, classification, breast-feeding,* and *drug therapy*; used singly or in combination.

Years:	1960 – November 1999
Limits:	full text, abstracts, English article, human
Abstracts reviewed	59
Full text reviewed	38

4.3 Transcutaeous Bilirubinometry

A MEDLINE, EMBASE and EBM database search was carried out using the key word strings *transcutaneous bilirubinometry, neonatal jaundice screening, phototherapy* and *serum bilirubin.* Searches were also made of bibliography references in standard textbooks, cross-references and reviews. All studies (observational or case-control) examining the use of transcutaneous bilirubinometry in neonates using paired transcutaneous bilirubin readings and standard determinations of serum bilirubin, were eligible.The outcome measures used were correlation coefficient between transcutaneous

bilirubin readings and serum bilirubin with corresponding determination of sensitivity, specificity, negative- and positive-predictive values of transcutaneous bilirubinometry; effect of gestational age, postnatal age, weights, disease states, concurrent exposure to phototherapy, site of reading on reliability of transcutaneous bilirubin readings; cost-effectiveness of transcutaneous bilirubinometry as a screening tool in neonatal jaundice.

The methodology of the review involved categorization of the retrieved studies based on quality of evidence (levels I to VIII, ranging from meta-analyses to purely observational studies) and creation of an evidence-table.

Necessarily, most studies were observational in nature (Level VIII). Case-control formats and retrospective analyses were adopted in studies analysing cost-effectiveness of transcutaneous bilirubinometry.

4.4 Phototherapy

The databases used were Medline and Embase using the Internet. The keywords used were *neonatal jaundice, phototherapy, green light phototherapy, blue light phototherapy, daylight phototherapy, fibreoptic phototherapy, conventional phototherapy, hyperbilirubinemia,* and *biliblankets*.

Limits	English, human, abstract, full article
Years	1985-1999
Total search	382
Relevant titles	25
Abstracts	35
Full text reviewed	18

4.5 Exchange Transfusion

Abstracts and full text reviews from the Medline database from 1966 - 1999.
Subject headings used were: *exchange transfusion, neonatal jaundice, adverse effects bilirubin / albumin ratio*
Number of titles: 445
Number of abstracts reviewed: 57
Number of full texts: 39

Each selected article was graded on the level of evidence according to the modified CAHTA scale (Appendix A).

5. RESULTS AND DISCUSSION

5.1 Classification of Hyperbirubinemia

In general, babies with hyperbilirubinemia can be classified into those with hemolysis and others with no hemolysis. A systematic review recommends instituting treatment to keep serum bilirubin levels between 400-500μmol/L (23.4 –29.2mg/dL) in babies with no

hemolysis, and in those babies with hemolysis, to provide treatment to maintain levels in the range of 300-400μmol/L (17.5 –23.4mg/dL). Thus, babies with jaundice should be followed closely, obtaining several laboratory tests in those with early jaundice or with bilirubin levels more than 12-13mg/dL (205-222 μmol/L), using phototherapy to try to keep bilirubin levels below 20mg/dL (342μmol/L), and carrying out exchange transfusions if phototherapy fails, regardless of the cause of the jaundice (Newman, 1992).

5.2 Breast Milk Jaundice

It has been found that supplementary feeding of water, dextrose or infant formula during the first few days of life did not reduce the hyperbilirubinemia of term breast fed infants (Hall, 1983; Nicoll, 1982; DeCarvalho, 1981). A review of 77 references states that early onset jaundice is associated with how often a mother breast feeds, how well baby sucks, amount and frequency of supplementary or complementary feeds, while in late onset jaundice, it was related to breast milk rather than manner of feeding (Auerbach, 1987). However, in a another study there was no significant difference in serum bilirubin levels, in the first three days of life, of infants whose mothers breast fed on demand, (an average of 6.5times per day) and those who fed more frequently (an average of 9 times per day)[Maisels, 1994]. Jaundice levels are notably higher in breast-fed babies compared to formula-fed babies (Gourhy 1999; Osborn; Saigal; Tudehope, 1991;Kuhr, 1982; Hall, 1983; Maisels, 1986). In a paper by Tan (1998), the response to phototherapy in decreasing order of effectiveness is seen in babies on breast feeding supplemented with formula feeds, then babies on formula feeds, and then lastly on breast fed babies.

5.3 Diagnosis of Hyperbilirubinemia

5.3.1 Laboratory diagnosis

The *diazo* reaction was the first method used to measure serum bilirubin and remains the most popular. The procedure involves several methods including the *Jendrassik – Grof* (JG), but unfortunately, these methods often produce variable results because the chemistry of the diazo reaction can be affected by several factors (Westwood, 1991). The accuracy of the JG method, can be improved, however by using a standard containing a matrix of human albumin (Schlebusch, 1990). In comparing the diazo with enzymatic methods the differences were found to be caused by bilirubin species (Nakayama, 1995).

In the *caffeine method of direct spectrophotometry*, combining a dilution step and the clearing influence on the turbidity of human sera will improve both the calibration and make the measurements more accurate (Vink, 986). These findings are also important for standardization because the diazo method of JG is also protein independent. The caffeine method is preferred in neonates since it is not influenced by haemolysis or albumin (Vinck, 1988). Direct Spectrophotometry when compared with the candidate reference method gives identical results and is therefore suitable for use in neonatalogy (Hajzer, 1989). Comparison between the diazo and spectrophotometric methods shows the methods correlated well for total bilirubin determination. Discrepancies were observed

for conjugated bilirubin due to the fractions (Francoual, 1993). However, when different methods including the diazo and spectrophotometric were compared with the candidate reference method, the values produced by these 2 methods were generally higher (Schlebusch, 1990).

The *enzymatic method employing bilirubin oxidase* is apparently unaffected by commonly used anticoagulants, serum preparation materials, and selected drugs (Perry, 1986). However, turbidity and haemoglobin concentration of 2G/L resulted in lower values when compared to the JG method. Differences were also caused by the presence of bilirubin species (Nakayama, 1995). A newer assay for selectively measuring conjugated bilirubin concentration has been found to be useful for the fractional determination of bilirubin (Kurosaka, 1998). Precision and accuracy were studied using automation (Schlebusch, 1991). Imprecision was found to be unacceptably high and accuracy had to be improved using calibrators with reference method values.

For healthy term infants, blood bilirubin concentrations are not a reliable index of total bilirubin production; the "gold standard" is estimation of *carbon monoxide in breath.* This method of estimation may also be helpful in understanding the mechanisms of jaundice (Stevenson, 1994). The end tidal carbon monoxide (ETCO) uses a portable breath analyser. The ETCO measurements reflect the rate of heme degradation and bilirubin production (Stevenson, 1997).

Bilirubin fractions are measured by the diazo reaction, *high performance liquid chromatography (HPLC),* direct spectrophotometry and enzymatic methods (Doumas, 1991). The accepted gold standard is HPLC (Gourley, 1999). When common clinical laboratory methods were compared against HPLC, significant differences were uncovered (Gourley, 1999). Comparing manual and automated methods with HPLC, it was found that automated methods gave reasonable values for clinical use (Rosenthal, 1990). The identification of specific bilirubin species by HPLC in jaundiced infants will help in the understanding and management of their disease (Ostrea, 1988). HPLC analysis is also recommended as a standard method for bilirubin measurement (Ihara, 1992).

Studies conducted on the *variability of interlaboratory* bilirubin measurements, showed that although there was consistent internal quality control in each of the 14 laboratories involved, bilirubin measurements differed significantly from established reference values at most of the participating laboratories (Stevenson, 1997). Similar conclusions were drawn from other studies (Schreiner, 1982; Hazjer, 1992; Vreman, 1996).

Problems in *standardization* of total bilirubin in neonatal serum stem from the suitability of commercial bilirubin standards and direct reading instruments (bilirubinometers) (Blijenberg, 1987). Differences existed between the stated values and the results obtained with the candidate reference method. Another study showed that no synthetic bilirubin standard could be used as the primary standard, and advocated the use of pooled neonatal serum (Blijenberg, 1987).

While the reliability of bilirubin analyses is especially important, *external quality control* surveys showed differences of up to 10% (Rohle, 1988). A large American study involving about 6000 laboratories showed surprising variability in the bilirubin measurements. These laboratories included the 12 largest peer groups in this survey group. This study also showed that a test that had been performed for nearly 90 years showed tremendous inter-laboratory variation during the QC challenges (Lott, 1993).

In The Netherlands, a bilirubin *calibrator* is available through a QC program, and a study carried out showed that after re-calibration, the inter-laboratory coefficients of variation (CV) could be improved. This study also proved that using a fixed calibration factor reduced the CV in comparison to a daily calibration procedure (Bakker, 1996). The calibration of bilirubinometers should be performed with neonatal serum as this procedure can help to reduce interlaboratory imprecision in neonatal bilirubin analysis (Brugmann, 1990). Another study recommends that a control sample should only be used as a calibrator if there is no significant difference between the values obtained between a candidate reference method and a correctly calibrated spectrophotometer (Blijenberg, 1993).

For early detection, *cord serum* total bilirubin levels can define a subgroup of infants who are at a higher risk of significant hyperbilirubinemia. Infants with bilirubin levels of < 2.0 mg/dL have a 4% chance of developing hyperbilirubinemia if level rises above 2.0mg d/L, the infant has a 25% chance of requiring phototherapy (Rosenfeld, 1986). Similar conclusions were also drawn from 3 other studies that advocate the routine measurement of umbilical cord bilirubin levels which provide an early and painless method to identify neonates at risk for hyperbilirubinemia (Hanna, 1999; Knudsen, 1989; Johnson, 1989). Another comparative study of cord blood, heel-prick and transcutaneous (TC) bilirubin values with serum bilirubin, however found that serum and TC measurements are better predictors of neonates at risk. Cord blood bilirubin with a cut-off point of 2.2mg/dL was not a useful predictor of neonatal jaundice (Carbonell, 1999). The in-vitro effect of *light* on serum bilirubin fractions shows the importance of shielding serum, to avoid generating bilirubin photoproducts that interfere with accurate determination (Ihara, 1992).

Studies of another *pre-analytical factor*, the *sampling sites* for serum samples, showed that there was no significant difference between capillary and arterial sites (Langbaum, 1994; Chance, 1988). However, it was felt prudent to measure venous rather than capillary bilirubin levels when the total serum bilirubin exceeded 10 mg/dL (Leslie, 1987).

In infants with respiratory distress, acidosis, hypoglycaemia it was shown that the total bilirubin binding capacity (TBBC) and *TBBC/albumin molar ratios* were quite low and therefore treatment should be initiated at lower serum bilirubin levels in these patients

(Satar, 1996). A *diurnal variation* in bilirubin levels exists, in that they are significantly higher in the morning that in the evening (Reif, 1995).

Comparison of bilirubin production in Japanese and Caucasian infants showed higher levels in the former (Fischer, 1988). In Melanesian babies, the bilirubin levels were higher than in Caucasian but lower than Asian babies *Environmental and genetic factors* were said to be contributory (Kia, 1985**)**.

(a) Cost of laboratory diagnosis in local laboratories

Cost of chemistry analyser (heavy-duty)	RM 150 000 - 450 000
Cost of reagents & consumables (direct & indirect bilirubin)	RM 2.00
Cost of HPLC Analyser	RM 200 000

(multi –purpose separation instrument used for drug screening, therapeutic drug monitoring, toxicology, & bilirubin fractionation).

Cost per test with HPLC *RM 50.00 - 100.00*

(depending on reagents used)

5.3.2 Transcutaneous bilirubinometry

(a) Reliability in detecting significant neonatal jaundice in term infants

There were 15 studies, involving well term infants (of all weights) between ages 0 to 6 days, that reported good correlation between transcutaneous bilirubinometry determinations and serum bilirubin levels with correlation coefficients ranging from 0.74 – 0.91 (Yamauchi, 1988; Hegyi, 1981; Lin, 1993; Fok, 1986; Kumar, 1994;Yamanouchi, 1980; Tan, 1985; Tan, 1996; Boo, 1982; Heick, 1982; Maisels, 1982; Uchida, 1988; Sheridan-Periera, 1982; Knudsen, 1979;). This good correlation appeared to occur over a narrow range of serum bilirubin, i.e. between 175 – 225 μmol/L (10 – 13 mg/dL) [Maisels, 1982; Heick, 1982; Tan, 1985; Knudsen, 1990; Laeeq, 1993; Tan, 1996). At higher serum bilirubin levels, the instrument was more useful for its high negative-predictive value (Maisels, 1982; Heick, 1982; Laeeq, 1993).

Three other studies showed a poor correlation, with correlation-coefficients ranging between 0.53 – 0.67 (Bourchier, 1987; Bhutta, 1991; Moscicka, 1994).

Most studies emphasize the need for generation of individualized correlation coefficients and action levels (i.e., the transcutaneous bilirubin readings that indicate need for phototherapy or blood sampling).

It can be concluded that transcutaneous bilirubinometry correlates well with serum bilirubin over the ranges that necessitate initiation of phototherapy (i.e., between 175 – 225 μmol/L), making it a reliable screening tool for detection of significant neonatal jaundice. The high negative-predictive value at higher serum bilirubin levels indicates that the possibility of underestimating severe neonatal jaundice with this method is low.

(b) Factors affecting reliability of transcutaneous bilirubinometry

There may be certain important factors that influence the reliability of transcutaneous bilirubinometry.

Gestational age of infant - Transcutaneous bilirubinometry is unreliable in predicting serum bilirubin levels in preterm infants. This has been attributed to the increased intrinsic dermal yellowness of preterm neonates, confounding transcutaneous readings. Further, preterm neonates often have coexistent illnesses (anemia, respiratory distress syndrome, sepsis, acidosis) that appear to decrease the reliability of dermal spectral reflectance (Tan, 1985; Tan, 1988; Knudsen, 1996). One study, which had 60 term and 10 pre-term babies, found good correlation between plasma bilirubin levels and transcutaneous bilirubinometry readings (Sheridan-Pereira, 1982).

Thus, transcutaneous bilirubilirubinometry is probably not reliable in detecting significant jaundice in preterm neonates.

Site of reading – In several studies, sternal readings were found to correlate better with serum bilirubin values than forehead readings (Lin, 1993; Fok, 1986; Heick, 1982), while one study showed forehead readings to possess a superior correlation (Yamauchi, 1991). It has also been demonstrated that averaging forehead and sternal readings provides better correlation with serum bilirubin than either individually (Yamauchi, 1988). The less reliable forehead readings may be attributed to the effect of daylight exposure on the intensity of dermal icterus at the forehead (Yamauchi 1989). Other cutaneous sites have proven unreliable in assessing jaundice, owing to variable epidermal thickness. However, a lack of effect of site on correlation with serum bilirubin levels has also been demonstrated (Tan, 1985; Tan, 1996).

Hence, despite the manufacturer's recommendation to use forehead readings (teleologically based on the rostrocaudal progression of dermal icterus), more evidence seems to favour sternal readings as better correlated with serum bilirubin values.

Phototherapy - Serial transcutaneous bilirubin readings are rendered significantly unreliable following exposure to phototherapy (Hegyi, 1981; Fok, 1986; Yamanouchi, 1980). It has been suggested that correlation can be preserved if covered or less-exposed sites like the antero-lateral aspect of the thigh are chosen (Lim, 1997; Hegyi, 1983; Dominguez, 1993). However, there were two studies that showed no effect, of phototherapy on transcutaneous bilirubinometry readings (Kumar 1994; Knudsen, 1990). This limitation may be attributed to the asynchrony between dermal and serum bilirubin clearance (Yamauchi, 1989).

It is thus suggested that transcutaneous bilirubinometry readings be best correlated with serum bilirubin values before initiation of phototherapy.

Skin-pigmentation and transcutaneous bilirubinometry – It has been demonstrated that there is continued reliability of transcutaneous bilirubinometry in infants from multi-ethnic societies with varying intensities of skin pigmentation (Tan, 1985; Tan, 1996). In infants of Malay, Chinese and Indian ethnicities from Singapore a uniform correlation was found between transcutaneous bilirubinometry and serum bilirubin despite varying skin pigmentation (Tan, 1998). In contrast, a local study encountered poor correlation with serum bilirubin levels in 30 Indian babies, but good correlation for babies of Malay and Chinese ethnicity (Boo, 1984). It has also been suggested that individualised correlation curves for various ethnic groups are more reliable (Linder, 1994).

Thus, it is rather difficult to come to a conclusion in the light of conflicting evidence.

(c) Cost-effectiveness of Transcutaneous Bilirubinometry

The high sensitivity of transcutaneous bilirubinometry renders it a cost-effective screening technique. This could be as a result of early identification of those neonates who require phototherapy (a 5-9% improvement in detection rates)[Dai, 1996]; decreasing readmission rates following early neonatal discharge. (Knudsen, 1995); Reducing the need for vene-punctures to determine serum bilirubin by 20-75%, by accurate identification of those babies who require invasive sampling (Strange, 1985; Schubiger, 1986; Suckling, 1995; Dai, 1996; Maisels, 1997). Cost-savings by these may be up to A$ 1600 – 2000 (Maisels, 1997).

In conclusion, the good correlation between transcutaneous bilirubinometry and serum bilirubin levels over ranges that necessitate phototherapy renders the former a cost-effective screening option, since it identifies only those babies who require serum bilirubin sampling, so that unnecessary tests are not carried out, leading to cost savings.

5.4 Treatment of Hyperbilirubinemia

5.4.1 Phototherapy

(a) Levels to start phototherapy

There does not seem to be a consistent serum bilirubin level at which phototherapy is to be commenced. However, it is generally agreed that treatment should be based on the infant's history, physical findings, and clinical judgement. The actual bilirubin level, its rate of rise, and the gestation at birth of the infant may help determine whether to begin phototherapy, since direct bilirubin measurements may vary substantially with individual laboratories.

The American Association of Paediatrics recommends that for the treatment of infants without illness or apparent hemolytic disease, total serum bilirubin levels should exceed 260 μmol/l at 25-48 hours to more than 340 μmol/l at age exceeding 72 hours (American Association of Paediatrics, 1994). Another study recommends that phototherapy is indicated if serum bilirubin exceeds 255 μmol/l (CMAJ, 1986). Where based on unconjugated bilirubin, it is recommended that phototherapy be commenced if levels are higher than 136-204 μmol/l in babies up to 48 hours of age, at 204-272μmol/l in 49-72 hours old babies, and if it exceeds 272 μmol/l in older babies (Cockington). A study by Roberton recommends that phototherapy be commenced in babies at serum bilirubin levels of 100-310 μmol/l, irrespective of age, excluding babies with Rhesus hemolytic disease of the newborn (Roberton, 1992). Another study recommends the critical levels of serum bilirubin to be exceeding 18, 20 and 22 mg/dL respectively for the three age groups, at which phototherapy should be administered (Gartner, 1994). On the other hand, according to Johnson, for the age group 25-48 hours, phototherapy is to be given if serum bilirubin levels exceed 150-250 μmol/l, at levels of 250-320 μmol/l at ages 49-72 hours, and exceeding a level of 320 μmol/l in babies more than 72 hours old. (Johnson, 1994) Another study by Finlay and Turner adopted from Dodd, recommends slightly higher levels - 170-250 μmol/l, 250-350 μmol/l and more than 350μmol/l for the three age groups. According to Newman, in well babies with no hemolysis, phototherapy need only be instituted at serum bilirubin levels of 300-375 μmol/l while in those likely to have hemolysis or in ill babies, phototherapy should be started at lower bilirubin levels of 225 -300 μmol/l (Newman, 1972). In a study in Singapore, it was recommended that for babies less than 72 hours old, phototherapy is indicated at serum bilirubin levels exceeding 13 mg/dL (222 μmol/l) or exceeding 15 mg/dL (257 μmol/l) in older babies (Tan, 1989). However, another paper suggests normal phototherapy for babies with serum bilirubin from 222 - 255 μmol/l and high intensity phototherapy for babies with bilirubin levels exceeding 300 μmol/l. Phototherapy is to be continued till serum bilirubin levels fall to 185 μmol/l (2 consecutive readings), and these babies are to be monitored. When the serum bilirubin level does not exceed 210 μmol/l, monitoring can be discontinued. If the serum bilirubin level exceeds 255 μmol/l, phototherapy has to be resumed, while if it exceeds 300 μmol/l, high intensity phototherapy has to be used (Tan, 1996).

While, the above applies to babies at full term, it has been suggested that for pre-term babies, the levels of serum bilirubin would vary with the period of gestation - for babies at 28 -31 weeks of gestation, phototherapy should be started at 75 μmol/l within the first 24 hours, to 150 μmol/l at 72 hours and beyond. For babies at 32-36 weeks, phototherapy is to be commenced at serum bilirubin levels of 75-200 μmol/l, and at 200 μmol/l in babies after 24 hours of age; in babies of gestation of beyond 37 weeks, in the first 24 hours. Appropriate serum bilirubin levels for phototherapy are from 50 -100 μmol/l, while from 24-72 hours, the levels for phototherapy would be from 100 -320 μmol/l (Johnson, 1994).

The levels of serum bilirubin at which phototherapy is recommended for babies at full term for differing periods of gestation is represented in the table below:

Table 1: Level of serum bilirubin at which phototherapy is recommended for babies at full term according to age

Author Year Age (hr)	Gartner 1984	Robert. 1986	Tan 1989	New 1992	Cockin. (UnSB)	AAP 1994	John. 1994	F & T 1994	CMAJ 1996
25-48	> 18*	100 - 310 (except RhHDN)	> 13*	300 - 375 (NH[#])	130-204	260	275 - 375	170-250	>255
49-72	➢ 20 *		> 15*	225 - 300	204-272		375	250-350	
> 72	> 22*				272			> 350	

*Note: all values in μmol/L except *values in mg/dL; [#] non-hemolytic*

Thus, it can be seen that there is really no consensus on the appropriate levels of serum bilirubin at which phototherapy is to be initiated, the values varying from as low as 100 μmol/l to as high as 375 μmol/l. The general trend, however, seems to be that phototherapy be considered at serum bilirubin levels of about 222 -260 μmol/L in healthy normal babies and earlier for pre-term and sick babies.

(b) Colour of light in phototherapy

Phototherapy can be provided in the form of white, blue or green light. In a study comparing special blue and green light it was found that both were equally effective in reducing plasma bilirubin levels (Vecchi, 1986). In a study of 262 neonates using blue and green light, both were found equally effective with respect to rate of fall of bilirubin levels, duration of phototherapy and serum bilirubin concentration at the end of treatment. There was also no significant difference in the rebound (Ayyash, 1987).

However, other studies found that there was more rapid response and less phototherapy rebound with blue light as compared to green light (Amato, 1991; Hodr 1990). A comparison of daylight (white), fluoresecent green and special blue lamps found that while all three were effective, the decline of serum bilirubin in response to phototherapy was most marked in the blue lamps, while the response to the daylight lamps was better than to the green lamps, so that the shortest exposure was required for blue lamps (Tan, 1989).

Green light filtered to remove blue component light emitting light in 480-600 nm spectral region was found to be a good alternative to other light sources used for phototherapy (Sbrana 1987). Blue green light when compared with blue light was found to produce a faster rate of fall and a shorter duration of exposure (Donzelli, 1995). White light phototherapy was also found to be efficacious and inexpensive in the treatment of non-hemolytic jaundice, and adequate in most cases, regardless of gestational age and birth weight (Tan, 1986). When compared to white light, high intensity blue light was twice as effective in reducing bilirubin levels, and thus would be the treatment of choice for

infants with rapidly increasing or high serum bilirubin levels not responding to white phototherapy (Tan, 1992).

Overall, blue light seems to be the most effective, followed by white and green the least effective of the three.

(c) Comparison of fiberoptic phototherapy & conventional phototherapy

An earlier study found that fibreoptic phototherapy (FOPT) is not as effective as conventional phototherapy, unless the irradiance could be increased to 35µW/cm^2 per nm (Holtrop, 1992). FOPT was, in addition, found to be as effective as home phototherapy using a conventional four-bulb "bililight" (Schuman, 1992). The later studies used an increased irradiance and found that FOPT is a safe and effective form of phototherapy for preterm infants, and as effective as white light phototherapy. FOPT offers greater convenience than CPT and is readily accepted by both parents and nursing staff (Tan, 1994; Costello, 1994; Larsen, 1995; van Kaam, 1998). It was also found to be less effective in term babies (Tan, 1994).

Double phototherapy, a combination of FOPT and conventional phototherapy, was also found to be more effective than conventional phototherapy in pre-term infants (Holtrop, 1992; Tan, 1994; Kang, 1995). A comparison of FOPT, blue light and white light indicated that FOPT as effective as white light, but less effective than blue light, although there was a reduction of stress and interference of care-giving to the neonate (Donzelli, 1996). Another study comparing standard FOPT, large FOPT, double-FOPT, and conventional phototherapy in full-term infants found that the efficacy of double-FOPT was comparable to conventional phototherapy, and that it was more efficacious than the other two forms of therapy. However, nursing personnel found single FOPT easier to use in comparison to double FOPT (Tan, 1997). A comparison of Ohmeda Biliblanket and Wallaby neonatal system found no significant difference in efficacy between the two systems (Maisels, 1998). A recent study found that there is no change in mesenteric flow response to feeding in FOPT as compared to conventional phototherapy (Pezzati, 2000).

It can be concluded that FOPT is as effective as conventional phototherapy in pre-term infants, but there is insufficient evidence of its effectiveness for term infants.

(d) Intensified phototherapy

Using seven daylight fluorescent tubes was found to be a simple and cheap method that resulted in a significantly greater decrease of serum bilirubin concentration, than by using expensive special blue light fluorescent tubes (de Carvalho, 1998). However, intensified phototherapy using high intensity blue lights with seven overhead lamps and four lamps placed below the infant was found to be twice as effective as standard phototherapy in decreasing serum bilirubin concentration, and also reducing the duration of phototherapy. Greatest response was obtained in small pre-term infants (Tan, 1992). High intensity double surface phototherapy on a fluid bed resulted in a significantly lower serum bilirubin after 24 hours as compared to conventional phototherapy, with a faster rate of fall. The system was well tolerated, and easily and economically provided (Garg, 1995).

Thus, intensified phototherapy may be considered for infants with rapidly increasing serum bilirubin, or with very high levels of serum bilirubin not responding to conventional daylight phototherapy.

(e) Factors influencing the effectiveness of phototherapy

Oral agar used concurrently with phototherapy has been shown to augment the efficacy of phototherapy (Odell, 1983; Caglayan 1993), while administration of agar alone did not show significant drop in levels of serum bilirubin in one trial, (Harold, 1973), but was found to be as effective as phototherapy in another (Caglayan, 1993). Cholestyramine used in combination with phototherapy also decreased serum bilirubin (Nicolopoulos, 1978), but another study found that that there was no effect (Tan, 1984). Vitamin E was also found to reduce serum bilirubin and reduce the duration of phototherapy (Gross, 1979).

There was insufficient conclusive evidence on factors influencing phototherapy.

(f) The safety of phototherapy

Effects on Vision - Eye-shielding is advocated, as changes in the visual functions are noted in non-shielded infants exposed to prolonged illumination (Abramov 1985). With proper eye-shielding however, there are no long-term differences in ophthalmologic functions (Valkeakari 1981). Eye protection with the conventional eye-patch has the disadvantages of increased purulent eye discharge, conjunctivitis, suffocation, frequent accidental eye exposure and behavioural changes. Eye protection using a modified light proof head box has been shown to decrease the above side effects (Fok 1995; Fok 1997)

Effects on Gastrointestinal Tract - Phototherapy associated diarrhoea is a common known side-effect and is postulated to be due to increased bile salts (Brent 1983) and increased intestinal peptides resulting in stimulation of intestinal water and electrolyte secretions (Gounaris 1998; De Curtis 1989).

Effects on Central Nervous System - it has been suggested that there are short-term adverse effects on visual and auditory orientation during phototherapy (Ju 1992). Cerebral auto-regulation in both low birth weight and term infants is not affected by phototherapy (Amato, 1991). Long-term follow-up has shown that there are no differences in growth, development***, social maturity,*** neurological or EEG recordings between non-photo treated and photo treated infants (Valkeakari 1981)

Effects on Biochemical Functions - phototherapy aggravated the postnatal decline in riboflavin status, though the outcome of such decrease is of equivocal clinical significance. However, riboflavin supplementation is not routinely recommended (Amin 1992, Wu 1994, Rudolph 1985, Sisson 1987).

Phototherapy also results in oxidation of parenteral lipid emulsion, and thus caution has been suggested in parentral feeding (Neuzil 1995). Phototherapy-induced, but mostly

clinically asymptomatic, hypocalcemia has been reported, although Vit.D3 is not advocated for treatment (Sethi 1993, Zecca 1983). There does not appear to be any effect of phototherapy on thyroid function (Tan 1995). The potential for phototoxicity of tin protoporphyrin, tin mesoporphyrin and tin diiododeuteroporphyrin under neonatal phototherapy conditions at very high doses of phototherapy with ultra-violet radiation has been suggested, but is reversible when phototherapy is discontinued (Fort 1989).

Effects on Skin - With regards to insensible water loss from skin, phototherapy does not increase such losses in thermally stable infants (Kjartanson 1992), but in pre-term babies, the losses can be ten times more (Stornowski 1983). In critically ill neonates nursed under the radiant warmer, the water loss can be 50% more when phototherapy is administered (Engle, 1981). Two cases of cutaneous burns from phototherapy has been reported, and these can be prevented by plexiglass shields (Siegtried, 1992). Phototherapy has caused bullous eruption (Mellon, 1997). Purpuric phototherapy induced eruption with a causal link to transient porphyrinemia has also been reported (Peller, 1997).

Another complication of phototherapy is the bronze baby syndrome. This is a greyish-green discolouration of the skin resulting from abnormal accumulation of an unknown brown pigment, probably unexcreted photo-products. It occurs in infants with cholestasis of thick bile fluids as a result of hepatic dysfunction or hepatic disease. This skin discoloration is transient and resolves spontaneously with time (Redermacher 1997; Rodot 1994; Tan 1982; Curveillier 1980; Onishi 1982)

Although there has been concern over the possibility of development of skin malignancy in babies exposed to phototherapy, a case control study involving 120 patients showed no significant risk of malignant melanoma after phototherapy after 18 years follow-up (Berg 1997).

Effects on Cardiovascular System - a randomised controlled trial involing 295 babies showed a 50 % increased incidence of reopening of the patent ductus arteriosus (PDA) in extremely low birth weight babies (Barefield, 1993). A similar result was obtained in preterm infants on phototherapy (Benders, 1998), while another comparative study of 74 premature babies found that chest shielding can ameliorate PDA reopening rate (Rosenfield 1986).

(g) Cost implications of phototherapy

A comparison of cost per day per baby of the various types of phototherapy is indicated in the table below:

Table 2: Cost of various types of phototherapy

Type of light	Double photo light		Wooden photo light	Blue light	Medela intensive photolight		Air Shield high intensity photolight		Biliblanket		
	Eq. Cost	Blue light	(4 babies each time)		Eq. cost	Blue tubes	Eq. cost	Bulbs	Eq.cost	Halogen bulb	Blan-ket
Total cost (RM)	4800	1680	700	2900	4900	1680	1500	180	800	150	-
Number of lights / tubes / bulbs needed	-	12	-	10	-	-	-	3	-	1	-
Cost of each light / tube / bulb / blanket (RM)	-	28	-	58	-	70	-	15	-	25	90
No. of times changed / year	-	5	-	-	-	-	-	4	-	-	-
Life span in years	5	-	5	5	5	6	5	-	5	6	-
Cost / day (RM)	0.60	4.60	0.38	7.94	2.70	4.60	0.82	0.49	4.38	0.40	0.25
Total cost / baby / day (RM)	**7.20**		**0.10**	**2.08**	**7.30**		**1.31**		**5.03**		

It must be noted that the above costing is based only on equipment and consumables costs and does not include building costs, cost of personnel, and other costs like utility, maintenance and the like.

5.4.2. *Exchange transfusion*

(a) Criteria for carrying out exchange transfusion

The critical serum bilirubin level at which exchange transfusion should be carried out has not been established prospectively. This may be due to the fact that to propose a study that exposes neonates to higher serum bilirubin concentrations than those previously allowed would be

ethically questionable. However, arbitrary guidelines have been tested clinically and modified where the incidence of kernicterus was unacceptable (Boggs, 1960; Kitchen, 1970; Guaran, 1992).

Studies on diagnosis of kernicterus have been based on autopsied findings (Weldon, 1968; Kitchen, 1970; Dikshit, 1989). However, it has been pointed out that kernicterus at autopsy may be just an intra-mortem event that may not be associated with *in vivo* toxicity, since some neonates with evidence of staining of basal ganglia did not have any clinical evidence of kernicterus (Guaran, 1992). Disruption or immaturity of the blood brain barrier, potentiated by acidosis, hypothermia and shock may predispose neonates to toxicity. It has been suggested that these factors might be as important as the level of unbound bilirubin in the pathogenesis of kernicterus. (Dikshit, 1989) However, there are studies, which also give a contrasting opinion (Kitchen, 1970).

The criteria for exchange transfusion in the National Institute of Child Health and Human Development Phototherapy Study have been widely used as a guideline for exchange transfusion. There are two groups critical bilirubin concentration based on whether the baby belongs to the standard risk group or the high risk group, and adjusted for weight. For babies in the standard risk group the level varies from 13mg/dL for babies less than 1 250 gm. to 20 mg/dL for those more than 2 500 gm. The cut-off levels are lower for babies in the high-risk group varying from 10 to 18 mg/dL. The high risk factors are condition at birth, albumin concentration as well as birth weight and illness (Boggs, 1960; Weldon, 1968).

There is evidence supporting the free bilirubin theory in the pathogenesis of kernicterus, and the significance of the albumin concentration - clinical evidence like auditory brain stem evoked responses (Panagppoulous, 1969; La Rosa, 1986; Kalpoyiannis, 1982), behavioural changes (Panagppoulous, 1969; Mantalenaki, 1975), and long term neurological abnormalities (Tan, 1975). Thus, it is suggested to use the bilirubin albumin ratio. If this is incorporated with standard risk, weight less than 1250 gm. bilirubin albumin ratio of 5.2 corresponds to serum bilirubin level of 13 mg/dL while for babies beyond 2500 gm. it is 18. Similarly for the high-risk group, the bilirubin albumin ratio ranges from 4.0 to 7.2 (Boggs, 1960).

(b) Technique for exchange transfusion

The automated method was found to be superior to the classical push-pull technique as post-exchange serum bilirubin concentration was significantly less and potential haemodynamic derangement may be ameliorated by the former (Jackson, 1997; Ammann, 1983). Peripheral vessels exchange transfusion was found to be simple, practicable, and safe with few complications (Tan, 1976). It was also found that exchange transfusion performed with fresh heparinised blood is safe (Touloukian, 1973).

(c) Mortality, morbidity and adverse events associated with exchange transfusion

Mortality rates attributable to exchange transfusion ranged from 0.65% - 3.2% in studies performed in the 1960s, and from 0.4% - 3.2% during the 1970s and 1980s. Most of the studies conducted regarding adverse events related to exchange transfusion were performed more than 20 years ago.The most frequently cited review of adverse events from exchange transfusion is from the 1974 - 1976 prospective NICHD phototherapy

study. Keenan et al reported that in this study, 6.7% of the exchange transfusions were associated with adverse problems and 5.2% had serious morbidity events while 3.7% had transient complications. The calculated mortality rate was 0.53% (Keenan, 1985).

Another study spanning 15 years found deaths attributable to exchange transfusion to be 2%, incidence of permanent serious sequelae to be <1%, serious prolonged complications to be 4 -5% and serious transient complications around 16-17 %(Jackson, 1997).

Another study in 1989 reported a high rate of complications, that is, 20.4% in term and 41.8% in preterm infants. Procedure related mortality was 3.2 per 100 exchange transfusions that declined to 0.9 per 100 exchanges after exclusion for high-risk patients. The overall mortality was 10.6/100 exchange transfusions. Anemia and clinical septicemia were major delayed complications (Dikshit, 1989). A study in Singapore of 122 infants who underwent 140 exchange transfusions, reported 2 procedure related deaths occurring 2 days after exchange transfusion (Tan, 1976).

Rare complications associated with exchange transfusion are intravascular hemolysis following exchange transfusion with G6PD deficient blood (Kumar, 1994) and acquired immunodeficiency in an infant who received multiple transfusions for rhesus disease (Ammann, 1983). In preterm babies failure of autoregulation resulting in intravascular hemolysis has been reported (Milligan, 1980).
In conclusion the mortality rate of exchange transfusion ranges from 0.5% - 2.0%, while the incidence of serious morbidity events ranges from 4 -5 %. The most common causes of mortality and morbidity were necrotising enterocolitis, septicemia and kernicterus.

(d) Complications associated with instrumentation

Peripheral vessel exchange transfusion is generally a safe, simple procedure (Fok, 1990). Umblical vein catheterisation has been associated with risk of infection. Rare complications included abdominal distension, bloody stools and bilious vomiting (Touloukian, 1973). Exchange transfusion using fresh heparinised blood was also generally safe when performed in babies who do not have serious complications prior to exchange transfusion (Hovi, 1985).

(e) Effects of exchange transfusion on serum immunoglobulins

Two papers involving small sample randomised controlled trials were reviewed. They showed that exchange transfusion suppressed the production of autologous IgG and IgA, whereas IgM synthesis was provoked (Mantalenaki, 1975). Another randomised controlled trial on whether neonatal jaundice or the exchange transfusion stimulated IgE synthesis was inconclusive (LA Rosa, 1986).

(f) Efficacy of exchange transfusion compared with phototherapy

Studies show phototherapy acts slowly but constantly to reduce serum bilirubin levels and the rebound is also small. Phototherapy is effective even in severe hemolytic jaundice

but its effectiveness is inversely related to degree of hemolysis. Exchange transfusion caused an immediate reduction in serum bilirubin but the rebound was rapid (Tan, 1982; Kalpoyiannis, 1982).

(g) Cost implications of exchange transfusion

The requirements for the procedure and the cost of each item used is as shown below:

Equipment	Disposable blood exchange set	83.00
	Disposable Intravenous drip set (x 2)	2.40
	Face mask	0.20
	Disposable needles 23G & 21G (x 4)	1.40
	Blade x 2	1.20
	Gloves x 1 pair	1.40
	Bandage x 1 roll	0.50
	Plaster	0.40
	Staff Nurse	2.54
	Doctor	4.72
Blood Products	Fresh whole blood x 1 pint	100.00
Investigations	Blood tests done before and after transfusion	40.00
Drugs	Drugs given during exchange transfusion	41.00
	TOTAL	**278.76**

5.4.2 Drug treatment

(a) Agar

A study comparing agar and phototherapy found that continuous phototherapy in the first four days is superior to agar in reducing serum bilirubin levels in low birth weight (Harold, 1973). Another trial comparing a combination of agar and phototherapy with phototherapy alone, found that the rate of decline of serum bilirubin was greater and more uniform in the agar supplemented, so that a shorter duration of phototherapy was required (Odell, 1983; Suat, 1993).

(b) *Cholestyramine*

A study on a combination of cholestyramine and phototherapy against phototherapy alone found the combination to produce superior results in reducing the duration of phototherapy needed (Nicolopoulos, 1978). However, another similar study found that adding cholestyramine did not lower serum bilirubin levels during phototherapy (Tan, 1984).

(c) Vitamin E

In the use of vitamin E in neonatal hyperbilirubinemia, it was found that serum bilirubin levels were lowered in low birth weight babies (less than 1.5 kg.), with shorter duration of phototherapy required. However, there was no significant difference in babies weighing more than 1.5 kg (Gross, 1979).

(d) Metalloporphyrin

A single dose of Sn-mesoporphyrin (SnMP) proved effective in controlling severe hyperbilirubinemia in full term breast-fed newborn as well as in premature infants (Martinez, 1999). In a series of five trials involving 517 newborns, a single injection of SnMP significantly reduced hyperbilirubinemia in newborns of al ages. It was superior to phototherapy in term infants without hemolytic jaundice of the newborn, since a shorter time was taken for the serum bilirubin levels to decline to preset levels. The only side effect demonstrated was transient erythema although there was lack of detailed follow up data in the published studies (Valaes, 1994). A comparison of a single dose of SnMP and phototherapy found that the drug could be a substitute for phototherapy in both term and preterm babies. There was also no rebound unlike in phototherapy (Kappas, 1995).

6. LOCAL DATA

With respect to the incidence of neonatal hyperbilirubinemia in Malaysia, over the years 1993-1997, of the total live births in Ministry of health facilities, an average of 23.9% (Peninsula Malaysia), 21.2% (Sabah) and 23% (Sarawak) were diagnosed as hyperbilirubinemia. Of these, 32% received phototherapy, 0.29% exchange transfusion and 1.29% received both phototherapy and exchange transfusion. Of these cases of neonatal hyperbilirubinemia, 0.032% developed kernicterus (Quality Assurance Programme, Ministry of Health Malaysia)

7. CONCLUSIONS

7.1 Classification of Hyperbilirubinemia

Neonates with jaundice should be investigated if bilirubin levels exceed 205-222μmol/l, administered phototherapy to keep the bilirubin levels below 342μmol/l, and exchange transfusion instituted if phototherapy fails.

7.2 Breast Milk Jaundice

Serum bilirubin levels are higher in babies on breast milk in comparison to formula-fed babies.

7.3 Diagnosis of Hyperbilirubinemia

7.3.1 Laboratory diagnosis

While a number of methods for bilirubin estimation like diazo method, caffeine method of direct spectrophotometry, and enzymatic method using bilirubin oxidase, the gold standard is estimation of carbon monoxide in breath. High performance liquid chromatography is the gold standard for measurement of bilirubin fractions. There is significant variability in bilirubin measurements due to various factors like problems with standardisation and quality control. Cord serum has not been found to be a useful predictor of hyperbilirubinemia in comparison to other methods of measurement.

7.3.2 Transcutaneous bilirubinometry

Transcutaneous bilirubinometry is a cheap, reliable, easy-to-use, non-invasive method of serum bilirubin estimation. It correlates well with serum bilirubin measurements over the ranges of bilirubin that are considered significant to initiate phototherapy (i.e., between 170 – 225 μmol/L), and is thus an effective screening tool in determining significant neonatal jaundice. Transcutaneous bilirubinometry rapidly loses its reliability once phototherapy is initiated.

However, the reliability of transcutaneous bilirubinometry in a multi-ethnic population of babies (as in Malaysia) with varying cutaneous pigmentation remains unresolved.

7.4 Treatment of Hyperbilirubinemia

7.4.1 Phototherapy

(a) Levels to start phototherapy

There is no consistent serum bilirubin level to commence phototherapy. The general trend is that phototherapy should be considered at serum bilirubin levels of 222-260 μmol/l in healthy normal babies and at lower levels for pre-term and ill babies.

(b) Colour of light in phototherapy

Blue light is the most effective, followed by white, with green light being the least effective.

(c) Fibreoptic phototherapy

Fibreoptic phototherapy is as effective as conventional phototherapy in pre-term babies, but there is insufficient evidence of its efficacy for term babies.

(d) Intensified phototherapy

There is evidence of its efficacy in infants with rapidly increasing serum bilirubin, or with very high levels of serum bilirubin not responding to conventional phototherapy.

(e) Safety of phototherapy

Eye-shielding using a modified light-proof head-box can reduce the dangers due to prolonged illumination including eye infections. The evidence on other effects of phototherapy is inconclusive.

(f) Cost implications of phototherapy

White light phototherapy is the cheapest, especially using the wooden photolight.

Overall, phototherapy is an effective tool for treating neonatal jaundice with acceptable side effects, which can be minimised with special precautions.

7.4.2 Exchange transfusion

(a) Criteria for exchange transfusion

Apart from serum bilirubin levels, the bilirubin/albumin ratio can also be used as criteria for decisions on the need for exchange transfusion. For babies at risk, other factors like low Apgar score, low birth weight, hemolysis, clinical condition and the like have to be considered.

(b) Safety of exchange transfusion

There is a degree of morbidity and mortality associated with exchange transfusions, mortality ranging from 0.4 - 10.6%, and morbidity ranging from 6.7 - 20.4%.

(c) Drug treatment

There is limited evidence on the effectiveness of tin mesoporphyrin

8. RECOMMENDATIONS

1. For bilirubin determination, the laboratory should select the appropriate method based on needs and availability of technical resources. Quality control programmes and other measures need to be instituted to increase accuracy of results.
2. Transcutaneous bilirubinometry should be carried out on a selective basis. Periodic instrument calibration and generation of individualised correlation curves (institutional or regional) between transcutaneous bilirubinometer indices and serum bilirubin levels should be instituted.

3. In the treatment of hyperbilirubinemia, phototherapy should be considered at serum bilirubin levels of 222-260μmol/l taking into account other clinical factors. White light phototherapy is recommended, using intensive or blue light phototherapy only if serum bilirubin levels are high and it does not respond to conventional phototherapy.
4. For treatment by exchange transfusions, serum bilirubin levels, bilirubin/albumin ratio and other clinical factors should be taken into consideration. All necessary precautions should be taken to limit morbidity and mortality.
5. Drug treatment is not recommended at present, until more evidence on efficacy is available. Local data on the reliability of transcutaneous bilirubinometry in a multi-ethnic population with varying intensities of skin pigmentation, as well as its cost effectiveness is needed.
6. More data is also needed with respect to laboratory diagnosis like the indications for use of the non-invasive end tidal carbon monoxide excretion (ETCOc) technique and the best method of bilirubin determination for identifying the infant at risk for kernicterus.

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EVIDENCE TABLE

PHOTOTHERAPY

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments & Grade
Effects on Vision				
1.	Fok T.K. et al Use of eyepatches in phototherapy : Effects on conjunctival bacterial pathogens And conjunctivitis Paediatric Infectious Disease Journal 1995 Dec; 14(12):1091-4	RCT 102 with eyepatch 101 with lightproof plastic headbox	Eyepatched group increase pathogens isolated and increase purulent eyedischarge and conjunctivitis	Good - Fair
2.	Fok TK et al Eye protection for newborns under Phototherapy: comparison between Modified head-box and conventional Eye-	Case randomisation	Side-effects of eye-patch: eye infection, suffocation, frequent accidental eye exposure behavioural changes abdominal distension	Good - Fair

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments & Grade
	patches Journal of Paediatrics & Child Health 1997 Mar; 33S(1):S169			
3.	Valkeakari T Follow-up study of phototreated FT Newborns Acta Paediatrica Scandinavia 1981 Jun; 70(1):21-25	Case control n=41 assessed at 3 yrs old	No difference in growth, development, social maturity, neurological or opthalmologic, EEG recordings or lab. determinations	Poor
4	Abramov Changes in visual functions in children Exposed as infants to prolonged Illumination Journal of the American Optometric Association 1985 Aug; 56(8):614-9	7 yr old	Not shielded – deficits in colour vision spatial contrast sensitivity, steropsis but not rod vision	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments & Grade
Effects on GIT				
1.	Latini G P36 Evaluation of the possible effects of Phototherapy on non-nutritive sucking Patterns in newborn infants Paediatria Medice.Chingica 1989 Mar - Apr; 11(2): 195-6	Randomised 2 gps	No effect on non-nutritive sucking	Good - Fair
2	De Curtis M Diarrhoea in jaundiced neonates treated with Phototherapy: role of intestinal secretion Archives of Diseases in Childhood 1989 Aug; 64(8):1161-4	n=30 NNJ matched with 30 controls	Absorption of H2O, with phototherapy resulting in NaCl,K impaired secretory diarrhoea	Good - Fair

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments & Grade
3.	Brent H Phototherapy associated diarrhoea The role of bile salts Acta Paediatrica Scandinavia 1983 Nov; 72(6):853-5	n=14 PT, 14 control	High concentration of bile salts found in colonic contents of neonates during PT actor in pathogenesis of PT associated diarrhoea	Poor
4.	Gounaris A Gut hormones levels in neonates under PT Early Human Development 1998 Apr; 51(1) :57-60	A=15 no NNJ B=15 mild NNJ C=15 marked NNJ + PT	Increased VIP, reduced gastrin no difference neurotensin and increase stools in C Increased VIP – increased stools from stimulation of intestinal water and electrolyte secretion	-
Effects on CNS				
1.	Amato M.Cerebral Haemodynamics in LBW infants' treated with photo therapy European Neurology 1991; 31(3) 178-180	Case study n=20	No functional disturbance of cerebral auto-regulation	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
2.	Ju SH The effect of moderate non-haemolytic jaundice And phototherapy on newborn behavior Journal Cheng Hua 1992 Jan/Feb; 32(1):31-41	n=29 Randomly assigned (Neonatal Behavioral Assessment Scales)	Phototherapy has short-term adverse effect on visual, auditory orientation	Fair
3	Amato M *Cerebral blood flow velocity in Term infants treated with photo therapy* Brain and Development 1991 Nov; 13(6) 417-9.	n=50	Effective cerebral autoregulation in term infants undergoing light therapy for NNJ	Fair
4	Valkeakari T Follow-up study of phototreated FT Newborns Acta Paediatrica Scandinavia1981June;70(1): 21-25	n=41 Assessed at 3 yrs old	No difference in growth, development, Social maturity, neurological or Opthalmologic, EEG recordings or lab determinations.	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
Effects on Biochemical Functions				
1.	Amin HJ Significance of phototherapy induced Riboflavin deficiency in FT neonate Biology of Neonate 1992; 61(2):76-81	n=8 10 controls Experimental	Riboflavin deficiency induced by phototherapy in FT neonates was not of sufficient severity to limit riboflavin-dependent fatty acid oxidation	Poor
2.	Kjartansson S Respiratory H2O loss and O2 consumption in newborn infants during phototherapy Acta Paediatrica 1992 Oct; 81(10) 769-73	n=11 FT 8 preterms	No significant difference between respiratory H2O loss and O2 consumption before, during and 1 hour after PT	Poor
3.	Wu ZL. Mechanism and prevention of hemolysis in Jaundiced infants on phototherapy Chinese Medical Journal	n=18 16 controls	Reduced Hb and time of jaundice disappearance during phototherapy more favourable in oral vitB2(5mg 3x/day) to overcome reduced GR activity	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
	1994 Jun; 74(6): 364-6,391-2			
4.	Neuzil Oxidation of parenteral lipid emulsion By combination with phototherapy: Potential toxicity of routine parenteral Feeding The Journal Of Paediatrics 1995 May 126(5):785-790	n=59	Triglyceride hydroperoxides during PT with lipid (despite vit E)	Fair
5.	Tan KL Effect of PT on TSH and Free Thyroxin levels Journal of Paediatrics & Child Health 1995 Dec; 32(6): 508-511	n=123 into 3 gps fibreoptic light, conventional daylight, combined PT	PT does not effect neonatal thyroid screening.	Good - Fair

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
On Biochemical Functions				
1.	Rudolph N Postnatal decline in pyridoxal phosphate and Riboflavin – accentuation by PT American Journal of Diseases of Children 1985 Aug; 139(8): 812-5	n=25 FT with PT 16 FT without PT	Both groups reduced levels but more so in PT group.	Poor
2.	Sisson TR Photodegradation of riboflavin in neonates Federation Proceedings 1987 Apr; 46(5): 1883-5	-	Photoreactivity and presence in almost all body fluids and tissues low stores and low intake of riboflavin and PT deficiency of riboflavin role of riboflavin supplementation	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
3.	Sato H Effect of PT on erythrocyte membrane proteins of FT and premature human newborn infants Acta Paediatrica Scandinavica	-	No qualitative and quantitative differences in erythrocyte membrane proteins.	Poor
4.	Sethi H Phototherapy induced hypocalcemia Indian Paediatrics 1993 Dec; 30(12): 1403-6	Preterm 20 PT 10 control Term 20 PT 10 control	90% preterm, 75% term on phototherapy developed hypocalcemia	Poor

5.	Zecca E Ineffectiveness of vit D3 in the prevention of hypocalcemia induced by phototherapy Paediatrica Medicae Chirurgica 1983Sept; 5(5):317-9t	n=100	Vit D3 has no effect.	Fair

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
Effects on Biochemical Functions				
1.	Fort FL Phototoxicity of tin protoporphyrin, tin Mesoporphyrin and tin diiododeuteroporphyrin Under neonatal phototherapy conditions Paediatrics 1989 Dec; 84(6) 103-7	-	SnMP<SnPP<Sn12DP SnMP phototoxic only at highest dose under PT with UV irradiation Reversible when discontinued	Fair

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
Effects on Skin				
1.	Peller Purpuric phototherapy induced eruption in Transfused neonates: relationship to Transient porphyrinemia American Academy of Paediatrics 1997 Sept; 100(3): 360	n=6	Purpuric light eruption should be considered as a transient benign cutaneous eruption in neonates who undergo PT. Discovery of significantly increased plasma porphyrin in 2 – link of cutaneous lesion after exposure to intense flourescent radiation 400nm	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
2.	Berg Is phototherapy in neonates a risk factor for malignant meloma development? A preliminary Archives of Paediatrics & Adolescent Medicine 1997 Dec; 151(12): 1185-1187	Case Control Study n=30(melanoma) 120 matched controls	No significant risk of developing childhood malignant melanoma after PT in neonates with NNJ. Median follow-up time 18 years	Poor
3.	Cabana **Phototherapy in neonates** Archives of Paediatrics & Adolescent Medicine 1998 Aug .152(8):818	Letter	Larger sample size to reach conclusion Small sample size, low statistical power and precision	-

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
4.	Siegfried EC UV light burns: a cutaneous complication of visible light phototherapy of NNJ Paediatric Dermatology 1992 Sept; 9(3): 278-82	Case Report n=2	Phototherapy induced erythema prevented by plexiglass shields	Poor
5.	Kjartanson S Insensible water loss from skin during Phototherapy in term and preterm infants Acta Paediatrica 1992 Oct; 81(10):764-8	n=10 FT 7 preterm	In thermally stable infants non-ionising radiation from phototherapy does not increase H2o loss from skin	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
6.	Stomowski C Water loss from skin of preterm and Newborn infants under PT with standard blue light Monatsschriff kinderheilkunde 1983 July; 131(7): 448-50	n=15 term 15 preterm	preterm>10x water loss cf. BW>1.9kg water loss is increased if more than one side of body irradiated	Poor
7.	Engle WD Insensible water loss in the critically ill neonate Combined effect of radiant-warmer power and PT American Journal of Disease of Children 1981 Jun; 135(6): 516-20	n=12	Increase insensible water loss with phototherapy – 45% increase 2.54ml/kg/hr increased to 3.73ml/kg/hr	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
8.	Redermacher EH *The bronze baby syndrome: A complication of phototherapy* Klinische Paediatrie 1997 Sept; 189(5):379-84	Case Report	Elevated coproporphyrins possible neurotoxic effects	Poor
9.	Rodot S Annales de Dermatologie et de **Bronze baby syndrome** Venerologies 1994; 121(8): 568-70	Case Report	Rh incompatibility complicated by cholestasis of thick bile fluids due to abnormal accumulation of unexcreted photoproducts but return to normal	Poor
10.	Tan KL **The bronze baby syndrome** Acta Paediatrica Scandinavica 1982 May; 71(3): 409-14	n=13	Associated wit hepatic dysfunction bronzing disappeared within 2 months spectroscopy .	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
11.	Curveillier JC *The bronze baby syndrome Apropos of 3 cases* Annales de Paediatricia 1980 Dec; 37(10) :669-71	-	Infrequent complication of phototherapy for NNJ in infants with liver diseases - bile duct galactosemia and TPN with cholestasis Bronze colour disappears spontaneously	Poor
12.	Onishi S Mechanism of development of bronze baby Syndrome in neonates treated with PT Paediatrics 1982 Mar. 69(3): 273-6	-	Unknown pigment – brown pigment main excretory pathway via biliary route	Poor

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
Factors Influencing Effectiveness Of Phototherapy				
1.	Caglayan Superiority of oral agar and phototherapy Combination in treatment of NNJ American Academy of Paediatrics 1993 July; 92(1):86-89	n=208 4 gps PT, PT & oral agar; oral agar, no treatment	Efficacy of PT augmented with oral agar	Good - Fair
2.	Tan KL Decreased response to phototherapy for NNJ in breastfed infants Archives of Paediatrics & Adolescent Medicine 1998 Dec;152(12):1187-1190	n=163 into 3 gps Formula Breastfeeding Breastfeeding & formula	The responses to phototherapy of gp 2 were significantly slower than gp 3 and 1. The addition of formula to feedings of totally breastfed infants without suspension of breastfeeding would enhance the efficacy of phototherapy and reduce exposure time	Good - Fair

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
3.	Gourhy Neonatal jaundice and diet Archives of Paediatrics & Adolescent Medicine 1999 Feb; 153(2): 184-8	n=20 x 3gps	Jaundice levels lower in babies fed on Nutramigen(casein) than Enfamil(whey) than breast milk.	Good - Fair
Comparison of Side-Effects of Different Phototherapy				
1.	Garg AK A controlled trial of high intensity double Surface phototherapy on a f,luid bed versus Conventional phototherapy in NNJ American Academy Of Paediatrics 1995:13	n=50	No more side-effects compared to conventional PT	Fair

2. .	Donzuli One day phototherapy of NNJ with Blue-green lamp Lancet 1995 July 15; .346(8968): 184-185	n=40 LBW	Shorter duration of blue-green light compared with special blue	Fair

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
Side-Effects on CVS				
1.	Barefield ES Association of PDA and phototherapy in Infants weighing less than 1000gm Journal of Perinatology 1993 Sept- Oct; 3(5):376-80	RCT n=295	Use of phototherapy associated with increased incidence of PDA in ELBW 76% with PT 53% without PT	Good

No	Title, Author, Journal, Year	Study type, Sample size, Follow up	Outcome &Characteristics	Comments, Grade of Evidence
2.	Rossenfield W Phototherapy effect on incidence of PDA In premature infants: prevention with Chest shielding Paediatrics 1986 July; 78(1): 10-14	n=74 2 gps	Shielding reduced incidence of PDA	Good - Fair
3.	Benders MJ The effect of phototherapy on renal blood flow Velocity in preterm infants Biology of Neonate 1998; 73(4): 228-34	n=30	PDA reopened >50%(16) renal blood flow velocity and renal vascular resistance did not return to baseline in ventilated patients	Fair

Drugs

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
1.	Nelson's Textbook of Paediatrics, 15th edition, 1996 *Jaundice and hyperbilirubinemia in the newborne 498*		Phenobarbitone: • enhance conjugation and excretion of bilirubin • limits development of physiological jaundice in newborn when administered to mother 90mg/24H prior to delivery or to infant at birth 10mg/kg/24hrs Not routinely recommended for treatment of jaundice in neonate • its effect on bilirubin metabolism not manifested until after several days of administration • it is less effective than PT in ↓SB • untoward sedative effect • does not add to response to PT Tin (Sn) protoporphyrin or tin mesoporphyrin • inhibits conversion of biliverdin to bilirubin by haem oxygenase • althogh bilirubin levels may decline the effect is no greater than that achieved by PT • complications: transient erythema if the infant is receiving PT	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
			• more data needed about its efficacy and toxicity before it can be recommended for therapy for hyperbilirubinemia •	
2.	Harold et. al Controlled trial comparing agar, intermittent phototherapy and continuous phototherapy for reducing neonatal hyperbilirubinemia Journal of Pediatrics 1973; 82(1) : 73-76	n=69	Continuous PT in first 4 days superior to either agar / intermittent PT in ↓SB in LBW Failure of agar to significantly ↓ NNJ 1. inability of agar to sequester bilirubin in the gut and prevent reabsorption from intestinal tract 2. variability of lot to lot in capcity of agar to sequester bilirubin 3. higher dosage required in LBW vs Term	Poor
3.	Gerard B Odell et al Enteral Administration of agar as an effective adjunct to phototherapy of neonatal hyperbilirubinemia Pediatrics Research 1983 17(10): 810-813	RCT Single blind n=52	The rate of declination of the plasma bilirubin conc after 24Hr of PT was greater and significantly more uniform in the agar supplemented infants (-1.59 +/- 2.3 vs 2.51+/- 1.44) Agar supplementation ↓duration of PT by 23%(37.6+/-3.2 vs 48.1+/-3hrs)	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
4.	Caglayan Suat et al Superiority of oral agar and PT combination In the treatment of NNJ Pediatrics 1993 July; 92 (1):86-89	Propective randomised controlled Clinical study n=208	In all 3 therapy groups, the time required to ↓ SB to either 15mg/dL or to 10mg/dL was significantly shorter than that required by the control gp. Although oral agar was found to be as effective as PT, the most significant ↓ in SB was in the combination group The efficacy of PT in ↓ SB level in NNJ can be augmented with the use of oral agar. Oral agar can be used as a single agent for the treatment of NNj since it is as effective as PT Advantage: no side effects, no maternal separation; no negative effect of agar on feeding	Poor
5.	D Nicolopoulos MD et al Combined Treatment of NNJ with cholestyramine and PT The Journal of Pediatrics 1978 684-687	n=40	Cholestyramine is a quatenary ammonium ion exchange cpmpoune with a strong affinity for bile salts. Side effects: with long term steatorrhoea, deficiency of fat soluble vitamins and folic acid, nausea, flatulence and constipation,intestinal obstrucation	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
6	Tan KL, Jacob E S; Karim MM *Cholestyramine and PT for NNJ* Journal of Pediatrics, Feb 1984 104 (2): 284-286	n=84	To determine the usefulness of cholestyramine as as adjunct to PT Normal healthy fullterm with non hemolytic NJ SB > 15mg % Control + PT n=42 cholestyramine 1.5gm.kg/day + PT Lack of effect of cholestyramine in ↓SB during PT S/effects: hyperchloremia, mild hyperkalemia, ↓tryglyceride;↑stool frequency Conclusion: little justification to use cholestyramine during PT	Poor
7	Vitamin E and neonatal bilirubinemia Pediatrics 1979; 64 (3): 321-323	Randomised Control not Blinded n=10	No detectable toxicity other than mild transient erythema and indurtation at site of injection Role of vit E (Roberton) PUFA ↑ vit E requirements Deficiency: increases red cell hemolysis ↑Intake to prevent hemolytic anemia in prem esp those receiving diet rich in PUFA Against giving↑ doses of vit E : sepsis and NEC with serum levels	Poor

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
8	Jorge C Martinez et al Control of severe hyperbilirubinemia in full term newborn with the inhibitor of bilirubin production Sn-Mesoporphyrin Pediatrics 1999 Jan; 103; (1): 1-5	Randomised control not double blinded n=40 and 44 in control 1yr study 2/11/96-26/11/97 Follow up at 3/12 and at 18months	Single dose of SnMP proved effective in controlling severe hyperbilirubinemia in full term breast fed newborn with high bilirubin between 48-96H SnMP eliminated need for PT and reduced use of medical resources	Good – Fair
9.	Timoes Valaes et al *Control of jaundice in prem by an inhibitor of bilirubin production: studies with tin mesoporphyrin* Pediatrics 1994 (93) 1-11		SnMP by inhibiting the production of Bilirubin, substantially moderates the development of hyperbiliruninemia in prem. This compound and similarly acting enzyme inhibitors merit futher clinical study as agents in neonatal populations for whom other treatment modalities are not available	Fair
10	Attalah Kappas et al Direct comparison of Sn Mesoporphyrin, an	Metera Masternity Hospital Athens Rockefeller University Hosp N York	• Single dose of SnMP can entirely substitute for PT in controlling hyperbilirubinemia in term and near term newborn	Good – Fair

No	Author, Title, Journal, Year	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
	inhibitor of bilirubin production and phototherapy in controlling hyperbilirubinemia in term and near term newborn Pediatrics 1995 Apr; 95 (4): 468-474	April 1993-Jan 1994 3/12 ; 18mths and 5yr follow up	• 44 SnMP treated : PT not required • Period of observation required for NNJ mx substantially shorter by > 30H in SnMP vs PT • 14/44 PT rx infants – rebound after PT stopped; 5 required 2nd course of PT; no rebound in SnMP Timely to initiate more extensive clinical trials of the safety and efficacy of enzyme inhibitors such as SnMP for the practical management of NNJ in various infant populations and in different medical and social settings	
11	Cooke RWI New approaches to prevention of kernicterus The Lancet; 1999 May 29; 353(9167): :1814-1815	Commentary	Sn-MP superior to phototherapy in term infants without HDN in time taken for SB levels to decline to preset levels Similar trial in breast fed infants without HDN confirmed the ability to abolish the need for phototherapy. Side effects: transient erythema. haematological changes suggestive of iron deficiency developed as did photosensitivity.	Poor

Breast Feeding And Jaundice

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
1.	Auerbach KG Gartner LM Breast feeding and human milk their association with jaundice in the neonate Clinics in Perinatology 1987 Mar; 14(1): 89-107,	Review 77 ref	**Early onset jaundice:** associated with feeding related factors: How often a mother breastfeeds How well the baby suckles How often and how much supplementary or complementary feeds of water, glucose or infant formula **Late onset: breast milk jaundice** Milk received rather than manner of feeding	Poor
2.	Adams JA. Hey DJ. Hall RT *Incidence of hyperbilirubinemia in breast vs formula fed infants* Clinical Pediatrics 1985 Feb; 24(2): 69-73	Retrospective Study n=233 Breast fed 101 Formula fed 117	Aim: to determine the effect of several variables on the development of hyperbilirubinemia (SB>12mg%) -15% (35) developed peak SB>12mg% in the 1st week of life -step wise multiple regression: **breast feeding was the most predictive** of a group of 8 variables **of developing NNJ >12mg%** -breast fed (12%)significantly higher incidence of hyperbilirubinemia >15mg% vs 2% of formula fed	Poor

3.	Osborn LM, Reiff MI Bolus R Jaundice in the full term neonate	Prospective N=866	Significant correlation between SB & method of birth, perinatal complications, bld gp incompatibilities, birth weight and method of feeding. **Breast feeding** was highly related to the development of exaggerated jaundice Most common occurrence of jaundice requiring PT was in breast feeding infants in whom no cause for the jaundice could be determined Relative caloric deprivation as an explanation of the increased incidence of hyperbilirubinemia found in breast fed newborn	Poor
No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
4.	Saigal S. Lunyk O. Bennett KJ. Patterson MC Serum bilirubin levels in breast and formula fed infants in the first 5 days of life CMAJ 1982 Nov 15; 127(10): 985-9	Prospective Study	The mean total bilirubin was significantly higher on each postnatal day in breast fed , as was the proportion of infants with peak levels >12mg%(28% vs 6%) The breast fed infants also had significantly higher proportional weight losses on each postnatal day than the formula fed.	Poor

5.	Tudehope D; Bayley G, Munro D, Townsend S Breast feeding practices and severe hyperbilirubinemia Journal of Paediatrics and Child Health 1991 Aug ;27(4): 240-4.	Case Control Study	Univariate analysis: less frequent breast feeds, greater weight loss and less frequent stools over the first 2days related to severe hyperbilirubinemia Multivariate analysis: maternal non smoking, less frequent breast feeding, less frequent stooling and excessive infant weight loss were the best predictors of severe hyperbilirubinemia	Fair
6	Kuhr M. Paneth N Feeding practices and early neonatal jaundice Journal of Paediatric Gastroenterology & Nutrition 1982;1 (4) 485-8	-	Breast fed infants had significantly higher rates of jaundice than bottle fed infants In a subset of breast fed infants, sugar water intake in the first 3 days of life was significantly and inversely related to estimated volume of breast milk intake on the 4^{th} day ($r=-0.35$, $p<0.05$). Breast fed infants with high sugar water intake in the first 3days and low breast milk intake on the 4^{th} day, tended tohave higher rates of jaundice, but these results were not statistically significant Data raises the possibility that breast fed infants sugar water intake may reduce the stimulus to nurse & thereby ↑ the risk of jaundice	Fair

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
7.	Maisels MJ. Grifford K Normal serum bilirubin levels in the newborn and the effect of breast feeding Pediatrics 1986 Nov; 78(5): 837- 43	n= 2416	Investigations for the cause of NNJ in healthy breast fed infants may not be indicated unless the SB >15mg/dl; whereas in bottle fed such investigations may be indicated if the SB>12mg/dl	Poor
8.	Hall RT. Braun WJ. CallenbachJC; Metzl K. et al Hyperbilirubinemia in breast vs formula fed infants in the first six weeks of life: relationship to weight gain American Journal of Perinatalogy 1983 Oct; 1 (1):47-51,	-	SB measurements weekly intervals from 1-6wks of age in 27 breast fed and 12 formula fed average size infants Mean SB significantly higher in breast fed infants at each age studied. Highest mean SB in each group was present at 1wk of life, higher in breast fed group 10.6 vs. 4.7 Mean birth weight not different in two groups, but breast fed infants lost significantly more weight (4.8%) by the time of discharge than formula fed infants (2.2%) Breast fed remained lighter at 6wks of life Analysis of variance and covariance revealed no significant correlation between body weight, and bilirubin levels in either group Mean bilirubin levels are significantly higher in breast fed infants compared with formula	Poor

			fed infants from 1-6wks of age Breast fed infants also have significantly greater weight loss during the first 4 days of life and remain lighter at 6wks of age There is no relationship of weight loss to bilirubin levels	
No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
9.	De Carvalho M. Hall M. Harvey D Effects of water supplementation on physiological jaundice in breast fed babies Archives of Disease in Childhood 1981 Jul; 56 (7): 568-9,		The effect of water supplementation in normal, term, breastfed babies with physiological jaundice was studied. Water supplementation was given to 120 babies and 55 received no extra fluids. There was no significant difference between the two groups when peak SB levels and incidence of phototherapy were compared.	Poor

10.	Nicoll A. Ginsburg R. Tripp JH Supplementary feeding and jaundice in newborns Acta Paediatrica Scandivania 1982 Sep ; 71(5): 759-61		In a survey it was found that the majority of full term breast fed infants received supplementary feeds of water, dextrose solution or infant formula during the first few days of life. Breast fed babies receiving water or dextrose supplements had higher plasma bilirubins on the 6^{th} day of life than bottle fed infants. Supplementation with water or dextrose did not reduce the hyperbilirubinemia of term breast fed infants. Suggest the practice of supplementation be abandoned.	**Poor**
11.	Maisels M et al The effect of breast feeding frequency on serum bilirubin levels American Journal of Obstetrics and Gynecology 1994 Mar 170(3) 880-883		There was no correlation between the frequency of breast- feeding and the SB level. Within the range of the frequency of nursing observed in this study, we could not demonstrate a significant effect on SB levels in the first 3days after birth. 2 main limitations in the study: Water and dextrose supplementation in both groups 11% frequent and 21% demand feeders SB measurements could not be measured beyond day 3 because of early discharge. Maximal SBs occur beyond day 3 ie. 4-5.	Poor

No.	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
12.	Maisels M Jeffrey MB. Newman, ThomasB *Kernicterus in otherwise healthy breast fed term newborns* Pediatrics, 1995 Oct; 96(4) 730-733		6 infants born between 1979&1991, met the criteria for the inclusion. Their peak recorded bilirubin levels occurred 4-10days after birth and ranged from 39-49mg/dl. All had one or more exchange transfusions. One infant had an elevated reticulocyte count 9% but no other evidence of hemolysis. The other infants had no evidence of hemolysis, and no cause was found for the hyperbilirubinemia (other than the breast feeding) Conc: although very rare, classic kernicterus can occur in apparently healthy full term breast fed newborn, who do not have hemolytic disease or any other discernable cause for their jaundice. Such extreme elevations of bilirubin are rare, we do not know how often infants with similar SB levels escape harm. We also have no reliable method for identifying these infants early in the neonatal period. Closer follow up after birth and discharge from the hospital might have prevented some of these outcomes, but rare sporadic cases of kernicterus might not be preventable unless we adopt an approach to follow up and surveillance of the newborn that is significantly more rigorous than has been practised.	Fair

Methods of Diagnosis – Various Laboratory Techniques to Measure Serum Bilirubin.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
1.	Perry B et al. *Measurement of total bilirubin by use of Bilirubin oxidase*. Clin Chem 1986 Feb 32 (2).:329-32.	(Comparative study n not stated	Total serum bilirubin was measured using bilirubin oxidase, an enzyme developed from a fungus. The day-to-day precision ranged from <1% to about 11% when the bilirubin concentration was 183 – 12 mg/L. Drugs, anticoagulants, serum preservatives::no effect Turbidity slight increase. Hb concentration @ 2gm/L: lower value by as much as 17 mg/L. Results were lower than those obtained by the J-G principle.	Poor
2.	Kurosaka K et al. *A new enzymatic assay for selectively measuring conjugated bilirubin concentration in serum with use of bilirubin oxidase (BOD*) Clin Chim Acta 1998 Feb; 269(2):125-36.	Descriptive Study	Using BOD, this assay measures conjugated bilirubin only; neither unconjugated nor delta bilirubin is measured , based on HPLC results. The lack of interference with coexisting substances in serum and the stability of reagent solutions is satisfactory from the point of ractical applications. These findings suggest that the conjugated bilirubin is useful for fractional determination of bilirubin in cteric sera.	Poor

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
3.	Nakayama K Differences between enzymatic and diazo methods for measuring DB Eur J Clin Chem Biochem 33(8), 1995 Aug: 513-17.	Comparative study	Disparities have been found in direct bilirubin(DB) values by diazo and enzymatic method. Samples were tested as above and then submitted for fractionation by HPLC. Conjugated bilirubin was largely responsible for the different values obtained by the 2 methods; incomplete oxidation (enzymatic) products are responsible for the disparity.Care must be exercised in the interpretation of DB measured by enzymatic method.	Poor
4.	Stevenson DK et al Bilirubin production in healthy term infants as measured by carbon monoxide (CO) in breath. Clin Chem 1994; 40(10):1934-9.	Control Study n= > 397	The results showed that in term infants,the ETCOc was 1.3 _+ 0.7 uL/L with the bilirubin level , 73 -+ 35 mg/L. In contrast, the ETCOc in those infants with ABO/Rh incompatibility or whose mothers had diabetes , was higher at 1.8 -+ 0.7 uL/L. This method of estimation indexed by ETCOc may be helpful in under-standing mechanisms of jaundice in healthy term infants.	Fair.
5.	Stevenson DK and Vreman HJ. Carbon Monoxide and bilirubin production in neonates. Pediatrics, 1997	Control Study N= not stated	The measurement of CO in breath or blood can be used as an index of bilirubin production in vivo. Using a portable noinvasive breath sampler instrument developed specifically for neonates, measurements in healthy and haemolytic term infants showed that an	Poor

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
	Aug; 100(2): 252-254.		ETCOc value of > or = to 3 ppm correlated with known haemolysis.	
6.	Schlebusch H et al . Comparison of 5 routine methods with the candidate reference method for the determination of bilirubin in neonatal serum. J Clin Chem Clin Biochem 1990 Apr ; 8(4) :203-210.	Comparative Study n = 77 neonatal serum samples	Using five routine methods (Jendrassik and Grof,Hertz, bilirubinometer, Vinck, and 2,5 dichlorophenyldiazonium) and the candidate reference method (CRM) of Doumas, total bilirubin (TB) was determined in the samples. Vinck's method differed neglibly from the CRM; the other 4 methods gave values that were generally higher. The accuracy of the 5 methods can be improved by using standards containing human albumin, or calibration with a serum pool..	Poor.
7.	Langbaum ME et al. Automated total and neonatal bilirubin values in newborns is a distinction clinically relevant? Clin Chem 1992 Sep;38(9): 1690-1693.	Comparative Study n = 500 paired serum samples in newborns < 15 days old.	An automated system which measures serum bilirubin by 2 dry-slide methods namely TBIL (Modified diazo) and NBIL (colorimetric), was used to test the serum samples and the values compared. A small statistically significant difference of $p< 0.0001$ between TBIL and NBIL was noted; this had no clinical significance. The study conclusions were that TBIL values could be used with caution; NBIL measurements were acceptable if guidelines developed for this purpose were used.	Poor.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
8.	Schlebusch H and Schneider C. Enzymatic determination of bilirubin in serum of **newborns** – any advantage over previous methods? Ann Clin Biochem 1991 May; 28(3): 290-296.	Comparative Study n = 70 sera from newborns.	Precision and accuracy were checked using an automated method which utilised enzymatic determination of total bilirubin. Imprecision (day-to-day) was unacceptable high using daily calibration: accuracy was checked against the Candidate reference method and improved by reference calibrators. Enzymatic measurement is also susceptible to oxidation products of Hb. No added advantage in using this method.	Poor.
9.	Vink LJ et al. Use of Caffeine Reagent in Direct Spectrophotometry of Bilirubin. Clinical Chemistry 1986;32(7),: 1389-93.	Experimental Study.	This article describes the development of a new method for bilirubin determination **in neonates**, using caffeine which is independent of the protein matrix. 14 sources of albumins and proteins (human & animal) mixed with bilirubin were used in the analysis by direct spectrophotometry. Results: Bilirubin determination in the presence of protein is accurate and precise using caffeine. The introduction of reliable inexpensive standard for bilirubin measurement by direct spectrophotometry is advocated.	Good.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
10.	VinkLJ et al. Direct Spectro. of Bilirubin in Serum of the serum of the Newborn, with use of Caffeine Reagent. Clinical Chemistry 1998; 34(1). 67-70.	Comparative Study. n=55 sera	Based on the above principle, the method for measuring unconjugated bilirubin in neonates is described and compared with the other methods name the diazo (Doumas) and borate (Hertz). The sera were divided into 3 groups based on the amount of haemolysis which affects the Doumas method. This method is shown to be independent of protein matrix and haemolysis, and therefore it is to be preferred in neonatology.	Good.
11.	Hajzer S. J *Comparison of direct spectr. determination of bilirubin with candidate reference method in sera of newborns.* Clin Chem Clin Biochem 1989 Jul; 27(7): 131-2.	Comparative Study. n=230 newborns.	The candidate method of Doumas was compared with direct spectrophotometry (DS) in the measurement of bilirubin. Spectr. showed statistically insignificant differences (p-0.5) in comparison to the reference method. Haemolysis & Doumas: B is unaffected at HbO2 conc. 5g/L. Haemolysis & DS:B is unaffected at HbO2 conc. 25g/L. The results are identical and comparable, and are not influenced by haemolysis: DS is therefore very suitable for use in neonatology.	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
12.	Lott JA; Basil T Doumas."Direct" and Total Bilirubin Tests: Contemporary Problems. Clinical Chemistry 1993; 39(4): 641-647.	n = 6000 F/ up: 2 years. (8 cycles of testing).	The analytical methods used by the 12 major clinical chemistry analysers, as part of a Comprehensive Chemistry Survey of the College of American. Pathologists were reviewed. A "wild card" specimen containing ditaurobilirubin was distributed to the participating laboratories. The results for DB (direct bilirubin) were highly variable amongst the 12 largest peer groups; also the results themselves differed from those obtained by a reference methods. The major causes for the differing results were calibration problems, and various faulty technical steps. Recommendations given to the manufacturers of analysers and reagents: the method employed must not measure unconj. bilirubin as direct bilirubin.	Good .
13.	Gourley et al. *Measurement of serum bilirubin in newborn infants: common clinical laboratory methods versus High Performance Liquid Chromato-graphy(HPLC*).	(Comparative Study n = 944 serum samples from newborns	The objective was to compare the accuracy and bias of various clinical methods used to measure total serum bilirubin (TSB) in neonates against HPLC, the "gold" standard. The 944 samples were analyzed by HPLC at one laboratory; the samples were then analyzed again at another, using automated analysers employing diazo, slide, or direct spectrophotometric technology.	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
	Pediatr Res 1999;45(4) Part 2of 2.		The results were compared. Those obtained \ from the clinical methods did not differ ($p<0.05$).; however there were significant differences from HPLC and between methods. In assessing the accuracy of methods to measure TSB data should include HPLC as well as multiple clinical methods.	
14.	Rosenthal P et al. *Total and direct-reacting bilirubin values by automated methods compared with liquid chromatography and with manual methods for determining delta bilirubin.* Clin Chem 1990 May; 36 (5) 788-791.	Comparative Study. n = 40	Reasonable estimations for routine clinical use can be obtained by the various methods. Each laboratory needs to select the appropriate method based on local conditions.	Poor.
15.	Francoual J et al. Investigation of total and conjugated bilirubin	Comparative Study n = 108 neonates	Total and conjugated bilirubin determinations are necessary to identify the origin of jaundice, predict its evolution and to treat it. In the 108 neonates, total bilirubin determination using 2 methods (diazoand	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
	determination during the neonatal period. Eur J Clin Chem Clin Biochem 1993 Aug; 31 (8) : 499-502.		colorimetric) correlated well($r > 0.96$). Discrepancies were observed for conjugated (direct) bilirubin with the same methods; HPLC revealed the presence of bilirubin fractions in the latter. During the neonatal period, conjugated bilirubin production needs further investigation by HPLC , whereas total bilirubin can be measured accurately by automatized methods.	
16.	Ostrea EM et al. The occurrence and significance of the bilirubin species, including delta bilirubin in jaundiced infants. J Pediatr. Gastroenterol Nutr 1988 Jul-Aug ; 7 (4): 511-16.	n=40	Indirect hyperbilirubinemia: 90% TSB was unconj B, 5% of delta B. Elevated direct SB (>-2 mg/dl): mono: diconj: 2:1. The standard diazo test underestimated direct B by as much as 34%. When the conc. of delta bilirubin ranged from 10-73%, it was related to the duration of the jaundice, rather than the cause. Identification of the specific bilirubin species in jaundiced infants helps in the management and understanding of their disease.	Fair.
17.	Doumas BT, Wu TW. *The measurement of bilirubin fraction in serum*. Crit. Rev. Clin Lab Sci	Review, tutorial.	This paper review the measurement of bilirubin fractions using 4 methods, namely HPLC, diazo reaction, spectr. , and enzymatic. HPLC is favoured but is impractical for routine use due to the cost and tedious techniques involved. Spectr. is limited as only 1 analyser	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
	1991; 28(6-5):415-45.		used this method. The diazo reaction can measure the fractions but not very accurately, and enzymatic reactions are largely dependent on the pH. For the application, diazo reaction should be replaced by methods specific for measuring conjugates of bilirubin.	
18.	Schreiner RL, Glick MR. Interlaboratory bilirubin variability Pediatrics 1982 Mar ;69(3): 277-81 .	-	Sera used for quality control analysed by ? labs: variability was high, where the results ranged from 10.9 to 24 mg/100ml .Unacceptable variability can be reduced by stabilized quality control sera.	Poor.
19.	Hajzer S et al. Evaluation of interlaboratory proficiency surveys of bilirubin determination in sera of newborns. Eur J Clin Chem Clin Biochem 1992 May; 30(5): 291-295.	Comparative Study n=66 laboratories. 2 cycles; control samples (1^{st}) and identical calibrant (2^{nd}).	Using the diazo technique and spectrophotometry, the control samples were analysed: also the interlaboratory precision and accuracy of these 2 different analytical principles were compared. Then, using an identical calibrant, the raw data from all the analyses were recalculated. Accuracy was determined as within ± 7% of the reference values. 1^{st} cycle: 60% of diazo results acceptable compared with 22% of spectr. 2^{nd} cycle: 74-82% (diazo) and 83-91% (spectr)	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
			were acceptable. Greater accuracy can be achieved through quality control using identical calibrants and standards.	
20.	Stevenson DK and Vreman HJ. CO and B production Pediatrics 1997 Aug; 100(2):252-254.	Quality Control. 14 Laboratories n = 564 samples	Studies were conducted on the variability of inetrlaboratory bilirubin measurements by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. Serum bilirubin was measured in 14 laboratories using automated analytical systems. Quality control was monitored through monthly aanalysis of commercial reference sera containing low, medium and high levels of bilirubin. The results showed that bilirubin measurements differed significantly from established reference values; there was no correlation between methodology used and the results obtained.	Good
21.	Vreman HJ et al. *Interlaboratory variability of bilirubin measurements*. Clinical Chemistry 1996 June; 42(6): 869-873.	Comparative Study. n=14 laboratories. n=292 samples	Using, automated analytical systems, 14 laboratories measured total bilirubin concentrations in control samples with known values; 5 to 9 blinded measurement of each concentration were made over a period of 8 months. 6 laboratories's values were consistently > 104% of actual value. 4 laboratories's values were consistently < 96% of actual value. Within each laboratory, the	Good.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
			variability across time (CV) ranged from 1.3% to 17.2%. Recommendations: Inspite of Schreiner and Glick's recommendations, there is no systematic distribution of bilirubin solution for calibration and QC in the range appropriate of neonatal populations. QAPs of the CAP should offer challenges at high B concentrations for neonatal bilirubin. This assumes greater importance in view of current early hospital discharge policies	
22.	Blijenberg BG et al. Reflections on the standardization of total bilirubin in neonatal serum. J Clin Chem Clin Biochem 1987 Mar; 25(3) 177-81.	Comparative Study	Surveys held in the Netherlands and Germany showed a wide variation in the determination of neonatal total bilirubin (TB). Commercial bilirubin standards used were tested as well as the direct measurement devices and the results compared to reference methods. Reference method/stated values of the control: differences in TB. Reference method/direct measurement device differences in TB. Recommendations were not stated.	Poor.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
23.	Blijenberg BG et al. Further studies on the standardization of neonatal bilirubin. J Clin Chem Clin Biochem 1987 Oct; 25(10): 737-41.	-	The standardization of bilirubinometers is investigated from the aspect of combination of pH and wavelength setting. There is no synthetic bilirubin standard; the pragmatic solution is to use a pool of neonatal serum.	Poor.
24.	Bakker AJ. Is better adjustment of analytical results between clinical laboratories achievable? Bilirubin as a model Nederlands Tijschrift voor de Klinische Chemie 1996; 21(2): 62-65.	Quality Control	The possibility of achieving a better adjustment of analytical results between clinical laboratories was studied in the Nederlands. All participating laboratories calibrated the bilirubin assay according to their daily practice. Then, the bilirubin standards were assayed with 2 QC samples. The results showed use of the same calibrator resulted in a better adjustment of analytical results, and a fixed calibration factor reduced the coefficient of variability.	Good .

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
25.	RohleG et al. *External Quality control in the determination of neonatal bilirubin. An approach to the improvement of results.* J Clin Chem Clin Biochem 1988 Jul ; 26(7): 441-446.	Quality Control	In external quality control surveys, when the mean values of the results were compared with reference method values ,diffrences of up to 10% were found. Further inaccuracy arose from interlaboratory imprecision interference from contamination of the samples with haemoglobin.	Poor.
26.	Brugmann G. Calibration of direct reading photometers in the determination of neonatal bilirubin. J Clin Chem Clin Biochem 1990 Feb ; 28(2): 83-89.	Comparative Study. n=61.	The determination of bilirubin using direct spectrophotometry and bilimeters, calibrated with commercial controls, showed the results were 13-19% higher when compared by the standard method (Vink's method). After recalibration with various neonatal sera (specimens drawn for various procedures), the results showed differences of 10%. Calibration should be performed with neonatal serum, rather than commercial, as the former is unbiased by matrix effect.	

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
27.	Blijenber BG et al. Calibrators and control samples for bilirubinometers. Eur J Clin Chem Biochem 1993 Jun;31(6) 367-74.	Comparative Study. n=72 laboratories & 4 specialist labs.	The different matrix properties of neonatal serum and commercial control samples can lead to errors in calibration of bilirubinometers. Using 16 different control samples, in several interlaboratory surveys, it was shown that a control sample can be used for calibration of a bilirubinometer if it meets certains preconditions. 1. There should be no significant difference between the bilirubin values determined with reference method and correctly calibrated Br. Bilirubin values higher than 300 µmol/L should not be measured by a bilirubinometer as it has a limited linear range.	Fair.
28.	Rosenfeld J. *Umbilical cord bilirubin levels as a predictor of subsequent hyperbilirubinemia*. J Fam Pract. 1986 Dec; 23(6) 556-8.	Retrospective Study n = 108 infants	The use of cord blood estimation of bilirubin was used to define a subgroup of infants who are at higher risk of developing hyperbilirubinemia and requiring Rx. Less than 2mg/dL, 4 % chance.(hyperbil.) and 1.4% needing Rx. More than 25	Fair

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
29.	Hanna G et al. Umbilical cord bilirubin levels are predictive of neonatal hyperbilirubinemia. Am of J Obstet Gynecol 1999 Jan; 180(1S-11) Suppl. : 148S.	Comparative Study n = 40 samples	The results showed that in 10 infants, further serum bilirubin testing was needed as the mean umbilical value was 2.5. In those normal neonates who did not need this further testing, the umbilical value (mean) was 1.9. 7 neonates had umbilical values above 2.1 but did not need the additional testing. There was no statistically significant difference in the maternal bilirubin values between the groups.An umbilical vein TB level of >2.1 was predictive of neonates who did not require evaluation for hyperbilirubinemia.	Fair.
30.	Knudsen A. Prediction of the development of neonatal jaundice by increased umbilical cord blood bilirubin. Acta Pediatr. Scan 1989; 78(2),:217-21.	Retrospective Studies. n = 291 newborns	This study, like the above, explored the possibility of defining subgroups of infants with significant risk of jaundice. Cord bilirubin <20µmol/L 2.9% developed jaundice. Cord bilirubin >40 µmol/L 85% developed jaundice; 57% need Rx. Cord bilirubin <40µmol/L, 9% would need Rx. Knowledge of infants at risk allows treatment measures to be introduced and facilitates early discharge from hospital.	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
31.	Johnson CA et al. Factors predictive of heightened third-day bilirubin levels a multiple stepwise regression analysis. Family Medicine 1989;21(4):283-287.	Prospective Study. n= 252 full-term healthy infants.	This study examines the variables contributing to the variance in third-day bilirubin levels in healthy full-term newborns. Six factors were found to be significant predictors of higher third-day bilirubin levels: higher **cord** bilirubin level; lower total serum protein; the child's sex; weight loss, breast-feeding, and use of promethazine HCl. This will have implications on clinical practice and treatment decisions.	Fair.
32.	Carbonell XE et al. Hyperbilirubinemia in fullterm newborns. Predictive factors. Anales Espan. de Pediatr. 1999; 50(4):389-392.	N =610 newborns.	Umbilical SB of 2.2mg/dl was not a useful predictor of neonatal jaundice. Correlation between SB and TCB was high ($p<0.0001$). At 24 hrs (SB>=6mg/dl) and 48 hrs (SB>=9mg/dl), there was a 100% sensitivity of predicting hyperbilirubinemia, specificity of 47.5% and 64.3% respectively. Bilirubin measurements must be performed at 48 and 72 hours of life if the SB at 24 and 48 hours are as stated above.	Good.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
33.	Ihara H et al. In vitro effects of light on serum bilirubin subfractions measured by routine methods. Clin Chem 1992 Oct; 38(10): 2124-9.		The effect of light on serum bilirubin subfractions in vitro were investigated by HPLC, diazo, spectr. and oxidase methods. The rates of photodegradation of the fractions were highest in HPLC and spectr. compared to the diazo and enzymatic methods. The importance of shielding serum from light to avoid generating byproducts which will interfere with accurate measurement of bilirubin subfractions is emphasized. HPLC is also recommended as a standard method for bilirubin analysis.	Fair.
34.	Leslie GI et al. *Capillary and venous bilirubin values.Are they really different*? Am J Dis Child 1987 Nov; 141(11):1199-200.	Comparative Study. n=79 jaundiced newborns (untreated) n=29 infants receiving photoRx.	Total SB was measured in paired capillary and venous samples in the study groups. Venous B > 10mg/dl: capillary B underestimated by –0.9 mg/dl (Gp1) and –1 mg/dl (Gp 2). Lower capillary values may be due to influence of environmental light. Venous B should be measured rather than capillary when TSB exceeds 10 mg/dl.	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
35.	Langbaum ME et al. Comparison of arterial and capillary bilirubin values in neonates with arterial lines. J Pediatr 1993 Nov; 123(5):794-6 .	N=13 infants. 35 paired samples.	Bilirubin samples are often drawn from indwelling arterial lines and the levels used for treatment decisions. This study showed the correlation between bilirubin values for capillary and arterial samples was high (r-0.993). Arterial samples may be substituted in newborns when capillary samples are difficult to obtain.	Poor.
36.	Satar M et al. The Influence of clinical status on Total Bili-rubin Binding Capacity (TBBC) in Newborn Infants. Tropical Paediatrics 1996,Feb;'42(1): 43-45.	Case- Control Study n = 83	The relationship between total bilirubin binding capacity and clinical status in 83 infants with jaundice was investigated; those infants with respiratory distress, acidosis, hyperglycaemia , sepsis, asphyxia-anoxia were accepted as ill , and the rest as well.Serum albumin, TBBC and TBBC/albumin ratios are over in ill premature and mature infants. In the management of jaundiced infants, the clinical condition can alter the binding of bilirubin to albumin resulting in lowered TBBC.	Fair .

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
37.	Chance KH et al. *Effect of blood sampling of bilirubin-albumin binding*. Scan J Clin Lab Invest1988, Sep; 48(5): 409-11.	n=10 neonates with hyaline membrane disease.	Total B and unbound B were measured on paired capillary and arterial serum samples. Results: No significant arterial/capillary difference in bilirubin binding. However, a small statistically significant but clinically insignificant difference in TSB was noted. Consistent blood sampling sites should be used for laboratory testing when results could differ, in lieu of therapeutic decisions.	Poor.
38.	Reif S et al. Diurnal variation in SB concentration in infants with neonatal jaundice. J Pediatr, 1995 Nov; 127(5); 801-3	Comparative Study n=124 healthy term newborns with nnj and SB>10mg/dl.	Intradaily changes in bilirubin levels were studied for at least 3 consecutive days, and starting from the second day of life, consistent changes were noted: morning levels were greater than evening ($p<0.001$). During the study period, body weight steadily increased. Diurnal variation in bilirubin levels should be considered in the follow-up and treatment of NNJ.	Good.
39.	Fischer AF et al. Comparison of bilirubin production in Japanese and	Comparative Study. N= not stated.	Bilirubin production measured by serum carboxy Hb was compared in a group of term healthy Jap. and Caucasian controls during the 2^{nd} and 3^{rd} day of life. The TSB was higher in Japanese infants (11.1	Fair.

No	Author, Title, Journal, Year,	Study Type, Sample size, Follow up	Outcome and Characteristics	Comments, Grade of Evidence
	Caucasian infants. J Pediatr Gastroenterol Nutr 1988 Jan-Feb; 7(1): 27029.		± 2.2 gm/dl in the Caucasians: this difference may be attributable to environmental and/or genetic factors.	
40.	Kia JP and Vince JD. *Serum bilirubin levels in Melanesian neonates*. Annals of Trop Paed. 1985; 5(3): 127-130.	N=98 term healthy babies.	The pattern of early neonatal serum bilirubin levels in the study population was noted to be: Mean cord blood SB: 1.2 mg/dl. 24-60 hours means SB: 8 mg/dl. In the early neonatal period, Melanesian babies have a mean SB level > than that reported for Caucasians but lower than Asian babies. Genetic factors are the most likely explanation for these differences.	Fair

Appendix A

LEVELS OF EVIDENCE SCALE (CAHTA)

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic reviews.
2	Good	Large sample of RCT
3	Good to fair	Small sample of RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN

Appendix B

INSTRUMENT	DISTRIBUTOR	PRICE
The Minolta-Air Shields Jaundice Meter Prototype meter, first described in 1980 (Yamanouchi I, Yamauchi Y, Igarashi I, Pediatr, 1980, 65:2, 195-202**).** Most published studies are with this meter	Perniagaan Med-Tech 14-17, Lot 204, Jalan TUDM, Kg. Baru Subang, 40150 Shah Alam, Selangor Tel: 03- 7463195 Fax: 03- 746 3694	RM 14,000
The Bili*Check* ™ (SpectRx Inc.) Limited studies: http://www.bilicheck.com	Insan Bakti (M) Sdn. Bhd. 10-B, Jalan Nirwana 37, Taman Niwana,, Ampang, Selangor 68000 Tel: 03- 9833080 Fax: 03-9849878	RM 18,000 per unit

THE FOLLOWING HTA REPORTS ARE AVAILABLE ON REQUEST:

REPORT	**YEAR**
1. LOW TEMPERATURE STERILISATION	1998
2. DRY CHEMISTRY	1998
3. DRY LASER IMAGE PROCESSING	1998
4. ROUTINE SKULL RADIOGRAPHS IN HEAD INJURY PATIENTS	2002
5. STROKE REHABILITATION	2002
6. MEDICAL MANAGEMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA	2002
7. CHILDHOOD IMMUNISATION	2002
8. VITAMIN K ADMINISTRATION AT BIRTH	2002
9. MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA	2002
10. SCREENING OF DIABETIC RETINOPATHY	2002
11. SCREENING OF CONGENITAL HYPERTHYROIDISM	2002
12. ROUTINE CHEST RADIOGRAPHS IN ROUTINE MEDICAL EXAMINATION	2002
13. MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA	2002