Hyperbilirubinemia of the Newborn (Jaundice)

Self Learning Module

Southern Health – Santé Sud
L Cassan Regional Obstetrical Education Facilitator RN BN
2014

"*Jaundice is the yellow color produced by the deposition of bilirubin in the skin and subcutaneous tissues*" (Wong, Bhutani, 2013). Jaundice can affect up to 60% of newborns and 80% of preterm infants. It usually progresses from head to toe, appearing in the face first. It may be seen in the newborn's skin, sclera and mucous membranes. Jaundice is more noticeable if the skin is blanched first by pressing a finger over a bony prominence (i.e. the sternum). If jaundice has progressed below the umbilicus, serum or transcutaneous testing for bilirubin should be done. Jaundice cannot be diagnosed by colour alone.

Asian infants, due to some genetic differences, often have a higher bilirubin level and the jaundice takes longer to resolve.

Neonates are born with high levels of fetal RBC's that are no longer needed once the neonate is breathing oxygen rich air. These fetal RBC's are broken down and replaced by neonatal RBC's, which have a shorter life span than adult RBC's. These two factors contribute to the increased amount of hemoglobin that is broken down, forming bilirubin.

Bilirubin is a by product of the hemolysis of hemoglobin from red blood cells. Hemoglobin is broken down into heme and globin. The heme is further broken down in the liver to unconjugated bilirubin. 80 -90% of bilirubin is formed this way.

There are two main types of jaundice – *Physiological* and *Pathological*.

Physiological Hyperbilirubinemia (Jaundice)

Physiological jaundice is the 'normal' jaundice that newborns may get and includes breast milk jaundice. This type of jaundice occurs due to the relative polycythemia of newborns, shortened erythrocyte life span of neonatal RBC's, immature liver and an increased enterohepatic circulation. Bilirubin levels usually peak by day 3-4 post birth.

Normal adjustment to extrauterine life includes having mild unconjugated (**indirect**) bilirubinemia. This primary jaundice is usually self resolving within one to two weeks of birth. These infants will often have a total serum or plasma bilirubin (TB) of > 1 mg/dL [17.1 micromol/L].

There are subtypes of physiological jaundice:

Neonatal jaundice occurs when there is an increased bilirubin production with a decrease in clearance of bilirubin and an increased enterohepatic circulation. This is the 'normal' jaundice.

Breastfeeding failure jaundice – When the infant does not receive enough breast milk which results in hypovolemia (dehydration). This causes decreased urine output. Jaundice occurs as bilirubin levels rise. Resolution occurs by increasing the amount of breast milk/ supplement taken by the infant. The infant should be breastfed at least 8 times in 24 hours. Supplementation may be necessary. This can be prevented by initiation of successful, frequent breastfeeding. Late preterm may be at greater risk for

this as they typically have a weaker suck and not enough energy to nurse for longer periods. This occurs within the first 7 days of life.

Breast milk jaundice is the persistence of jaundice beyond the first week of age and occurs in infants who are breastfeed exclusively. It peaks later than normal jaundice, around day 3-5 days of life (late onset is 6 – 14 days of life). It is thought to occur due to the maternal milk inhibiting normal bilirubin metabolism and the newborns immature liver and intestines, although the underlying cause is unknown. It may last up to twelve weeks, peaking within 2 weeks of life. This is a benign condition and will self resolve. It is not due to a decreased intake, as is the breastfeeding failure jaundice.

Bilirubin formation/transport/conjunction/excretion:

- Red blood cells are broken down (hemolysis) into heme and globin
- Bilirubin is formed as a product of heme catabolism
- Bilirubin is bound to albumin
- Hepatic uptake – bilirubin is transported to the liver by albumin. Here it separates from the albumin and is taken up by hepatocytes.
- Once in the hepatocytes, bilirubin forms a conjunction with glucuronic acid, forming a conjugated bilirubin (direct) that is more water soluble than unconjugated bilirubin (indirect). This is excreted in bile.
- The bile is excreted into the digestive tract where, in adults, it is broken down into urobilin by bacteria. As infants have a sterile gastrointestinal tract, very little bilirubin is broken down. Instead, the bilirubin is unconjugated by beta-glucuronidase in the intestine mucosa and passed out of the intestinal wall to be recycled into circulation (enterohepatic circulation of bilirubin). A small amount is excreted in the stool.
- Now the bilirubin must be taken up by albumin again and transported to the liver to start the process over again.

Pathological Hyperbilirubinemia (Jaundice)

Pathological Jaundice is jaundice that is not physiological in cause. The cause of this jaundice is not 'normal'. The bilirubin level may rise to dangerous levels and cause permanent disabilities. There may be underlying causes to the jaundice such as sepsis, rubella, cholestasis, toxoplasmosis, among others. Pathological jaundice is often marked by an increased level of conjugated (direct) bilirubin. Bilirubin may not be cleared due to the blockage of pathways (e.g. illeus), certain disorders (e.g. Crigler-Najjar syndrome, Gilbert's syndrome), cholestasis etc...

Suspect Pathological hyperbilirubinemia if:

- Jaundice occurs within the first 24 hours of life or after 2 weeks of life.
- The total serum bilirubin (TB) level is higher than the 95th percentile.
- The TB level rises by more than 0.2 mg/dL per hour or 5 mg [86 micromol/day]
- Direct (conjugated) bilirubin concentration is > 1 mg/dL if the total bilirubin is <5 mg/dL [86 micromol/L]

Or

- If the direct (conjugated) bilirubin is more than 20% of the total bilirubin if the total bilirubin is >5 mg/dL.

Elevated direct (conjugated) bilirubin levels are never normal and may be indicative of cholestasis, liver and/or biliary tract disease.

Hyperbilirubinemia is a disorder of the newborn where the bilirubin level in the newborn rises to above the 95th percentile on the Bhutani nomogram. Above 25-30 mg/dl [**428 – 513** micromol/L] is associated with an increased risk for bilirubin induced neurologic dysfunction (BIND). BIND has a permanent sequelae called kernicterus. Even with appropriate treatment, some babies will develop kernicterus. The acute phase of BIND is called acute bilirubin encephalopathy (ABE).

Signs and Symptoms of Hyperbilirubinemia:

Jaundice within 24 hours of birth

Rapid rise in TB levels

TB levels not responding to phototherapy

Excessive weight loss

Pallor

Vomiting

Lethargy

Poor feeding

Apnea

Temperature instability

Tachypnea

Testing

Transcutaneous device – Bilirubin may be measured using a transcutaneous device (TcB) (Note: this will not be accurate with high levels of bilirubin. If the bilirubin is above 257 micromol/L, confirm with a blood test. This test is also not accurate if the infant has undergone phototherapy.)

Blood test – Total Serum or Plasma Bilirubin (TB) is the sum of conjugated and unconjugated bilirubin in the blood. This may be broken down in direct and indirect bilirubin levels.

If bilirubin is above the 95th %, then the following additional tests are recommended:

- Blood type and direct Coombs' test
- Complete blood count and smear
- Reticulocyte count
- Glucose-6-phosphate dehydrogenase (G6PD) measurement, if clinically appropriate
- Direct or conjugated bilirubin

Note: Coomb's test is also called antiglobulin test (AGT) and can be ordered as direct or indirect. It tests for autoimmune hemolytic anemia. This condition may be caused by an Rh negative mother having an Rh positive infant or a blood type O mother having an infant with blood type A or B. If there was a mixing of the two bloods, the mother would produce antibodies against the infant's blood. These antibodies may transfer to the infant in utero. The antibodies then attack the infant's blood, causing hemolysis of the red blood cells.

Note: G6PD is an enzyme that assists in the newborn's ability to conjugate bilirubin. If the newborn is deficient in G6PD they are at increased risk for severe hyperbilirubinemia. This deficiency may cause up to 35% of the kernicterus occurrences. TB levels may rise very rapidly in these newborns. Newborns of Asian/African/Mediterranean and Middle Eastern descent are at risk for this deficiency.

Causes of hyperbilirubinemia are:

1) **Increased production of bilirubin** by:

   ABO incompatibility – isoimmune-mediated hemolysis of RBC's

   Inherited RBC membrane defects

   Erythrocyte enzymatic defects

Sepsis that causes hemolysis

Polycythemia – hematocrit or hemoglobin concentration that is higher by two standards than the normal levels.

Cephalohematoma – accumulation of blood in the periosteum, usually across the parietal or occipital bone. Does not cross the suture line.

2) **Decreased clearance**
   a. Crigler-Najjar syndrome – defects in the gene which allows the conjugation of bilirubin to glucuronic acid
   b. Gilbert's syndrome – mutation of the same gene. May cause breast milk jaundice.
   c. OATP-2 polymorphism – polymorphism of the same gene
   d. Maternal diabetes
   e. Congenital hypothyroidism
   f. Galactosemia – elevated blood galactose concentration

3) Increased enterohepatic circulation
   a. Breast milk jaundice – persistent jaundice beyond the first week of life, may develop later than other types of jaundice. Is benign and is not the same as breastfeeding failure jaundice. Infants TB levels often >5 mg/dL for several weeks. Does not require intervention as long as the bilirubin remains unconjugated and does not increase. Resolution by week 12 usually. Breast milk seems to increase the absorption of bilirubin from the intestinal tract.
   b. Intestinal obstruction

Newborns should be visually assessed for jaundice every 8 – 12 hours post birth and at discharge. Transcutaneous bilirubin or serum levels may be done. If you suspect jaundice, get a bilirubin level. Do not rely on colour alone. Remember - once the bili light has been established the yellow skin may be 'bleached' and no longer appear jaundice even though the serum levels may still be high. A newborn undergoing phototherapy cannot have the bilirubin level tested by transcutaneous bilirubin devices as this method is unreliable once phototherapy has begun.

If a bilirubin is not routinely done on discharge (as is the standard), the newborn should be visually assessed and if risk factors or signs & symptoms exist (jaundice, lethargy, inadequate feeding), a bilirubin should be ordered prior to discharge home.

RISK FACTORS for severe hyperbilirubinemia and BIND:

TB or transcutaneous bilirubin (TcB) in the high risk zone (>95 th percentile)

Jaundice within the first 24 hours of life (usually caused by increased hemolysis - ABO or Rh incompatibility)

Hemolytic disease – i.e. ABO incompatibility (the administration of WinRho has greatly decreased this)

Gestational age between 35 – 36^{6} weeks (These newborns are often cared for as if they are term, however, they are at an increased risk because they may have inadequate intake due to decreased strength of suck and an even more immature liver than term newborns)

Sibling with previous hyperbilirubinemia

Cephalohematoma or significant bruising (especially post vacuum/forceps delivery)

Exclusively breastfeeding (especially if inadequate)

Excessive weight loss post birth

East Asian/African/ Mediterranean/Middle Eastern/ Native American race

Genetic factors (i.e. Crigler-Najjar/Gilbert's syndrome)

Drugs - Maternal – diazepam, oxytocin

- Infant – chloramphenicol, Pediazole®

Infections – TORCH panel (**T**oxoplasmosis, **O**ther – syphilis, Hepatitis B, coxsackie virus, Epstein-Barr virus, varicella-zoster virus , human parvovirus, **R**ubella, **C**ytomegalovirus (CMV), **H**erpes simplex virus (HSV))

Minor risks: TB above 75^{th} percentile, jaundice prior to discharge, macrosomic infant of a diabetic mother, polycythemia, male gender, maternal age ≥ 25 years old

NEUROLOGICALLY

Bilirubin is a neurotoxin. Free or indirect bilirubin (not attached to albumin) is free to cross the blood brain barrier and can cause significant damage.

Acute bilirubin encephalopathy (the acute phase of BIND) can be reversible or can cause permanent damage called kernicterus. According to Wong and Bhutani (2013b), it typically has three phases:

Early phase - Infant is sleepy, arousable with mild to moderate hypotonia (lack of tone) and a high pitched cry.

Intermediate phase – persistent hyperbilirubinemia. The infant may become lethargic with a poor suck, irritable/jittery with a strong suck, have a shrill cry, become inconsolable, become febrile. Mild to moderate hypertonia may occur (backward arching of the neck and trunk)

*an emergent exchange transfusion might prevent permanent BIND if done at this stage.

Advanced phase – apnea, inability to feed, fever, seizures, semi-comatose state progressing to a comatose state. Cry may be inconsolable, weak or absent. Hypertonicity is apparent with bicycling or twitching of feet and hands. Death is due to respiratory failure or intractable seizures.

**12.4% of infants with severe hyperbilirubinemia (TB >24.8 mg/dL [424 micromol/L]) in Canada were diagnosed with ABE (as reported by Wong et al, 2013)

When the amount of bilirubin exceeds the amount of albumin available 'free' bilirubin occurs. Kernicterus occurs when bilirubin is 'free', unconjugated and is deposited in the brain. Albumin bound bilirubin may also cross the blood brain barrier if it is damaged by asphyxia, hypoxia, sepsis etc...Kernicterus is chronic and permanent. It involves Choreoathetoid Cerebral Palsy, hearing loss (auditory neuropathy, usually high frequency), gaze abnormalities (especially paralysis of upward gaze) and dental dysplasia. Cognitive function is usually preserved, may have mild mental retardation. Defects are usually apparent by 1 – 3 years of age.

TREATMENT:

The use of phototherapy has greatly decreased the need for exchange transfusions and decreased the risk of severe hyperbilirubinemia.

Treatment includes phototherapy, improving efficiency/frequency of breastfeeding (increasing volume) and/or supplementing as needed, exchange transfusion.

Phototherapy converts bilirubin to lumirubin that is then excreted in bile and urine. Lumirubin does not convert back to bilirubin in the intestines. For bilirubin levels above 20 mg/dL [342 micromol/L], phototherapy should be constant. Once below this, phototherapy may be interrupted for feedings/visits.

Infants under the bili-lights should have their eyes covered and not be wearing a diaper (to maximize the amount of skin exposed).

Phototherapy helps keep the bilirubin levels from rising to levels that put the infant at risk for BIND/kernicterus.

A decline of 6 – 20% can be expected in the first 18 – 24 hours of phototherapy.

Infants under phototherapy need increased monitoring of VS, hydration status, TB level. Hydration is important as lumirubin is excreted primarily through urine.

Phototherapy can be discontinued when levels reach at or below the levels at which phototherapy was initiated (as the infant is now older and the acceptable level has increased).

Loose stools may occur due to the excretion of bilirubin.

Phototherapy is not indicated in conjugated hyperbilirubinemia (usually due to cholestasis and hepatic disease)

Adverse effects of phototherapy:

Transient erythematous rash

Loose stools

Hyperthermia

Dehydration

"Bronze Baby" - a rare complication in babe's with cholestatic jaundice. It includes a discoloration of the skin (dark, grey/brown), serum and urine. Self resolves after discontinuation of phototherapy – may take several weeks. It is unknown if there are neurotoxic effects.

Possible Retinal degeneration (if the eyes are not covered)

If phototherapy does not lower the bilirubin levels, exchange transfusion may be necessary. This involves exchanging partially hemolyzed antibody coated RBC's with uncoated RBC's that lack the sensitizing antigen.

Recommendations to prevent/manage hyperbilirubinemia:

- Promote and establish successful breastfeeding (8 or more times in a 24 hour period)
- Standing orders to obtain a TB level if required
- Tb or TcB upon discharge (if not done on all infants, then TB/TcB on all newborns with signs & symptoms or risk factors)
- TB level of all newborns with jaundice within 24 hours of birth
- Awareness of unreliability of visual diagnosis, especially with darker skinned newborns
- Effective teaching to parents re jaundice, signs & symptoms to watch for
- Effective communication with public health, especially in regards to newborns with risk factors
- Awareness that a late preterm is at higher risk than a term newborn
- Systematic assessment of the newborn at discharge, including S&S of hyperbilirubinemia
- Prompt treatment (phototherapy) of newborns with hyperbilirubinemia

Canadian Paediatric Society Guidelines (2011) for treatment of hyperbilirubinemia

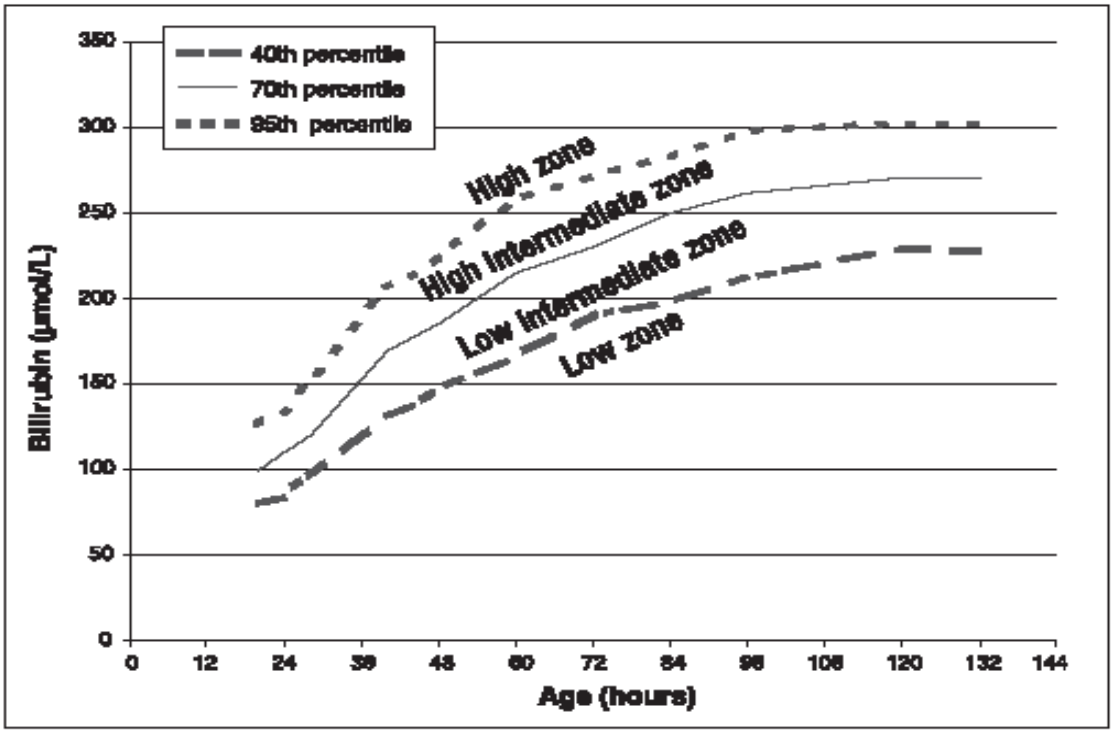

Figure 1) *Nomogram for evaluation of screening total serum bilirubin (TSB) concentration in term and later preterm infants, according to the TSB concentration obtained at a known postnatal age in hours. Plot the TSB on this figure, then refer to Table 4 for action to be taken*

Response to results of bilirubin screening			
ZONE	**> 37 WEEKS & DAT NEGATIVE**	**35 – 37.6 WEEKS OR DAT POSITIVE**	**35 – 37.6 WEEKS AND DAT POSITIVE**
HIGH	Further testing or treatment required	Further testing or treatment required	Phototherapy required
HIGH - INTERMEDIATE	Routine Care	Follow up within 24 – 48 hours	Further testing or treatment required
LOW - INTERMEDIATE	Routine Care	Routine Care	Further testing or treatment required
LOW	Routine Care	Routine Care	Routine Care
**Arrangements must be made for a timely (e.g., within 24 h) re-evaluation of bilirubin by serum testing. Depending on the bilirubin level , treatment with phototherapy may also be indicated. DAT Direct antiglobulin test*			

Table 4 (Barrington, K. Sankaran, K. (2011, February 1). Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants. Canadian Paediatric Society. *Paediatr Child Health* 2007; 12 (Suppl B); 1B-12B)

Intensive Phototherapy Guidelines:

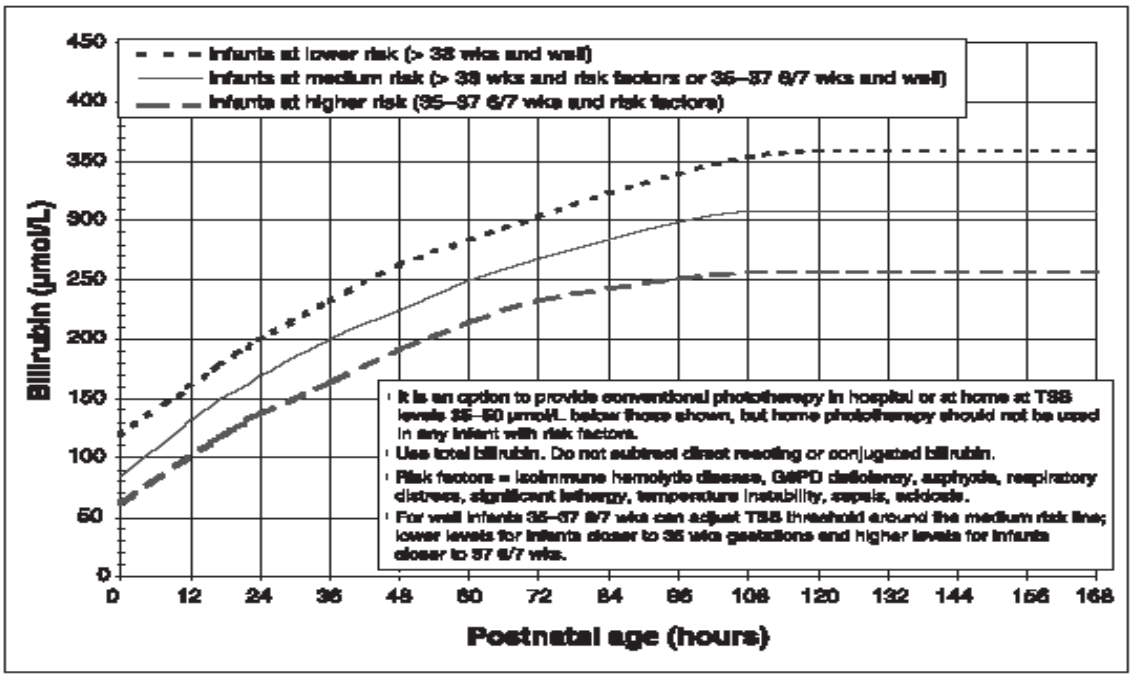

Figure 2) *Guidelines for intensive phototherapy in infants of 35 or more weeks' gestation. These guidelines are based on limited evidence and the levels shown are approximations. Intensive phototherapy should be used when the total serum bilirubin (TSB) concentration exceeds the line indicated for each category*

- If the infant has mild jaundice (not severe enough for phototherapy):

  Encourage the mom (if breastfeeding) to feed often (at least 8 times in 24 hours). Explain the rational for this.

  If the infant is dehydrated, encourage supplementation. The mom may pump post feeds and give this to the babe (preferred) or use formula.

Infants are at risk for severe hyperbilirubinemia and kernicterus due to exclusively breastfeeding and early discharge home where successful breastfeeding is not properly established.

(Wong, Bhutani, 2013b)

Therefore - it is important to successfully initiated breastfeeding early. The length of the postpartum stay should be increased if breastfeeding is not well established. Exclusive breastfeeding should still be encouraged. Supplementation should be done with expressed breast milk as much as possible.

REFERENCES

Abrahms, S., Shulman, R. (2013, September 3). Causes of neonatal cholestasis. Accessed on January 6, 2014 from www.uptodate.com/contents/causes-of-neonatal-cholestasis.

Barrington, K. Sankaran, K. (2011, February 1). Guidelines doe detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants. Canadian Paediatric Society. *Paediatr Child Health* 2007; 12 (Suppl B); 1B-12B

Garcia-Prats, J. (2013, October 5). Neonatal polycythemia. Accessed on September 9, 2013 from www.uptodate.com/contents/neonatal-polycthemia.

Lucile Packard Children's Hospital at Stanford. (2013) Hyperbilirubinemia and Jaundice. Accessed on September 10, 2013 from www.lpch.org/DiseaseHealthInfo/HealthLibrary/hrnewborn/hyperb.html

McKee-Garrett, T. (2013, August 15). Overview of the routine management of the healthy newborn infant. Accessed on September 6, 2013 from www.uptodate.com/contents/ overview-of-the-routine-management-of-the-healthy-newborn-infant.

Porter, M. (2002, February 15). Hyperbilirubinemia in the Term Newborn. *American Family Physician* 15:65(4), 599-607. Accessed on September 10, 2013 from www.aafp.org/afp/2002/0215/p599.html.

Wong, R., Bhutani, V. (2013a, Jun 11). Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn. Accessed on September 6, 2013 from www.uptodate.com/contents/ pathogenesis-and-etiology-of-unconjugated- hyperbilirubinemia -in-the-newborn.

Wong, R., Bhutani, V. (2013b, August 6). Clinical manifestations of unconjugated hyperbilirubinemia in term and late preterm infants. Accessed on September 6, 2013 from www.uptodate.com/contents/clinical-manifestations-of- unconjugated-hyperbilirubinemia -in-term-and-late- preterm-infants.

Wong, R., Bhutani, V. (2013c, August 7). Treatment of unconjugated hyperbilirubinemia in term and late preterm infants. Accessed on September 6, 2013 from www.uptodate.com/contents/ treatment-of- unconjugated-hyperbilirubinemia-in-term -and-late- preterm-infants

Wong, R. Bhutani, V. (2014, August 7). Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants. Accessed on January 6, 2014 from www.uptodate.com/contents/evaluation-of-unconjugated-hyperbilirubinemia-in-term-and-late-preterm-infants.

Yamamotoa, L. (2008, October). Hyperbilirubinemia Learning Package. Hamilton Region Hospitals. Accessed on September 10, 2013 from http://view.officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fwww.stjosham.on.ca%2Fmedia%2FHyperbili%2520Learning%2520Pkg%2520Ottawa%2520Oct%252016%252008.doc