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Hyperbilirubinemia Consensus

MANAGEMENT AND DEFINITION OF HYPERBILIRUBINEMIA

1. Guideline treatment of the **Hemolytic and Non-Hemolytic > 2500 gram newborn see graph 1***
   Guideline treatment of the **Hemolytic and Non-Hemolytic < 2500 gram newborn see graph 2***
   *Use total serum bilirubin if the direct bilirubin < 1 mg/dL
2. Need to distinguish between hemolytic and non-hemolytic hyperbilirubinemia
3. Hyperbilirubinemia due to hemolysis will be considered in a term infant as meeting any of the following criteria
   - reticulocyte count $\geq$ 8%
   - Hct < 40 % in a term infant and < 35 % in a preterm infant in the absence of acute blood loss
   - rate of rise > 0.5 mg/dL/hour
   - peripheral smear
   - Coomb's positive (consider dilutional studies if clinically confident of a hemolytic process with a negative coomb's test)
   - known familial hemolytic disorder
   - clinically septic
4. Any patient that is placed under phototherapy must have the following done
   - CBC with differential
   - reticulocyte count
   - RBC morphology
   - blood type and Coomb's
   - total and direct bilirubin

   - G-6PD **only** in the presence of the following
     - at risk ethnic background including African Americans
     - either sex (may have a heterozygote female)
     - hemolytic picture **without**…… blood group or Rh incompatibility
       proven infection
       abnormal smear for RBC wall defects
       other alternative explanations
5. How often to check bilirubin levels
   - see graphs
   - at least q 24 hrs if under phototherapy
   - in a patient with hemolysis q 4-8 hrs
   - in a patient that the bilirubin has not yet peaked q 8-24 hrs
6. Serum bilirubin levels $\leq$ 12 mg/dL at > 48 hrs in either hemolytic or non-hemolytic term infant, who has not received prior phototherapy, may be discharged to home with a 2% chance of readmission.
7. Any baby with a serum bilirubin level > 12 mg/dL at 48 hours of life needs to have follow-up with a primary care professional within 3 days from discharge.
8. Any baby treated with phototherapy needs to have follow-up with a primary care professional within 7 days from discharge.
9. Term infants in Zone 3 whose serum bilirubin is still rising needs to have follow-up with a primary care professional within 1-3 days from discharge.
10. High risks infants are defined as follows:
    - family history of hemolytic disease
    - the presence of hemolysis
    - polycythemia
    - hematoma
    - GI bleeding or other internal bleeding
    - swallowed maternal blood
    - small or large bowel obstruction
    - signs and symptoms consistent with sepsis
    - signs and symptoms consistent with hypothyroidism
    - signs and symptoms consistent with galactosemia

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PHOTOTHERAPY

The response to phototherapy depends on the light wavelength and intensity, the surface area exposed, and the rate at which isomerized bilirubin is removed from skin and blood.

To ensure maximal benefit from phototherapy one must ensure

1. **Maximal wavelength**
2. **Maximal light intensity**
3. **Maximal surface area exposed**

Microwatts

Recommend starting at 12 microwatts and increase to maximum of 25 microwatts. At an irradiance of 25 microwatts in the 425-475 nm range, serum bilirubin can be decreased by 50-60% in a 24-hour period. One may consider using 8 microwatts as a means to wean phototherapy.

Bilimeters should be used to ensure and document adequate microwattage.

Light Source

Recommend blue light, which carry a narrow spectrum of wavelengths at approximately 450 nm.

There is reasonable data to conclude that daylight lamps when used in adequate dosage and in particular with two light sources is adequate for the therapy of hyperbilirubinemia.

Spotlights are inadequate for term neonates but data describe no difference in its efficiency in preterm infants. There maybe a role for spotlight use as an additional light source.

Bili-blankets are advisable as it increases surface area. They should be used according to availability.

Exposure

Infants need to be **fully exposed**. This can be accomplished by eliminating blankets or clothing; minimizing diaper coverage; and surrounding the infant with white sheeting for its reflective capabilities in order to optimize exposed surface area.

All infants should have their eyes and gonads shielded while under phototherapy

Prophylactic phototherapy

There is no current data to support prophylactic phototherapy. In fact prophylactic therapy increases time of exposure without further benefit.

Continuous phototherapy

Continuous phototherapy is no more effective than intermittent but is easier to administer. The rate-limiting step for good treatment depends on the phototherapy chemical reaction of bilirubin in the skin that takes between 1 to 3 hours. Therefore, it is recommended that the infant not be out from under the lights for greater than 3 hours at a time and is limited to those infants who are stable and not close to exchange transfusion level. Infants approaching exchange level should not be off phototherapy for greater than 1 hour.

Coming off Phototherapy

Consider discontinuing phototherapy if the bilirubin level is below the range for beginning phototherapy for age/time **and** has been stable or decreasing over the past 24 hours.

Rebound

Despite anecdotal experience, data suggest rebound hyperbilirubinemia is a very unlikely occurrence in the average neonate with exaggerated physiologic jaundice. However, it is suggested that preterm infants and infants with hemolysis have follow-up serum bilirubin levels checked at least in 24 hours post phototherapy or as clinically indicated.

Home Phototherapy

Where available, home phototherapy may be provided in a healthy full term infant with established follow-up within the next 1-2 days, who has good enteral intake, reliable guardians, and who is not approaching exchange transfusion levels.

Home phototherapy may be initiated **only** in the healthy, full-term infant with the following criteria:

- normal CBC with differential
- > 48 hours
- bilirubin level < 20 mg/dL
- no history of hemolytic disease
- access to reliable transportation
- ability to communicate with care provider by phone
- maternal and infant blood types are known
- rate of rise is < 1 mg/dL in 3-4 hours
- adequate social support at home
- no elevation of direct bilirubin
- a primary physician willing to manage home care

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EXCHANGE TRANSFUSION

Exchange transfusion should be reserved for infants in whom intensive phototherapy with maximal area of exposure and at an irradiance of more than 12 microwatts has failed and for whom risk of encephalopathy exceeds the risks of complications and death from a double volume exchange.

Morbidities and Mortality form double volume exchange include:

- Mortality 0.5 – 5%
- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Hypernatremia
- Hyperkalemia
- Acidosis
- Thrombocytopenia
- Volume overload
- Dysrhythmias
- NEC
- Hypoperfusion injury
- Hypothermia
- Infections
- Graft versus host disease
- Drug loss

The <u>total</u> blood volume for a double volume exchange should be approximately 160ml/kg for term infants.

The <u>total</u> blood volume for a double volume exchange should be approximately 200ml/kg for pre-term infants.

Blood transfused should be CMV (-), irradiated and < 14 days old. The anticoagulant to be used is CPD (citrate-phosphate-dextrose).

ABO-compatible Rh-negative cells are used in Rh incompatibility.

Type O Rh-specific PRBCs are used for ABO incompatibility.

O (-) blood should be used if the etiology of hemolysis is unknown.

Double volume exchange should take approximately 1-2.5 hours in any infant.

Blood aliquots for exchange transfusion are 5, 10, 15, and 20 mls for infants weighing < 1500, 1500-2500, 2500-3500, and > 3500 grams, respectively. Alternatively, one may use 10% of the patient's blood volume as aliquots to be exchanged.

Refer to "Atlas of Procedures in Neonatology" edited by Fletcher, MacDonald, and Avery for the different techniques of exchange transfusion. The procedure for isovolemic transfusion is performed by withdrawing aliquots of blood from peripheral or umbilical arterial catheter and infusing the same amount into a venous line simultaneously. Alternatively if the umbilical venous catheter is central (above the diaphragm), the entire exchange can done through the UVC, withdraw and infusion. If a single catheter, "push-pull" method is utilized through the UVC, smaller aliquots and slower rates of transfusion should be considered. There is no consistent data to recommend a particular method for exchange transfusion.

Labs

The 1st aliquot from the exchange transfusion to be send for…

- CBC with differential
- bilirubin
- other miscellaneous labs

The last aliquot from the exchange transfusion to be sent for…

- CBC with differential
- basic electrolyte panel
- platelets
- bilirubin
- calcium
- type and cross

In 4-6 hours follow-up labs should include…

- hematocrit
- calcium
- basic electrolyte panel
- bilirubin

The blood should be ordered as follows…
"<u>*X blood type*</u> and Rh <u>*Y*</u> <u>*Z*</u> cc's of PRBC reconstituted in FFP to a hematocrit of 45-50%"

Prior to the initiation of a double volume exchange procedure, the involved attendings need to be in clear communications with each other and bedside care giver. Once the decision is made to proceed with a double volume exchange plans should not be altered.

All double volume exchange transfusions are to be performed in the ICU in the presence of a fellow and/or attending.

IVIG

Recommended **only** for antibody mediated hemolysis. This includes ABO, Rh, and minor blood group incompatibilities. Consider administering IVIG when in **Zone 4** for preterm infants and when in **Zone 5** for term infants. Data is less established for the use of IVIG in pre-term infants with anti-body mediated hemolysis.

Dose = 500 mg/kg/dose IV over 4 hours

May repeat at 12 hour intervals x 3 doses

PHENOBARITAL

There is no convincing data to support post-natal use of phenobarbital for the treatment of hyperbilirubinemia, especially as adjunctive therapy with phototherapy. It may be a consideration in special circumstances at the discretion of the attending of record.

HYDRATION

There is no clinical benefit to over/excessive hydration or albumin boluses.

Term infant should be hydrated enterally when possible. Supplemental PO hydration maybe as effective as IV hydration in breastfed-jaundiced infants.

Adequate hydration should be maintained at all times. Dehydration should be assessed by physical exam and by serum electrolytes.

When starting phototherapy, preterm infants will most likely need supplemental increase in their fluid intake by 10-20 cc/kg/day.

GLYCERIN SUPPOSITORIES

There is modest evidence that the administration of glycerin suppositories, until the first transitional stool, results in a minimal decrease in bilirubin. This therapy should be considered in infants not regularly stooling.

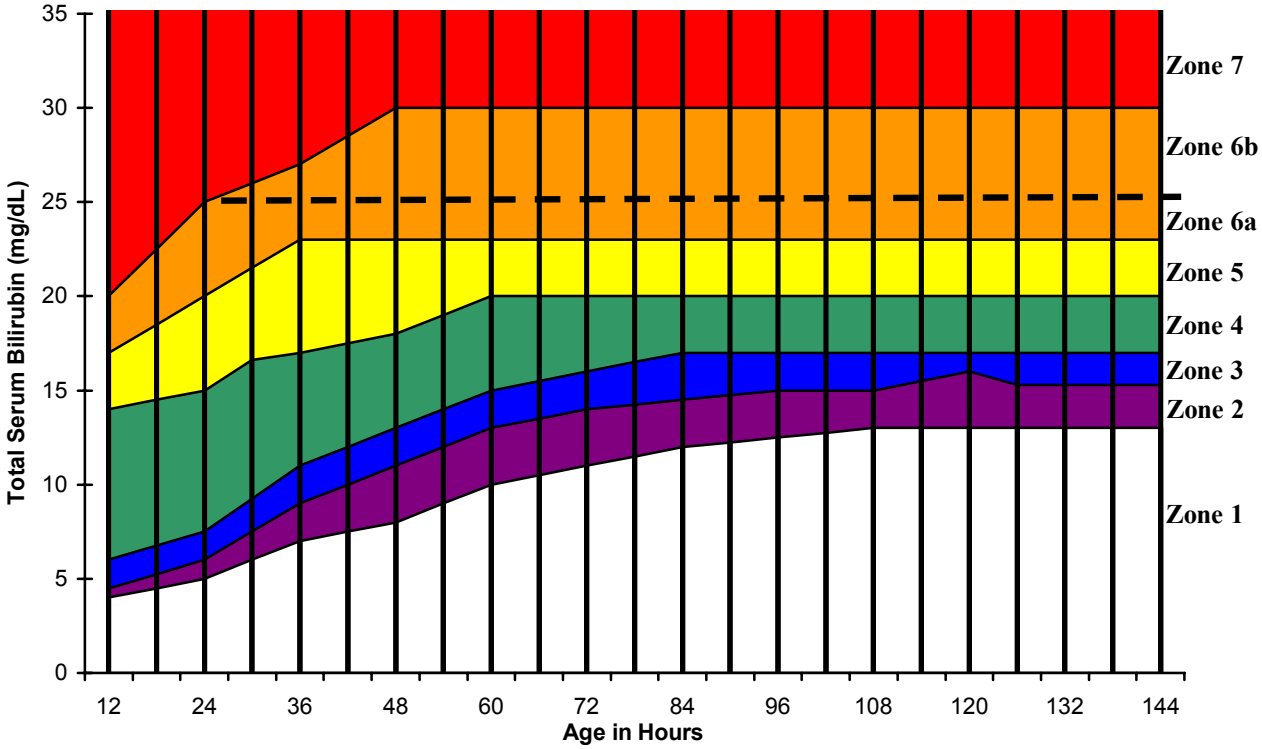
INTRALIPIDS

Data suggests that intralipids should be limited to $\leq$ 1 gm/kg in $\leq$ 30 weeks EGA. There is no data for > 30 weeks. Intralipids should be kept covered.

FUTURE

A consensus group will be re-established to review newer and developing science regarding hyperbilirubinemia. Other interventions and therapies like metalloporphyrins, exhaled CO, and skin monitoring should be regularly addressed as they become more established and available.

Treatment Options for Term Infants > 2500 grams



ZONE	HEMOLYTIC	BILI	NON-HEMOLYTIC	BILI
1	Follow bili until decreasing x 2	q 12-24^0	Observe	prn
2	Consider PTX	q 12^0	Follow bili until decreasing x 1	q 24^0
3	PTX	q 12^0	Consider PTX	q 12-24^0
4	PTX-M > consider IVIG	q 8-12^0	Consider PTX	q 12-24^0
5	PTX-M > IVIG > consider exchange	q 6-8^0	PTX > PTX-M	q 8-12^0
6a	PTX-M > IVIG > Exchange	q 4-8^0	PTX-M > consider exchange	q 6-12^0
6b	EXCHANGE			
7	EXCHANGE	q 4-8^0	EXCHANGE	q 4-8^0

Risk factors: history of hemolytic disease; the presence of hemolysis; polycythemia; GI bleeding or other internal bleeding; swallowed maternal blood; hematoma; bowel obstruction; signs and symptoms of sepsis, hypothyroidism, or galactosemia

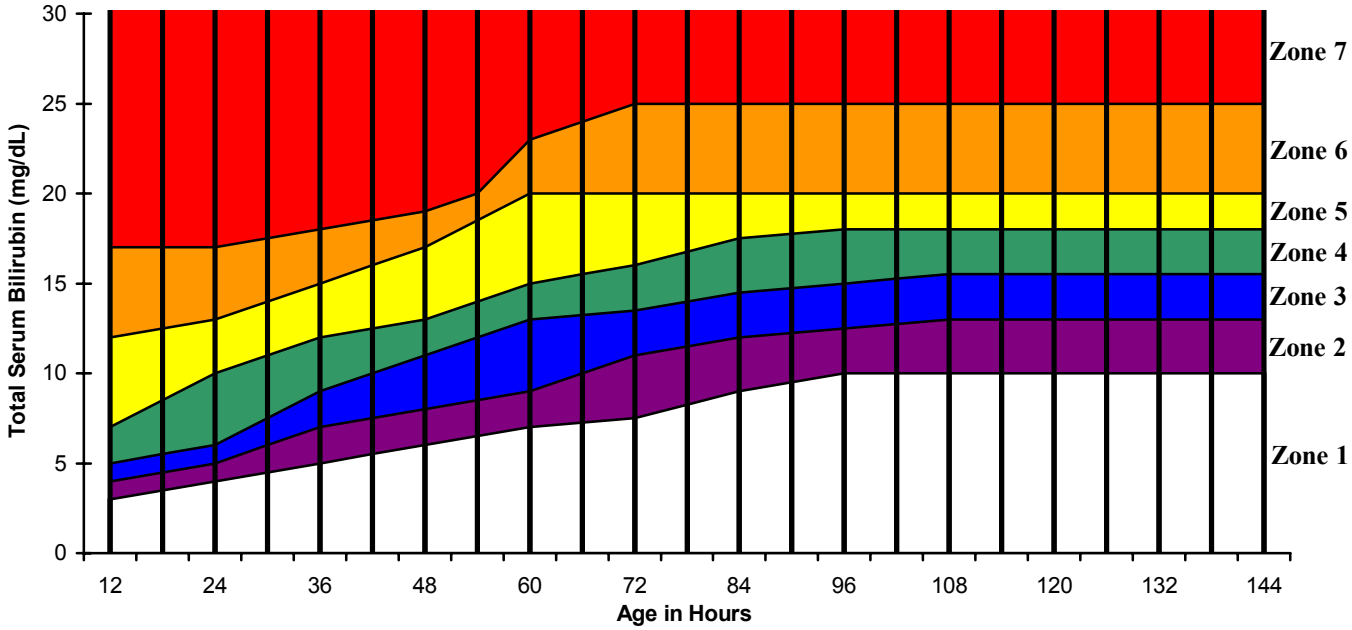
Consider => if infant sick/bruised, bili is increasing (>0.5 mg/dl/hr) despite therapy or near upper zone border

PTX => start phototherapy

PTX-M => maximize skin surface area exposure, and light source wave length and intensity

IVIG => 500 mg/kg/dose over 2 hours, may repeat q 12 hours x 3 doses, only indicated for antibody mediated hemolysis i.e. ABO or Rh sensitization

Treatment Options for Pre-Term Infants < 2500 grams



ZONE	BIRTH WEIGHT	HEMOLYTIC	BILI	NON-HEMOLYTIC	BILI
1	<1000	Consider PTX*	q 12-24^0	Follow bili till < 5	q 12-24^0
	1000-1500	Follow bili till <5	q 12-24^0	Follow bili / Observe	prn
	1500-2500	Follow bili / Observe	prn	Observe	prn
2	<1000	PTX	q 8-12^0	Consider PTX*	q 12-24^0
	1000-1500	Consider PTX	q 12^0	Follow bili till < 5	q 24^0
	1500-2500	Follow bili till <5	q 12-24^0	Follow bili / Observe	± q 24^0
3	<1000	PTX > consider IVIG	q 6-12^0	PTX	q 12-24^0
	1000-1500	PTX	q 8-12^0	Consider PTX	q 12-24^0
	1500-2500	Consider PTX	q 12-24^0	Consider PTX	q 24^0
4	<1000	PTX-M > IVIG > consider exchange	q 4-8^0	PTX-M	q 8-12^0
	1000-1500	PTX-M > consider IVIG	q 6-12^0	PTX	q 12^0
	1500-2500	PTX	q 12^0	PTX	q 12-24^0
5	<1000	PTX-M > IVIG > consider exchange, but exchange at 15 mg/dL at any hour of age	q 4-8^0	PTX-M > consider exchange	q 6-8^0
	1000-1500	PTX-M > IVIG > consider exchange	q 6-8^0	PTX-M	q 8^0
	1500-2500	PTX-M > consider IVIG	q 6-12^0	PTX-M	q 8-12^0
6	<1000	PTX-M > IVIG > exchange	q 4-8^0	PTX-M > exchange	q 4-8^0
	1000-1500	PTX-M > IVIG > exchange	q 4-8^0	PTX-M > consider exchange	q 4-8^0
	1500-2500	PTX-M > IVIG > consider exchange	q 6-8^0	PTX-M > consider exchange	q 6-12^0
7	ALL	EXCHANGE	q 4-6^0	EXCHANGE	q 4-6^0

Risk factors: history of hemolytic disease; the presence of hemolysis; polycythemia; GI bleeding or other internal bleeding; swallowed maternal blood; hematoma; bowel obstruction; signs and symptoms of sepsis, hypothyroidism, or galactosemia

Consider => if infant sick/bruised, bili is increasing (>0.5 mg/dl/hr) despite therapy or near upper zone border

PTX => start phototherapy

PTX-M => maximize skin surface area exposure, and light source wave length and intensity

IVIG => 500 mg/kg/dose over 2 hours, may repeat q 12 hours x 3 doses, only indicated for antibody mediated hemolysis i.e. ABO or Rh sensitization

Bibliography

Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. *Pediatrics* vol. 93(3), March 1994.

Alkay, A., Sola, A. Neonatal jaundice guidelines. *Neonatal Intensive Care* vol. 13, no 3, May/June 2000.

Alpay F, et al. High-dose Intravenous immunoglobulin therapy in neonatal immune haemolytic jaundice. *Acta Paediatrica* vol. 88(2), February 1999.

Anand NK, Gupta AK. What constitutes a "safe" level of bilirubin concentration in pre-term and full-term infants. *Indian Journal of Pediatrics* vol. 60(4), July-August 1993.

American Academy of Pediatrics; Practice Parameter: Management of hyperbilirubinemia in healthy term newborns. *Pediatrics* vol. 94(4), October 1994.

American Academy of Pediatrics; Committee on Fetus and Newborn. Home phototherapy. *Pediatrics* vol. 76, 1985.

Bhutani V, et al. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics* vol. 103(1), January 1999.

Brown AK, et al. Efficacy of phototherapy in prevention and management of neonatal hyperbilirubinemia. *Pediatrics* vol. 75(supp), 1985.

Cashore WJ. Bilirubin and jaundice in the micropremie. *Clinics in Perinatology* vol. 27(10), March 2000.

Cashore WJ. The neurotoxicity of bilirubin. *Clinics in Perinatology* vol. 17(2), June 1990.

Cloherty JP. Neonatal hyperbilirubinemia. In: Manual of neonatal care. Cloherty JP, Stark AP, editors. Second edition, Boston: Little, Brown and Company, 1985.

Dagoglu T, et al. High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. *Journal of International Medical Research* vol. 23(4), July-August 1995.

Dennary, P., Seidman, D., Stevenson, K. Neonatal hyperbilirubinemia. *New England Journal of Medicine* vol. 344(8), February 22, 2001.

Eberhard BA, Drew JH. Perhaps Vigintiphobia should only apply to infants with rhesus erythroblastosis. *Journal of Pediatrics and Child Health* vol. 30(4), August 1994.

Edwards MC, Avery MA. Exchange Transfusions. In: Atlas of Procedures in Neonatology. Avery MA, MacDonald MG, Avery GB, editors. First edition: J. B. Lippincott Company, 1983.

Gartner LM. Neonatal Jaundice. *Pediatrics in Review* vol. 15(11), November 1994.

Gustafson PA, Boyle DW. Bilirubin index: a new standard for intervention. *Medical Hypothesis* vol. 45(5), November 1995.

Hammerman C, et al. Intravenous immune globulin in neonatal immune hemolytic disease: Does it reduce hemolysis. *Acta Paeditrica* vol. 85(11), November 1996.

Hammerman C, et al. Intravenous immune globulin in neonatal ABO isoimmunization: Factors associated with clinical efficacy. *Biology of the Neonate* vol. 70(2), 1996.

Hammerman C, Caplan M. Recent development in the management of neonatal hyperbilirubinemia. *Pediatric in Review Neo Reviews* 2000; 1.

Holotrop PC, et al. Double versus single phototherapy in low birth weight infants. *Pediatrics* vol. 90, 1992.

Holotrop PC, et al. A clinical trial of fiberoptic phototherapy versus conventional phototherapy. *American Journal of Diseases in Childhood* vol. 146, 1992.

Johnson L, Bhutani VK. Guidelines for management of the jaundiced term and near-term infant. *Clinics in Perinatology* vol. 25(3), September 1998.

Kjartansson S, et al. Insensible water loss from the skin during phototherapy in term and pre-term infants. *Acta Paediatrica* vol. 81(10), October 1992.

Kjartansson S, et al. Respiratory water loss and oxygen consumption in newborn infants during phototherapy. *Acta Paediatrica* vol. 81(10), October 1992.

Lucey JF. The unresolved problems of kernicterus in the susceptible low birth weight infant. *Pediatrics* vol. 49, 1972.

Maisels MJ. Neonatal jaundice. In: Effective care of the Newborn. Sinclair JC, Bracken MB, editors. First edition: Oxford University Press, 1992.

Maisels MJ, Newman TB. Kernicterus in otherwise healthy breast-fed term newborns. *Pediatrics* vol. 96, 1995

Mills JF, Tudehope D. Fiberoptic phototherapy for neonatal Jaundice. *The Cochrane Database of Systematic Reviews* vol. (issue 1), 2001.

OH W, Karecki H. Phototherapy and insensible water loss in the newborn infant. *American Journal of Diseases in Childhood* vol. 124, 1972.

Petrec SM. Management of neonatal Rh disease. *Clinics in Perinatology* vol. 22(3), September 1995.

Rubo J, et al. High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. *Journal of Pediatrics* vol. 121(1), 1992.

Tanyer G, et al. Multiple dose IVIG treatment in neonatal immune hemolytic jaundice. *Journal of Tropical Pediatrics* vol. 47(1), February 2001.

Valaes, T., Harvey-Wilkes, K. Pharmacologic approach to the prevention and treatment of neonatal hyperbilirubinemia. *Clinics in Perinatology* vol. 17(2), June 1990.

Voto LS, et al. Neonatal administration of high-dose intravenous immunoglobulin in rhesus hemolytic disease. *Journal of Perinatal Medicine* vol. 23(6), 1995.

Wennberg RP. The blood-brain barrier and bilirubin encephalopathy. *Cellular and Molecular Neurobiology* vol. 20(1), February 2000.

Watchko JF, Claassen D. Kernicterus in premature infants: Current prevalence and relationship to NICHD phototherapy study exchange criteria. *Pediatrics* vol. 93(6), June 1994.