Hemolytic Disease of the Fetus and Newborn

Eremciuc Rodica

1

Introduction

- Almost all newborn infants develop a total serum or plasma bilirubin (TB) level >1 mg/dL (17 micromol/L), which is the upper limit of normal for adults.
- As TB levels increase, **neonatal hyperbilirubinemia** can develop, noticeable as **jaundice**, a visible yellowish discoloration of the skin and/or conjunctiva, caused by bilirubin deposition (TB levels of 4 to 5 mg/dL [68 to 86 micromol/L]).
- Term and late preterm infants (gestational age ≥35 weeks) with a TB >25 mg/dL (428 micromol/L) or **"severe" hyperbilirubinemia** are at risk for developing **bilirubin-induced neurologic dysfunction** (BIND), which occurs when bilirubin crosses the blood-brain barrier, subsequently binds to brain tissue, and induces neurotoxicity.

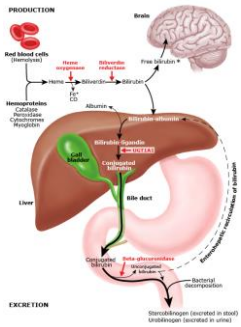
2

Bilirubin metabolism

Bilirubin production

Bilirubin is a product of heme catabolism.
In newborns, approximately 80 to 90 percent of bilirubin is produced during the breakdown of hemoglobin from red blood cells or from ineffective erythropoiesis.
The remaining 10 to 20 percent is derived from the breakdown of other heme-containing proteins, such as cytochromes and catalase.

Bilirubin is produced in two steps
- The enzyme heme oxygenase (HO), located in all nucleated cells, catalyzes the breakdown of heme, resulting in the formation of equimolar quantities of iron, CO, and biliverdin.
- Biliverdin then is rapidly converted to bilirubin by the enzyme biliverdin reductase.



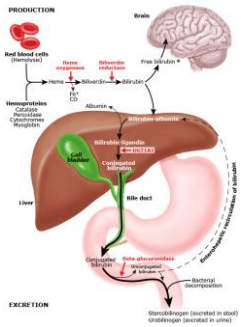
3

Bilirubin metabolism

Bilirubin clearance and excretion

1. Hepatic uptake
Circulating bilirubin bound to albumin is transported to the liver. Bilirubin then dissociates from albumin and is taken up by hepatocytes, where it is processed for excretion.

2. **Conjugation**
In hepatocytes, the enzyme uridine diphosphogluconurate glucuronosyltransferase (UGT1A1) catalyzes the conjugation of bilirubin with glucuronic acid, producing bilirubin diglucuronides and, to a lesser degree, bilirubin monoglucuronides.



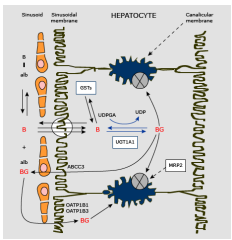
4

Bilirubin metabolism

Bilirubin clearance and excretion

3. Biliary excretion
Conjugated bilirubin, which is more water-soluble than unconjugated bilirubin, is secreted into the bile in an active process that depends upon canalicular transporters, and then excreted into the digestive tract.

4. Enterohepatic circulation
The secreted conjugated bilirubin cannot be reabsorbed by the intestinal epithelial cells.
At birth an infant's gut is sterile and, subsequently, infants have far fewer bacteria in the gut, so very little, if any, conjugated bilirubin is reduced to urobilin.
In the infant, beta-glucuronidase in intestinal mucosa deconjugates the conjugated bilirubin.
The unconjugated bilirubin can then be reabsorbed through the intestinal wall and recycled into the circulation, a process known as **the enterohepatic circulation of bilirubin.**



5

BENIGN NEONATAL HYPERBILIRUBINEMIA

- ***Benign neonatal hyperbilirubinemia*** (also previously referred to as "**physiologic jaundice**") results in unconjugated (indirect-reacting) bilirubinemia that occurs in nearly all newborns.

- It is a **normal** transitional phenomenon caused by:
  - the turnover of fetal red blood cells,
  - the immaturity of the newborn's liver to efficiently metabolize (conjugate) bilirubin,
  - increased enterohepatic circulation.

6

BENIGN NEONATAL HYPERBILIRUBINEMIA

Peak total serum or plasma bilirubin (TB) and time to resolution vary by an infant's diet, ethnicity, and gestational age (GA), likely because of differences in hepatic uptake, clearance, and excretion.

TIME TO RESOLUTION

- Visible jaundice resolves within the first one to two weeks after birth.
- Jaundice resolves by three weeks in approximately 65 percent of exclusively breastfed newborns, although approximately one in five are still jaundiced at four weeks of age.
- Persistence of hyperbilirubinemia beyond two weeks of age has been labelled as **prolonged hyperbilirubinemia/jaundice** and these infants require an assessment of their direct or conjugated bilirubin levels to rule out cholestatic jaundice.

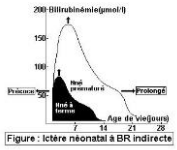


Figure : Ictère néonatal à BR indirecte

7

CAUSES OF SIGNIFICANT UNCONJUGATED NEONATAL HYPERBILIRUBINEMIA

- Identification of an underlying pathologic cause of neonatal hyperbilirubinemia is useful in determining whether therapeutic interventions are needed and timing of intervention to prevent severe hyperbilirubinemia.
- Any increase in bilirubin load resulting in significant hyperbilirubinemia is due to either or both an increase in bilirubin production or a decrease in bilirubin clearance

Increased production	Decreased clearance
Isoimmune-mediated hemolysis (eg, ABO or Rh[D] incompatibility)	**Inherited defects in the gene that encodes the enzyme UGT1A1**, which catalyzes the conjugation of bilirubin with glucuronic acid, decrease bilirubin conjugation. This reduces hepatic bilirubin clearance and increases total serum or plasma bilirubin (TB) levels. These disorders include Crigler-Najjar syndrome types I and II and Gilbert syndrome.
Inherited red blood cell membrane defects (eg, hereditary spherocytosis and elliptocytosis).	
Erythrocyte enzymatic defects (eg, G6PD deficiency, pyruvate kinase deficiency, and congenital erythropoietic porphyria).	**Other causes:** • maternal diabetes • congenital hypothyroidism • Galactosemia • Panhypopituitarism
Sepsis	
Macrosomic infants of diabetic mothers (IDM) have increased bilirubin production due to either polycythemia or ineffective erythropoiesis.	

8

Increased enterohepatic circulation of bilirubin

- *Causes of hyperbilirubinemia due to increased enterohepatic circulation of bilirubin include:*
  - *impaired intestinal motility caused by functional or anatomic obstruction*
  - *possibly breast milk jaundice*

Breast milk jaundice	Lactation failure jaundice
Breast milk jaundice is defined as **the persistence of benign neonatal hyperbilirubinemia beyond the first two to three weeks of age.** It typically presents after the first three to five days of life, peaks within two weeks after birth, and progressively declines to normal levels over 3 to 12 weeks	Lactation (breastfeeding) failure jaundice **typically occurs within the first week of life, as lactation failure leads to inadequate intake of fluids and calories resulting in hypovolemia and significant weight loss**. This results in hyperbilirubinemia (jaundice) and, in some cases, hypernatremia defined as a serum sodium >150 mEq/L. Decreased intake also causes slower bilirubin elimination and increases enterohepatic circulation of bilirubin that contribute to an elevated TB level.

Establishment of successful breastfeeding, one of the mainstays of preventing hyperbilirubinemia.

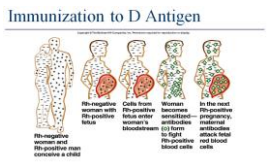
9

Hemolytic disease of the fetus and newborn

10

Definition

- Hemolytic disease of the fetus and newborn (HDFN), also known as **alloimmune HDFN** or **erythroblastosis fetalis**, is caused by the destruction of red blood cells (RBCs) of the neonate or fetus by maternal immunoglobulin G (IgG) antibodies.
These antibodies are produced when fetal erythrocytes, which express an RBC antigen not expressed in the mother, gain access to the maternal circulation.



11

TYPES OF HDFN

RhD hemolytic disease	The original description of HDFN was due to RhD incompatibility, which is associated **with the most severe** form of the disease (hydrops fetalis). To note, in the absence of transfusion, Rh HDFN generally does not occur in the first pregnancy. The introduction of antenatal Rh(D) immune globulin prophylaxis has significantly reduced alloimmune sensitization in pregnant women who are RhD negative.
ABO hemolytic disease	Although ABO incompatibility occurs in approximately 15 percent of all pregnancies, it results in neonatal hemolytic disease in only 4 percent of such pregnancies. Infants with ABO HDFN generally have **less severe disease** than those with RhD incompatibility. Affected infants are usually asymptomatic at birth and have either no or mild anemia. They generally develop hyperbilirubinemia within the first 24 hours of birth. Phototherapy is usually sufficient therapy for most infants with ABO HDFN.
Other blood group antibodies	Several blood groups other than those of the ABO and Rh group are associated with HDFN and include Duffy, MNS, and P. Antibodies may develop in response to exposure to these antigens from a previous transfusion or pregnancy or from exposure to bacteria or viruses that express these antigens. The clinical disease associated with HDFN due to these other blood groups ranges from mild (hyperbilirubinemia) to severe, including hydrops fetalis. The variability is, in part, dependent upon the blood group

12

CLINICAL PRESENTATION

- The severity of HDFN is **variable**, ranging from only laboratory evidence of mild hemolysis to severe anemia with compensatory hyperplasia of erythropoietic tissues, leading to massive enlargement of the liver and spleen.
- When hemolysis exceeds the compensatory capacity of the hematopoietic system, profound anemia occurs and results in pallor, signs of cardiac decompensation (cardiomegaly, respiratory distress), massive anasarca, and circulatory collapse.
- This clinical picture of excessive abnormal fluid in 2 or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), termed **hydrops fetalis**, frequently results in death in utero or shortly after birth.

13

Hydrops fetalis

- Infants with **severe life-threatening anemia** (eg, hydrops fetalis) present with skin edema, pleural or pericardial effusion, or ascites.
- Infants with RhD and some minor blood group incompatibilities, such as Kell, are at risk for hydrops fetalis, especially pregnancies without antenatal care.
- ABO HDFN is generally less severe than that caused by the Rh and Kell systems; however, there are case reports of hydrops fetalis due to ABO incompatibility.
- Because of the lower severity of hydrops fetalis in neonates with ABO incompatibility, other causes for the severe hemolysis should be sought.
- Neonates with hydrops fetalis may present at delivery with shock or near shock and require emergent transfusion.

14

Clinical assessment

- Clinical assessment consists of routine evaluation of the newborn for the onset and progression of jaundice while in the hospital and determining if there are risk factors for severe hyperbilirubinemia in addition to an elevated TB measurement.
- Onset and progression of jaundice — All term and late preterm infants should be routinely assessed for the onset and progression of jaundice when vital signs are taken while in the hospital as part of the routine newborn management

Major risk factors include:

- GA of 35 to 36 weeks
- Suboptimal intake of exclusive breastfeeding
- Hemolytic disease
- Significant bruising (eg, cephalohematoma from birth trauma)
- Sibling who received phototherapy
- Being East Asian and certain ethnicities with high risk of having G6PD deficiency

15

Kramer zones

Zone	Affected region	Indirect serum bilirubin level, media
1	Head and neck	100
2	Apper part of the trunk	150
3	Lower abdomen	200
4	Arms and legs	250
5	Palms and plants	>250

16

Bilirubin measurements

Bilirubin measurements (TB or TcB) should be performed in the following settings when jaundice is detected. However, because visual assessment is not a reliable indicator of the degree of hyperbilirubinemia, a low threshold for measuring bilirubin is appropriate. Bilirubin measurements should be performed for:

- Any infant who develops jaundice before 24 hours of age.
- Any infant >24 hours of age when jaundice appears to be excessive for age (eg, jaundice below the level of the umbilicus).
- Failure of jaundice resolution after seven days of age in a formula-fed infant or 10 to 14 days in a breastfed infant.
- Infants who are still jaundiced at age two weeks must have a measurement of direct or conjugated bilirubin.

17

Transcutaneous Monitoring

- Transcutaneous bilirubinometry can be adopted as the first-line screening tool for jaundice in well, full-term babies.
- This leads to about 50% decrease in blood testing.

18

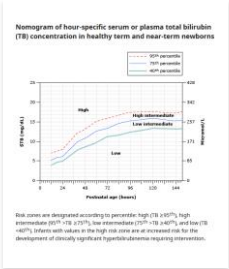
Bilirubin conversion unit

- Formula for calculation of mg/dl from mmol/l: **mg/dl = 18 × mmol/l**
- Formula for calculation of mmol/l from mg/dl: **mmol/l = mg/dl / 18**

19

CHOICE OF BILIRUBIN TEST FOR SCREENING

- The gold standard for neonatal bilirubin testing is measuring total serum or plasma bilirubin (TB). However, transcutaneous bilirubin (TcB) is a reasonable alternative because it decreases the need for phlebotomy, reduces laboratory costs, and appears to be as effective as TB as a screening tool in detecting the risk of developing severe hyperbilirubinemia.
- TB and TcB values are compared with age-specific percentile-based nomograms.



20

Evaluation of HDFN

Initial tests to perform in newborns with suspected HDFN include:

- Maternal and infant blood type (ABO and RhD)
- Direct antiglobulin test (DAT)
- Bilirubin level
- Complete blood count (CBC) and peripheral blood smear
- Reticulocyte count

21

Diagnosis

The diagnosis of HDFN is confirmed when **ALL** of the following criteria are fulfilled:

- Demonstration of incompatible blood types between the infant and mother
- Laboratory evidence of hemolysis (eg, unconjugated hyperbilirubinemia, anemia with elevated reticulocyte count, and/or peripheral blood smear findings consistent with hemolysis)
- Positive DAT (if the DAT is negative but other diagnostic criteria are met, a positive indirect antiglobulin test [IAT] supports the diagnosis of HDFN)

The differential diagnosis for HDFN includes other causes of neonatal jaundice and/or hemolytic anemia. Alloimmune HDFN is differentiated from these disorders by the presence of a positive DAT and/or IAT.

22

INTERVENTIONS USED TO PREVENT AND TREAT SEVERE HYPERBILIRUBINEMIA and HDFN

23

Phototherapy

Phototherapy is the most commonly used intervention to treat and prevent severe hyperbilirubinemia. It is an effective intervention to lower total serum or plasma bilirubin (TB) and has been considered a safe intervention based upon its extensive use in millions of infants and only infrequent reports of significant adverse effects and long-term neurologic complications.

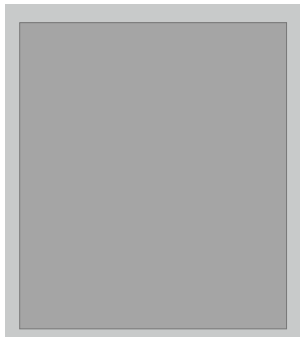
Phototherapy reduces TB levels and decreases or blunts the trajectory or the rate of rise of TB in almost all cases of hyperbilirubinemia, regardless of the patient's ethnicity or the etiology of the hyperbilirubinemia. The primary benefit of phototherapy is to prevent the TB from rising to a level at which exchange transfusion is recommended. Phototherapy might also decrease the risk of the development of chronic bilirubin encephalopathy (CBE), previously referred to as kernicterus, although the recommended treatment thresholds for phototherapy are generally considered to be well below those at which bilirubin neurotoxicity occurs

24

Phototherapy

- Effective phototherapy results in a decline of TB of at least 2 to 3 mg/dL (34 to 51 micromol/L) within four to six hours. A decrease in TB can be measured as soon as two hours after initiation of treatment. Twenty-four hours of phototherapy can effectively result in a 25 to 40 percent decrease in initial TB levels.
- During phototherapy, infants should be placed supine, body exposed with the area covered by the diaper minimized (for hygiene only), and eyes shielded with an opaque blindfold. Care should be taken to prevent the blindfold from covering the nose or sliding off the orbits.

25



Phototherapy

- Although several light sources are available for phototherapy, we use devices that incorporate blue LED lamps as their light source, as it is the safest and most efficacious.
- Other alternate light sources include fluorescent tubes or halogen bulbs.
- During feedings when overhead lighting is temporarily ceased, LED-based pads/mattresses or fiberoptic blankets or pads/mattresses can be used.

26

Monitoring of phototherapy

During treatment, the dose of phototherapy (irradiance) and the infant's temperature, hydration status (intake and output), time of exposure, and TB **should be monitored daily**.

Excessive fluid loss may be associated with phototherapy, which may increase insensible skin fluid loss.

LED-based devices emit lower levels of heat than other light sources, and thus fluid loss due to hyperthermia is less of a concern when using these types of devices

27

Discontinuation of phototherapy

It is recommended to discontinue phototherapy:

- For infants who have been readmitted for phototherapy, when their TB levels are 12 to 14 mg/dL (205 to 239 micromol/L).
- For those who required phototherapy during the birth hospitalization, when the TB has fallen to, or below, the level at which phototherapy was initiated.

After discontinuation of phototherapy, TB is best measured after 18 to 24 hours to assess for rebound hyperbilirubinemia.

28

EXCHANGE TRANSFUSION

Exchange transfusion, an intervention with known risks, should be avoided.

In infants with Rhesus isoimmunization, it was a life-saving emergency procedure that acutely reduced total serum or plasma bilirubin (TB) levels and removed offending antibodies.

However, exchange transfusion is an increasingly rare, expensive, time-consuming procedure, which requires clinical expertise and experience.

The need for exchange transfusions has decreased with the prevention of Rhesus (Rh) isoimmune hemolytic disease.

29

EXCHANGE TRANSFUSION

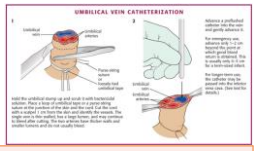
Procedure

- The procedure involves umbilical catheter placement and removing and replacing blood in aliquots that are approximately 10 percent or less of the infant's blood volume. Urgent and intensive phototherapy is provided during the interim time period needed to set up for the exchange transfusion.
- On admission, a type and cross-match of the infant's blood and placement of an umbilical catheter are performed promptly, so that exchange transfusion, if needed, can be started as quickly as possible.

30

Goals of Exchange Transfusion

- Remove sensitized cells.
- Reduce level of maternal antibody.
- Removes about 60 percent of bilirubin from the plasma, resulting in a clearance of about 30 percent to 40 percent of the total bilirubin.
- Correct anemia by providing blood that will have normal survival.
- Replacement with donor plasma restores albumin and any needed coagulation factors.
- Rebound – usually a 2 volume exchange is needed as bilirubin in tissues will return to blood stream.



Blood volume to be exchanges is about double the blood volume of infant :

2*85 mL * Bwt

31

EXCHANGE TRANSFUSION

Post-procedure management

- Following exchange transfusion, phototherapy is reinitiated (ideally, phototherapy should not be discontinued and continued at the same therapeutic dose used prior to exchange).

- TB is measured within two hours following the procedure and management decisions are made dependent on the level of TB.

32

COMPLICATONS OF EXCHANGE TRANSFUSION

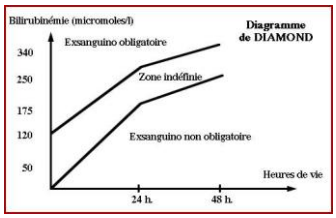
The risks of exchange transfusion result from the use of blood products and from the procedure itself.

Complications include:

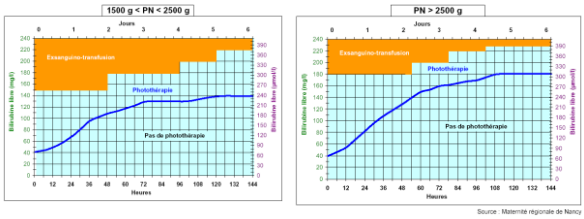
- Blood-borne infections
- Thrombocytopenia and coagulopathy
- Graft versus host disease
- Necrotizing enterocolitis
- Portal vein thrombosis
- Electrolyte abnormalities (eg, hypocalcemia and hyperkalemia)
- Cardiac arrhythmias

33

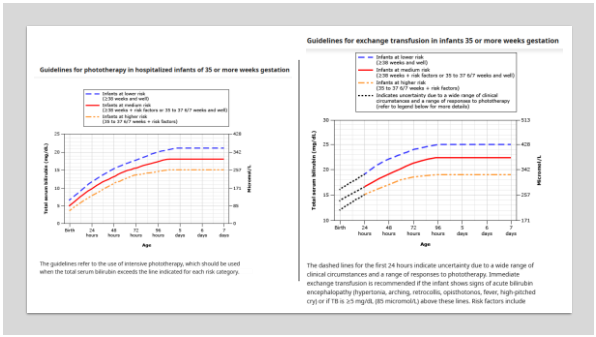
Diamond diagramme



34



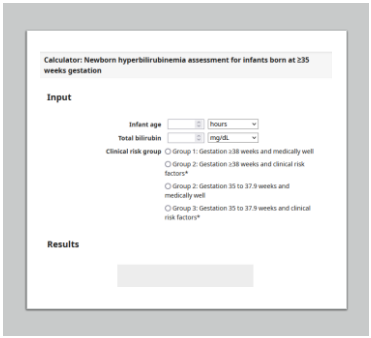
35



36

Management

- The risk for severe hyperbilirubinemia and the threshold for intervention either with phototherapy or exchange transfusion may be determined using the newborn hyperbilirubinemia assessment calculator based on TB values and the presence of concomitant risk factors
- **Age limitation** - Results are not available for infants greater than 6 days of age or newborns less than 12 hours of age.



37

Clinical risk factors

The risk for severe hyperbilirubinemia and the threshold for intervention are used to determine the clinical risk group, which is based upon the hour-specific bilirubin value, gestational age, and the presence of the following clinical risk factors:

- Isoimmune hemolytic disease or glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Asphyxia or lethargy
- Unstable temperature, sepsis, or acidosis
- Hypoalbuminemia (less than 3 g/dL [30 g/L], a risk factor when considering phototherapy, not transfusion)

38

Management of HDFN

The postnatal management for HDFN is dependent on both the severity of anemia and hyperbilirubinemia.

- **Early life-threatening anemia (hydrops fetalis)** – Infants with life-threatening anemia (hydrops fetalis) require emergency transfusion using group O, RhD-negative RBCs.
- **Early severe anemia and/or severe hyperbilirubinemia** – For patients with early severe symptomatic anemia (hematocrit <25 percent) and/or severe hyperbilirubinemia (based upon hour-specific bilirubin values), it is recommended exchange transfusion rather than simple transfusion. However, if there is a delay or inability to perform an exchange transfusion, simple RBC transfusion and treatment with intravenous immunoglobulin (IVIG) are reasonable options.
- **Moderate to severe anemia and nonsevere hyperbilirubinemia** – For patients with moderate to severe anemia (hematocrit between 25 and 35 percent) and nonsevere hyperbilirubinemia (ie, not requiring exchange transfusion it is recommended simple transfusion. Selection of RBCs for transfusion depends on the type of HDFN.

39

Management of HDFN

The postnatal management for HDFN is dependent on both the severity of anemia and hyperbilirubinemia.

- **Hyperbilirubinemia due to HDFN** is managed in the same manner as for neonatal unconjugated hyperbilirubinemia more broadly. The mainstays of management include serial monitoring of serum bilirubin levels, oral hydration, and phototherapy.
  For neonates in whom the bilirubin level continues to rise despite intensive phototherapy or is within 2 or 3 mg/dL (34 to 51 micromol/L) of the threshold for exchange transfusion, it is recommended IVIG.

- **Mild anemia and nonsevere hyperbilirubinemia** – Patients with hematocrit >35 percent generally do not require transfusion. Management of these newborns focuses on monitoring and treating hyperbilirubinemia.

40

Other options of treatment

- **Ursodeoxycholic acid (UCDA)** – UDCA enables the emulsification of bile in the biliary ducts. It increases bile flow, bile elimination into the gut, and helps to lower TB levels. It is useful in the treatment of cholestatic jaundice (direct bilirubin >2 mg/dL). As a result, it is recommended to use UCDA in infants with combined unconjugated and conjugated hyperbilirubinemia in addition to phototherapy, and those with conjugated hyperbilirubinemia alone.

- **Phenobarbital** – Phenobarbital increases the conjugation and excretion of bilirubin and decreases postnatal TB levels when given to pregnant women or infants. However, prenatal administration of phenobarbital may adversely affect cognitive development and reproduction. As a result, it is **not** recommend phenobarbital be used routinely used to treat neonatal unconjugated hyperbilirubinemia because of its clinically significant adverse effects.

- **Metalloporphyrins** – There are studies showing that synthetic metalloporphyrins (SnMP), such as tin mesoporphyrin, reduce bilirubin production by competitive inhibition of heme oxygenase. However, SnMP (or other metalloporphyrins) are **not** approved to treat neonatal hyperbilirubinemia and is not available for general use.

41

OUTCOME

When infants with hyperbilirubinemia are identified and treated appropriately, the outcome is excellent with minimal or no additional risk for adverse neurodevelopmental sequelae.

But….

42

Clinical case: Kernicterus spectrum disorders in children of preterm birth

43