



Hyperbilirubinemia in the Newborn

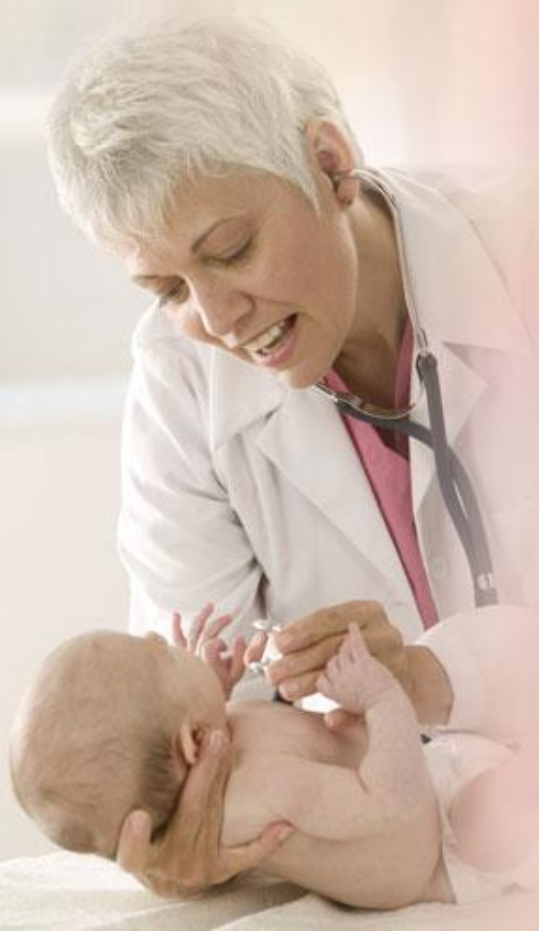
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MBCHB, FICSM, MRCPCh

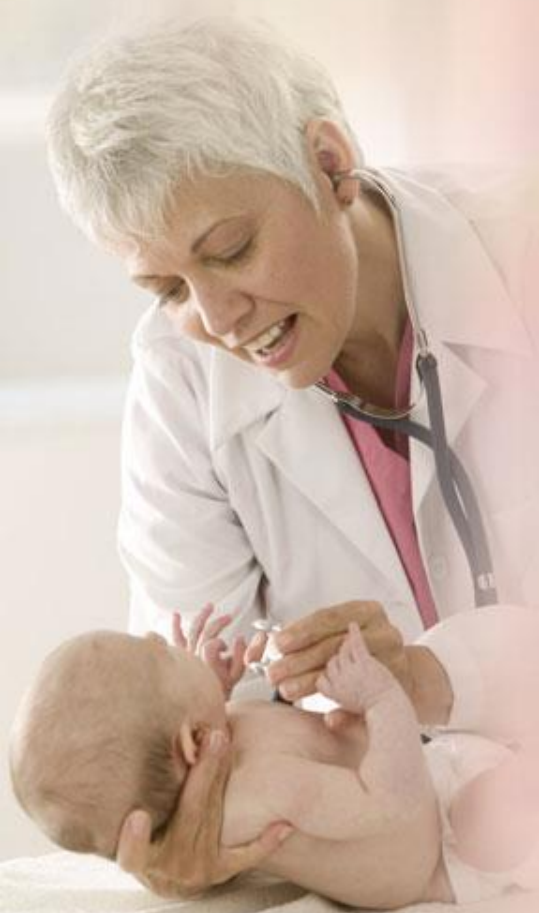


JAUNDICE (ICTERUS).

- Def.: Yellow discoloration of the sclera, skin, and mucous membranes
- Clinically apparent jaundice in children and adults occurs when the serum concentration of bilirubin reaches 2–3 mg/dL (34–51 $\mu\text{mol/L}$);
- the neonate may not appear icteric until the bilirubin level is >5 mg/dL (85 $\mu\text{mol/L}$).



Types of jaundice

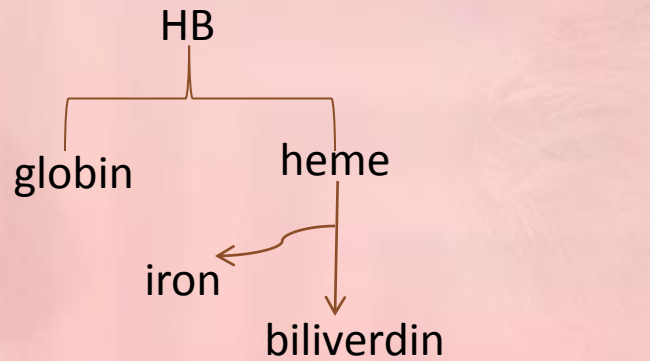
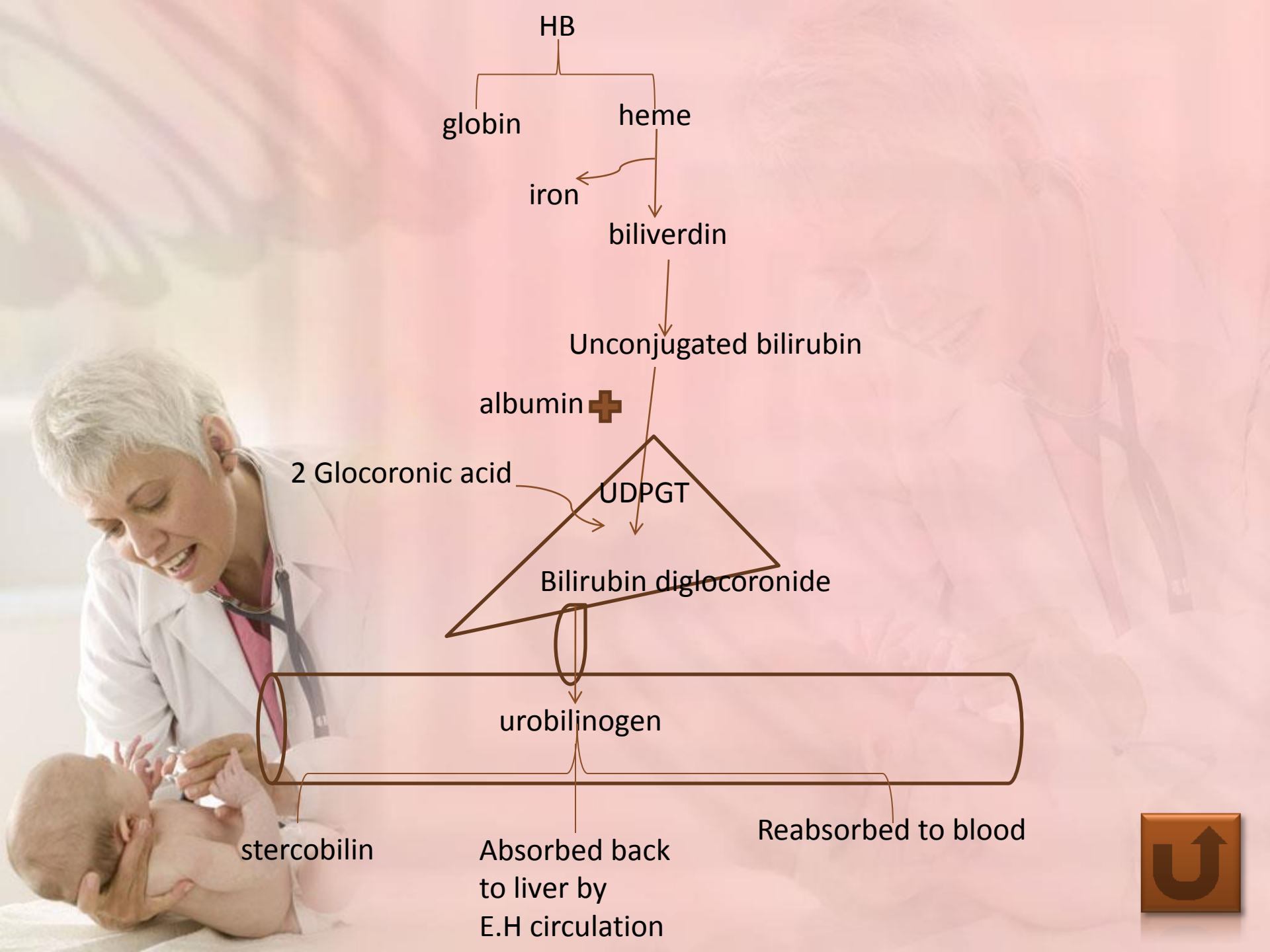


Unconjugated (indirect)

- unconjugated, nonpolar, lipid-soluble bilirubin
- .This unconjugated bilirubin(designated **indirect acting** by nature of the Van den Bergh reaction)
- is an end product of heme-protein catabolism from a series of enzymatic reactions in the reticuloendothelial cells.
- unconjugated bilirubin are potentially neurotoxic

Conjugated (direct)

- conjugated bilirubin,
- the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid)UDP(-glucuronyl transferase .
- the polar, water-soluble glucuronide of bilirubin (**direct reacting**)
- is not neurotoxic, direct hyperbilirubinemia indicates serious hepatic disorders or systemic illness



Unconjugated bilirubin

albumin +

2 Glucuronic acid

UDPGT

Bilirubin diglucoronide

urobilinogen

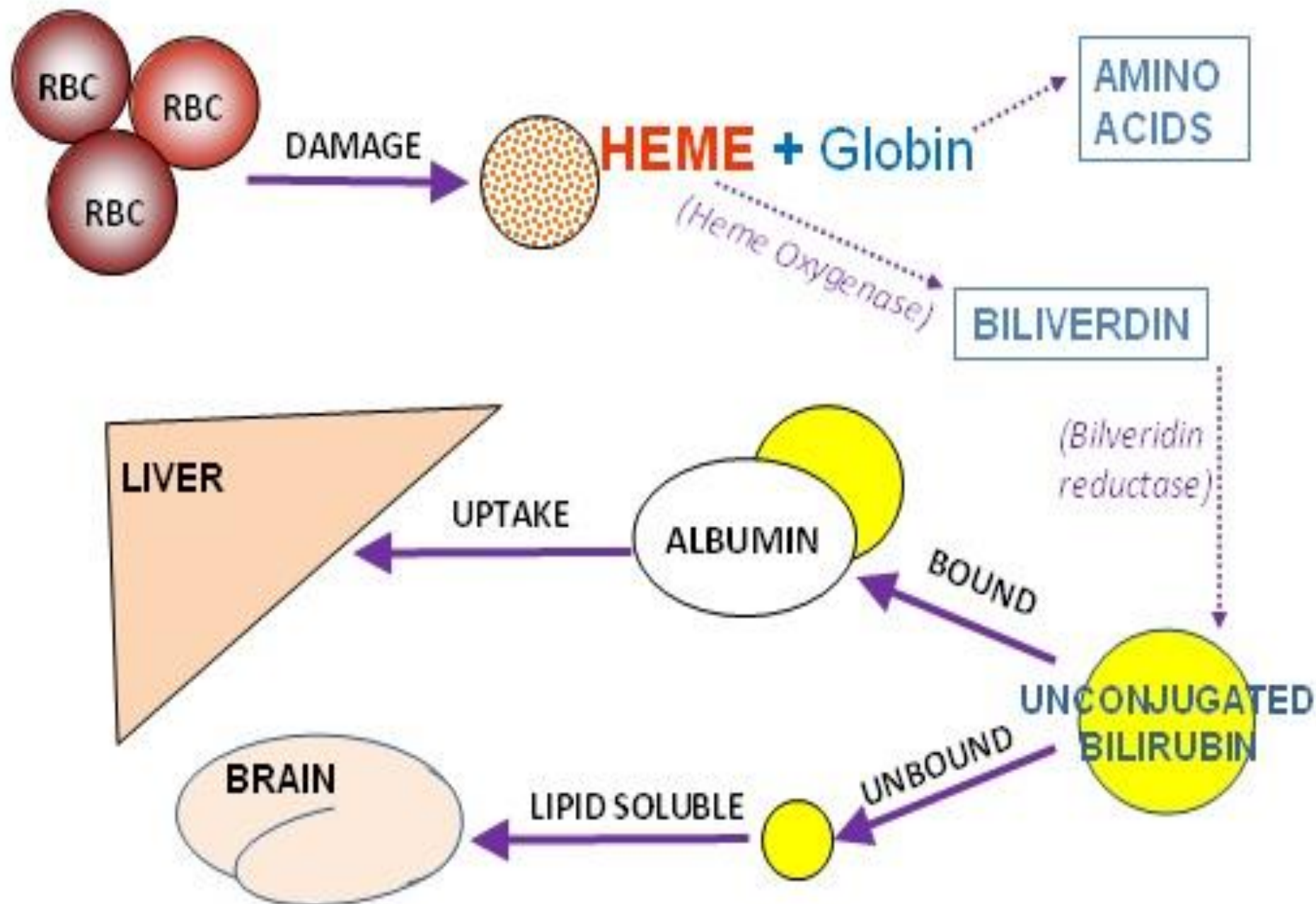
stercobilin

Absorbed back to liver by E.H circulation

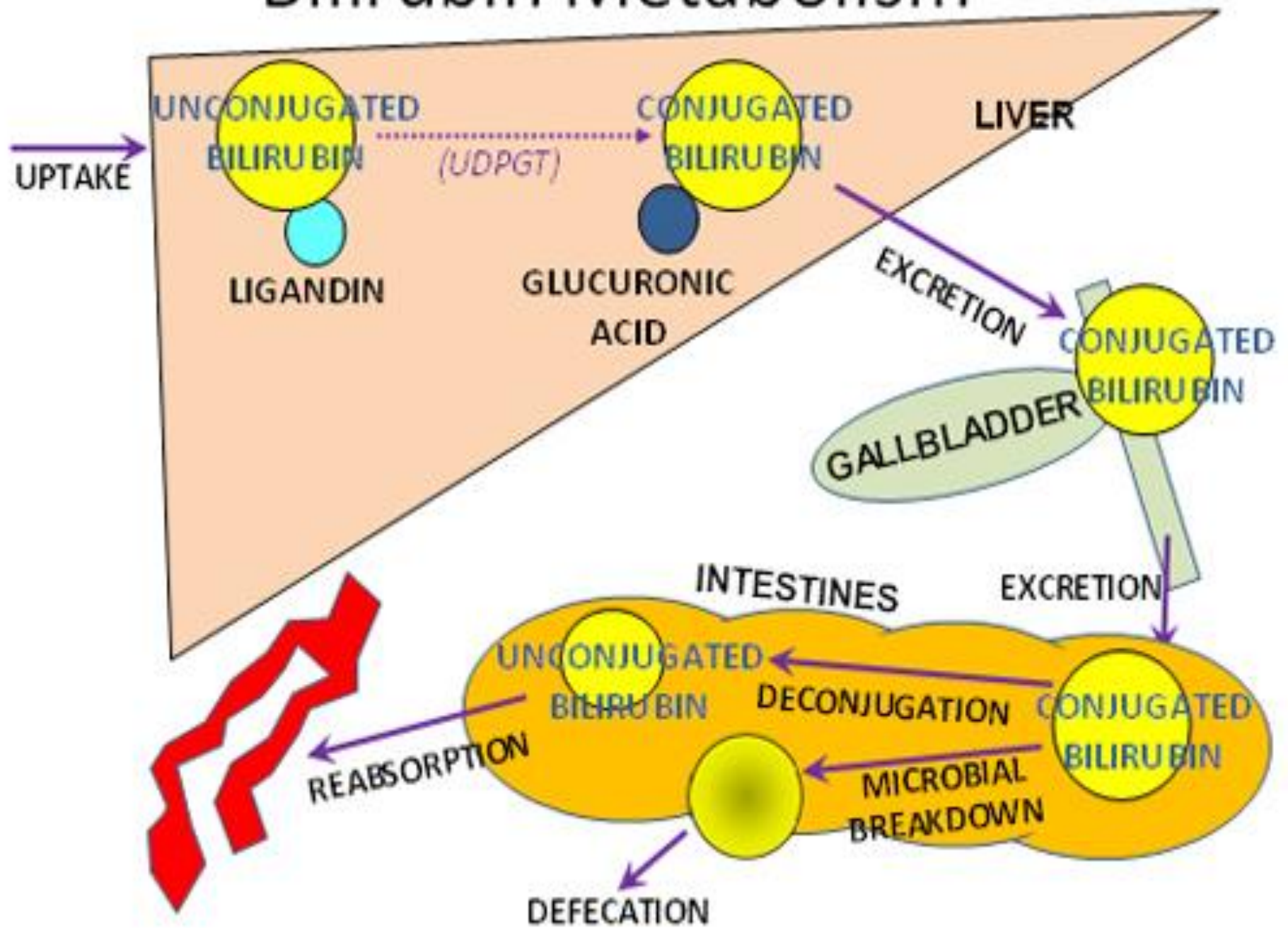
Reabsorbed to blood



Bilirubin Metabolism

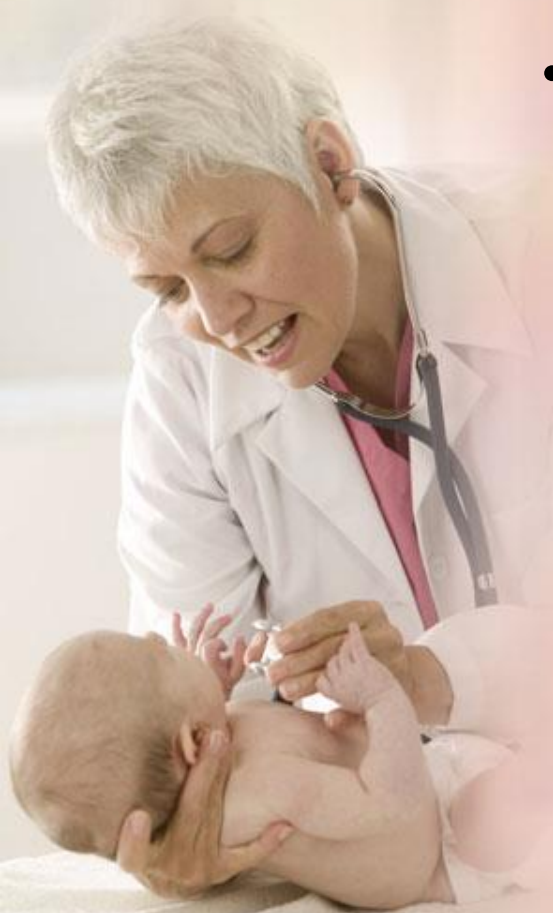


Bilirubin Metabolism



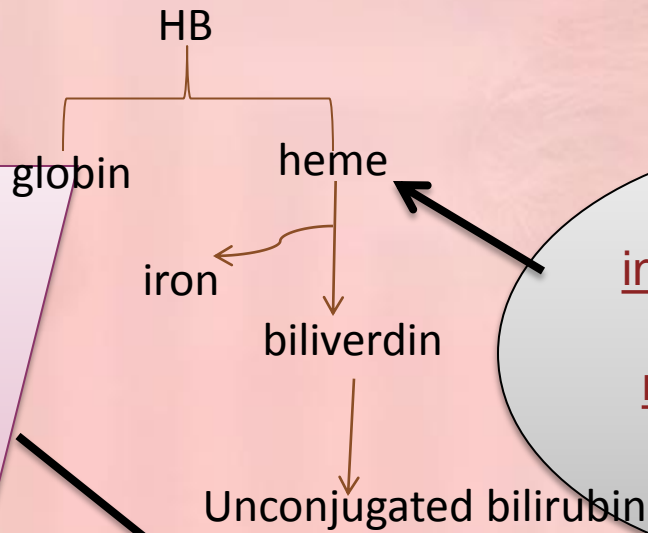
Jaundice and Hyperbilirubinemia in the Newborn

- Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st wk of life in approximately 60% of term infants and 80% of preterm infants.



ETIOLOGY .

- Unconjugated hyperbilirubinemia may be caused or increased by any factor that:
 1. increases the load of bilirubin to be metabolized by the liver)hemolytic anemias, polycythemia, shortened red cell life as a result of immaturity or transfused cells, increased enterohepatic circulation, infection(;
 2. damages or reduces the activity of the transferase enzyme or other related enzymes)genetic deficiency, hypoxia, infection, thyroid deficiency(;
 3. competes for or blocks the transferase enzyme drugs and other substances requiring glucuronic acid conjugation.
 4. leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells)genetic defect, and prematurity .(



damages or reduces the activity of the transferase enzyme or other related enzymes

increases the load of bilirubin to be metabolized by the liver

albumin

UDPGT

competes

leads to an absence or decreased amounts of the enzyme

- hemolytic anemias
- polycythemia,
- shortened red cell life as a result of immaturity or transfused cells,
- increased enterohepatic circulation,
- infection

genetic defect, and prematurity

Absorbed back to liver by E.H. circulation

genetic deficiency, hypoxia, infection, the decrease



5. The toxic effects of elevated serum levels of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation hypoproteinemia,

6. displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and

increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia



5. Factors that increase the toxic effects of elevated serum levels of unconjugated bilirubin

factors that reduce the retention of bilirubin in the circulation

displacement of bilirubin from its binding sites on albumin binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia

Unconjugated bilirubin + albumin

2 Glucuronic acid

UDPGT

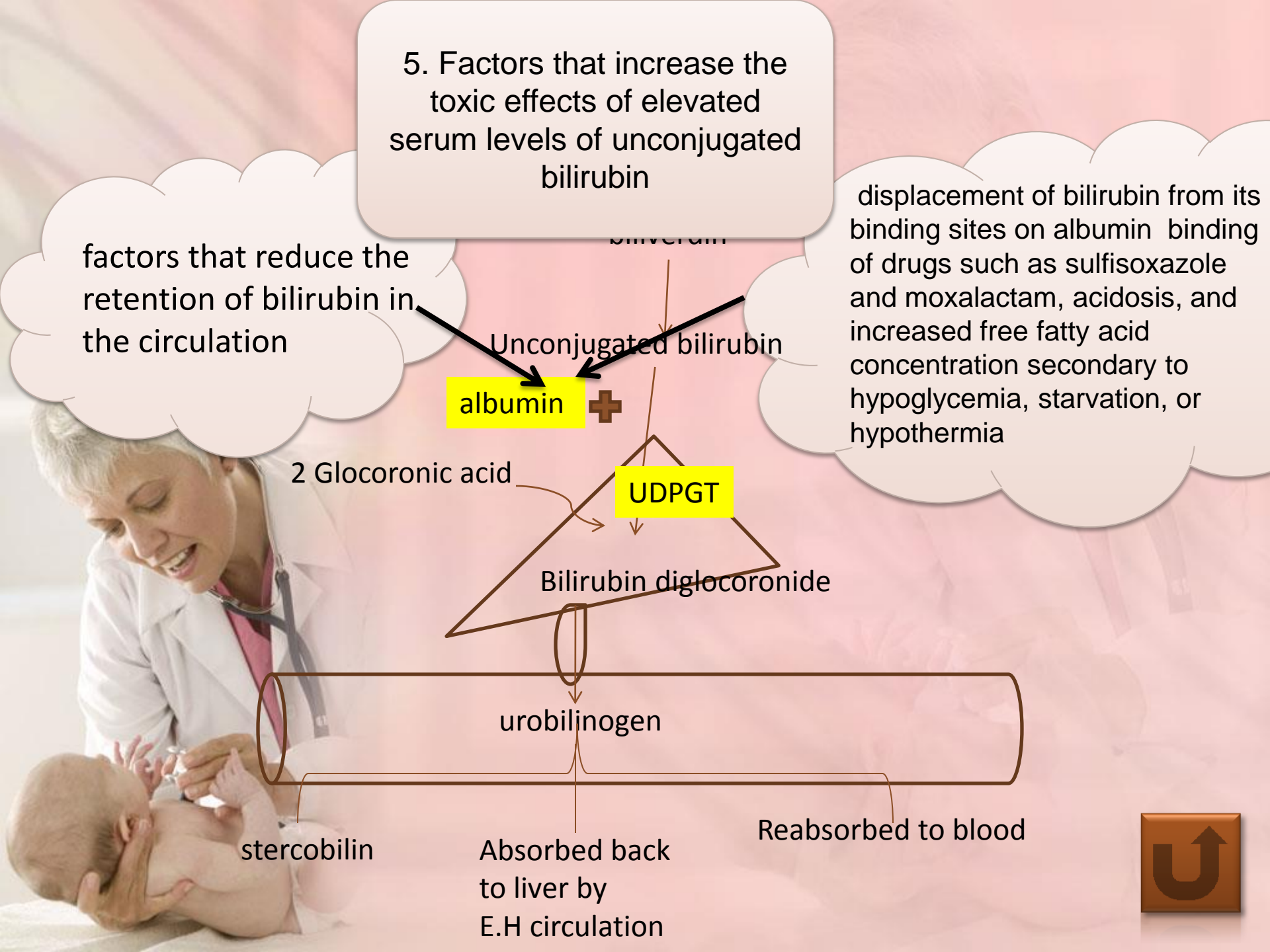
Bilirubin diglucoronide

urobilinogen

stercobilin

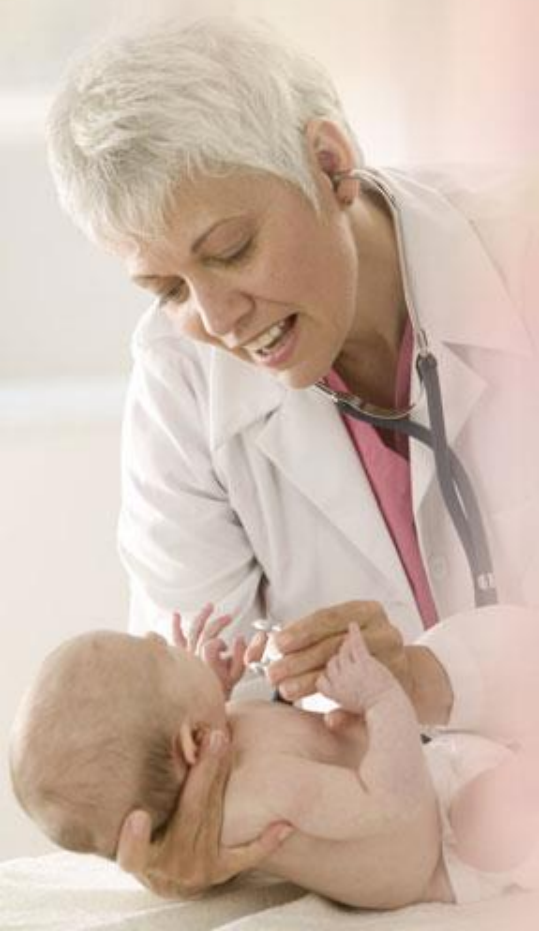
Absorbed back to liver by E.H circulation

Reabsorbed to blood

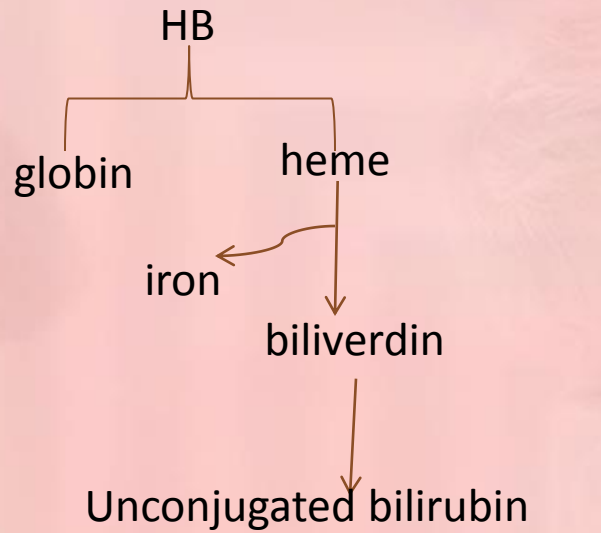




- the permeability of the blood-brain barrier neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection .
- Early and frequent feeding decreases whereas breast-feeding and dehydration increase serum levels of bilirubin
- The neonatal production rate of bilirubin is 6–8 mg/kg/24 hr)in contrast to 3–4 mg/kg/24 hr in adults



- Delay in passage of meconium, which contains 1 mg bilirubin /dL, may contribute to jaundice by enterohepatic circulation after deconjugation by intestinal glucuronidase)
- Drugs such as oxytocin and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia



albumin +

2 Glucuronic acid

UDPGT

Bilirubin diglucoronide

urobilinogen

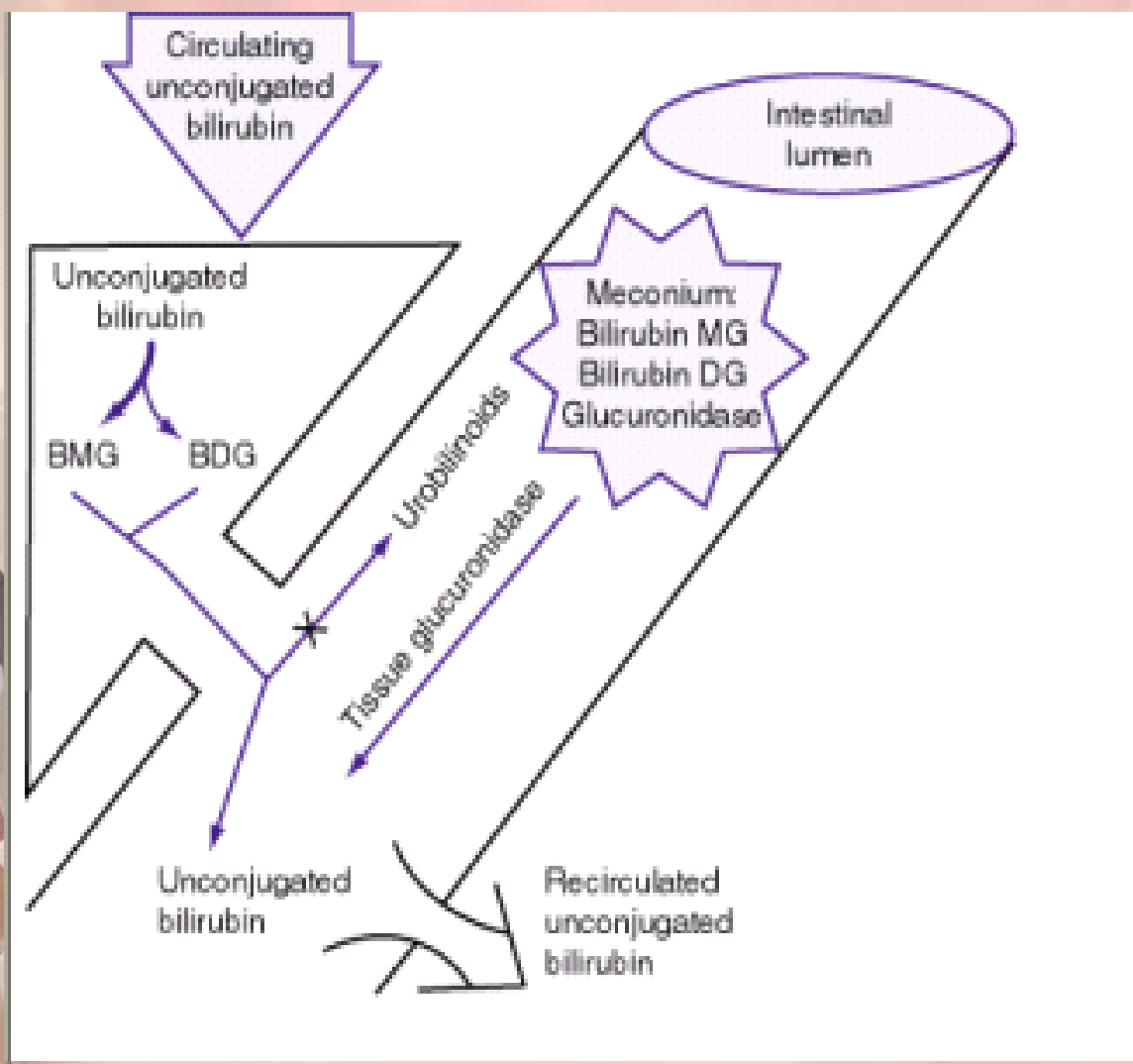
stercobilin

Absorbed back to liver by E.H circulation

Reabsorbed to blood

.Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic circulation after deconjugation by intestinal glucuronidase





CLINICAL MANIFESTATIONS

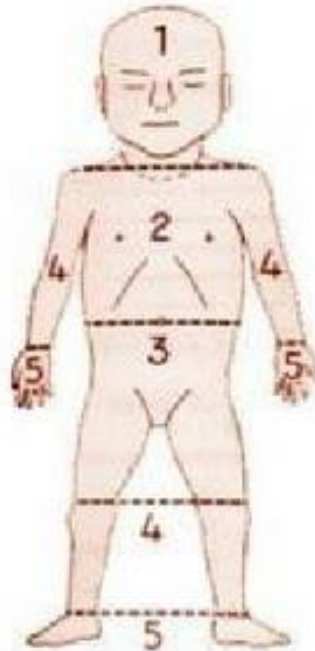
- Jaundice usually becomes apparent in a cephalocaudal progression starting on the face and progressing to the abdomen and then feet, as serum levels increase



- Dermal pressure may reveal the anatomic progression of jaundice face, =5 mg/dL; mid-abdomen, =15 mg/dL; soles, =20 mg/dL , but clinical examination cannot be depended on to estimate serum levels .

Grading of extent of jaundice

Schema for grading extent of jaundice

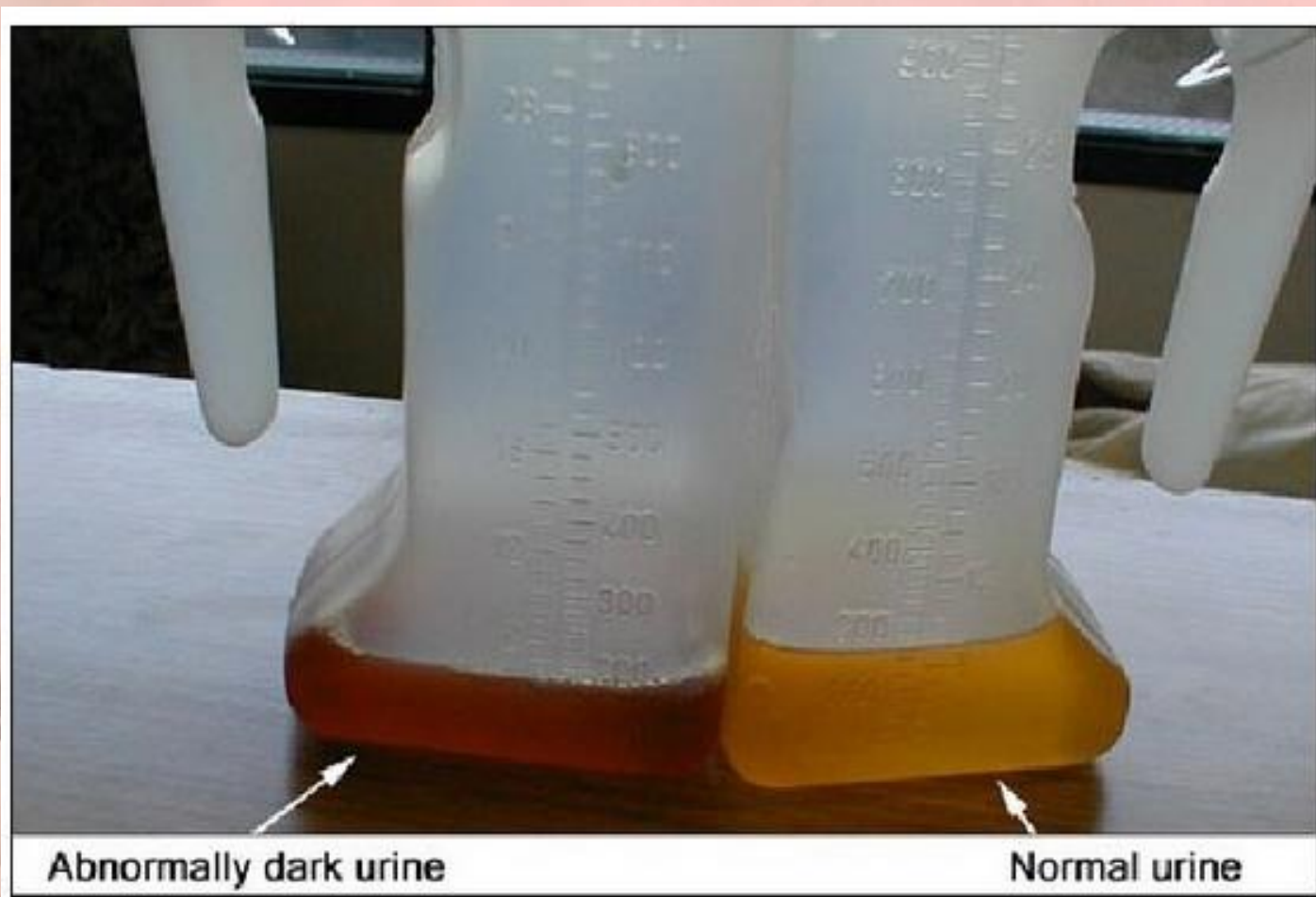


Grade	Extent of Jaundice
0	None
1	Face and neck only
2	Chest and back
3	Abdomen below umbilicus to knees
4	Arms and legs below knees
5	Hands and Feet





- jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange,
- jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast .
- Although signs of kernicterus rarely appear on the 1st day, affected infants may present with lethargy and poor feeding and, without treatment, can progress to acute bilirubin encephalopathy



Abnormally dark urine

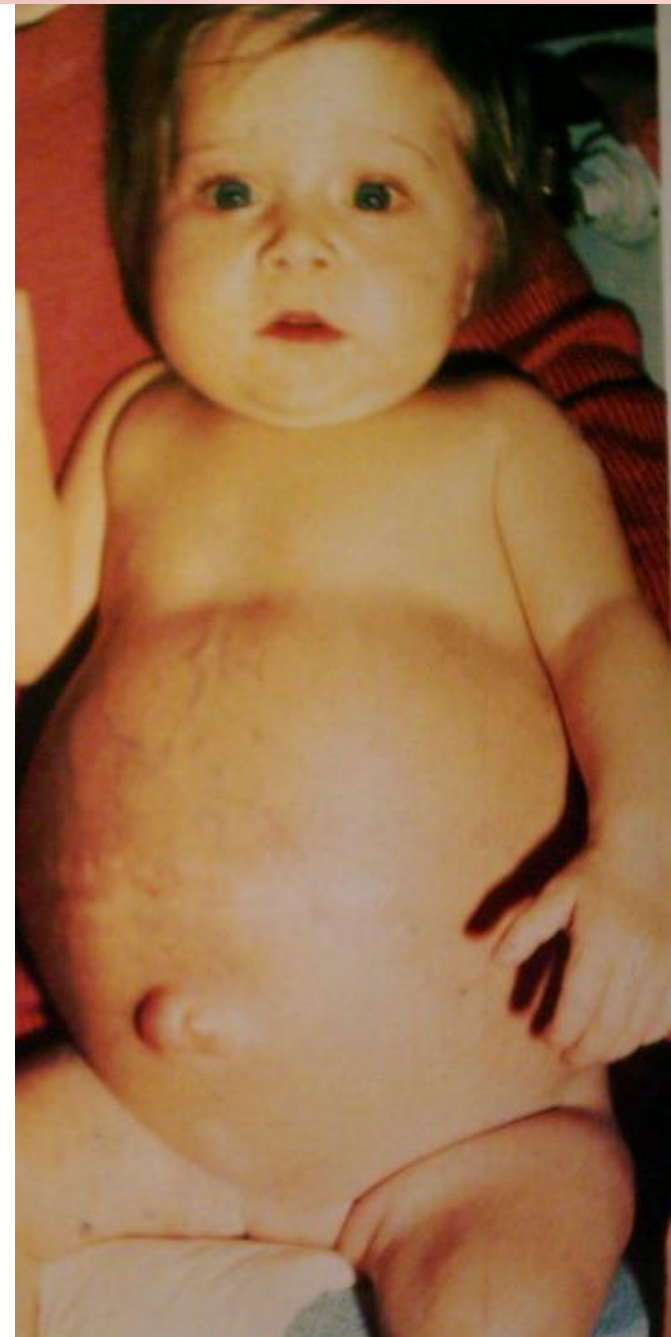
Normal urine



Fig. 114a Jaundice



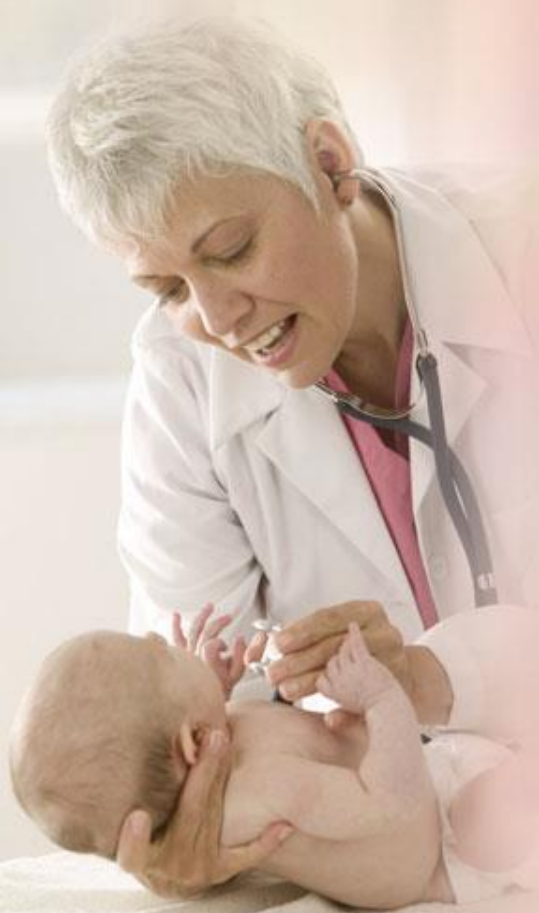
Fig. 114b Obstructive jaundice



DIFFERENTIAL DIAGNOSIS .

Jaundice that is present at birth or appears within the 1st 24 hr of life

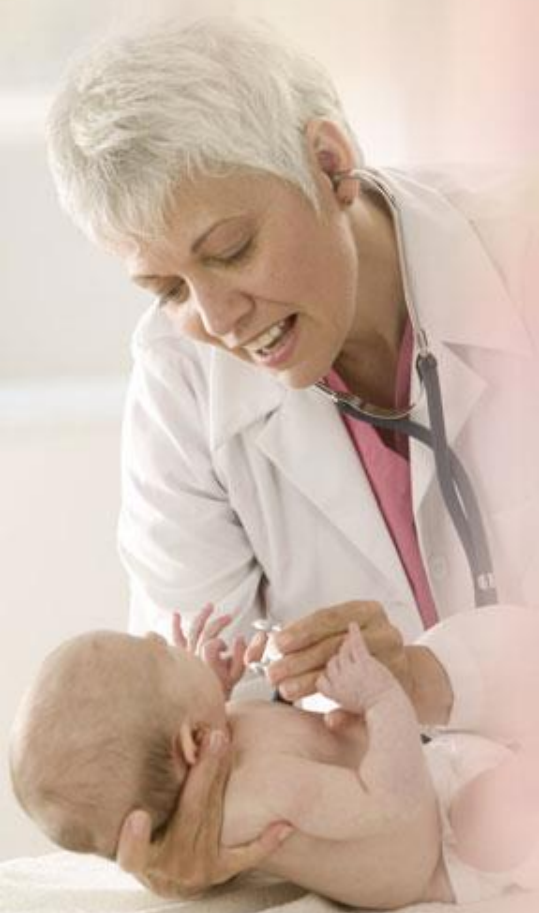
1. erythroblastosis fetalis,
2. concealed hemorrhage,
3. sepsis,
4. congenital infections, including syphilis, cytomegalovirus, rubella, and toxoplasmosis



Jaundice that 1st appears on the 2nd or 3rd day

is

- usually **physiologic** but may represent a more severe form.
- Familial non-hemolytic icterus (**Crigler-Najjar syndrome**)
- early-onset breast-feeding jaundice.



.Jaundice appearing after the 3rd day and within the 1st wk:

- bacterial sepsis
- urinary tract infection;
- it may also be due to other infections, notably syphilis, toxoplasmosis, cytomegalovirus, (TORCH) or enterovirus

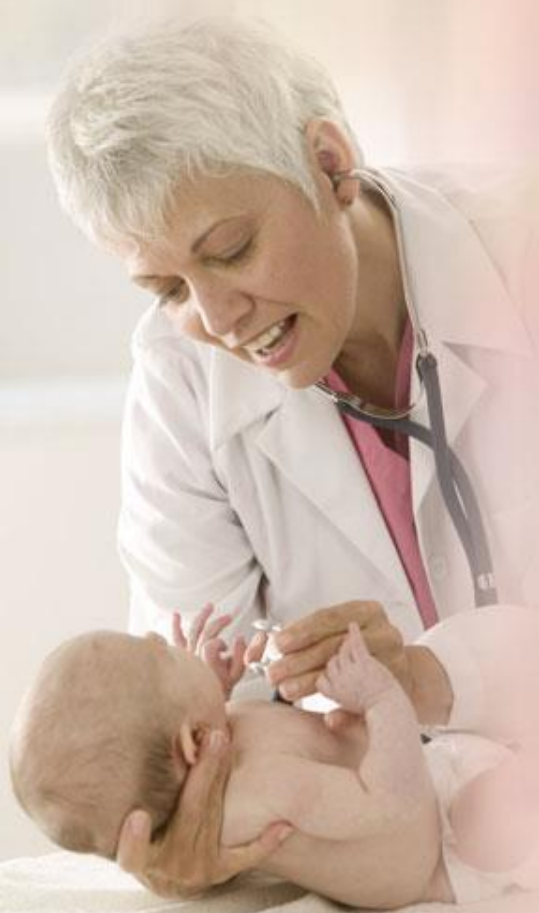


1st recognized after the 1st wk of life

There is a long differential diagnosis for jaundice :

Including

- breast-milk jaundice,
- septicemia,
- congenital atresia or paucity of the bile ducts, hepatitis,
- galactosemia,
- hypothyroidism,
- CF,
- congenital hemolytic anemia crises related to red cell morphology and enzyme deficiencies (spherocytosis, G6PD, pyruvate kinase def.)





DIAGNOSIS

Investigations for early jaundice

- Serum bilirubin level
- FBC and film
- Blood group
- Maternal blood group
- Direct coombs test
- Consider G6PD level



The differential diagnosis for persistent jaundice during the 1st mo of life:

- cholestasis,
- hepatitis
- , cytomegalic inclusion disease, syphilis, toxoplasmosis,
- familial non-hemolytic icterus,
- congenital atresia of the bile ducts,
- galactosemia, or
- inspissated bile syndrome following hemolytic disease of the newborn .
- Rarely, physiologic jaundice may be prolonged for several wk, as in infants with hypothyroidism or pyloric stenosis .



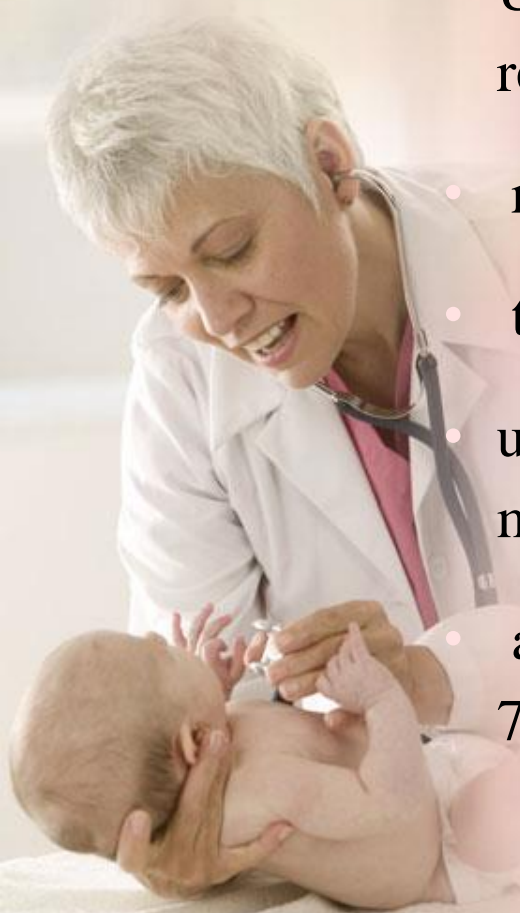
Investigations for prolonged jaundice

- Serum bilirubin level
- Conjugated fraction of bilirubin
- Liver function test (GGT, ALT, AST, Albumin)
- Coagulation profile (PT, PTT, INR)
- Abdominal ultrasound (gallbladder)
- HIDA scan (with follow through)
- Thyroid function test (TSH, free T4)
- Metabolic screen (urine for reducing substance)
- Hepatitis screen (TORCH)
- Liver biopsy (bile duct proliferation)
- FBC and film
- Blood group
- Maternal blood group
- Direct coombs test



PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)

- Under normal circumstances, the level of indirect-reacting bilirubin in umbilical cord serum is 1–3 mg/dL
- rises at a rate of <5 mg/dL/24 hr;
- thus, jaundice becomes visible on the 2nd–3rd day,
- usually peaking between the 2nd and 4th days at 5–6 mg/dL
- and decreasing to below 2 mg/dL between the 5th and 7th days of life



Cause of physiological jaundice

increased bilirubin production resulting from

- increased RBC mass,
- shortened RBC life span,
- hepatic immaturity of glucuronosyltransferase.



Risk factors for elevated indirect hyperbilirubinemia include:

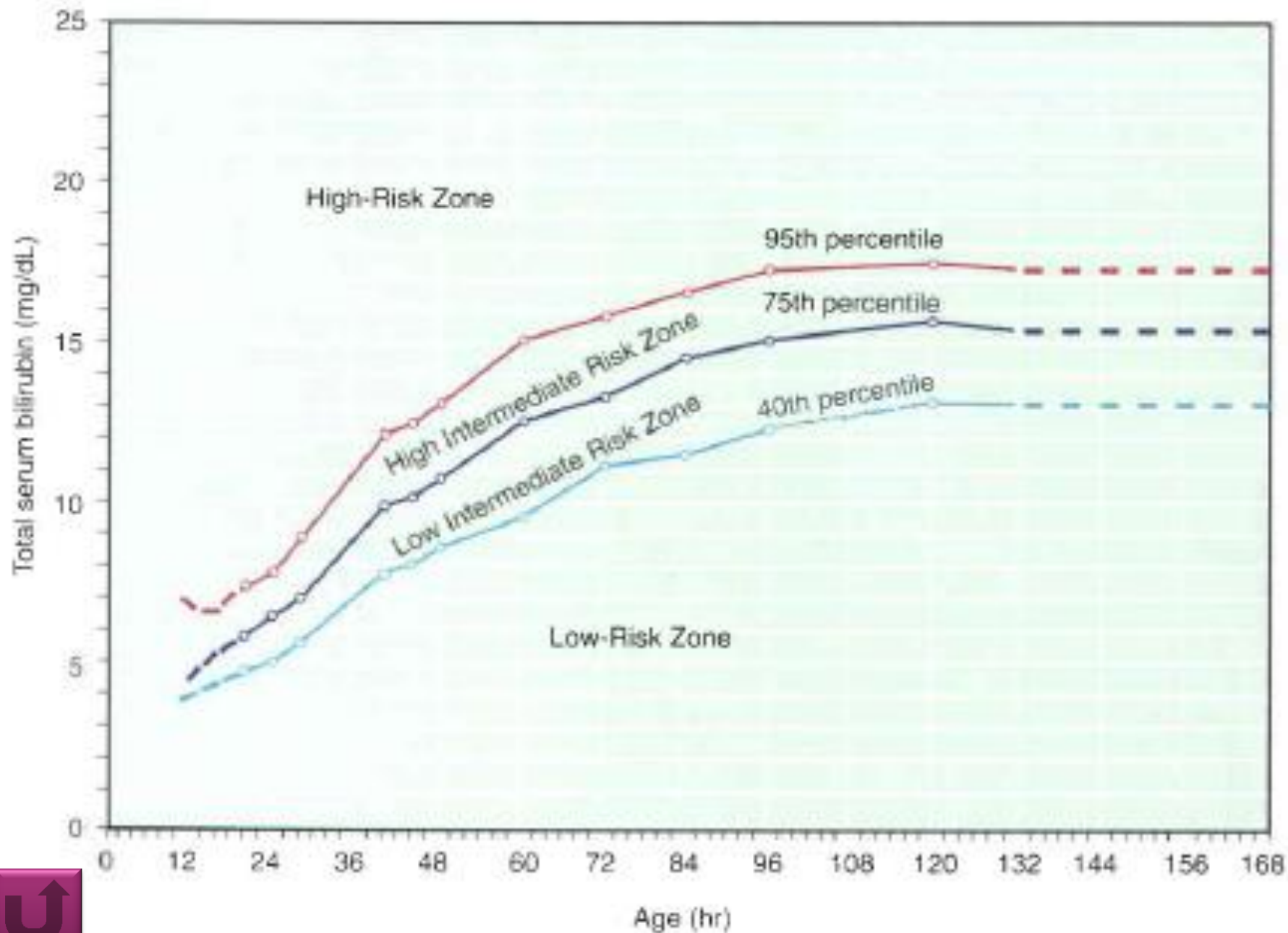
- maternal age, race (Chinese, Japanese, Korean, and Native American),
- maternal diabetes,
- oxytocin induction,
- prematurity,
- drugs vitamin K₃
- polycythemia,
- male sex,
- trisomy 21,
- cutaneous bruising, blood extravasation (cephalohematoma),
- breast-feeding,
- weight loss (dehydration or caloric deprivation),
- delayed bowel movement, and
- a family history/sibling who had physiologic jaundice)



Prediction of which neonates are at **risk for exaggerated physiologic jaundice** can be based on hour-specific bilirubin levels in the 1st 24–72 hr of life (Fig)

Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dl) by 10–14 days of life .





In **premature infants**, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants.

- Peak levels of 8–12 mg/dL are not usually reached until the 4th–7th day,
- and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion .



Pathological jaundice is suspected if :

1. it appears in the 1st 24–36 hr of life.
2. serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr,)
3. serum bilirubin is >12 mg/dL in full-term infants (especially in the absence of risk factors) or 10–14 mg/dL in preterm infants,
4. jaundice persists after 10–14 days of life,
5. direct-reacting bilirubin is >2 mg/dL at any time .



6. Other factors suggesting a nonphysiologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower bilirubin, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, and signs of kernicterus



JAUNDICE ASSOCIATED WITH BREAST-FEEDING

breast-feeding jaundice

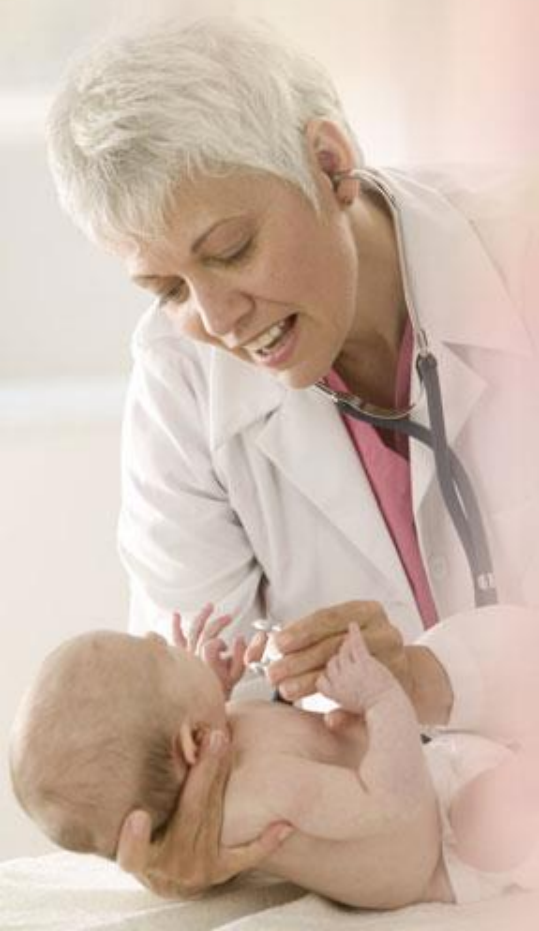
- occurs in the 1st week of life, in breast-fed infants who normally have higher bilirubin levels than formula-fed infants .
- Hyperbilirubinemia (>12 mg/dL) develops in 13 %of breast-fed infants in the 1st wk of life
- may be due to decreased milk intake with dehydration
- and/or reduced caloric intake .
- More in primi- mother,C/S





- Giving supplements of glucose water to breast-fed infants is associated with higher bilirubin levels,
- in part because of reduced intake of the higher caloric density of breast milk.





- Frequent breast-feeding(>10/24 hr),
- rooming-in with night feeding,
- discouraging 5 %dextrose or water supplementation,
- and ongoing lactation support may reduce the incidence of early breast-feeding jaundice

JAUNDICE ASSOCIATED WITH BREAST-FEEDING .

breast-milk jaundice

- Significant elevation in unconjugated bilirubin (breast-milk jaundice) develops in an estimated 2 % of breast-fed term infants
- after the 7th day of life,
- with maximal concentrations as high as 10–30 mg/dL reached during the 2nd–3rd week
- If breast-feeding is continued, the bilirubin gradually decreases but may persist for 3–10 wk at lower levels .



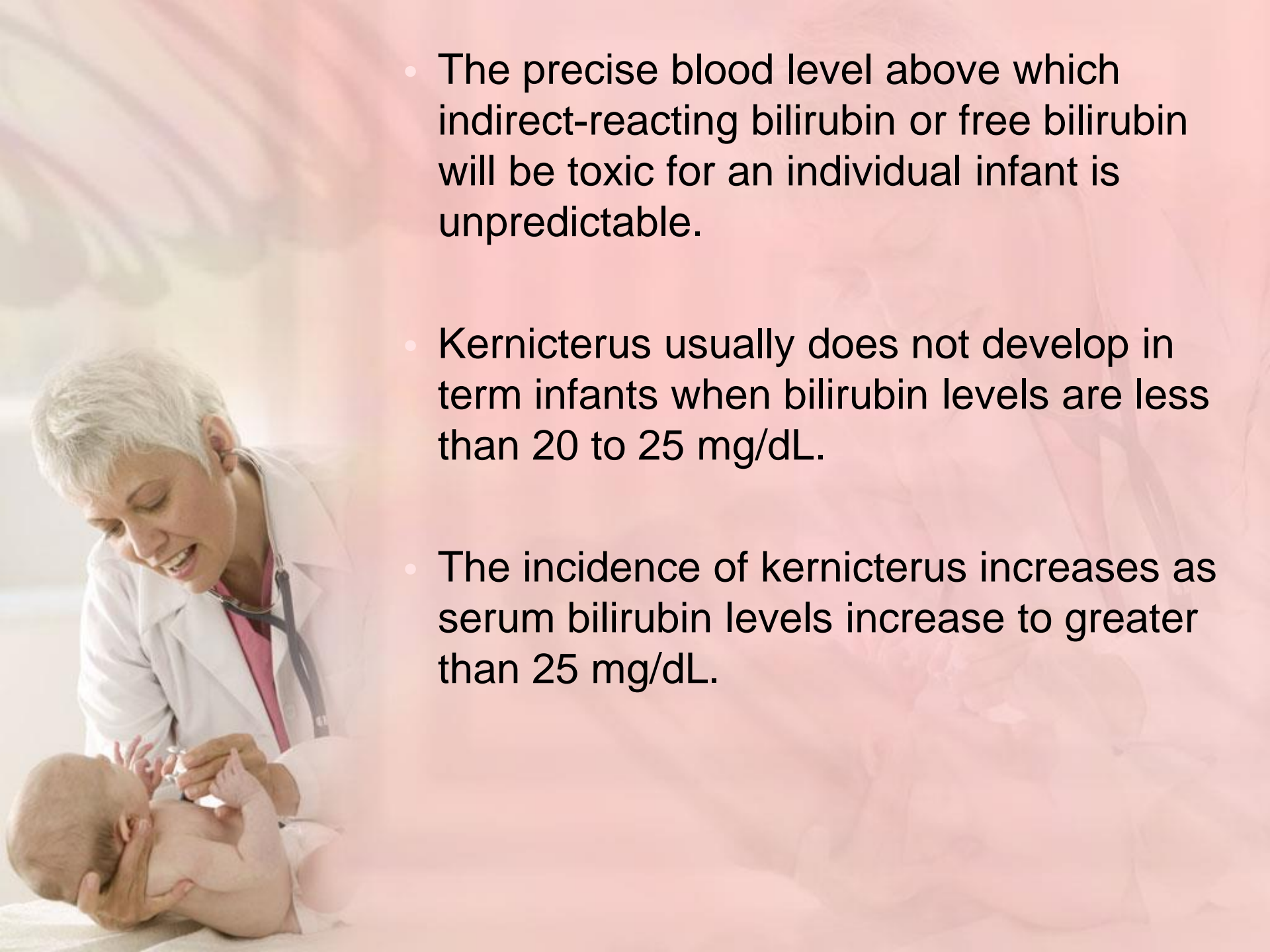


- If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal levels within a few days .
- With resumption of breast-feeding, bilirubin levels seldom return to previously high levels .
- Phototherapy may be of benefit .
- Although uncommon, kernicterus can occur in patients with breast-milk jaundice .
- The etiology of breast-milk jaundice is not entirely clear, but may be attributed to the presence of **glucuronidase** in some breast milk.

KERNICTERUS

- Kernicterus: or *bilirubin encephalopathy*, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei.

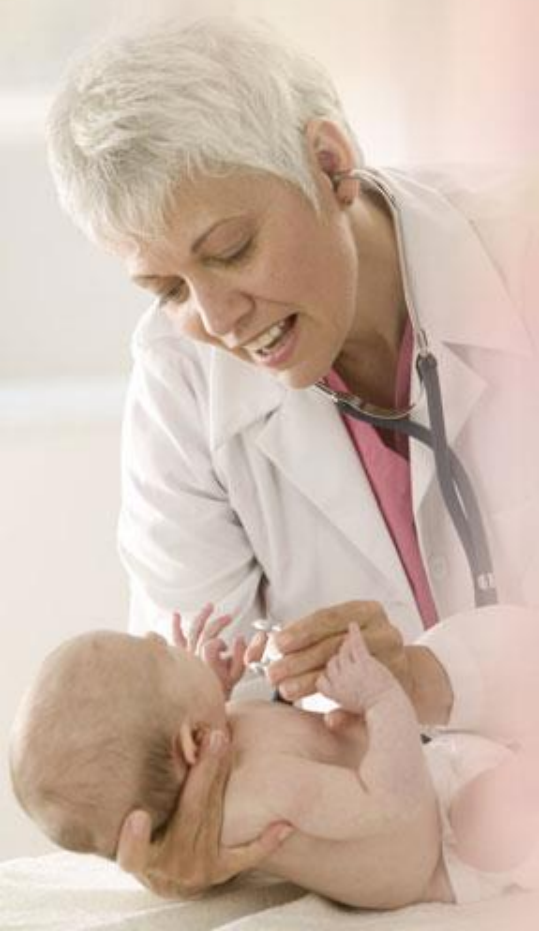




- The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable.
- Kernicterus usually does not develop in term infants when bilirubin levels are less than 20 to 25 mg/dL.
- The incidence of kernicterus increases as serum bilirubin levels increase to greater than 25 mg/dL.

- Kernicterus may be noted at bilirubin levels less than 20 mg/dL → in the presence of sepsis, meningitis, hemolysis, asphyxia, hypoxia, hypothermia, hypoglycemia, bilirubin-displacing drugs (sulfa drugs), and prematurity.
- Other risks for kernicterus in term infants are hemolysis, jaundice noted within 24 hours of birth, and delayed diagnosis of hyperbilirubinemia.
- .



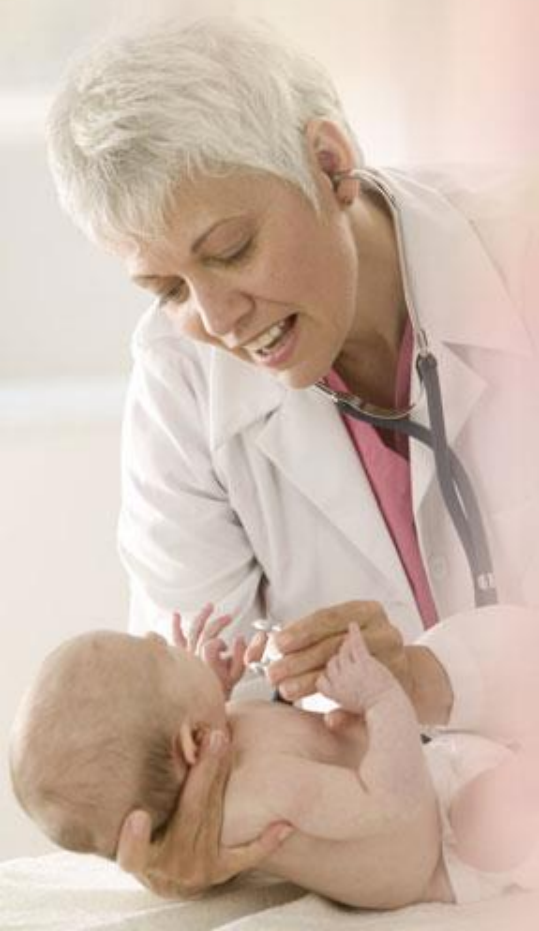


- In previously healthy, predominantly breast-fed term infants, kernicterus has developed when bilirubin levels exceed 30 mg/dL.
- Onset is usually in the 1st wk of life, but may be delayed to the 2nd–3rd wk
- Kernicterus has developed in extremely immature infants weighing less than 1000 g when bilirubin levels are less than 10 mg/dL because of a more permeable blood-brain barrier associated with prematurity.

CLINICAL MANIFESTATIONS

- Signs and symptoms of kernicterus usually appear 2–5 days after birth in term infants
- and as late as the 7th day in premature infants,
- but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period .





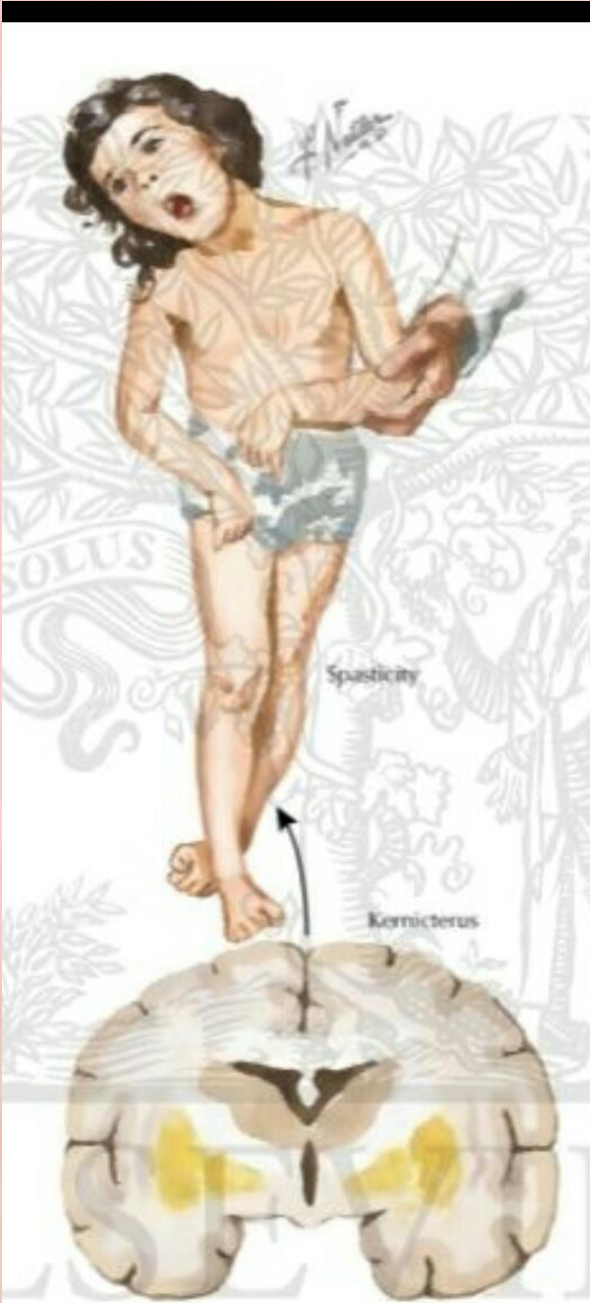
- The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate.
- Lethargy, poor feeding, and loss of the Moro reflex are common initial signs.
- Subsequently, the infant may appear gravely ill and prostrated, with diminished tendon reflexes and respiratory distress.
- **Opisthotonos** with a bulging fontanel, twitching of the face or limbs, and a shrill high-pitched cry may follow.



Opisthotonos



- In advanced cases, convulsions and spasm occur,
- with affected infants stiffly extending their arms in an inward rotation with the fists clenched .Rigidity is rare at this late stage.
- Infants with severe cases of kernicterus die in the neonatal period.
- Spasticity resolves in surviving infants, who may manifest later nerve deafness, choreoathetoid cerebral palsy, mental retardation, enamel dysplasia, and discoloration of teeth as permanent sequelae.



CLINICAL FEATURES OF KERNICTERUS

ACUTE FORM

Phase 1 (1st 1–2 days): poor sucking, stupor, hypotonia, seizures

Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever

Phase 3 (after the 1st wk): hypertonia

CHRONIC FORM

First year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills

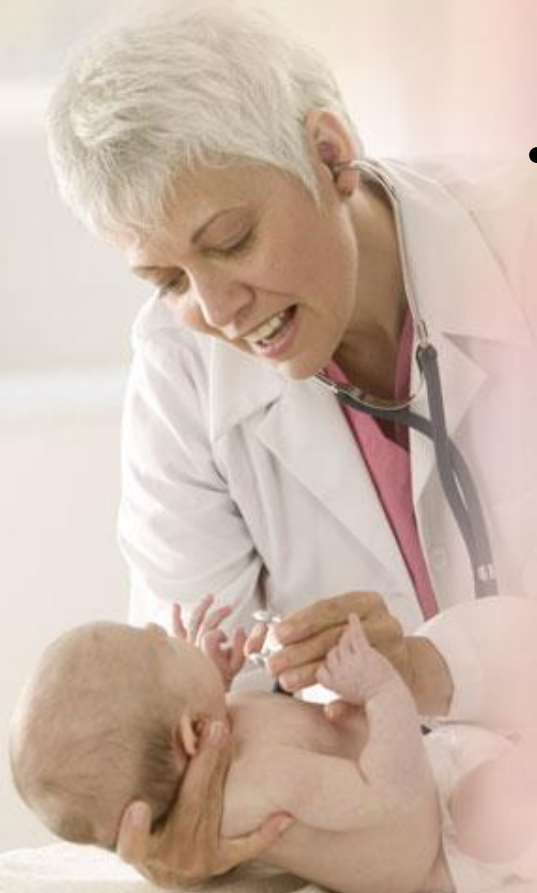
After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

THERAPY OF INDIRECT HYPERBILIRUBINEMIA

Phototherapy

is an effective and safe method for reducing indirect bilirubin levels.

- Bilirubin absorbs light maximally in the blue range (420–470 nm).
- Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels



MODE OF ACTION OF PHOTOTHERAPY

photochemical reaction
producing

configurational isomer

- the **reversible**, more water-soluble
- bypassing the liver's conjugation system
- **excreted in bile** without conjugation.

Unconjugated
bilirubin
(4Z, 15Z
configuration)

phototherapy
(light 425- to
475-nm)

- a more water-soluble **structural isomer** which does not spontaneously revert to unconjugated native bilirubin (**irreversible**)
- can be **excreted in urine**.

isomer 4Z,
15E
bilirubin

lumirubin

Conventional phototherapy

- is applied continuously, and the infant is turned frequently for maximal skin surface area exposure
- . It should be discontinued as soon as the indirect bilirubin concentration has reduced to levels considered safe with respect to the infant's age and condition.



Maximal intensive phototherapy

- Such therapy includes “special blue” fluorescent tubes,
- placing the lamps within 15–20 cm of the infant,
- and placing a fiberoptic phototherapy blanket under the infant's back to increase the exposed surface area.





- Because phototherapy may require 6–12 hr to have a measurable effect,
- it must be started at bilirubin levels below those indicated for exchange transfusion.
- In term infants, phototherapy is begun when indirect bilirubin levels are between 16 and 18 mg/dL.
- Phototherapy is initiated in premature infants when bilirubin is at lower levels

SUGGESTED MAXIMAL INDIRECT SERUM BILIRUBIN CONCENTRATIONS (MG/DL) IN PRETERM INFANTS

BIRTHWEIGHT (g)	UNCOMPLICATED	COMPLICATED ^[*]
1,000>	13–12	12–10
1,250–1,000	14–12	12–10
1,499–1,251	16–14	14–12
1,999–1,500	20–16	17–15
2,500–2,000	22–20	20–18



- Phototherapy is usually started at 50–70% of the maximal indirect level.
- If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximal bilirubin level, or if signs of kernicterus are evident, exchange transfusion is indicated.



- Serum bilirubin levels and hematocrit should be monitored every 4–8 hr in infants with hemolytic disease or those with bilirubin levels near toxic range for the individual infant.
- Others, particularly older infants, may be monitored less frequently.
- Serum bilirubin monitoring should continue for at least 24 hr after cessation of phototherapy in patients with hemolytic disease because unexpected rises in bilirubin may occur and require further treatment.

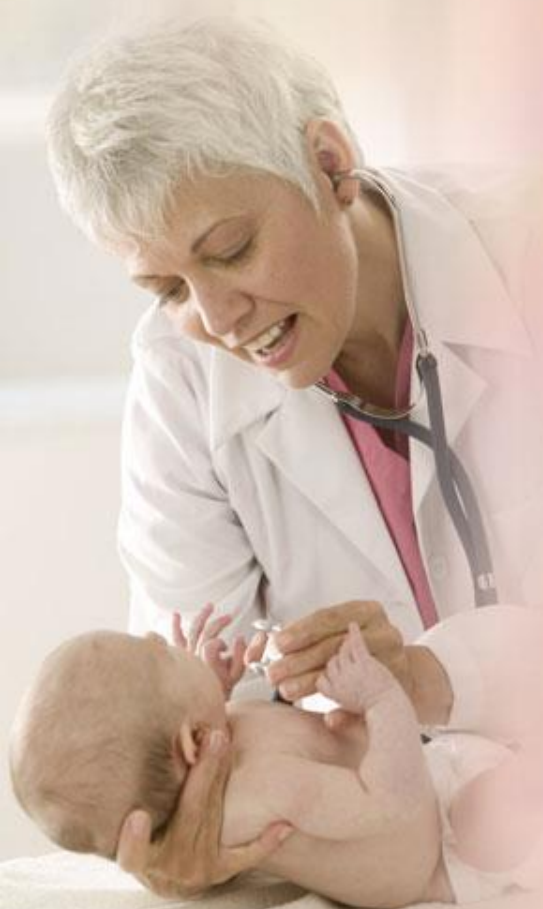
NOTES

- 👤 Skin color cannot be relied on for evaluating the effectiveness of phototherapy;
the skin of babies exposed to light may appear to be almost without jaundice in the presence of marked hyperbilirubinemia.
- 👤 Although not necessary for all affected infants, intravenous fluid supplementation added to oral feedings may be beneficial in dehydrated patients or those with high bilirubin levels nearing exchange transfusion.
- 👤 Dark skin does not reduce the efficacy of phototherapy.



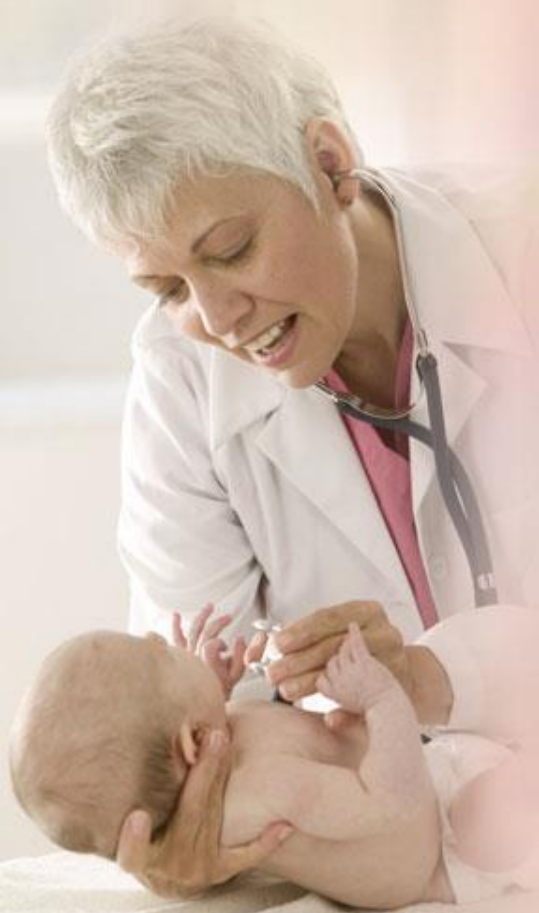
Complications of phototherapy

- increased insensible water loss
- diarrhea
- dehydration
- macular-papular red skin rash
- lethargy
- masking of cyanosis
- nasal obstruction by eye pads
- potential for retinal damage
- Skin bronzing may be noted in infants with direct-reacting hyperbilirubinemia



Exchange transfusion

- usually is reserved for infants with dangerously high indirect bilirubin levels who are at risk for kernicterus.
- As a rule of thumb, a level of 20 mg/dL for indirect-reacting bilirubin is the "exchange number" for infants with hemolysis who weigh more than 2000 g.
- Asymptomatic infants with physiologic or breast milk jaundice may not require exchange transfusion, unless the indirect bilirubin level exceeds 25 mg/dL.

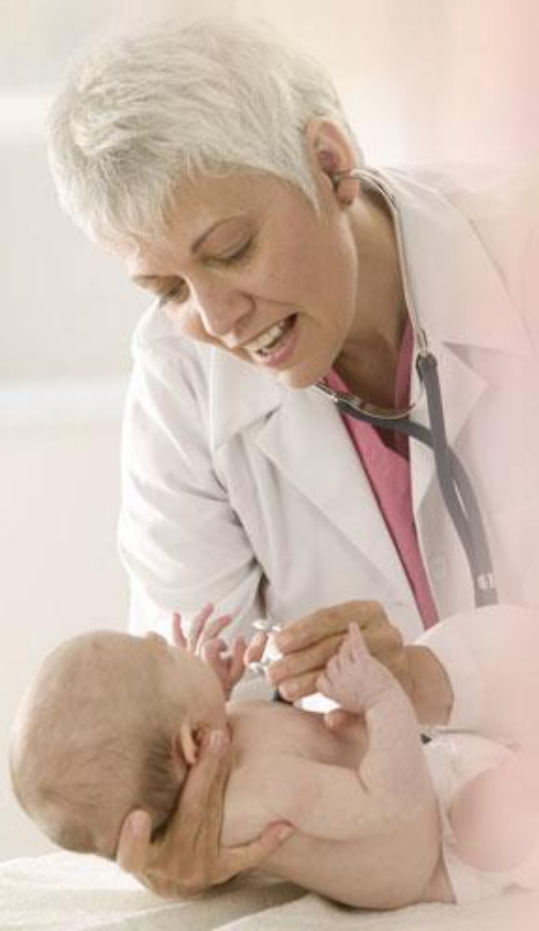


- The exchangeable level of indirect bilirubin for other infants may be estimated by calculating

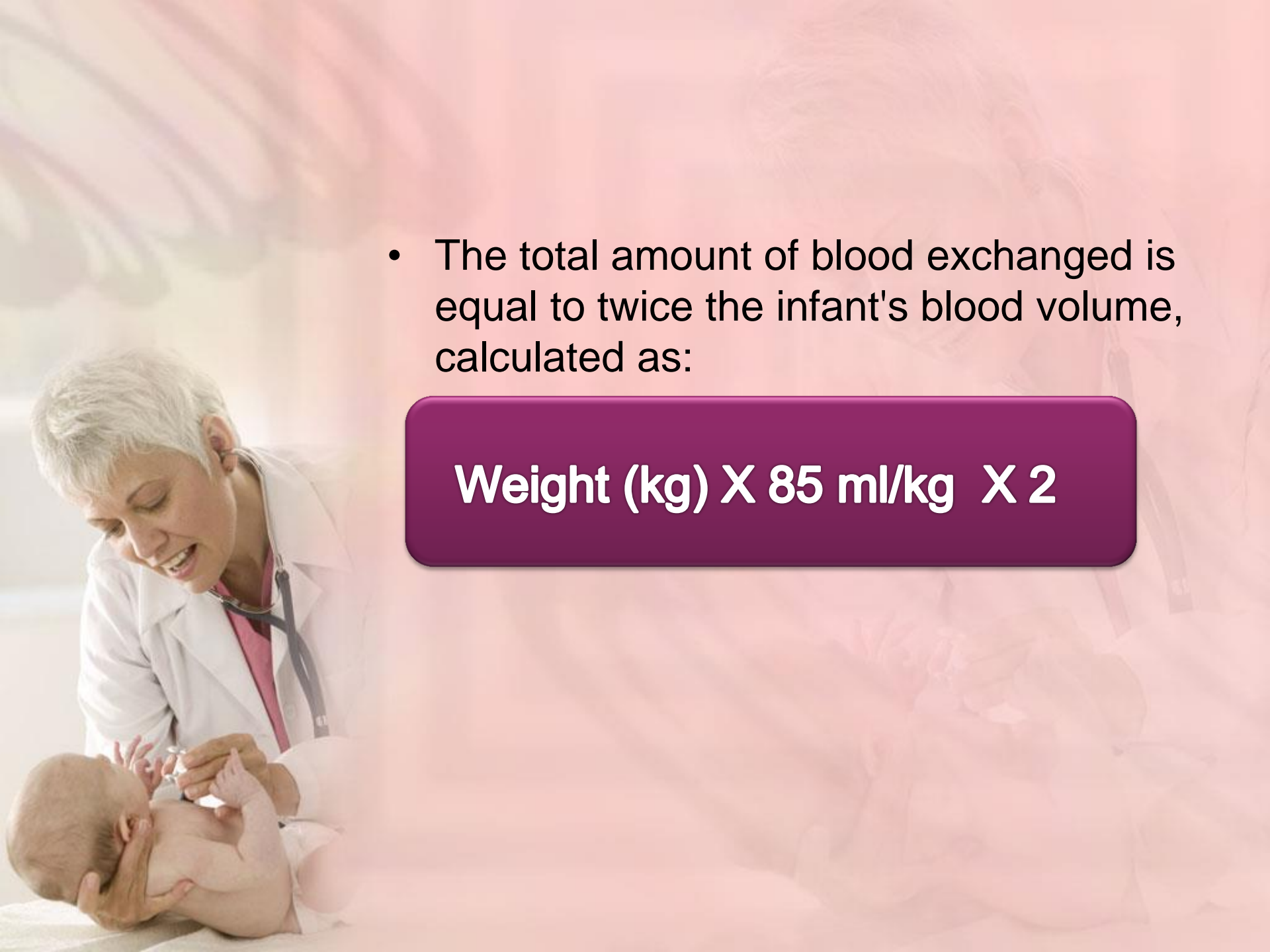
10% of the birth weight in grams

- the level in an infant weighing 1500 g would be 15 mg/dL. Infants weighing less than 1000 g usually do not require an exchange transfusion until the bilirubin level exceeds 10 mg/dL.





- Small infusions of fresh whole blood crossmatched with that of the mother and infant
- are alternated with withdrawals of an equivalent quantity of the infant's blood, which is discarded.
- Depending on the size of the infant, aliquots of 5 to 20 mL per cycle are withdrawn and infused,
- with the total procedure lasting 45 to 60 minutes.



- The total amount of blood exchanged is equal to twice the infant's blood volume, calculated as:

$$\text{Weight (kg)} \times 85 \text{ ml/kg} \times 2$$



- This volume should remove 85% of the infant's RBCs (the source of bilirubin), maternal antibodies.
- The exchange transfusion usually is performed through an umbilical venous



- The level of serum bilirubin immediately after the exchange transfusion declines to levels that are about half of those before the exchange;
- levels rebound 6 to 8 hours later as a result of continued hemolysis and redistribution of bilirubin from tissue stores.

Complications of exchange transfusion

Related to the blood	Graft versus reaction	
	infection	Hepatitis B,C ,HIV,CMV..)
	Metabolic	Hypoglycemia Hypocalcemia Hypomagnesemia hyperkalemia
	Anemia/polycythemia	
Related to the catheter	Perforation	
	Haemorrhage	
	vasospasm	
Related to the procedure	Hypo-or hyperthermia	
	Volume overload	
	Necrotizing enterocolitis	
	arrythmia	
Late complications	Late anemia	
	Inspissated bile syndrome	persistent icterus with significant elevations in direct and indirect bilirubin in infants with hemolytic disease. The cause is unclear, but the jaundice clears spontaneously within a few weeks or months.
	Portal vein thrombosis and portal hypertension	

Thank you

