Neonatal Jaundice

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2019/2020

Definition

Neonatal jaundice:

Yellowish discoloration of the skin and/or conjunctiva caused by bilirubin deposition

Definition

Hyperbilirubinemia

Bilirubin > normal level

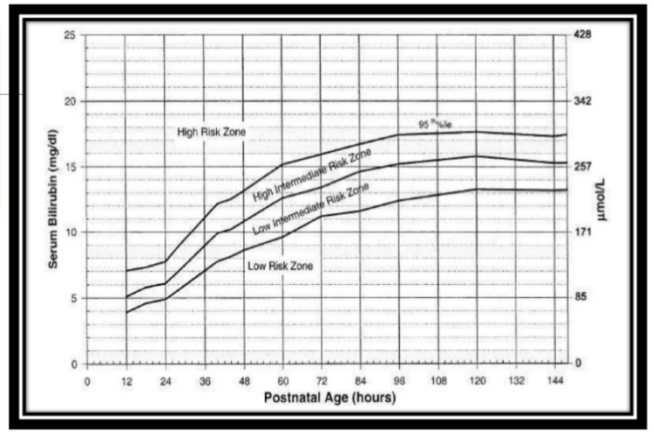
- The state of excessive amount of bile pigment billirubin in the blood visibly manifested as jaundice.

Definitions
Other Defenetions

Neonatal hyperbilirubinemia in infants ≥35 weeks gestational age (GA)

Normogram for designation of Hyperbilirubinemia risk based on hour specific bilirubin values.

Adapted from bhutani et al.



Diagnose hyperbilirubinemia
Bilirubin measured at >95th percentile for age in hours. Using Bhutani nomogram

Definitions

Severe neonatal hyperbilirubinemia

Defined as a Total serum Bilirubin

>25 mg/dL (428 micromol/L) in Term Newborns .

Ref

A *Bhutani VK, Johnson LH*

Clin Chem. 2004 Mar; 50(3):477-80.

It is associated with an increased risk for bilirubin-induced neurologic dysfunction (BIND).

Real Life Scenario

- 3 days old (73 hrs),
- 2.7 kg
- male,
- born at 36 wks.
- Mom is primi,
- group A +.

- ❑ He is breast feeding exclusively.
- ❑ Mother brings him to your office because he is sleepy and feeding less today.
- ❑ Exam: he is hard to arouse and has shrill cry.
- ❑ looks jaundiced.
- ❑ Weight 2.3kg.

✓ Total bili 25 mg/ dl (425 µmol/L).
✓ Indirect 23 mg/dl (391 µmol/L).
✓ Hgb 13.5 gm/dl
✓ direct Coombs is negative.

What is your diagnosis? (BIND)

- Bilirubin-Induced Neurologic Dysfunction (BIND)
  - Acute signs = Acute Bilirubin Encephalopathy (ABE) include: **poor feeding, lethar**gy, hypertonia and retrocollis, opithotonus, **shrill cry**; and irritability alternating with **increasing lethargy.**
    - Acute advanced signs are cessation of feeding, bicycling movements, inconsolable irritability and crying, possible seizures, fever, and coma
  - Kernicterus is the chronic and permanent sequelae of BIND.

Objectives

Why this lecture

Bilirubin metabolism

What special in neonates

Types and Causes of neonatal Jaundice

Breast feeding and hydration

Assessment of neonate at risk of sever hyperbilirubinemia

Management

- Guidelines
- Work UP

Treatment

- Prevention
- treatment

Epidemiology of Jaundice

- 85% of infants > 35 weeks gestation have visible jaundice due to hyperbilirubinemia in the first week after birth – Bhutani, Stark et al, J Pediatr 2012 Epub
- Nearly all preterm newborns have hyperbilirubinemia

- However 10% term -25% of late preterm require intervention

Has a complication

Bilirubin-Induced Neurologic Dysfunction (BIND)

- ***Acute sequelae*** **of BIND :**

Acute signs (**Acute Bilirubin Encephalopathy**)

- ***Chronic and permanent sequelae*** **of BIND**

Kernicterus :it is chronic sequelae

Neonatal Jaundice is HOT topic in Paediatric Journals

Original Art

Eur J Pediatr (2011) 170:461–467
DOI 10.1007/s00431-010-1310-8

ORIGINAL PAPER

Early intravenous immunoglobin (two-dose regimen) in the management of severe Rh hemolytic disease of newborn—a prospective randomized controlled trial

Mohsen Saleh Elalfy · Nancy Samir Elbarbary · Heba Wegdan Abaza

Received: 14 August 2010 / Accepted: 15 September 2010 / Published online: 6 October 2010

Neonatology

Original Paper

Neonatology 2011;100:57–63
DOI: 10.1159/000321990

Received: April 21, 2010
Accepted after revision: September 28, 2010
Published online: January 5, 2011

Severe Neonatal Hyperbilirubinemia and Adverse Short-Term Consequences in Baghdad, Iraq

2011

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Vinod K. Bhutani[b]

[a]Division of Pediatrics, College of Medicine, Baghdad University and Children Welfare Teaching Hospital Medical City Complex, Bab Al-Muadham, Baghdad, Iraq; [b]Department of Neonatal and Developmental Medicine, Lucile Packard Children's Hospital, Stanford University, Palo Alto, Calif., USA

Key Words

Severe neonatal hyperbilirubinemia · Newborn jaundice · Acute bilirubin encephalopathy · Kernicterus

Abstract

Background: Severe neonatal hyperbilirubinemia, when unmonitored or untreated, can progress to acute bilirubin encephalopathy (ABE). Initiatives to prevent and eliminate post-icteric sequelae (kernicterus) are being implemented to allow for timely interventions for bilirubin reduction. ***Objectives:*** We report an observational study to determine the clinical risk factors and short-term outcomes of infants admitted for severe neonatal jaundice. ***Methods:*** A post-discharge medical chart review was performed for a cohort of infants admitted for management of newborn jaundice to the Children Welfare Teaching Hospital during a 4-month period in 2007 and 2008. Immediate outcomes included severity of hyperbilirubinemia, association of ABE, need and impact of exchange transfusion, and survival. Short-term post-discharge follow-up assessed for post-icteric sequelae. ***Results:*** A total of 162 infants were admitted for management of severe jaundice. Incidences of severe sequelae were: advanced ABE (22%), neonatal mortality within 48 h of admission (12%) and post-icteric sequelae (21%). Among the cohort, 85% were <10 days of age (median 6 days, IQR 4–7 days). Readmission total serum bilirubin ranged from 197 to 770 μM; mean 386 ± 108 SD μM (mean 22.6 ± 6.3 SD mg/dl; median 360, IQR 310–445 μM). The major contributory risk factor for the adverse outcome of kernicterus/death was admission with advanced ABE (OR 8.03; 95% CI 3.44–18.7). Other contributory factors to this outcome, usually significant, but not so for this cohort, included home delivery, sepsis, ABO or Rh disease. Absence of any detectable signs of ABE on admission and treatment of severe hyperbilirubinemia was associated with no adverse outcome (OR 0.34; 95% CI 0.16–0.68). ***Conclusions:*** Risks of mortality and irreversible brain injury among healthy infants admitted for newborn jaundice are urgent reminders to promote education of communities, families and primary health care providers, especially in a fractured health system. Known risk factors for severe hyperbilirubinemia were overwhelmed by the effect of advanced ABE.

Introduction

All newborns are at risk for jaundice or some degree of hyperbilirubinemia [1, 2]. Extreme neonatal hyperbilirubinemia, especially when unmonitored or untreated, is associated with chronic bilirubin encephalopathy or

1 March 2019

Obstet Gynecol. 2019 Mar 11. doi: 10.1097/AOG.0000000000003172. [Epub ahead of print]

Association of a Delayed Cord-Clamping Protocol With Hyperbilirubinemia in Term Neonates.

Yang S[1], Duffy JY, Johnston R, Fall C, Fitzmaurice LE.

Author information

Abstract

OBJECTIVE: To evaluate the implementation of a delayed cord-clamping protocol at an academic medical center, and its short-term associations on term neonates.

METHODS: This was a retrospective cohort study of women aged 18 years or older delivering a term neonate at an academic medical center before and 5-7 months after implementation of a universal delayed cord-clamping protocol (October-December 2015 and October-December 2016, respectively). The primary outcome measure was the mean peak neonatal transcutaneous bilirubin level, with secondary outcome measures including mean initial transcutaneous bilirubin levels, mean serum bilirubin levels, number of serum bilirubin levels drawn, incidence of clinical jaundice, and phototherapy.

RESULTS: Protocol adherence was 87.8%. Data are presented on 424 neonates. The mean peak neonatal transcutaneous bilirubin levels were significantly higher among neonates in the postprotocol group (10.0±3.4 mg/dL vs 8.4±2.7 mg/dL, P<.01). More neonates in the postprotocol group were diagnosed with jaundice (27.2% vs 16.6%; odds ratio [OR] 1.88; 95% CI 1.17-3.01) and required serum blood draws (43.7% vs 29.4%; OR 1.86; 95% CI 1.25-2.78). However, there were no differences in mean peak serum bilirubin levels between groups (9.7±3.0 mg/dL vs 9.1±3.1 mg/dL, P=.17) or need for phototherapy (5.2% vs 6.6%, OR 1.28; 95% CI 0.57-2.89).

CONCLUSION: Implementation of a delayed cord-clamping protocol for term neonates was associated with significantly higher mean transcutaneous bilirubin levels, an increased number of serum blood draws, and more clinical diagnoses of jaundice, although there was no increase in the incidence of phototherapy.

PMID: 30870273 DOI: 10.1097/AOG.0000000000003172

1. **Neonatal Jaundice** and Developmental Impairment among Infants in Kilifi, Kenya.
Magai DN, Mwaniki M, Abubakar A, Mohammed S, Gordon AL, Kalu R, Mwangi P, Koot HM, Newton CR.
Child Care Health Dev. 2020 Jan 24. doi: 10.1111/cch.12750. [Epub ahead of print]
PMID: 31978271
Similar articles

2. Efficacy of double versus single phototherapy in treatment of **neonatal jaundice**: a meta-analysis.
Nizam MA, Alvi AS, Hamdani MM, Lalani AS, Sibtain SA, Bhangar NA.
Eur J Pediatr. 2020 Jan 22. doi: 10.1007/s00431-020-03583-x. [Epub ahead of print]
PMID: 31970487
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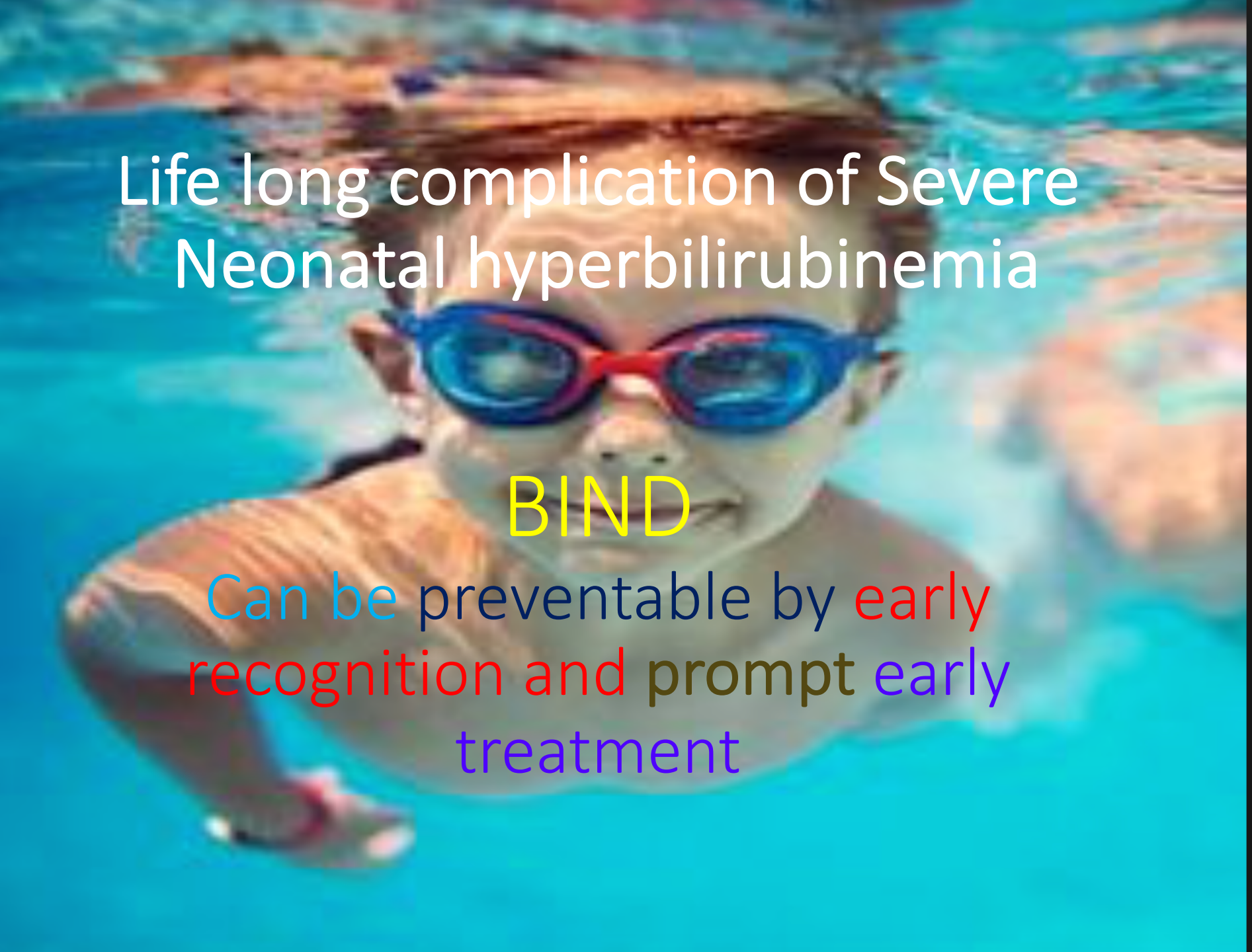
3. Use of multiple nursing interventions (cluster nursing) in ABO hemolytic disease of neonates and evaluation of its effect.
Wang W, Tang C, Ji QL, Xiu H, Shao H, Yu XM.
J Int Med Res. 2020 Jan;48(1):300060519887630. doi: 10.1177/0300060519887630. No abstract available.
PMID: 31939321
Similar articles

4. Baby-Friendly Hospital Initiative Is Associated with Lower Rates of **Neonatal** Hyperbilirubinemia.
Hudson JA, Charron E, Maple B, Krom M, Heavner-Sullivan SF, Mayo RM, Dickes L, Rennert L.
Breastfeed Med. 2020 Jan 14. doi: 10.1089/bfm.2019.0220. [Epub ahead of print]
PMID: 31934778
Similar articles

5. Breastfeeding during breast milk **jaundice** - a pathophysiological perspective.
Prameela KK.
Med J Malaysia. 2019 Dec;74(6):527-533.
PMID: 31929480 **Free Article**
Similar articles

6. Timing of umbilical cord clamping and **neonatal jaundice** in singleton term pregnancy.
Qian Y, Lu Q, Shao H, Ying X, Huang W, Hua Y.
Early Hum Dev. 2020 Jan 8;142:104948. doi: 10.1016/j.earlhumdev.2019.104948. [Epub ahead of print]
PMID: 31927308 **Free Article**



Life long complication of Severe Neonatal hyperbilirubinemia

BIND

Can be preventable by early recognition and prompt early treatment

Objectives

Why this lecture

Bilirubin metabolism

Bilirubin measurement

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- Work UP

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- treatment

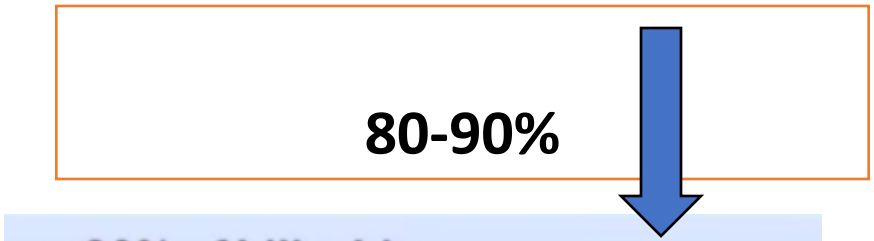
Why to know the bilirubin production and metabolism

To Know the cause

- Physiologic

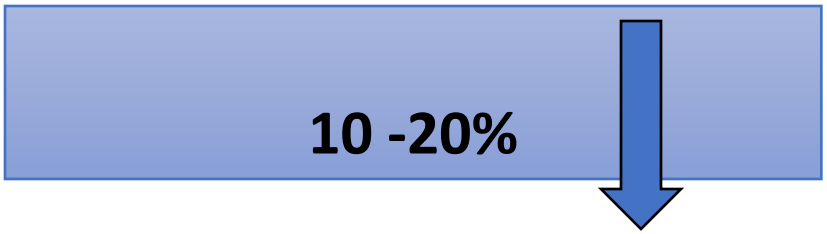
- Pathologic

Bilirubin production: Source



- 80% of bilirubin
  - Degradation of the hemoglobin
    - Old or injured RBCs

-Or from Ineffective erythropoiesis



- Breakdown of hemoproteins in the liver
  - Catalases
  - Cytochrome oxidases

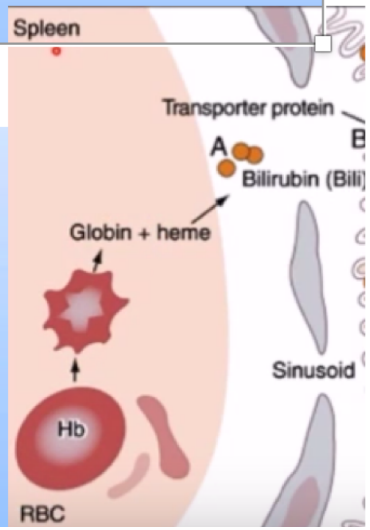
Note:

Ineffective erythropoiesis =. Destruction of newly formed RBC in bone marrow itself

Site of bilirubin metabolism

- Reticuloendothelial system
- Consists primarily of monocytes and macrophages

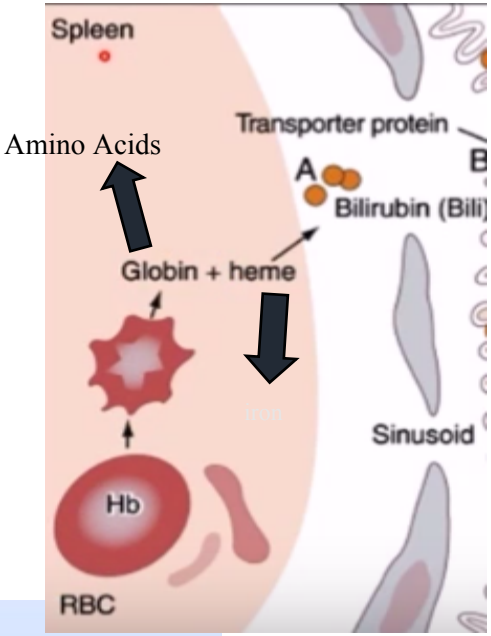
- Spleen
  - Largest unit
- Liver
- Bone marrow



Bilirubin synthesis

Macrophages

- Remove old erythrocytes from the circulation
  - Lifespan of RBCs =120 days
- Hemoglobin broken down into
  - Iron
    - Reutilized
  - Globin
    - Degraded and returned to the amino acid pool



Heme

Heme ---------- Biliverdin (green color) + CO + Iron

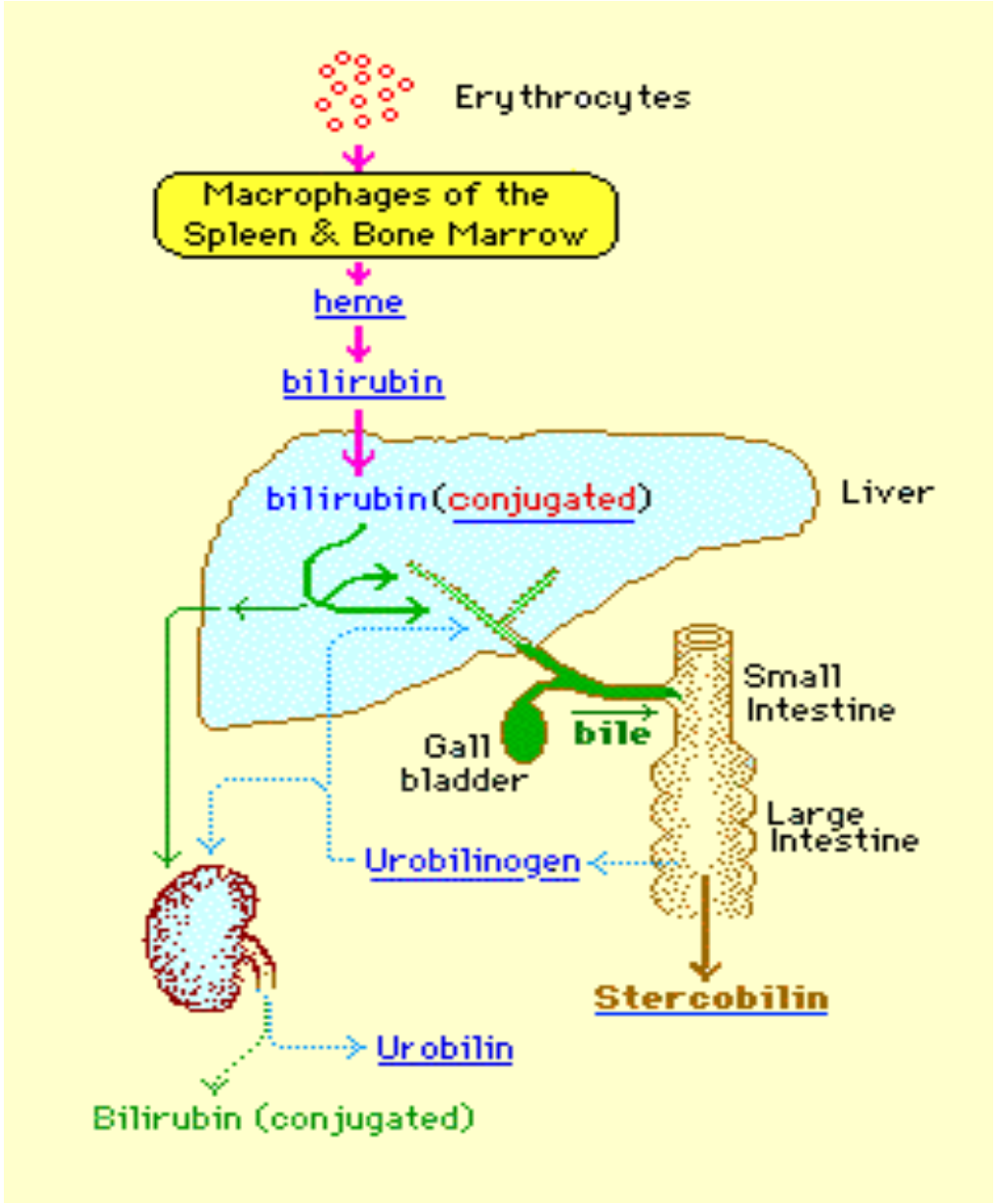
oxygenase

↓ Biliverdin reductase

↓

Bilirubin

(released into blood)

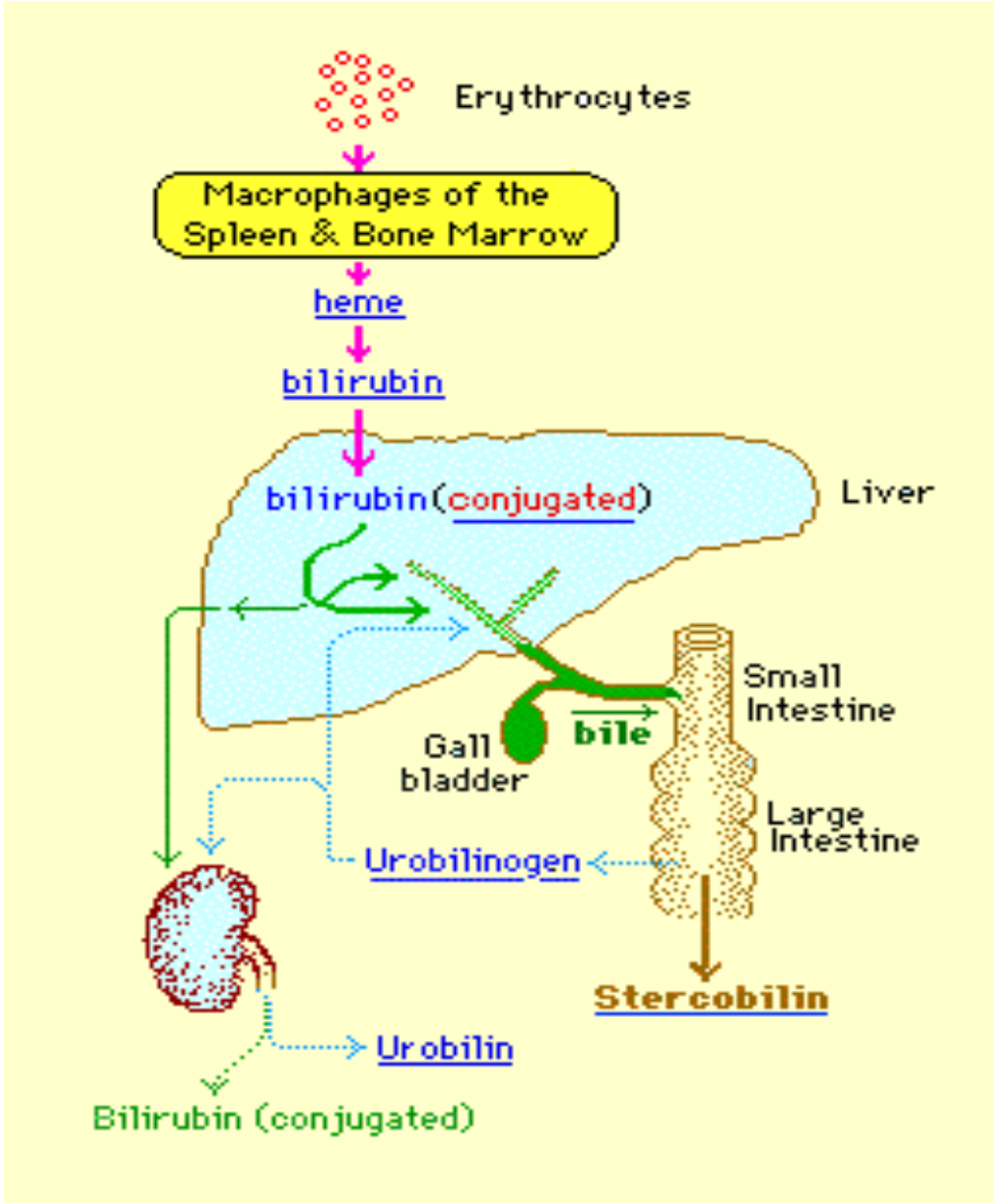


Why to know the

Bilirubin Production

&

Metabolism



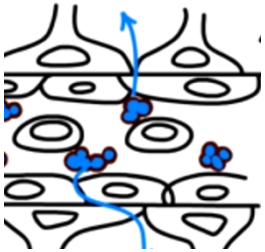
Why to know the

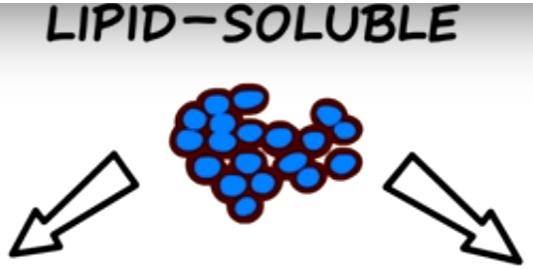
Bilirubin Production

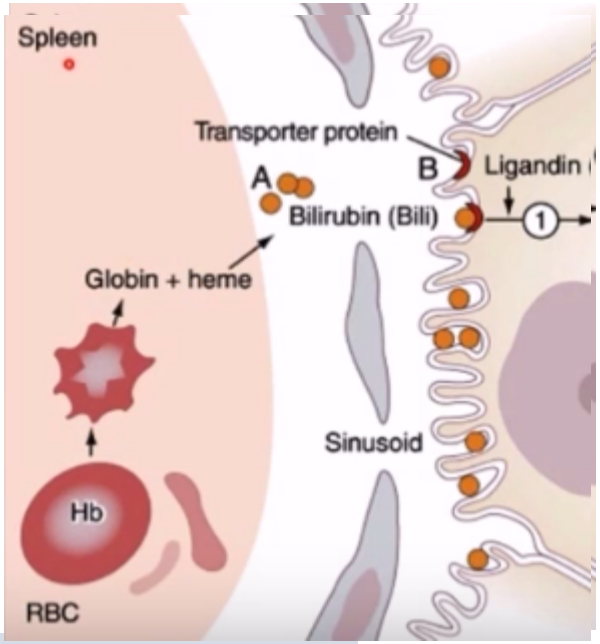
&

Metabolism

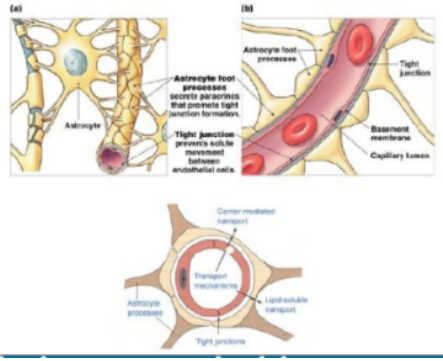
Unconjugated Bilirubin in plasma





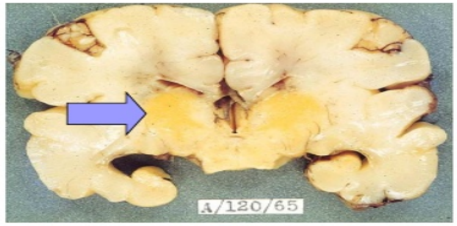


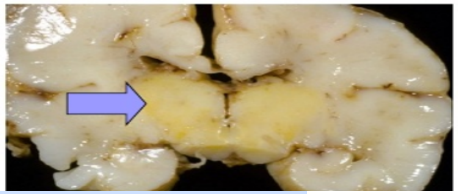
Blood-brain barrier



- Bound to albumin (reversible binding)
- Can be displaced if
  - Drugs (valium, ceftriaxone, sulfa)
  - Free fatty acids

Unconjugated Bilirubin (UB)





- Not soluble in water
- Potentially toxic
- Made soluble and less toxic by its reversible, binding to albumin

No bilirubin in urine

- Bilirubin in blood tightly bound to albumin
- Cannot appear in the urine
  - Albumin not filtered by glomerulus

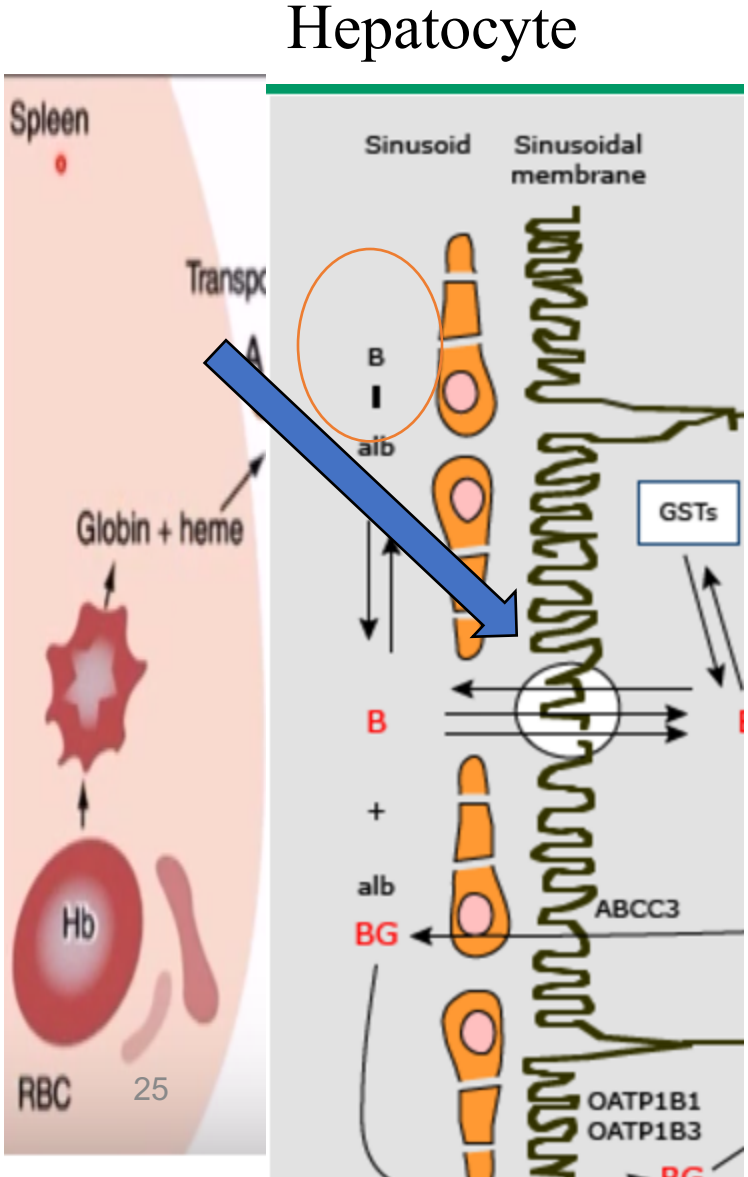
Normal level

- < 1.5 mg/dL
  - Almost entirely bilirubin (unconjugated)
    - Tightly but reversibly bound to albumin

Unless
- Liver disease
- Biliary obstruction

Hepatic uptake – Circulating bilirubin

- Bilirubin is transported to the liver Through carrier proteins
  - organic anion transporter protein OATP-2



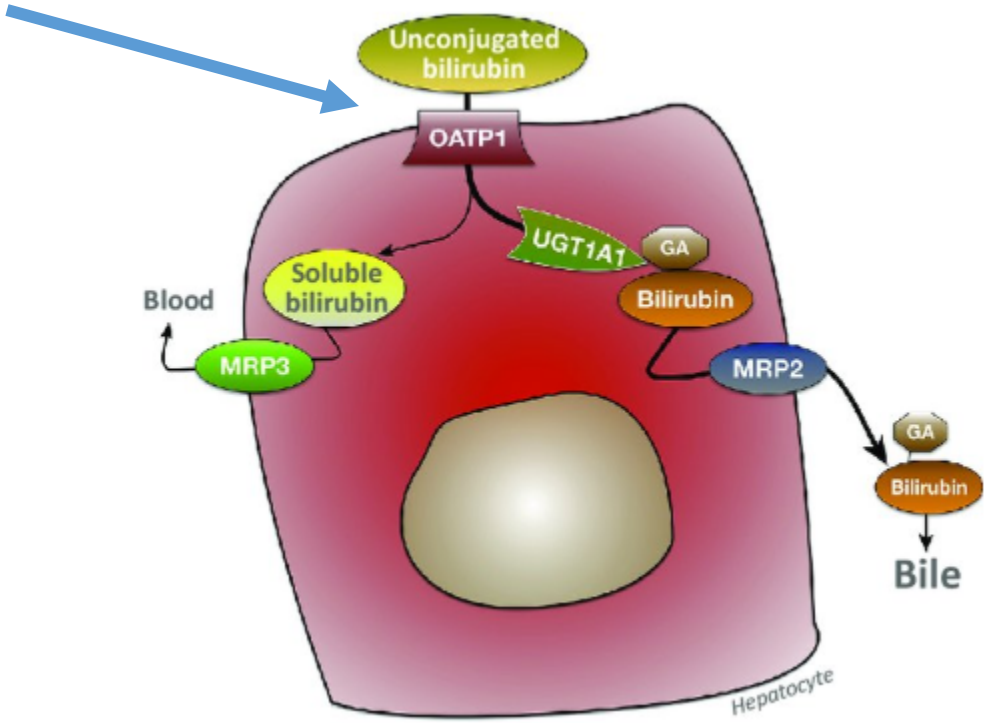
Role of **u**ridine diphosphate **g**lycosyl**t**ransferase

conjugation is catalyzed by the enzyme **u**ridine diphosphate **g**lycosyl **t**ransferase 1A1

” *UGT1A1* gene (ID: 54658) is a part of a complex locus **encoding** 13 UDP-**g**lucu**rono**syltransferases)

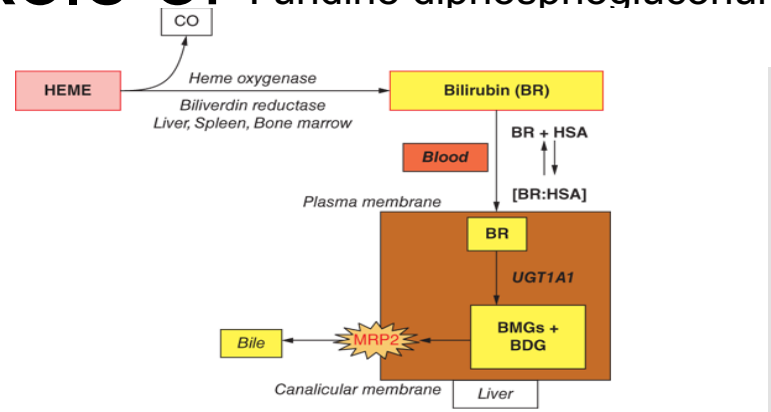
What does UGT1 stand for?
UGT1 stands for
"UDP-glucuronosyltransferase family 1

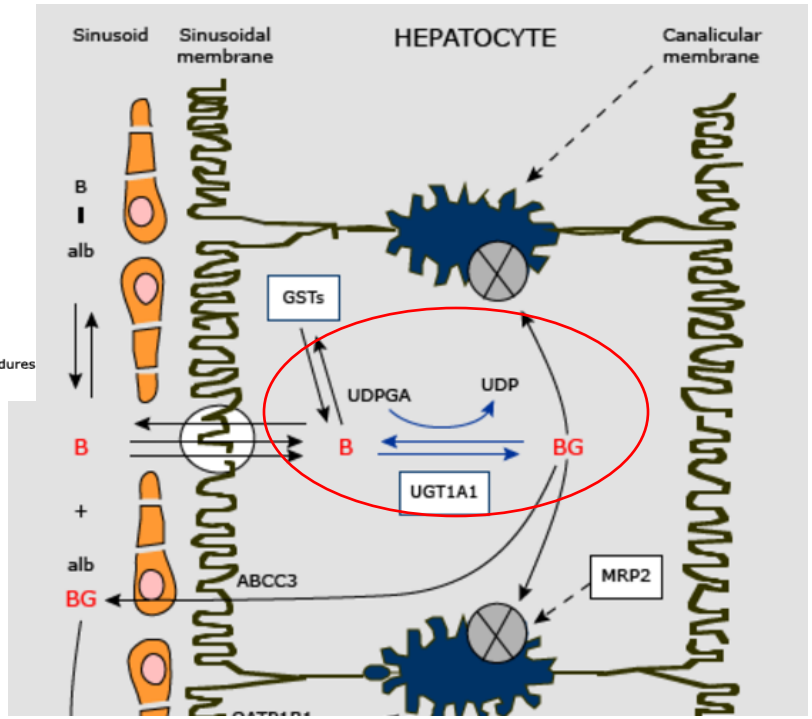
Hepatic uptake – Circulating bilirubin



Conjugation – In Hepatocytes

Role of : uridine diphosphogluconurate glucuronosyltransferase (UGT1A1)





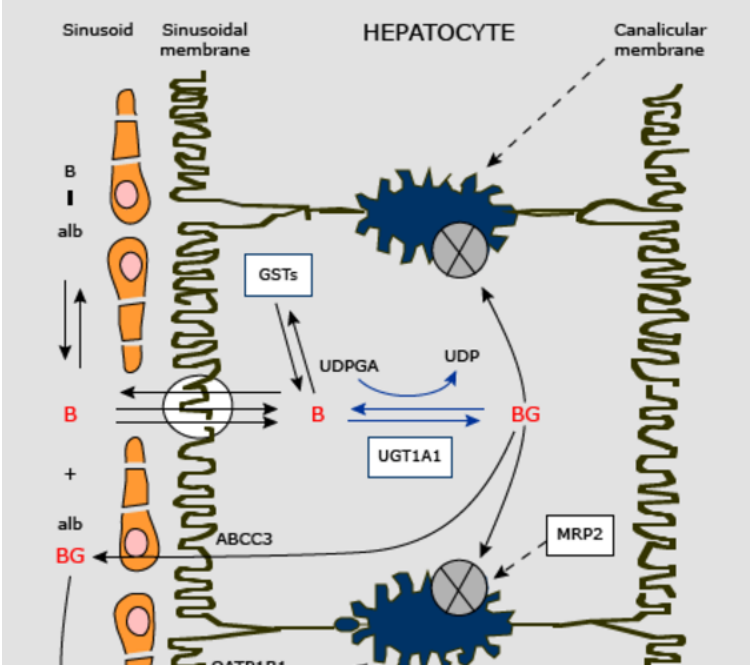
- Actively excreted into bile

Bilirubin in bile

- 85%
  - Diglucuronides
- 15%
  - Monoglucuronide

Ethnic variation in conjugation ability

- Polymorphisms in the UGT1A1 gene
  - Due to differences in the number of thymine-adenine (TA) repeats in the promoter region of the gene
  - vary among individuals of Asian, African, and Caucasian ancestry
  - These polymorphisms correlate with decreases in UGT1A1 enzyme activity resulting in increased total bilirubin levels.



Bilirubin Conjugation abnormalities in liver

Conjucation abnormalities:

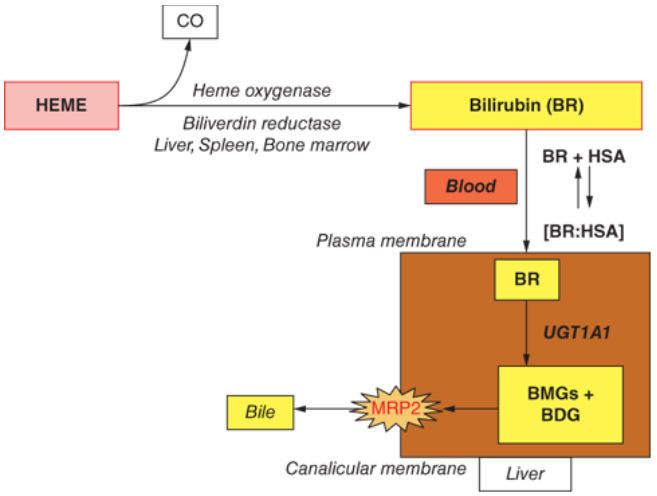
- UGT1A1 polymorphism
- Crigler –Najar Syndrome
- Gilber Syndrome
- Inhibitory factors for hepatic UGT1A!

Inhibitory factor(s) for hepatic UGT1A1

- Can be secreted in the milk of some mothers (breast milk jaundice).

- Can be present in maternal plasma may be transplacentally transferred to the fetus (the Lucey Driscoll syndrome).

Biliary excretion –for Hepatocytes
Role of : **Multi resistant associated proteins 2 (MRP2)**



Source: David K. Stevenson, Ronald S. Cohen, Philip Sunshine: Neonatology: Clinical Practice and Procedures
www.accesspediatrics.com

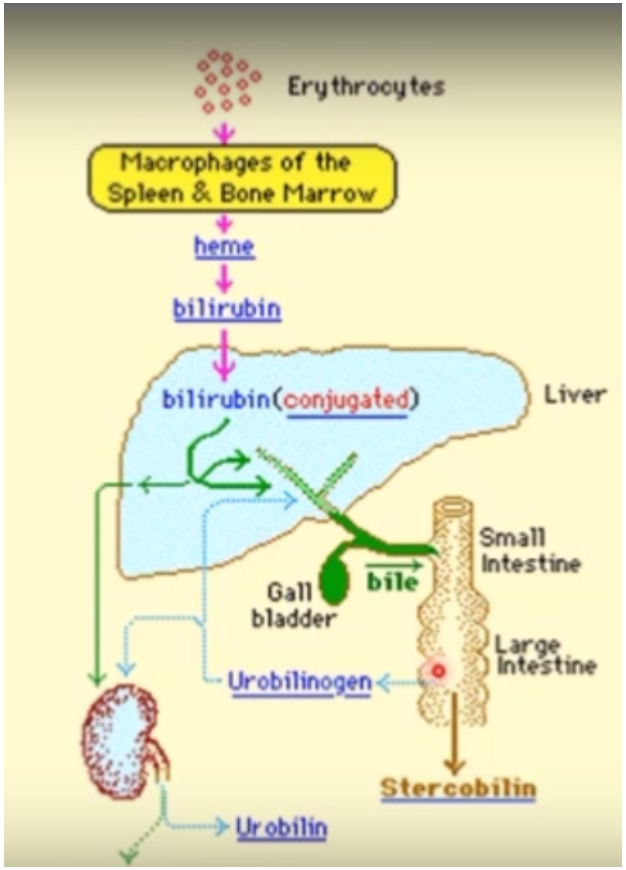
- Actively transported into the bile canaliculus
  - ATP-dependent export pump
    - Protein in the hepatocyte apical membrane
      - Multidrug resistance-associated protein 2

Enhanced bile flow by phenobarbital

Dubin-Johnson syndrome

- Abnormal MRP2 (multidrug resistance-associated protein 2)
- Failure to actively excrete conjugated bilirubin into the biliary cannaliculi
  - Conjugated bilirubin increases in the blood

Bilirubin metabolism In adult



Unconjugated bilirubin

- Reduced by normal gut bacteria
  - Colorless urobilinogen

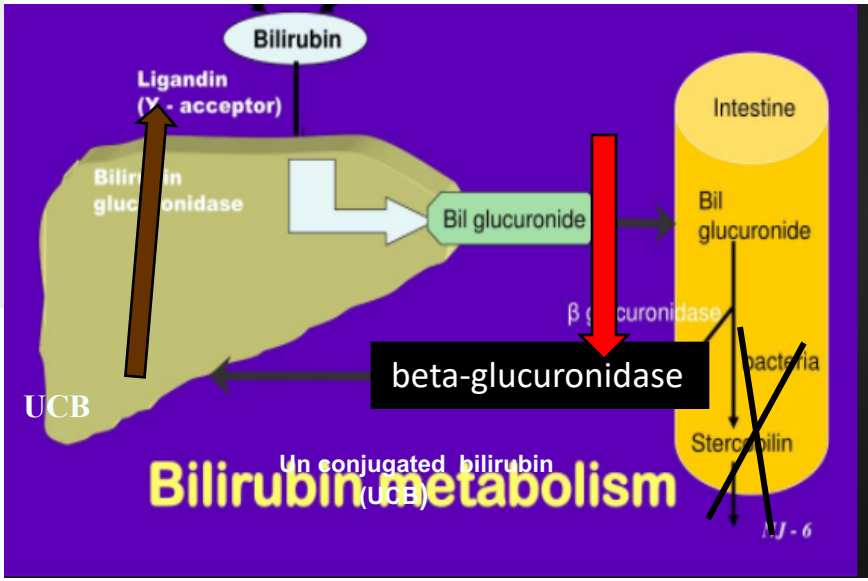
Urobilinogen

- Oxidized in the colon to colored stercobilinogen
- 85%
  - Excreted in feces as stercobilinogen
- 15%
  - Enterohepatic circulation
    - Passively absorbed into the portal venous blood
      - Enter the liver
      - Re-excreted by liver into the intestine

Some is urobilonogen go to the blood reach the kidney and excreted as o urobilin that give yellow color.

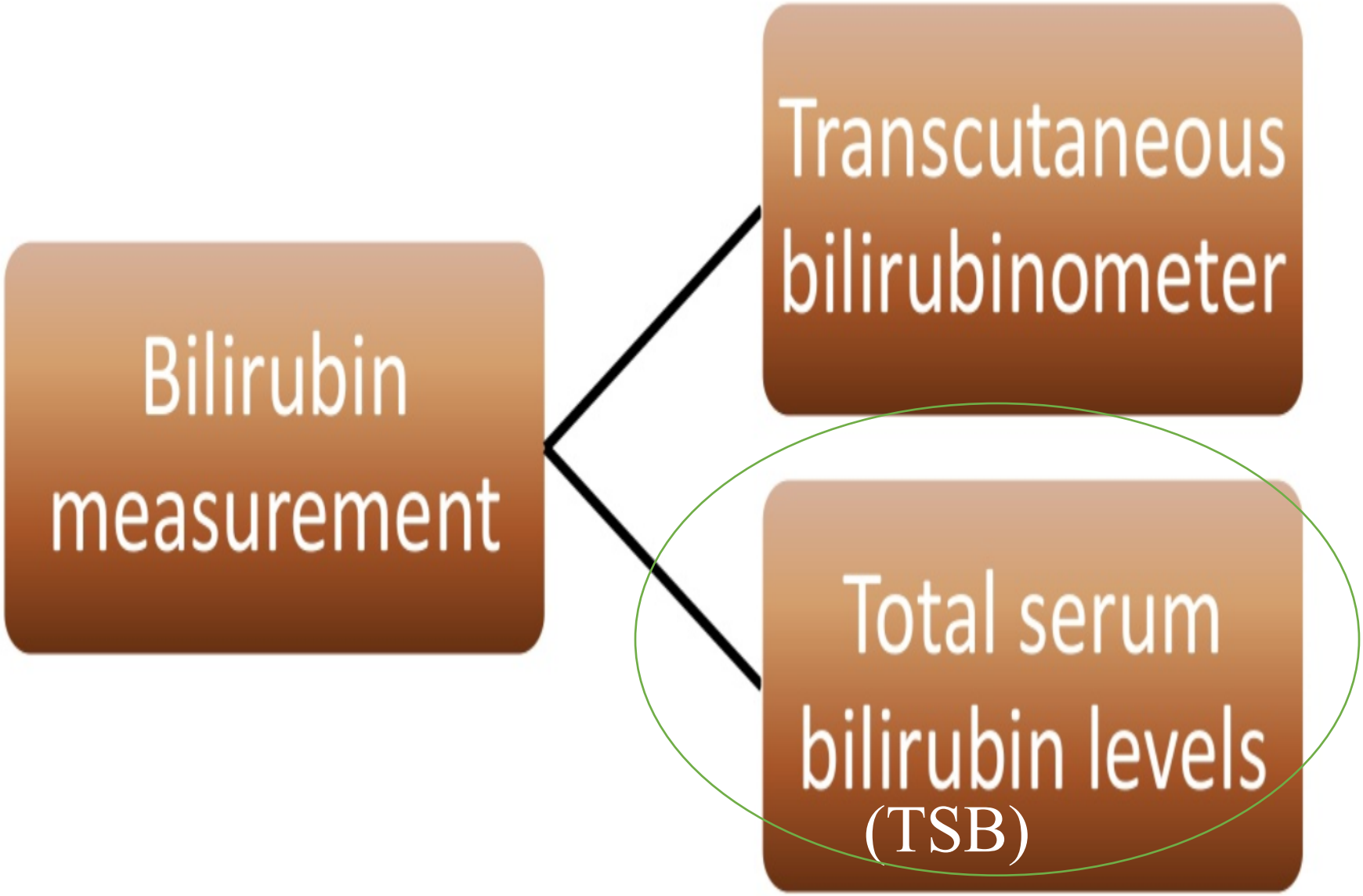
Bilirubin metabolism in neonate (Entero hepatic circulation EHC)

- Neonates have beta-glucuronidase in the intestinal mucosa
- It deconjugates the conjugated bilirubin to **unconjugated bilirubin** (UCB)



UCB fraction is partially reabsorbed through the intestinal wall and recycled into the circulation, a process known as the “EHC of bilirubin".
undergoes EHC

Excessive amounts of bilirubin are available for reabsorption in : obstruction of the upper intestinal tract, delayed passage of meconium, or fasting (decrease transient time)


Bilirubin measurement
Transcutaneous bilirubinometer
Total serum bilirubin levels
(TSB)

Transcutaneous bilirubinometer (TcB)

- TcB is a useful adjunct to TSB measurement and routine employement of TcB can reduce the need for blood sampling.
- TcB can be used in infants of 35 wks or more gestation & after 24 hrs of life.
- TcB has a good correlation with TSB levels but becomes unreliable once the TSB level goes beyond 14 mg/dl.
- Trends in TcB values 12 hrs apart have a better predictive value than a single reading.
- A TcB value more than 12 – 14 mg/dl needs confirmation by TSB examination.

Objectives

Why this lecture

Bilirubin metabolism

Bilrubin measurement

What special in neonates

Types and Causes of neonatal Jaundice

Breast feeding and hydration

Assessment of neonate at risk of sever hyperbilirubinemia

Management

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Types of Neonatal Jaundice

Physiological Jaundice

Pathological Jaundice

Breast-milk Jaundice

Breast-feeding Jaundice

Related to breast milk

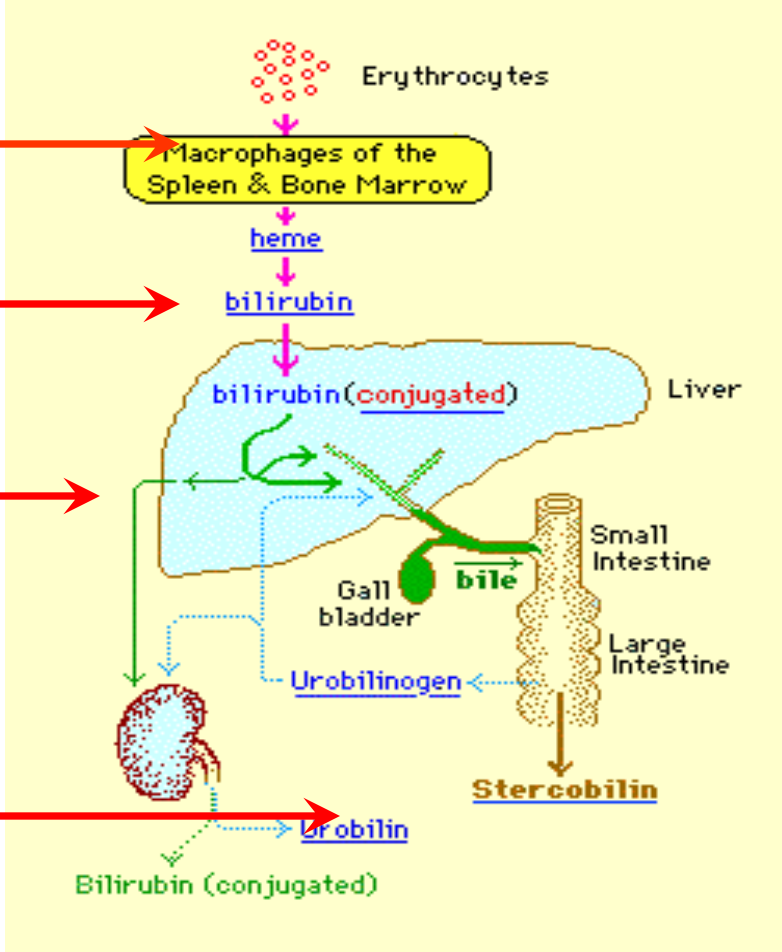
Mechanism of Physiologic Jaundice

Increased rbc's
and ineffective erythropoiesis

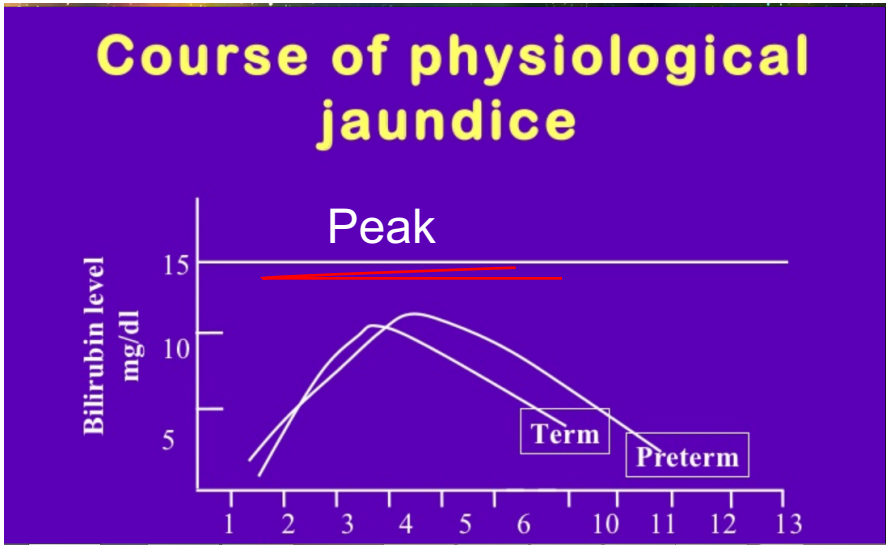
Shortened RBC lifespan

Immature hepatic uptake & conjugation (paucity of ligandin and decrease UGTA1)

Increased enterohepatic Circulation
(Increase B glucuronidase)



Physiologic Jaundice: Has Pattern



- usually *disappear*
- by 4 – 5 days (rarely by 7 -10 days) in full term
- & usually by 7 - 9 days (rarely by 10 days - 2wk) in preterm .

Peak 5- 7 days in preterm

Physiologic Jaundice

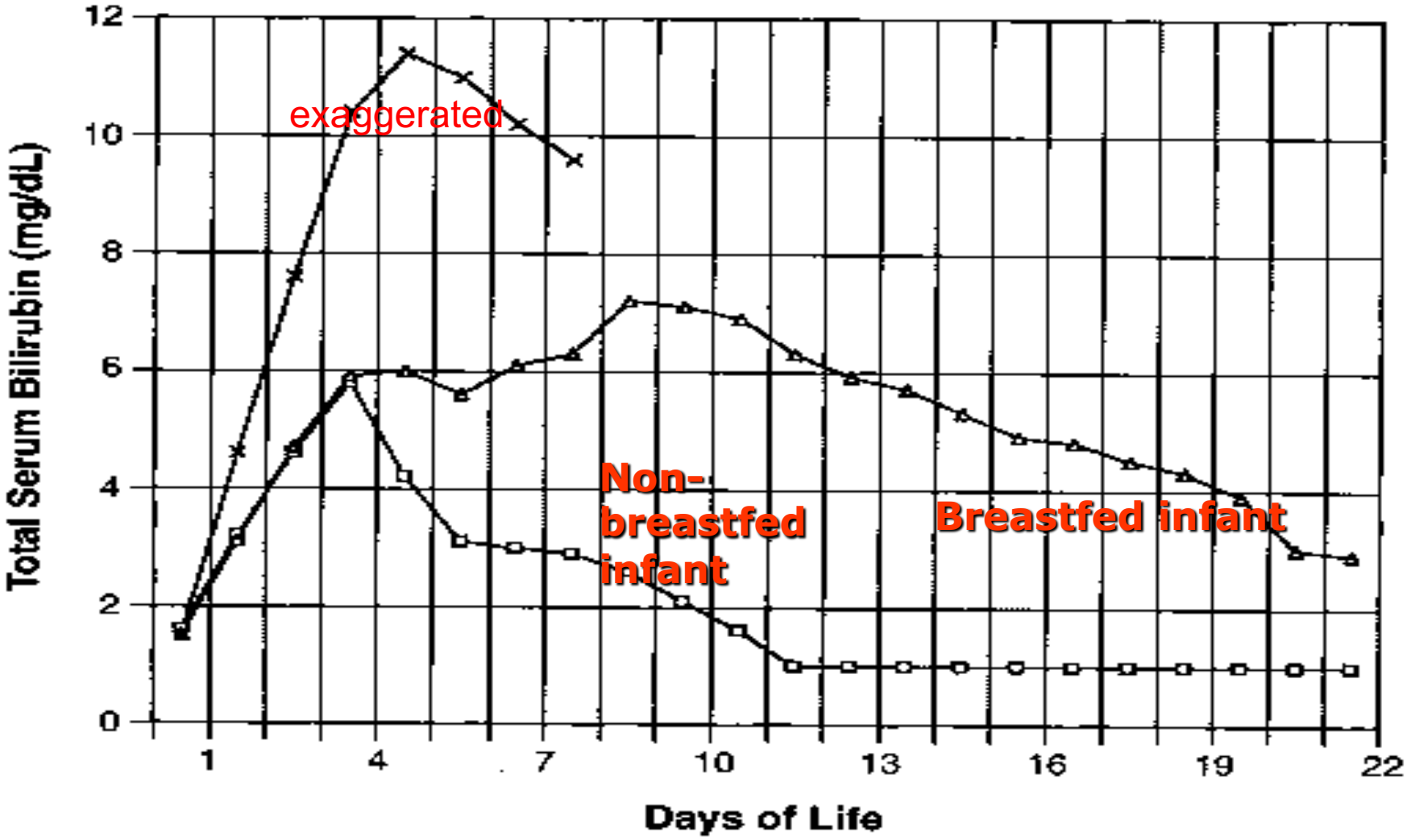
Increase should <than 0.2 mg/dL / hour.

- Rate of rise should <5 mg/dL per Day

- Mean Peak is according to race (less than 15)

- May be exaggerated

Physiologic Jaundice: pattern



Physiological jaundic may be exaggerated (increase peak & duration)

- when there is a risk factors as ; breast feeding , male sex , cephal hematoma , cutanouse bruising , polycythemia , weigh loss , dehydration , caloric deprivation , delay bowel movement , maternal DM , drug (K3 , novobiocin oxytocin), trisomy

Breast feeding Jaundice

- Elevated unconjugated bilirubin
  - (can exaggerate Physiologic Jaundice)
- There is mild dehydration and weight loss + low caloric intake
  - Weight loss more than 8% of birth weight
  - **May** associated with increase serum Na level and fever
- Elevated bilirubin in the 1st week of life
    - in the first few days of life
- Mandates improved/increased breastfeeding (for hydration)
  - No water or dextrose supplementation
  - Formula (OK)
  - May need phototherapy
  - Give feed every 2-3 hours

Physiologic Jaundice

Clinical jaundice should resolve within the first one to two weeks after birth,

Persistence of hyperbilirubinemia beyond two weeks of age merits further evaluation.

this is called

Prolonged Jaundice

Prolonged Jaundice

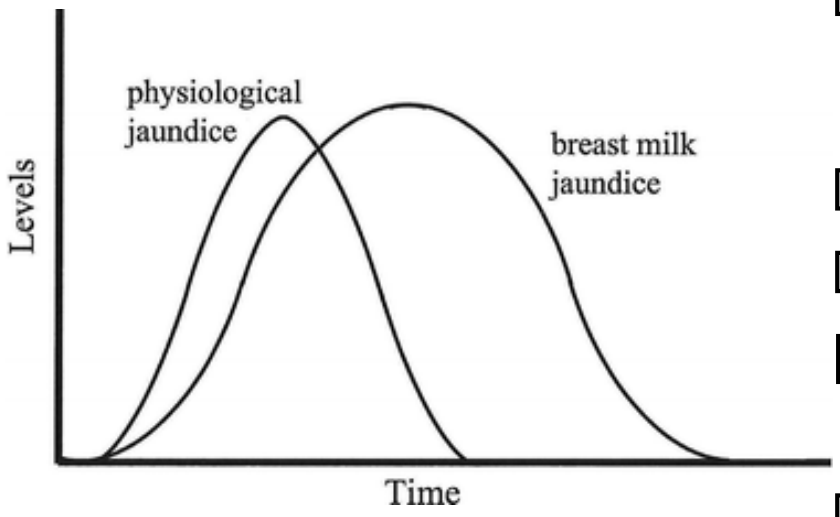
>2 weeks in term
> 3 weeks preterm

- **Common & important causes**
  - Breast milk jaundice
  - Obstructive jaundice
  - Neonatal hepatitis
  - Haemolysis
  - Metabolic - Hypothyroidism

Work UP
✓CBC & reic
✓BBG $ MBG
✓DCT
✓TSB& direct
✓G6PD
✓TFT
✓Urine (Reducing substances
✓ urine culture

- ❑ Urinary tract infection
- ❑Erly galactosemia

Breast Milk Jaundice



- Type of neonatal Jaundice
- Associated with breastfeeding
- characterized by indirect hyperbilirubinemia in an otherwise healthy breastfed newborn

- Develops after the first 4-7 days of life, persists longer than physiologic jaundice
- May Familial
- May last 3-12 weeks
- Rare to cause BIND unless bilirubin > 25 mg/dl
- has no other identifiable cause
- main cause of prolonged Jaundice
- ?Milk inhibitors and genetic factor
  - substances in the breast milk that inhibits (UDPGA1)
  - beta glucuronidase activity in breast milk

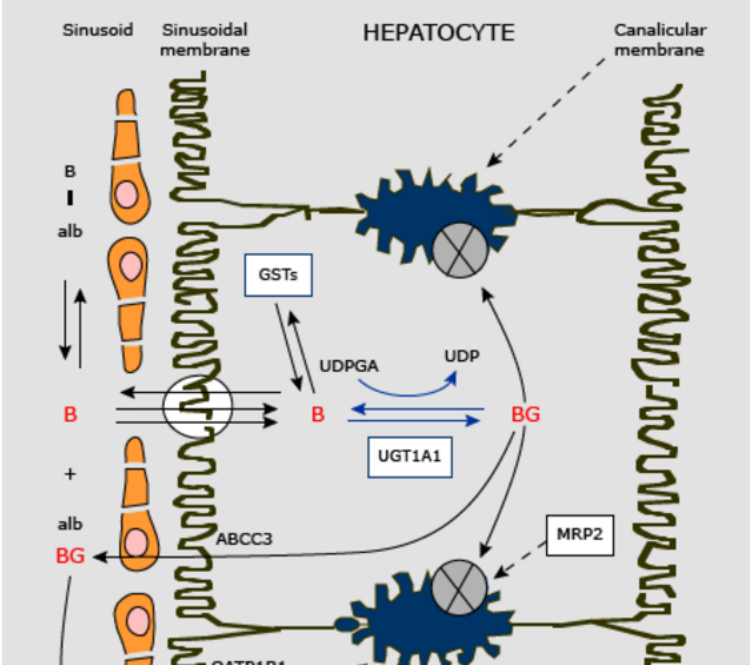
Ethnic variation in conjugation ability

Polymorphisms in the UGT1A1 gene

-Due to differences in the number of thymine-adenine (TA) repeats in the promoter region of the gene

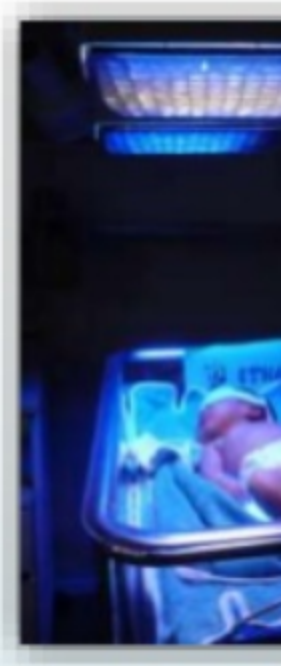
- vary among individuals of Asian, African, and Caucasian ancestry

- These polymorphisms correlate with decreases in UGT1A1 enzyme activity resulting in increased total bilirubin levels.

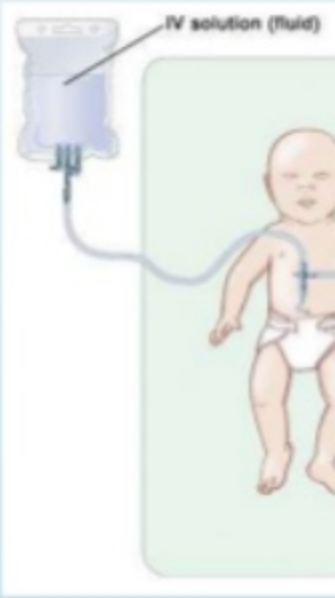


MANAGEMENT OF BREASTMILK JAUNDICE:

- Phototherapy is indicated, if serum bilirubin exceeds 20 mg/dl.



- Exchange transfusions, if serum bilirubin reaches 25-30 mg/dl.



- Temporary interruption of breastfeeding may be followed by fall in serum bilirubin values.

- However, in majority of cases the jaundice can be managed without need of stopping breastfeeding.

Jaundice and Breast milk

Breastfeeding Jaundice versus Breastmilk Jaundice

Parameters	Breastfeeding Jaundice	Breastmilk Jaundice
Onset	3rd-4th day of life	defined as the persistence of "physiologic jaundice" beyond the first week of age
Pathophysiology	Low caloric intake Dehydration Increase EHC	Unknown; probably due to B-glucuronidase in breastmilk which increase enterohepatic circulation; Normall Liver Function Test, (-) Hemolysis **Genetic cause**
Management	Fluid and caloric supplementation Feed every 2-3 hours	Stop breast milk ?? Mange by photo if needed

polymorphisms of the UGT gene
Gilbert syndrome
is the most common inherited disorder of bilirubin glucuronidation.
It results from a mutation in the promoter region of the UGT1A1 gene

6/30/2017

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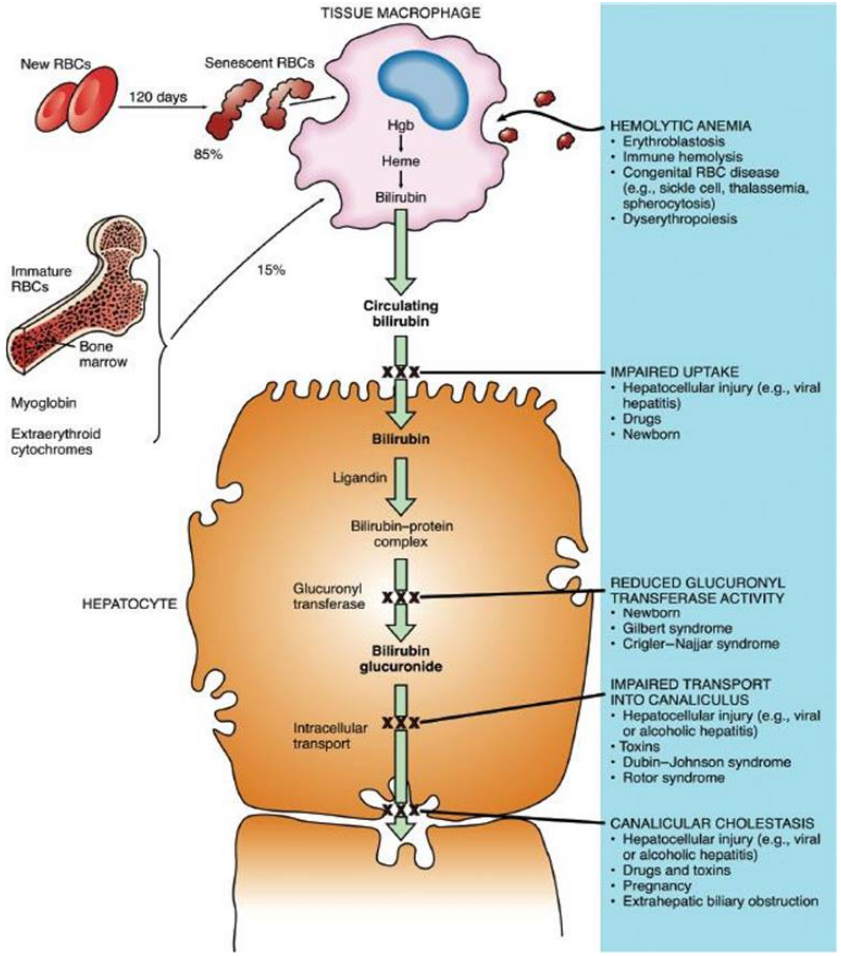
Objectives

- Why this lecture
- Bilirubin metabolism
- What special in neonates
- **Types and Causes of neonatal Jaundice**
- Breast feeding and hydration

- Assessment of neonate at risk of sever hyperbilirubinemia

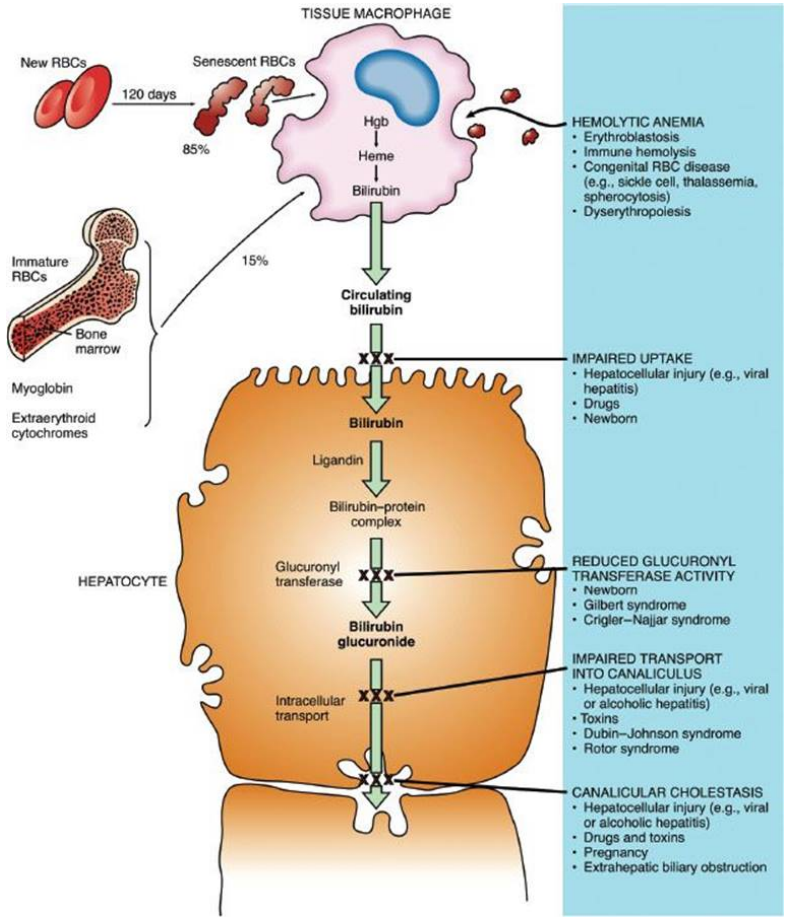
- Management
  - Guidelines
  - Work UP
- Treatment
  - Prevention
  - treatment

Pathologic Jaundice

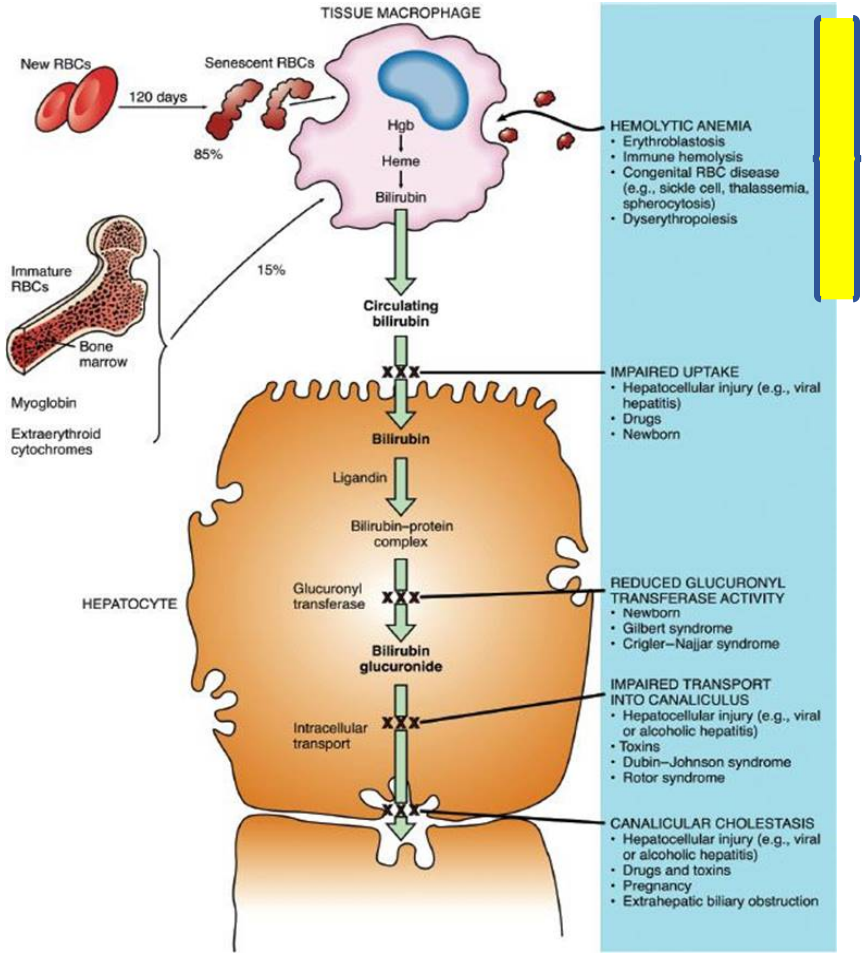


- is a medical emergency.-

Causes of Pathologic indirect hyper bilirubinemia causing Jaundice



Pathologic Jaundice: Causes



Increased production

- **Hemolysis**
  - - Isoimmune-mediated hemolysis (eg, ABO or Rh(D) or minor blood group incompatibility
  - -Inherited red blood cell membrane defects (eg, hereditary spherocytosis and elliptocytosis-
- -- Erythrocyte enzymatic defects (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency , pyruvate kinase deficiency, and congenital erythropoietic porphyria
- **Sepsis**
- **increased red blood cell breakdown**
- -polycythemia
- - sequestration of blood within a closed space, which occurs in cephalohematoma.
- **Ineffective erythropoiesis)-**
- **Galactosemia**

Causes of unconjugated hyperbilirubinemia in neonates[4-6]

Increased bilirubin production	Increased enterohepatic circulation	Decreased clearance of unconjugated bilirubin	Metabolic conditions	Inborn errors of metabolism
Hemolysis (immune-mediated, heritable)	Insufficient breast milk/ feeding	Prematurity	Hypothyroidism	Galactosemia
Extravasation (cephalohematoma)	Pyloric stenosis	G6PD deficiency	Hypopituitarism	Gilbert syndrome
Polycythemia	Bowel obstruction			Crigler-Najjar syndrome (I and II)
Sepsis	Ileus			Breast milk jaundice due to other bilirubin UGT1A1 mutations
Disseminated intravascular coagulation				Tyrosinemia
Macrosomic infants of diabetic mothers				Hypermethioninemia

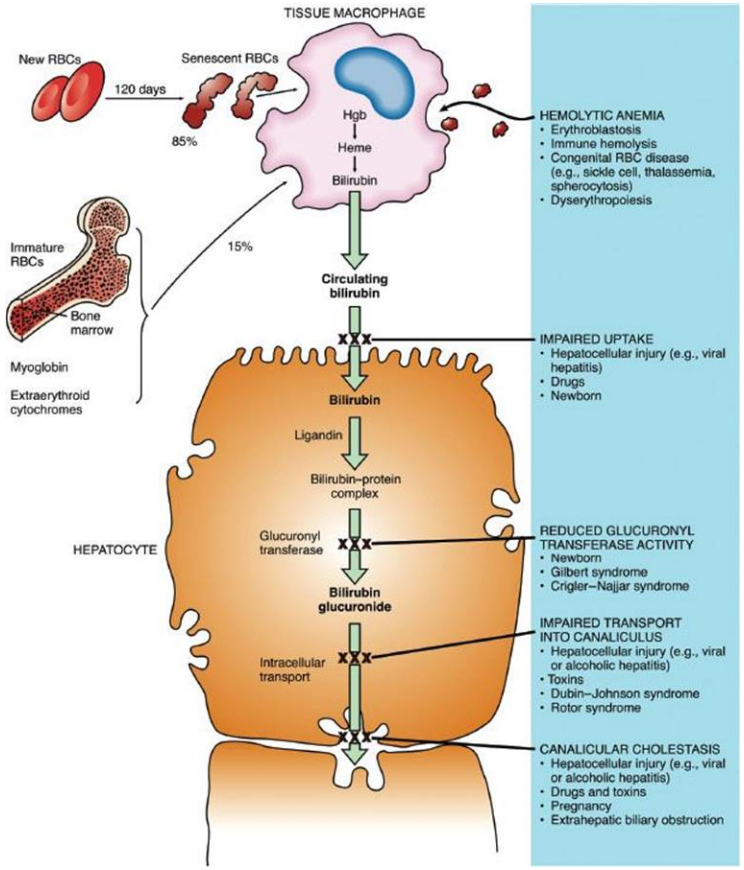
G6PD, glucose-6-phosphate dehydrogenase; UGT1A1, uridine diphosphate-glucuronosyltransferase, family 1, polypeptide A1.

Examples Of increased production

ABO Incompatibility

- Early onset jaundice – within 24 hour after birth
- Baby blood group A or B, Mother blood group O
- Direct Coomb's test +ve
- Blood smear show increase spherocytes
- Usually can be controlled with phototherapy

Pathologic Jaundice Causes



Decreased clearance

And excretion

Inherited

- Galactosemia

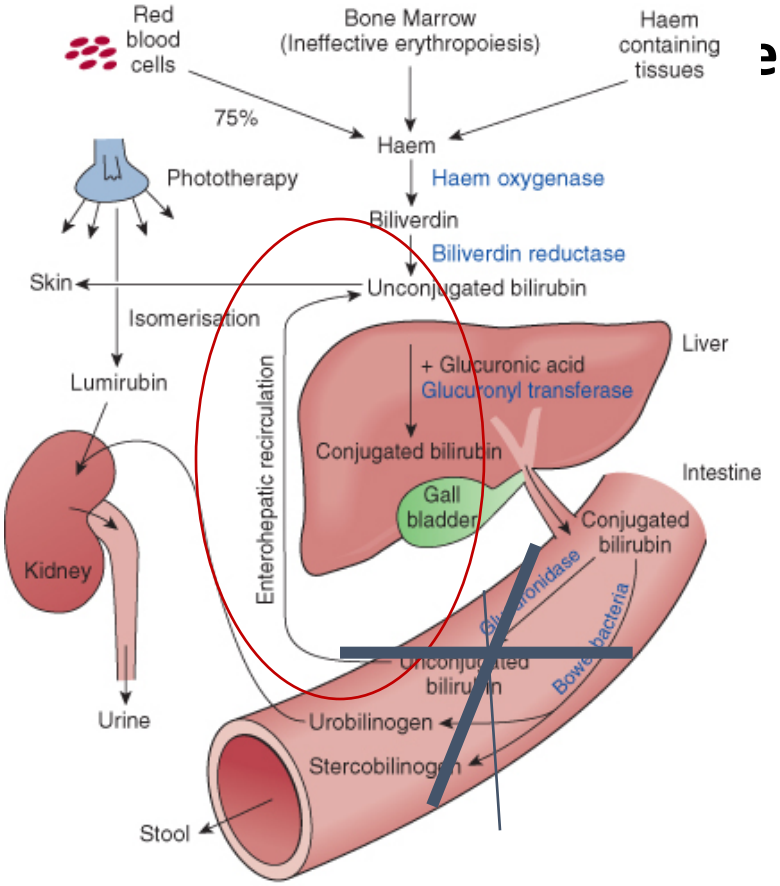
- Defects in the gene that encodes UGT1A1

- - Crigler-Najjar syndrome types I and II
- - Gilbert syndrome,I.
- - OATP-2 polymorphism

Other causes —

congenital hypothyroidism

Pathologic Jaundice Causes: increase in enterohepatic circulation (EHC)



-NPO

-Obstruction

Pathologic jaundice: How to recognize

Suspicion 1:

Cord blood

TSB at 24 hour

Pathologic jaundice: How to recognize

Jaundice in 1st 24 hrs

Table-3: Mean± standard deviation of cord blood and 1st day TSB levels

	Cases developed significant hyperbilirubinemia	Cases did not develop significant hyperbilirubinemia	P value
Cord bilirubin mg/dL	2.68± 1.2	1.24±0.38	<0.01
1st day bilirubin mg/dL	6.41±1.8	3.2±1.32	<0.01

P value <0.01is highly significant

Cord blood bilirubin level of >2.38 mg/dL cut off value is achieved by ROC curve analysis (figure 1) with sensitivity (83.3%), specificity (88.8%), positive predictive value (58.1%) and negative predictive value (96.6%) are shown in table 4, also the cut off point of first day bilirubin >5 mg/dL shows sensitivity (91.1%), specificity (79.8%), positive predictive value (46.3%) and the negative predictive value was (97.7%).

Figure-1: ROC curve for cut off value of the cord blood bilirubin for prediction of significant hyperbilirubinemia

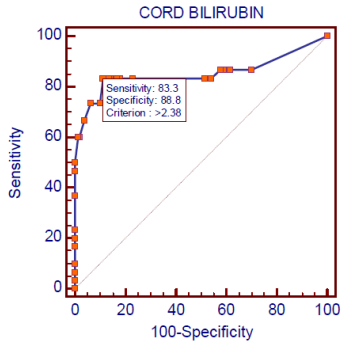


Table-4 :Sensitivity, specificity, positive predictive value and negative predictivevalues of cord and 1st day bilirubin levels for prediction of hyperbilirubinemia

High sensitivity and specificity to develop sever hyperbilirubimimeia if

-Cord total bilirubin > 2.38mg\dl

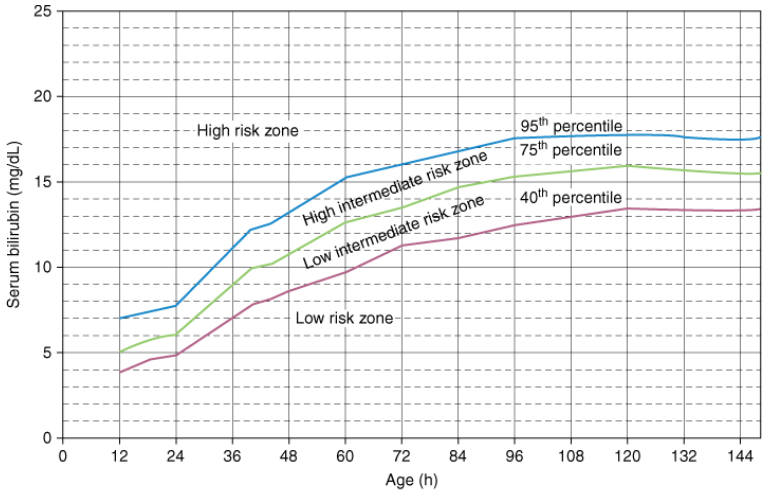
- Total Serum bili level at 24 hor of life > 5 mg\dl

Suspicion 2:
Pattern of rise

Pathologic Jaundice: How to recognize

- **Pattern of rise**
  - Rapidly rising TSB (> 5 mg/dL per day)
  - > o.2 mg/dl/hour
  - TSB high risk zone (> 75Th)

Study 1



Source: Stevenson DK, Maisels MJ, Watchko JF: *Care of the Jaundiced Neonate*: www.accesspediatrics.com

Table 3. Risk of Developing a Total Serum Bilirubin (TSB) Level of 20 mg/dL (342 µmol/L) or Higher by TSB Percentile Group

TSB Percentile at <48 h	No. of Patients	No. (%) of Patients With a TSB of ≥20 mg/dL
<40th	994	5 (0.50)
40-74.9	1508	11 (0.73)
75-94.9	1780	58 (3.26)
≥95th	1424	196 (13.76)
Total	**5706**	**270** (4.73)

Suspicion 3:
COAURSE

Pathologic Jaundice: How to recognize

- Jaundice in a term newborn after two weeks of age.

Suspicion 4:
Type

Pathologic Jaundice: How to recognize

- Direct (conjugated) bilirubin concentration

Definition of direct bilirubin

-Direct Bilirubin more than 20 percent of the total bilirubin if the total bilirubin is >5 mg/ dL

- Direct bilirubin > 1 mg/ dL if the total bilirubin is <5 mg/ dL

Suspicion 5 :

Assess Risk factors

Pathologic Jaundice: How to recognize

Major Risks	Minor Risks	Decreased Risk
Predischarge TcB or TSB in high-risk zone	Predischarge TcB or TSB in high intermediate-risk zone	TSB or TcB in low-risk zone
Jaundice in first 24 hr.	Gestation age 37-38 wk	Gestation age ≥41 wk.
Blood group incompatibility with positive DAT, other known hemolytic disease, elevated $ETCO_2$	Jaundice observed before discharge	Exclusive bottle feeding
Gestation age 35-36 wk	Sibling with jaundice	Black race
Sibling received phototherapy	Macrosomic infant of diabetic mother	Discharge from hospital after 72 hr.
Exclusive breastfeeding, particularly with excessive weight loss	Maternal age ≥25 yr.	
East Asian race	Male gender	

Objectives

Why this lecture

Bilirubin metabolism

What special in neonates

Types and Causes of neonatal Jaundice

Breast feeding and hydration

Assessment of neonate at risk of sever hyperbilirubinemia

Management

- Guidelines
- Work UP

Treatment

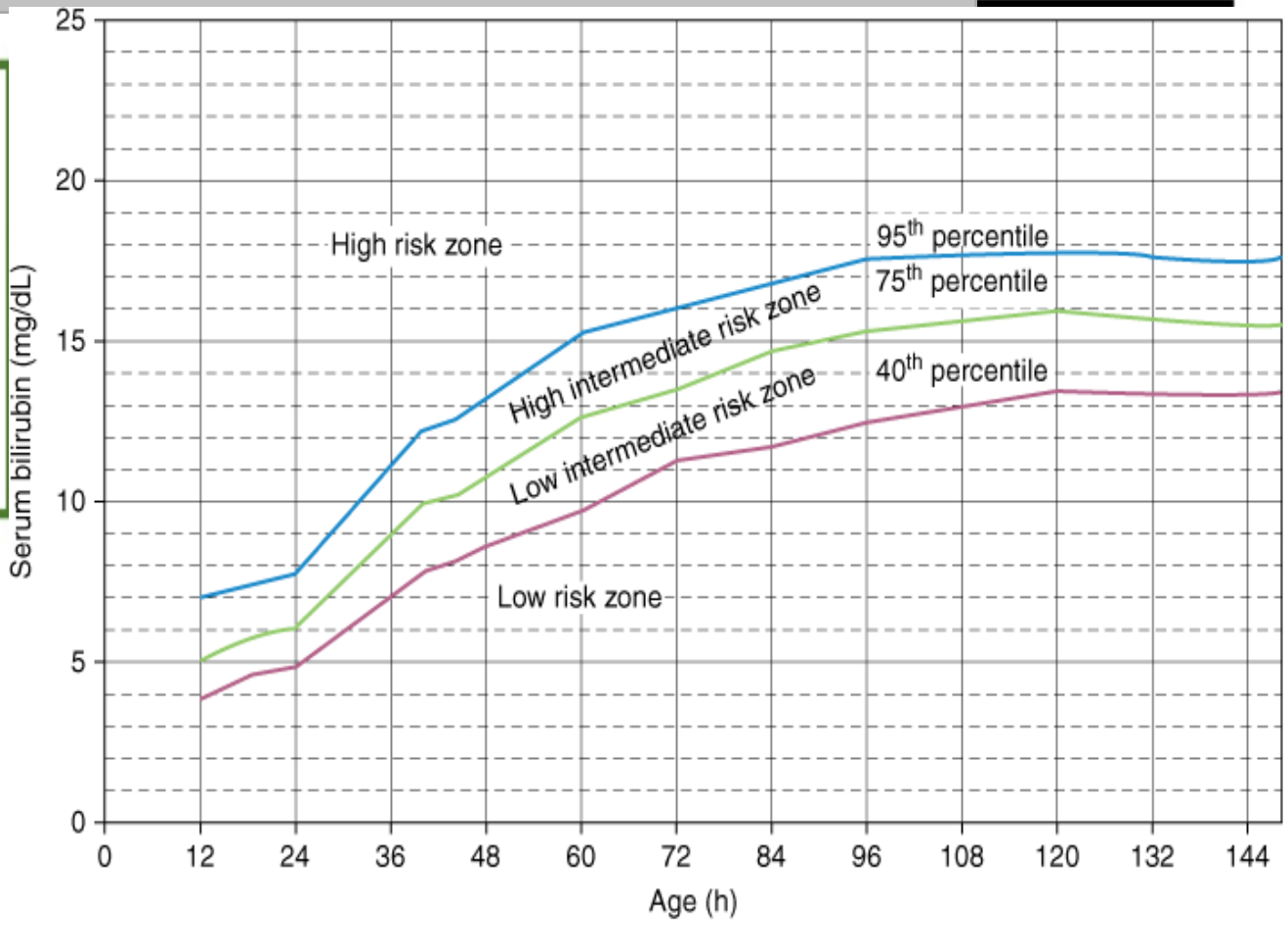
- Prevention
- treatment

1-Assess the risk Zone

1- Hyperbilirubinemia risk factor by Nomogram for those > 35 weeks

Normogram for designation of Hyperbilirubinemia risk based on hour specific bilirubin values.

Adapted from bhutani et al.

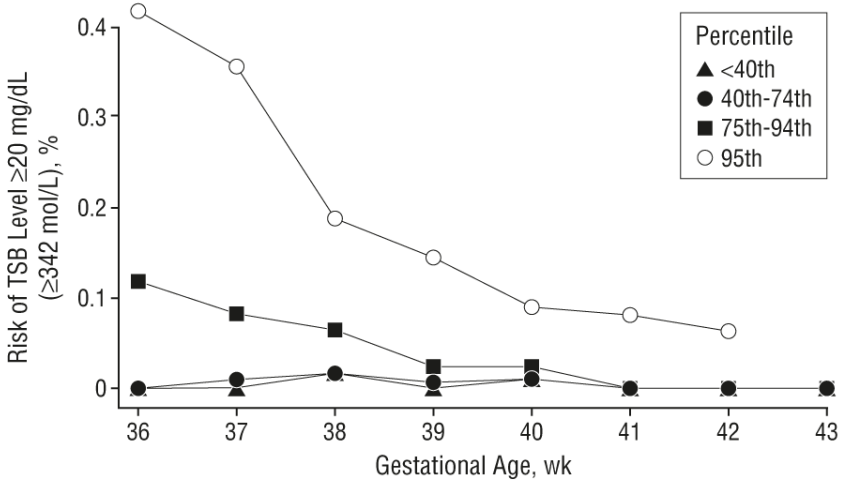


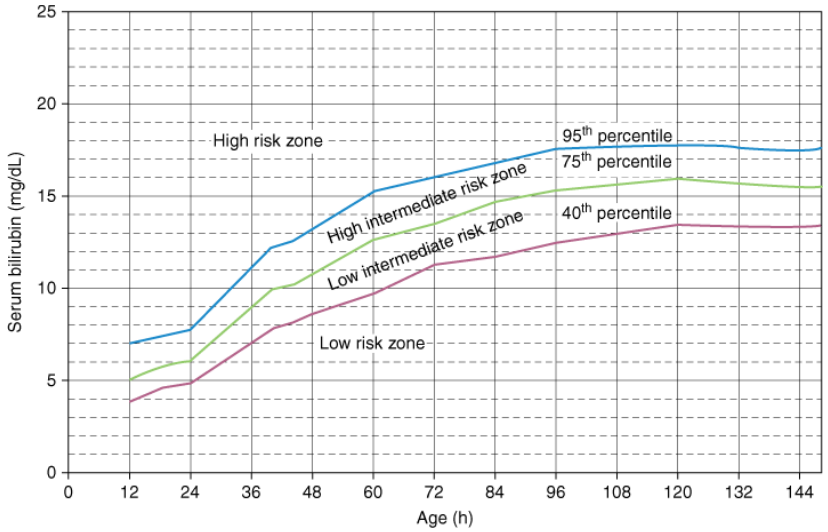
Source: Stevenson DK, Maisels MJ, Watchko JF: *Care of the Jaundiced Neonate*: www.accesspediatrics.com

1-Assess the Gestation Age

Risk of Jaundice By gestation age (GA)

Clinical risk factor





Source: Stevenson DK, Maisels MJ, Watchko JF: *Care of the Jaundiced Neonate*: www.accesspediatrics.com

Increase risk of sever hyper bilirubinemia risk with decrease GA

Study on those >36 weeks

At Discharge

- Assess risk
  - 1.. Do Predischarge bilirubin (serum or transcutaneous)
    - Use nomogram to determine risk zone
  - **2. And/or Assessment of risk factors**

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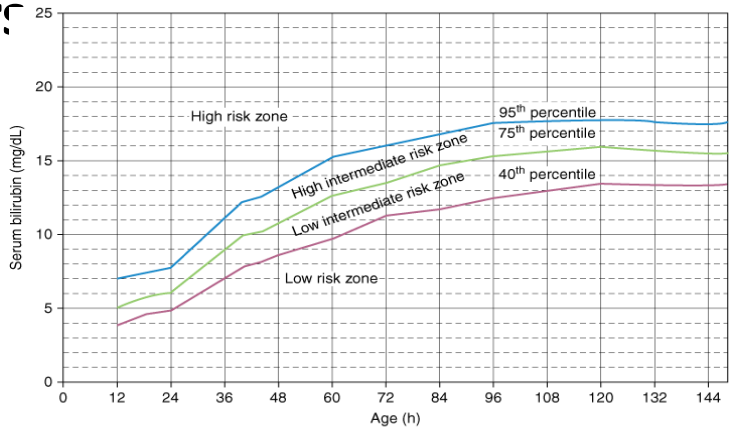

Source: Stevenson DK, Maisels MJ, Watchko JF: *Care of the Jaundiced Neonate*: www.accesspediatrics.com

2. Do Clinical Risk Factors Assessment for Severe Hyperbilirubinemia

4-Assess the other

- **Major risk factors**
-
  - Predischarge bili in high-risk zone
  - Jaundice in 1st 24 hrs
  - **Blood group incomp** with + direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency)
  - Gestational age 35–36 wk
  - **Previous sibling** received phototherapy or exchange
  - **Cephalohe**matoma or significant bruising
  - **Exclusive breastfeeding**
  - East Asian race

- Minor risk factors
-
  - Bili in high intermed-risk zone
  - Gestational age 37–38 wk
  - Jaundice before discharge
  - Previous sibling with jaundice
  - Macrosomia infant with diabetic mother
  - Maternal age ≥ 25
  - Male

- **Decreased Risk**
  - Bili in low-risk zone
  - ≥ 41 wks gestation
  - Exclusive bottle feed
  - Black race
  - D/c from hospital > 72hrs

Why to know risk factors
potentially correctable causes: Kernicterus cases

- **Failure to check bilirubin level if onset in first 24 hours**
- Early discharge (<48hrs) without f/u within 48 hrs
- Visual assessment underestimate of severity
- Delay in testing jaundiced newborns or treating elevated levels
- Lack of concern for presence of **jaundice** or parental concern
- ***Failure to note risk factors***

- Pediatrics 2001; 108:763-765

Monitoring

After Birth

- All newborns should be routinely assessed for jaundice.
- Jaundice is visible when Sr. Bilirubin >5mg/dl.

During their Vital signs monitoring

- Newborns to be observed for 72 hrs for jaundice appearance. In case of discharge before 48hrs, Bilirubin risk factors and Hyperbilirubinemia risk as per Normograms should be assessed and followup to be advised accordingly.
- A predischarge TSB or Transcutaneous bilirubin reading to be done if discharge is before 72 hrs of life.

Know the risk factors

Pre discharge screen

2- High bilirubin clinical Risk factor

(risk for sever hyperbilirubinemia)

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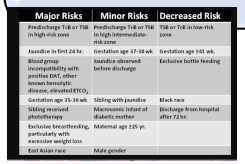
Screening recommendations lack consensus

NEED TO SCREEN :128,600 to prevent 1 case of kernicterus (COST ISSUE)

AAP

Universal screening of infants ≥35 weeks' gestation prior to discharge with measurement of TSB/TcB and/ or clinical assessment



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East Asian race	Male gender	

Pediatrics. 2004;114:297-316.

NICE/UK

:Do Bilirubin at 24 hour of age

As selective screen (for at risk)

recommends against routine monitor-ing of bilirubin levels in infants who do not appear jaundiced.

https://www.nice.org.uk/guidance/cg98. Updated October 2016. Accessed October 17, 2018.

The Canadian Pediatric Society CPS

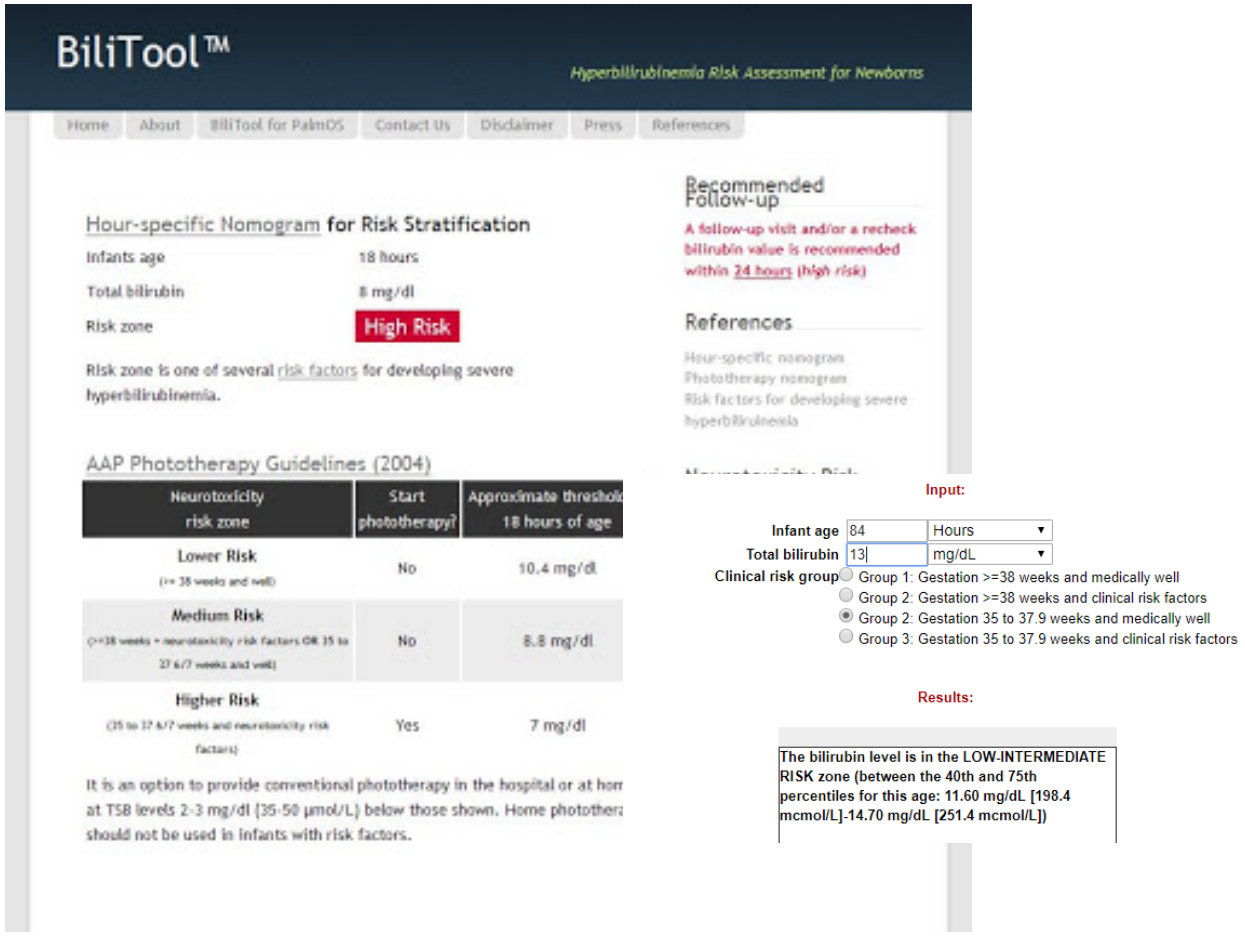
: universal screening with TSB/TcB measurement in all infants in the first 72 hours of life. :

Paediatr Child Health. 2007;12:401-418.

Diagnosis & Evaluation

- History and Physical Exam
  - Jaundice = Bilirubin > 5 mg/dL
- Laboratory
  - Blood
  - Transcutaneous
    - Generally within 2mg/dL of serum test
    - Most useful if serum bili < 15

Mobile Application
to asses risk factors : AAP



When to Do Lab Investigation

- Clinical Jaundice

- **Screen at 24 hoarse**
- **- If MBG is Rh Negative**
- **- ABO**

  (follow Hospital Protocol) : AS SUGGETED BY AAP
- **-Baby expected to have isoimmune H anemia**
- **bilirubin concentrations reach phototherapy levels Do more tests**

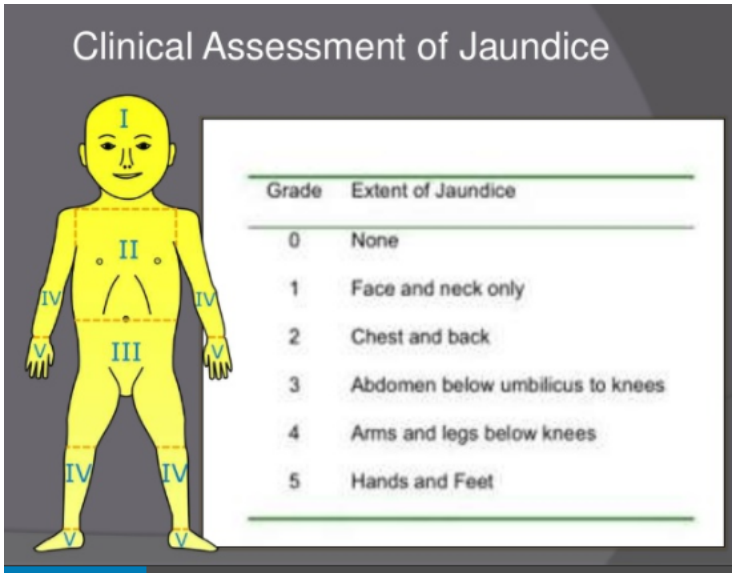
Post-discharge follow-up

Infants discharged before 72 hours of life should be seen within 2 days of discharge.

Those infants with significant risk factors for development of severe hyperbilirubinemia should be seen within 1 day.

Assessment of hyperbilirubinemia by visual assessment

- Unreliable
- Testing bilirubin level is more correct



Objectives

Why this lecture

Bilirubin metabolism

What special in neonates

Types and Causes of neonatal Jaundice

Breast feeding and hydration

Assessment of neonate at risk of sever hyperbilirubinemia

Aproach

Management

- Guidelines
- Work UP

Treatment

- Prevention
- treatment

How to manage if baby is Jaundice

Use A guideline

NICE guidelines (UK)

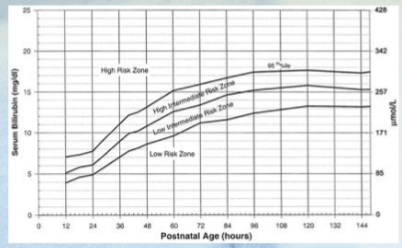
AAP guidelines (USA)

Measuring bilirubin in all babies with jaundice

Do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice.

AAP Clinical Practice Guideline

- Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation



Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values.

AAP Subcommittee on Hyperbilirubinemia. *Pediatrics.* 2004;114:297–316

Help to diagnose , investigate and treat

Objectives

Why this lecture

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Management

- Guidelines
- Work UP

Treatment

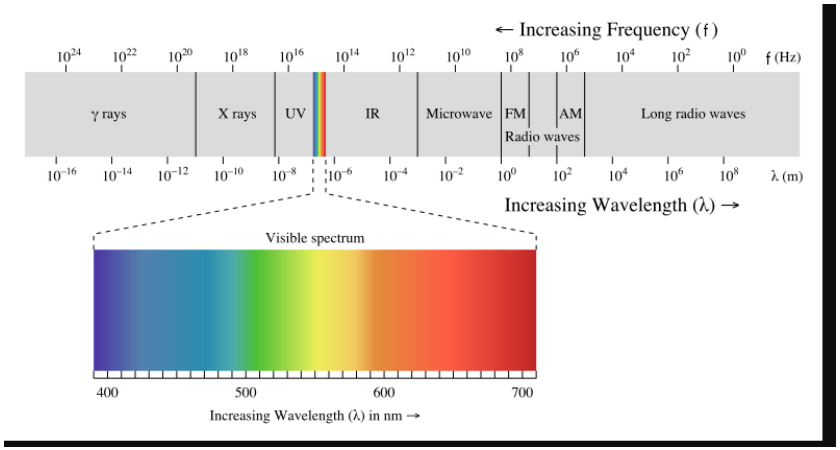
- Prevention
- treatment

Therapeutic Options

- Phototherapy for neonat
with mild jaundice

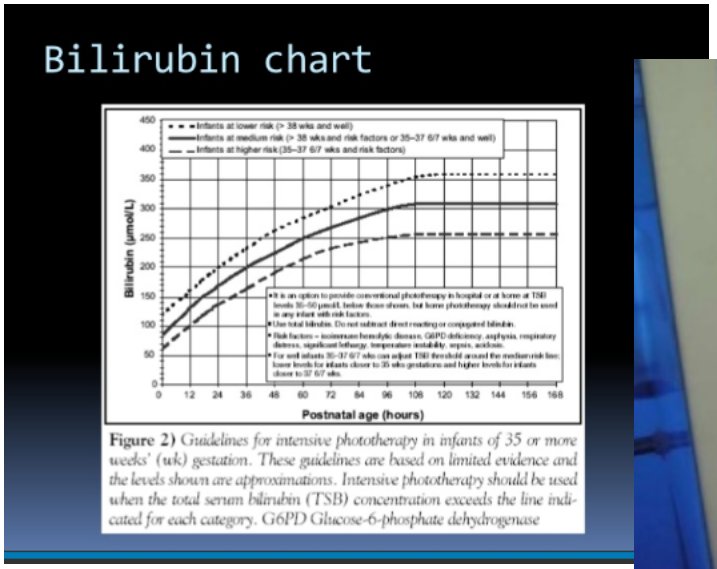
- Exchange transfusion i
Severe cases

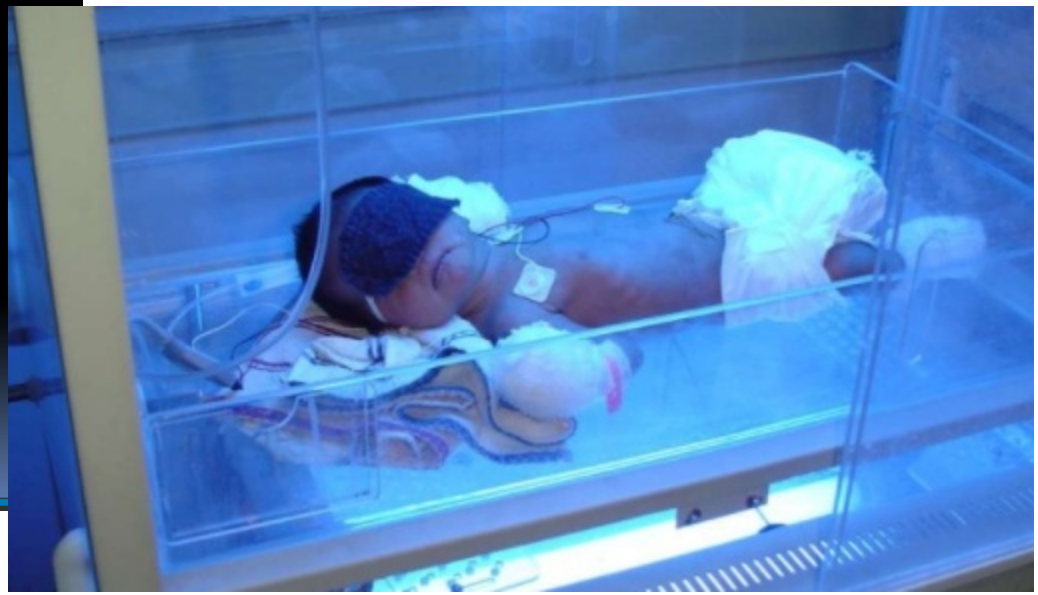
Intravenous Immune globulin



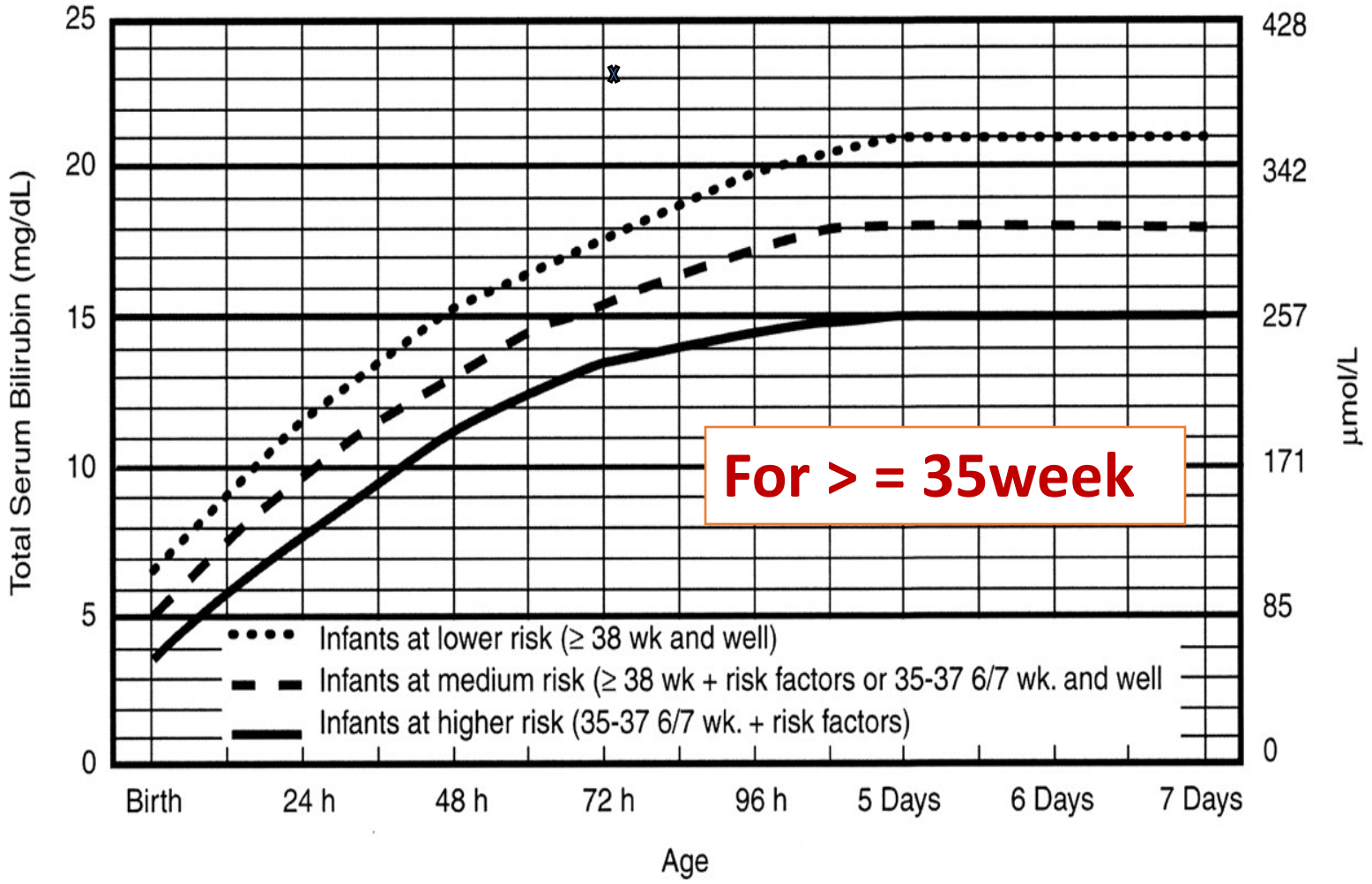
Phototherapy

- Goal: to treating neonatal hyperbilirubinemia and prevent related neurotoxicity
- Decreases the need for exchange transfusion
- Exposure of the skin of the jaundiced baby to blue or cool white light of wavelength 425-475 nm
- Toxic bilirubin molecule isomerizes to non-toxic product





Guidelines for Phototherapy in infants of 35 or more weeks' gestation



Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316

Who need photo therapy ?

PEDIATRICS®

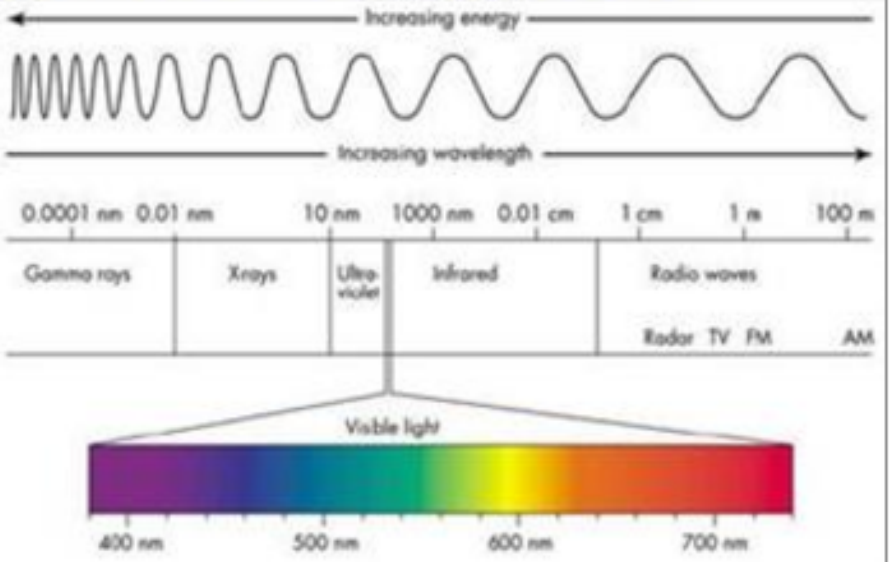
Factors affecting Phototherapy

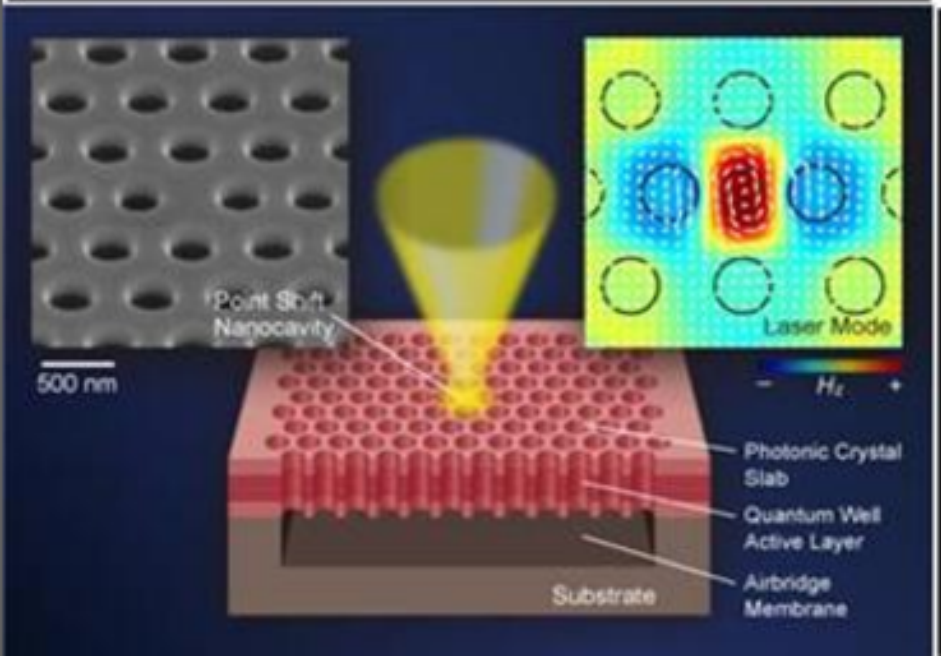
Wavelength

Narrow spectrum of wavelengths at approximately 450 nm (425-475 nm)

light used in wavelengths

White Blue Green





Microwatts / Irradiation

8 -12 µW/cm2/nm

Irradiance of 25 µW in the 425-475 nm range, TSB can be decreased by 50-60% in a 24-hour period

Phototherapy – Mechanism of action

3 reactions can occur when unconjugated bilirubin is exposed to light

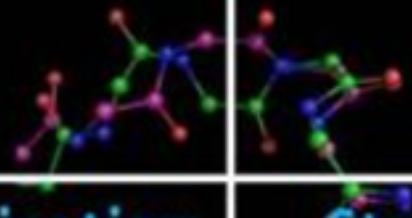


Photo oxidation

The process is slow

believed to contribute only minimally to the therapeutic effect

Configurational Isomerization

very rapid process

Changes bilirubin isomer to *water-soluble isomers*

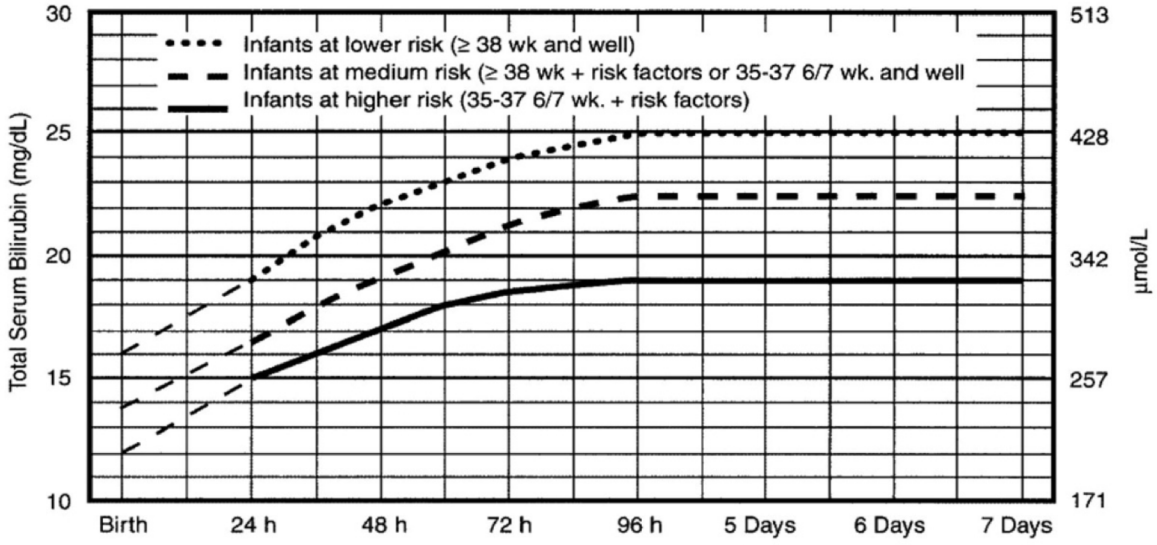
Not influenced significantly by the intensity of light.

Structural Isomerization

Intramolecular cyclization resulting in the formation of lumirubin

Enhanced by increasing the intensity of light.

Exchange photo therapy



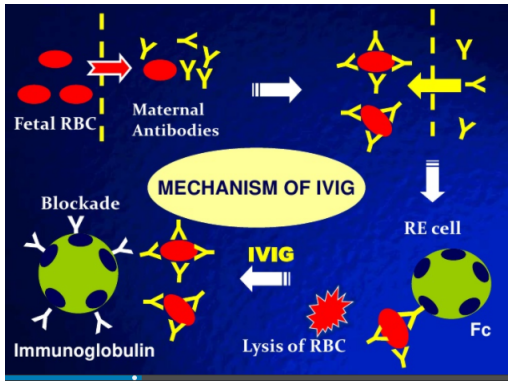
- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Figure 2 Guidelines for exchange transfusion in infants of 35 and more weeks' gestation.

Exchanges transfusion: indication

- bilirubin levels >25 mg/dL,
- those who are not responding to phototherapy,
- those with evidence of acute bilirubin encephalopathy

Intravenous immune globulin



- Dose
  - (IVIG; dose 0.5 to 1 g/kg over two hours)
  - The dose may be repeated in 12 hours if necessary
- is recommended in
  - infants with **isoimmune hemolytic** disease and if the **TSB level is rising despite phototherapy**
  - or is within 2 or 3 mg/dL of the threshold for exchange transfusion.

- Thank you