

Neonatal Jaundice

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Fifth year medical students

Definition



Neonatal jaundice:

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

Definition

Hyperbilirubinemia

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

Bilirubin > normal level

TSB >> 1 mg/dL
(17.1 micromol/L),



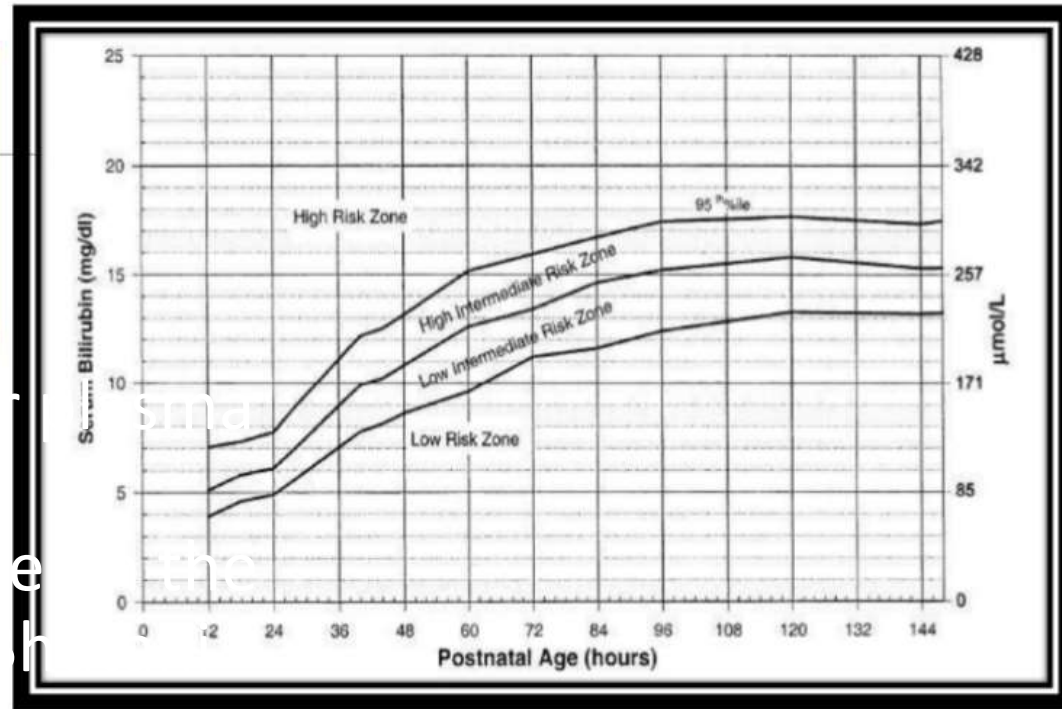
Definitions

Significant neonatal hyperbilirubinemia in **infants ≥ 35** weeks gestational age (GA) is defined as :

TB >95 percentile on the hour-specific Bhutani nomogram

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

Adapted from bhutani et al.



erh

*Diagnose hyperbilirubinemia
Bilirubin measured at >95th
percentile for age in hours.*

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).

BIND

Bilirubin-
Induced
Neurologic
Dysfunction

- Due to brain damage from free bilirubin
- that crosses the blood-brain barrier and binds to brain tissue as evidenced by both molecular
- and cause cytological injuries of brain cells

Real Life Scenario

- 3 days old (**73** hrs),
- BW=2.7 kg
- male,
- born at **36** wks.
- Mom is primi,
- **Mother B.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 μ mol/L).
- ✓ Indirect 23 mg/dl (391 μ mol/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, lethargy**, hypertonia and retrocollis, opithotonus, **shrill cry**; and irritability alternating with **increasing lethargy**.

Acute advanced signs are cessation of feeding, bicycling movements (possible seizures), inconsolable irritability and crying,, fever, and coma

Kernicterus is the chronic and permanent sequelae of BIND.

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Objectives

Why this lecture

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



Why this lecture

Common

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

Bilirubin-Induced Neurologic Dysfunction (BIND)

Why this
lecture

- *Acute sequelae* of BIND :

Acute signs (Acute Bilirubin
Encephalopathy)

Has a complication

- *Chronic and permanent sequelae* of BIND

Kernicterus :it is chronic sequelae

Neonatal Jaundice is HOT topic in Paediatric Journals

Why this lecture

Always Hot topic in research



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

Numan Nafie Hameed^a Alaa' Muhamed Na' ma^a Rohan Vilms^b
Vinod K. Bhutani^b

^aDivision of Pediatrics, College of Medicine, Baghdad University and Children Welfare Teaching Hospital Medical City Complex, Bab Al-Muadham, Baghdad, Iraq; ^bDepartment 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.

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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

Format: Abstract ▾

Send to ▾

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 S¹, 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



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- [Association between neonatal jaundice and autism spectrum disorders among children: a meta-analysis](#)
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Ghana Med J. 2019 Dec; 53(4): 267-272. doi: 10.4314/gmj.v53i4.3
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- [Long-term neurodevelopmental outcomes of significant neonatal jaundice in Taiwan from 2000-2003: a nationwide, population-based cohort study](#)
Pei-Chen Tsao, Hsin-Ling Yeh, Yu-Shih Shiau, Yen-Chen Chang, Szu-Hui Chiang, Wen-Jue Soong, Mei-Jy Jeng, Kwang-Jen Hsiao, Po-Huang Chiang
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A young child with brown hair is swimming in a pool, wearing blue and red goggles. The child is looking towards the camera. The background is a bright blue pool with some ripples on the surface.

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

What special in neonates

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Why to know the bilirubin production and metabolism

To Know the cause

- Physiologic

- Pathologic

Bilirubin production: Source

80-90%

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

-Or from Ineffective erythropoiesis

10 -20%

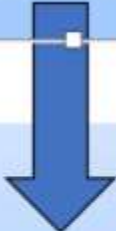
- ▣ Breakdown of hemoproteins in the liver
 - ▣ Catalases
 - ▣ Cytochrome oxidases

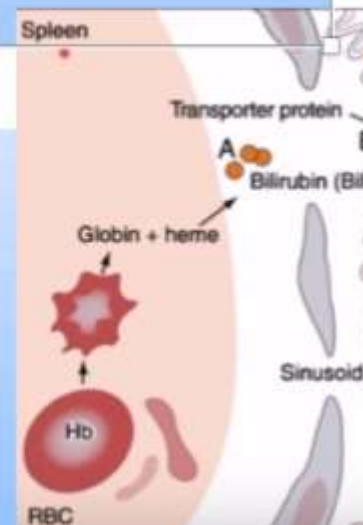
Note:

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

Site of bilirubin metabolism

- Reticuloendothelial system
 - Consists primarily of monocytes and macrophages

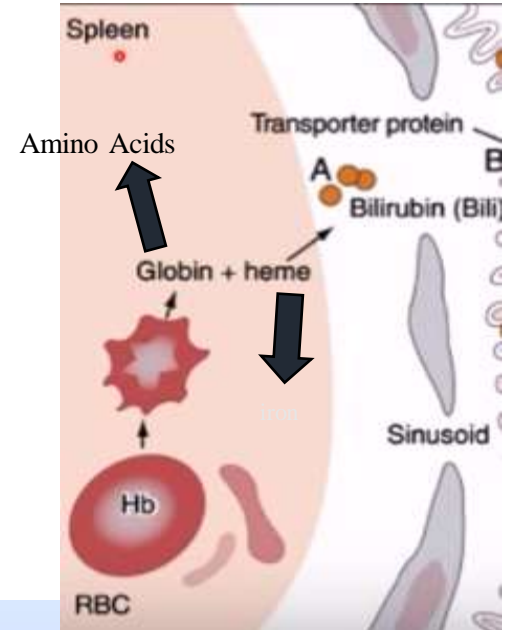
- 
- Spleen
 - Largest unit
 - Liver
 - Bone marrow

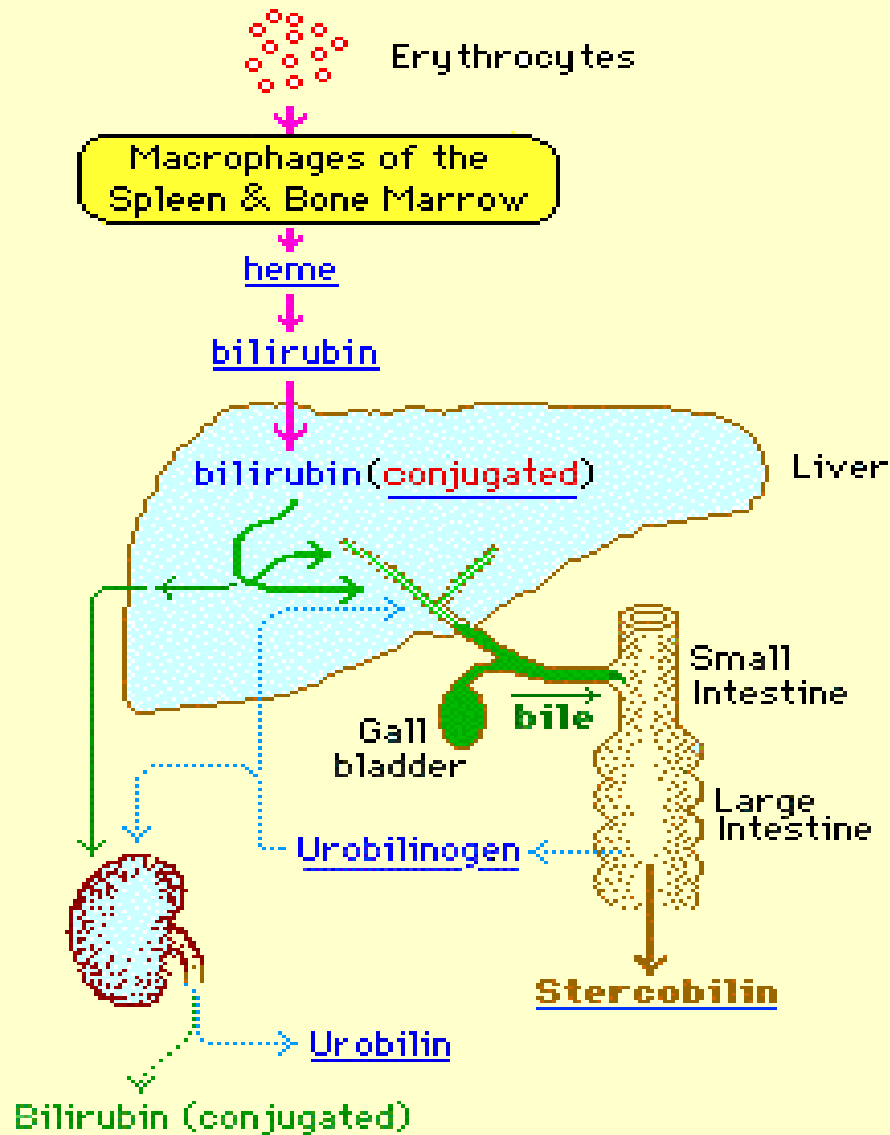


Bilirubin synthesis

Macrophages

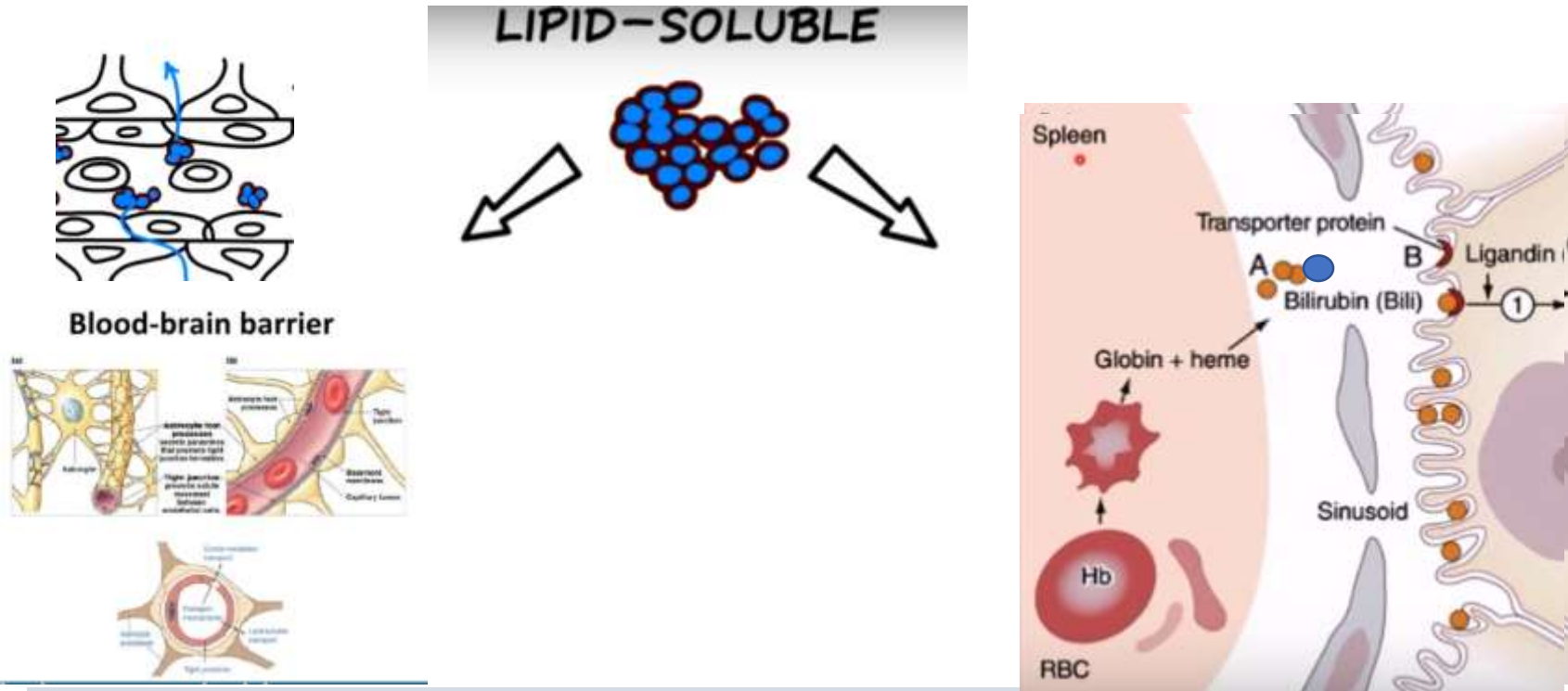
- Remove old erythrocytes from the circulation
 - Lifespan of RBCs = 120 days
- Hemoglobin broken down into
 - Iron
 - Reutilized
 - Globin
 - Degraded and returned to the amino acid pool





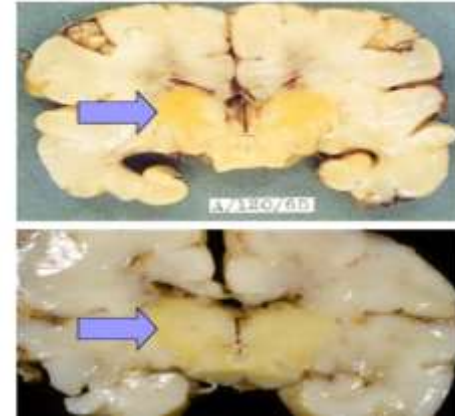
Why to know the **Bilirubin Production & Metabolism**

Unconjugated Bilirubin in plasma



- 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
- ▣ Liver disease
- ▣ Biliary obstruction

Normal level

▣ $< 1.5 \text{ mg/dL}$

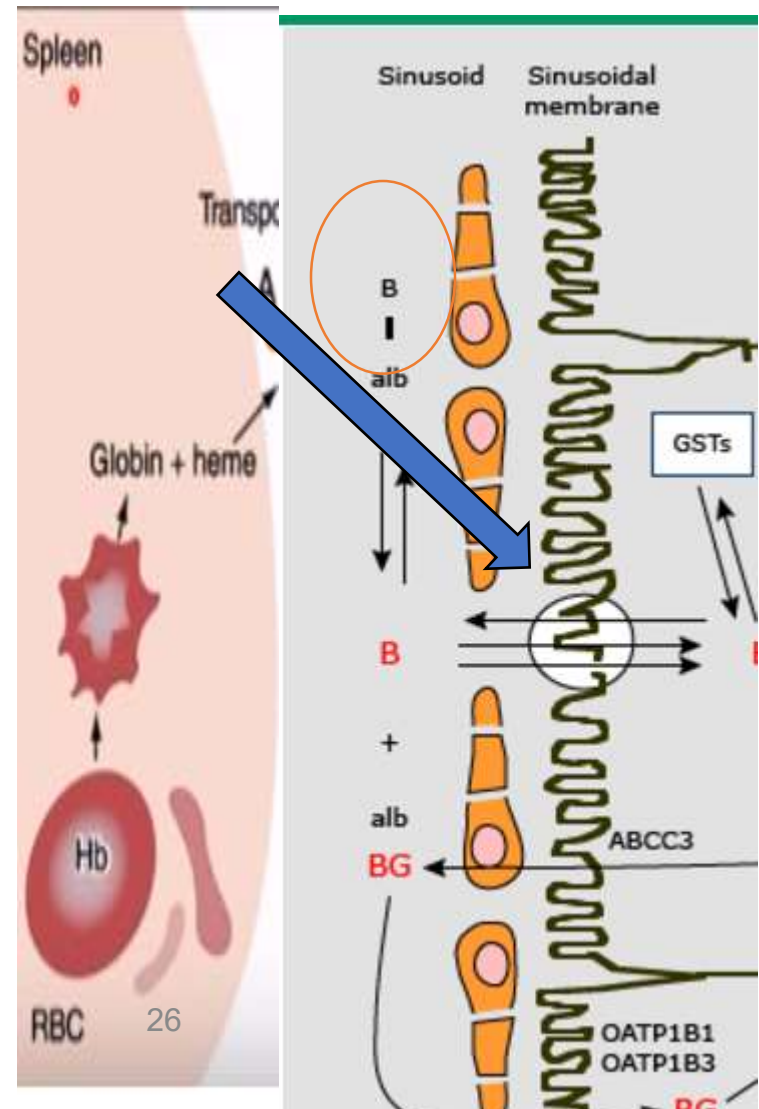
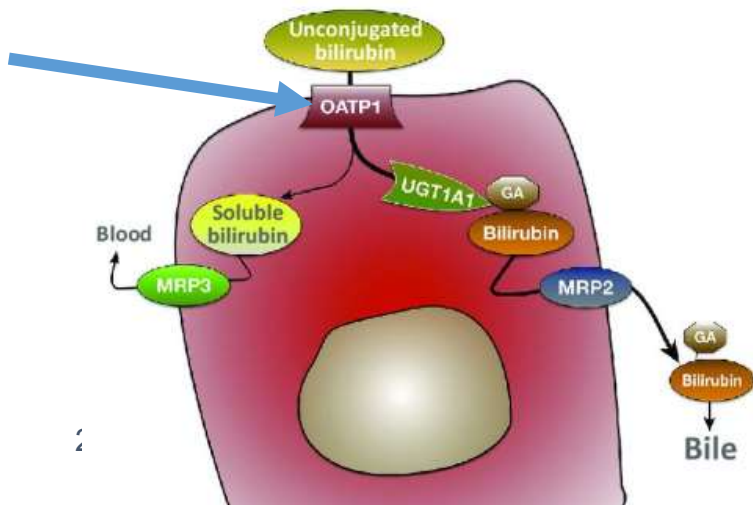
- ▣ Almost entirely bilirubin (unconjugated)
 - ▣ Tightly but reversibly bound to albumin

Unless

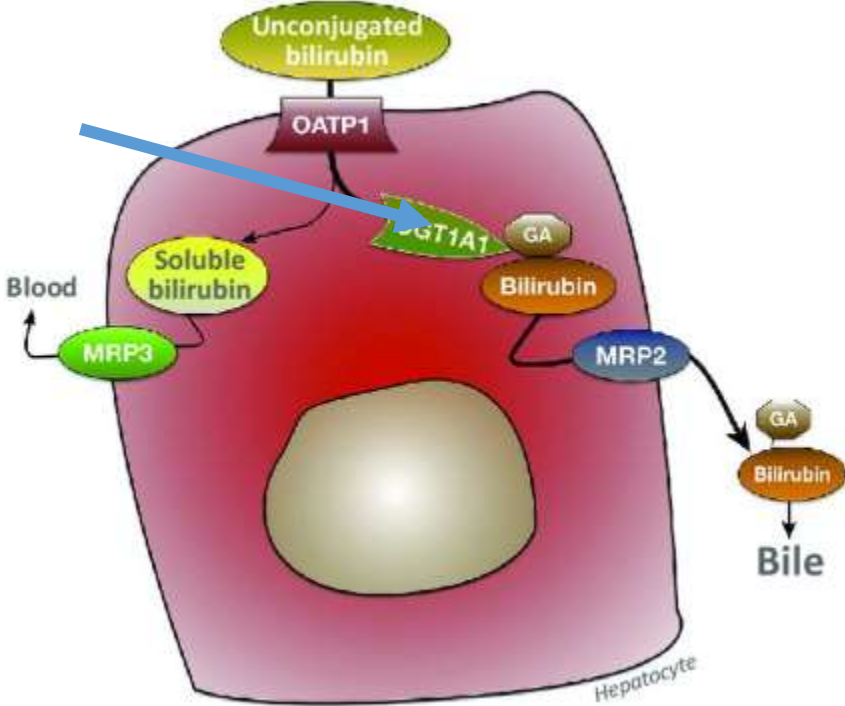
Hepatic uptake – Circulating bilirubin

Hepatocyte

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



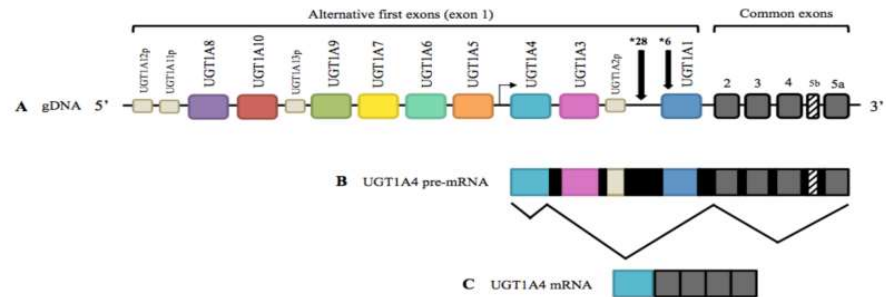
conjugation



Role of uridine diphosphate glycosyltransferase Enzyme

conjugation is catalyzed by the enzyme **Uridine diphosphate glycosyl transferase 1A1 (UGT1A1 Enzyme)**

” *UGT1A1* gene (ID: 54658) is a **part of a complex locus encoding 13 UDP-glucuronosyltransferases**)

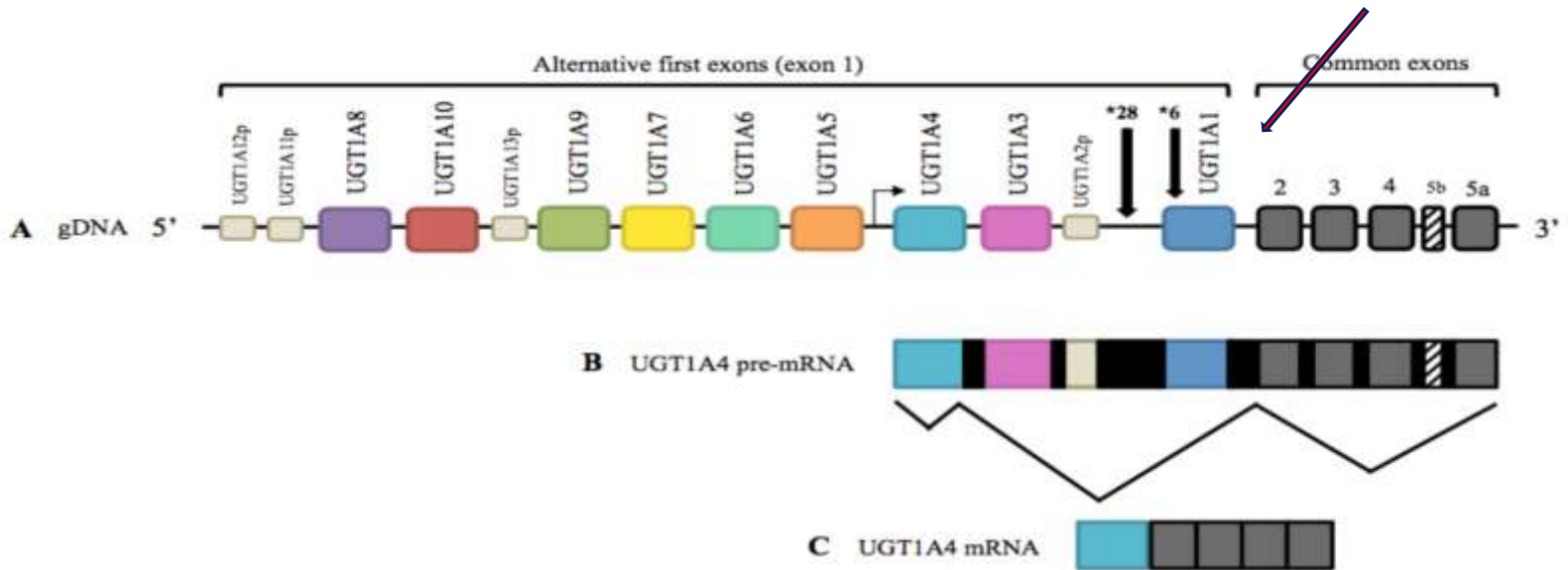


What does UGT1 stand for?

UGT1A1 stands for

"UDP-glucuronosyltransferase family 1

gene : uridine diphosphate-glucuronosyltransferase-1A1
(UGT1A1)

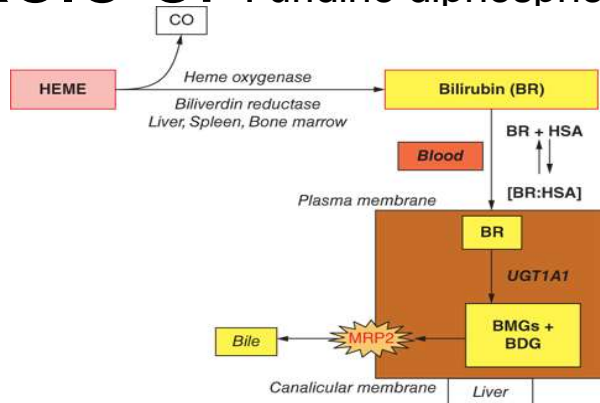


conjugation is catalyzed by the enzyme **U**ridine diphosphate
glycosyl **t**ransferase 1A1 (UGT1A1 Enzyme)

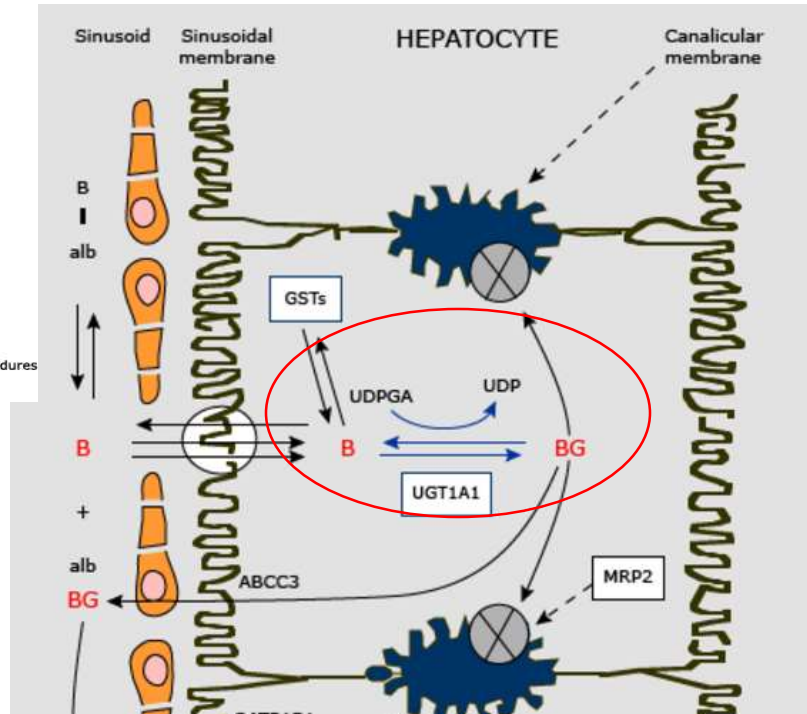
” *UGT1A1* gene (ID: 54658) is a **part of a complex locus**
encoding 13 UDP-**g**lucuronosyltransferases)

Conjugation – In Hepatocytes

Role of : uridine diphosphogluconurate glucuronosyltransferase (UGT1A1)



Source: David K. Stevenson, Ronald S. Cohen, Philip Sunshine: Neonatology: Clinical Practice and Procedures www.accesspediatrics.com Copyright © McGraw-Hill Education. All rights reserved.



Actively excreted into bile

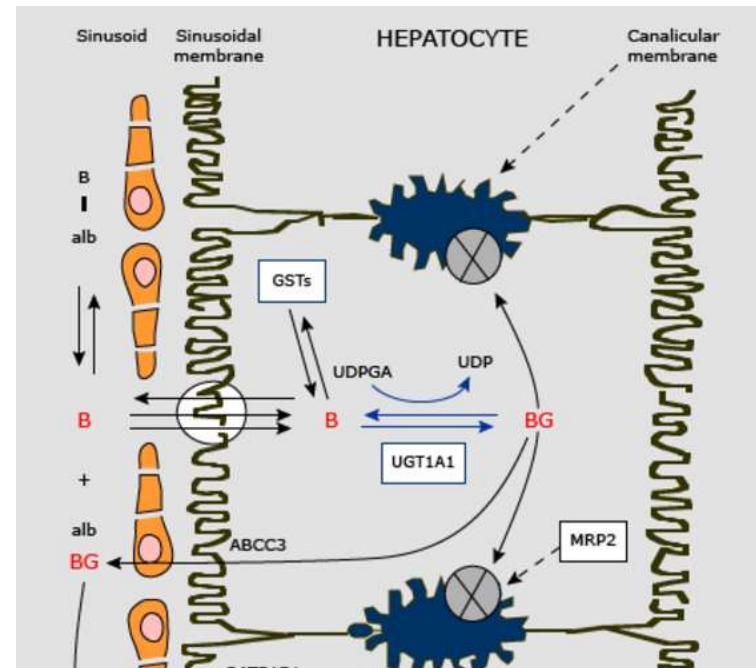
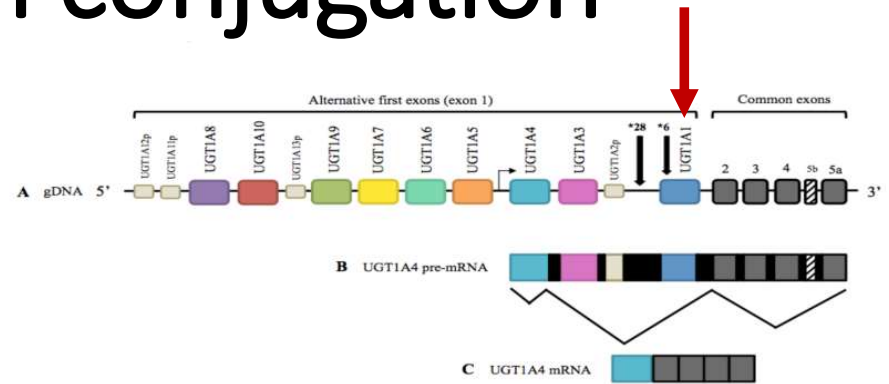
Bilirubin in bile

- 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

Conjugation abnormalities:

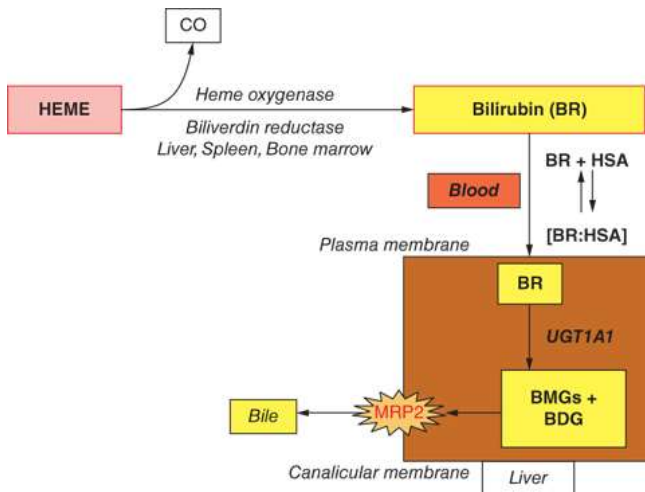
- UGT1A1 polymorphism
- Crigler –Najar Syndrome
- Gilbert Syndrome
- Inhibitory factors for hepatic UGT1A1!

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)



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

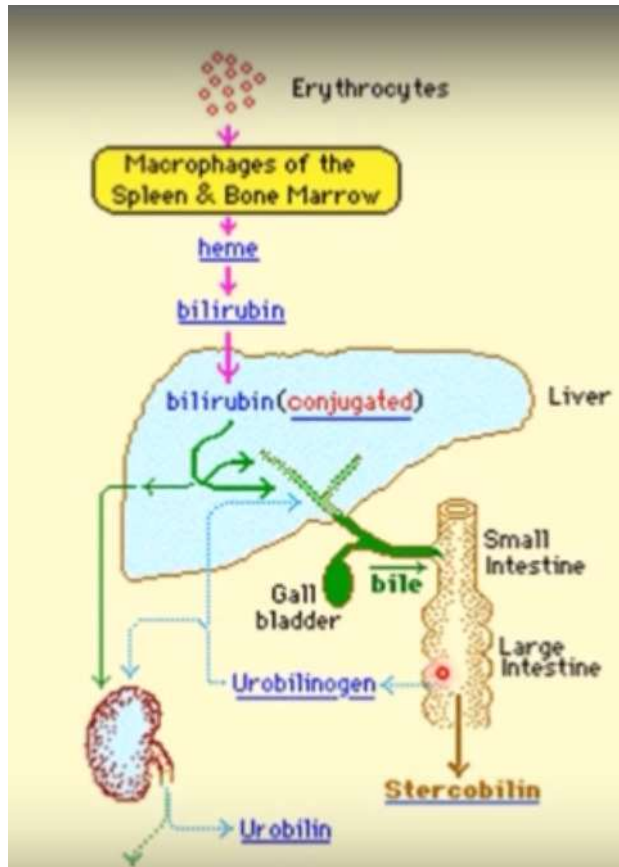
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Enhanced bile flow
 by phenobarbital

Dubin-Johnson syndrome

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

Bilirubin metabolism In adult



Unconjugated bilirubin

- ▣ Reduced by normal gut bacteria
 - ▣ Colorless urobilinogen

Urobilinogen

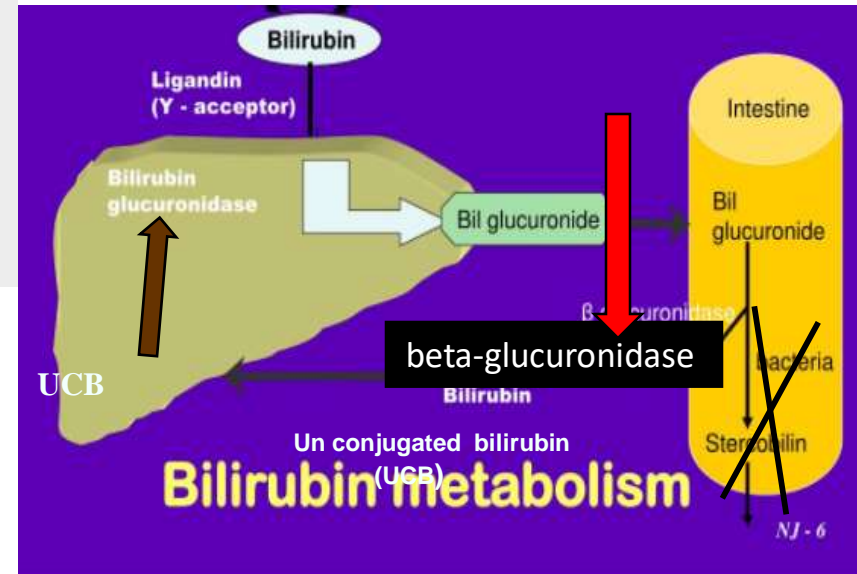
- ▣ Oxidized in the colon to colored stercobilin
- ▣ 85%
 - ▣ Excreted in feces as stercobilinogen
- ▣ 15%
 - ▣ Enterohepatic circulation
 - ▣ Passively absorbed into the portal venous blood
 - ▣ Enter the liver
 - ▣ Re-excreted by liver into the intestine

Some is urobilinogen go to the blood reach the kidney and excreted as 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

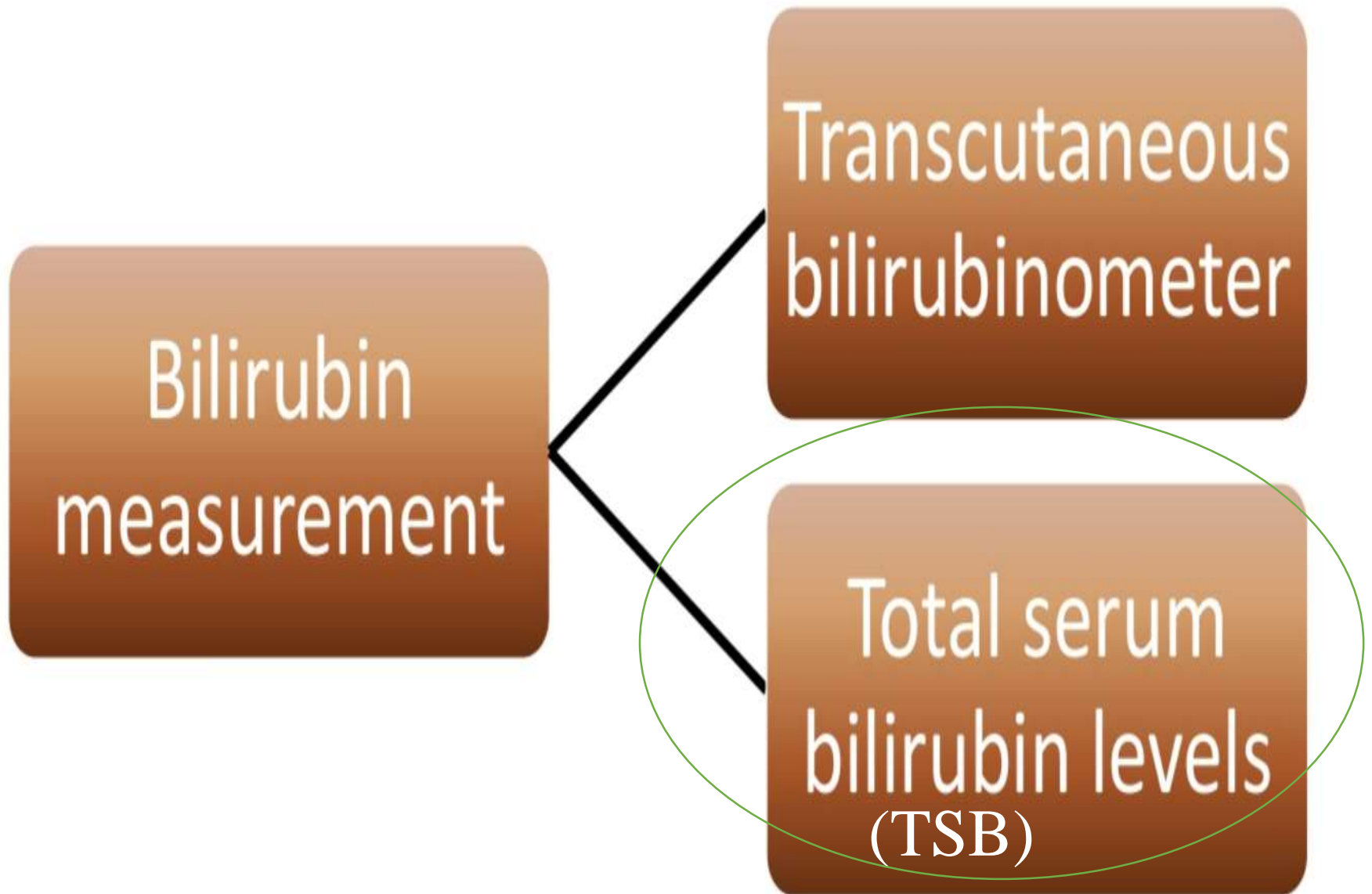


Excessive amounts of bilirubin are available for reabsorption in : obstruction of the upper intestinal tract, delayed passage of meconium, or fasting (decrease transient time)

Break 1



معبد هرقل: قام بتشييده الإمبراطور الروماني أوريليوس سنة 161م، ولم يبق منه إلا الواجهة المؤلفة من ستة أعمدة، ارتفاعه كل عمود حوالي 30 قدم: جبل القلعه



Transcutaneous bilirubinometer (TcB)

Clipboard

- TcB is a useful adjunct to TSB measurement and routine employment 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.



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treatment

Types of Neonatal Jaundice

Physiological Jaundice

Pathological Jaundice

Breast-milk Jaundice

Breast-feeding Jaundice

Related to
breast milk



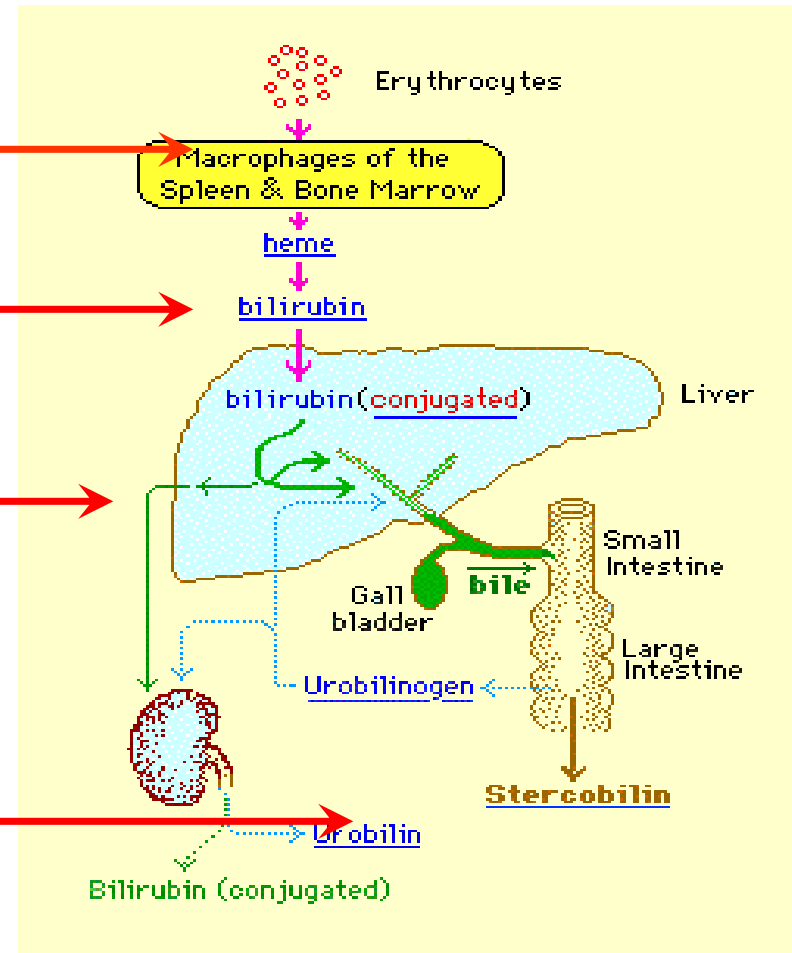
Mechanism of Physiologic Jaundice

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

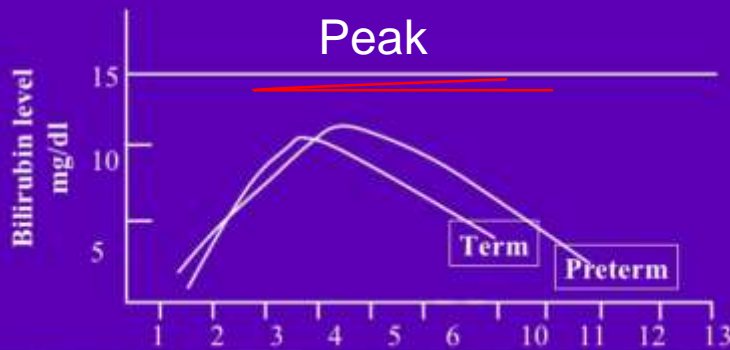
Physiologic Jaundice:

1. Has Pattern

HAS PEAK

Peak
3-4 DAYS IN TERM
5- 7 days in preterm

Course of physiological jaundice



- 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 .

Physiologic Jaundice: 2. Baby is well



Physiologic Jaundice

3. - Bilirubin rise trend

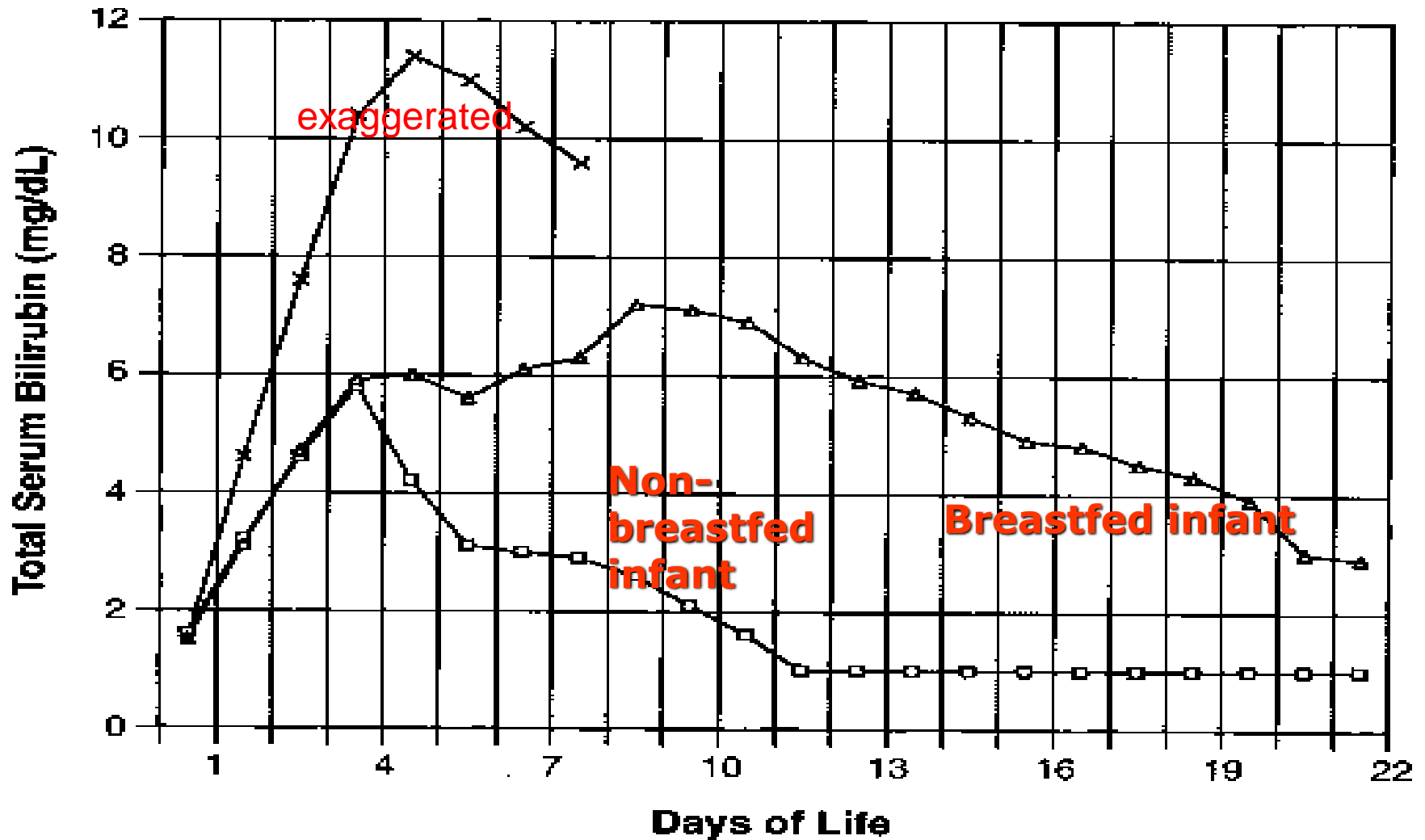
Increase should <than 0.2 mg/dL / hour.

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

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

Physiologic Jaundice:

4. May be exaggerated



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

Why Breastfeeding can cause exaggerated Physiologic Jaundice

- Can exaggerate the peak of physiologic Jaundice
- Through Breast feeding Jaundice (BFJ)

Types of Neonatal Jaundice

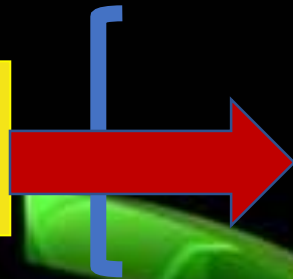
Physiological Jaundice

Pathological Jaundice

Breast-milk Jaundice

Breast-feeding Jaundice

Related to
breast milk



What is Breast feeding Jaundice (BFJ)?

- 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 (day 3-4)
 - **May** associated with **increase serum Na** level and Dehydration fever **fever**
- It is. The Elevated bilirubin in the first few days of life
- Mandates improved/increased breastfeeding (for hydration)
 - No water or dextrose supplementation
 - Formula (OK)
 - May need phototherapy (**shared decision with parents**)
 - Give feed every 2-3 hours

Physiologic Jaundice

Has a pattern ..continue

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

What is 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

Types of Neonatal Jaundice

Physiological Jaundice

Pathological Jaundice

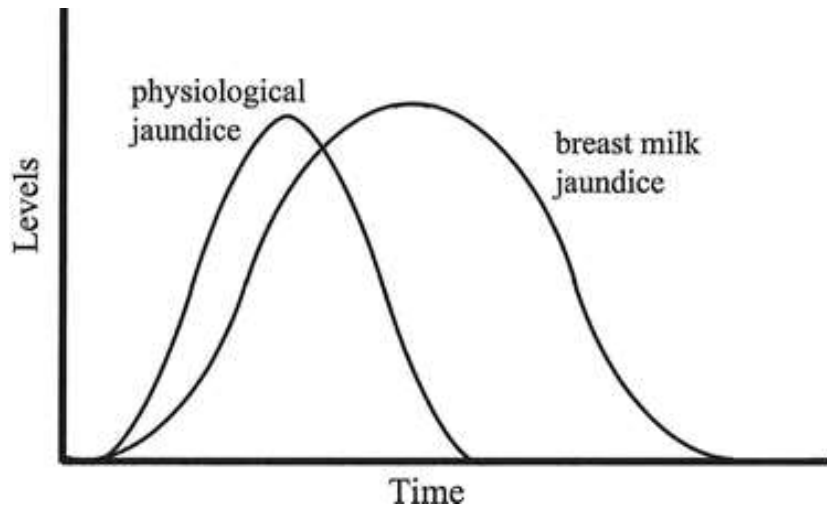
Breast-milk Jaundice

Breast-feeding Jaundice

Related to
breast milk



Breast Milk Jaundice (BMJ)



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

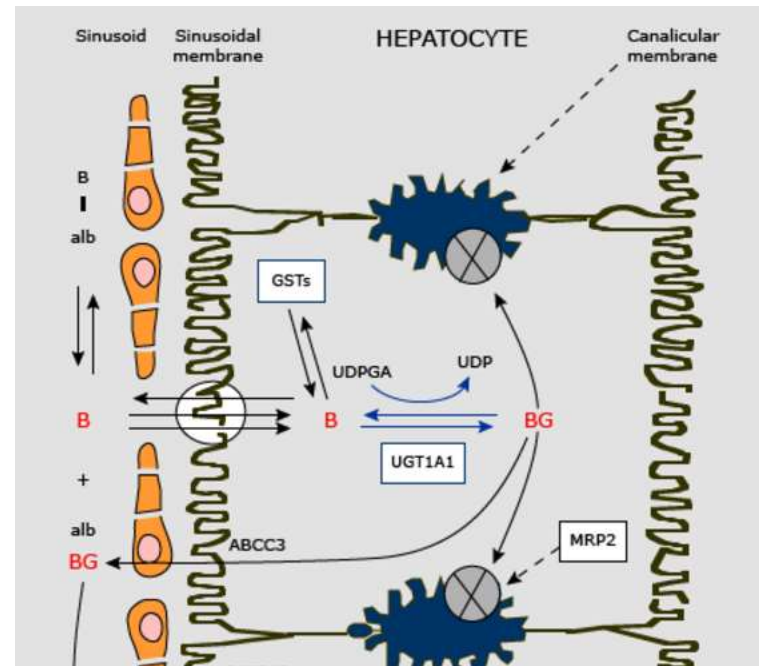
- Develops after the first 4-7 days of life, persists longer than physiologic jaundice
- May be Familial
- May last 3-12 weeks
- Rare to cause BIND unless bilirubin > 25 mg/dl
- has no other identifiable cause
- main cause of prolonged Jaundice
- ?Milk inhibitors and genetic factor
 - substances in the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

Prolonged Jaundice :causes

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.



Jaundice and Breast milk

Breastfeeding Jaundice versus Breastmilk Jaundice

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

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

Types of Neonatal Jaundice

Physiological Jaundice



Pathological Jaundice

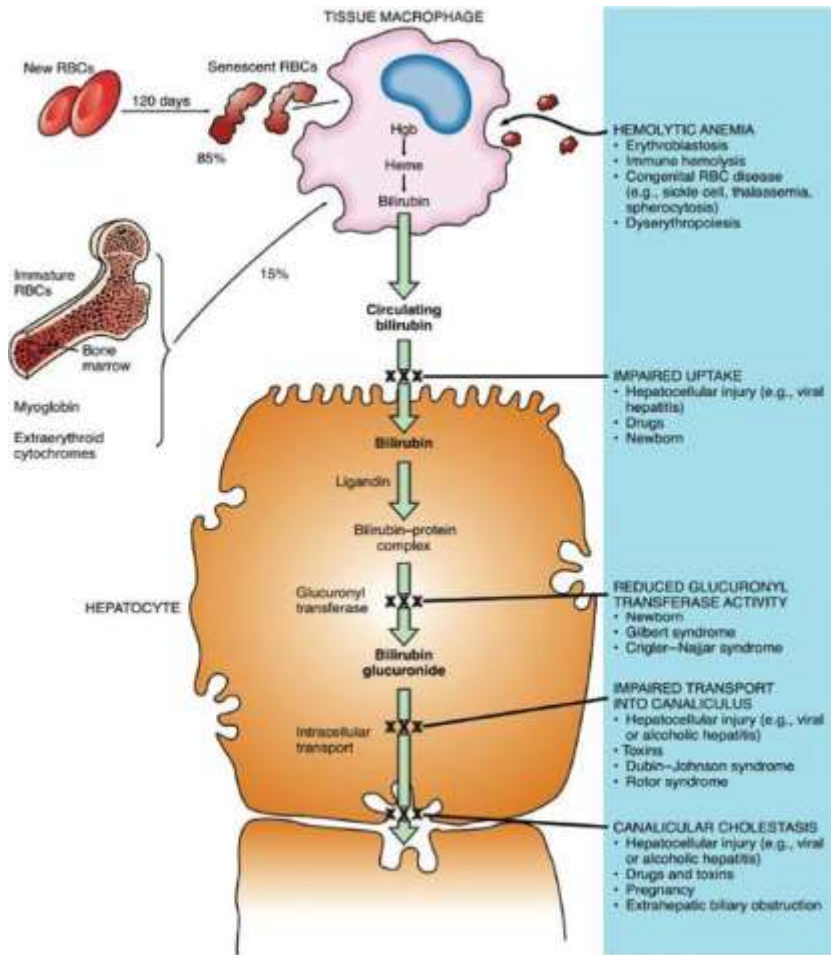
Breast-milk Jaundice

Breast-feeding Jaundice



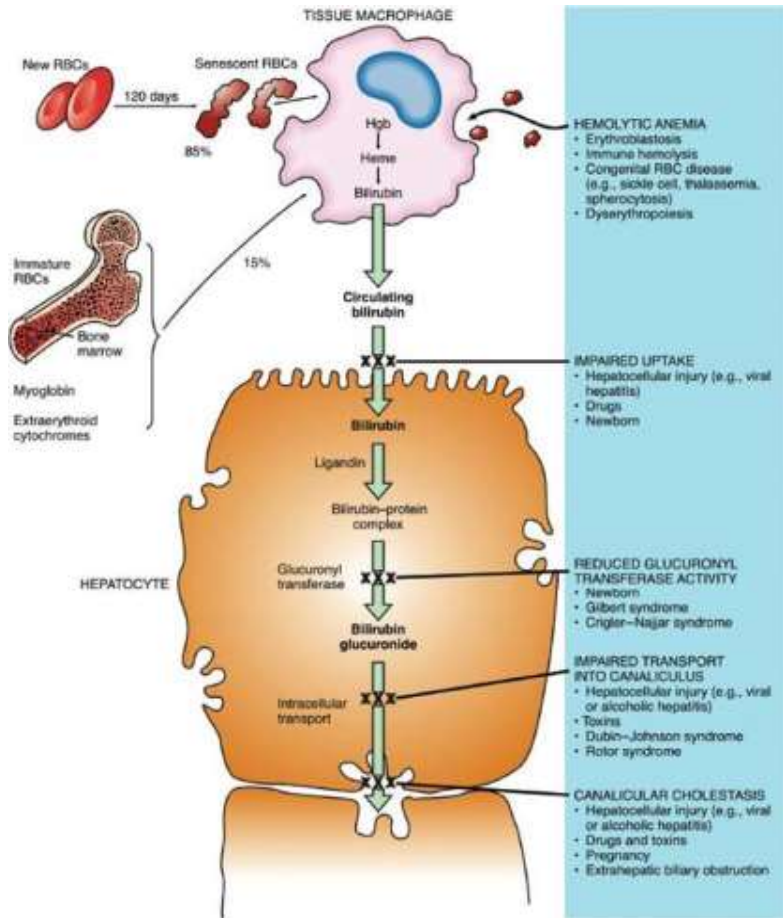
➤ **Types and Causes of neonatal
Jaundice (Pathological Jaundice)**

Pathologic Jaundice

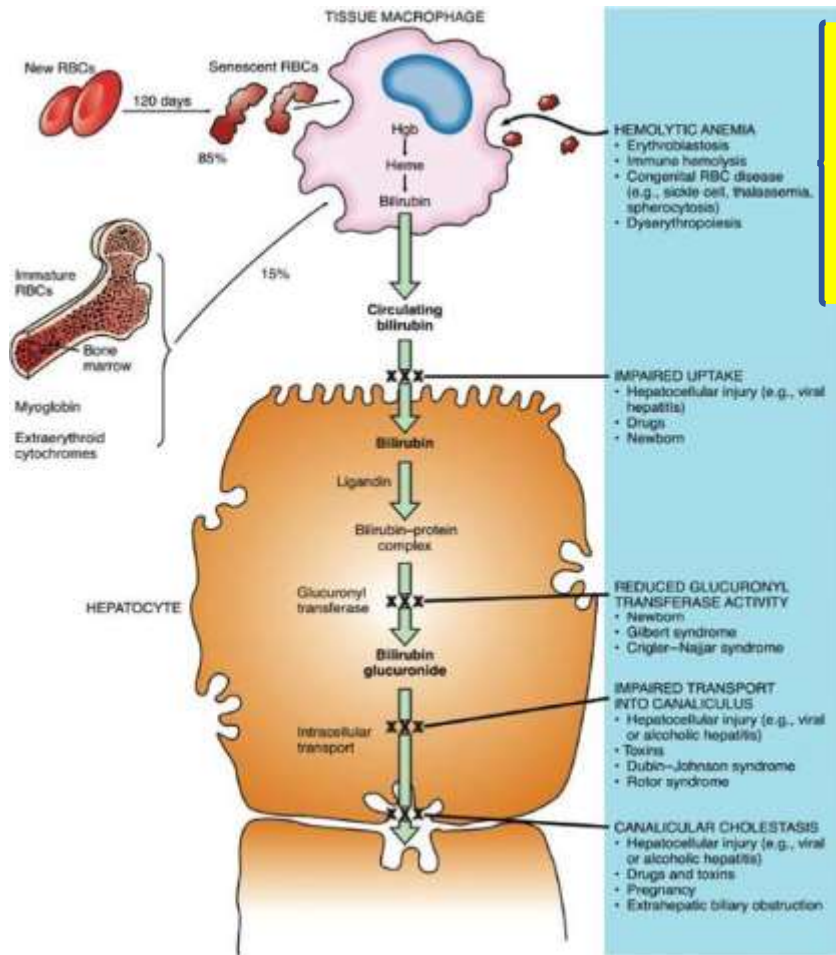


- is a medical emergency.-

Causes of Pathologic indirect hyperbilirubinemia 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)-

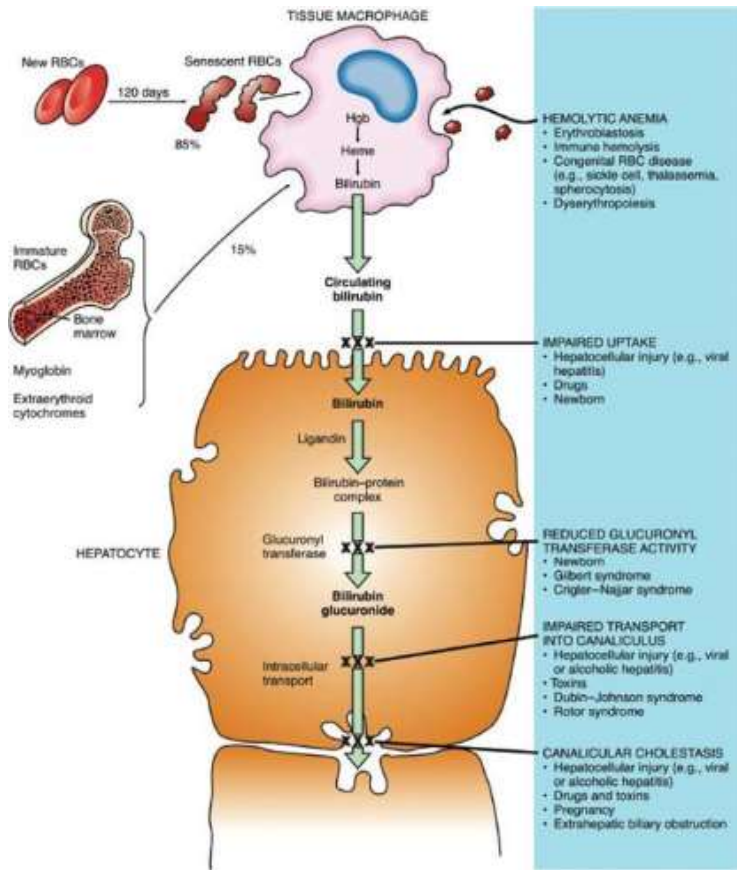
•Galactosemia

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**

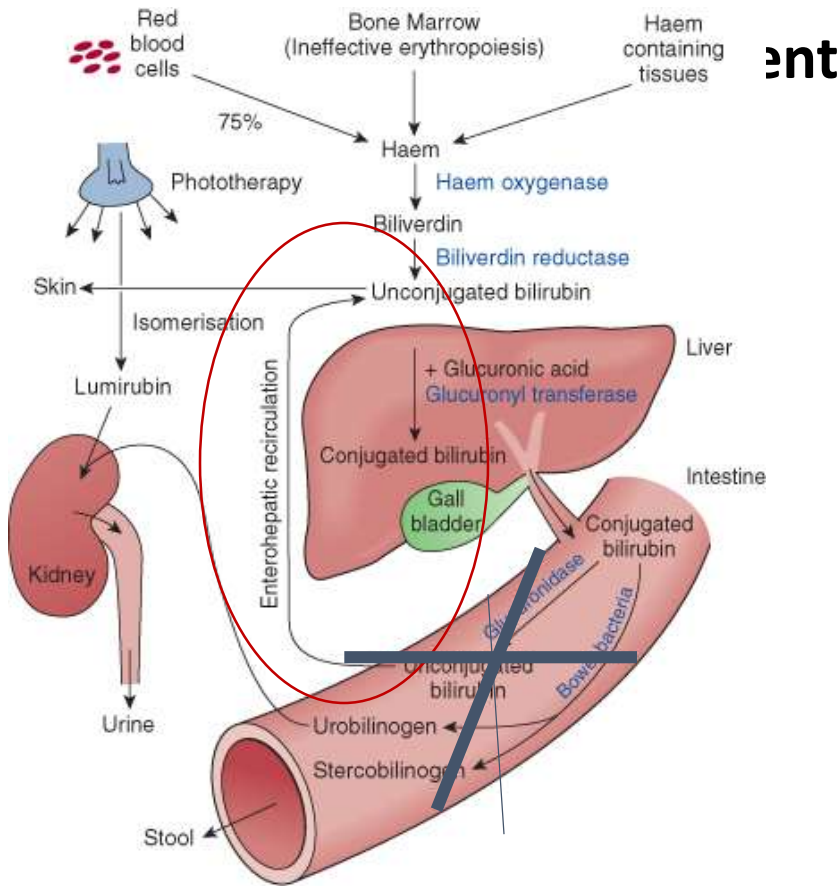
- **Defects** in the gene that encodes UGT1A1

- - 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

Causes of unconjugated hyperbilirubinemia in neonates⁴⁻⁶

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

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

Pathologic jaundice:

How to recognize



القصر الأموي: جبل القلعه

Suspicion 1:

Cord blood
TSB at 24 hour

Pathologic jaundice: How to recognize

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
1 st day bilirubin mg/dL	6.41±1.8	3.2±1.32	<0.01

P value <0.01 is 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

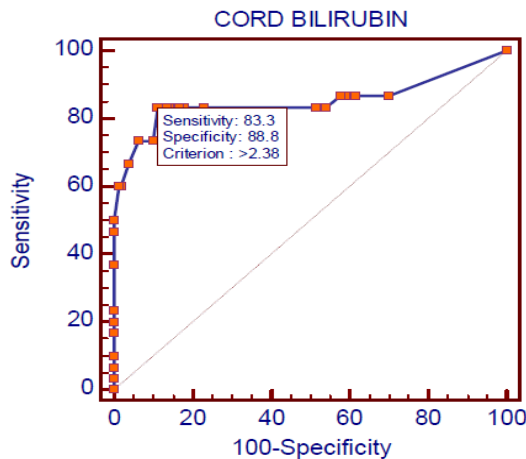


Table-4 :Sensitivity, specificity, positive predictive value and negative predictive values of cord and 1st day bilirubin levels for prediction of hyperbilirubinemia

Jaundice
in 1st 24
hrs

High sensitivity and specificity
to develop severe
hyperbilirubinemia if

cord total bilirubin > 2.38mg/dl
total Serum bili level at 24 hor of
> 5 mg/dl

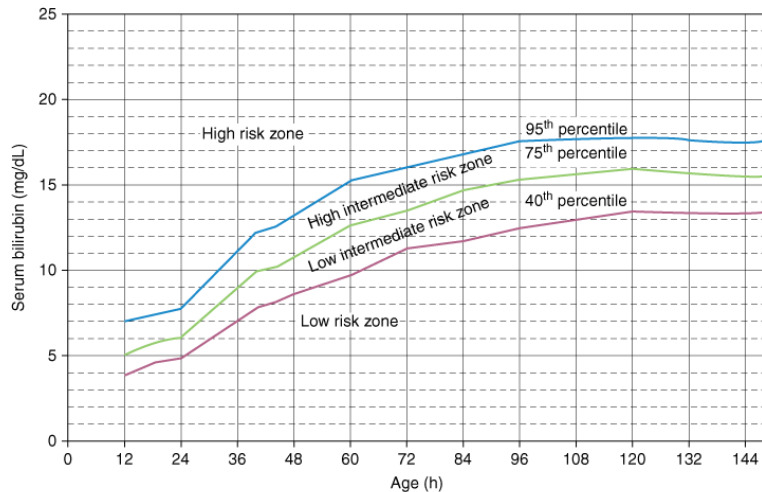
Suspicion 2: Pattern of rise

Pathologic Jaundice: How to recognize

• Pattern of rise

- Rapidly rising TSB (> 5 mg/dL per day)
- > 0.2 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

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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

How to asses of neonate at risk of sever hyperbilirubinemia ?

Management

Guidelines

Work UP

Treatment

Prevention

treatment

How to asses of neonate at risk of sever hyperbilirubinemia ?

My Baby

Is he at risk to develop sever

Hyperbilirubinemia: ???

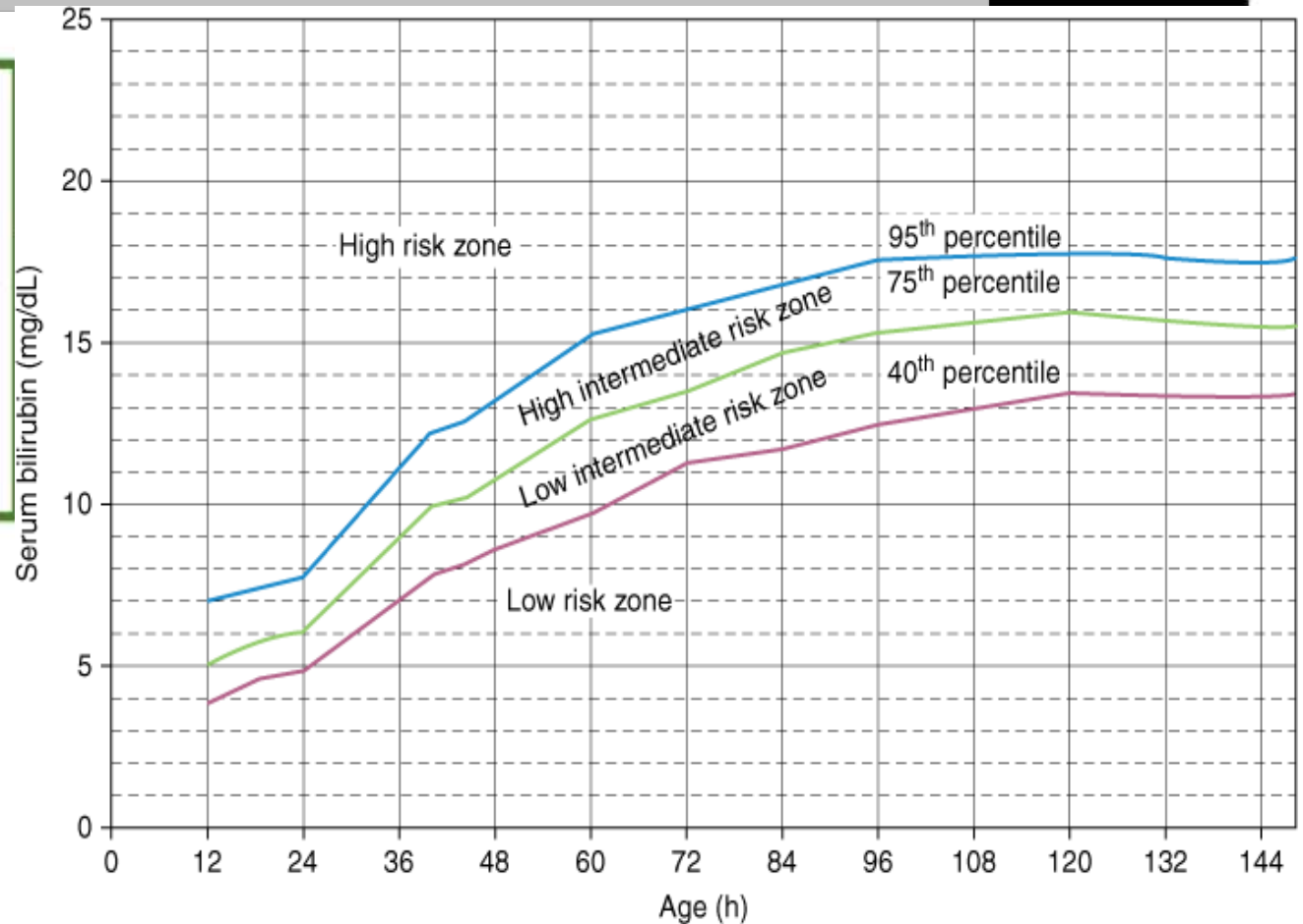


1-Assess the risk Zone

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

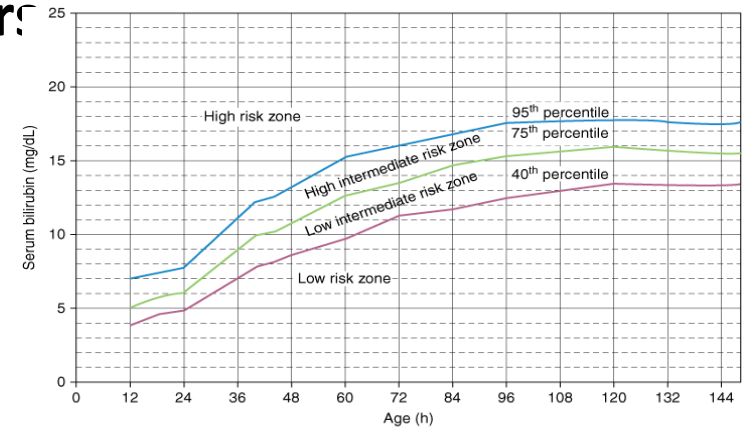
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At Discharge

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

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

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 - **2. And/or Assessment of risk factors**

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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	

Know the risk factors

Pre discharge screen

3- High bilirubin clinical Risk factors (by taking History)

(risk for sever hyperbilirubinemia)

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
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You can use Mobile Application to asses risk factors : AAP

BiliTool™
Hyperbilirubinemia Risk Assessment for Newborns

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Hour-specific Nomogram for Risk Stratification

Infants age: 18 hours
 Total bilirubin: 8 mg/dl
 Risk zone: High Risk

Risk zone is one of several [risk factors](#) for developing severe hyperbilirubinemia.

AAP Phototherapy Guidelines (2004)

Neurotoxicity risk zone	Start phototherapy?	Approximate threshold 18 hours of age
Lower Risk <small>(≥ 35 weeks and well)</small>	No	10.4 mg/dL
Medium Risk <small>(≥ 38 weeks + neurotoxicity risk factors OR 35 to 37 w/7 weeks and well)</small>	No	8.8 mg/dL
Higher Risk <small>(35 to 37 w/7 weeks and neurotoxicity risk factors)</small>	Yes	7 mg/dL

It is an option to provide conventional phototherapy in the hospital or at home at TSB levels 2-3 mg/dL [35-50 μmol/L] below those shown. Home phototherapy should not be used in infants with risk factors.

Recommended Follow-up

A follow-up visit and/or a recheck bilirubin value is recommended within 24 hours (high risk).

References

Hour-specific nomogram
 Phototherapy nomogram
 Risk factors for developing severe hyperbilirubinemia

Input:

Infant age: Hours
 Total bilirubin: mg/dL

Clinical risk group: Group 1: Gestation ≥38 weeks and medically well
 Group 2: Gestation ≥38 weeks and clinical risk factors
 Group 2: Gestation 35 to 37.9 weeks and medically well
 Group 3: Gestation 35 to 37.9 weeks and clinical risk factors

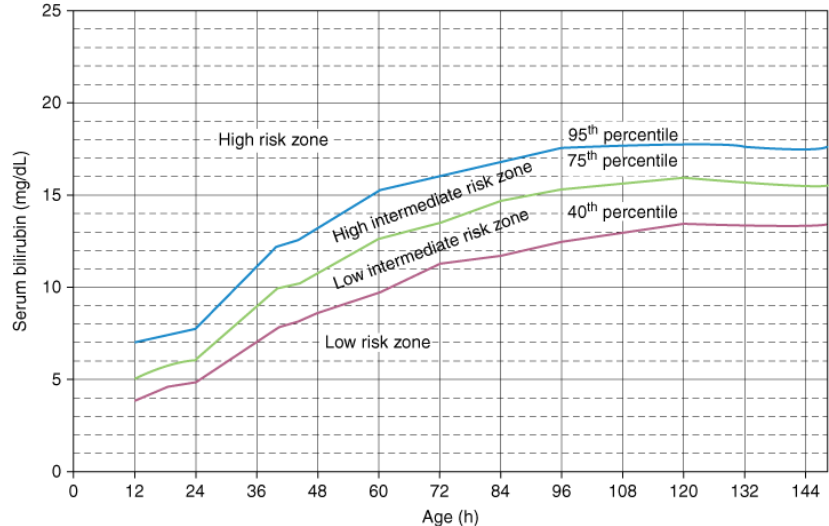
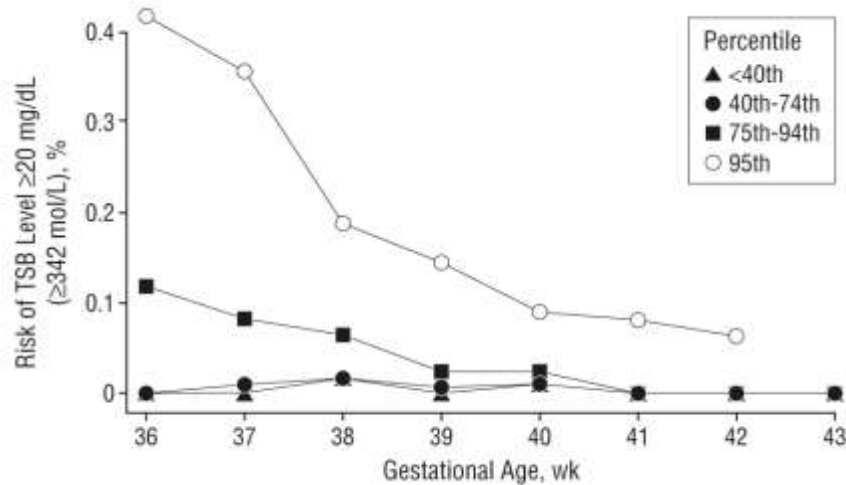
Results:

The bilirubin level is in the **LOW-INTERMEDIATE RISK** zone (between the 40th and 75th percentiles for this age: 11.60 mg/dL [198.4 μmol/L]-14.70 mg/dL [251.4 μmol/L])

2-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

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Increase risk of severe hyperbilirubinemia risk with decrease GA
Study on those >36 weeks

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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	

Why to know risk factors
potentially correctable causes:

Kernicterus cases –[Pediatrics Journal](#)

- **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

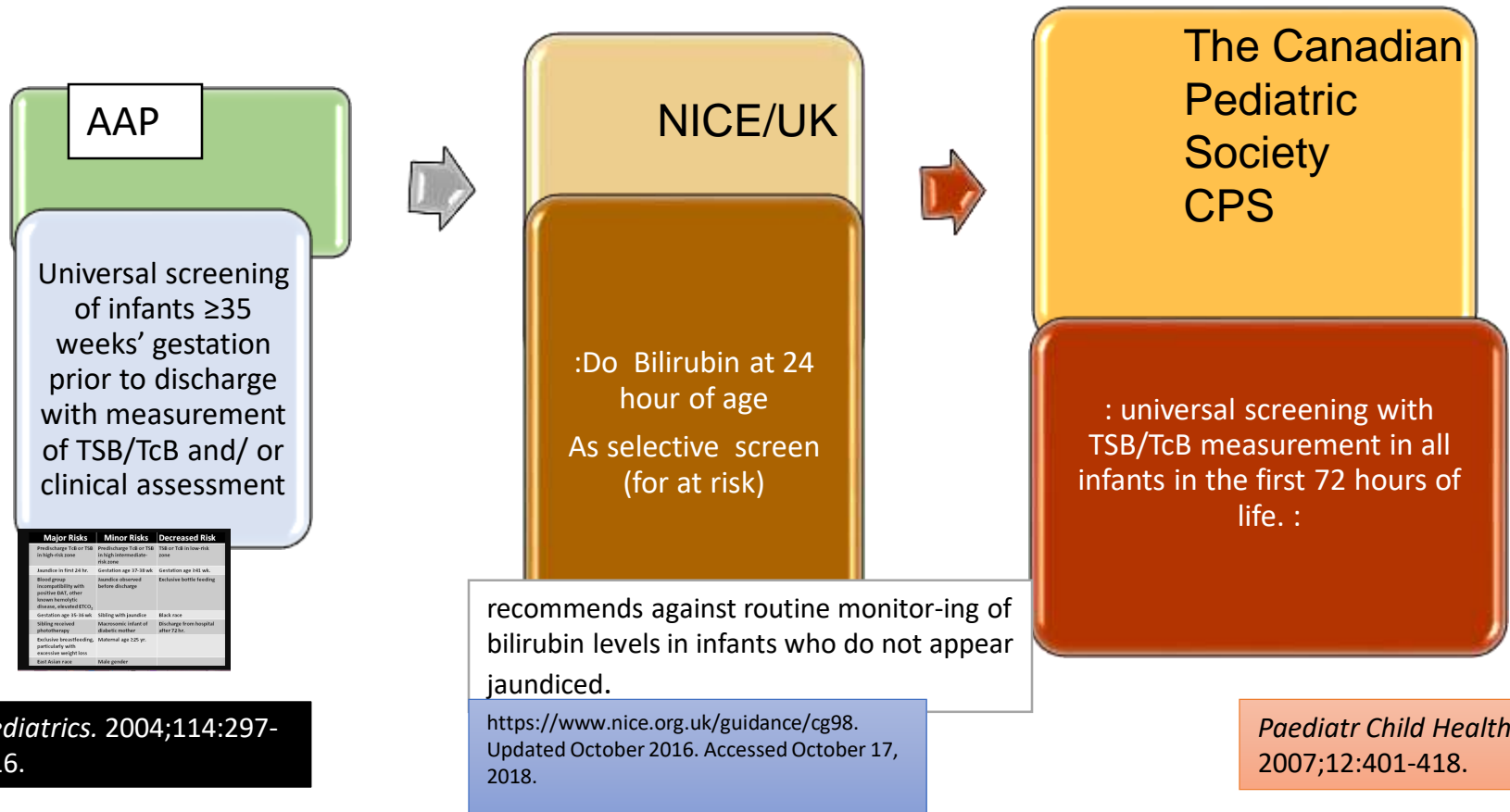
- All newborns should be routinely assessed for jaundice.
- Jaundice is visible when Sr. Bilirubin $>5\text{mg/dl}$.

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.

Screening recommendations lack consensus

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



Pediatrics. 2004;114:297-316.

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

Mobile Application to assess risk factors : AAP

BiliTool™
Hyperbilirubinemia Risk Assessment for Newborns

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 Total bilirubin: 8 mg/dl
 Risk zone: High Risk

Risk zone is one of several [risk factors](#) for developing severe hyperbilirubinemia.

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A follow-up visit and/or a recheck bilirubin value is recommended within **24 hours (high risk)**.

References

Hour-specific nomogram
 Phototherapy nomogram
 Risk factors for developing severe hyperbilirubinemia

AAP Phototherapy Guidelines (2004)

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Input:

Infant age: Hours
 Total bilirubin: mg/dL

Clinical risk group: Group 1: Gestation ≥ 38 weeks and medically well
 Group 2: Gestation ≥ 38 weeks and clinical risk factors
 Group 3: Gestation 35 to 37 9 weeks and medically well
 Group 3: Gestation 35 to 37 9 weeks and clinical risk factors

Results:

The bilirubin level is in the **LOW-INTERMEDIATE RISK** zone (between the 40th and 75th percentiles for this age: 11.60 mg/dL [198.4 µmol/L]-14.70 mg/dL [251.4 µmol/L])

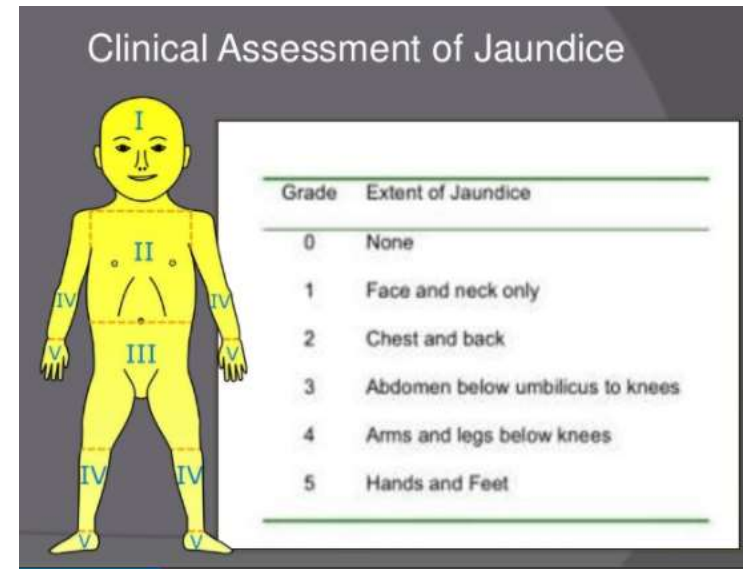
Post-discharge follow-up

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 severe hyperbilirubinemia

Approach

Management

Guidelines

Work UP

Treatment

Prevention

treatment

How to manage if baby is Jaundice

Use A guideline

NICE guidelines (UK)

Measuring bilirubin in all babies with jaundice

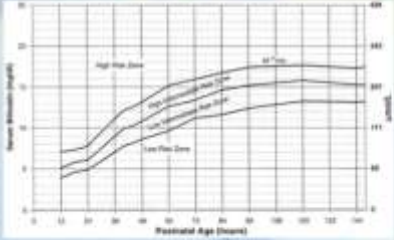
Do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice.



AAP guidelines (USA)

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

Bilirubin metabolism

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Types and Causes of neonatal Jaundice

Breast feeding and hydration

Assessment of neonate at risk of sever hyperbilirubinemia

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Guidelines

Work UP

Treatment

Prevention

treatment

Therapeutic Options

- Phototherapy for neonates with mild jaundice

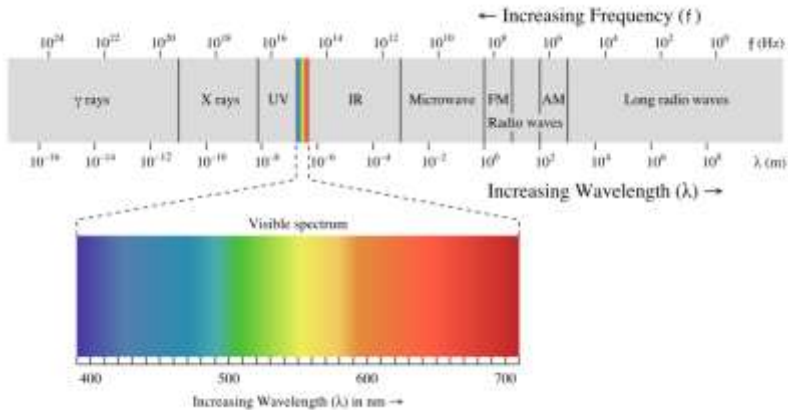


- Exchange transfusion in severe cases



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

Bilirubin chart

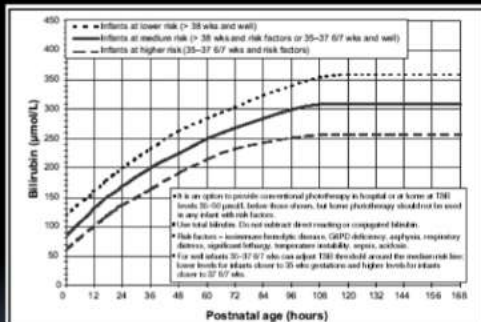
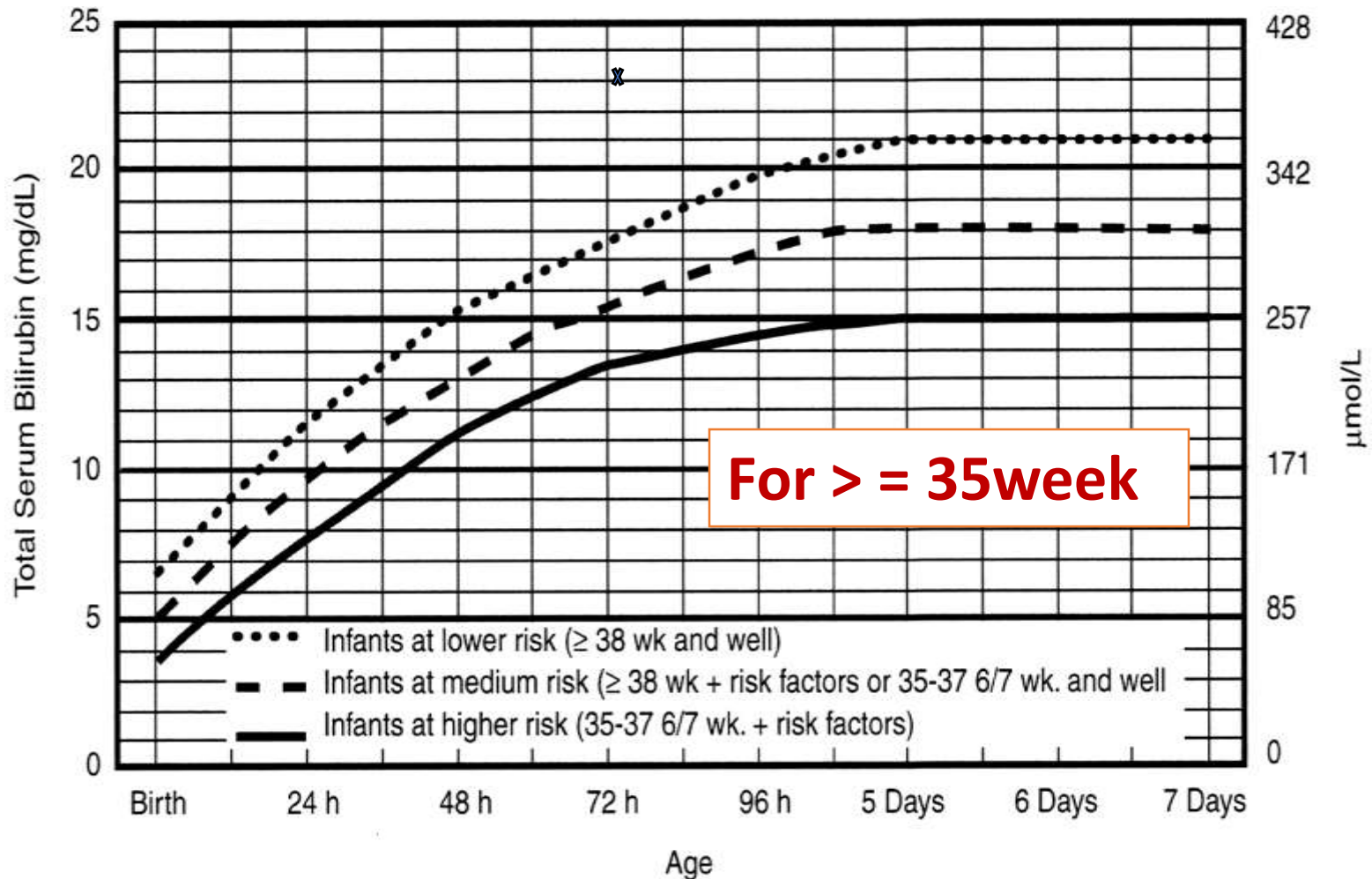


Figure 2) Guidelines for intensive phototherapy in infants of 35 or more weeks' (wk) gestation. These guidelines are based on limited evidence and the levels shown are approximations. Intensive phototherapy should be used when the total serum bilirubin (TSB) concentration exceeds the line indicated for each category. G6PD Glucose-6-phosphate dehydrogenase



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



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

Who need photo therapy ?

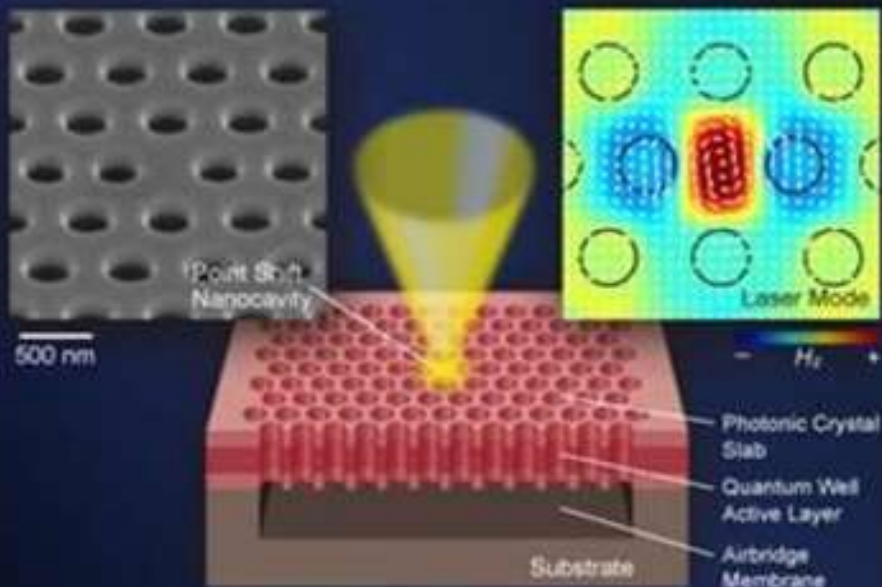
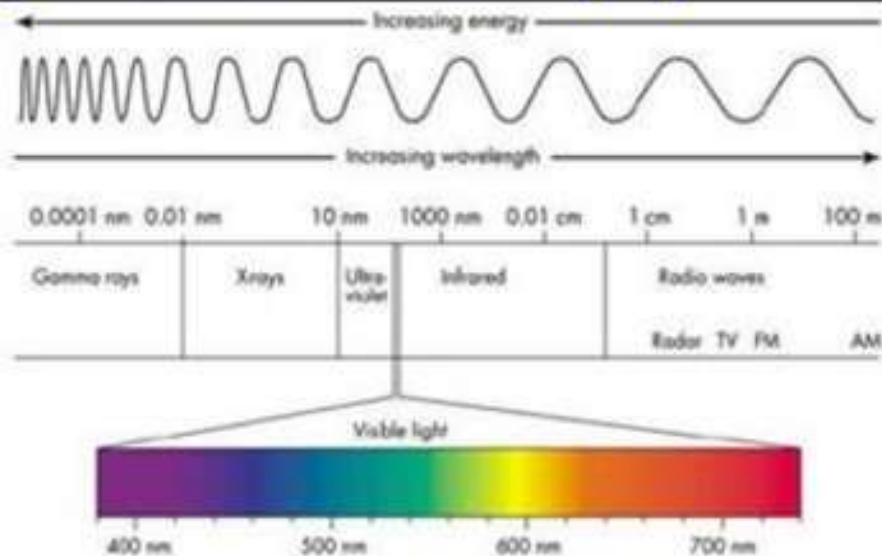
Factors affecting Phototherapy

Wavelength

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

light used in wavelengths

White Blue Green



Microwatts / Irradiation

8 -12 $\mu\text{W}/\text{cm}^2/\text{nm}$

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

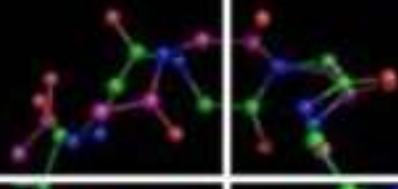


Photo oxidation

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*

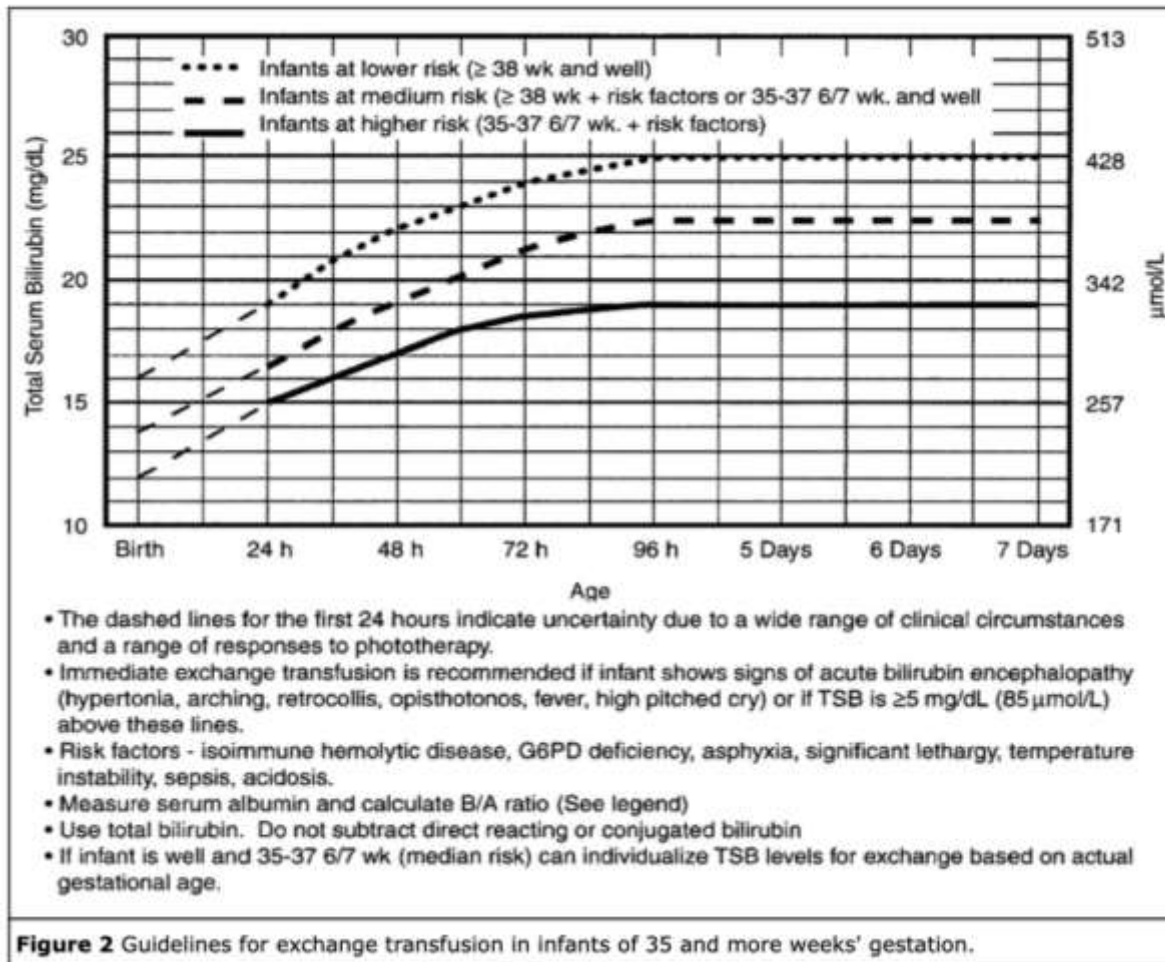
Not influenced significantly by the intensity of light.

Structural Isomerization

Intramolecular cyclization resulting in the formation of lumirubin

Enhanced by increasing the intensity of light.

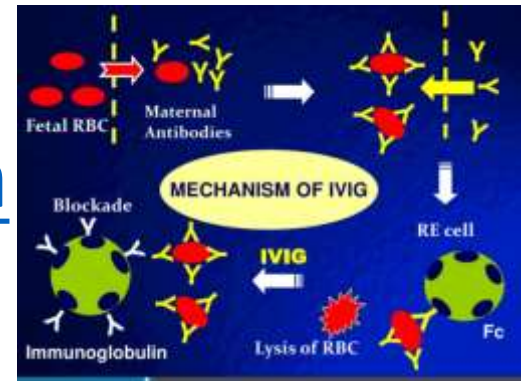
Exchange photo therapy



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

Neonatal Jaundice

Eman Badran
Professor of Pediatrics

Fifth year medical students

Ophthalmologic Problem In neonates



Case based study



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Learning Objectives

- Recognize manifestation of common ophthalmologic problems
- Understand the emergency Neonatal Ophthalmologic problems
- Understand management of common Neonatal Ophthalmologic problems
- Identify the needed work up for Neonatal Ophthalmologic problems

1-Watery eyes



2- Squint



3-Abnormal red reflex



Urgent

A

Source: Lueder GT: *Pediatric Practice Ophthalmology*:
www.accesspediatrics.com

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1- Watery eyes



CASE 1

Common scenario

- 37 week gestation
- Male
- Mother is primigravida's
- At 2 weeks of age Visit
 - the infant came to the clinic with history **excessive lacrimation** (tearing) with **mucoïd discharge** from the eyes or eye

<https://www.medscape.com/viewarticle/902470>

What Is the next step

History

- Duration: 1 wk
- Type of discharge:
Mucoid
- Uni/Bilateral:
Unilateral
- Eye redness: NO
- Course: Constant

Exam

- Cornea: Negative and clear
- Extra ocular movement: Negative
- Conjunctiva: Negative
- Scleral : Negative
- Pupil: round and reactive
- General exam Normal

Case 1

What is Diagnosis

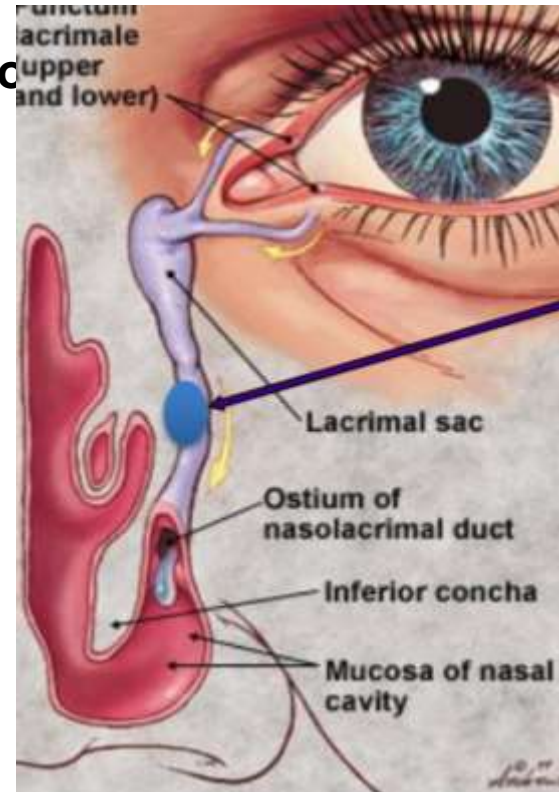


The parents would like to ask why is this pro

The pathogenesis of CNLDO :

- lies in a mechanical obstruction

located distally in the nasolacrimal duct (NLD) at the valve of Hasner, where this structure enters the nose



The parents Ask
you is this
common

- Occurs in 20% of cases
of infants



Congenital Naso-lacrimal duct obstruction

Affect approximately 20% in the first year of life

- Almost 95% of affected showed symptoms at one month of age
- Higher prevalence of CNLDO reported in premature infants
 - Developmental process

Parents were concerned

- How to treat?

Management

- simple observation
- Clean eye
- massage of the lacrimal sac (Crigler)
 - 10 massage s each time 3 times /day
- Application of topical antibiotics when a bacterial superinfection occurs

Parents Ask you

- What will happen
- When it will resolve

- Mostly resolve by one year (90% resolve)

- No improvement : Propping

Family asked

- Do we need to go to Ophthalmologist

Exclude Other Differential diagnosis

- PRIMARY CONGENITAL GLUCOMA (PGG)
- Foreign body
- Corneal infections

- If you are not sure
 - Pediatric Ophthalmology consult

Case 1

Reference

Congenital Nasolacrimal Duct Obstruction (CNLDO): A Review

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313586/pdf/diseases-06-00096.pdf>

Nasolacrimal Duct Obstruction: The Right Way to Teach Parents

<https://www.medscape.com/viewarticle/902470>

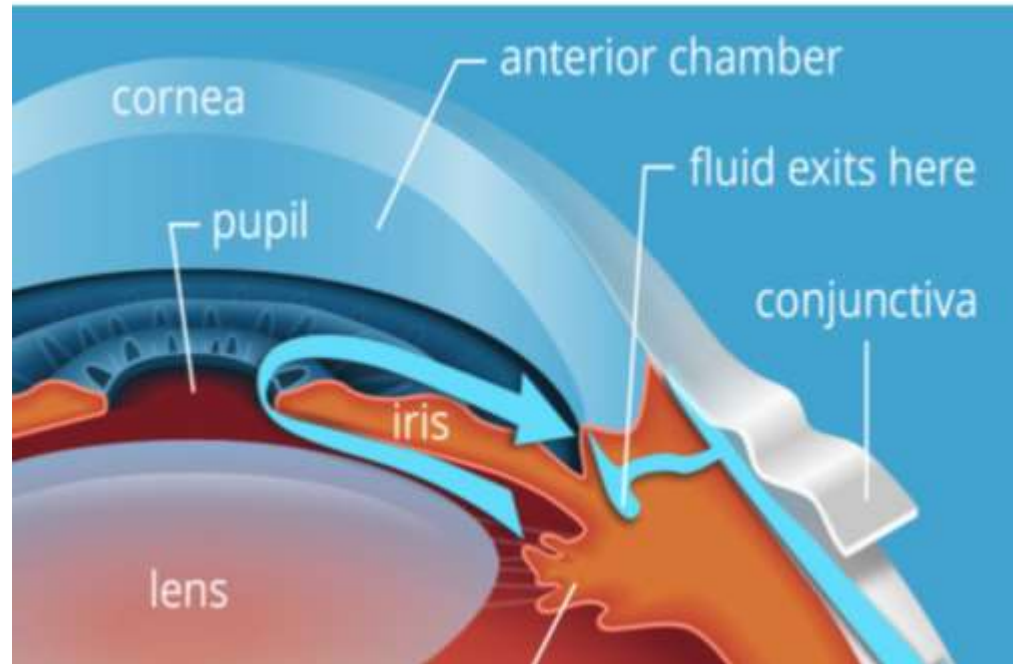
PRIMARY CONGENITAL GLAUCOMAS (PGG)

Due to **defect** in the developmental of the trabecular meshwork and anterior chamber angle

that prevent adequate drainage of aqueous humor,

resulting in elevated intraocular pressure (IOP)

stretching of the sclera that produces an enlarged globe (buphthalmos).



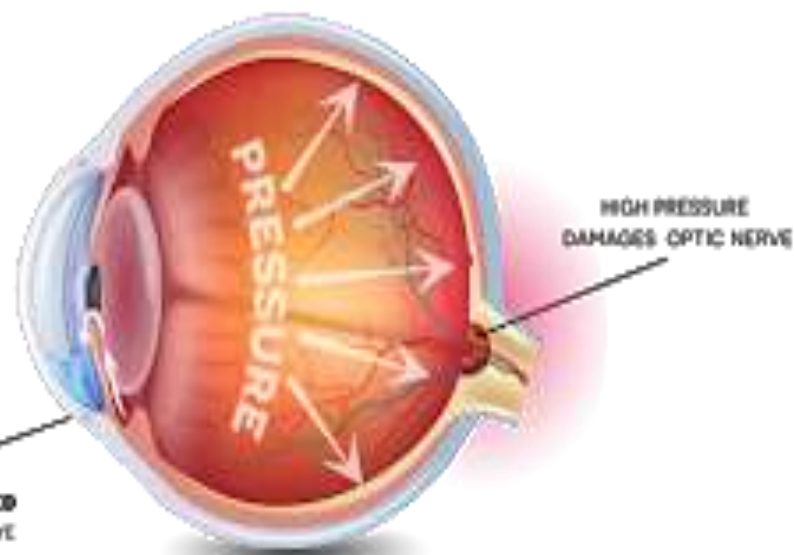
<https://www.kceyeclinic.com/our-services/glaucoma/types-of-glaucoma/>

GLAUCOMA



NORMAL EYE

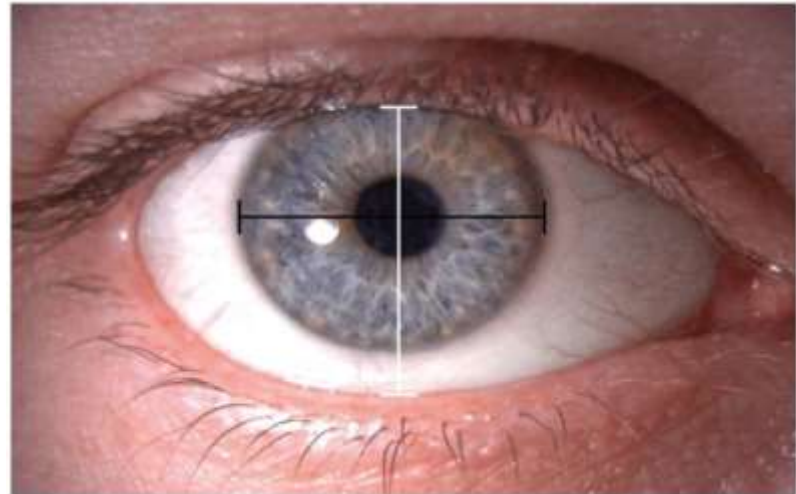
DRAINAGE CANAL BLOCKED
TOO MUCH FLUID STAYS IN THE EYE
THIS INCREASES PRESSURE



GLAUCOMA

Symptoms of [congenital glaucoma](#)

normal horizontal **corneal** diameter is 10.5 mm



Symptoms of [congenital glaucoma](#)

measurements greater than 12 mm are highly indicative of glaucoma.



Top emergency : need surgery
Can neve some damage as Optic nerve

symptoms of [congenital glaucoma](#)

- Tearing (Watery)
- Light sensitivity



Symptoms of congenital glaucoma

- Cloudiness of the cornea due:
 - Edema with opacification of the cornea.
- Enlargement of the eye globe (buphthalmos)
 - (STRECHING OF CORENEA)
- Photophobia
- Blepharospasm,
- **Usually Bilateral**> Unilateral
- Occur in 1:10,000



RISK FACTOR

Family history of congenital glaucoma

Genetic consult do: exome sequencing and genome sequencing
[pathogenic variant\(s\)](#)

CAN BE :

Autosomal recessive inheritance:

Autosomal dominant inheritance:

Prenatal diagnosis for pregnancies at increased risk is possible if the PCG-causing [pathogenic variant\(s\)](#) in the family are known.

Risk factors for Congenital Glaucoma

Sturge-Weber syndrome

facial port-wine stain involving the **upper** and **lower** eyelids



Risk factors

- congenital [rubella](#) (rare)

DDX : of PRIMARY CONGENITAL GLAUCOMAS (PGG)

- Infantile CG (may present in neonatal period)
 - Have another causes as part of syndromes and trisomy's
 - Important to be defeminated for genetic counseling

Squint



Case 2

- During 2 weeks Neonatal visit
- Parents noticed that their baby has **squint**
 - They said it is (**intermittent** side ways)
- His history and **Physical exam is unremarkable**
- He was **healthy**
- **Red reflex** were normal and symmetrical corneal reflex

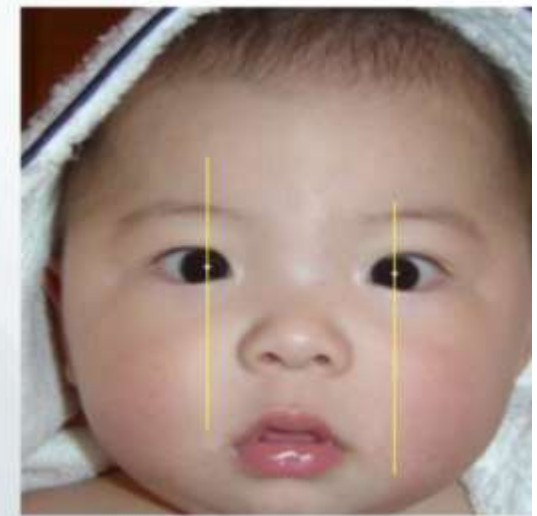
Strabismus – “squint that goes away”

Transient neonatal strabismus



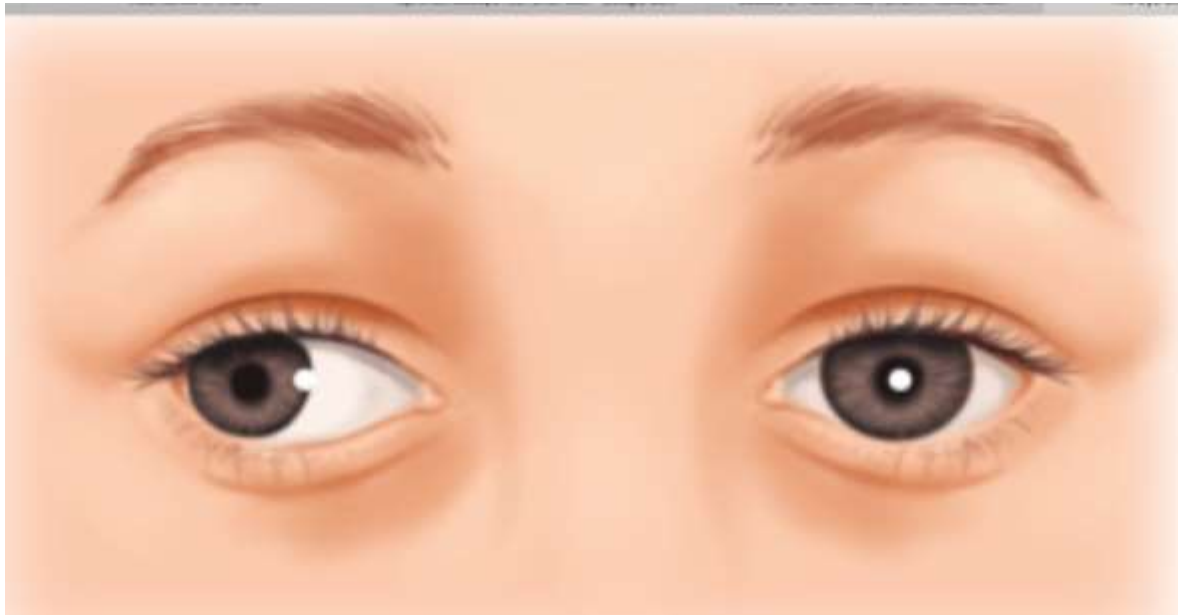
- *NORMAL ocular alignment*
- intermittent
- **Resolves by 2-4 months**^{1,2}

Pseudo-strabismus: Optical Illusion



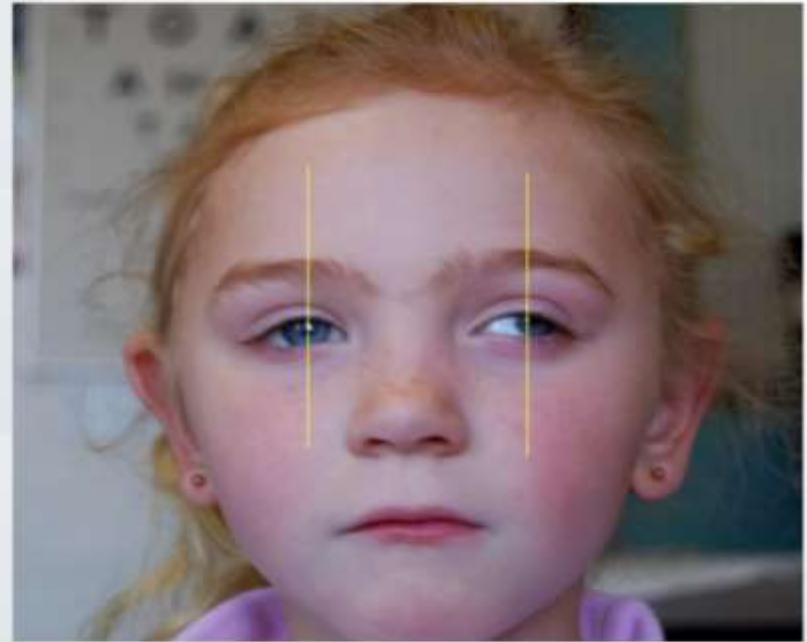
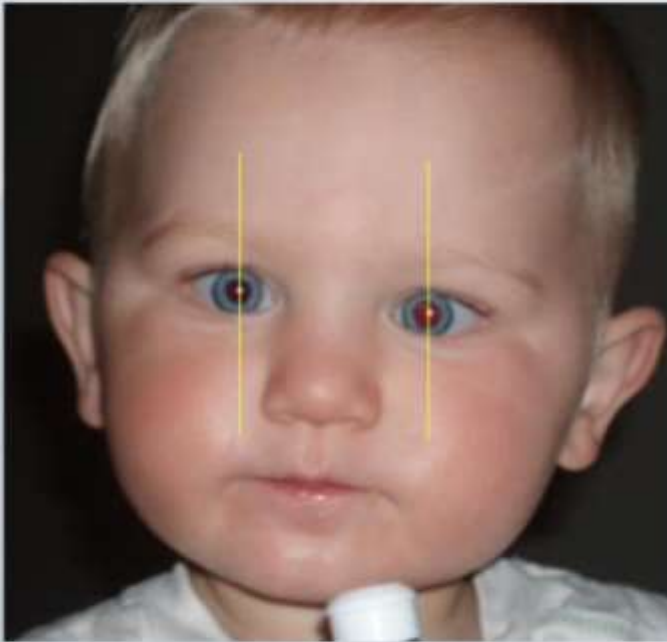
- Wide nasal fold/bridge of nose
- Intermittent – looking sideways
- “see both ears”
- Corneal light reflex - symmetry

¹Horwood A. 1993, JAAPOS; ²Sondhi N. et al. 1988 JAAPOS



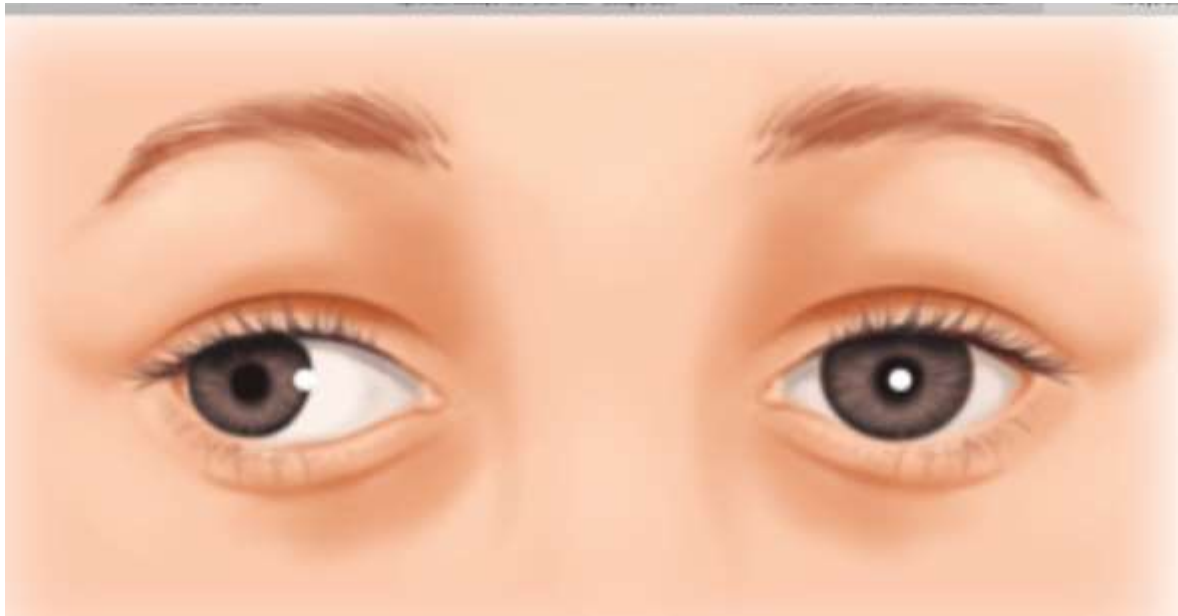
Asymmetrical pupillary reflex

True strabismus – variable direction, size and frequency



Consider:

- CAUSE? – *secondary cause until proven otherwise*
- EFFECT ON VISION DEVELOPMENT – AMBLYOPIA



Asymmetrical pupillary reflex

At what time you screen
the baby for red reflex

Why IT is important

Red reflex

Should be done before newborn discharge



Good Red Reflex

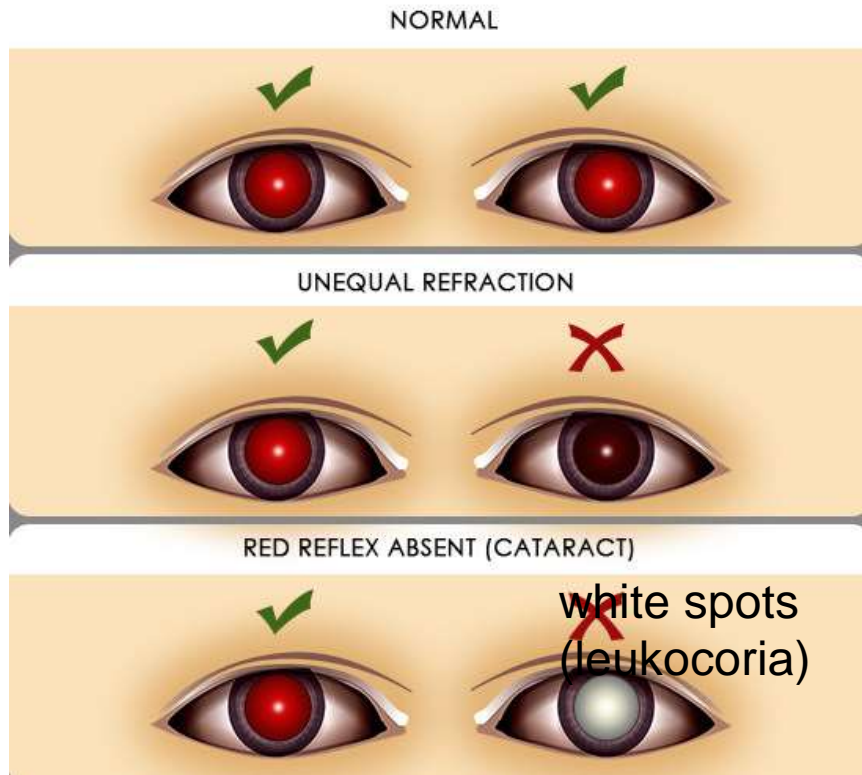
- Bright red
- Symmetric
- How to acquire the reflex?
 - Dim room
 - Direct ophthalmoscope
 - Simultaneous viewing of both eyes at arm's length



Red reflex should be equal in both eyes

Use direct ophthalmoscope from 2 to 3 ft away from the patient in a darkened room. The infant will usually be interested in the light and look directly toward it.

Interruption of Abnormal red reflex



Leukocoria

Strabismus may be early signs

“Leuko” – white
“Coria” – pupil



“Isn’t it just the camera flash?”



estimate is 1 case of retinoblastoma per 18,000-30,000 live births,

Congenital cataract



Urgent

Congenital Cataract

- Occur in about 3:10000 live birth.
- 2/3 of case are bilateral (half of the cause can be identified)
- The most common cause is genetic mutation usually AD
- It can cause ambyopia in infants.
- It is divided to:
 1. **Systemic** association
 2. **Non-systemic** association

Systemic association

1. Metabolic:

- Galactosaemia, galactokinase deficiency, Lowe syndrome, others (hypoparathyroidism, pseudohypoparathyroidism, mannosidosis)

2. Prenatal infection:

- Congenital rubella (~ 15% of cases), other intrauterine infection (toxoplasmosis, cytomegalovirus, herpes simplex varicella)

3. Chromosomal Abnormalities:

- Down syndrome ~ 5%
- Patau (trisomy 13)
- Edward (trisomy 18) syndrome.

Non-systemic association

1. Isolated hereditary cataract

- About 25% of cases.
- Most frequently **AD**, but maybe **AR** or **X-linked**
- Better visual prognosis than coexisting ocular and systemic abnormalities

Causes of cataract in healthy neonate



Hereditary

(usually dominant)

Idiopathic

With ocular anomalies

- PHPV
- Aniridia
- Coloboma
- Microphthalmos
- Buphthalmos



Intrauterine infections

- Rubella
- Toxoplasmosis
- Cytomegalovirus
- Varicella

Metabolic disorders

- Galactosaemia
- Hypoglycaemia
- Hypocalcaemia
- Lowe syndrome

Learning Objectives

for common eye problems

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