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 billirubin in the blood visibly manifested as jaundice.

Bilirubin > normal level

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

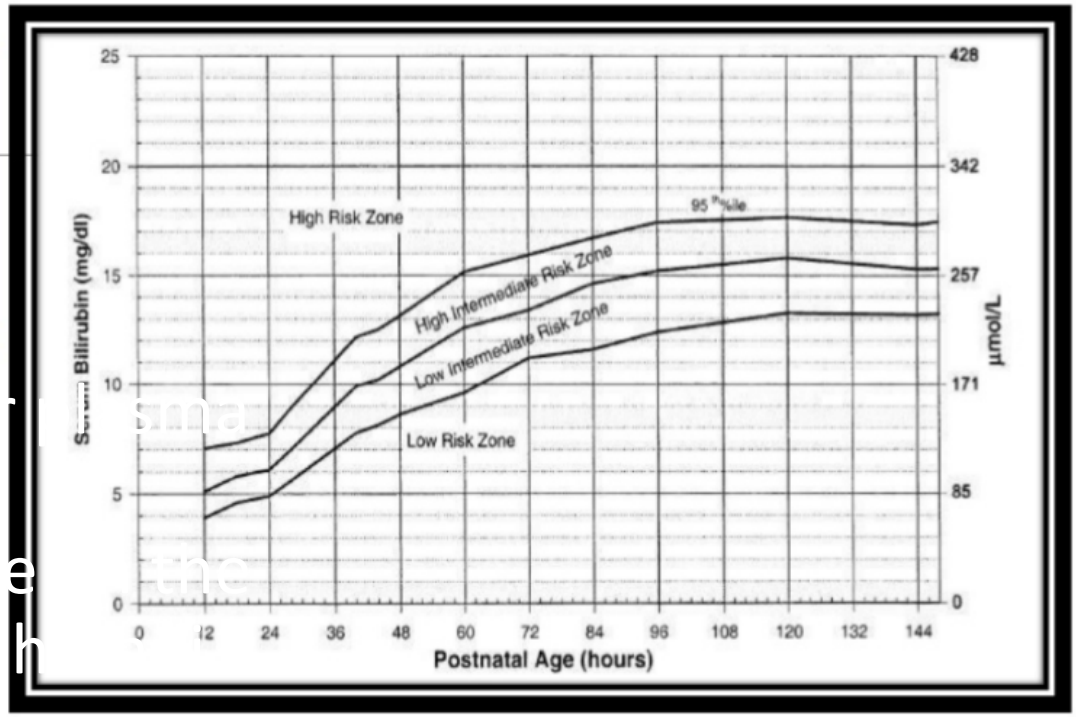
Definitions

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.



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 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 (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

Commmon

- 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

Alwys Hot topic in research

(2011) 170:461–467

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

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Neonatology

Original Paper

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

Received: April 21, 2010
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Published online: January 5, 2011

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

2011

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[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

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 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

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   BMJ Paediatr Open. 2020; 4(1): e000830. Published online 2020 Sep 18. doi: 10.1136/bmjpo-2020-000830
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3. Association between **neonatal jaundice** and autism spectrum disorders among children: a meta-analysis
   Ensiyeh Jenabi, Saeid Bashirian, Salman Khazaei
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4. **Neonatal Jaundice**: awareness, perception and preventive practices in expectant mothers
   Kokou H Amegan-Aho, Catherine I Segbefia, Naa Djama O Glover, Gloria A Ansa, Taiba J Afaa
   Ghana Med J. 2019 Dec; 53(4): 267–272. doi: 10.4314/gmj.v53i4.3
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5. 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
   Sci Rep. 2020; 10: 11374. Published online 2020 Jul 9. doi: 10.1038/s41598-020-68186-w
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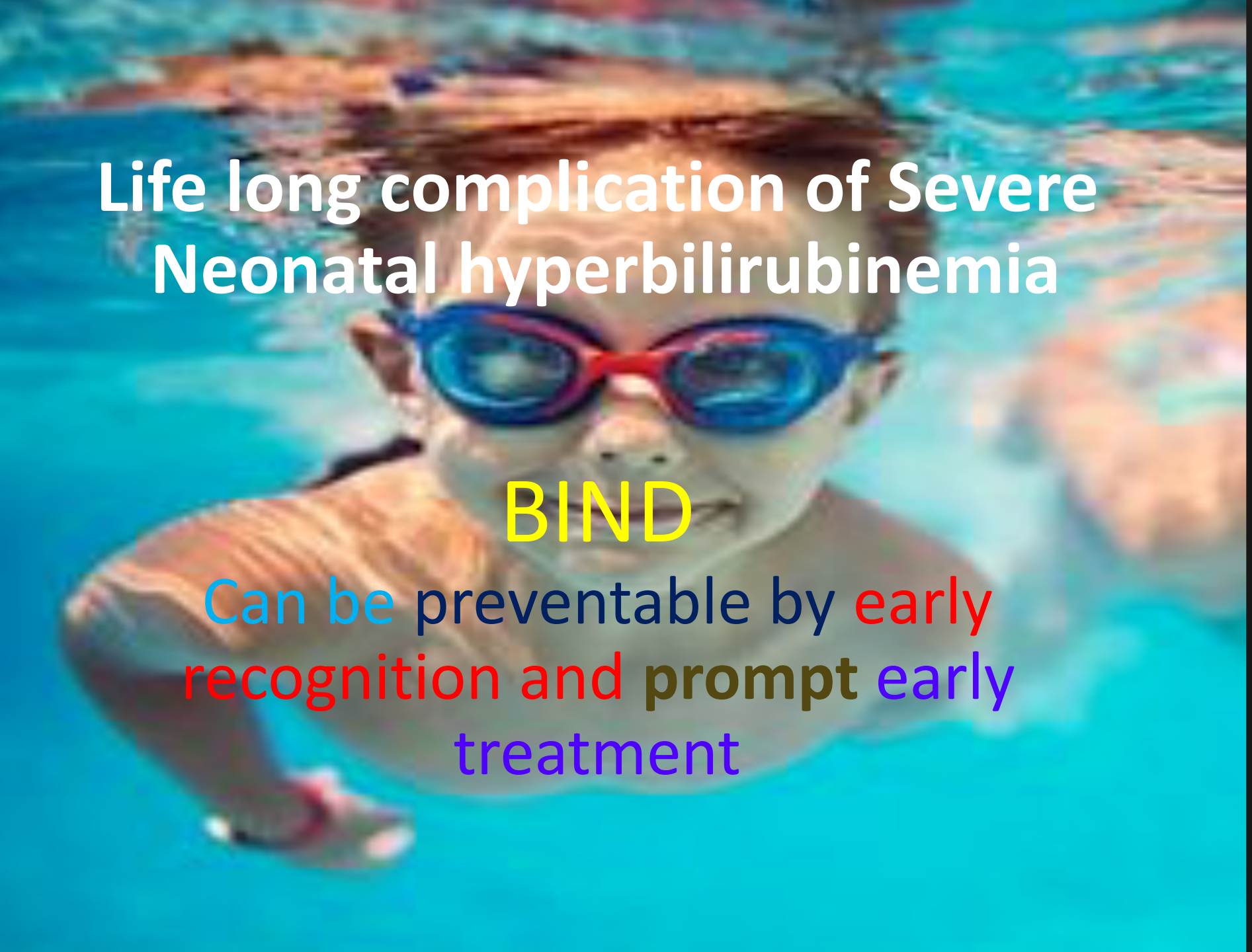


Life long complication of Severe Neonatal hyperbilirubinemia

BIND

Can be preventable by early recognition and **prompt** early treatment

Objectives

Why this lecture

Bilirubin metabolism

Bilirubin measurement

What special in neonates

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

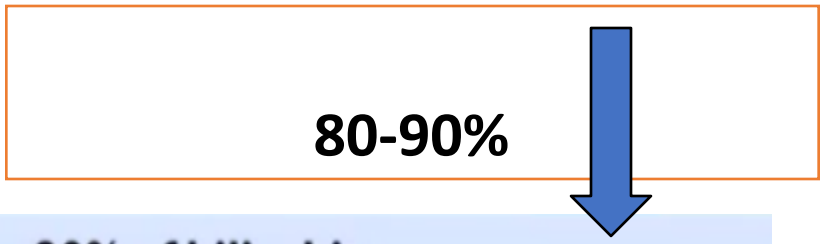
Why to know the bilirubin production and metabolism

To Know the cause

- Physiologic

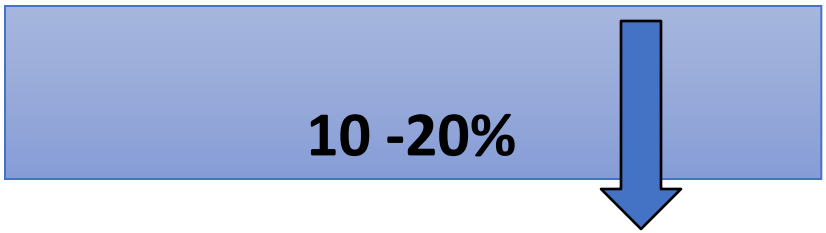
- Pathologic

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

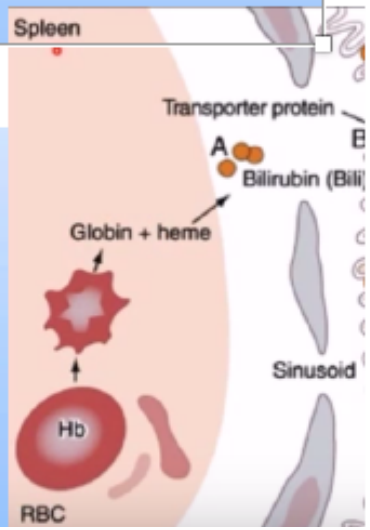
Note:

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

Site of bilirubin metabolism

- Reticuloendothelial system
- Consists primarily of monocytes and macrophages

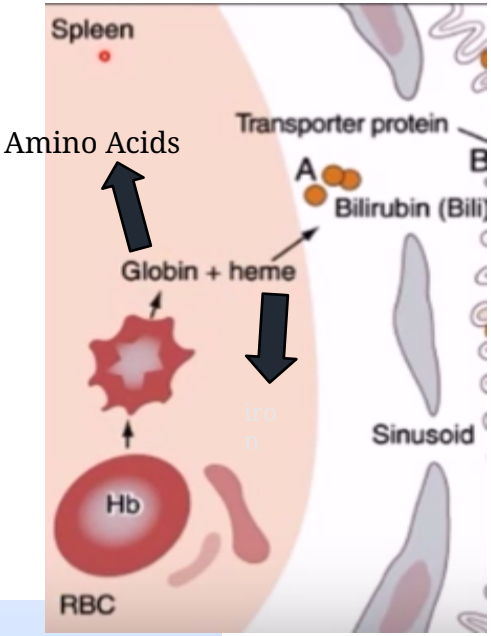
- Spleen
  - Largest unit
- Liver
- Bone marrow



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

e

oxygenase

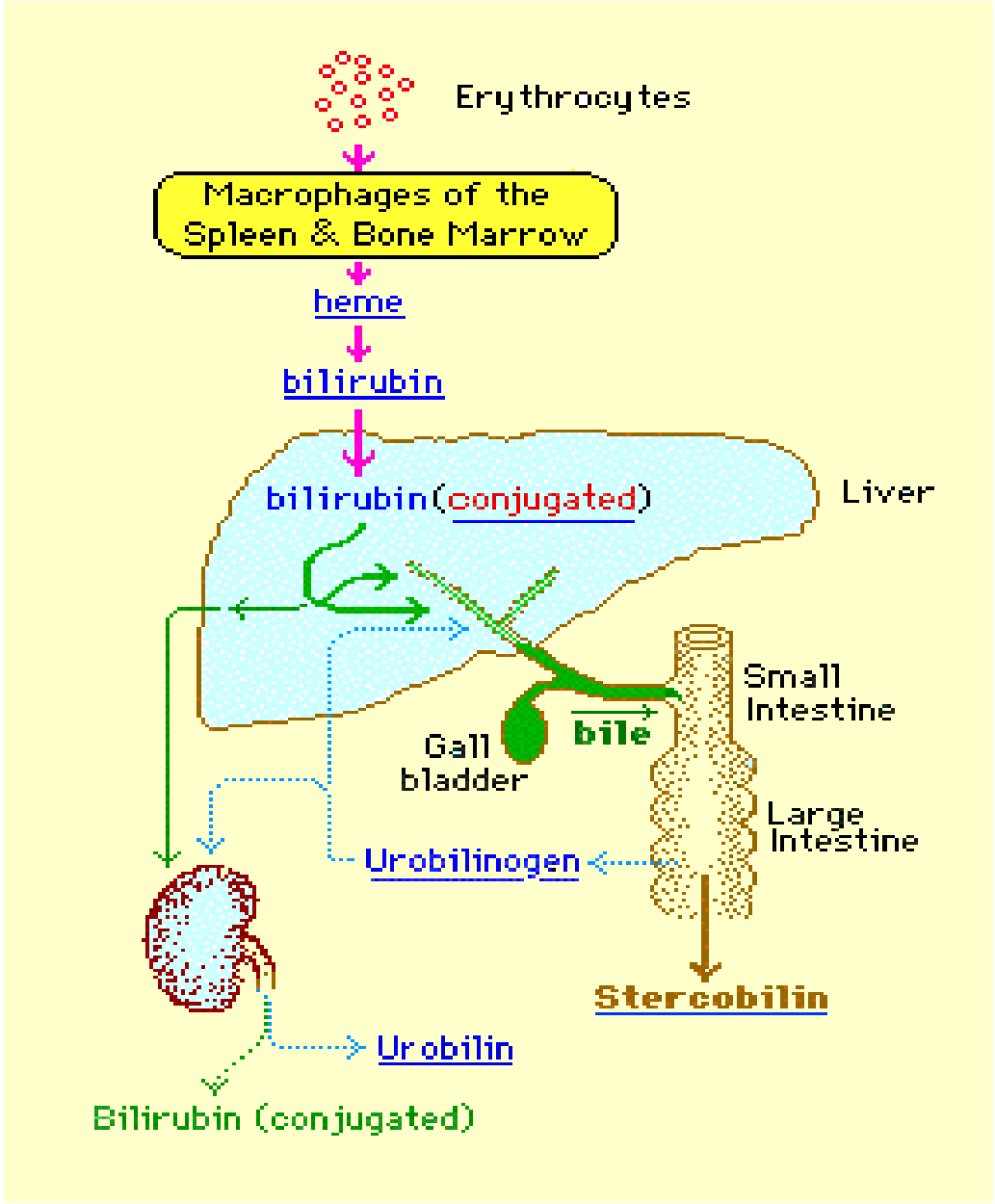
↓

↓ Biliverdin reductase

↓

Bilirubin

(released into blood)



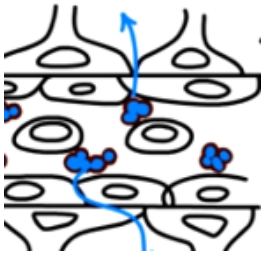
Why to know the

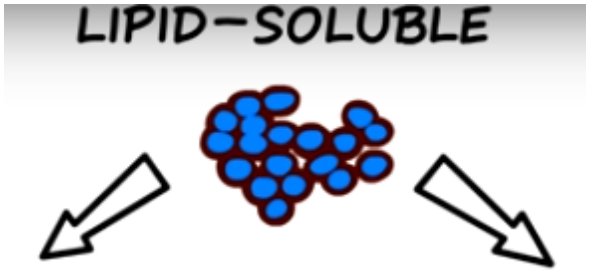
Bilirubin Production

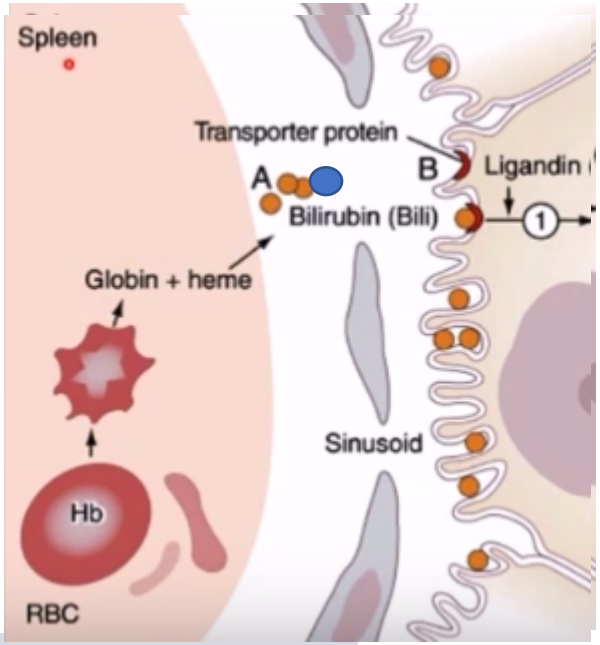
&

Metabolism

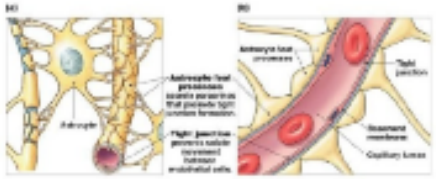
Unconjugated Bilirubin in plasma

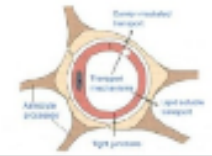






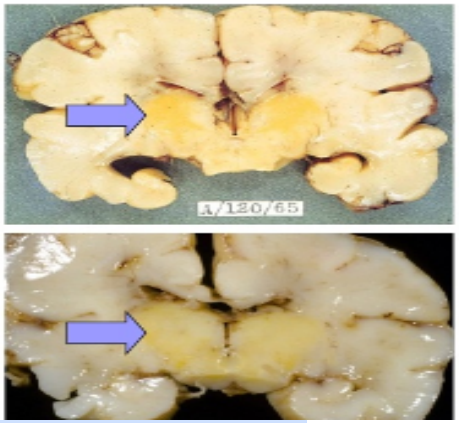
Blood-brain barrier





- 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

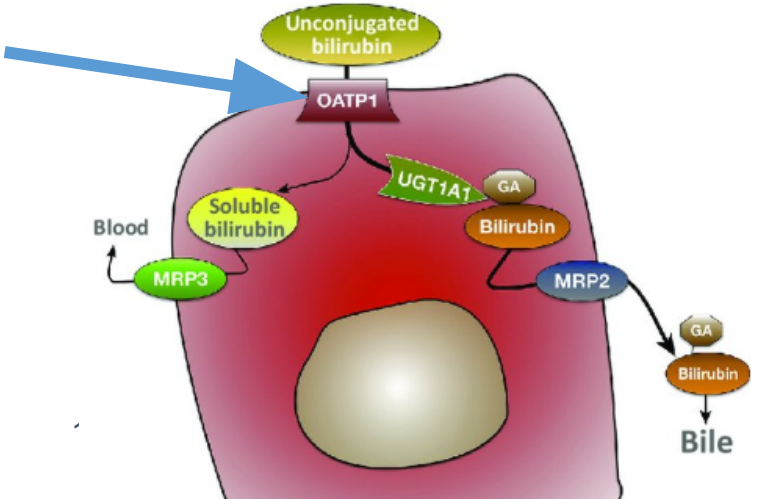
- < 1.5 mg/dL
  - Almost entirely bilirubin (unconjugated)
    - Tightly but reversibly bound to albumin

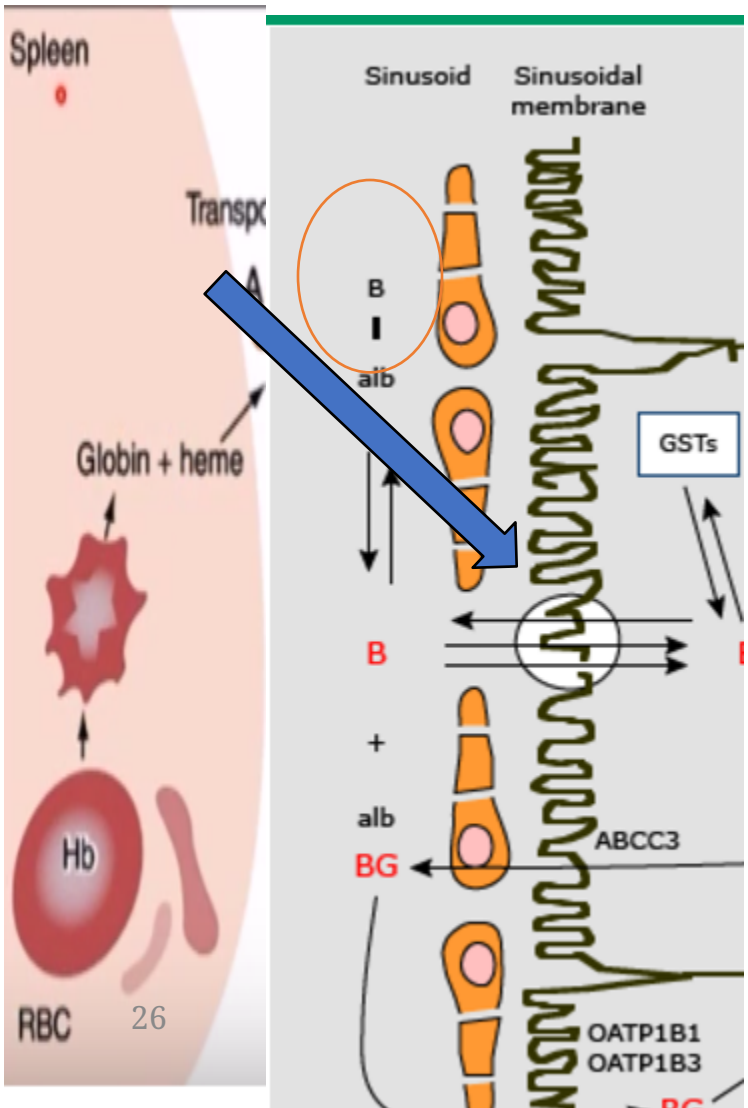
- Liver disease
- Biliary obstruction

Unless

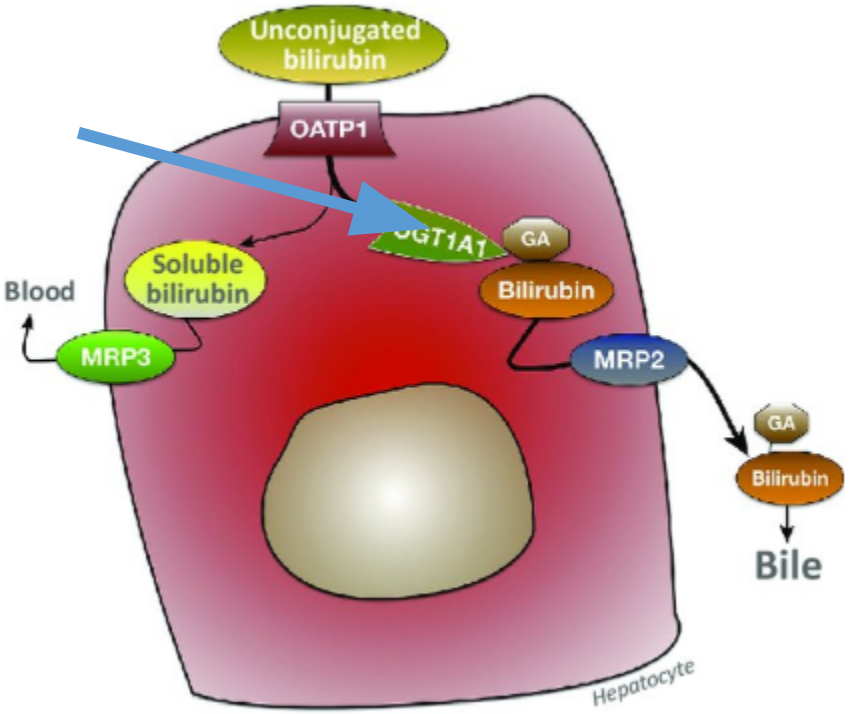
Hepatic uptake – Circulating bilirubin

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





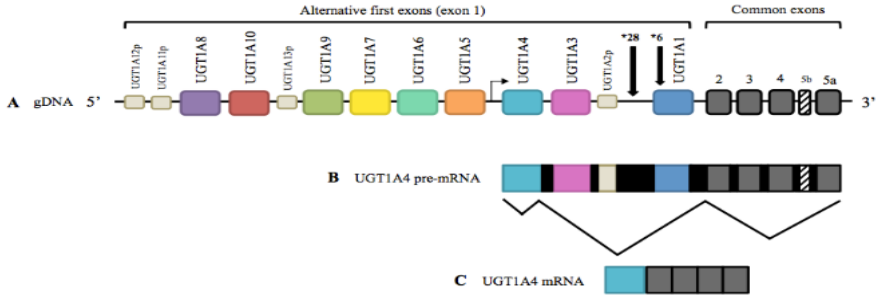
conjugation



Role of uridine diphosphate glycosyltransferase Enzyme

conjugation is catalyzed by the enzyme **u**ridine diphosphate **g**lycosyl **t**ransferase 1A1 (UGT1A1 Enzyme)

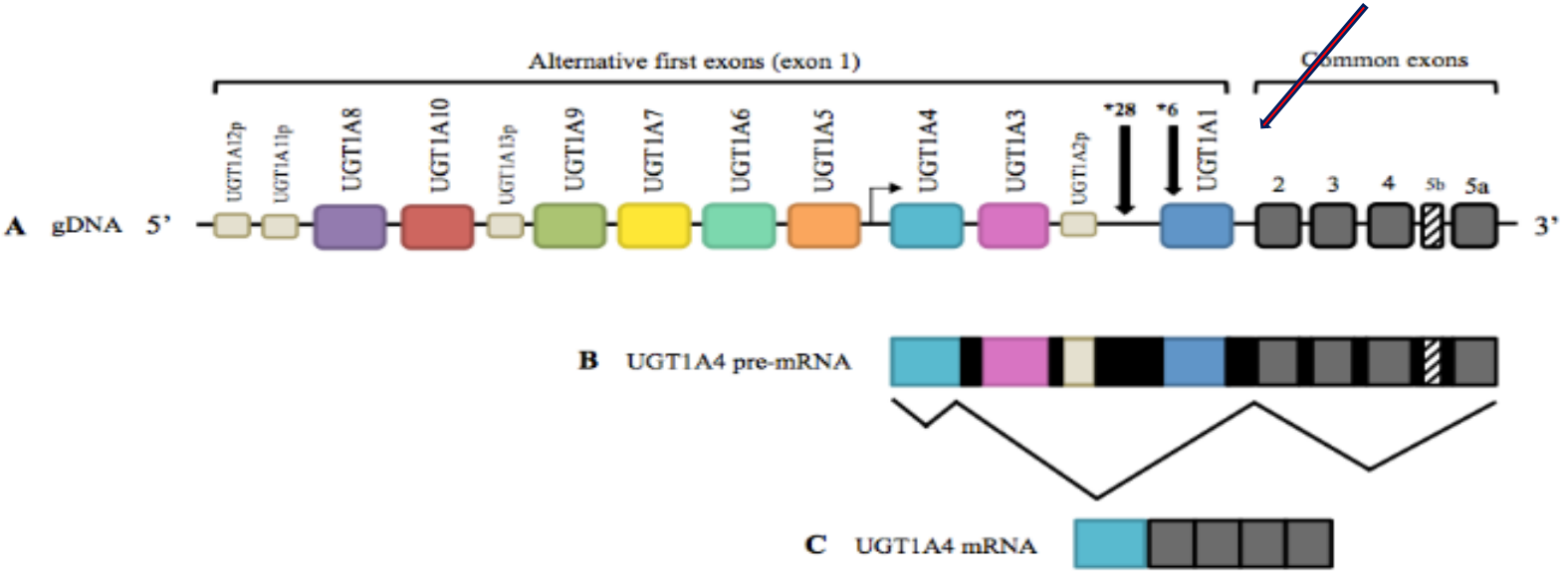
" *UGT1A1* gene (ID: 54658) is a part of a complex locus **encoding** 13 UDP-**g**lucu**rono**syltransferas**es**)



What does UGT1 stand for?

UGT1A! stands for "UDP-glucuronosyltransferase family 1

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



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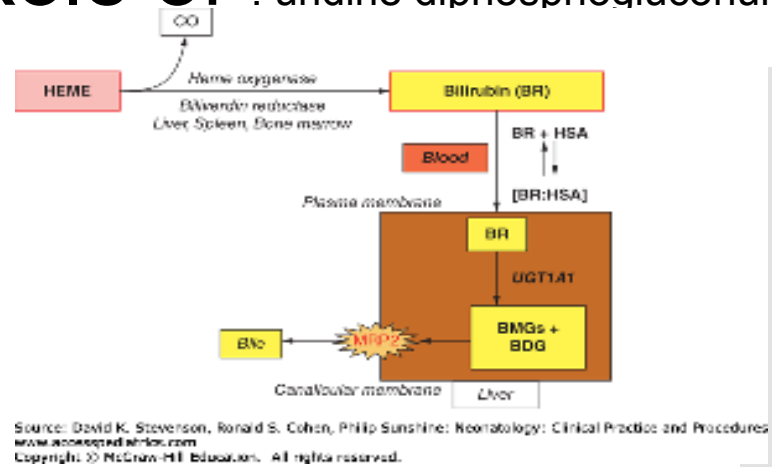
" *UGT1A1* gene (ID: 54658) is a part of a complex locus **encoding** 13 UDP-**g**lucu**rono**syltransferas**es**)

Conjugation – In Hepatocytes

Role of : uridine diphosphogluconurate glucuronosyltransferase (UGT1A1)



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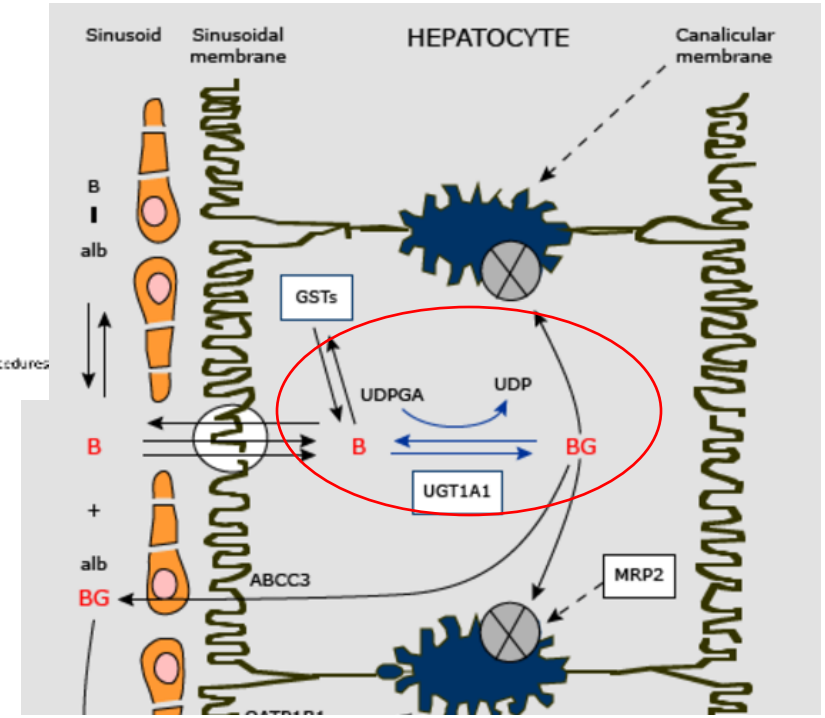
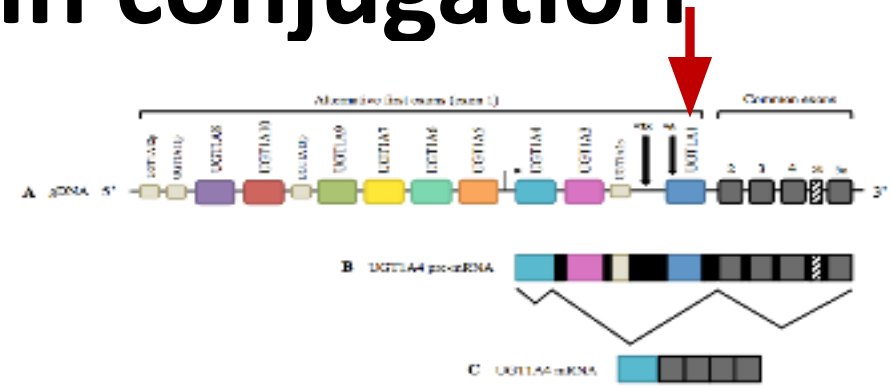


- Actively excreted into bile

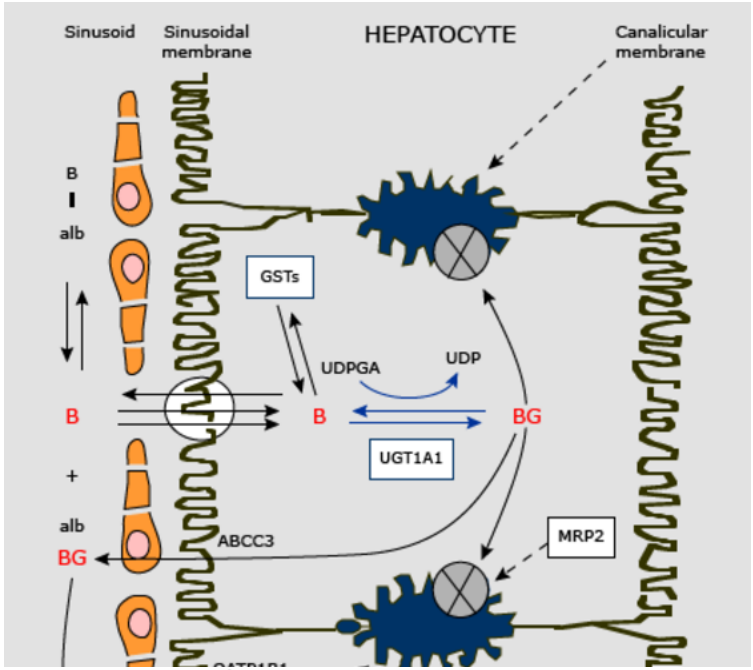
Bilirubin in bile

- 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:

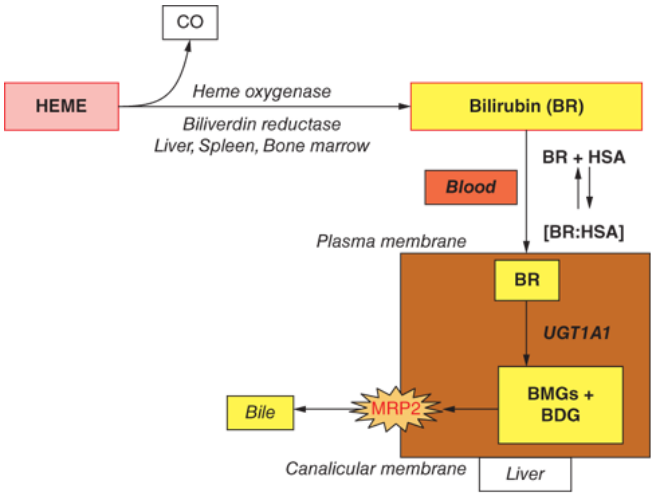
- UGT1A1 polymorphism
- Crigler –Najar Syndrome
- Gilber Syndrome
- Inhibitory factors for hepatic UGT1A!

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

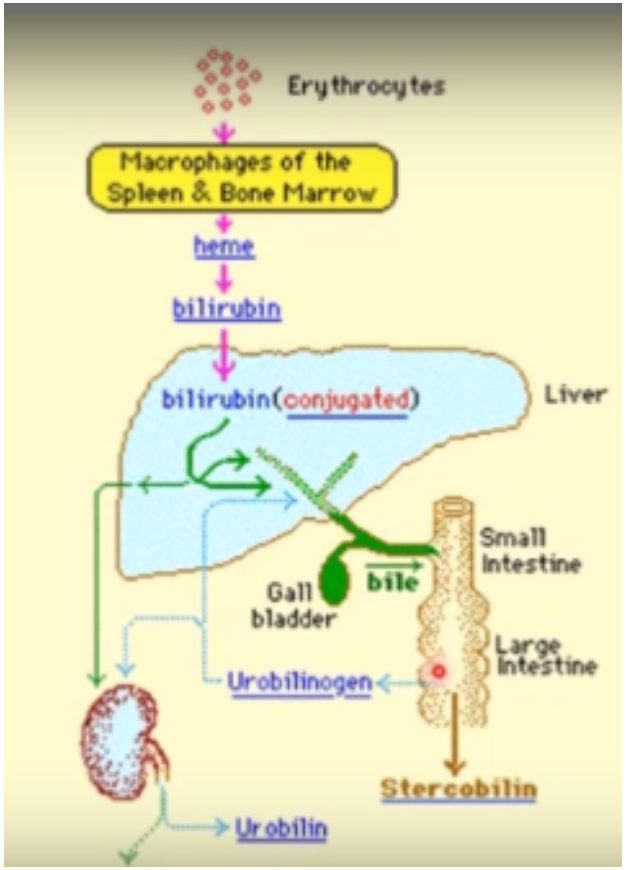
- Actively transported into the bile canaliculus
  - ATP-dependent export pump
    - Protein in the hepatocyte apical membrane
      - Multidrug resistance-associated protein 2

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

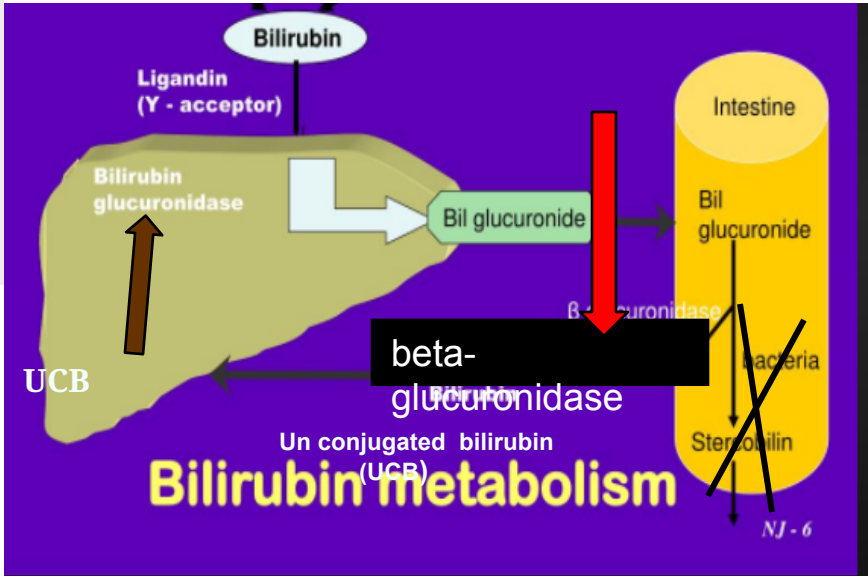
Urobilinogen

- 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

Bilirubin metabolism in **neonate** (Entero- hepatic circulation **EHC**)

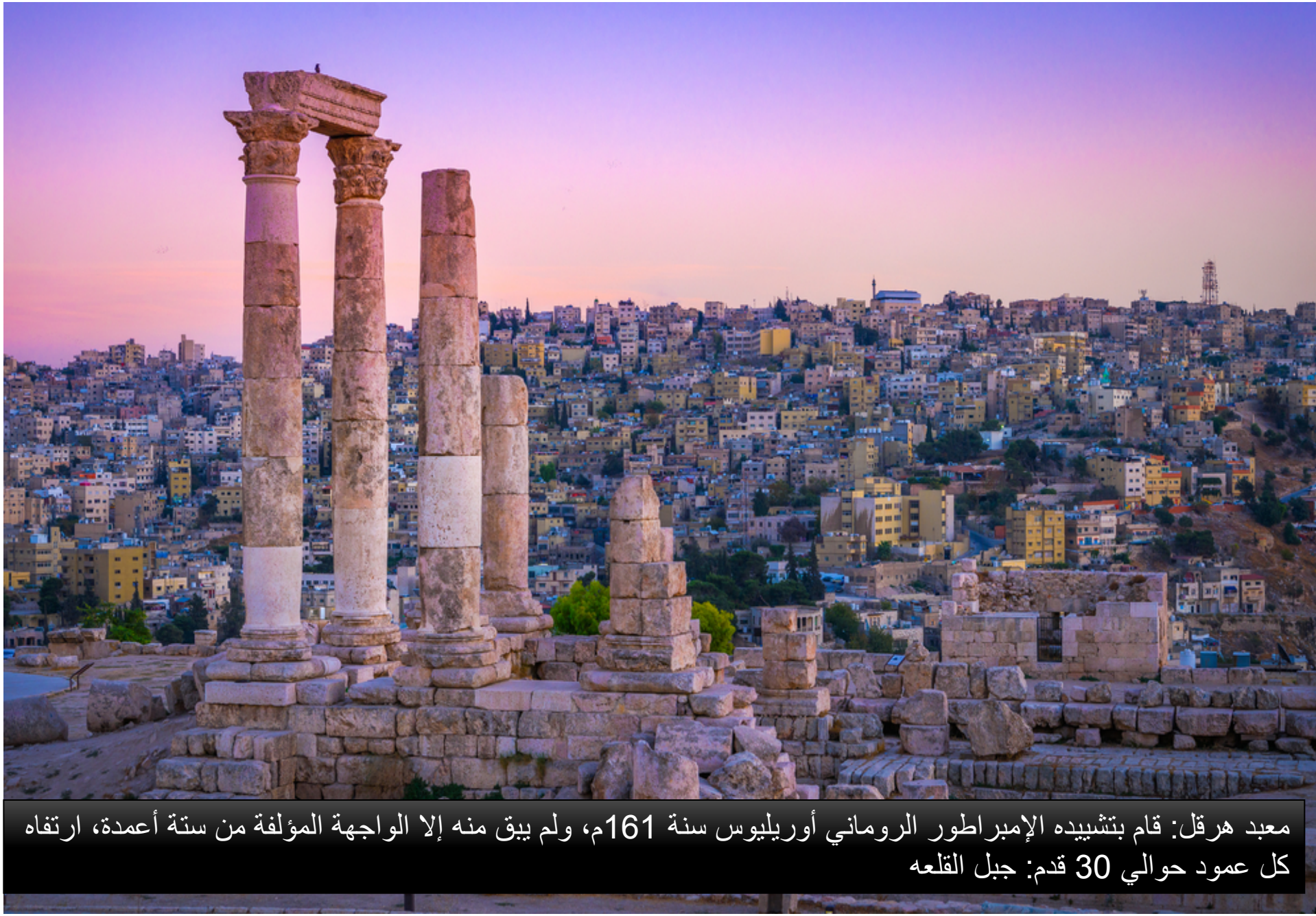
- Neonates have beta-glucuronidase in the intestinal mucosa
- It deconjugates the conjugated bilirubin to **unconjugated bilirubin** (UCB)



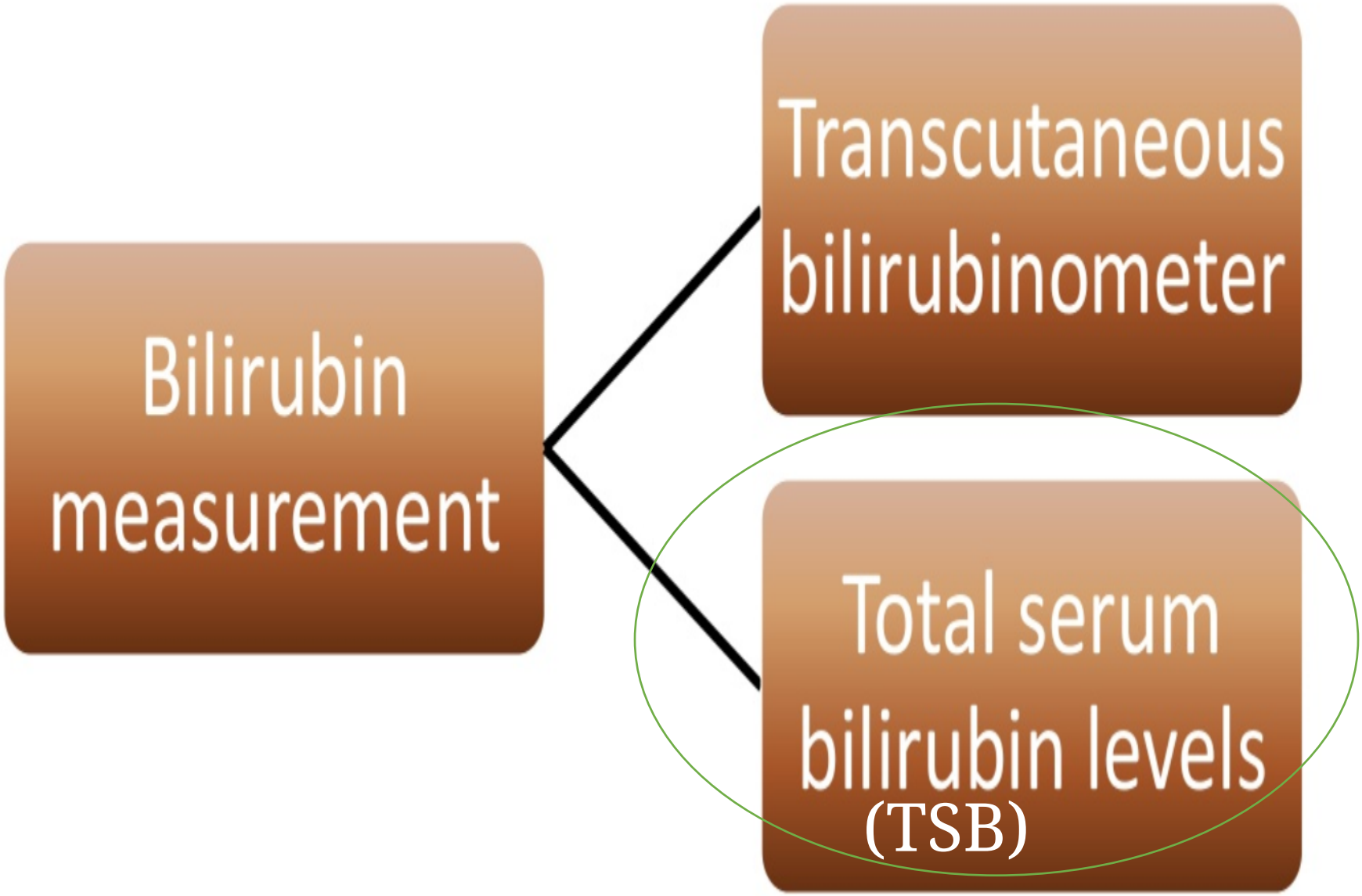
UCB fraction is partially reabsorbed through the intestinal wall and recycled into the circulation, a process known as the “EHC of bilirubin".
undergoes EHC

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، ارتفاه كل عمود حوالي 30 قدم: جبل القلعه


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

- Guidelines
- Work UP

Treatment

- Prevention
- treatment

Types of Neonatal Jaundice

Physiological Jaundice

Pathological Jaundice

Breast-milk Jaundice

Breast-feeding Jaundice

Related to breast milk

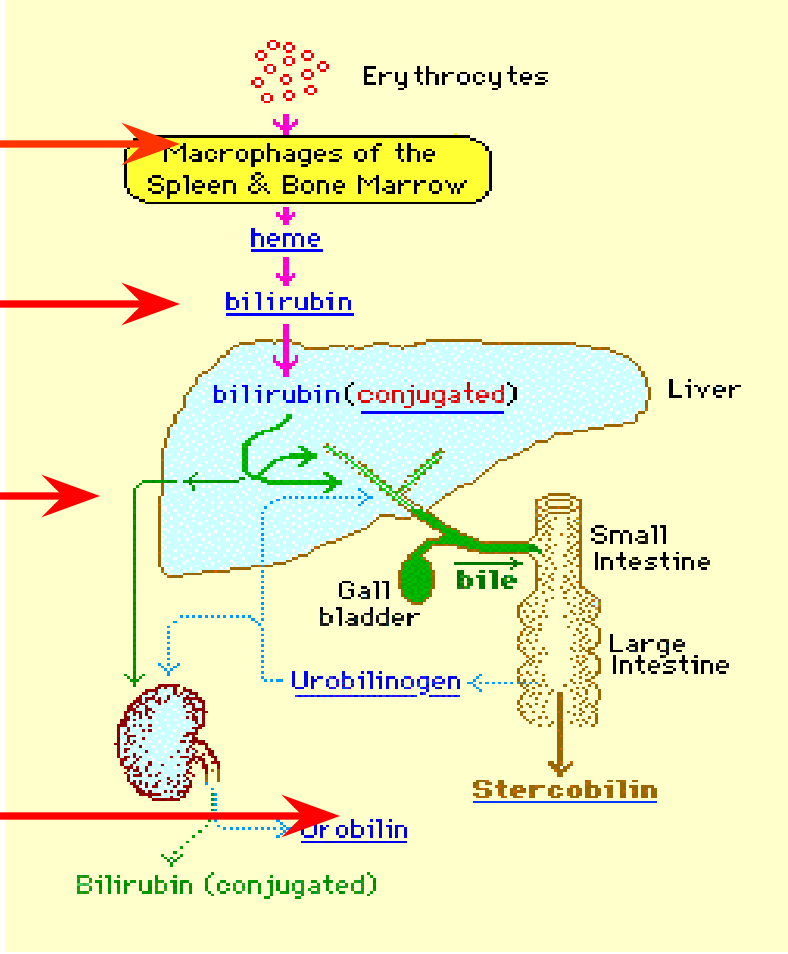
Mechanism of Physiologic Jaundice

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)

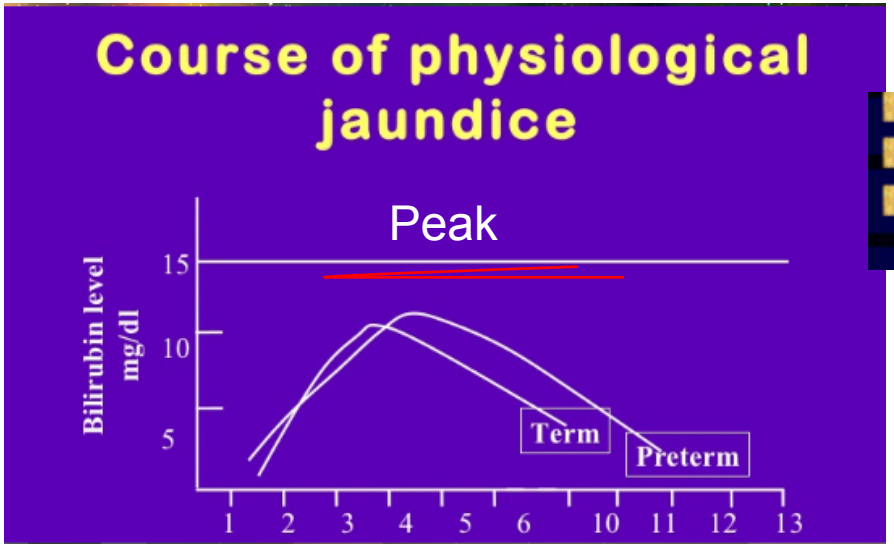


Physiologic Jaundice

Physiologic Jaundice:
1. Has Pattern

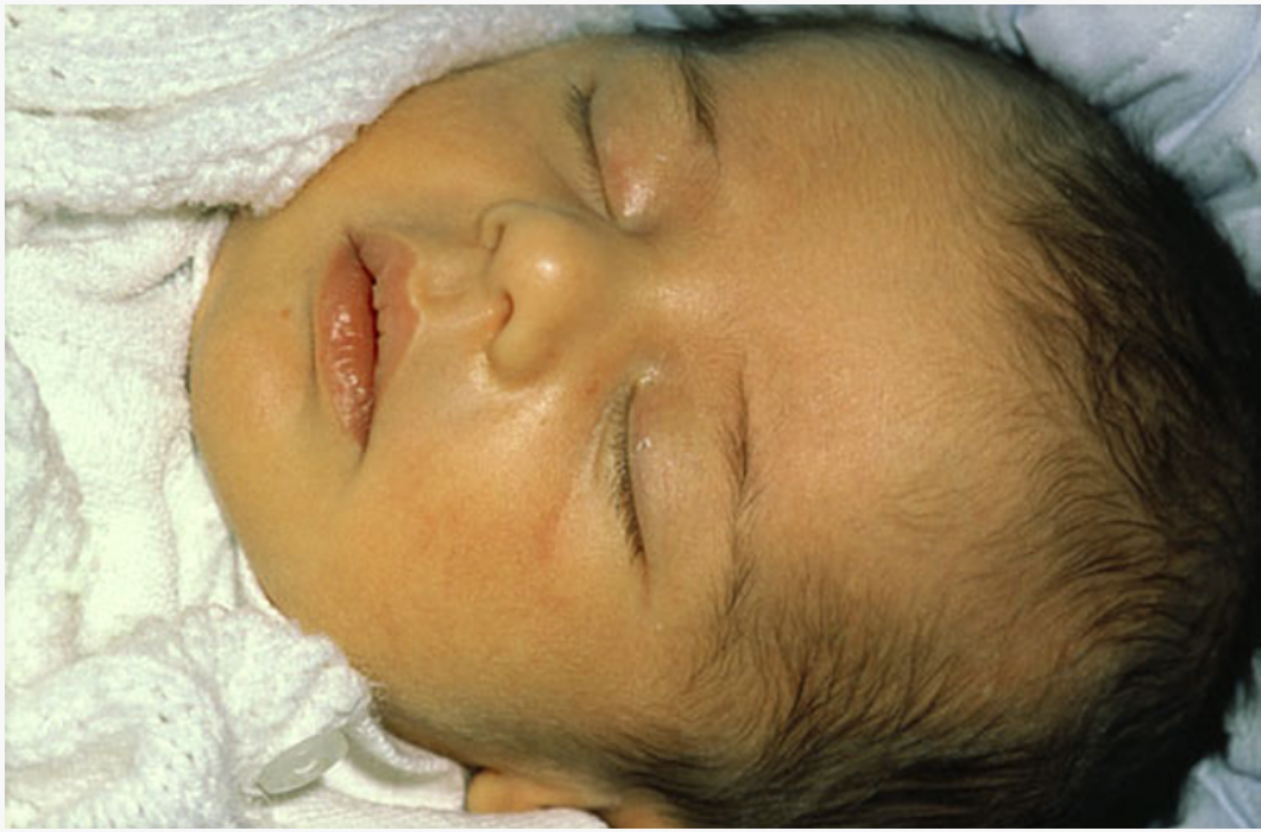
HAS PEAK

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



- 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



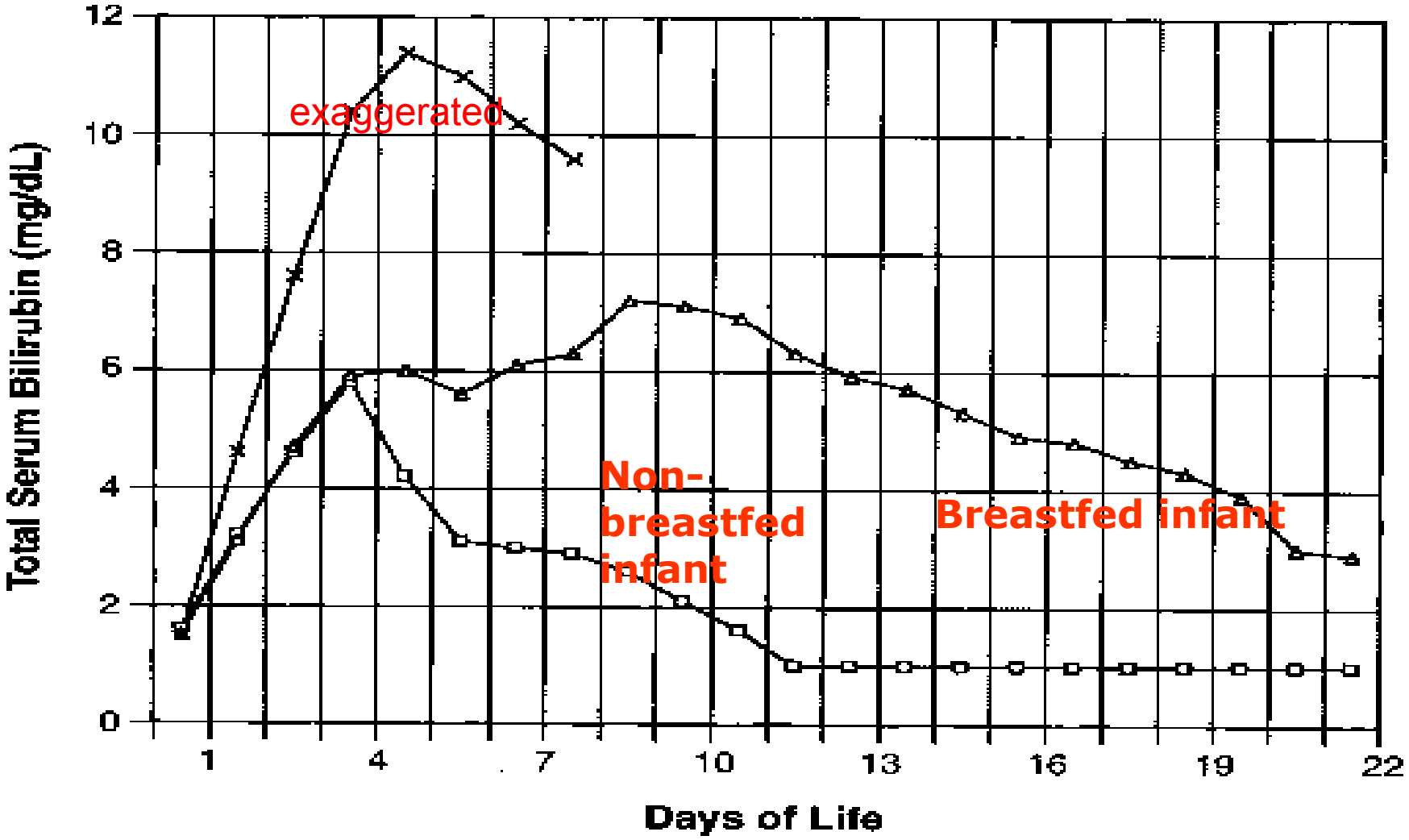
Physiologic Jaundice
3. - Bilirubin rise trend

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 exagerated Physiologic Jaundice

- Can exagerate the peak of physiologic Jaundice
- Throgh Breast feeding Jaundice (BFJ)

Types of Neonatal Jaundice

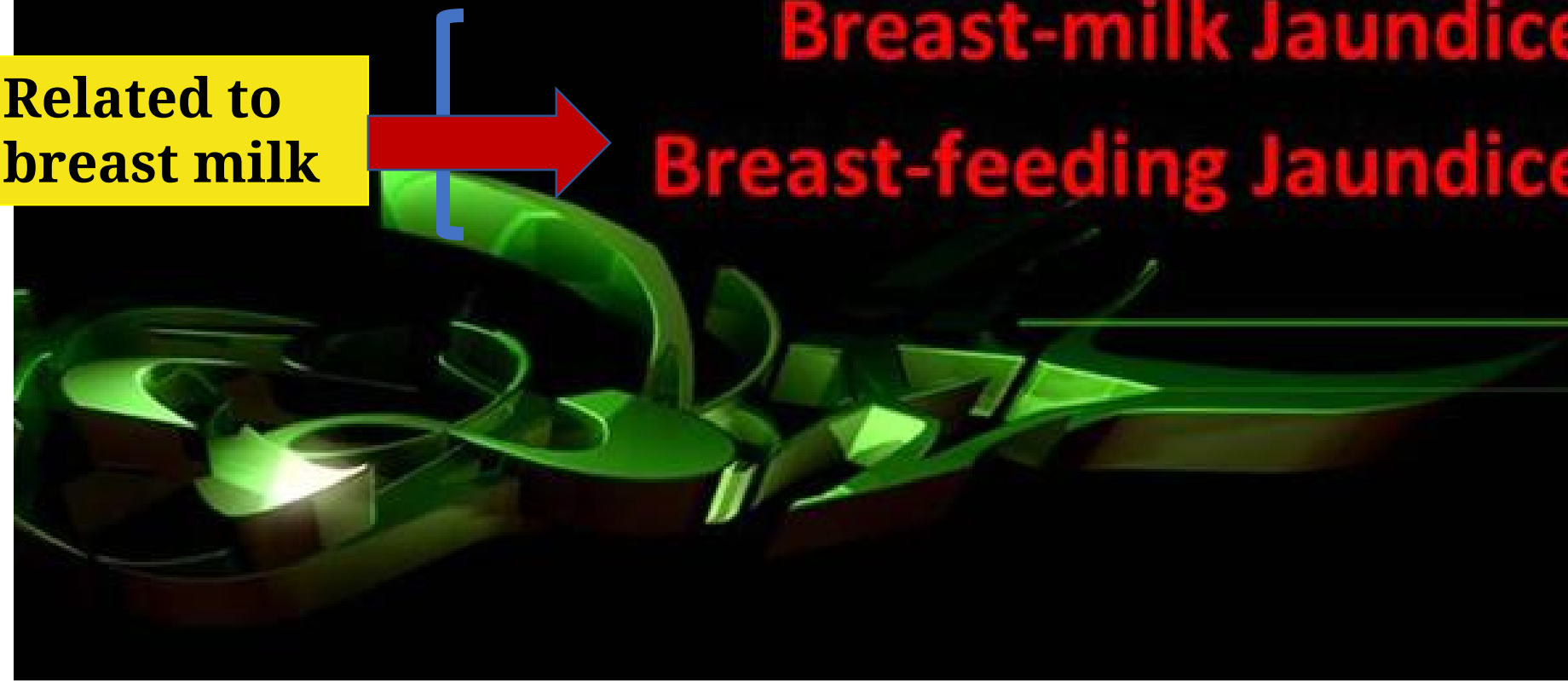
Physiological Jaundice

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

Related to breast milk

- Breast-milk Jaundice
- Breast-feeding Jaundice

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 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

Prolonged Jaundice :causes

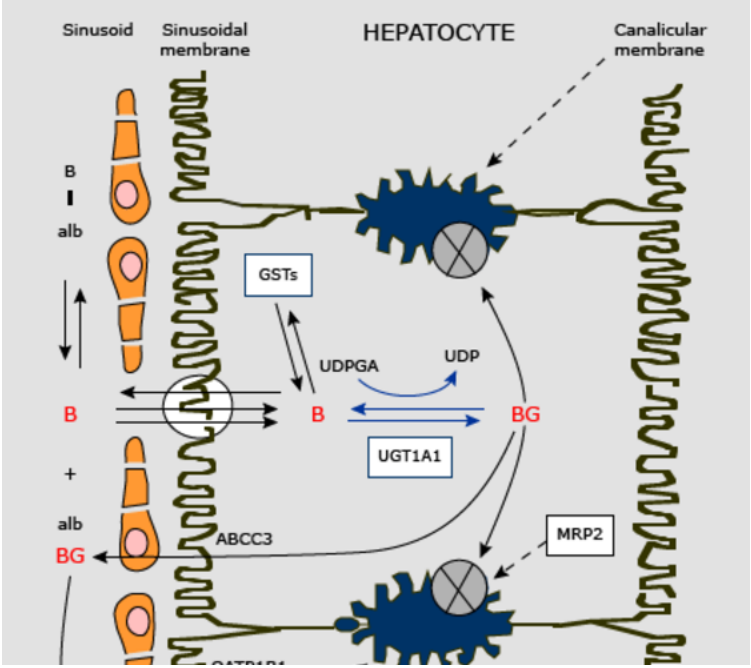
Ethnic variation in conjugation ability

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	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

6/30/2017

33

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

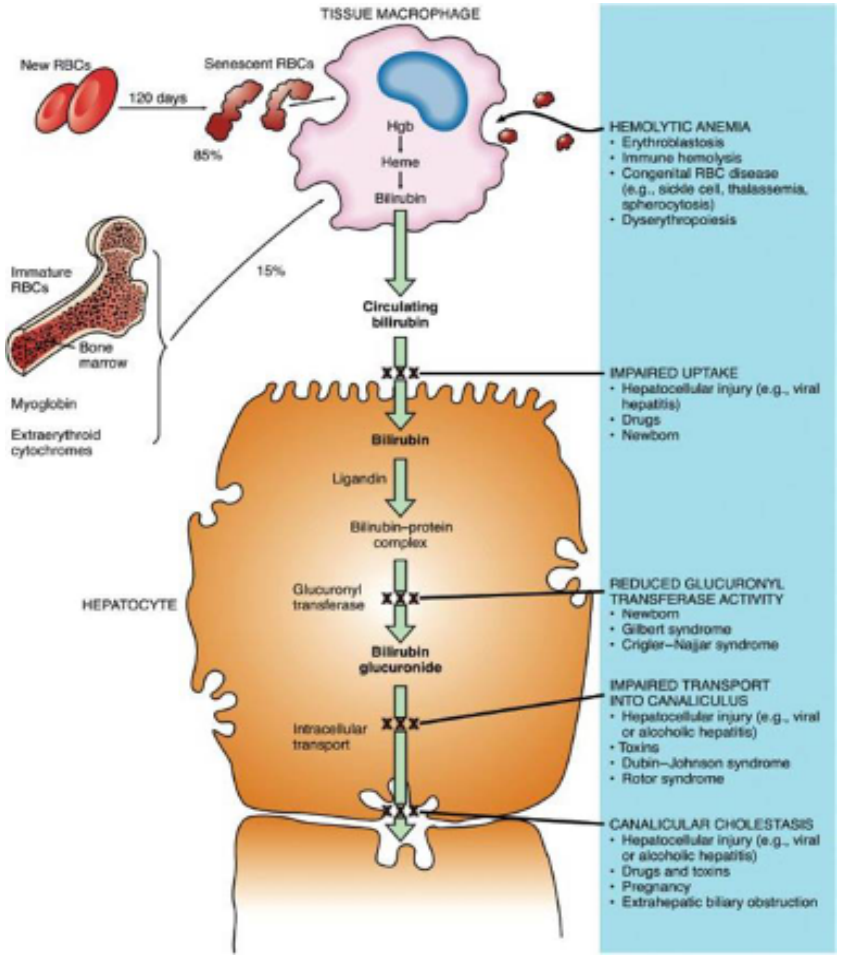
Pathological Jaundice

Breast-milk Jaundice

Breast-feeding Jaundice

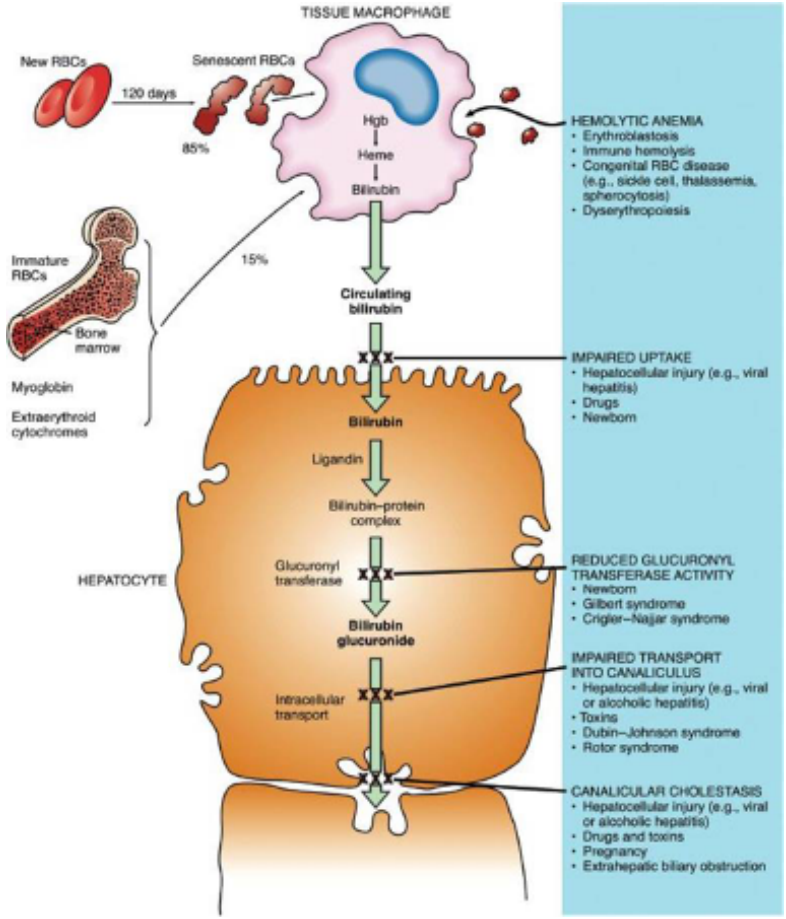
- **Types and Causes of neonatal Jaundice (Pathological Jaundice)**

Pathologic Jaundice

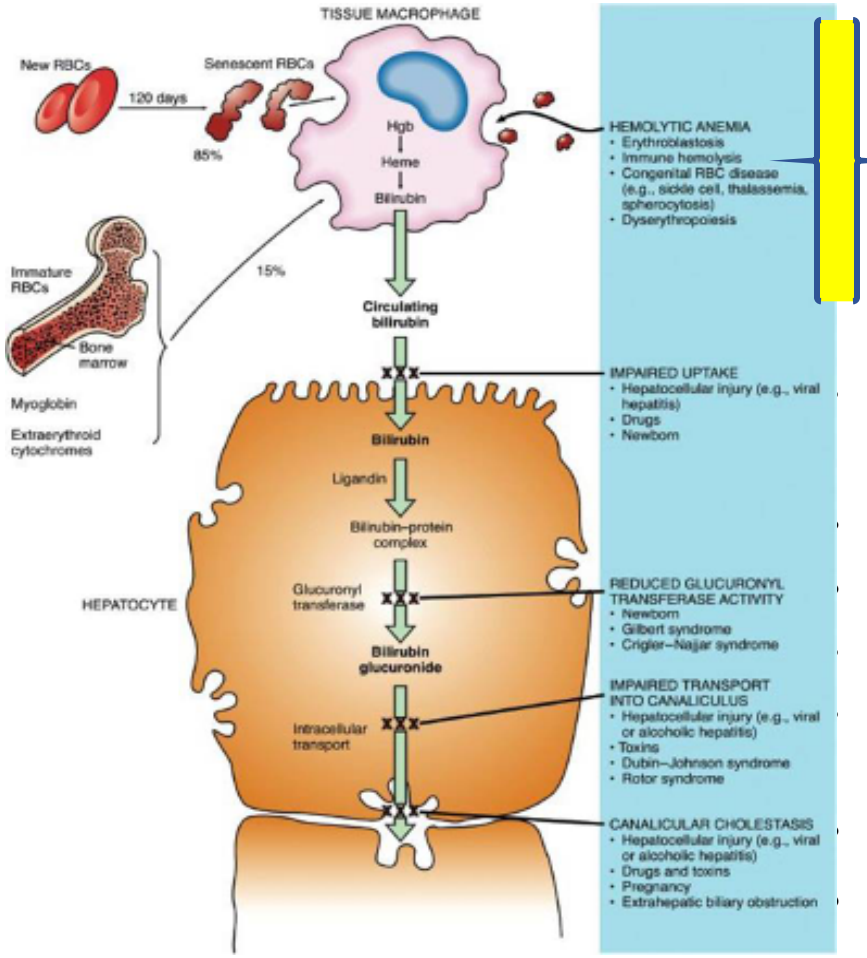


- is a medical emergency.-

Causes of Pathologic indirect 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)-

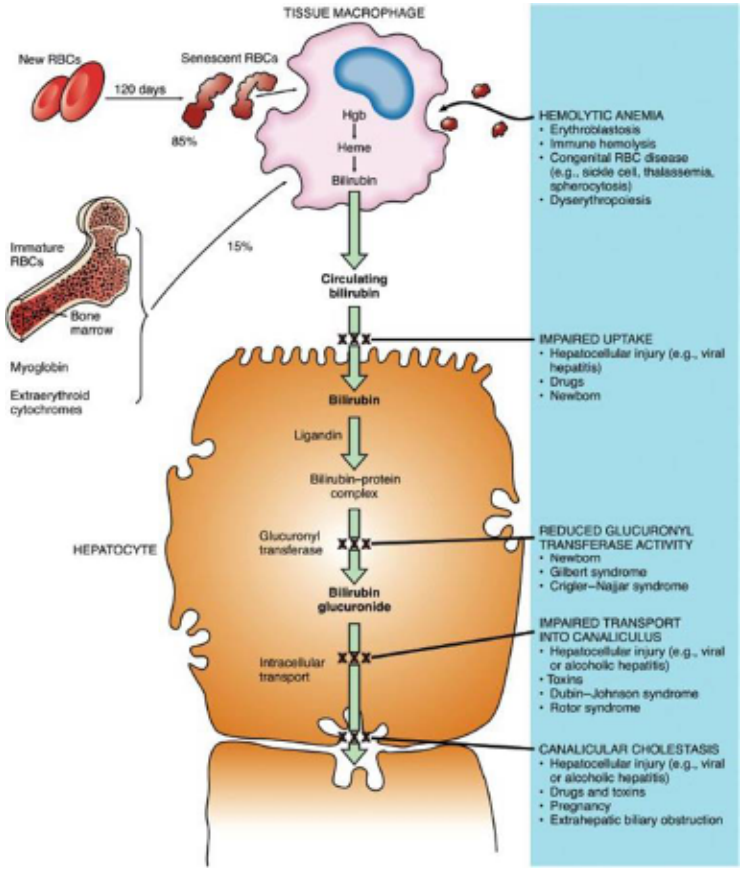
Galactosemia

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

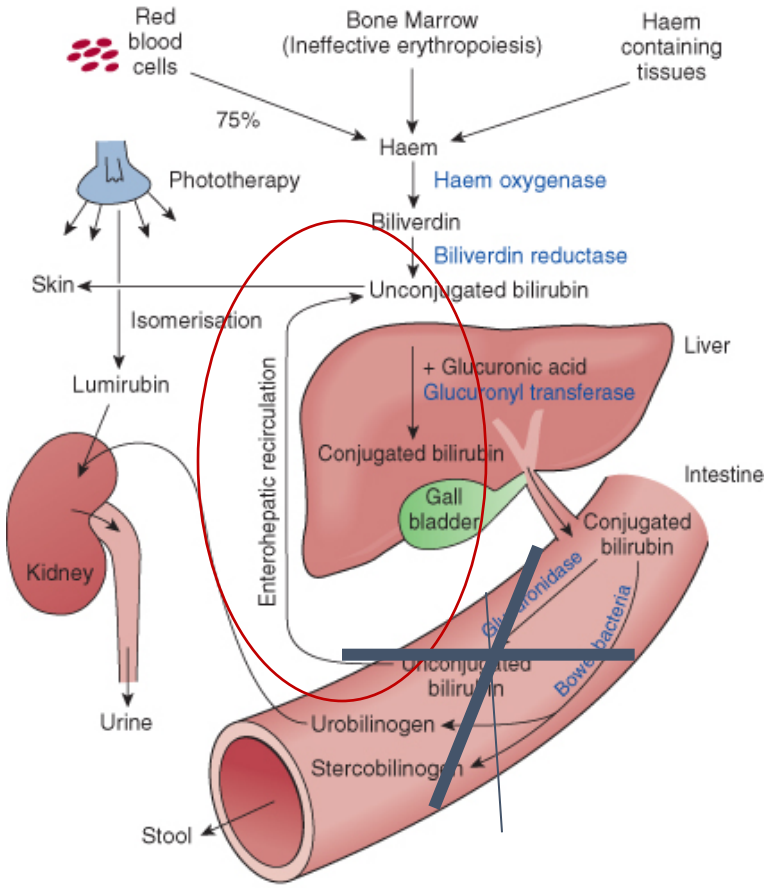
- Defects in the gene that encodes UGT1A1

- - 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 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.

Pathologic jaundice:

How to recognize

القصر الأموي: جبل القلعه

Suspicion 1:

Cord blood

TSB at 24 hour

Pathologic jaundice: How to recognize

Jaundice in 1st 24 hrs

High sensitivity and specificity to develop sever hyperbilirubimimeia if

-CCord 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) Study 1
- > o.2 mg/dl/hour
- TSB high risk zone (> 75Th)

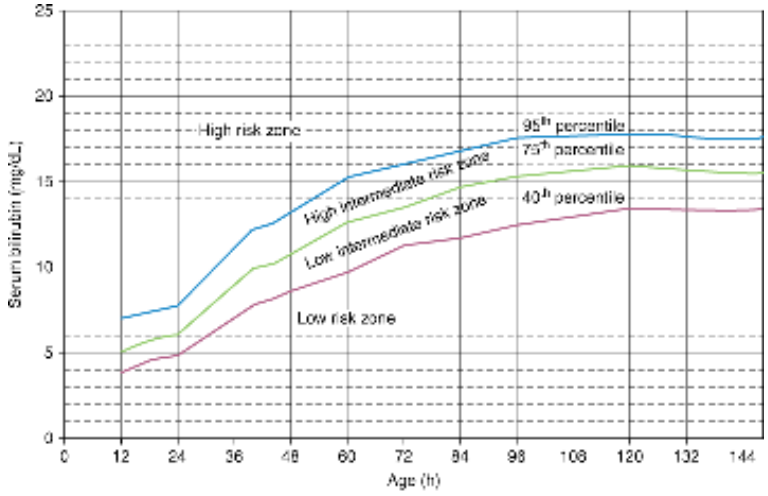


Table 3. Risk of Developing a Total Serum Bilirubin (TSB) Level of 20 mg/dL (342 µmol/L) or Higher by TSB Percentile Group

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 ?

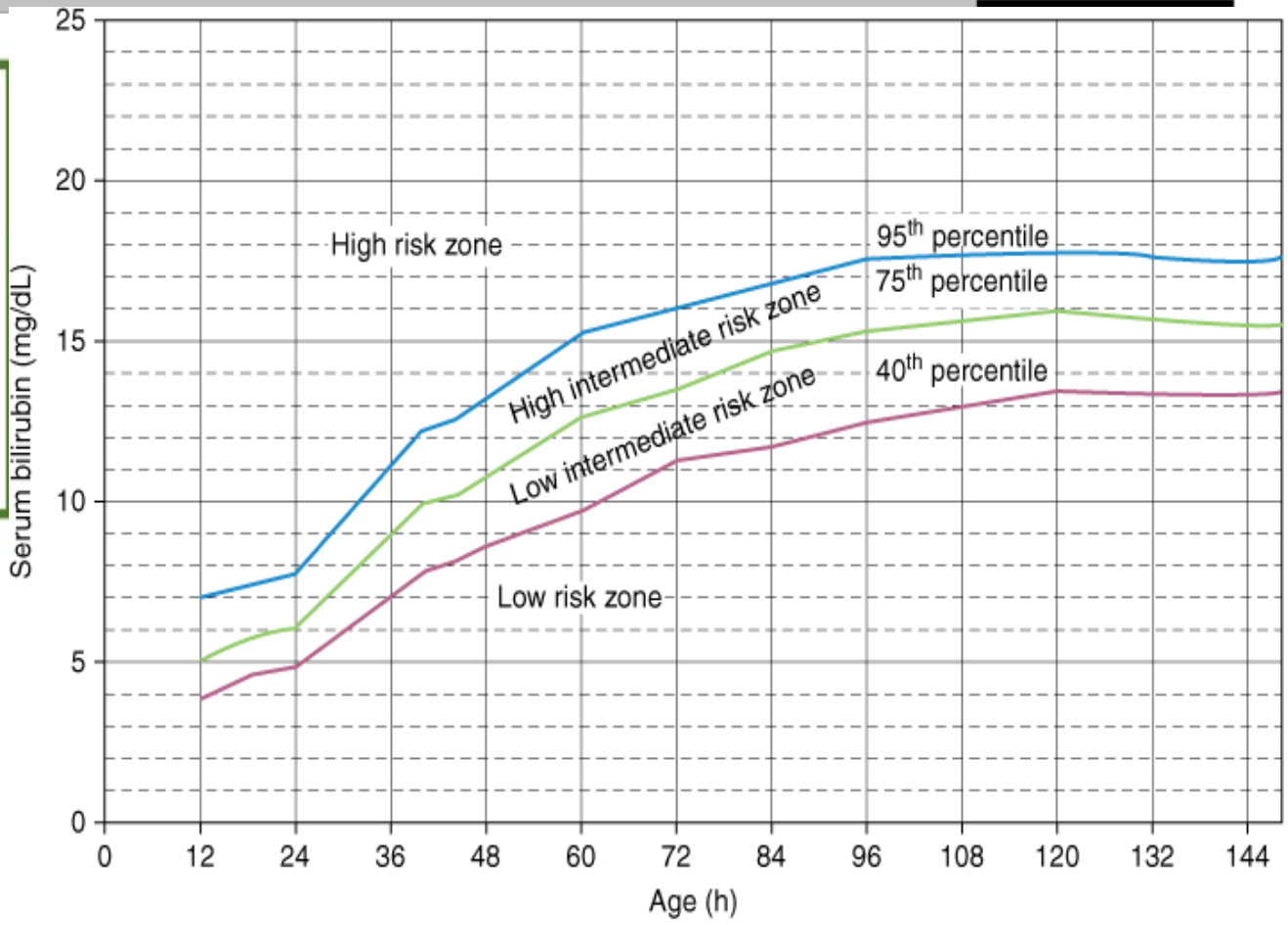
My Baby
Is he at risk to develop sever
Hyperbilirubinemia: ???

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.

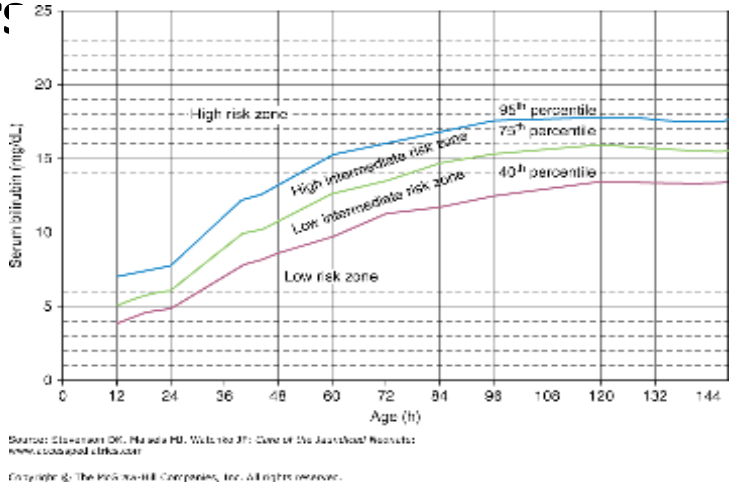
Adapted from bhutani et al.



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

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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Know the risk factors

3- High bilirubin clinical Risk factors (by taking History

(risk for sever hyperbilirubinemia)

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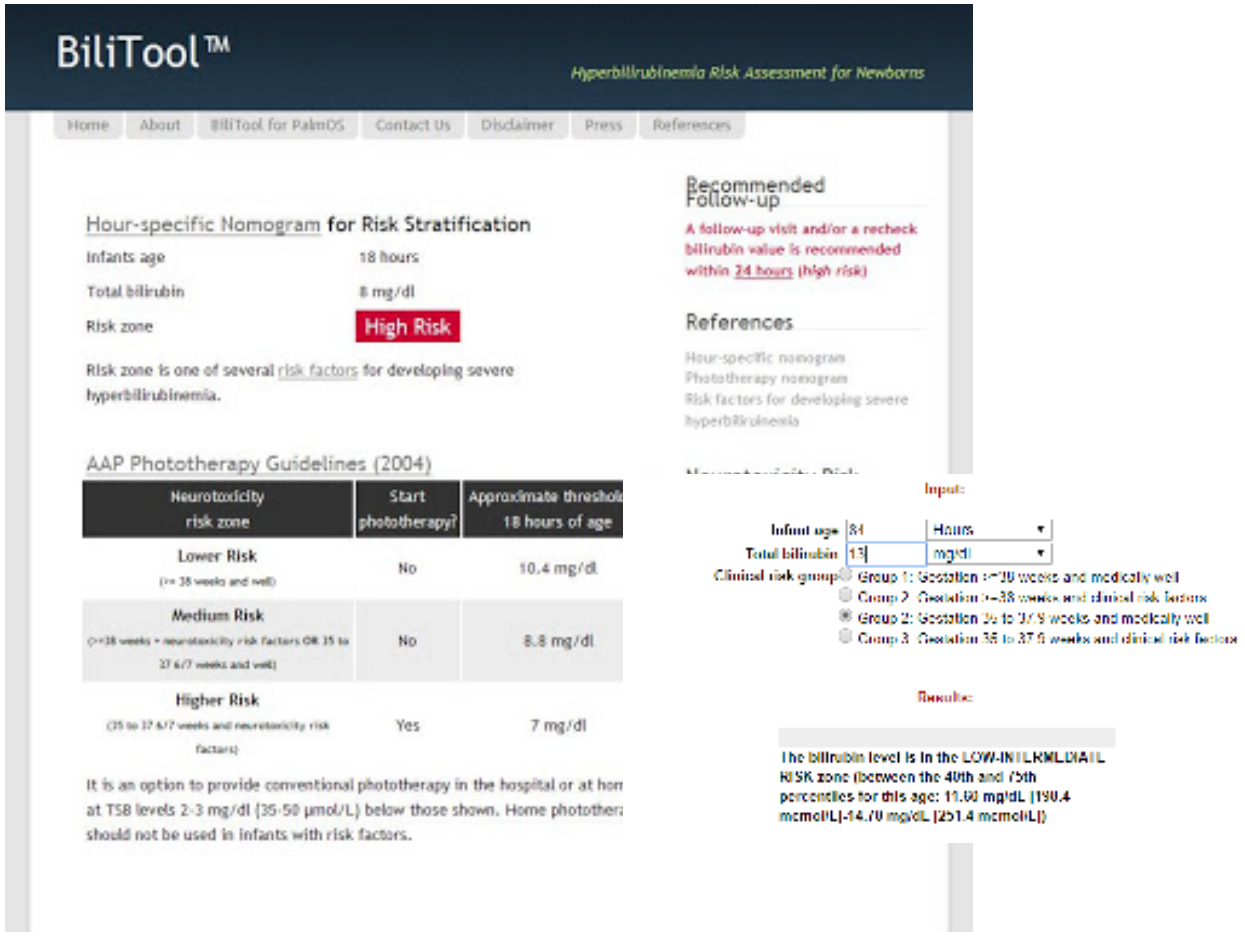
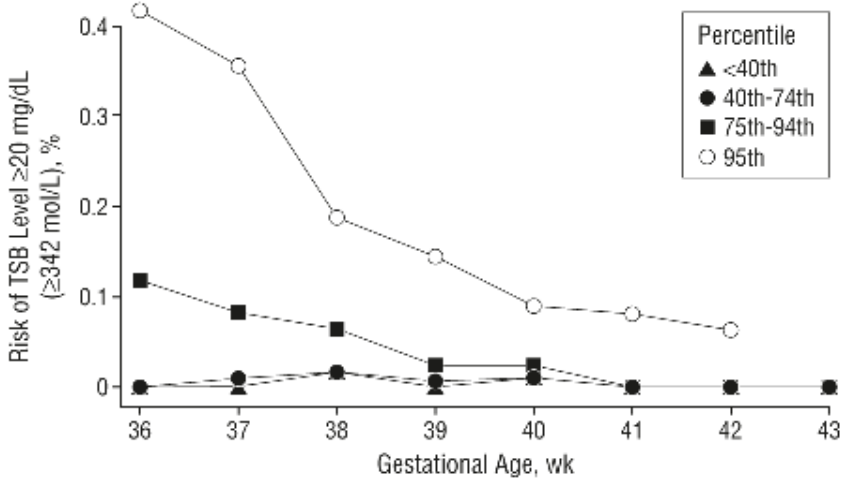
You can use Mobile Application to asses risk factors : AAP

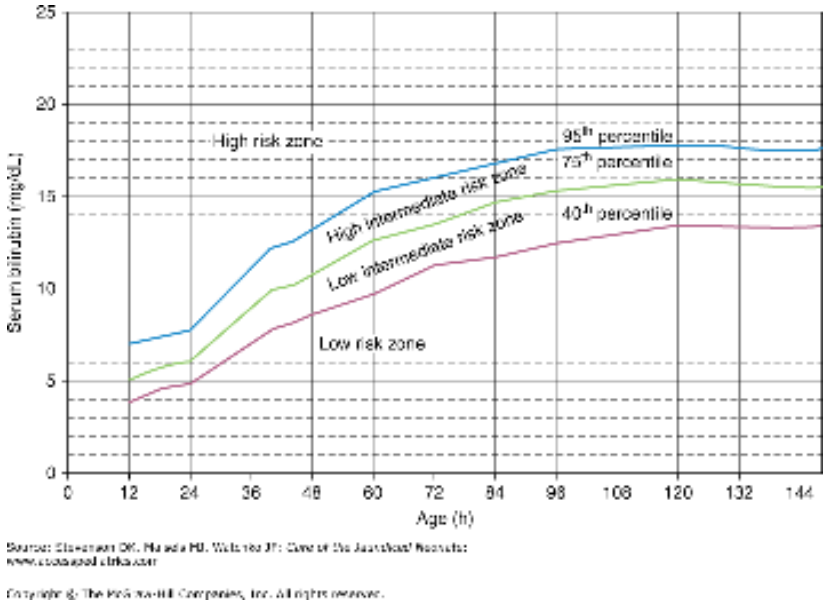


2-Assess the Gestation Age

Risk of Jaundice By gestation age (GA)

Clinical risk factor





Increase risk of sever hyper bilirubinemia risk with decrease GA
Study on those >36 weeks

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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 >5mg/dl.

→ During their Vital signs monitoring

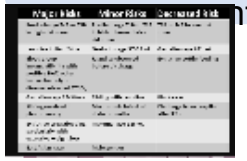
- Newborns to be observed for 72 hrs for jaundice appearance. In case of discharge before 48hrs, Bilirubin risk factors and Hyperbilirubinemia risk as per Normograms should be assessed and followup to be advised accordingly.
- A predischarge TSB or Transcutaneous bilirubin reading to be done if discharge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

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



Pediatrics. 2004;114:297-316.

NICE/ UK

:Do Bilirubin at 24 hour of age

As selective screen (for at risk)

recommends against routine monitoring of bilirubin levels in infants who do not appear jaundiced.

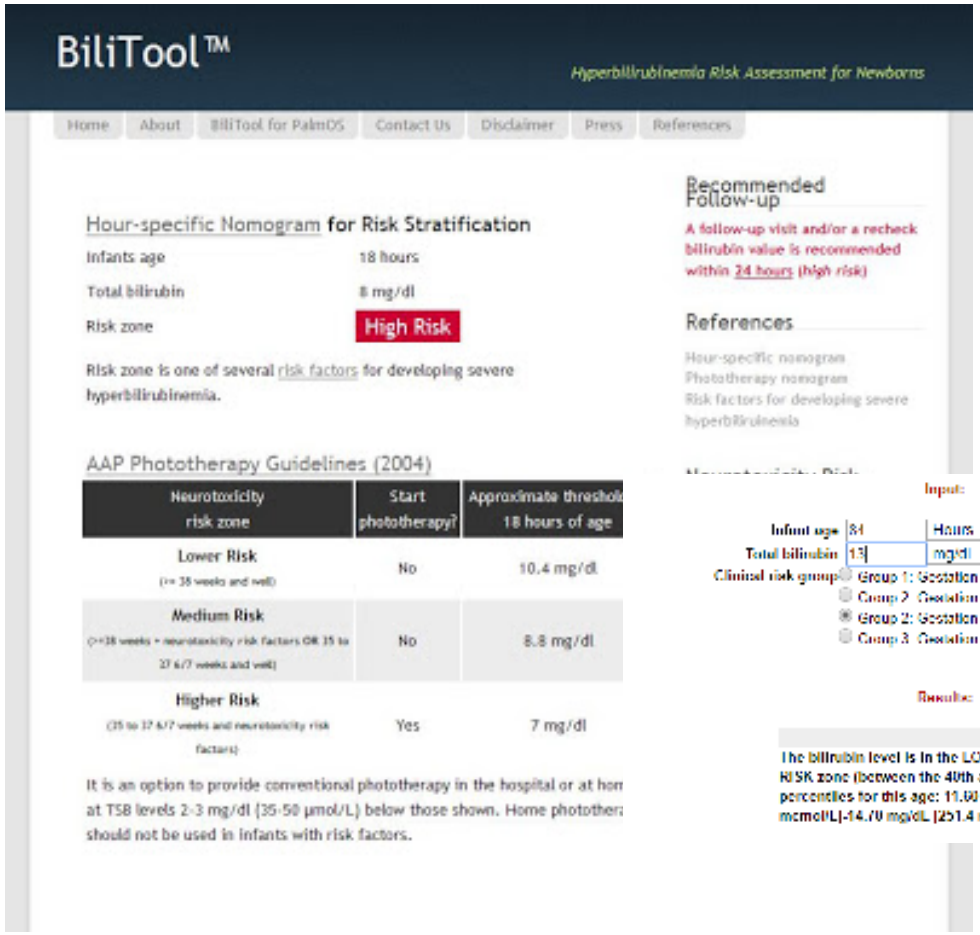
https://www.nice.org.uk/guidance/cg98. Updated October 2016. Accessed October 17, 2018.

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.

Mobile Application
to asses risk factors : AAP



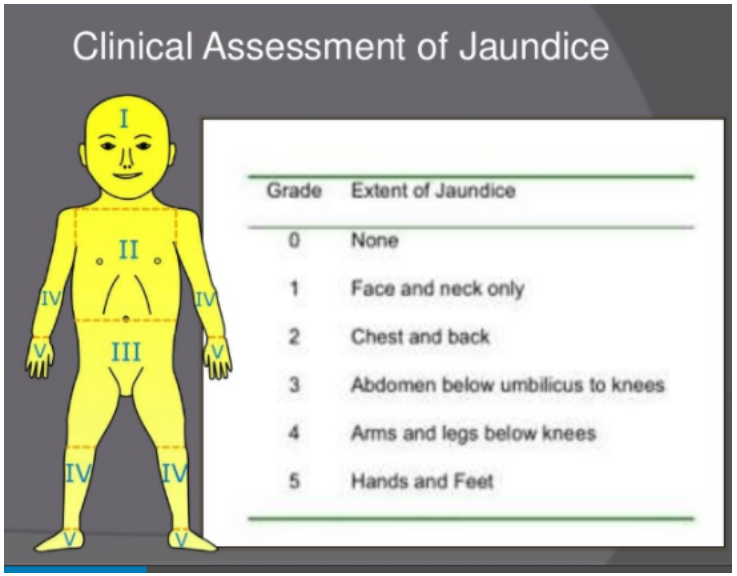
Post-discharge follow-up

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



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Aproach

Management

- Guidelines
- Work UP

Treatment

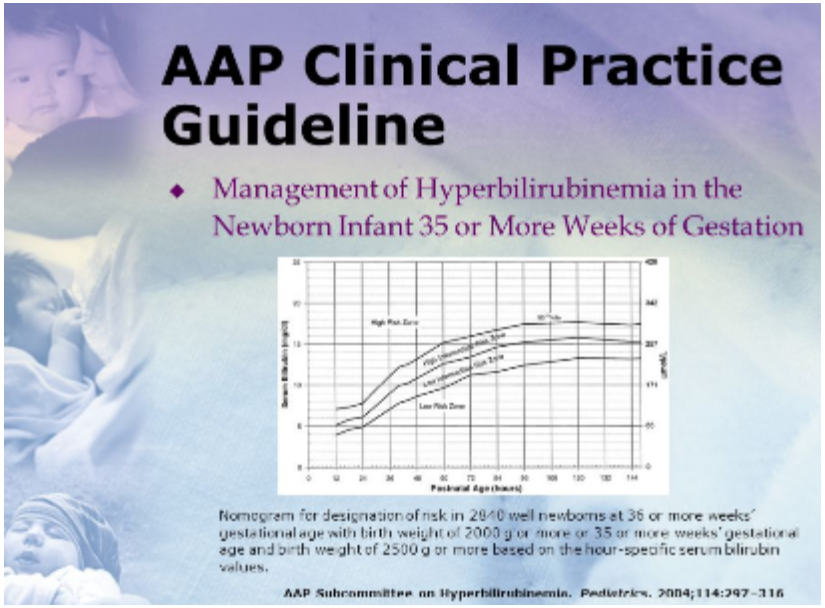
- Prevention
- treatment

How to manage if baby is Jaundice

Use A guideline

NICE guidelines (UK)

AAP guidelines (USA)



Help to diagnose , investigate and treat

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

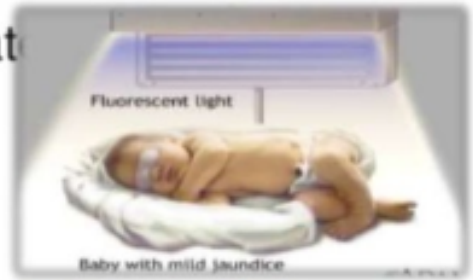
- Guidelines
- Work UP

Treatment

- Prevention
- treatment

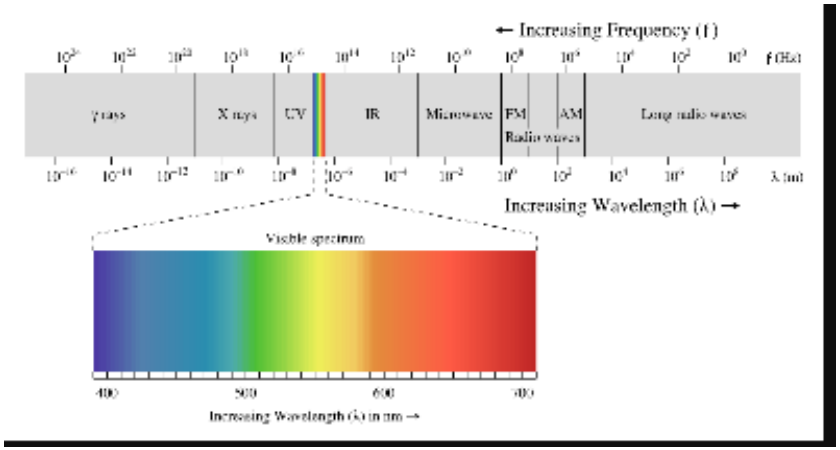
Therapeutic Options

- 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

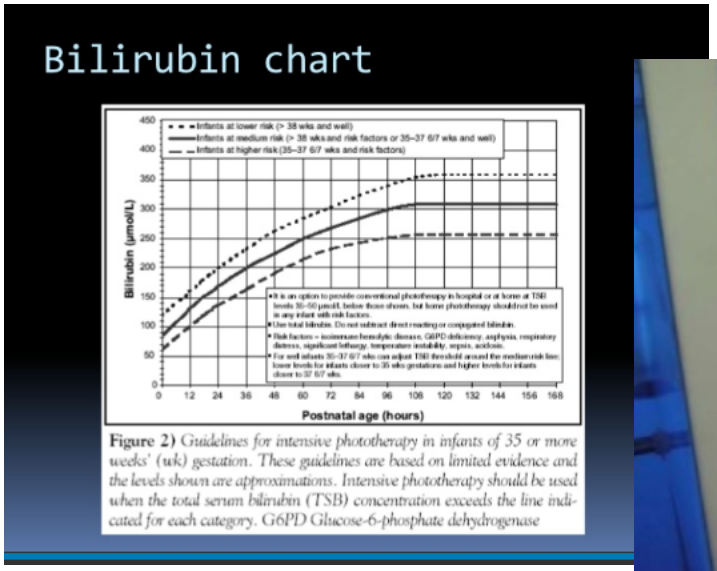
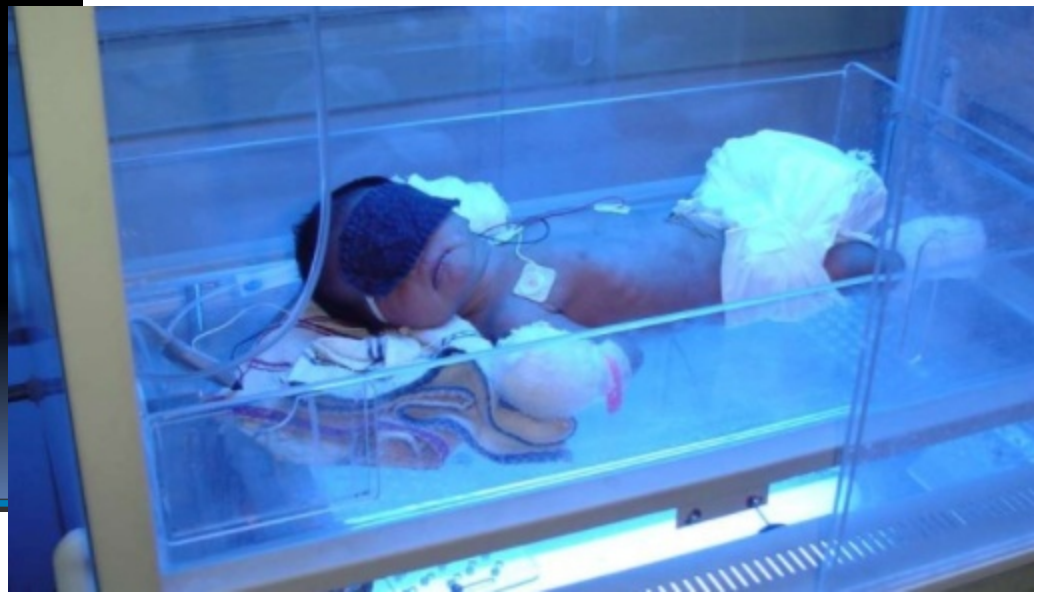
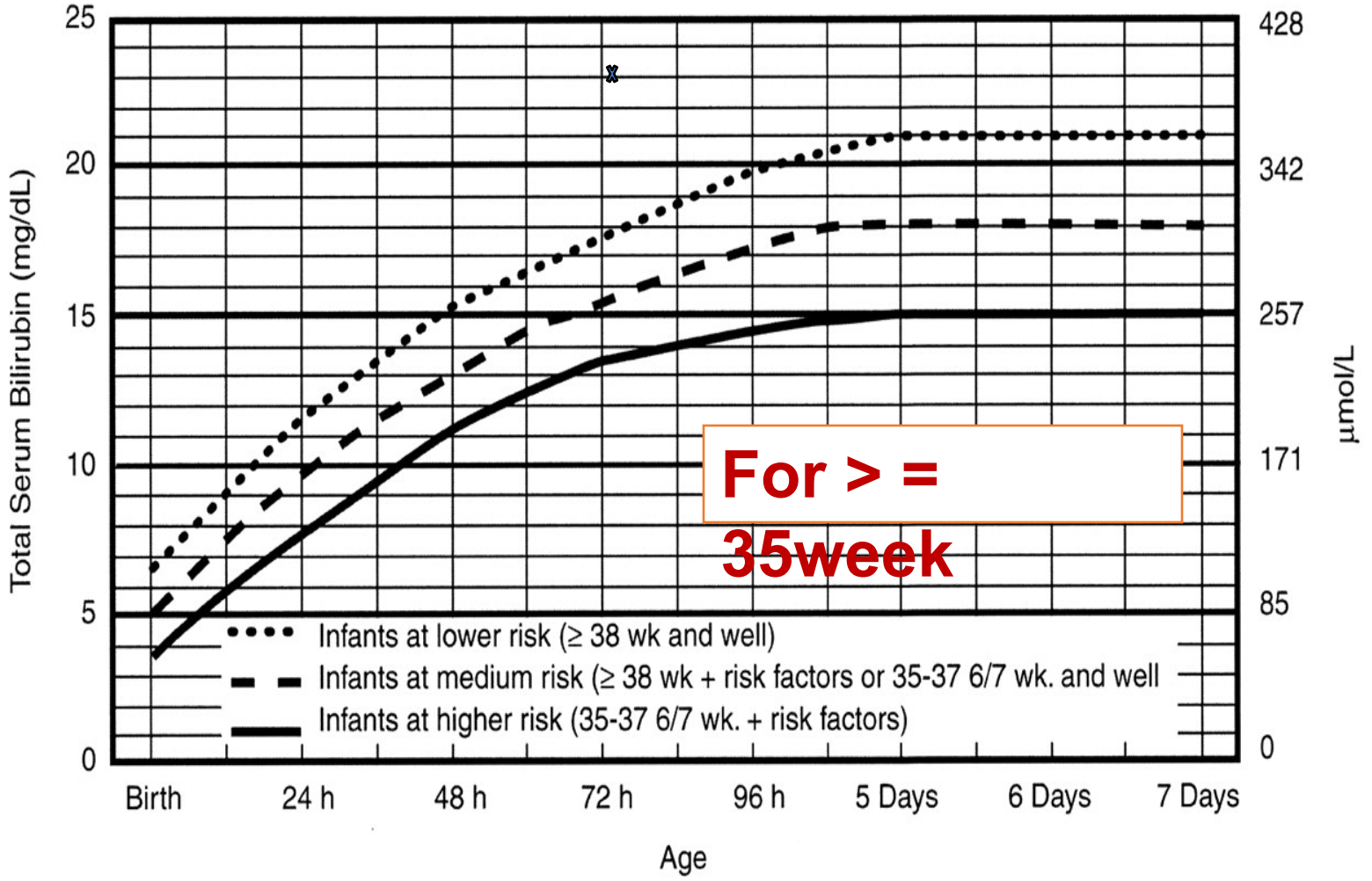


Figure 2) *Guidelines for intensive phototherapy in infants of 35 or more weeks' (uk) gestation. These guidelines are based on limited evidence and the levels shown are approximations. Intensive phototherapy should be used when the total serum bilirubin (TSB) concentration exceeds the line indicated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



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



Subcommittee on Hyperbilirubinemia, Pediatrics

Who need photo therapy ?

PEDIATRICS®

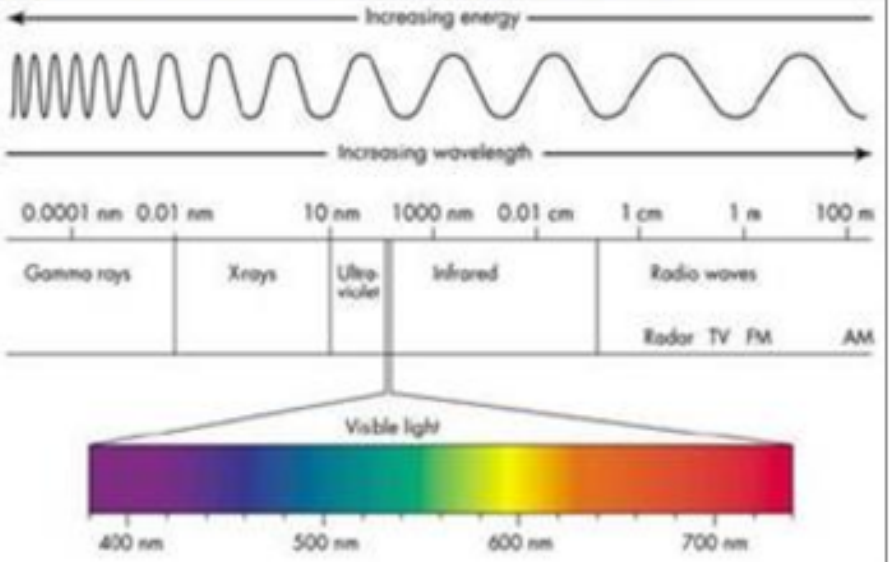
Factors affecting Phototherapy

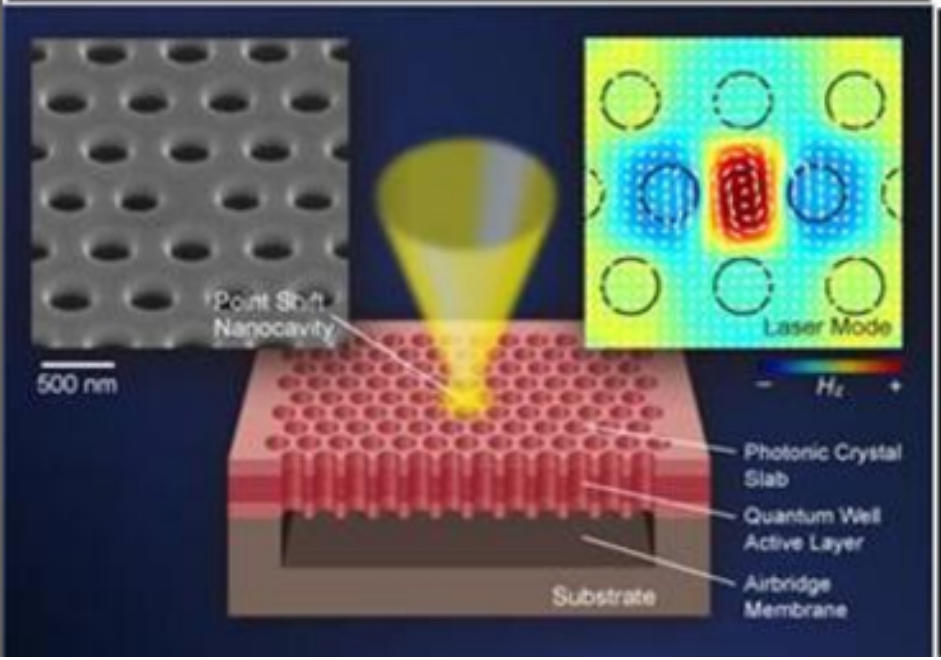
Wavelength

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

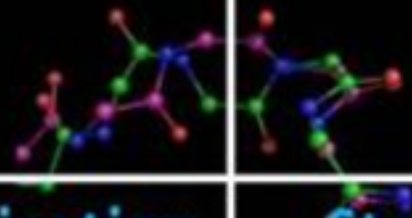


Photo oxidation

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*

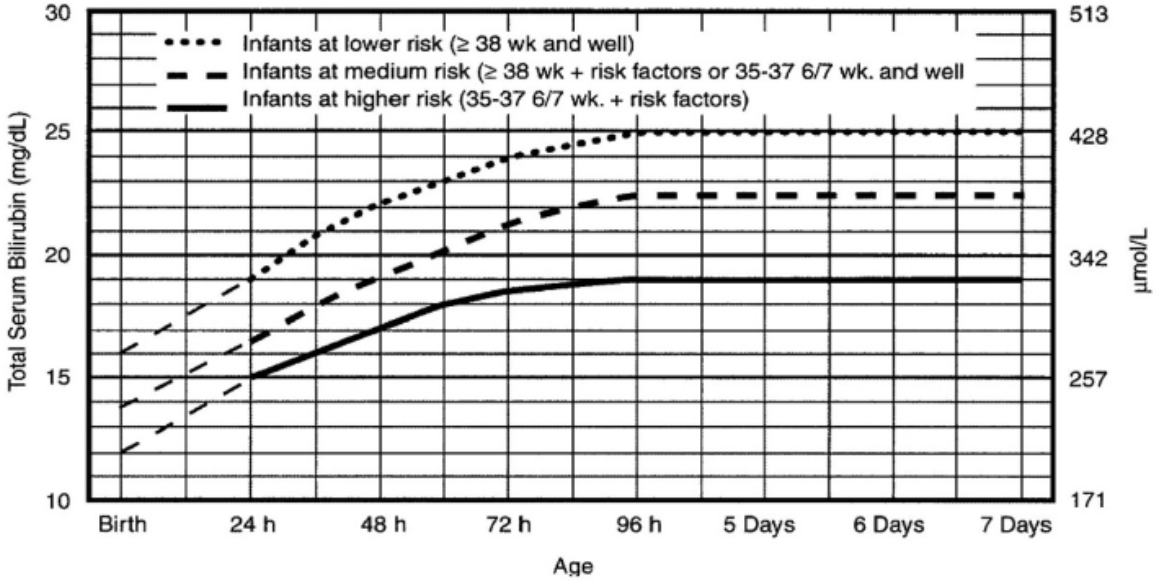
Not influenced significantly by the intensity of light.

Structural Isomerization

Intramolecular cyclization resulting in the formation of lumirubin

Enhanced by increasing the intensity of light.

Exchange photo therapy



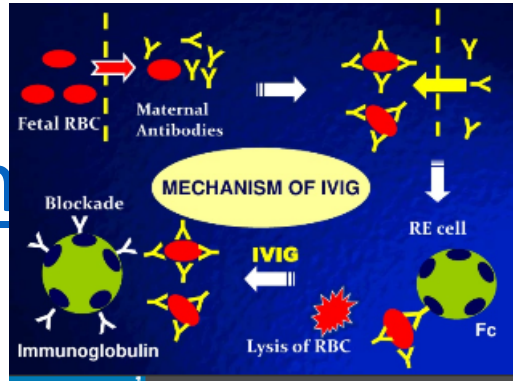
- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, 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.

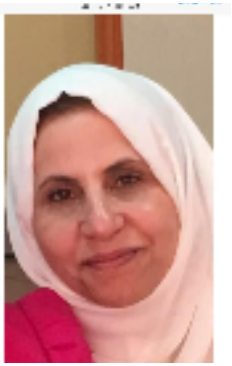
- Thank you

Neonatal Jaundice

Eman Badran
Professor of Pediatrics

Fifth year medical students

Ophthalmologic Problem In neonates



Case based study

Eman F. Badran
Professor of Pediatrics
University of Jordan
School of Medicine
Pediatric Department
Neonatal Division

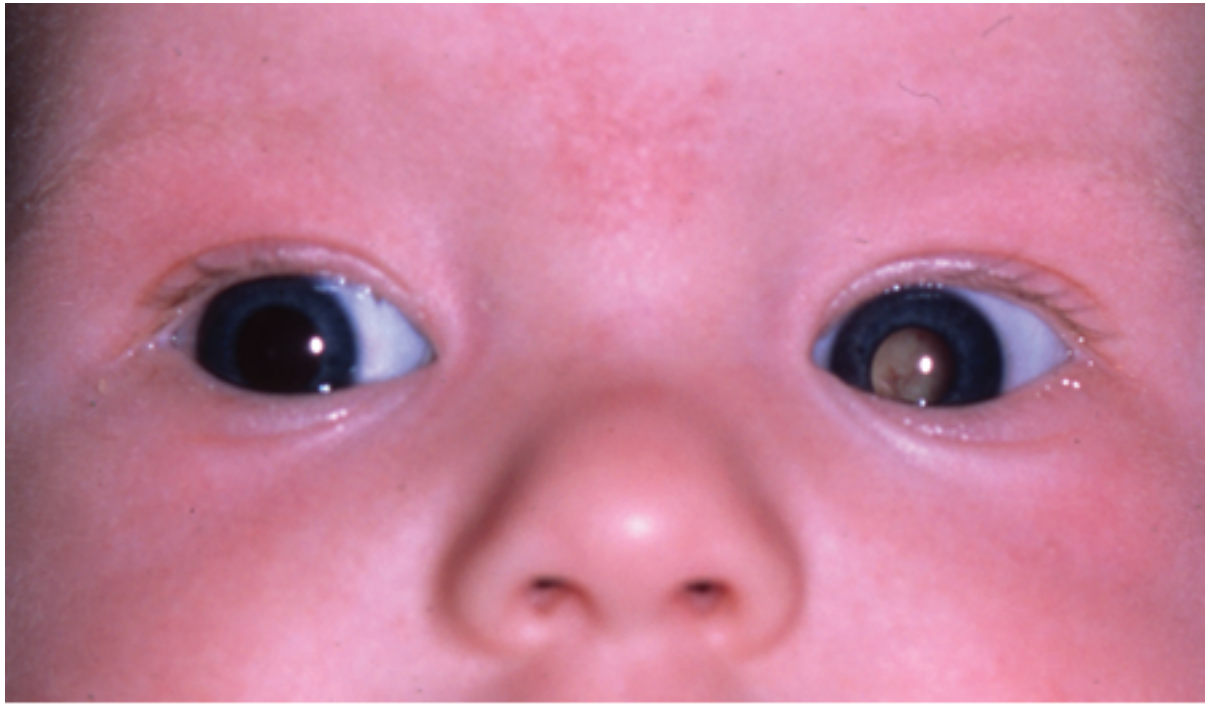
Learning Objectives

- 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



A

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

Urgent

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 **mucoid discharge** from the eyes or eye

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

What Is the next step

History

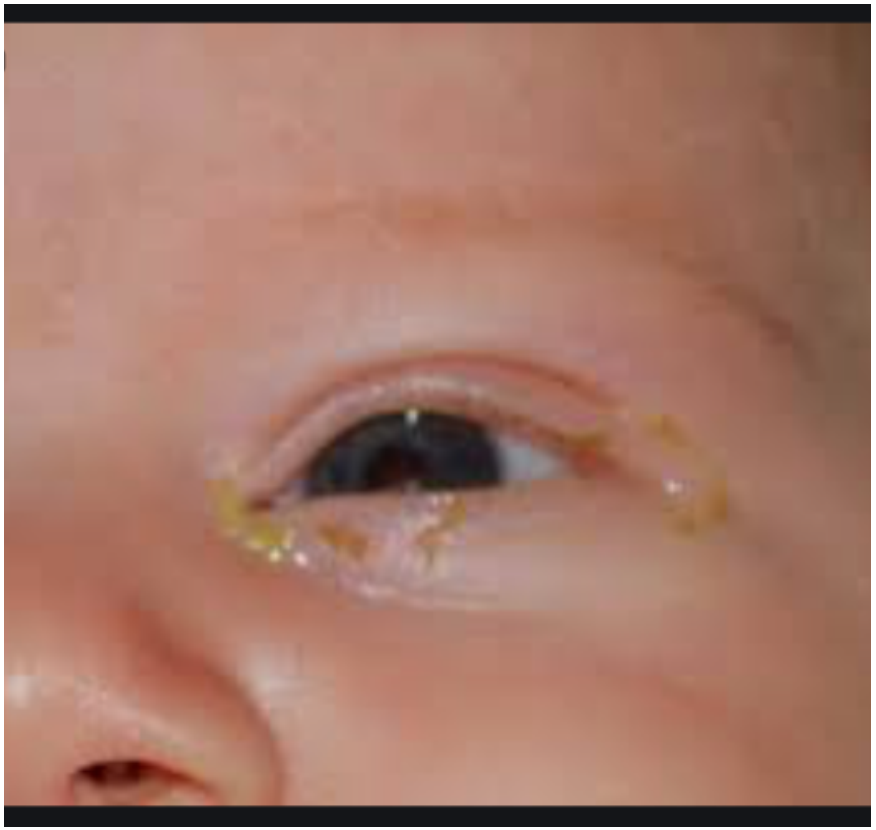
- Duration: 1 wk
- Type of discharge: Mucoid
- Uni/Bilateral: Unilateral
- Eye redness: NO
- Course: Constant

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

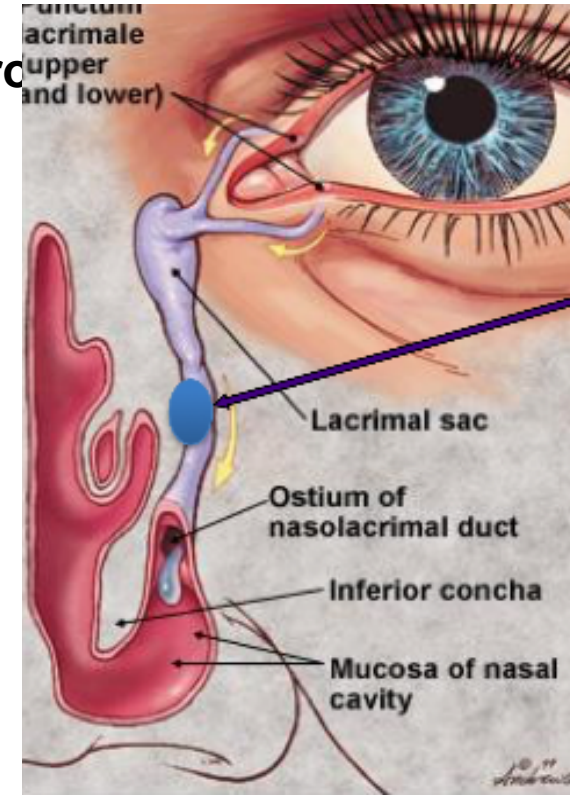


The parents would like to ask why is this pro

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

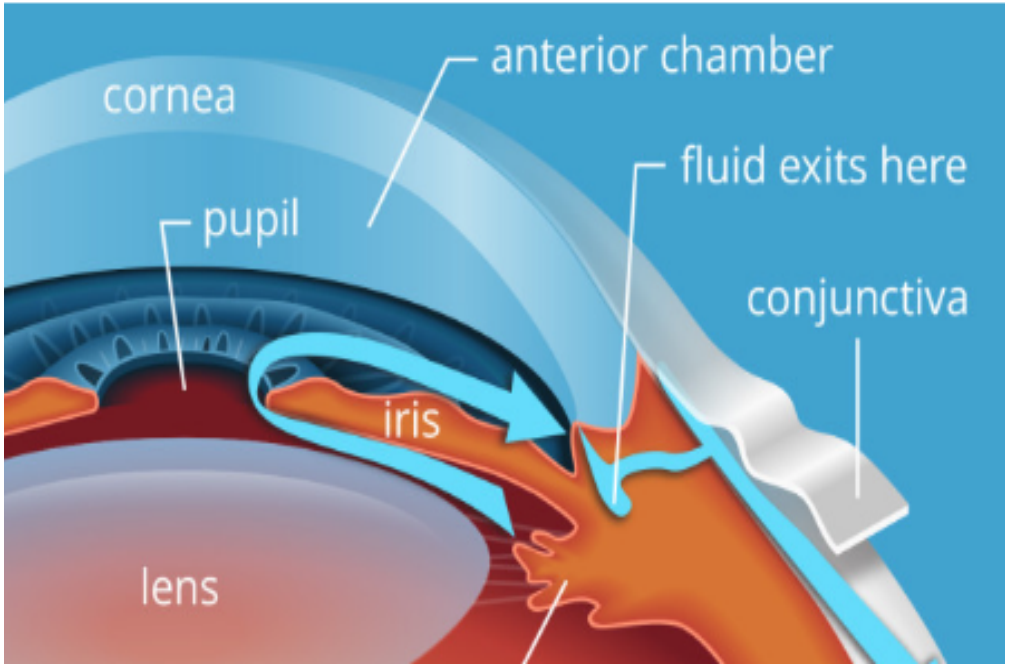
PRIMARY CONGENITAL GLAUCOMAS (PGG)

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

that prevent adequate drainage of aqueous humor,

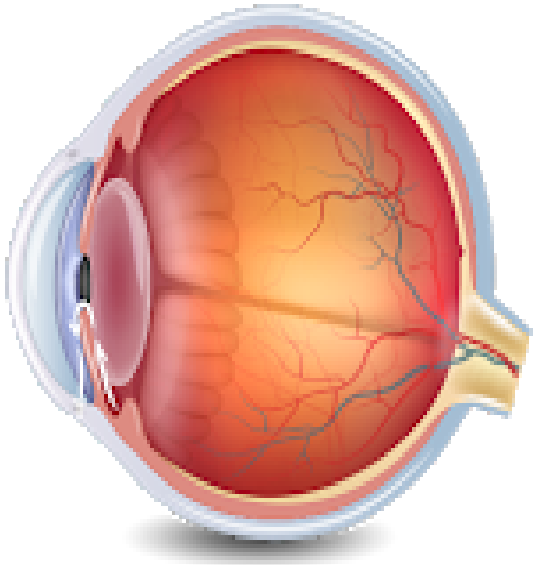
resulting in elevated intraocular pressure (IOP)

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

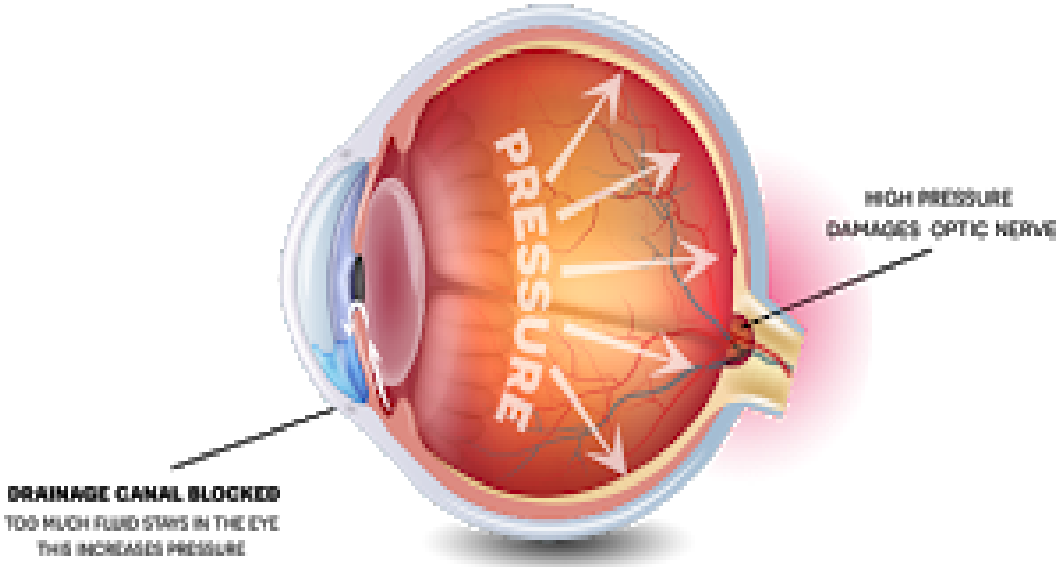


https://www.kceyeclinic.com/our-services/glaucoma/types-of-glaucoma/

GLAUCOMA



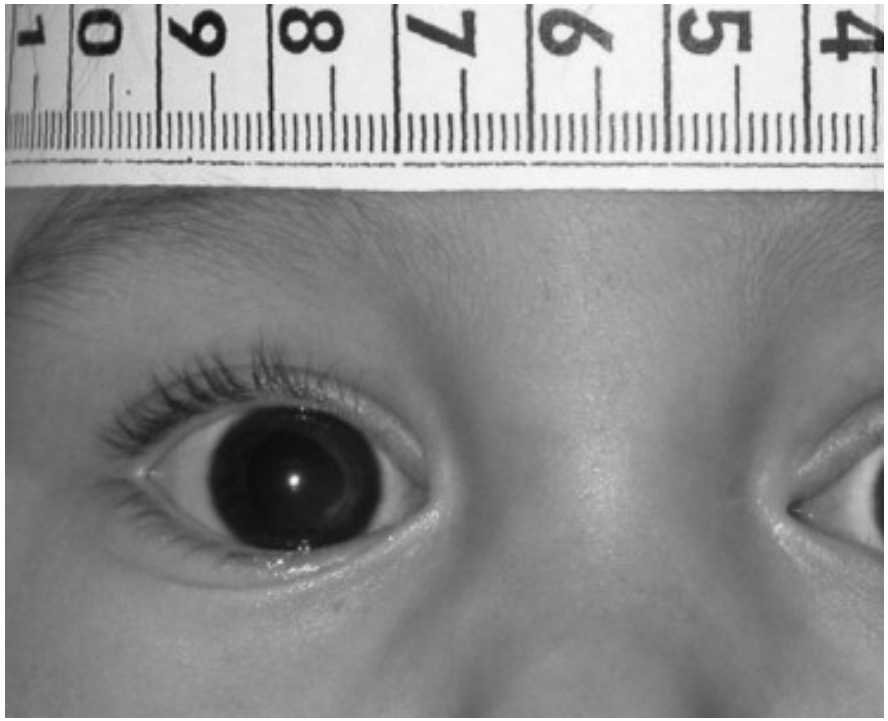
NORMAL EYE

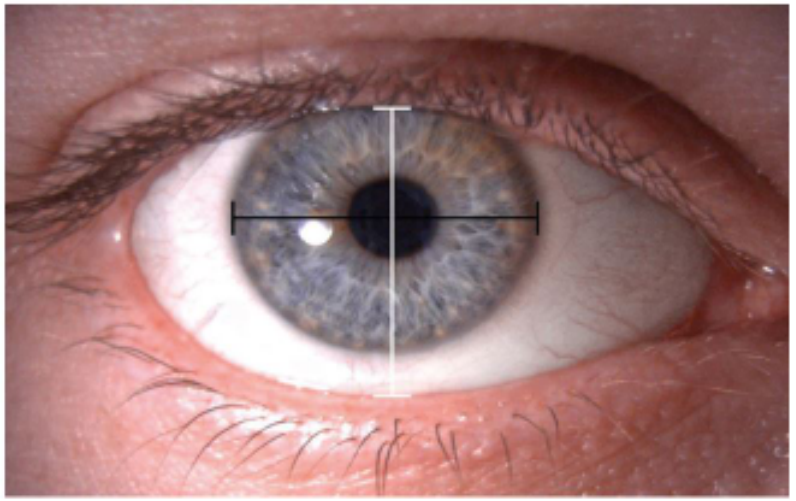


GLAUCOMA

Symptoms of congenital glaucoma

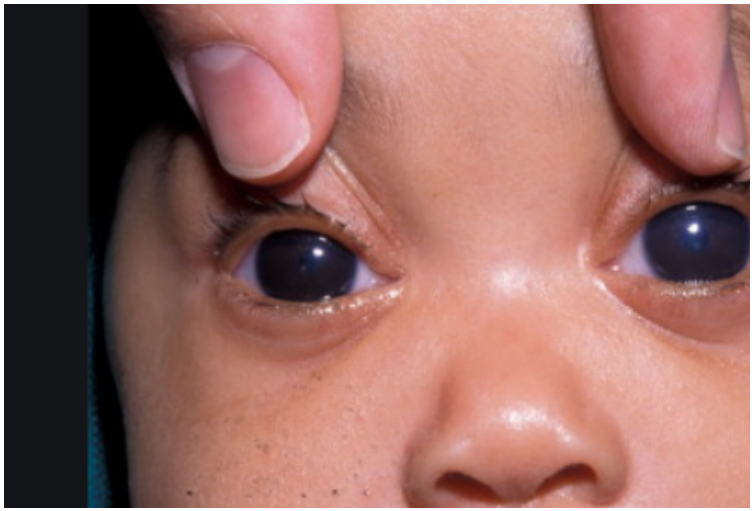
normal horizontal **corneal** diameter is 10.5 mm





Symptoms of congenital glaucoma

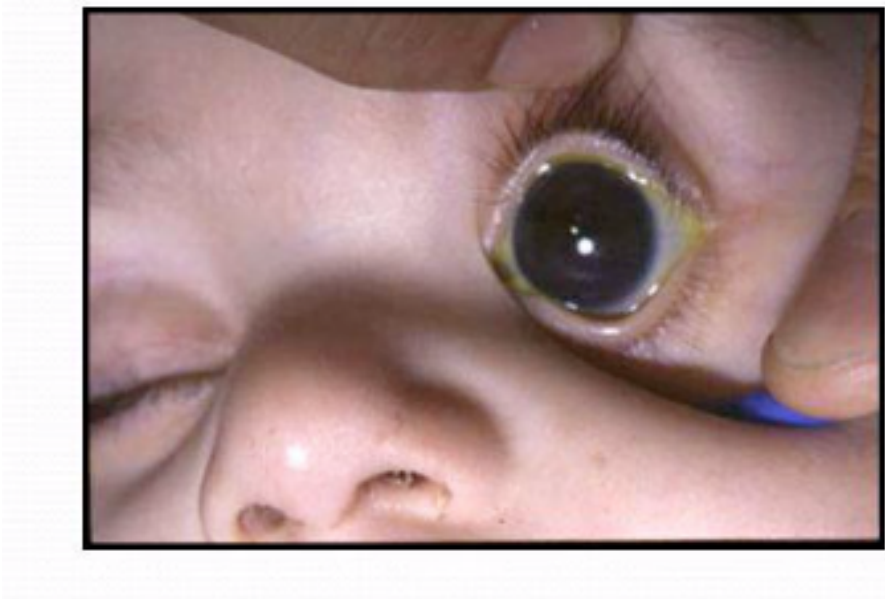
measurements greater than 12 mm are highly indicative of glaucoma.



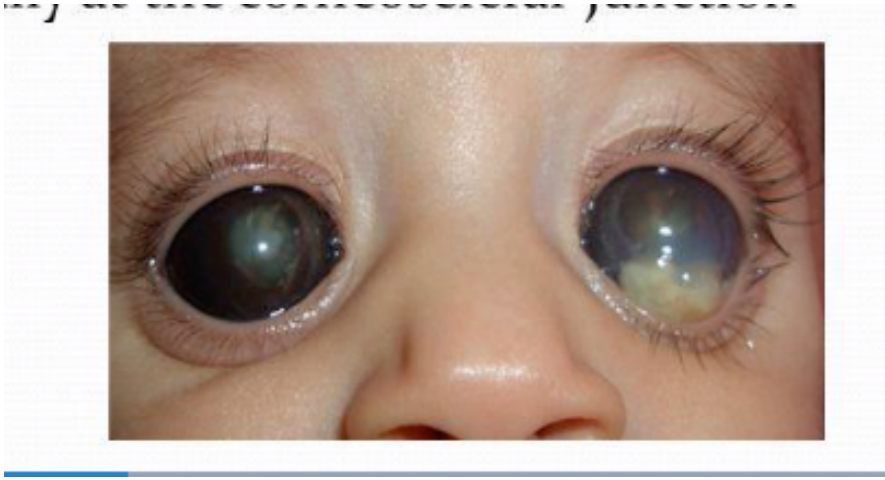
Top emergency : need surgery
Can neve some damage as Optic nerve

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 Glucoma

Sturge-Weber syndrome

facial port-wine stain involving the **upper** and l**ower** 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

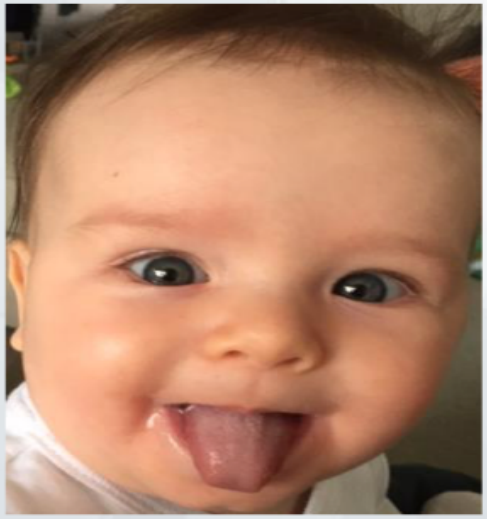
- During 2 weeks Neonatal visit
- Parents noticed that their baby has **squint**
  - They said it is (**intermittent** side ways)
- His history and **Physical exam is unremarkable**
- He was **healthy**
- **Red reflex** were **n**ormal and symmetrical corneal reflex

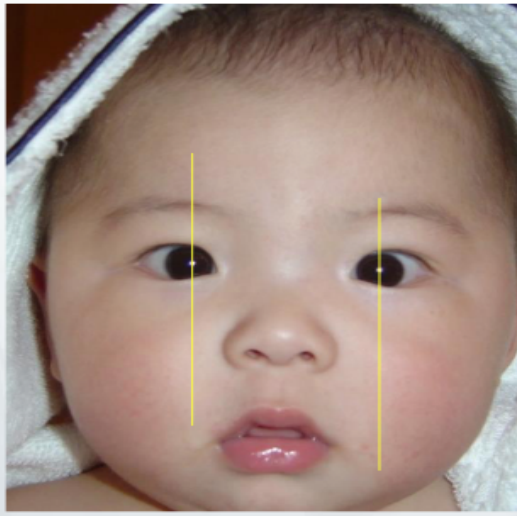
Strabismus – "squint that goes away"

Transient neonatal strabismus

- *NORMAL ocular alignment*
- intermittent
- ***Resolves by 2-4 months[1,2]***

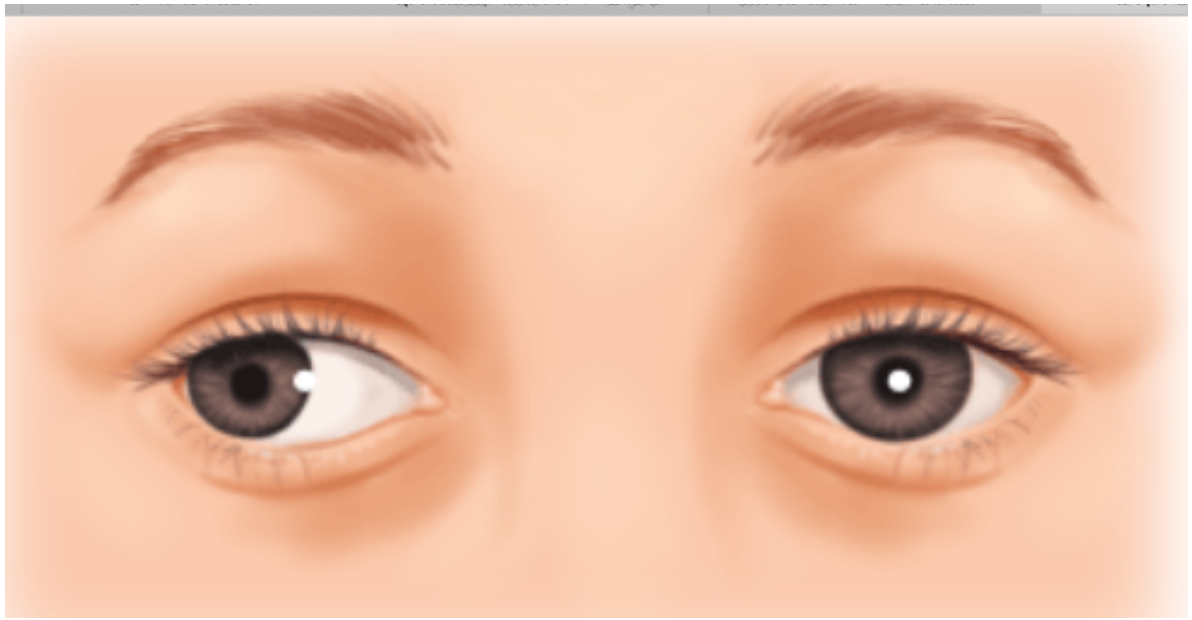
Pseudo-strabismus: Optical Illusion





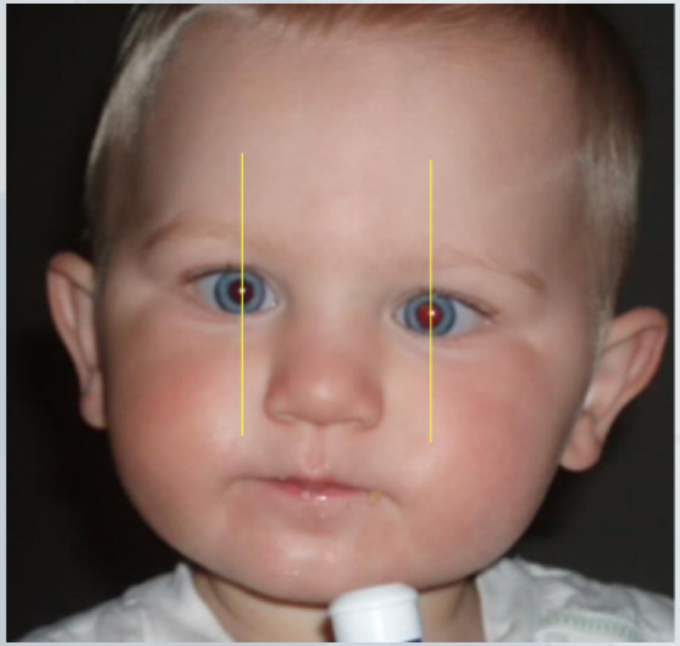
- Wide nasal fold/bridge of nose
- Intermittent – looking sideways
- "see both ears"
- Corneal light reflex - symmetry

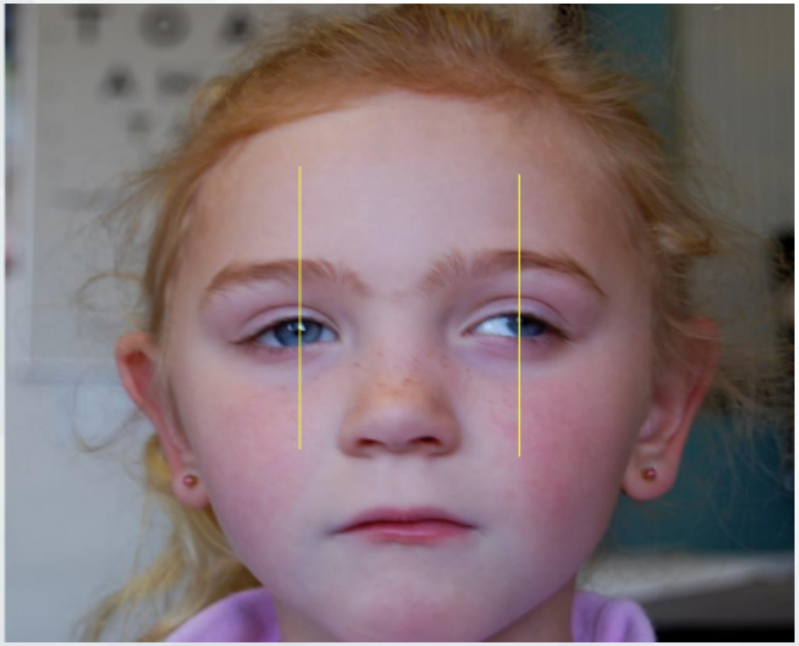
[1]Horwood A. 1993, JAAPOS; [2]Sondhi N. et al. 1988 JAAPOS



Asymmetrical pupillary reflex

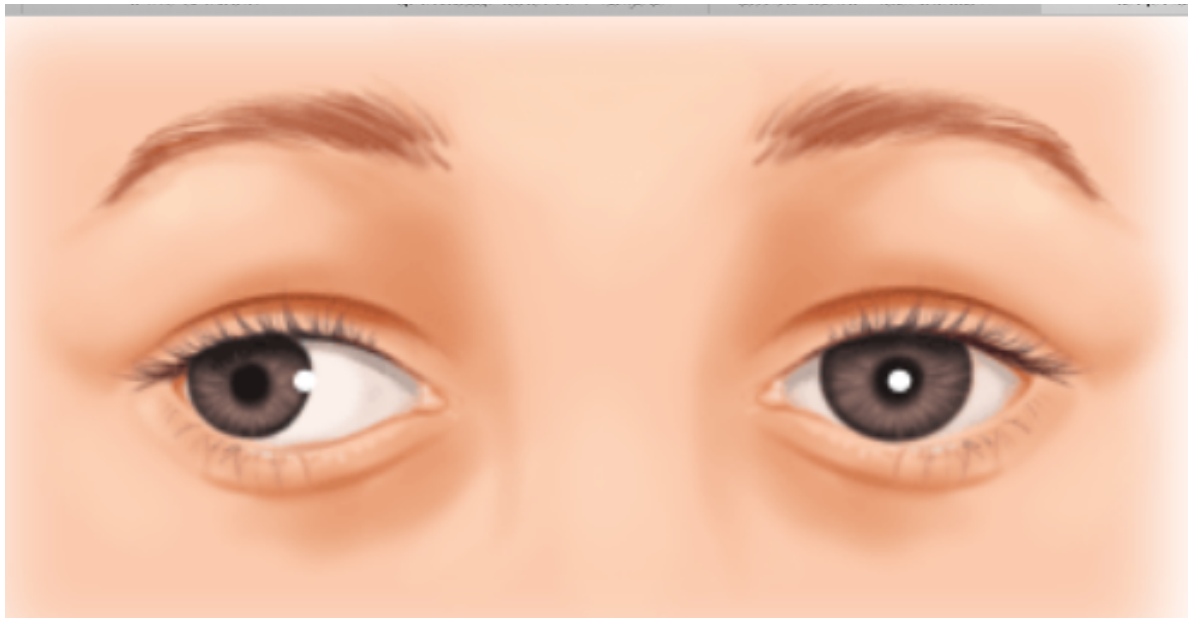
True strabismus – variable direction, size and frequency





Consider:

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



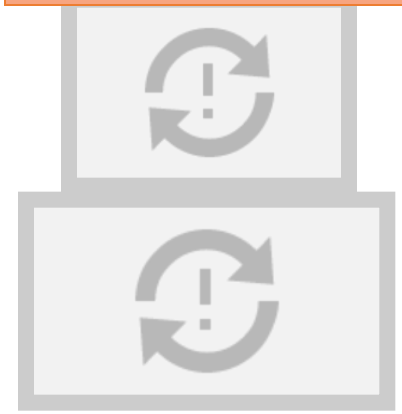
Asymmetrical pupillary reflex

At what time you screen the baby for red reflex

Why IT is important

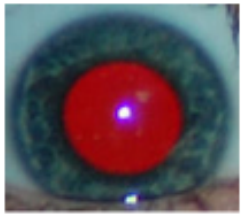
Red reflex

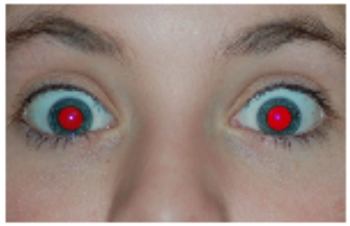
Should be done before newborn discharge



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.

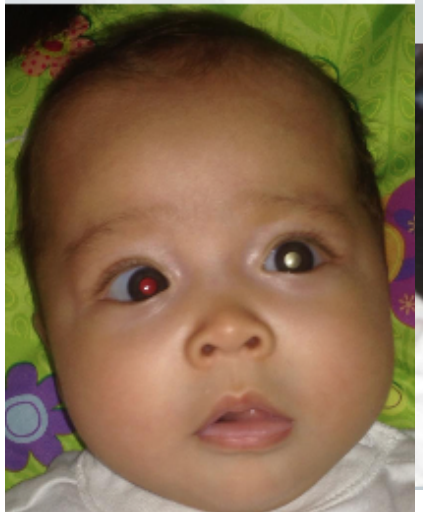
Interruption of Abnormal red reflex

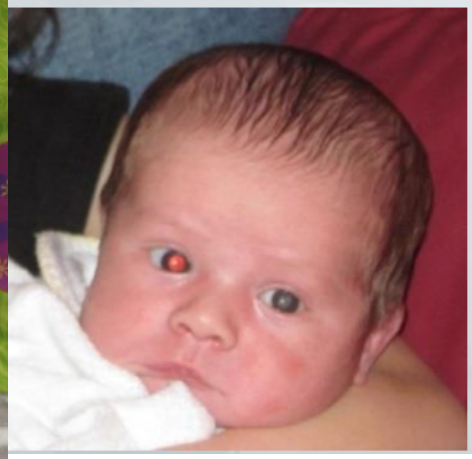
white spots
(leukocoria)

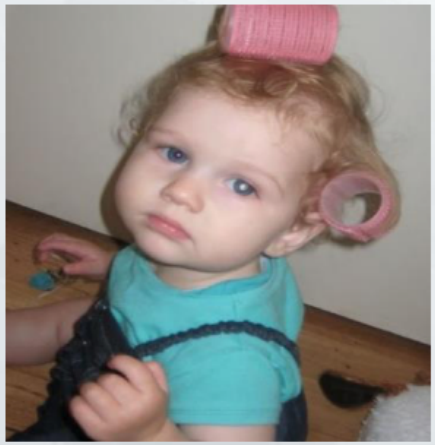
Leukocoria

Strabismus may be early signs

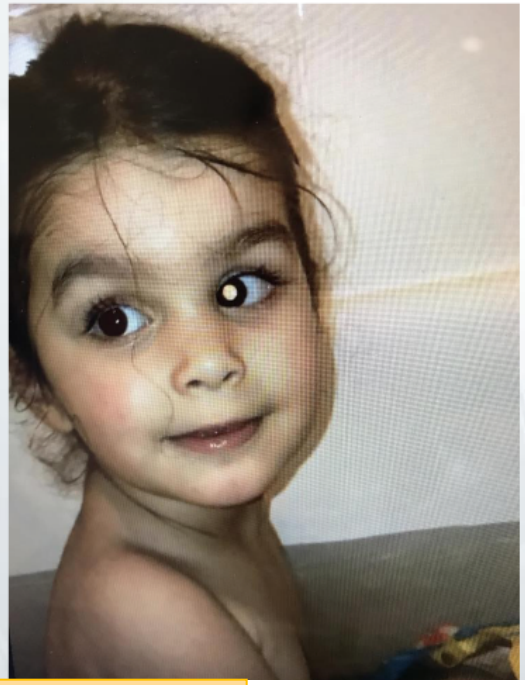
"Leuko" – white
"Coria" – pupil







“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 ambylopia in infants.
- It is divided to:
  1. **Systemic** association
  2. **Non-systemic** association

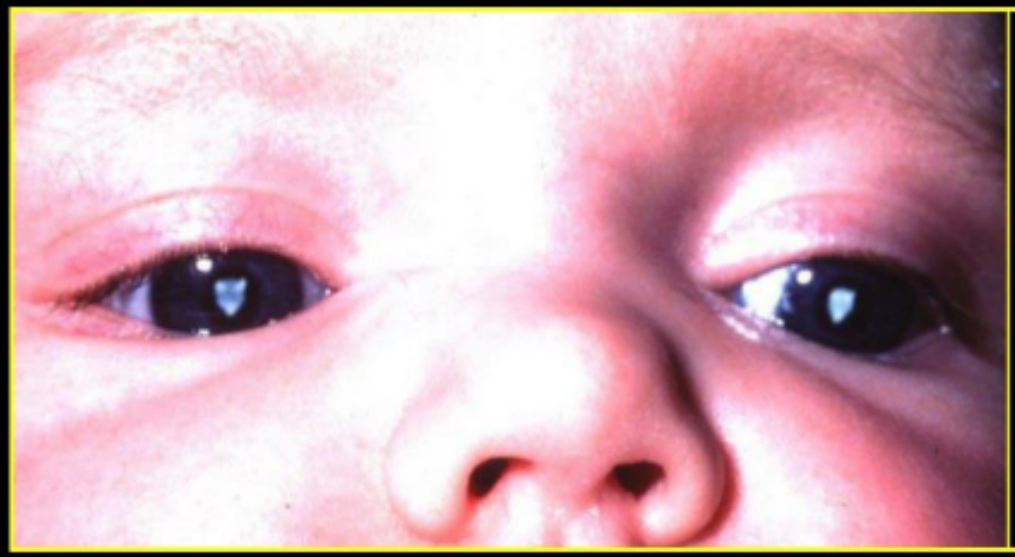
Systemic association

1. Metabolic:
   - Galactosaemia, galactokinase deficiency, Lowe syndrome, others (hypoparathyroidism, pseudohypoparathyroidism, mannosidosis)
2. Prenatal infection:
   - Congenital rubella (~15% of cases), other intrauterine infection (toxoplasmosis, cytoegalovirus, 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

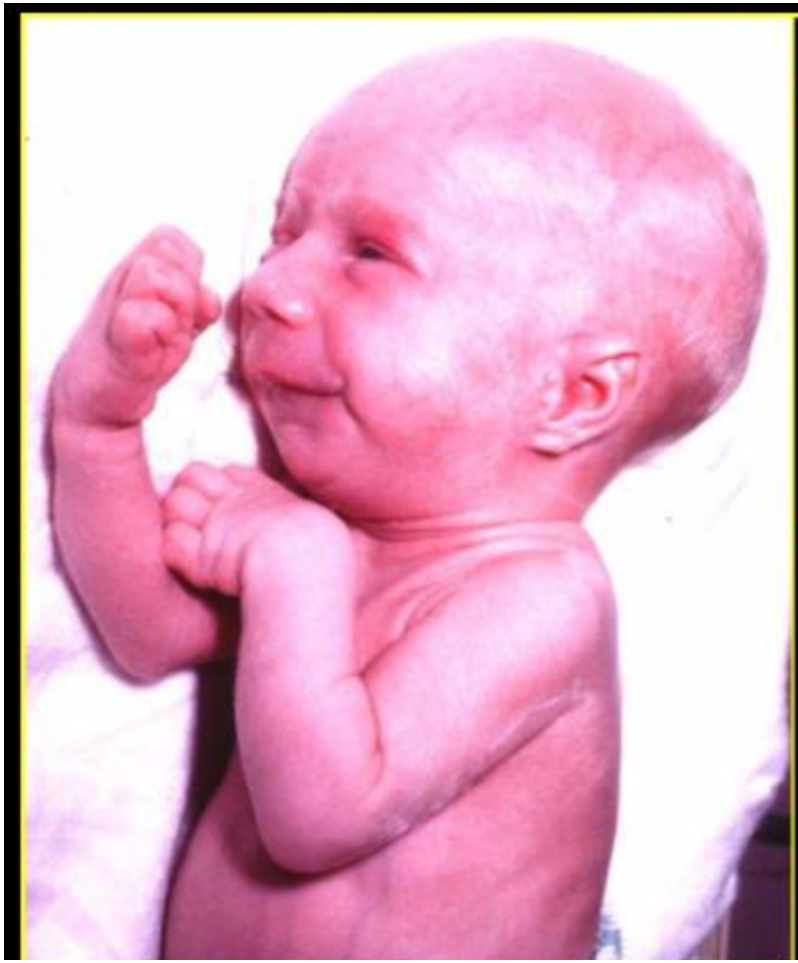


Hereditary
(usually dominant)

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

- 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