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

Bilirubin > normal level

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

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

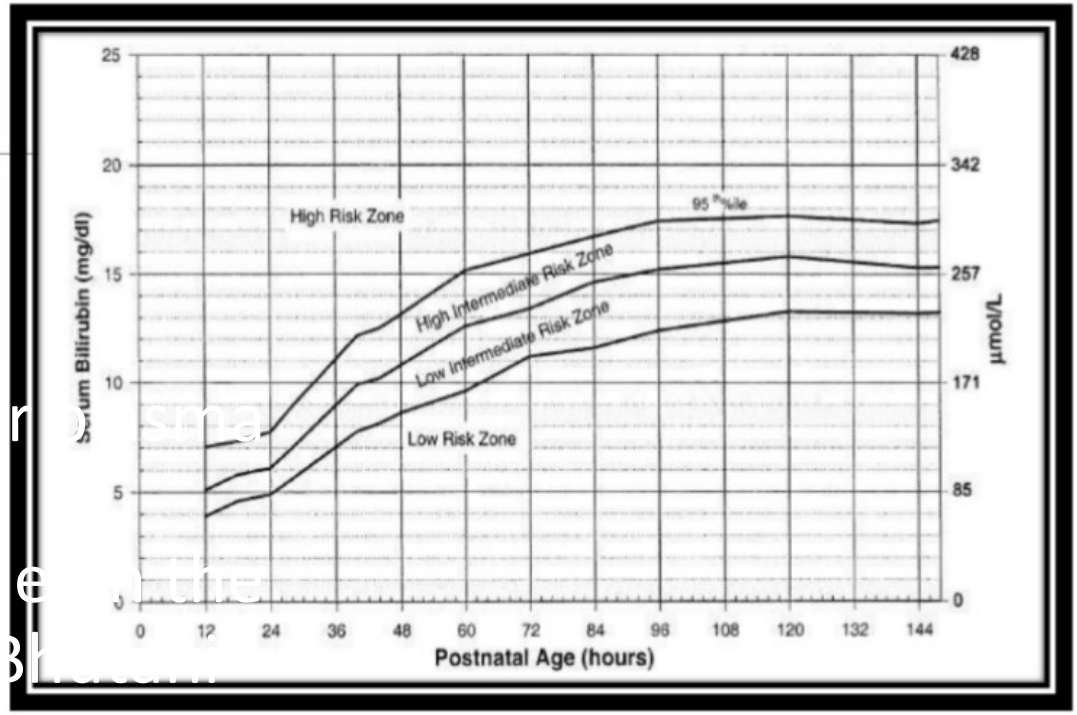
Definitions

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

TSB >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.



significant elevation of total serum bilirubin (TSB) levels:

it means requiring close surveillance or treatment

Definitions

Severe neonatal hyperbilirubinemia

Defined as a Total serum Bilirubin

>25 mg/dL (425 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:
      - **Change level of consciousness (l**irritability alternating with **increasing lethargy** then and coma)
      - **poor feeding then** cessation of feeding
      - hypertonia (retrocollis, opithotonus, **shrill cry**;
      - Seizure bicycling movements (possible seizures),
      - fever
  - Kernicterus is the chronic and permanent sequelae of BIND.

Real Life Scenario

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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

Has a complication

- *Acute sequelae* of BIND :

Acute signs (**Acute Bilirubin Encephalopathy**)

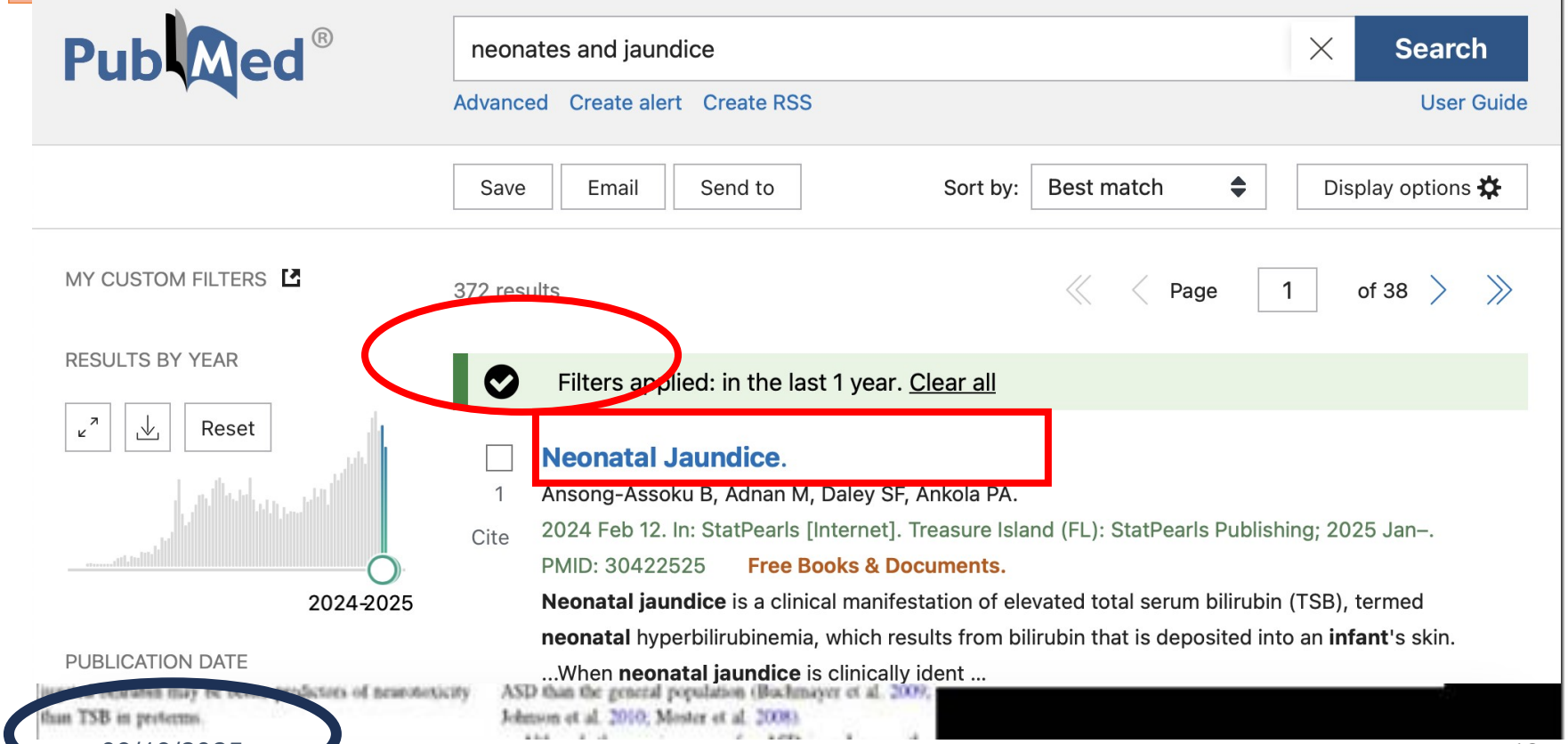
- *Chronic and permanent sequelae* of BIND

Kernicterus :it is chronic sequelae

Neonatal Jaundice is HOT topic in Paediatric Journals

Why this lecture

Alwys Hot topic in research



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Neonatology

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

2011

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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


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

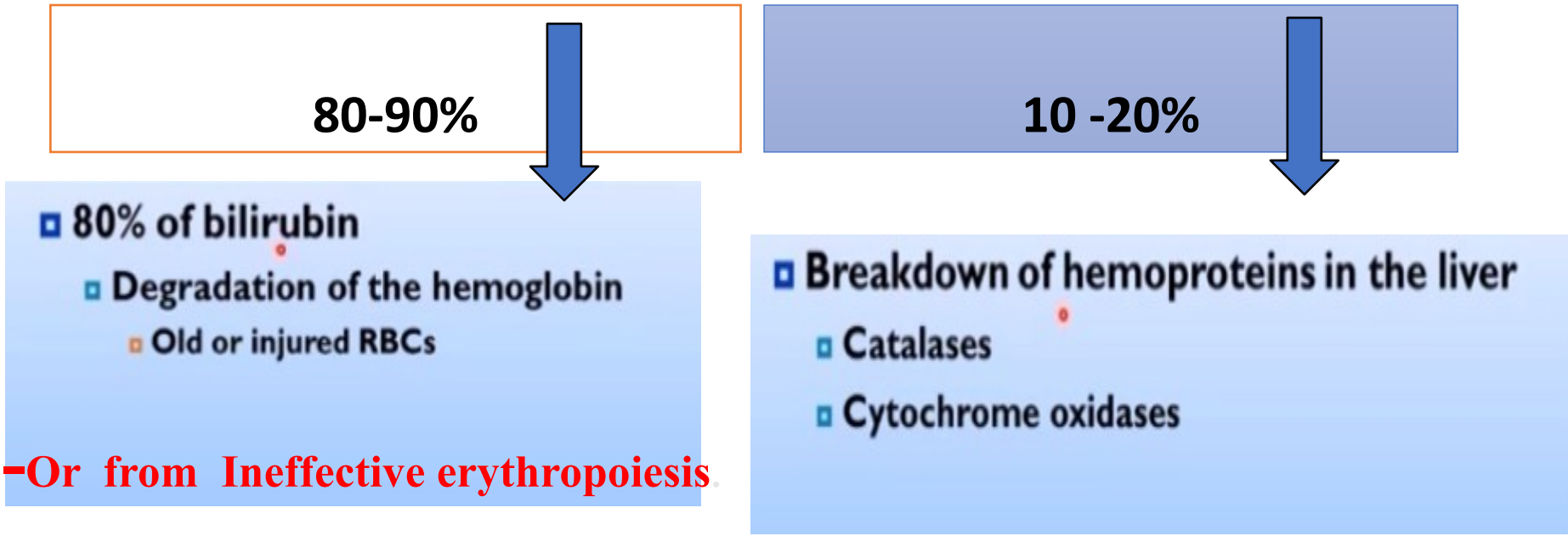
- Physiologic

- Pathologic

This is review

Can be skipped slide 20- 37

Bilirubin production: Source



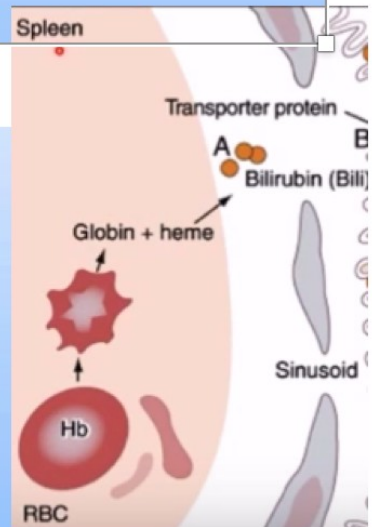
Note:

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

Site of bilirubin metabolism

- Reticuloendothelial system
- Consists primarily of monocytes and macrophages

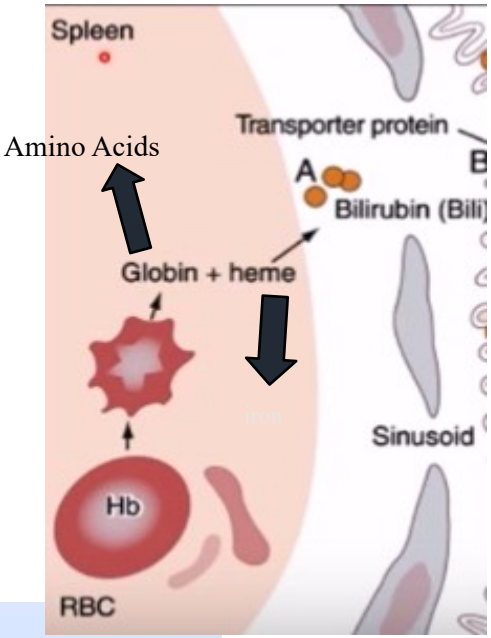
- Spleen
  - Largest unit
- Liver
- Bone marrow



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

C

oxygenase

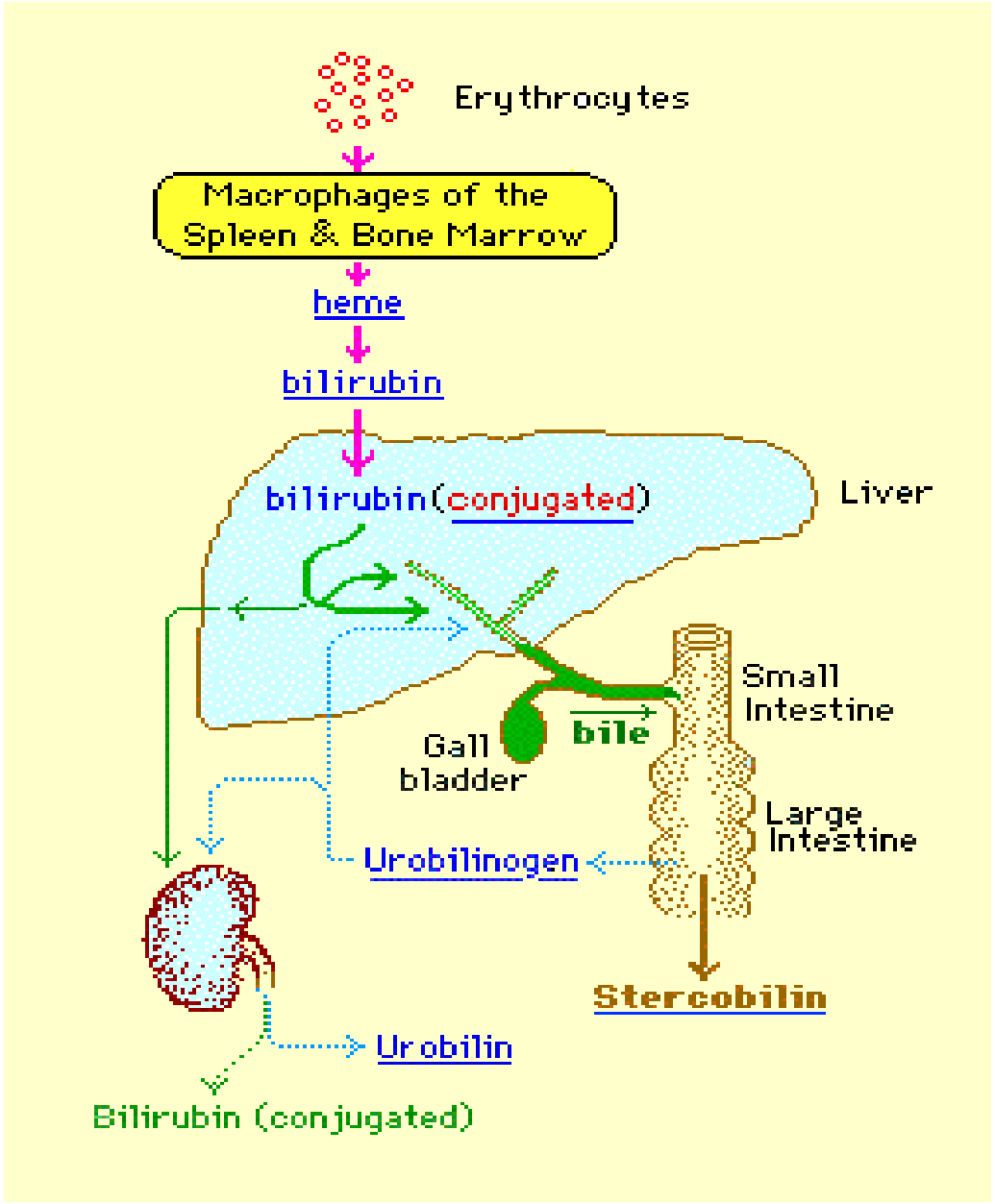
↓

↓ Biliverdin reductase

↓

Bilirubin

(released into blood)



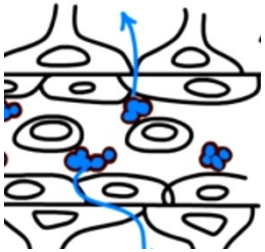
Why to know the

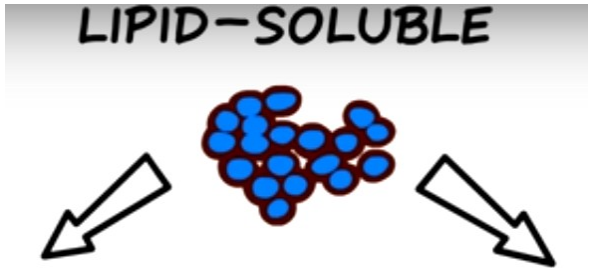
Bilirubin Production

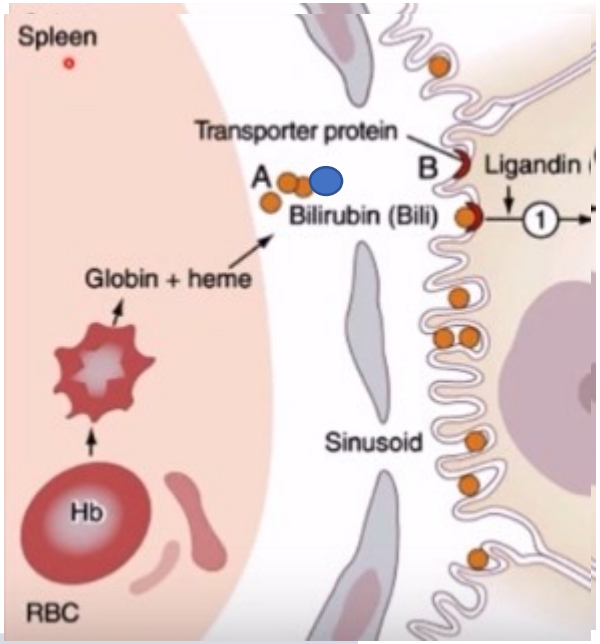
&

Metabolism

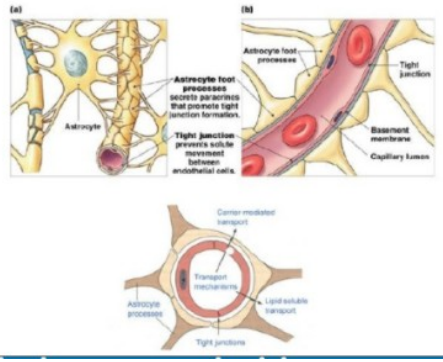
Unconjugated Bilirubin in plasma





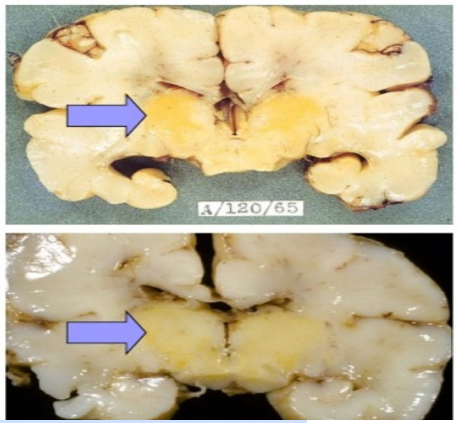


Blood-brain barrier



- 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

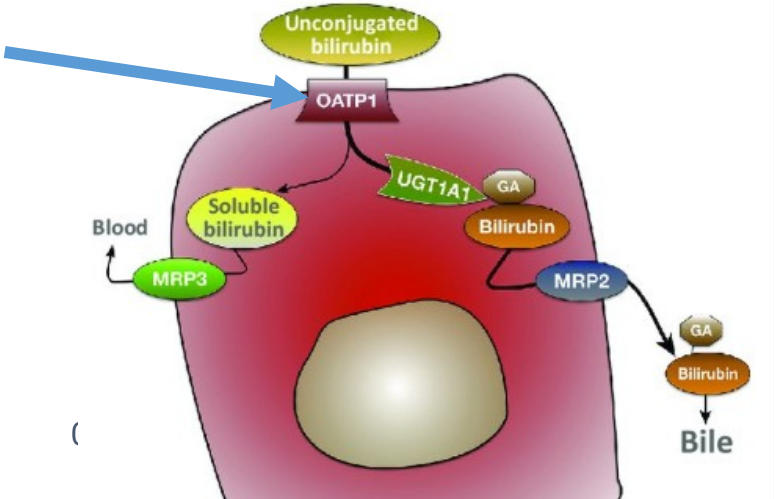
Normal level

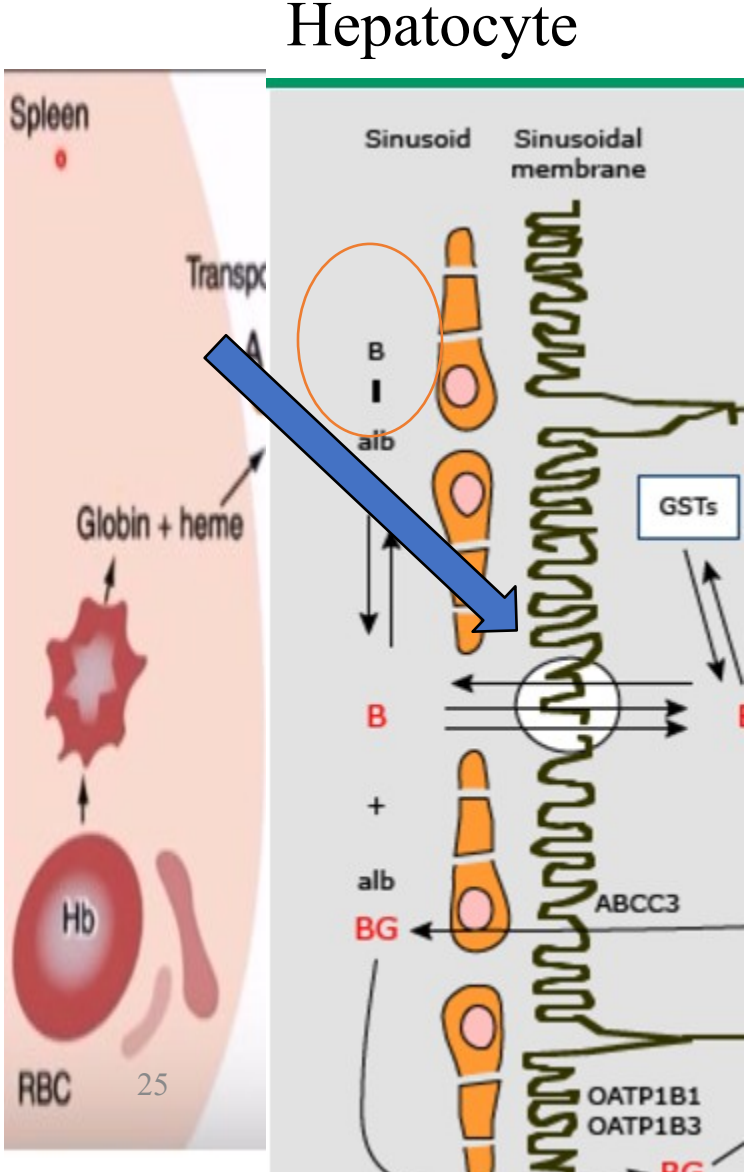
- < 1.5 mg/dL
  - Almost entirely bilirubin (unconjugated)
    - Tightly but reversibly bound to albumin

Unless
- Liver disease
- Biliary obstruction

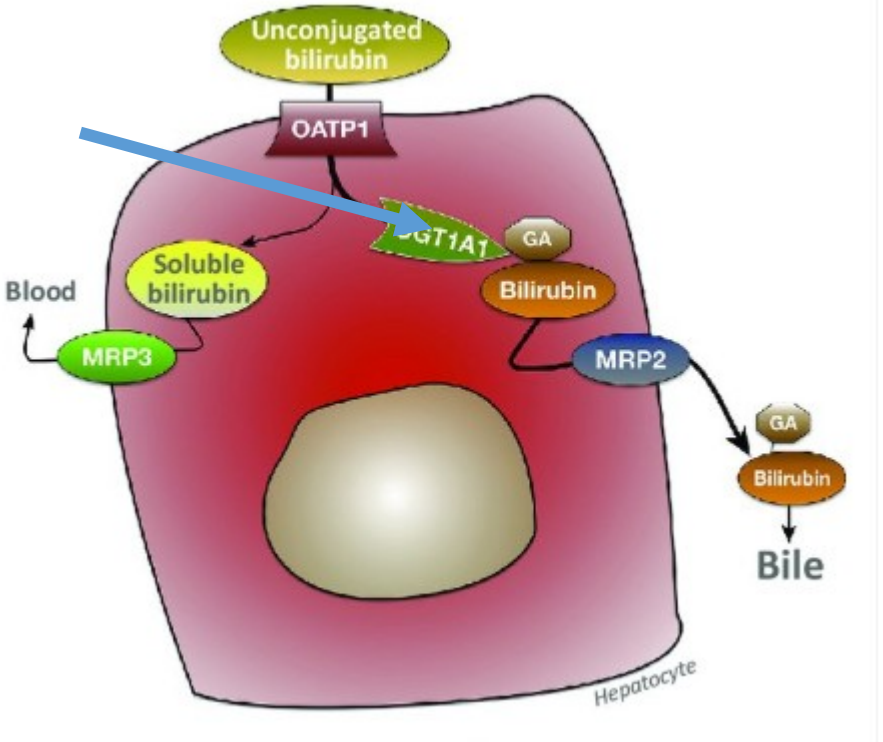
Hepatic uptake – Circulating bilirubin

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





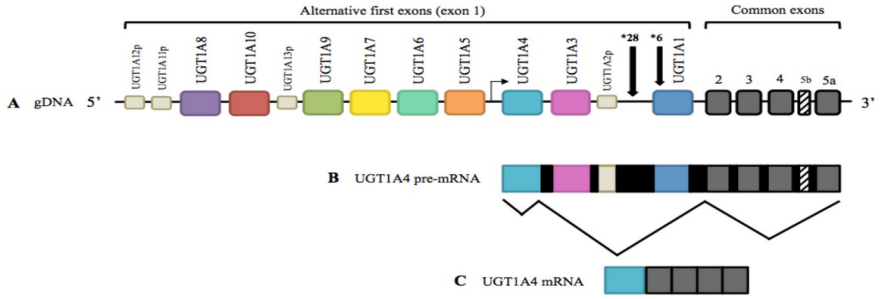
conjugation



Role of uridine diphosphate glycosyltransferase Enzyme

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

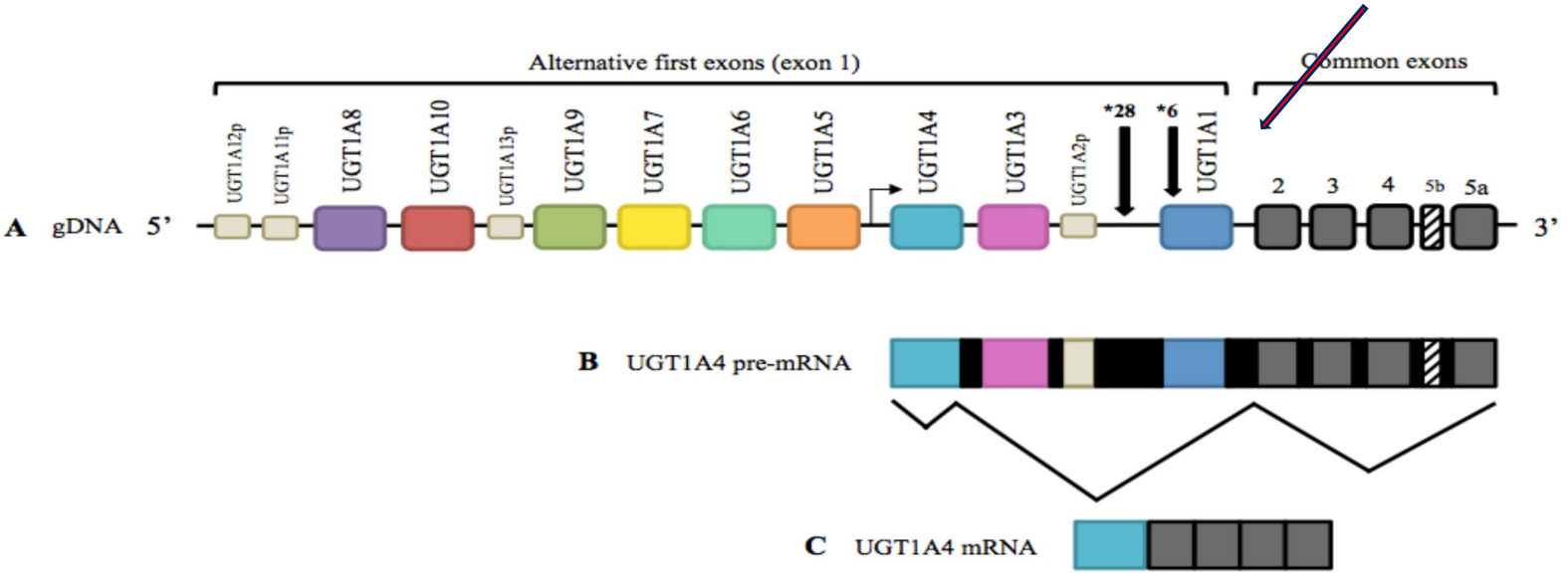
" *UGT1A1* gene (ID: 54658) is a part of a complex locus **encoding** 13 UDP-**g**lucu**rono**syltransferas**es**)



What does UGT1 stand for?

UGT1A! stands for "UDP-glucuronosyltransferase family 1

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



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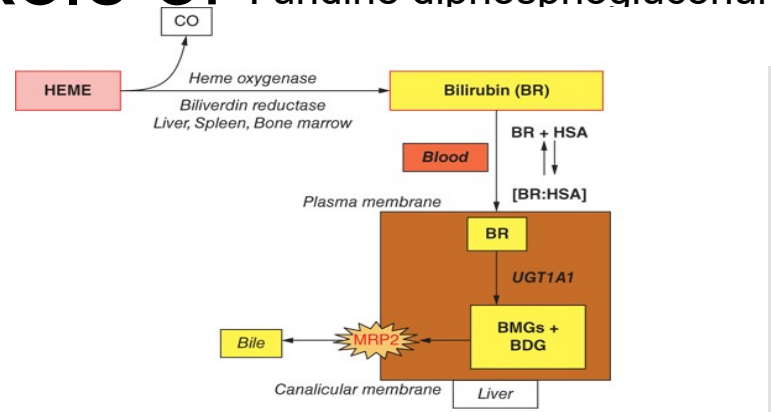
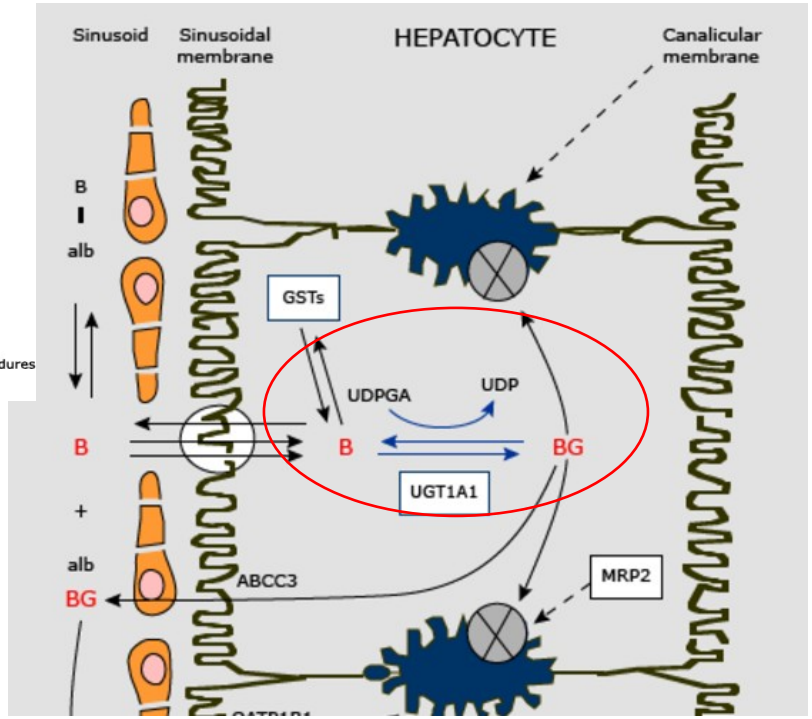
Conjugation – In Hepatocytes

Role of : uridine diphosphogluconurate glucuronosyltransferase (UGT1A1)





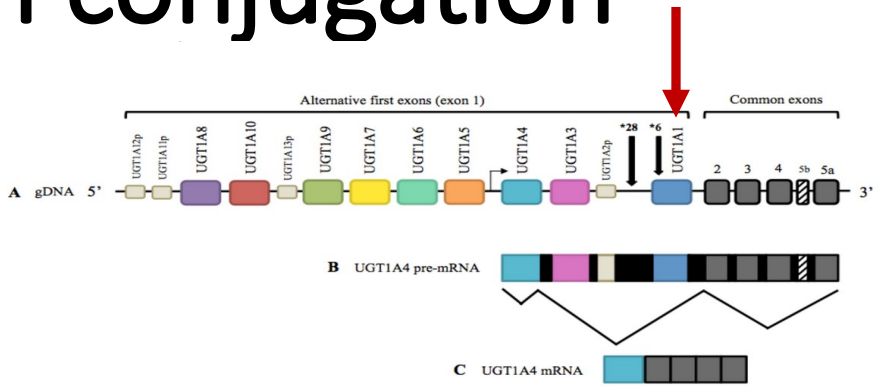
- Actively excreted into bile

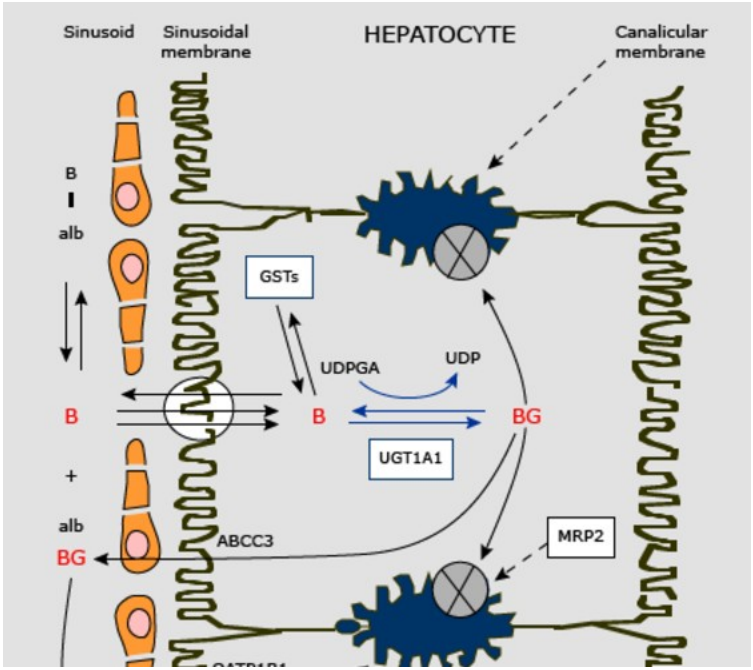
Bilirubin in bile

- 85%
  - Diglucuronides
- 15%
  - Monoglucuronide

Ethnic variation in conjugation ability

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





Bilirubin Conjugation abnormalities in liver

Conjucation abnormalities:

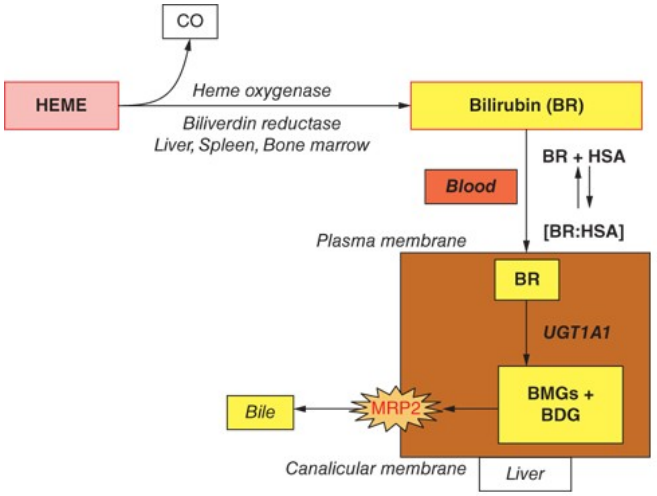
- UGT1A1 polymorphism
- Crigler –Najar Syndrome
- Gilber Syndrome
- Inhibitory factors for hepatic UGT1A!

Inhibitory factor(s) for hepatic UGT1A1

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

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

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



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

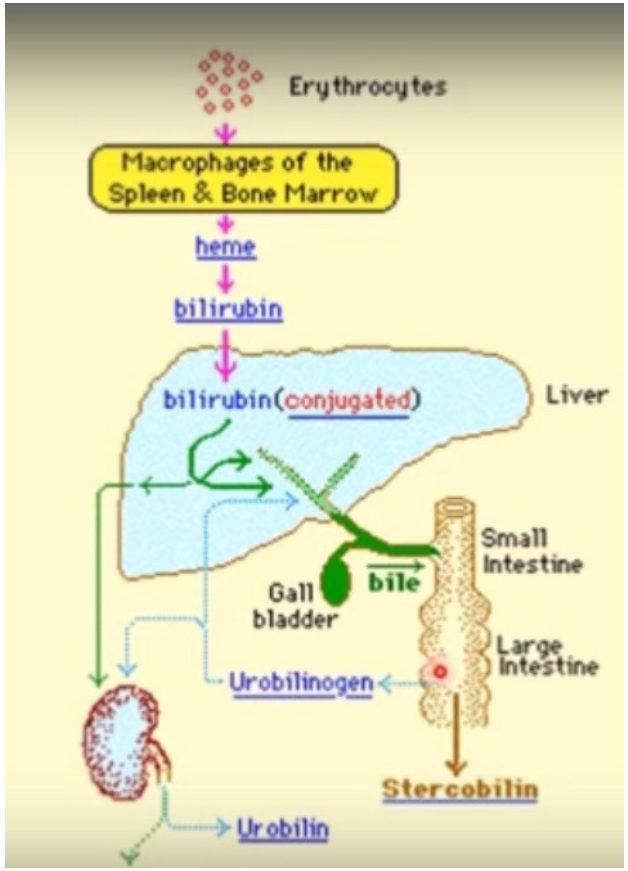
- Actively transported into the bile canaliculus
  - ATP-dependent export pump
    - Protein in the hepatocyte apical membrane
      - Multidrug resistance-associated protein 2

Enhanced bile flow by phenobarbital

Dubin-Johnson syndrome

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

Bilirubin metabolism In adult



Unconjugated bilirubin

- Reduced by normal gut bacteria
  - Colorless urobilinogen

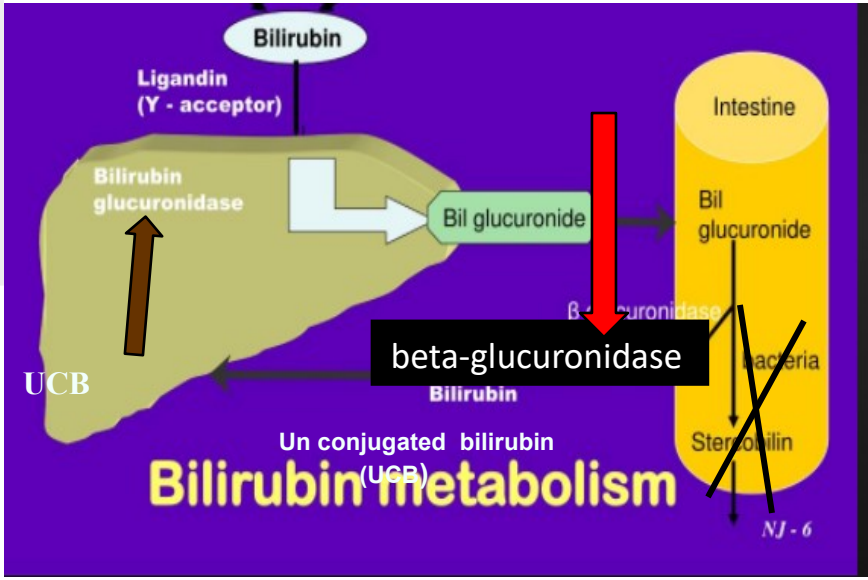
Urobilinogen

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

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

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

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

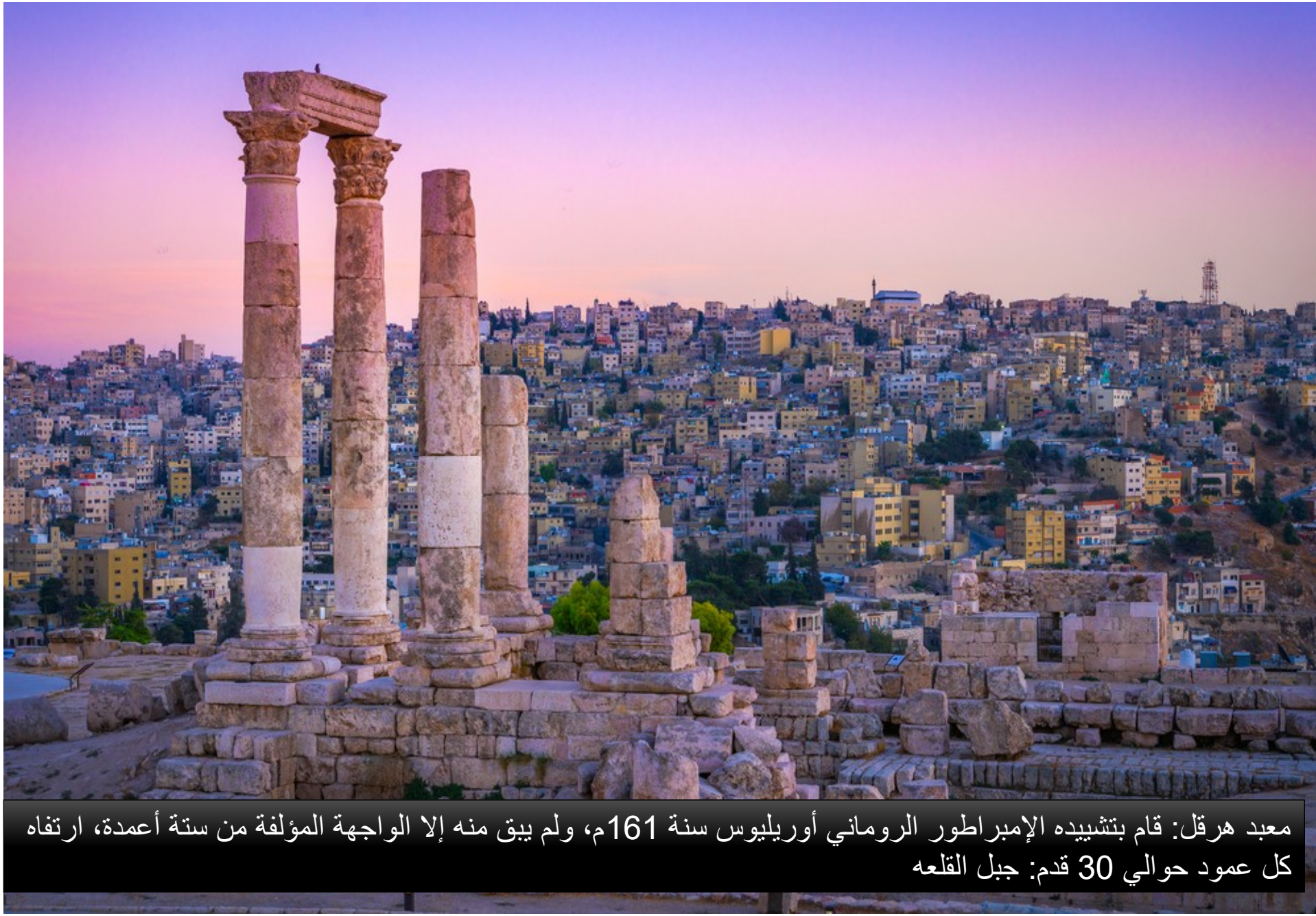


UCB fraction is partially reabsorbed through the intestinal wall and recycled into the circulation, a process known as the “EHC of bilirubin".
undergoes EHC

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

Table1: Risk Factors for Developing Significant Hyperbilirubinemia[19]
Lower gestational age (i.e. risk increases with each additional week less than 40 weeks)
Predischarge total serum bilirubin (TSB) concentration close to the phototherapy threshold
Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB of >0.3 mg/dL per hour in the first 24 hour or >0.2 mg/dL per hour thereafter.
Phototherapy before discharge
Parent or sibling requiring phototherapy or exchange transfusion
Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate dehydrogenase (G6PD) deficiency
Exclusive breastfeeding with suboptimal intake
Scalp hematoma or significant bruising
Down syndrome
Macrosomic infant of a diabetic mother

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

When to Measure TSB

- **If Jaundice < 12 hours**
- **All babies ≥12 h old** must have TSB or TcB measured before discharge
- If baby is discharged before 12 h (e.g., home births) → arrange bilirubin check within the first day.

When to Measure TSB

- **If test newborn screen is needed**
- A baby with **jaundice <24 h** or rapid rise in bilirubin → always get a **serum TSB**
- **All babies ≥12 h old** (even no jaundice)must have TSB or TcB measured **before discharge**
  - If baby is discharged before 12 h (e.g., home births) → arrange bilirubin check within the first day.

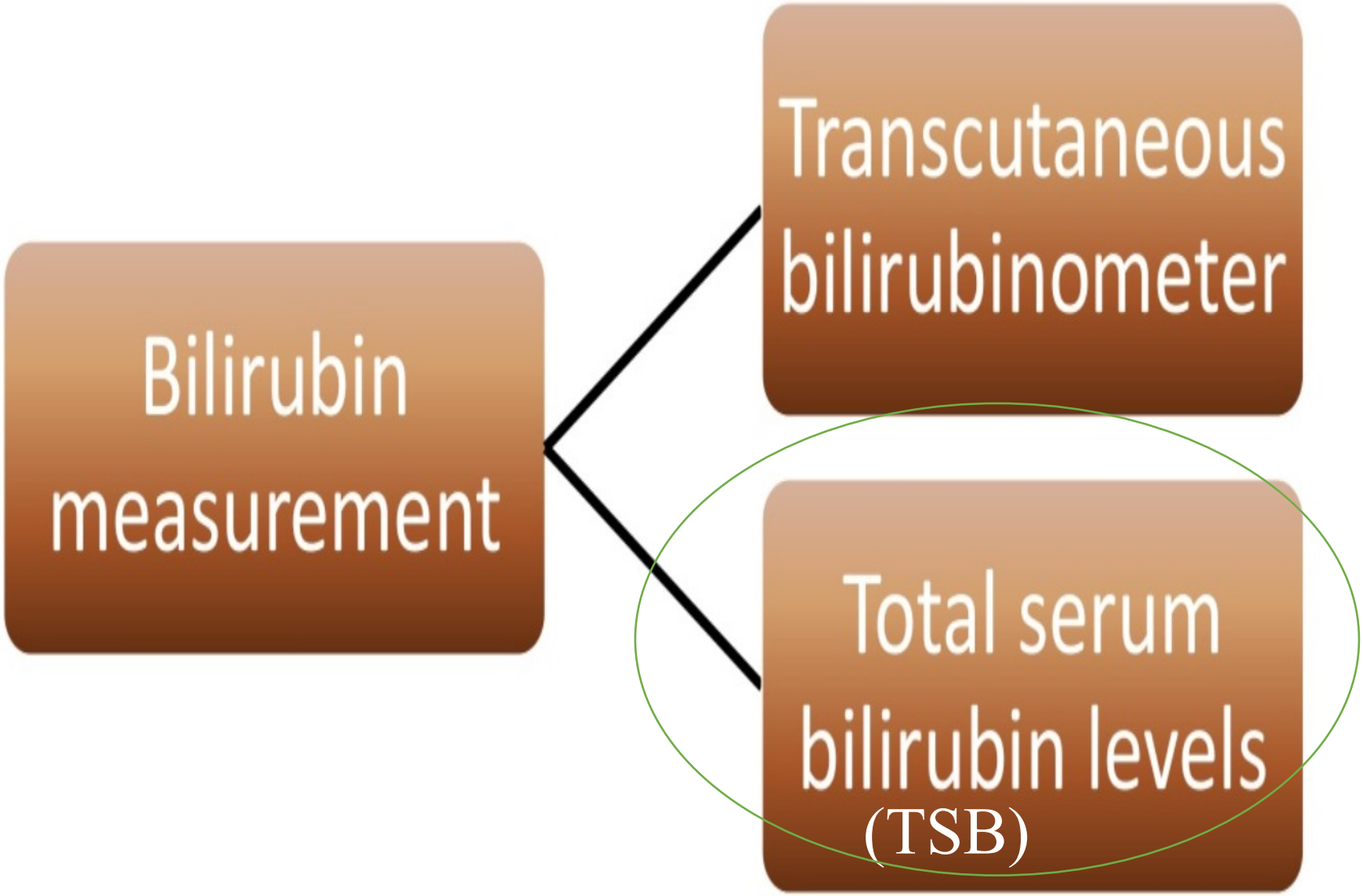
When test newborn screen is needed

- Test screen for
  - Maternal blood group (ABO and Rh)

  and

  - red cell antibody as part of routine prenatal care.

- **Do test newborn screen**
- **If the maternal antibody screen is positive or unknown at time of delivery, newborn**
- **testing should include all :**
  - **Atotal serum bilirubin (TSB),**
  - **Hemoglobin, reticulocyte count, blood smear**
  - **Direct antiglobulin test (DAT), and blood group**
- **preferably obtained from cord blood.**
- **Monitor these neonates closely for the development of early (<24 hours postnatal age) hyperbilirubinemia.**


Bilirubin measurement
Transcutaneous bilirubinometer
Total serum bilirubin levels
(TSB)

3. When to Confirm TcB with Serum TSB

Transcutaneous bilirubinometer (TcB)

Remember:
A baby with **jaundice <24 h** or rapid rise in bilirubin → always get a **serum TSB**

- A TcB value more than 12 – 14 mg/dl needs confirmation by TSB examination.

Situation	Action
TcB is **within 50 µmol/L (≈ 3 mg/dL)** of phototherapy threshold	Do a confirmatory **TSB**
TcB is **above 250 µmol/L (≈ 14.6 mg/dL)**	Do a confirmatory **TSB**
TcB clearly below threshold, baby well	TcB alone is acceptable (but always interpret with clinical context)

Objectives

Why this lecture

Bilirubin metabolism

Bilrubin measurement

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Types and Causes of neonatal Jaundice

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Assessment of neonate at risk of sever hyperbilirubinemia

Management

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Types of Neonatal Jaundice

Physiological Jaundice

Pathological Jaundice

Breast-milk Jaundice

Breast-feeding Jaundice

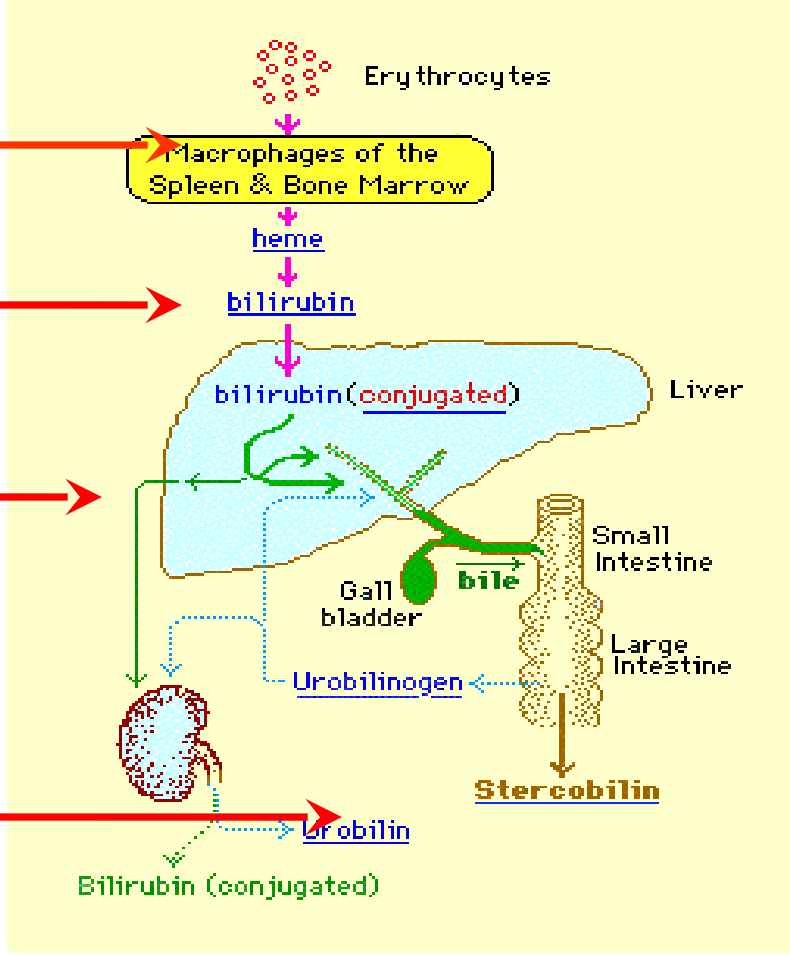
Related to breast milk

Mechanism of Physiologic Jaundice

1-Increased bilirubin production

Increased rbc's
and ineffective erythropoiesis

Shortened RBC lifespan



2-Immaturity

Immature hepatic uptake
immature conjugation (paucity of ligandin and decrease UGTA1)
decreased hepatic excretion of bilirubin

3-Increased enterohepatic Circulation

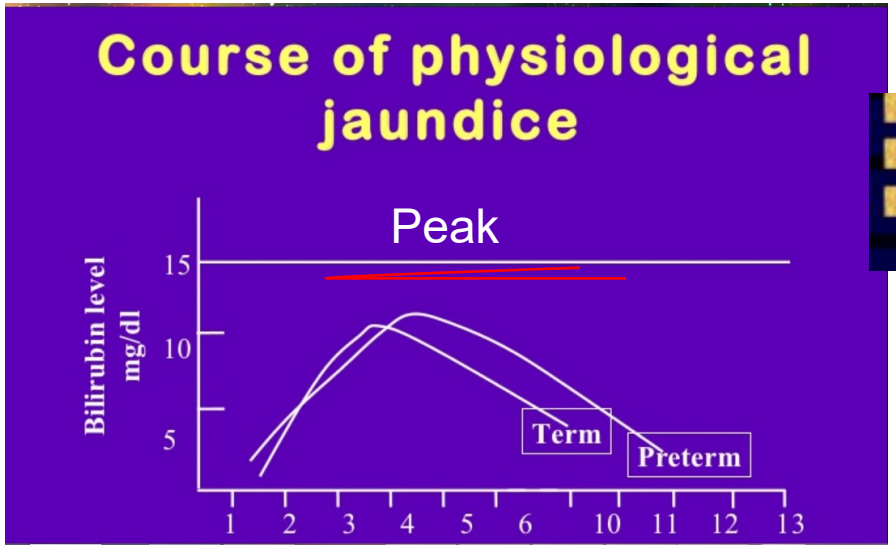
(Increase B glucuronidase)

Physiologic Jaundice

Physiologic Jaundice:
1. Has Pattern

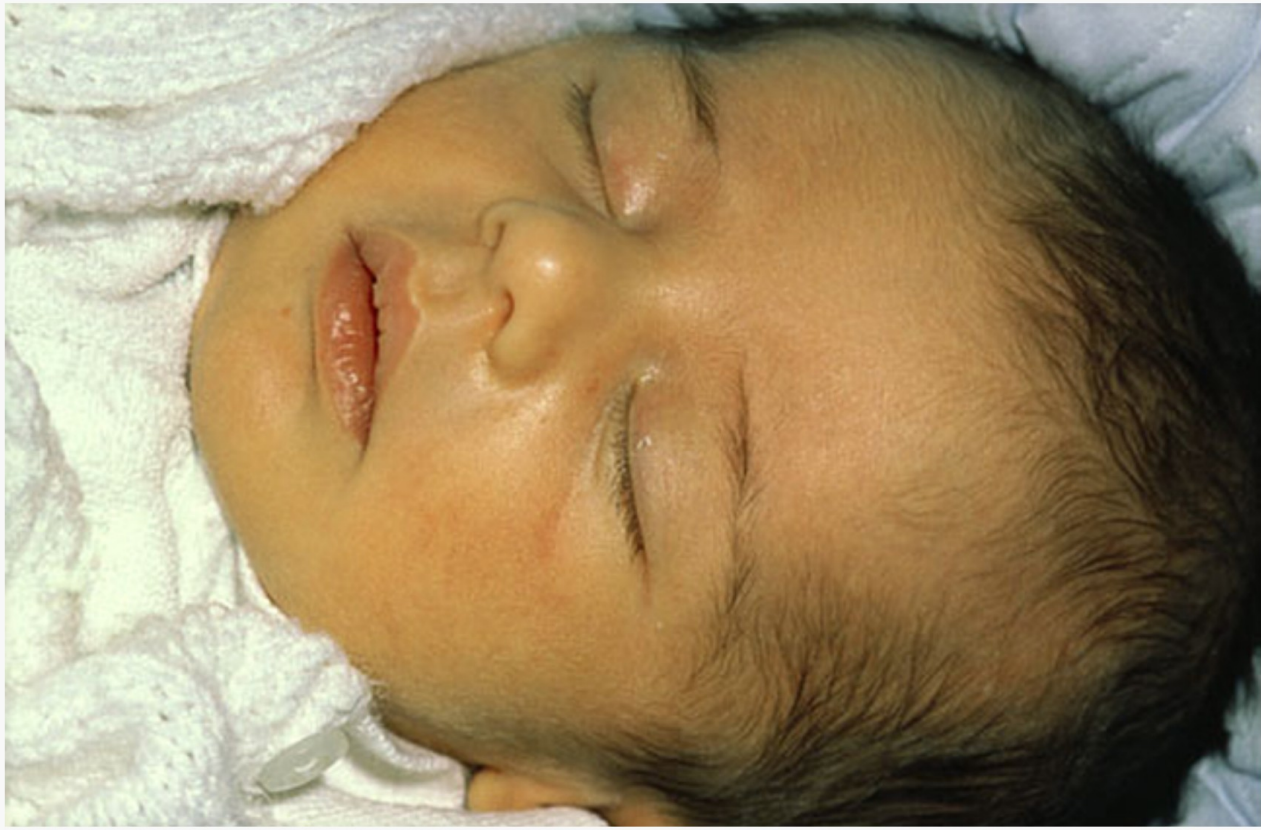
HAS PEAK

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



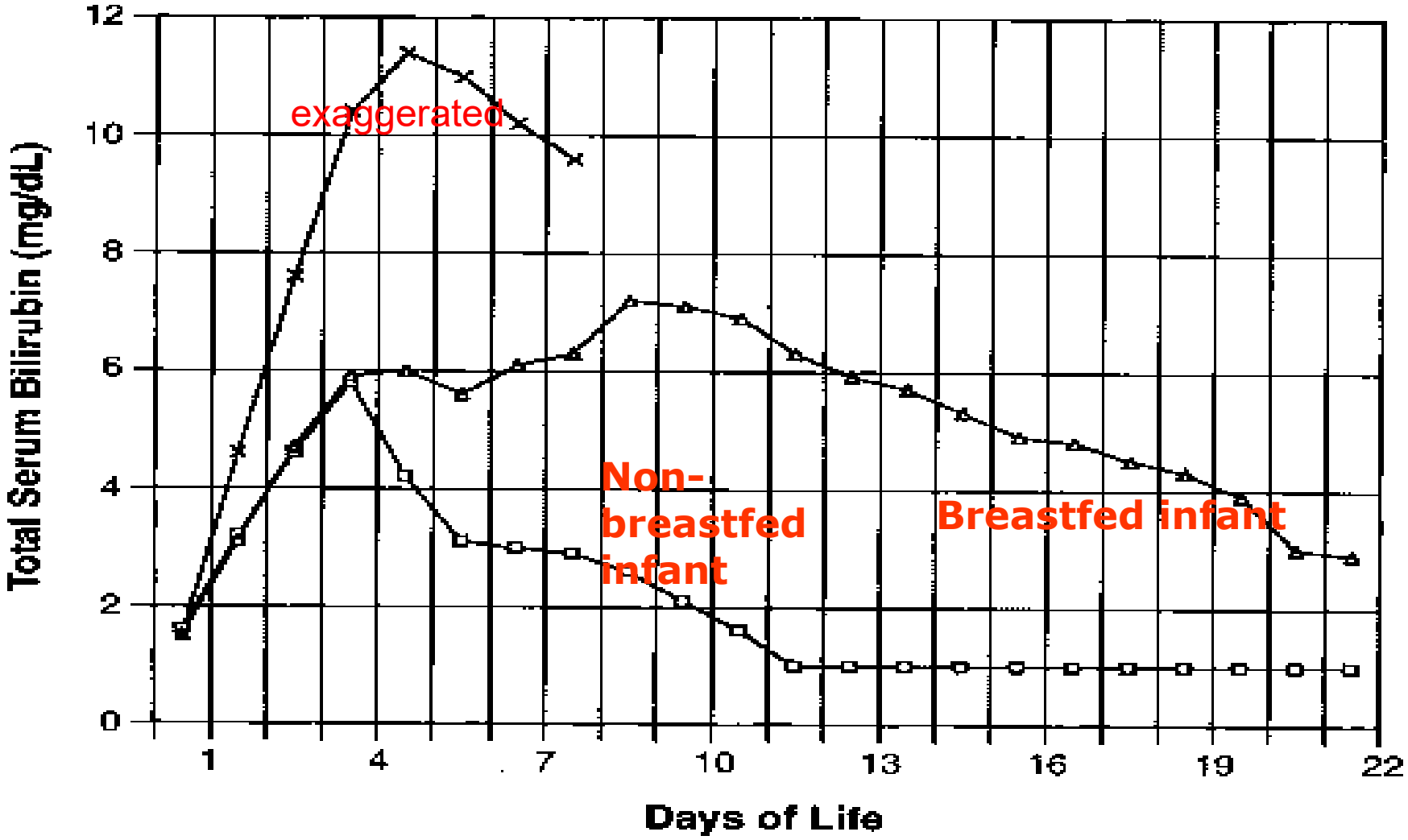
Physiologic Jaundice
3.- Bilirubin rise trend

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

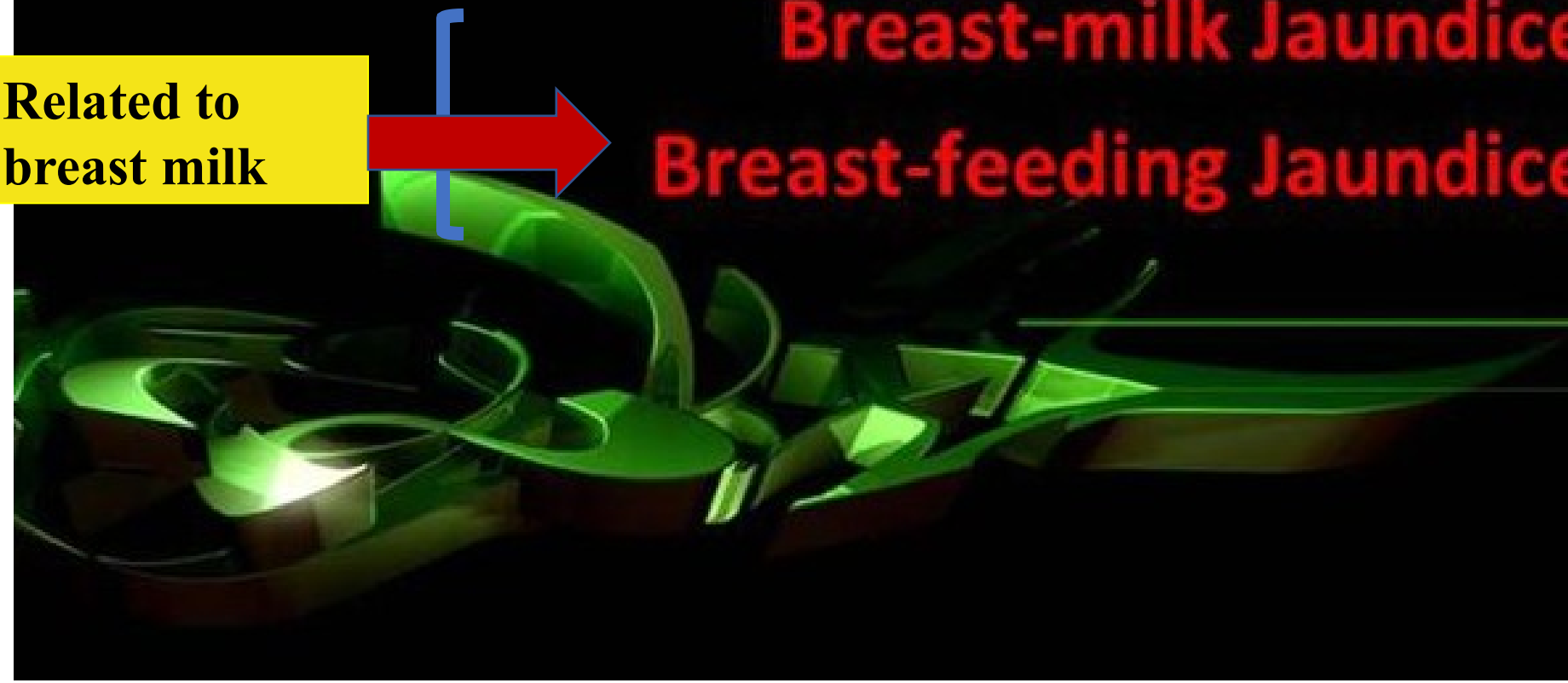
Physiological Jaundice

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

Types of Neonatal Jaundice

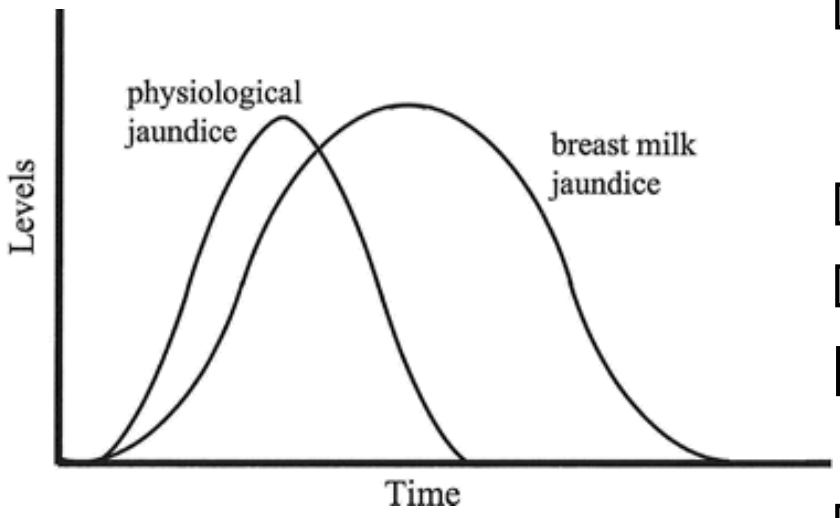
Physiological Jaundice

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 (2-4%)
- Last longer (May last 3-12 weeks)
- Rare to cause BIND unless bilirubin > 25 mg/dl
- has no other identifiable cause
- ?Milk inhibitors and genetic factor
  - substances in the breast milk that inhibits (UDPGA1)
  - High beta glucuronidase activity in breast milk
  - May be genetics

Prolonged Jaundice :causes

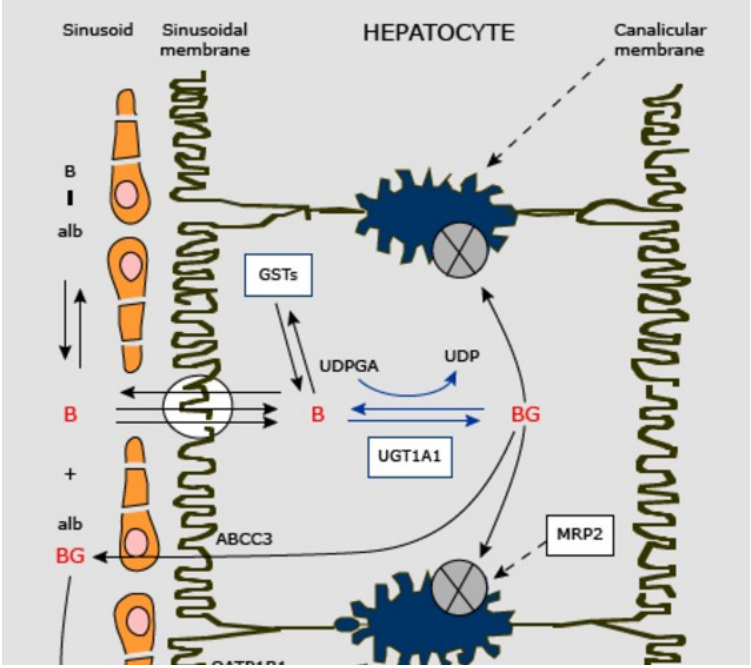
Ethnic variation in conjugation ability

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.



Prolonged jaundice

Prolonged jaundice = clinically significant jaundice (TSB within **35 µmol/L [≈2 mg/dL]** of the phototherapy threshold) that **persists beyond 14 days of life** in:

Causes of Prolonged Jaundice

- **Unconjugated hyperbilirubinemia causes** (indirect fraction):
  - Hemolytic disease (e.g., G6PD deficiency, ABO/Rh incompatibility).
  - Congenital hypothyroidism.
  - Genetic syndromes: Crigler–Najjar, Gilbert syndrome.
- **Conjugated hyperbilirubinemia causes** (direct fraction):
  - Cholestatic liver diseases (e.g., **biliary atresia**).
  - Metabolic/infectious causes (inborn errors of metabolism, sepsis, UTI).

Why Direct Bilirubin is Important

Always check **direct (conjugated) bilirubin** when jaundice persists >14 days.

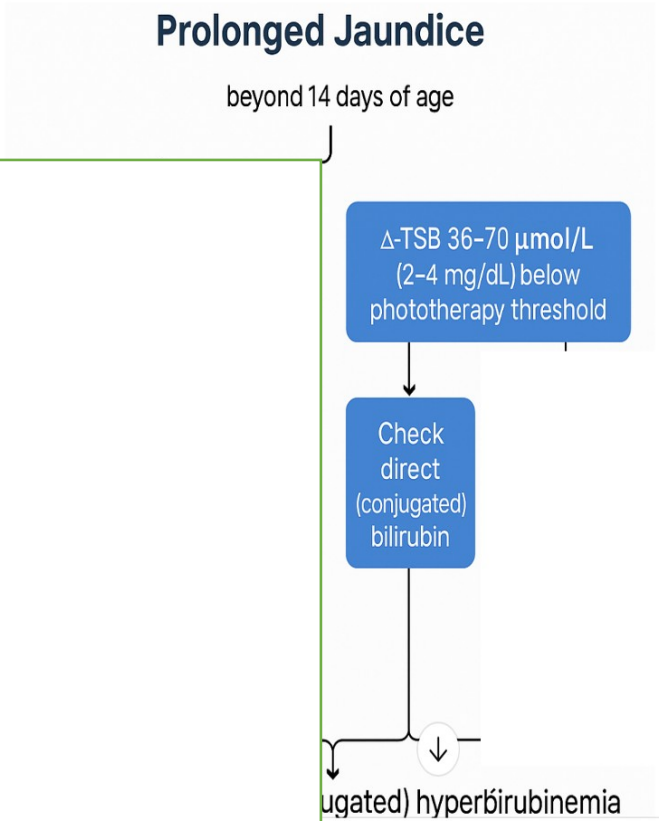
Abnormal result:

- Direct bilirubin **>17 µmol/L (≈1 mg/dL)** is considered abnormal.
- May indicate **cholestasis**.

Why urgent:

- **Biliary atresia** and some cholestatic diseases need **early surgery/treatment** for best outcomes.

Prolonged jaundice



Types of Neonatal Jaundice

Physiological Jaundice

Pathological Jaundice

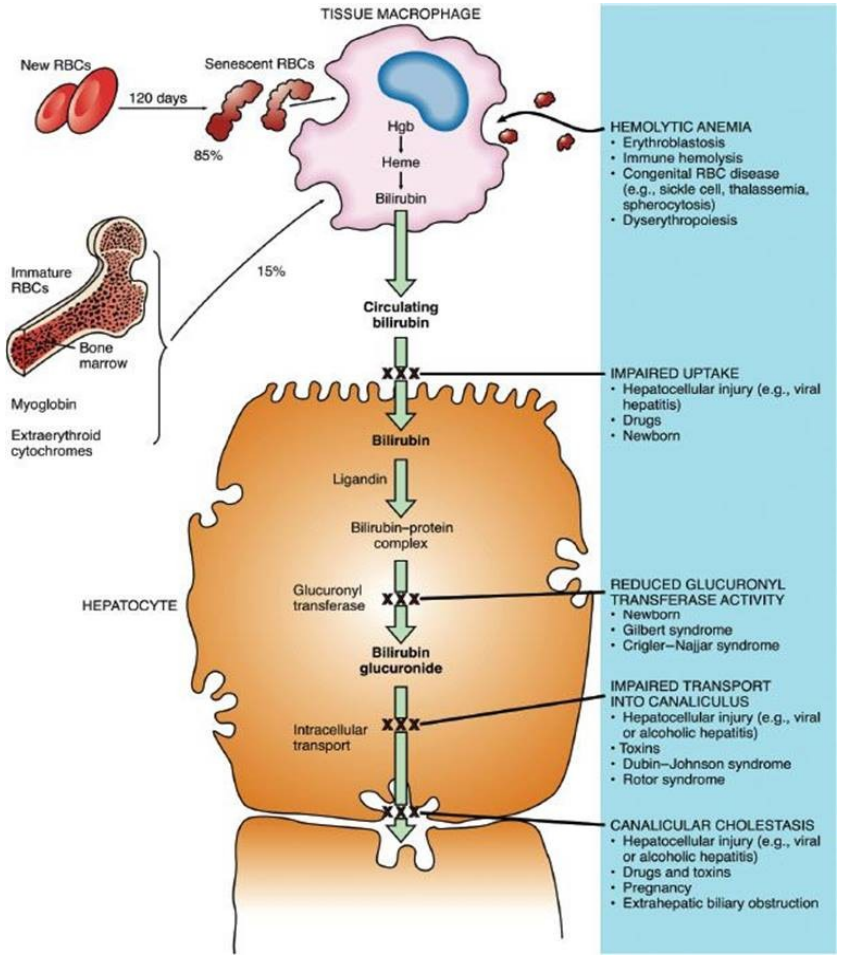
Breast-milk Jaundice

Breast-feeding Jaundice

Types and Causes of neonatal Jaundice (Pathological Jaundice)

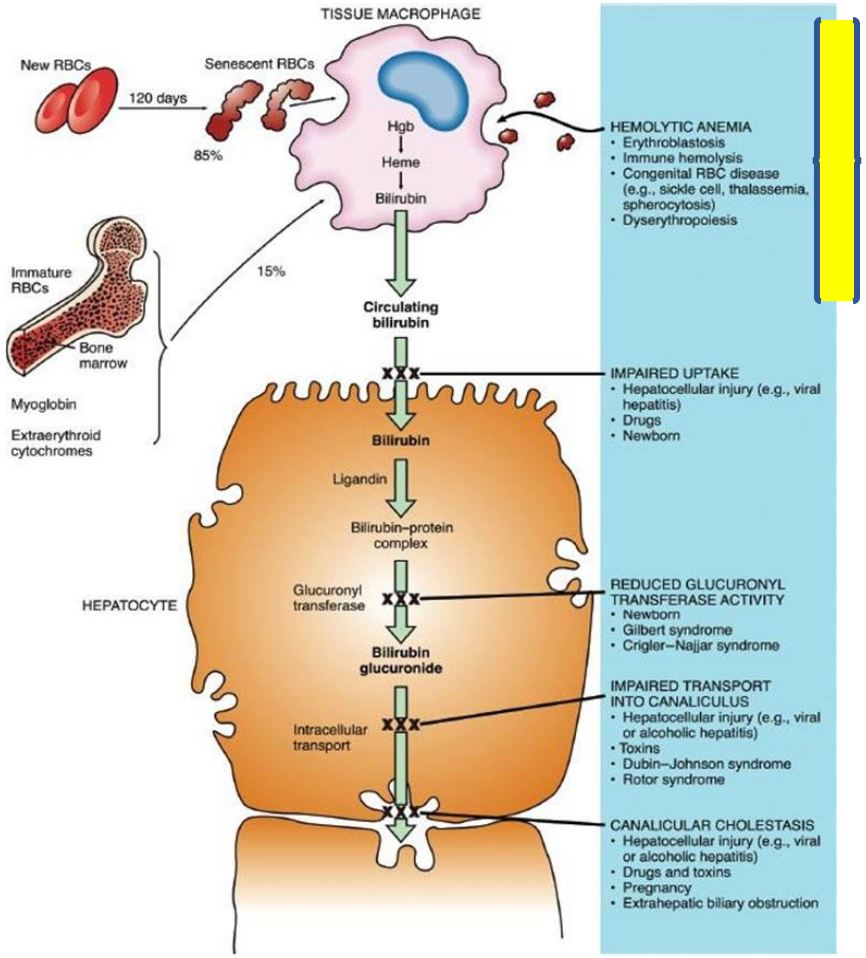
- ˇ Onset of jaundice < 24 h of birth
- Rise of serum bilirubin of >0.3 mg/dL/h in the first 24 hours or ≥0.2 mg/dL/h thereafter
- Signs of illness (e.g., lethargy, poor feeding, vomiting, apnea, tachypnea, temperature instability, excess weight loss)

Pathologic Jaundice



- is a medical emergency.-

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

- Viral or bacterial infections (sepsis)

•Increased red blood cell breakdown

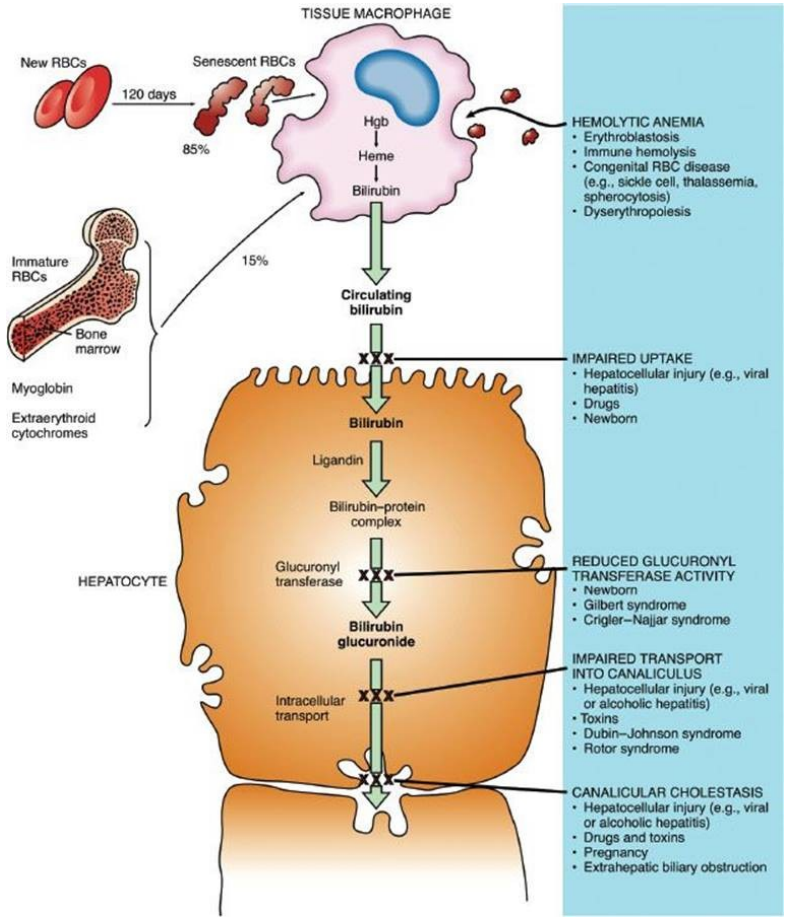
• -polycythemia

• - sequestration of blood within a closed space, which occurs in cephalohematoma.

•Ineffective erythropoiesis)-

•Inherited biochemical abnormalities as **Galactosemia**

Causes of Pathologic indirect hyper bilirubinemia causing Jaundice



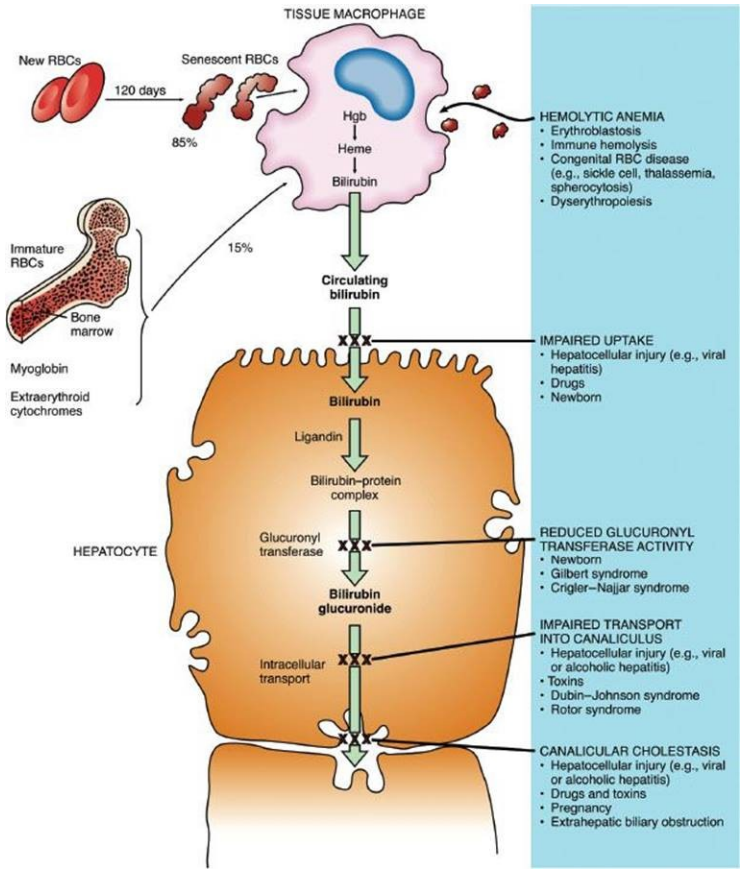
- **Testing for G6PD**
- **Initial testing:**
  - Do a **G6PD enzyme assay** in all babies with jaundice that:
    - Doesn't respond to phototherapy, OR
    - Appears without other obvious risk factors.
- **Caution in acute hemolysis:**
  - Test may be **falsely normal** because newly circulating young RBCs still have enough enzyme.
- **If suspicion remains:**
  - Repeat testing at **3 months of age**, when RBC population has stabilized.

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

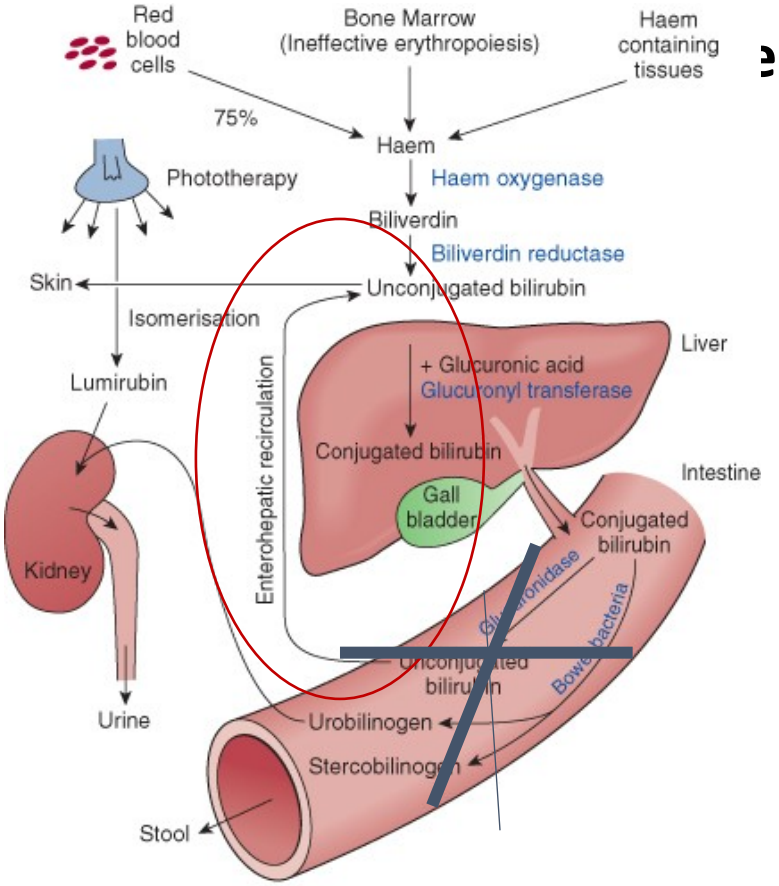
- - Crigler-Najjar syndrome types I and II
- - Gilbert syndrome,I.
- - OATP-2 polymorphism

Other causes —

congenital hypothyroidism

GI/Liver diseases (including metabolic liver disease)

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

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

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

P value <0.01is highly significant

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

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

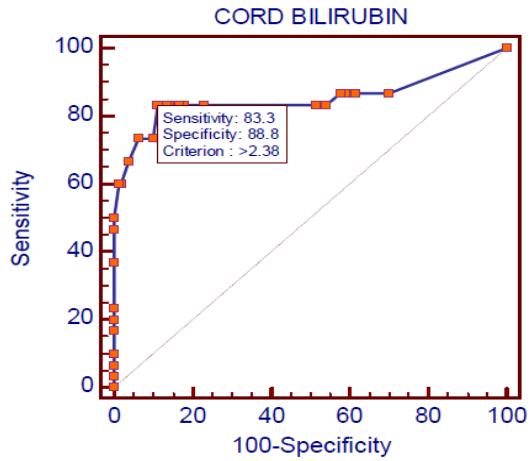


Table-4 :Sensitivity, specificity, positive predictive value and negative predictivevalues of cord and 1st day bilirubin levels for prediction of hyperbilirubinemia

Jaundice in 1st 24 hrs

High sensitivity and specificity to develop sever hyperbilirubimimeia if

ord total bilirubin > 2.38mg\dl

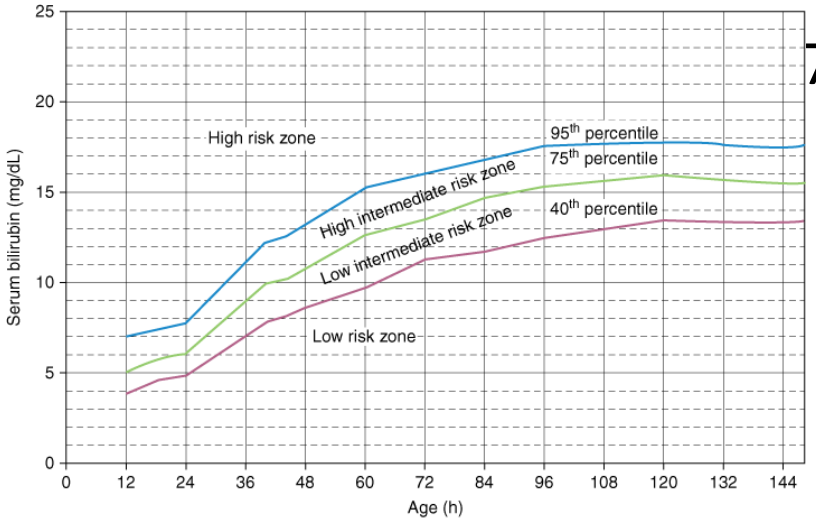
tal Serum bili level at 24 hor of > 5 mg\dl

Suspicion 2:

Pattern of rise

Pathologic Jaundice: How to recognize

- **Pattern of rise**
  - Rapidly rising TSB (> 5 mg/dL per day)
    - > Hemolysis : rapid rate of increase in the TSB of >0.3 mg/dL per hour in the first 24 hour
    - or >0.2 mg/dL per hour thereafter



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

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

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

Suspicion 3:
COAURSE

Pathologic Jaundice: How to recognize

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

Suspicion 4:

Type

Pathologic Jaundice: How to recognize

- Direct (conjugated) bilirubin concentration

Definition of direct bilirubin

Direct bilirubin > 1 mg/

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 assess of neonate at risk of sever hyperbilirubinemia ?

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

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.

Or Use Calculate Δ-TSB rule

1-Use SCREENING FOR HYPERBILIRUBINEMIA

AAP AND CPS guidelines March 2025

- **Test screen for**
  - **Maternal blood group (ABO and Rh) and**
  - **red cell antibody as part of routine prenatal care.**

- **If the maternal antibody screen is positive or unknown at time of delivery, newborn testing should include all :**
  - **Atotal serum bilirubin (TSB),**
  - **Hemoglobin, reticulocyte count, blood smear**
  - **Direct antiglobulin test (DAT), and blood group**
- **preferably obtained from cord blood.**
- **Monitor these neonates closely for the development of early (<24 hours postnatal age) hyperbilirubinemia.**

2- Always do Risk factor developing significant hyperbilirubinemia

Infants with risk factors for hyperbilirubinemia require closer monitoring than infants without risk factors.

o Lower gestational age
o Jaundice in the first 24 h after birth
o Predischarge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) concentration close to the phototherapy threshold o Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB or TcB of >0.3 mg/dL per hour

in the first 24 h or >0.2 mg/dL per hour thereafter.
o Phototherapy before discharge
o Parent or sibling requiring phototherapy or exchange transfusion
o Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate

dehydrogenase (G6PD) deficiency
o Exclusive breastfeeding with suboptimal intake o Scalp hematoma or significant bruising
o Down syndrome
o Macrosomic infant of a diabetic mother

Patients at high risk for developing hyperbilirubinemia neurotoxicity have the risk factors below.

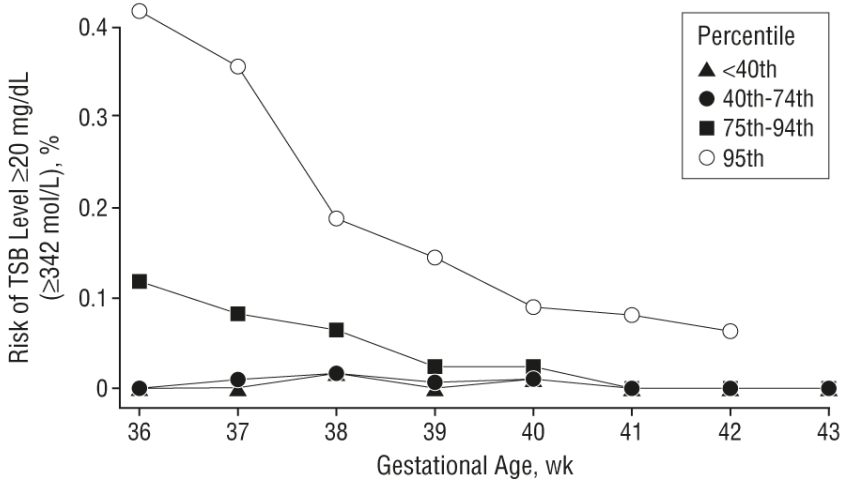
o Gestational age <38 wk and this risk increases with the degree of prematurity
o Albumin <3.0 g/dL
o Isoimmune hemolytic disease (i.e., positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions o Sepsis
o Significant clinical instability in the previous 24 h

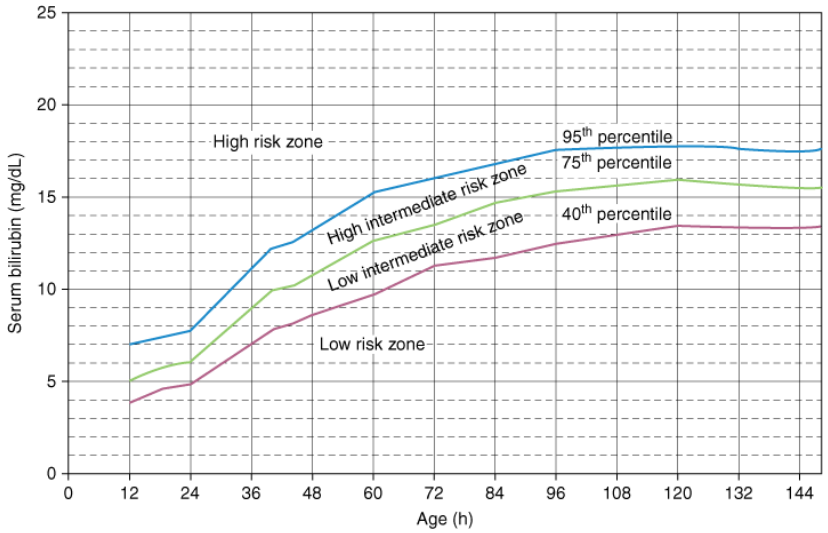
The presence of these risk factors lower the threshold for treatment with phototherapy and the level at which care should be escalated.

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

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

3- know phototherapy figures

Figure1 :

Risk with no Neurotoxicity

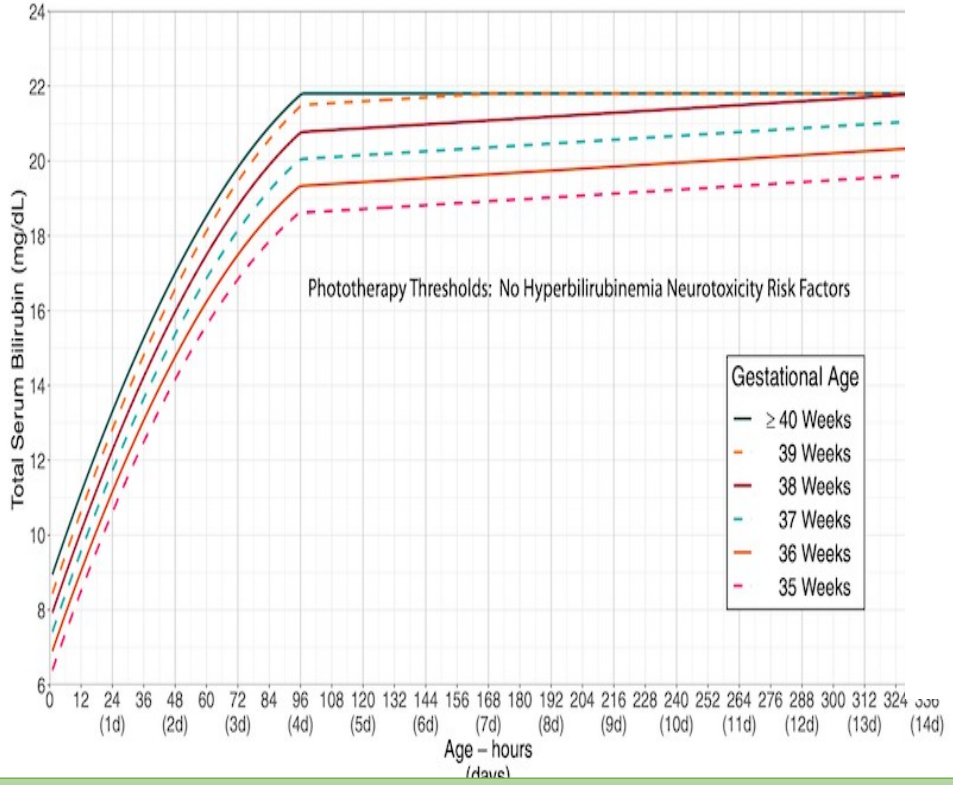
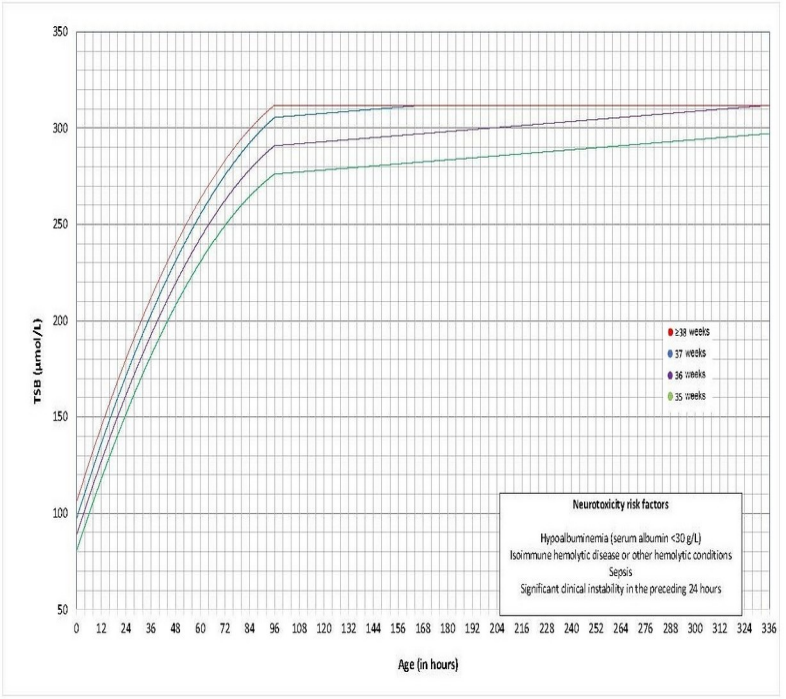


Figure 2 :

Risk with risk of neurotoxicity



Intensive phototherapy is recommended at the total serum bilirubin phototherapy threshold on the basis of gestational age, hyperbilirubinemia neurotoxicity risk factors, and age of the infant in hours.

Step 4.

A- Measure Before Discharge

Every baby should have TSB or TcB measured ≥12 h of life.

B-Step 2. Calculate Δ-TSB

Step 4. Cont--

Do Timed TSB measurement to determine the ΔTSB

△TSB = = Treatment threshold – Measured bilirubin.

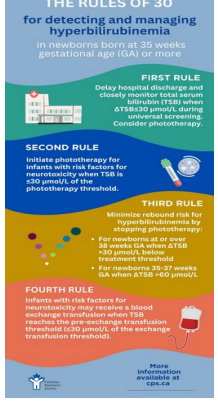
Timed TSB:

Measure **a pre-discharge total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) in all newborns at a ≥ of 12 hours post-birth**

-check phototherapy level

Δ-TSB (mg/dL + µmol/L) with Risk Factors Included

Δ-TSB (µmol/L)	Δ-TSB (mg/dL)	What it means	What to do
≤30 µmol/L	**≤1.8 mg/dL**	Baby is **very close to treatment line** → high risk	**Urgent action**: start phototherapy OR recheck in **6–12 h**. Keep in hospital if risk factors present.
31–60 µmol/L	**1.9–3.5 mg/dL**	Baby may reach treatment line soon	**Early follow-up**: recheck in **12–24 h**. If risk factors (prematurity, hemolysis, poor feeding, sepsis) → consider sooner.
61–100 µmol/L	**3.6–5.9 mg/dL**	Baby below threshold but still needs watching	**Recheck in 1–2 days**. If risk factors → shorten interval.
>100 µmol/L	**>6 mg/dL**	Baby well below treatment threshold	**Routine follow-up** in **2–3 days**. If risk factors present → follow-up earlier.



Use rule of 30

Example

Baby 24 h old

37 wks GA

Example. https://hyperbili.com

- Baby: **37 weeks GA, no risk factors**, 48 hours old.
- Phototherapy threshold at this age ≈ **250 µmol/L (14.6 mg/dL)**.
- If measured TSB = **245 µmol/L (14.3 mg/dL)**:
  - Δ-TSB = **5 µmol/L (0.3 mg/dL)** → at/near threshold. Start **intensive phototherapy immediately**.
- Baby: **37 weeks GA, with sepsis (risk factor)**, 48 hours old.
- Threshold is lower ≈ **220 µmol/L (12.9 mg/dL)**.
- If measured TSB = **200 µmol/L (11.7 mg/dL)**:
  - Δ-TSB = **20 µmol/L (1.2 mg/dL)** below threshold.
  - Because of **Rule of 30 #2**, you may **start phototherapy early**.

Step 5

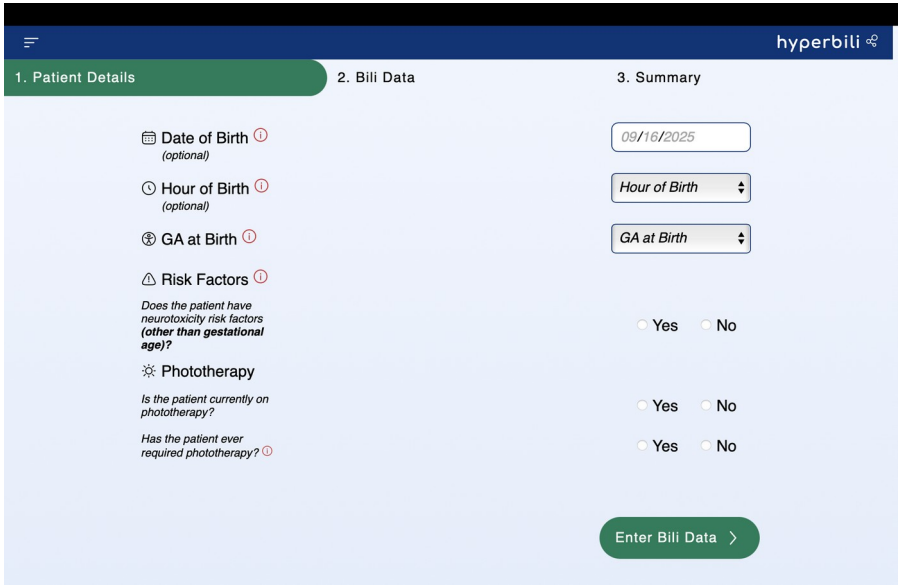
- **. Communicate Clearly to Families**
- Always give parents **written + verbal info** in their **first language**:
  - Baby's bilirubin level(s)
  - Age at testing
  - Calculated Δ-TSB
  - Next steps (e.g., "Come back tomorrow at 10 a.m. for a repeat test")
- Teach them **warning signs**: jaundice in first 24 h, poor feeding, excessive sleepiness, dark urine, pale stools.

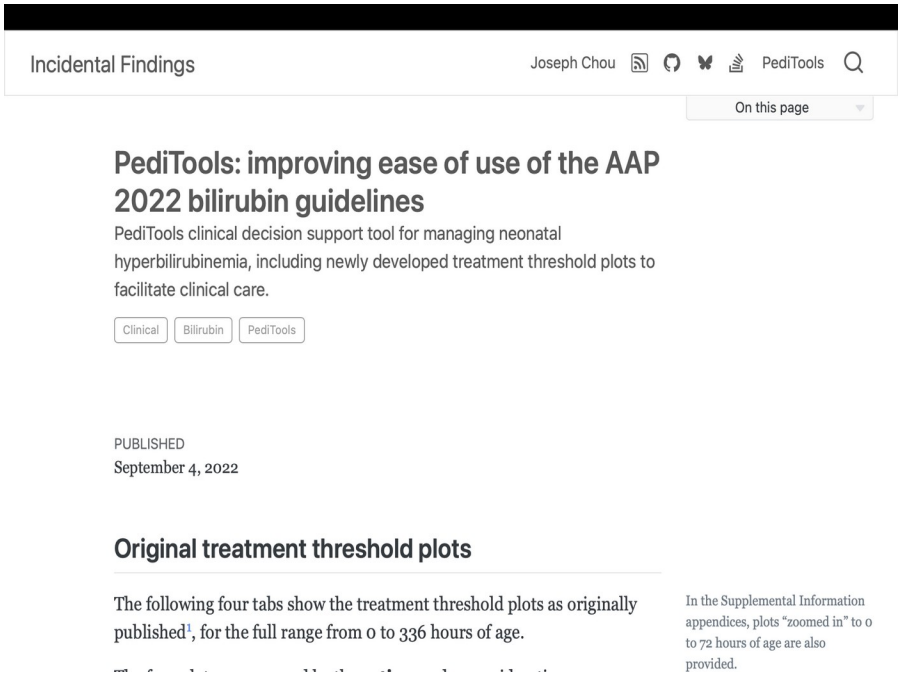
Step 6

- **Step 5. Support Breastfeeding**
- Breastfed babies have a slightly higher risk of jaundice, but **breastfeeding is strongly beneficial**.
- Support measures:
  - Early **skin-to-skin**
  - Frequent feeding (8–12 times/day)
  - Monitor **weight, urine, stool output**
  - Arrange community resources (lactation clinics, hotlines)
- Recommendation: **Every family should have access to breastfeeding support until feeding is well established.**

You can use Mobile Application

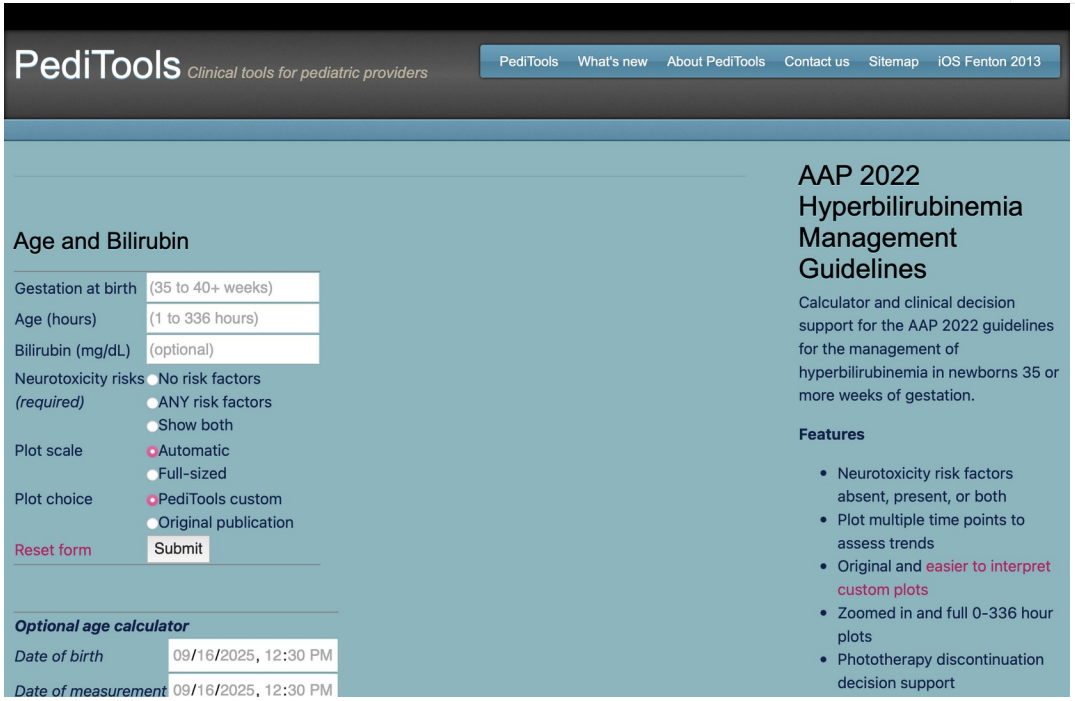
[Canadian](https://hyperbili.com)
https://hyperbili.com

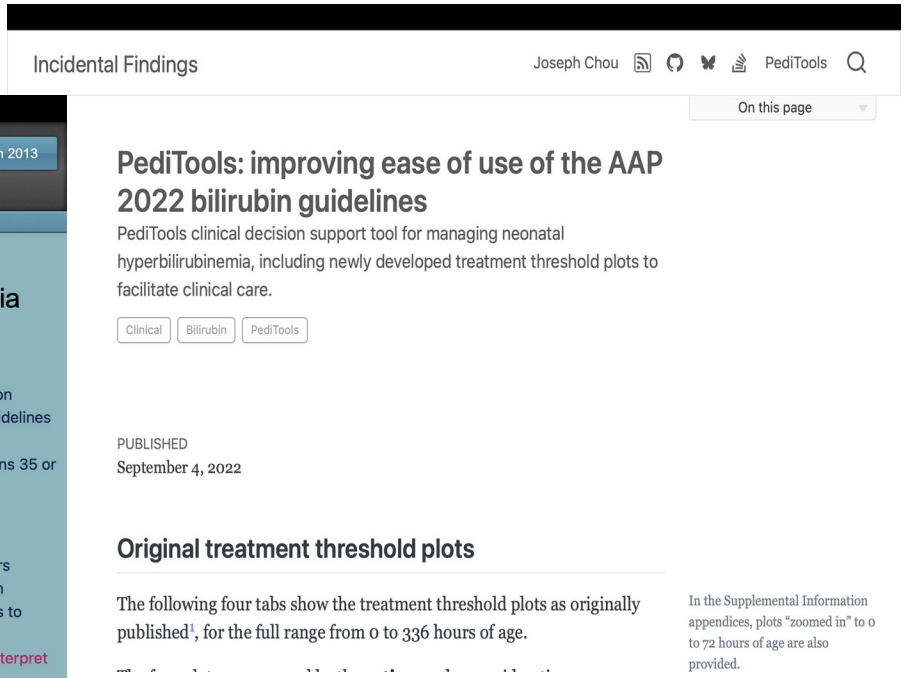




You can use Mobile Application AAP 2022

https://peditools.org/bili2022/



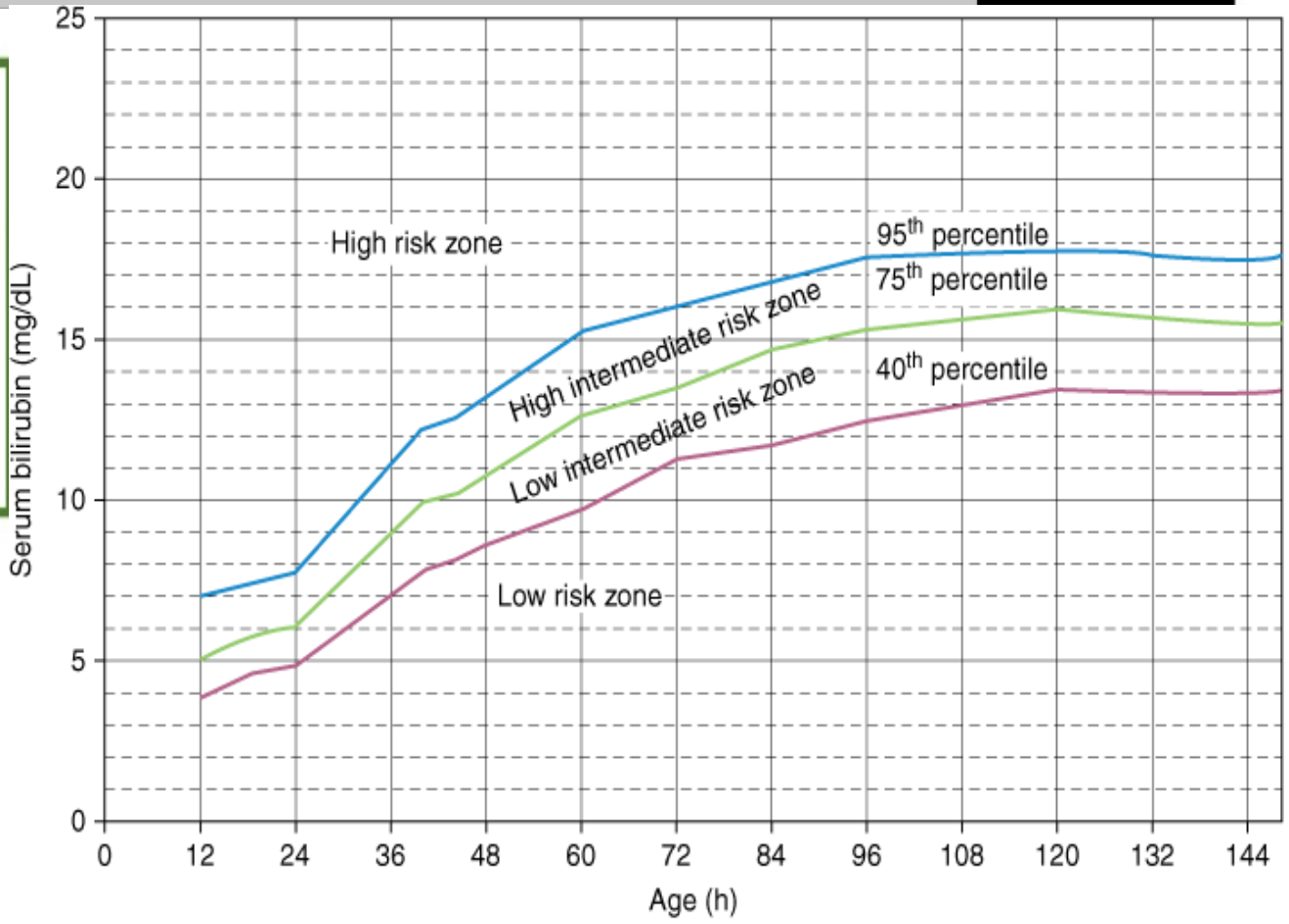


1-Assess the risk Zone :A predictive nomogram AAP 2022

nogram for those > **35** weeks

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

Adapted from bhutani et al.



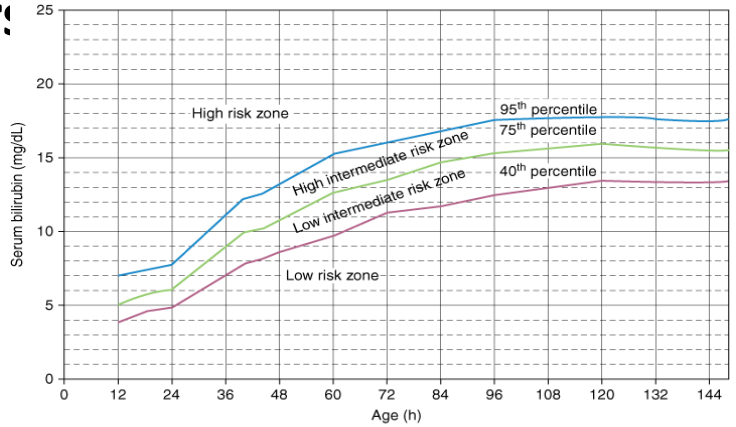
Source: Stevenson DK, Maisels MJ, Watchko JF: *Care of the Jaundiced Neonate*: www.accesspediatrics.com

At Discharge

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

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)



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

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

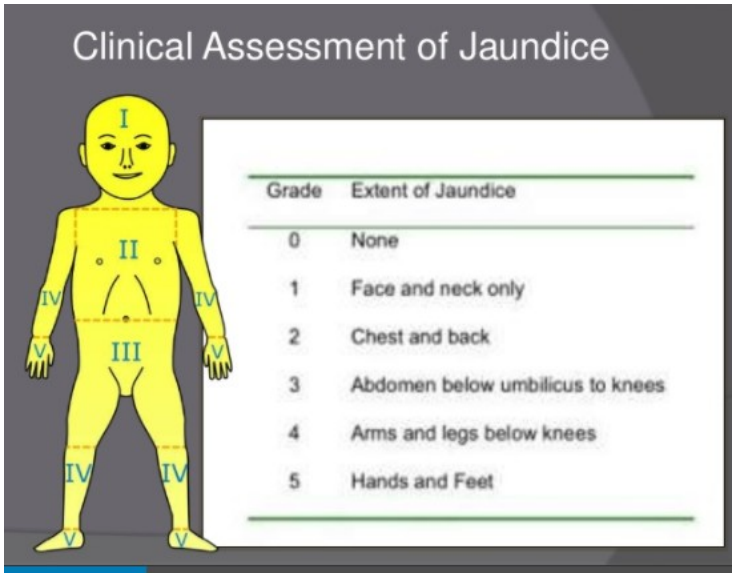
Post-discharge follow-up

Infants discharged before 48 hours of life should be seen within 2 days of discharge.

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

Assessment of hyperbilirubinemia by visual assessment

- Unreliable
- Testing bilirubin level is more correct



Objectives

Why this lecture

Bilirubin metabolism

What special in neonates

Types and Causes of neonatal Jaundice

Breast feeding and hydration

Assessment of neonate at risk of sever hyperbilirubinemia

Aproach

Management

- Guidelines
- Work UP

Treatment

- Prevention
- treatment

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

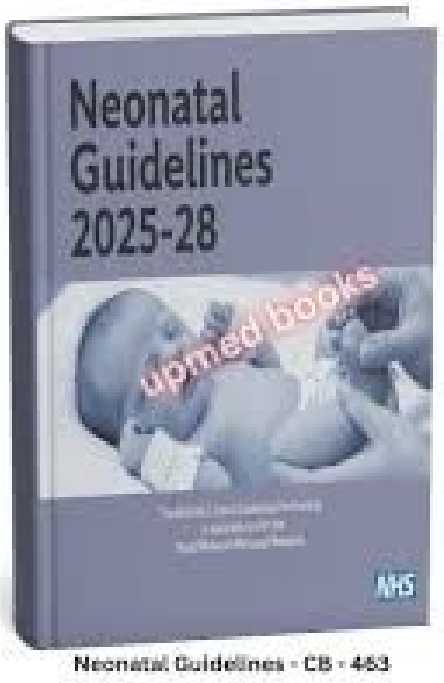
Treatment

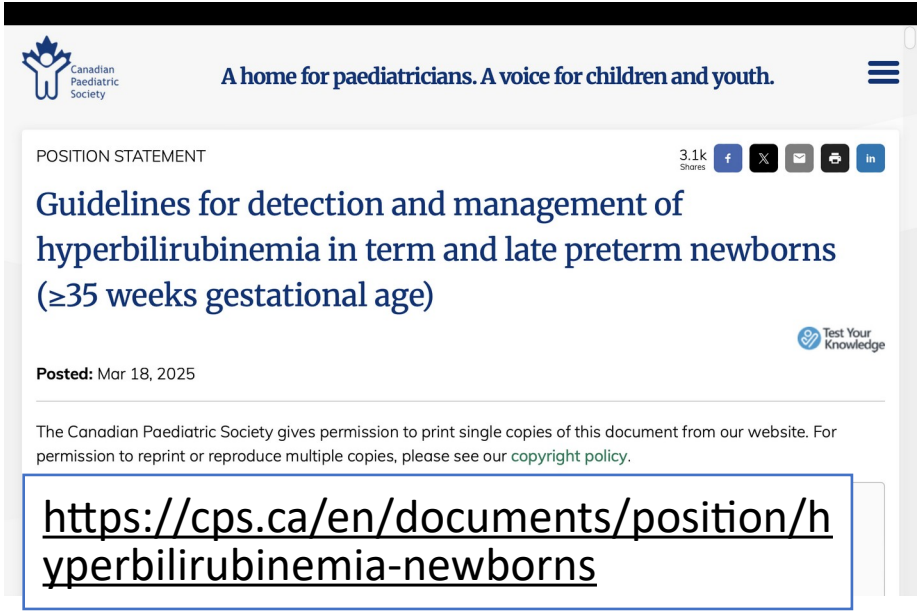
- Prevention
- treatment

How to manage if baby is Jaundice

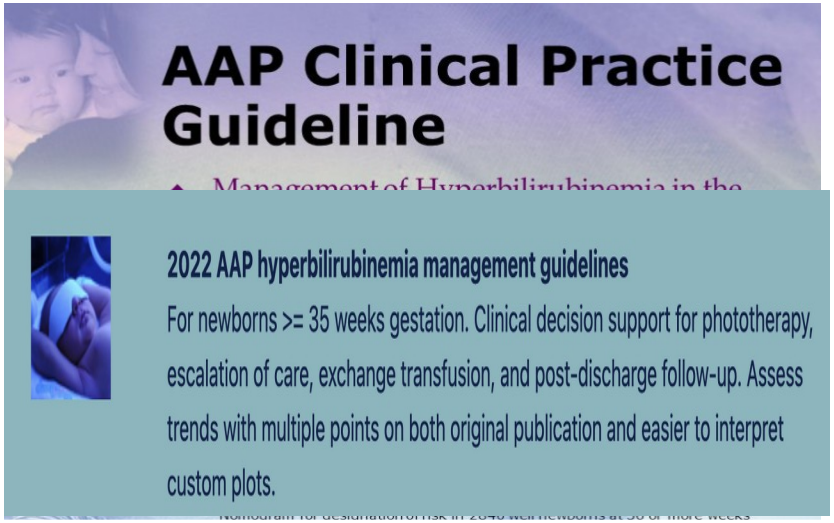
Use A guideline

NICE guidelines (UK)





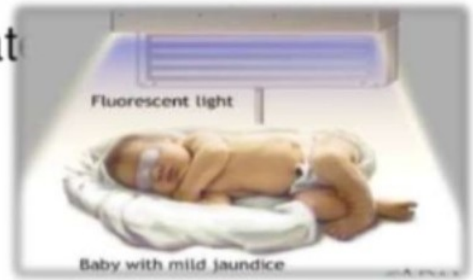
https://cps.ca/en/documents/position/hyperbilirubinemia-newborns



https://publications.aap.org/pediatrics/article/150/3/e2022058865/188725/Technical-Report-Diagnosis-and-Management-of?autologincheck=redirected

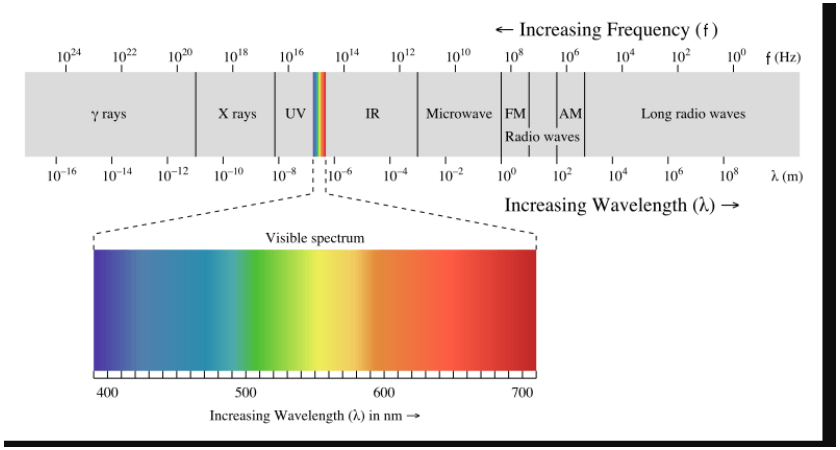
Therapeutic Options

- Phototherapy for neonat
with mild jaundice



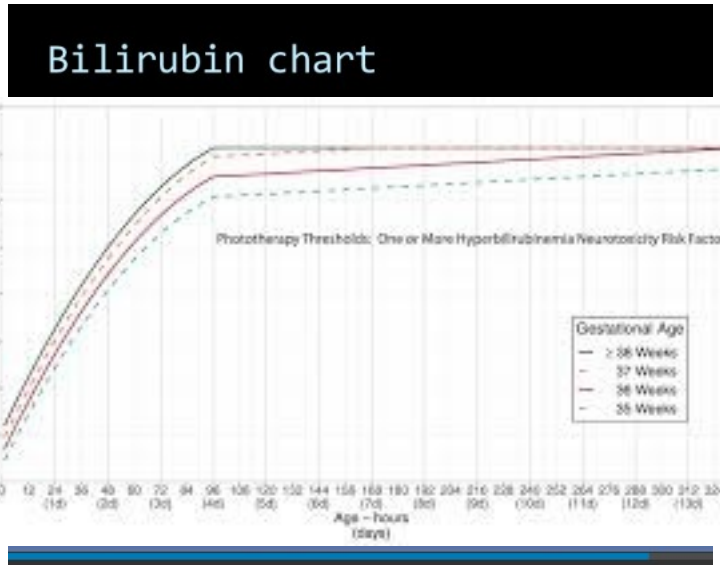
- Exchange transfusion i
Severe cases

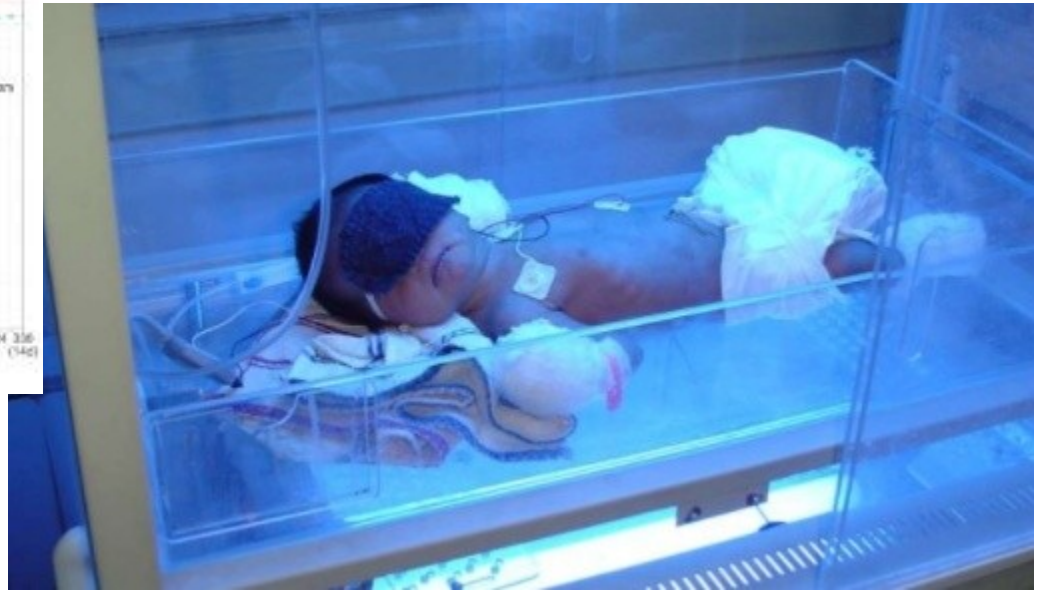
Intravenous Immune globulin



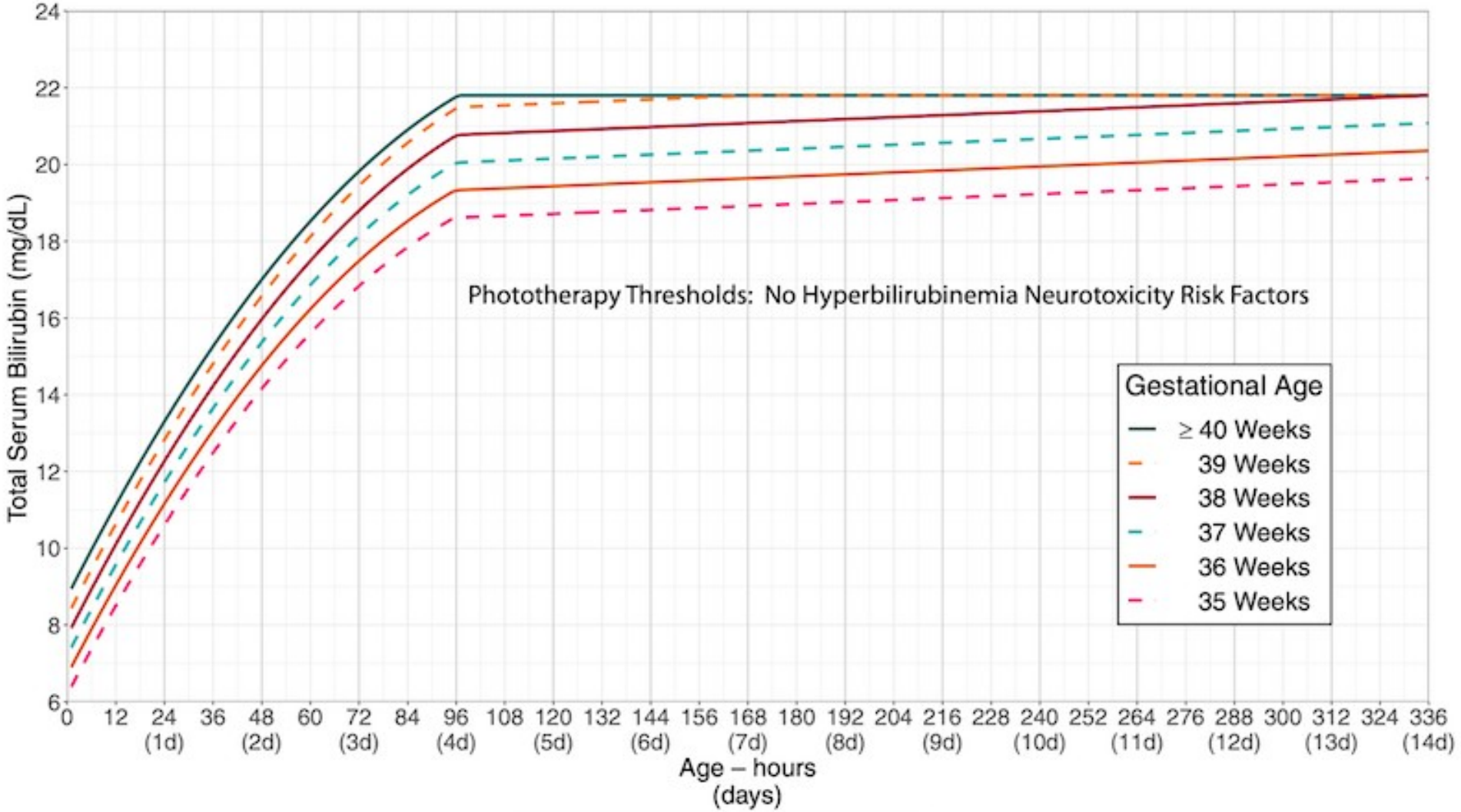
Phototherapy

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





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

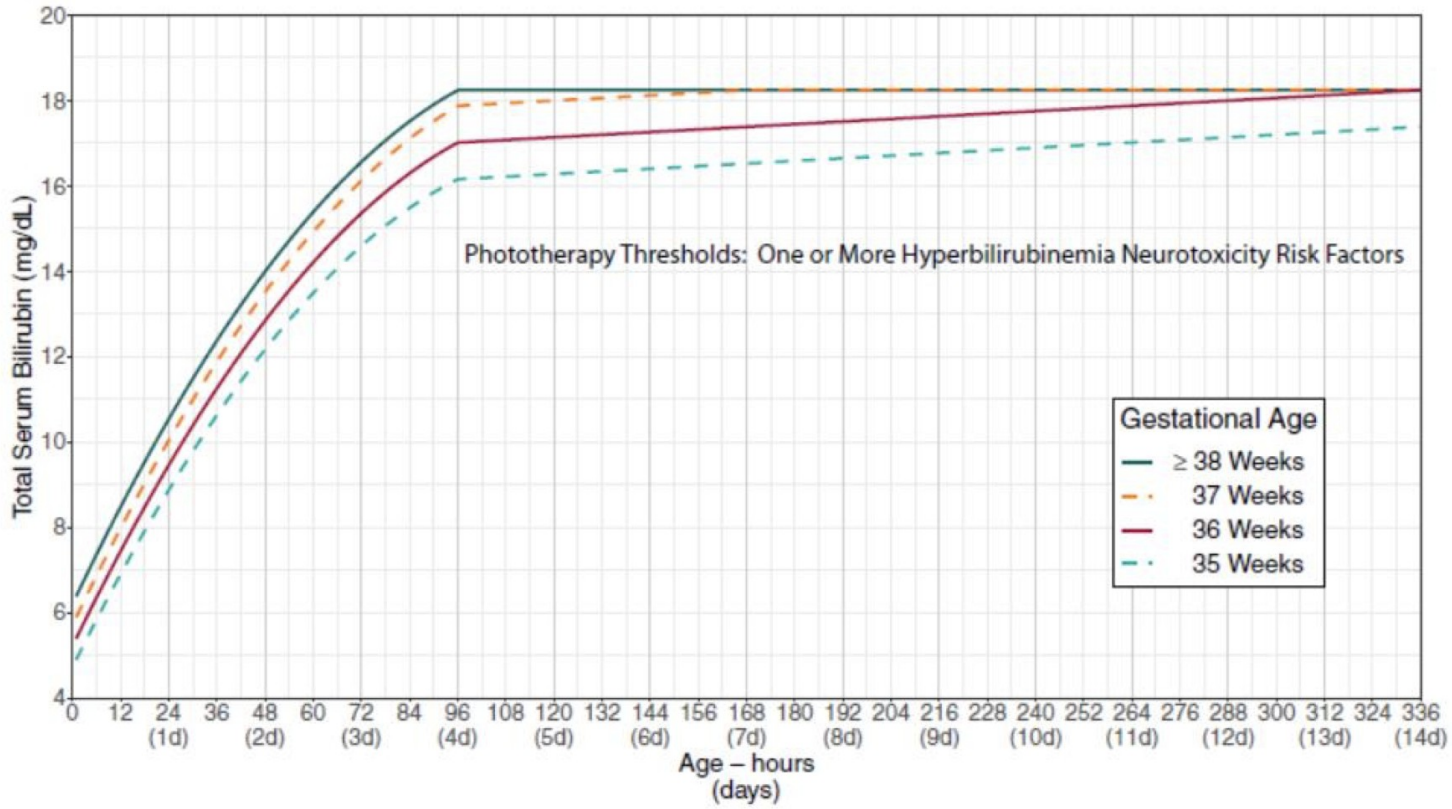


Subcommittee on Hyperbilirubinemia," Pediatrics 2004;114:297-316

Who need photo therapy ?

PEDIATRICS®

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



Subcommittee on Hyperbilirubinemia, Paediatrics 2022

Who need photo therapy ?

PEDIATRICS®

Adverse Effects of Phototherapy

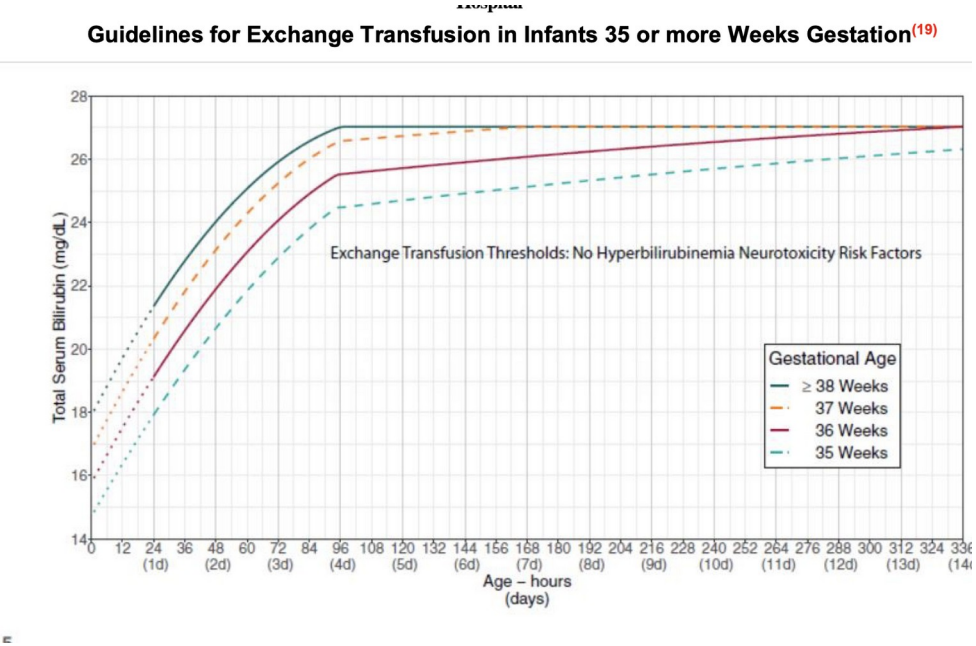
- Phototherapy is **safe and lifesaving**, but studies have suggested possible long-term associations with:
  - Asthma
  - Allergies
  - Blood cancers
  - Epilepsy
- **Important:** Evidence is **weak** and confounded.

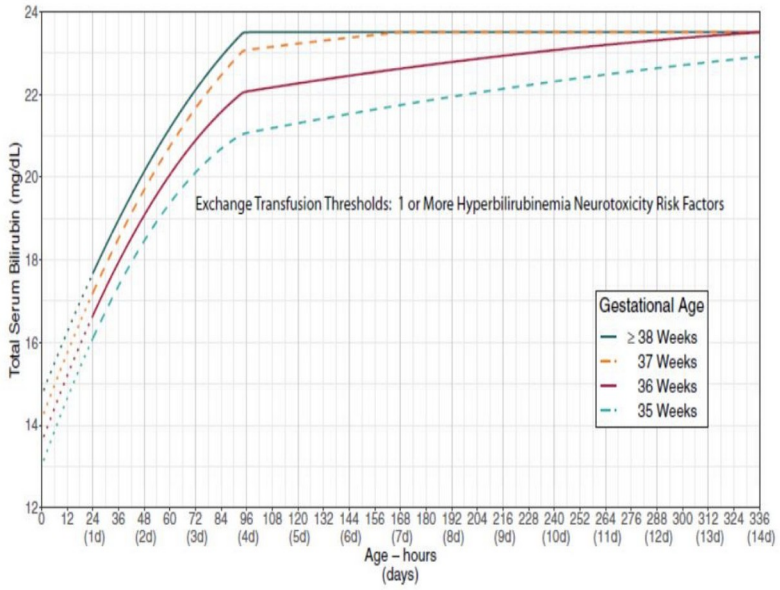
- Clinical message: **Benefits outweigh risks** — use phototherapy whenever threshold is reached.

Exchange photo therapy

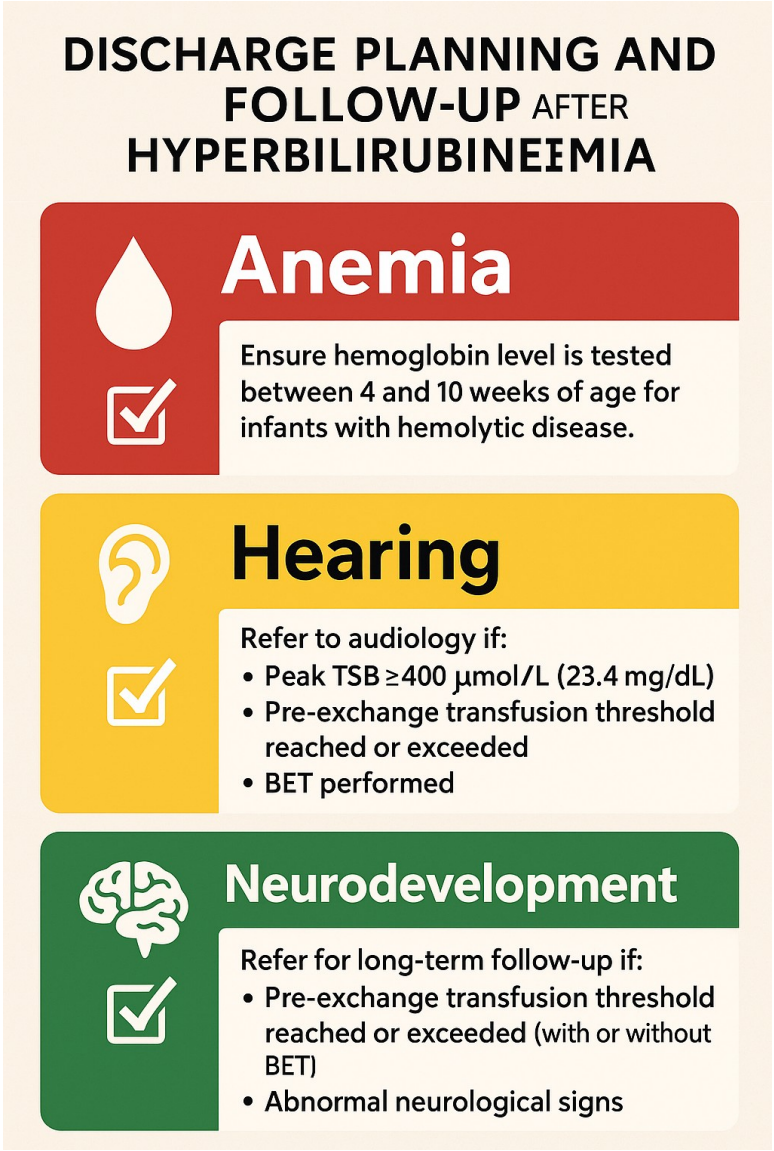
No risk factor

With neurotoxicity risk factor





Follow up Recommendations

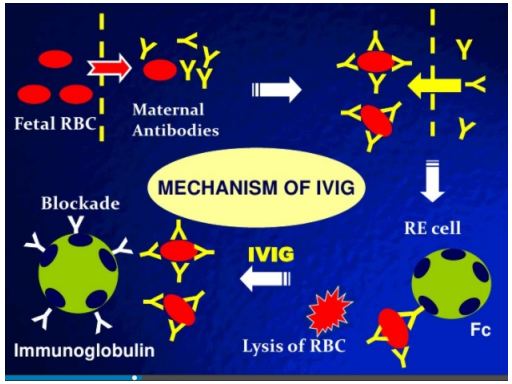


BET: blood exchange transfusion

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

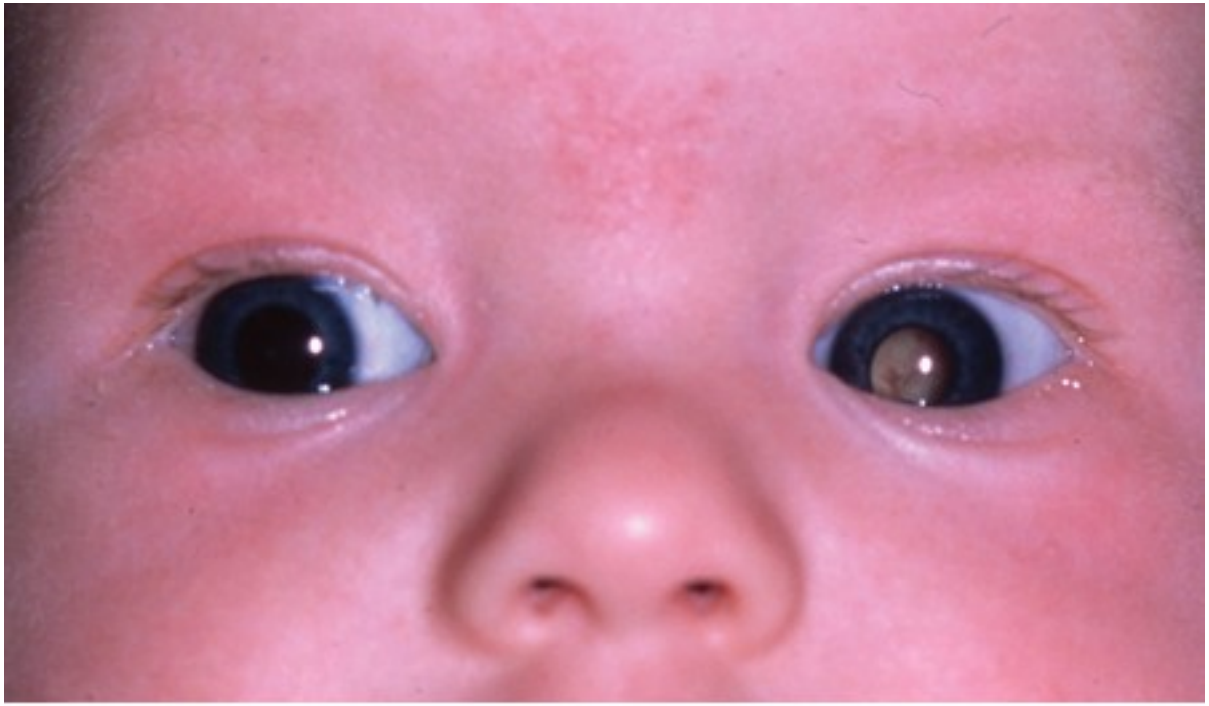
Learning Objectives

- 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



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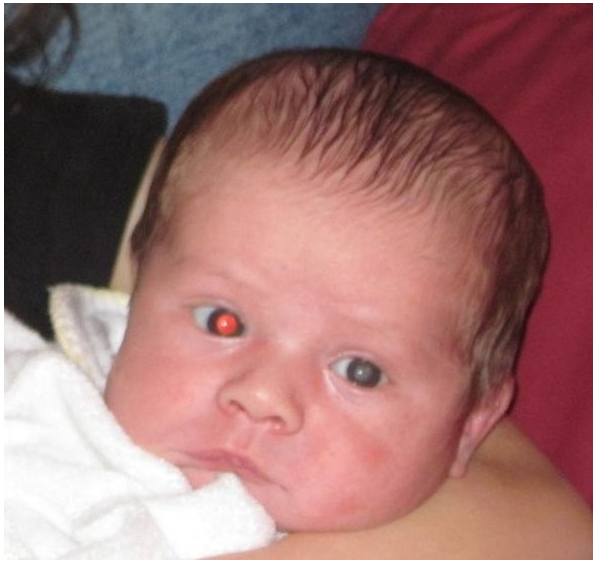
Source: Lueder GT: *Pediatric Practice Ophthalmology:*
www.accesspediatrics.com



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

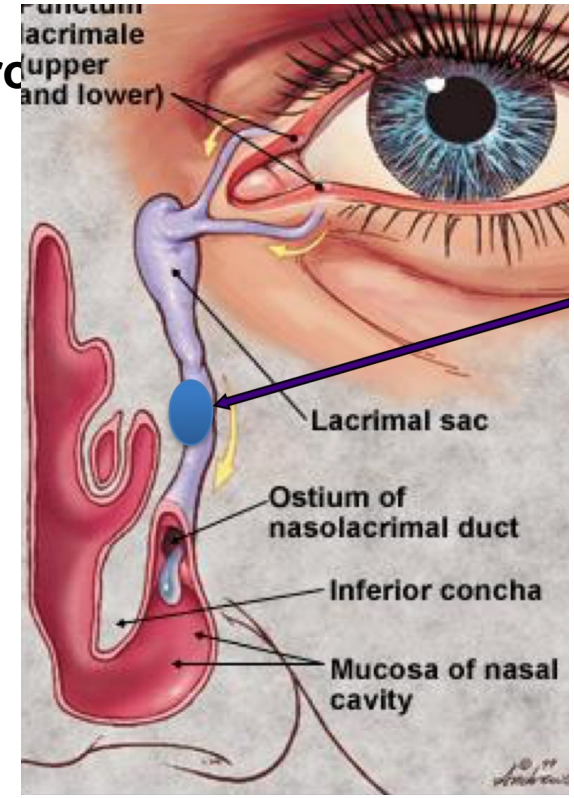
What is Diagnosis

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

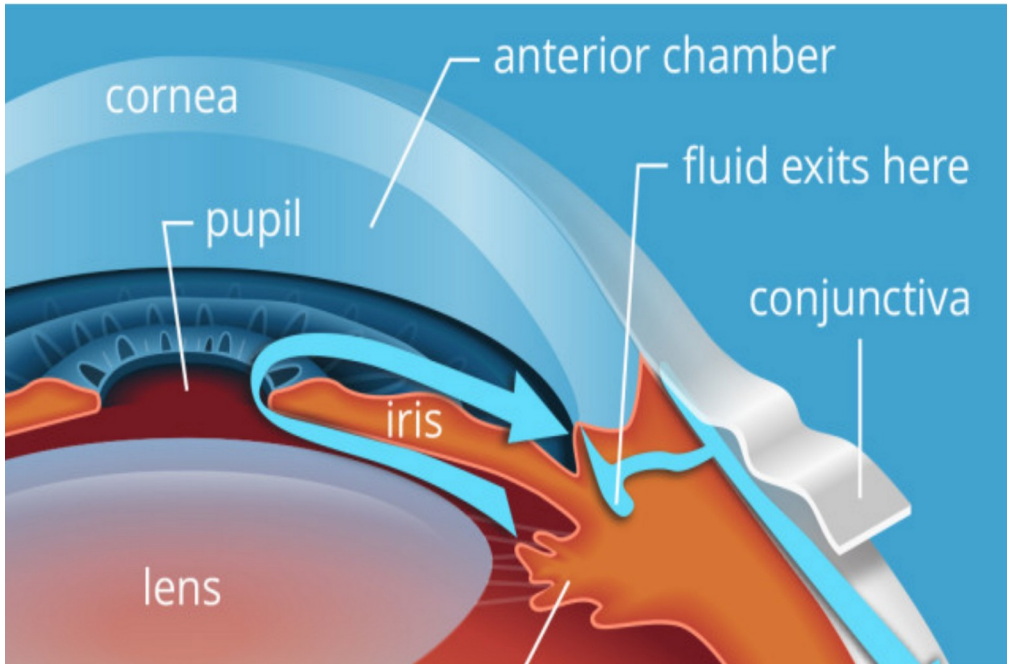
PRIMARY CONGENITAL GLAUCOMAS (PGG)

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

that prevent adequate drainage of aqueous humor,

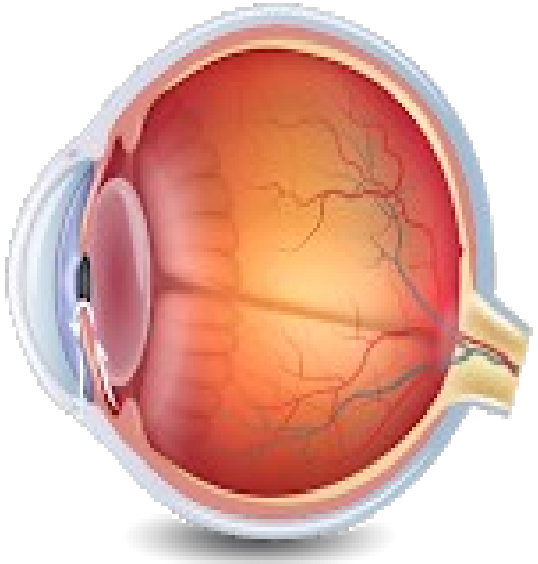
resulting in elevated intraocular pressure (IOP)

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

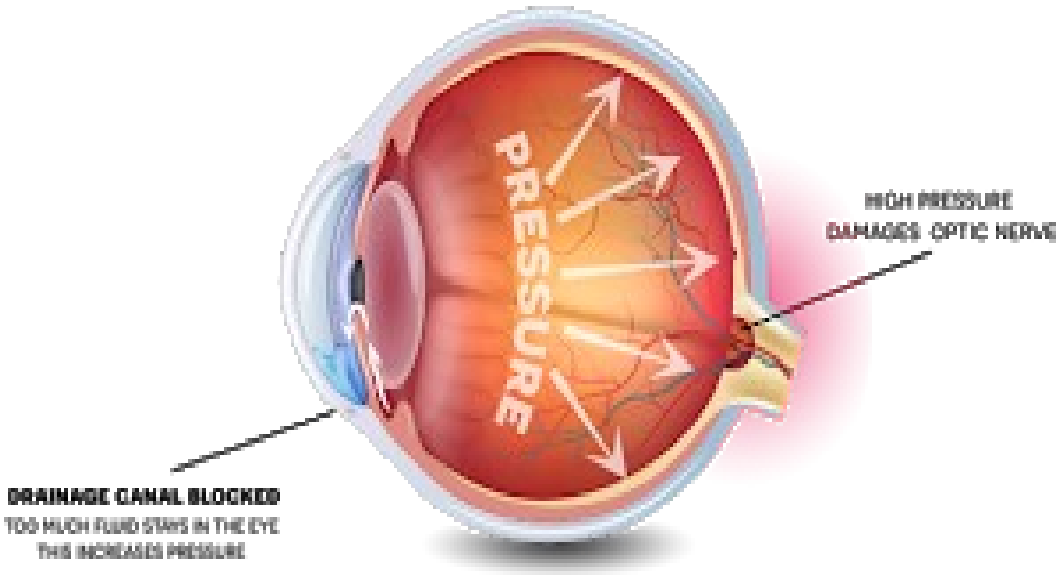


https://www.kceyeclinic.com/our-services/glaucoma/types-of-glaucoma/

GLAUCOMA



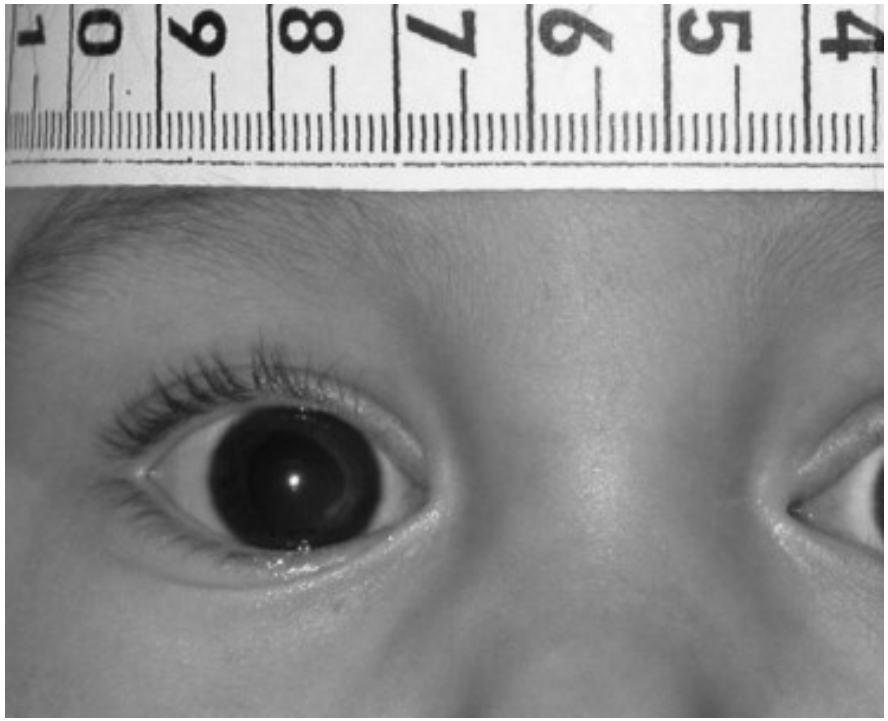
NORMAL EYE

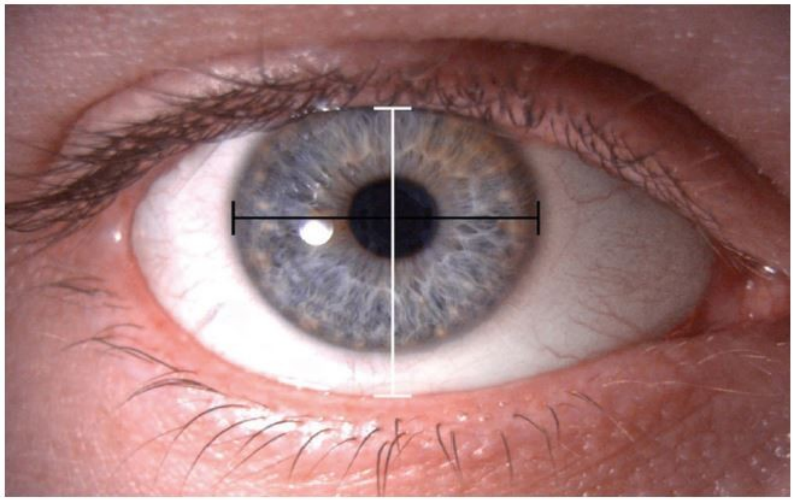


GLAUCOMA

Symptoms of congenital glaucoma

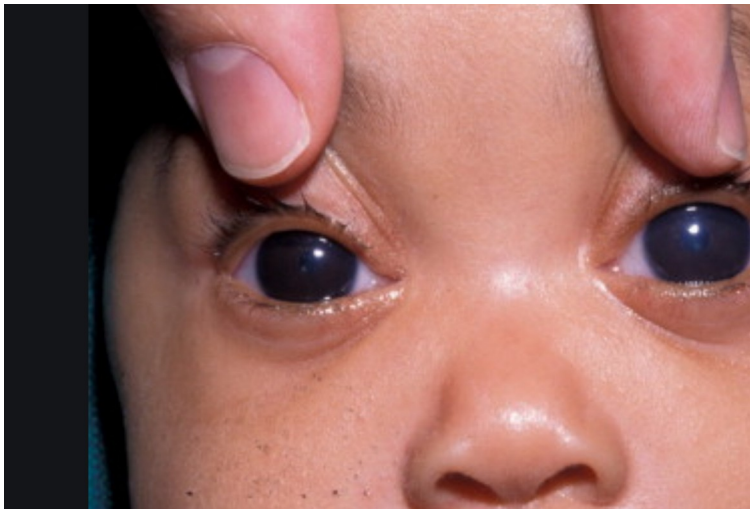
normal horizontal **corneal** diameter is 10.5 mm





Symptoms of congenital glaucoma

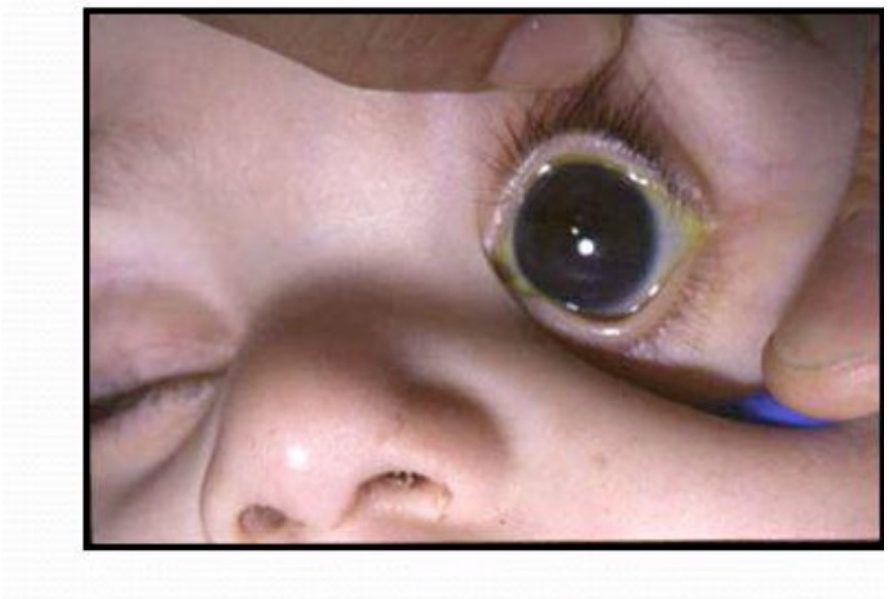
measurements greater than 12 mm are highly indicative of glaucoma.



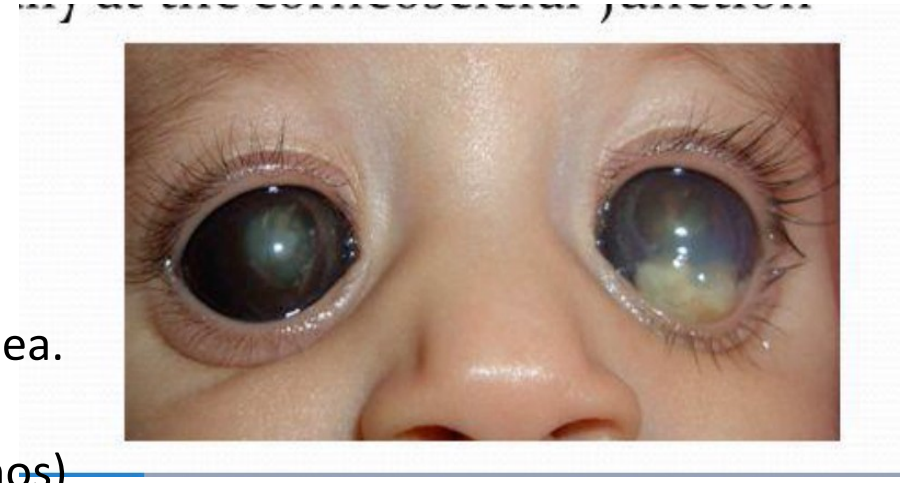
Top emergency : need surgery
Can neve some damage as Optic nerve

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)

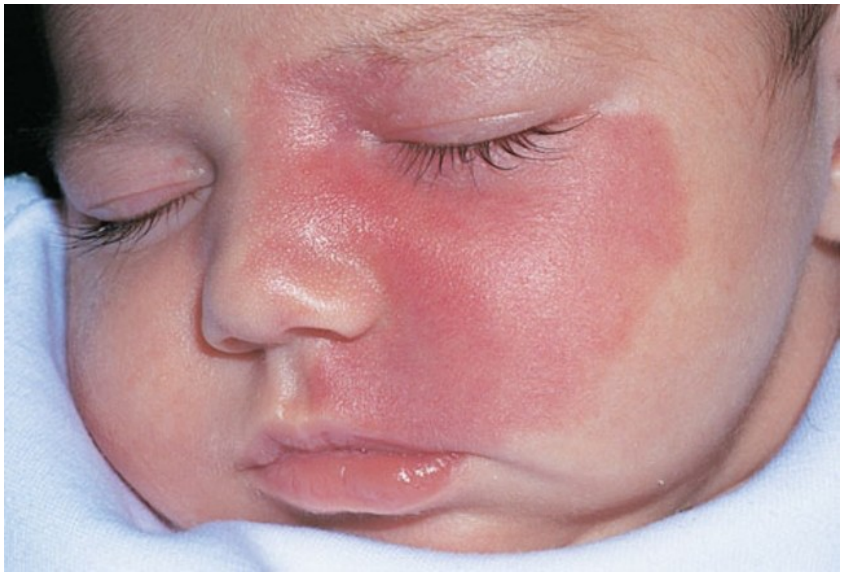
CAN BE :

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

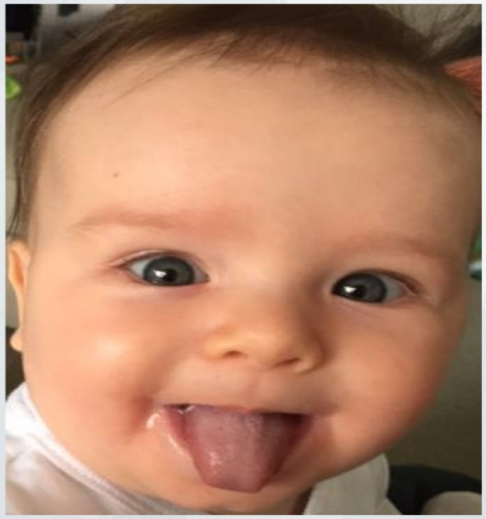
- During 2 weeks Neonatal visit
- Parents noticed that their baby has **squint**
  - They said it is (**intermittent** side ways)
- His history and **Physical exam is unremarkable**
- He was **healthy**
- **Red reflex** were **n**ormal and symmetrical corneal reflex

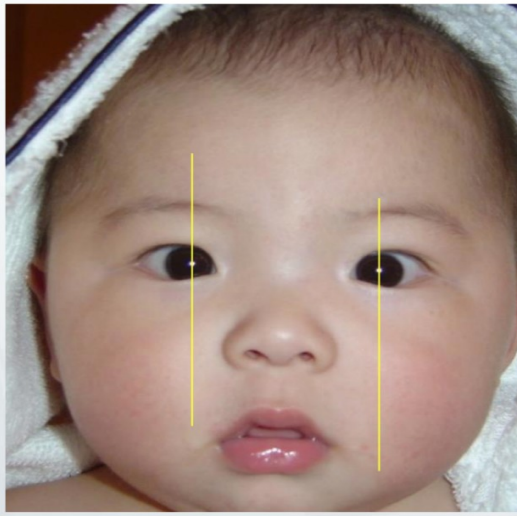
Strabismus – "squint that goes away"

Transient neonatal strabismus

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

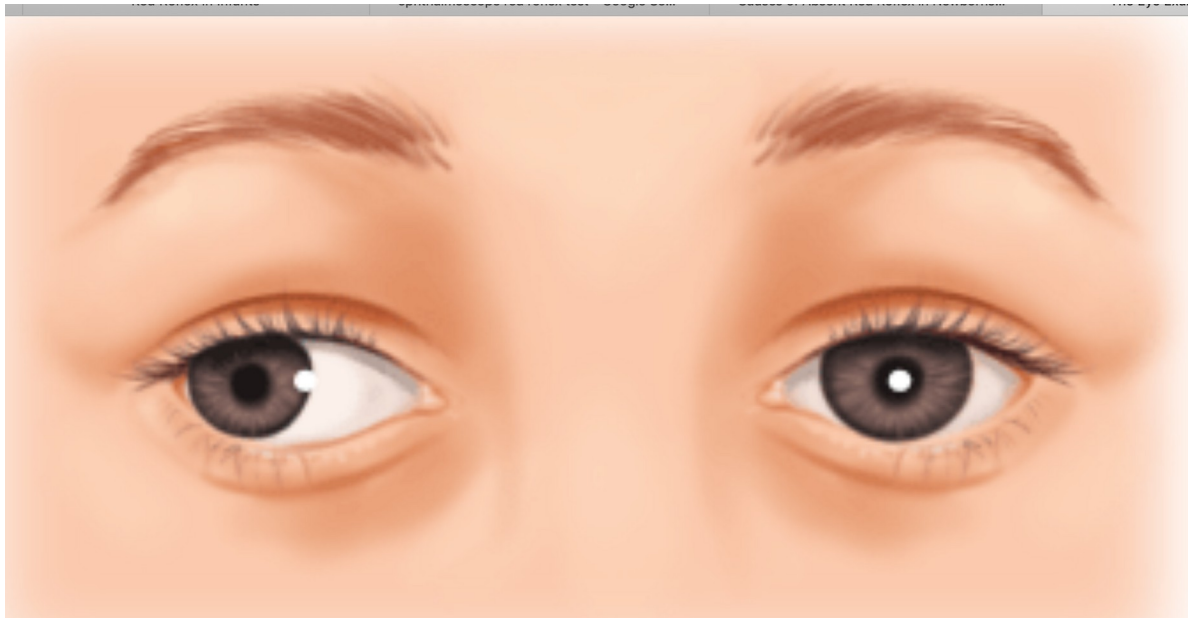
Pseudo-strabismus: Optical Illusion





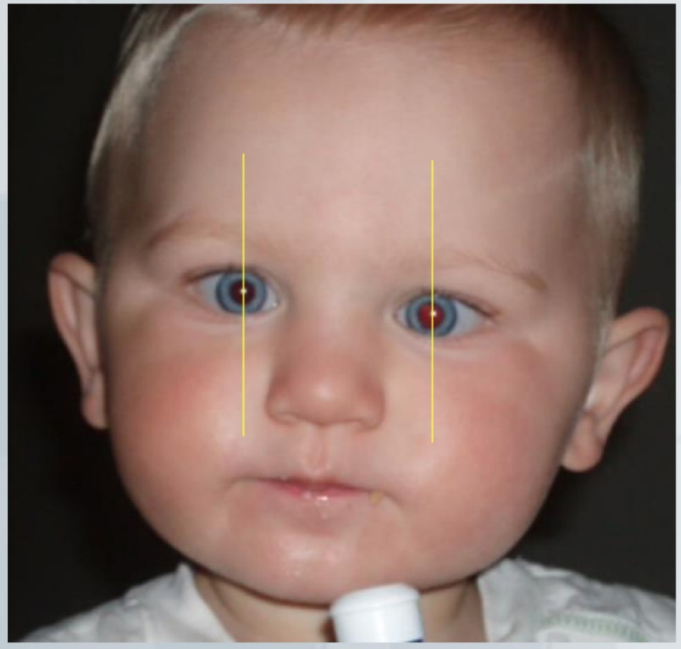
- Wide nasal fold/bridge of nose
- Intermittent – looking sideways
- "see both ears"
- Corneal light reflex - symmetry

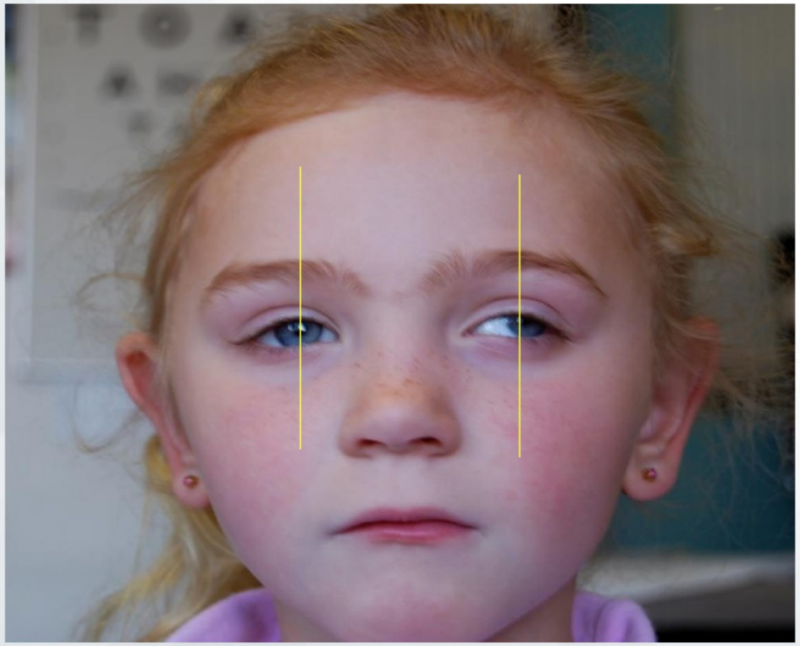
[1]Horwood A. 1993, JAAPOS; [2]Sondhi N. et al. 1988 JAAPOS



Asymmetrical pupillary reflex

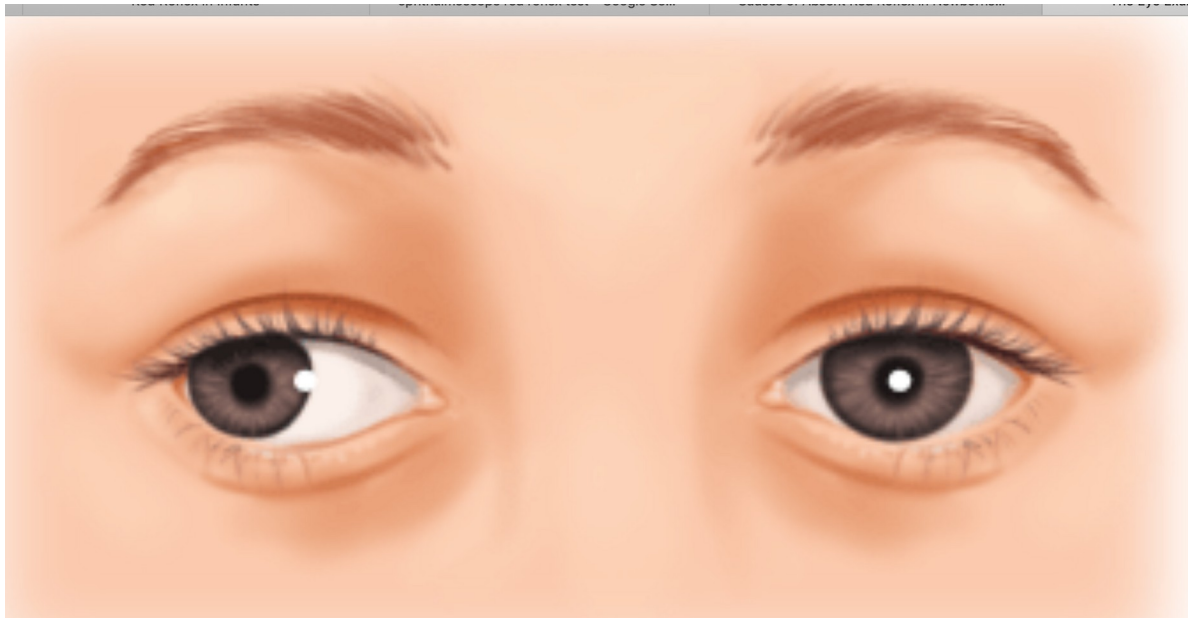
True strabismus – variable direction, size and frequency





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

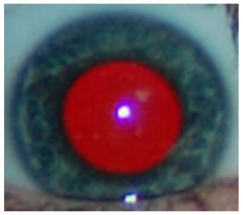
Why IT is important

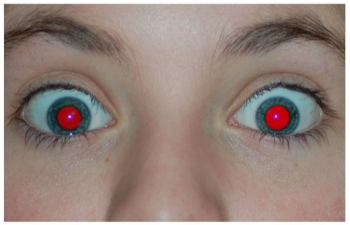
Red reflex

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

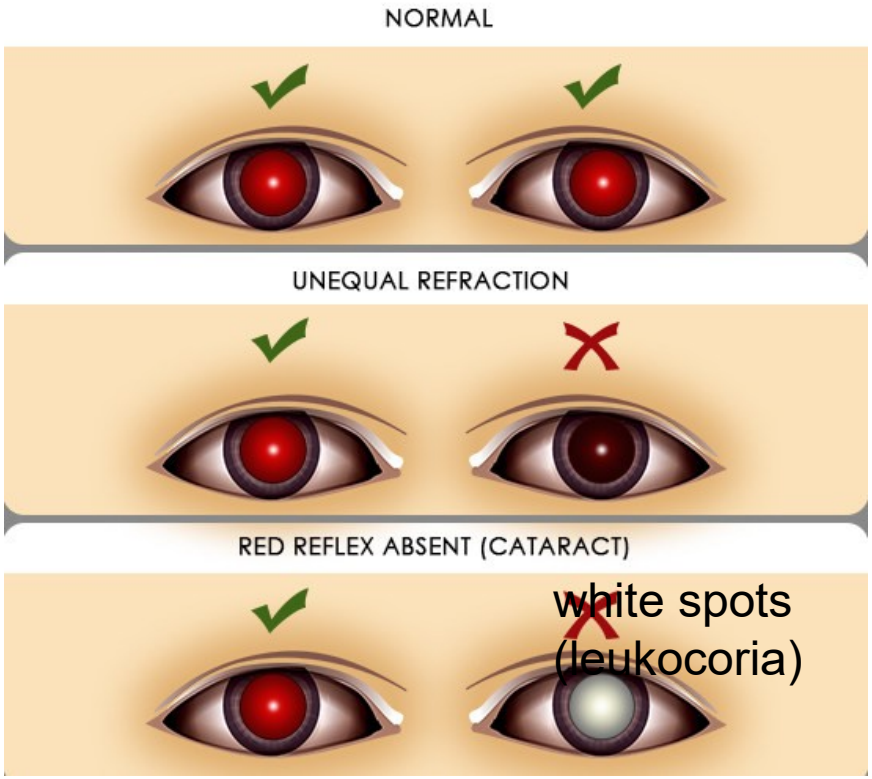




Red reflex should be equal in both eyes

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.

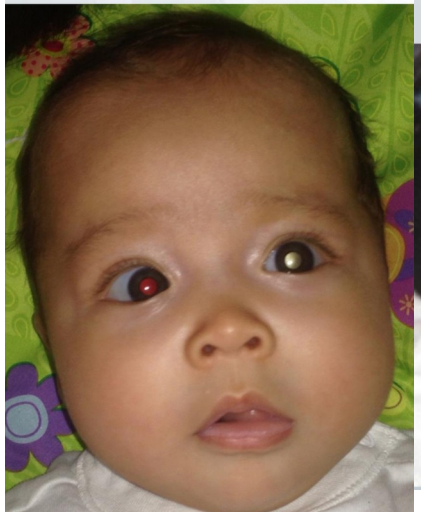
Interruption of Abnormal red reflex

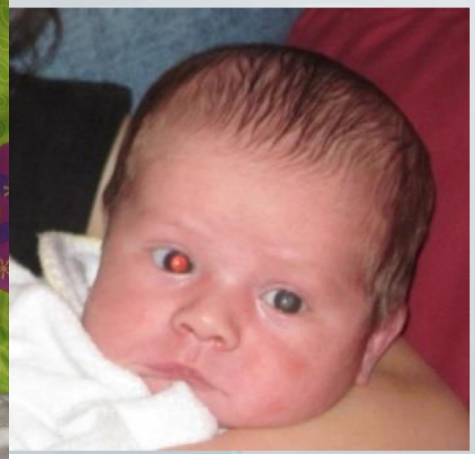


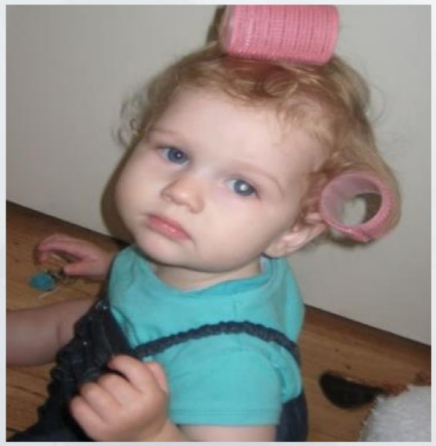
Leukocoria

Strabismus may be early signs

"Leuko" – white
"Coria" – pupil



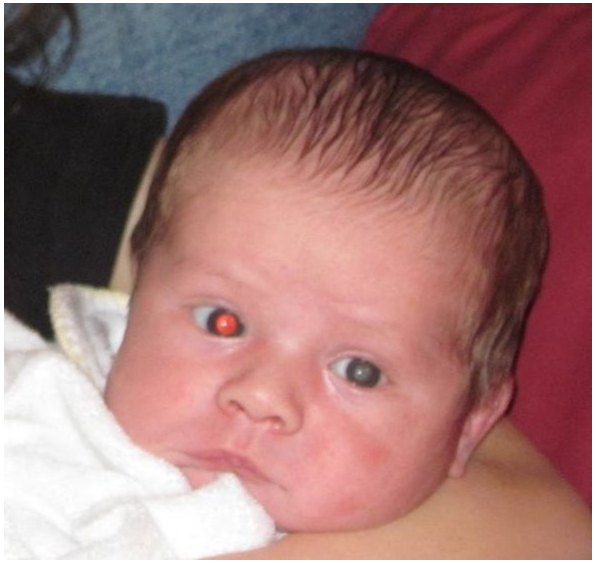




“Isn’t it just the camera flash?”

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

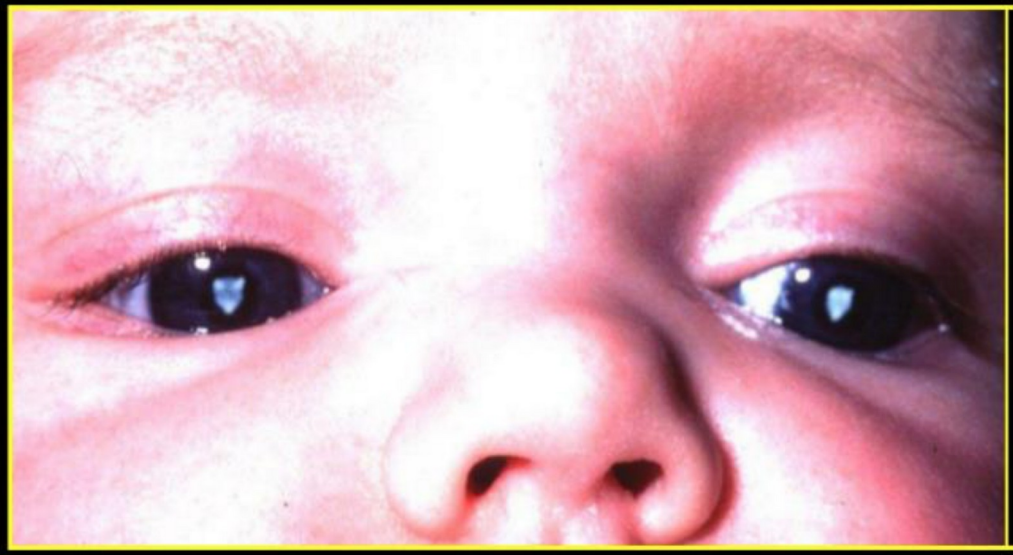
Systemic association

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

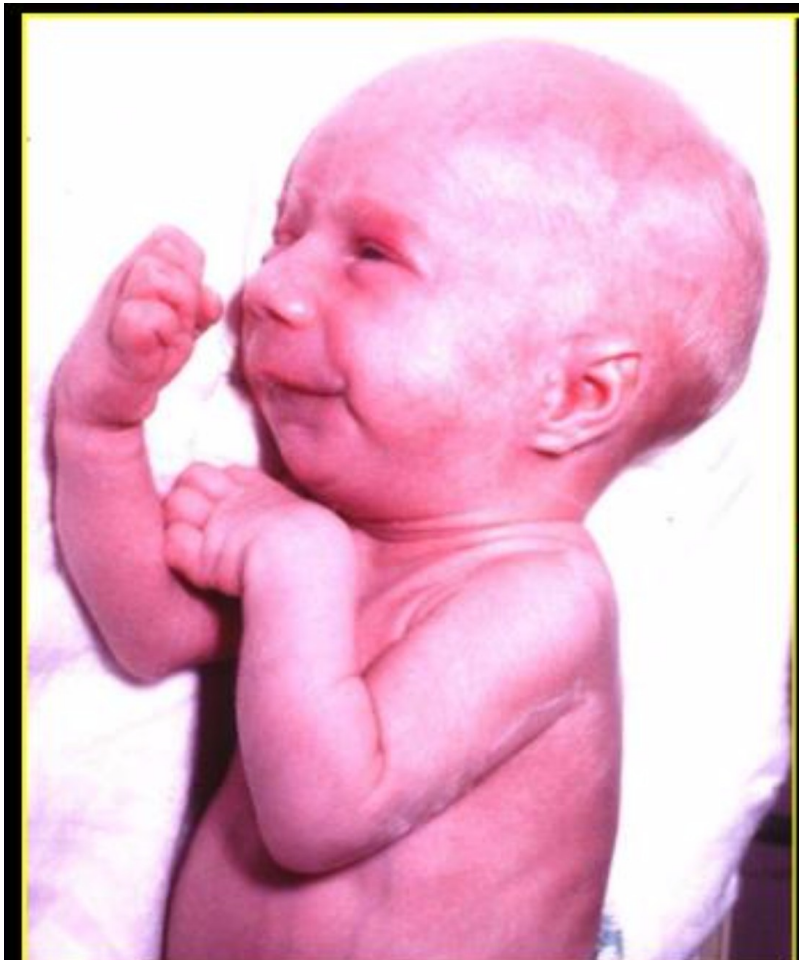


Hereditary
(usually dominant)

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