EVIDENCE-BASED UPDATE · AAP 2022 · CPS 2025 · NICE

Neonatal Indirect Hyperbilirubinemia

From bilirubin metabolism to a safe, modern management plan

Prof. Eman F. Badran

Neonatology — School Fifth year *medical students (2026-2027)*

START WITH A BABY, NOT A NUMBER

Meet Baby Zaid — Day 4 of life

THE STORY

- **Born at 36 weeks (late preterm)**

Exclusively breastfed; latch still being established

Lost 12 % of birth weight

Discharged home at 30 hours of age

Day 4: yellow to the chest, sleepy, feeding poorly

Mother: "Is this the normal newborn yellow… or something serious?"

PAUSE · THINK · PAIR · SHARE

1. What single question about timing would help you most?
2. Which features here worry you — and which reassure you?
3. What is the ONE test that decides everything?
4. Would you treat now, repeat later, or send home?

WHERE WE ARE GOING

Learning objectives

A Explain neonatal bilirubin metabolism and why newborns are uniquely prone to jaundice

B Distinguish physiologic from pathologic — and unconjugated from conjugated

C Classify the causes; separate breast-milk from breastfeeding jaundice

D Separate hyperbilirubinemia risk factors from neurotoxicity risk factors

E Apply AAP 2022 / CPS 2025 / NICE thresholds and build a management plan

F Recognise the RED FLAGS that prevent kernicterus

WHY THIS TOPIC MATTERS

~60–80%

of newborns become visibly jaundiced in the first week

~10%

have clinically significant hyperbilirubinemia needing surveillance or treatment

#1

cause of hospital readmission in the first week of life

Preventable

kernicterus is almost entirely avoidable with timely care

The clinical paradox: we must not over-treat the 80% who are fine, **while never missing the 1 in thousands whose bilirubin is climbing toward the brain.**

AAP 2022 (Pediatrics 150:e2022058859); Canadian Paediatric Society 2025.

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

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).

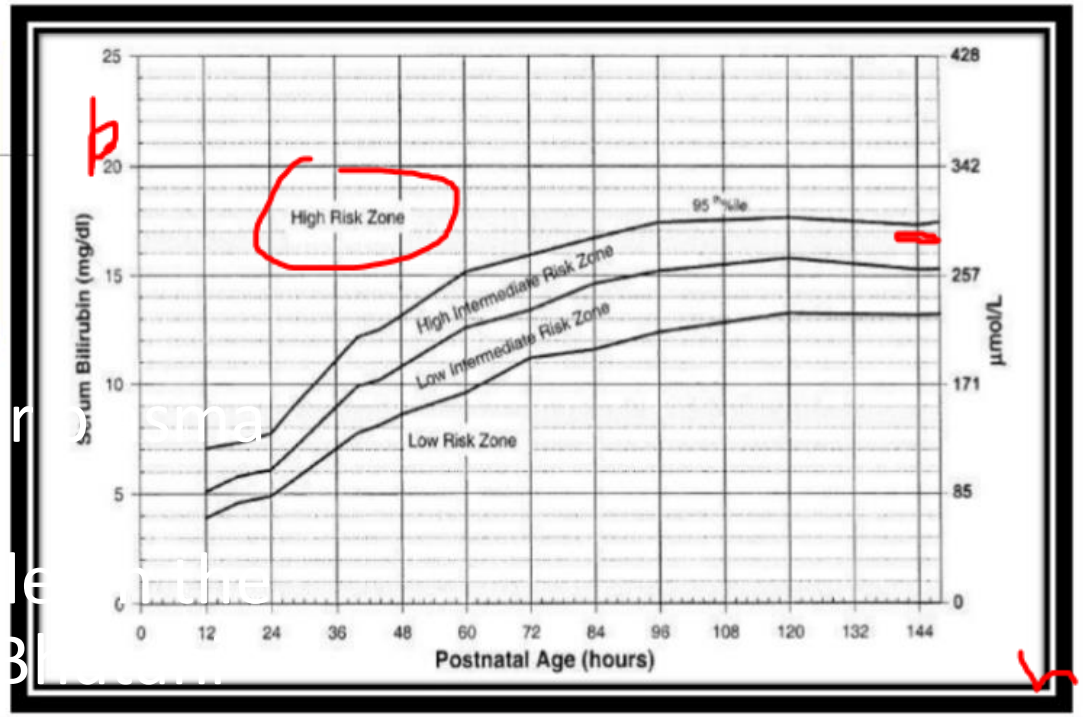
Definitions

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

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.**

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.

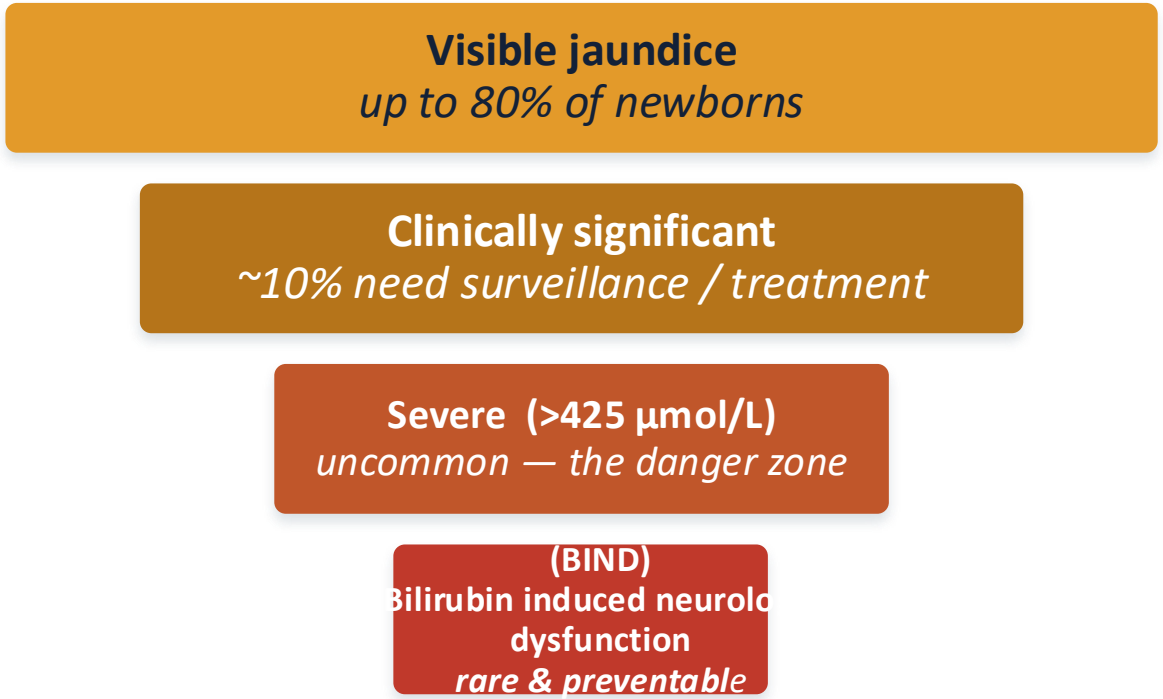
- Do test newborn screen
- If the maternal antibody screen is positive
- or unknown at time of delivery, newborn
- What tests?
  - Testing should include all :
    - Atotal serum bilirubin (TSB),
    - Hemoglobin, reticulocyte count, blood smear
    - Direct antiglobulin test (DAT), and blood group
  - Preferably obtained from cord blood.

  - Monitor these neonates **closely for the development of early (<24 hours postnatal age) hyperbilirubinemia.**

EPIDEMIOLOGY

How common, how severe, and where the burden falls

THE JAUNDICE FUNNEL



Almost universal at the top; the rare tip is what we work to prevent

Up to 80% develop visible jaundice; ~60% of term, ~80% of preterm

~10% reach a level needing surveillance or phototherapy

>425 µmol/L (~25 mg/dL) defines severe hyperbilirubinemia — uncommon but the danger zone

REGIONAL LENS — JORDAN & THE MIDDLE EAST

- High G6PD-deficiency prevalence and frequent consanguinity make inherited haemolytic causes especially relevant.
- ABO incompatibility is common.
- Severe cases and kernicterus persist mainly where screening and follow-up are inconsistent.

CPS 2025; AAP 2022; global burden data — kernicterus concentrated in low-resource settings.

THE REASON WE DO ALL OF THIS

Bilirubin Induced neurotoxicity (BIND) — acute encephalopathy & kernicterus

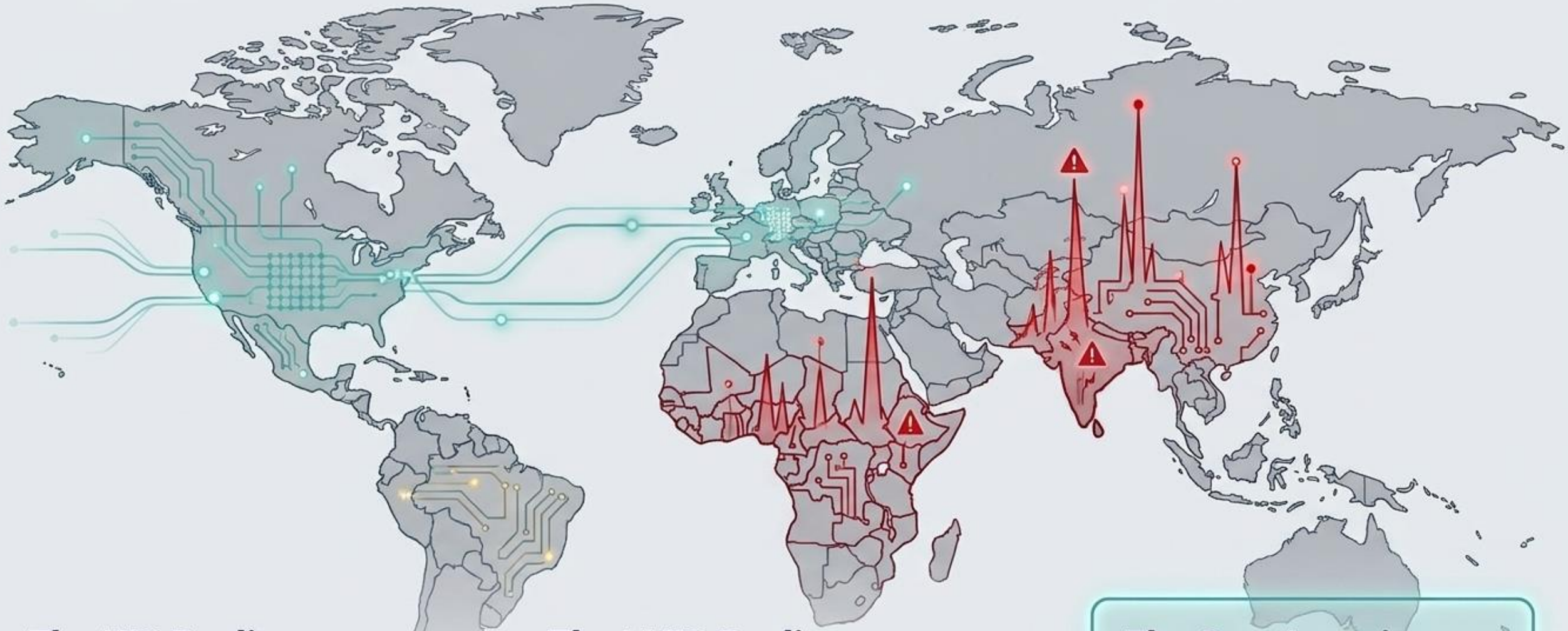
ACUTE BILIRUBIN ENCEPHALOPATHY (ABE) — evolves in phases

EARLY	INTERMEDIATE	ADVANCED
Lethargy, hypotonia, poor feeding	Hypertonia, irritability, high-pitched cry, retrocollis	Opisthotonos, apnoea, seizures, fever, coma

CHRONIC KERNICTERUS (permanent)

Athetoid cerebral palsy · gaze palsy (upward) · sensorineural hearing loss · dental enamel dysplasia. **Basal ganglia (globus pallidus) staining — the hallmark.**

Free, unconjugated bilirubin crosses the blood–brain barrier. **ABE is a medical emergency — at these levels, escalate and prepare exchange transfusion NOW.**



The HIC Reality

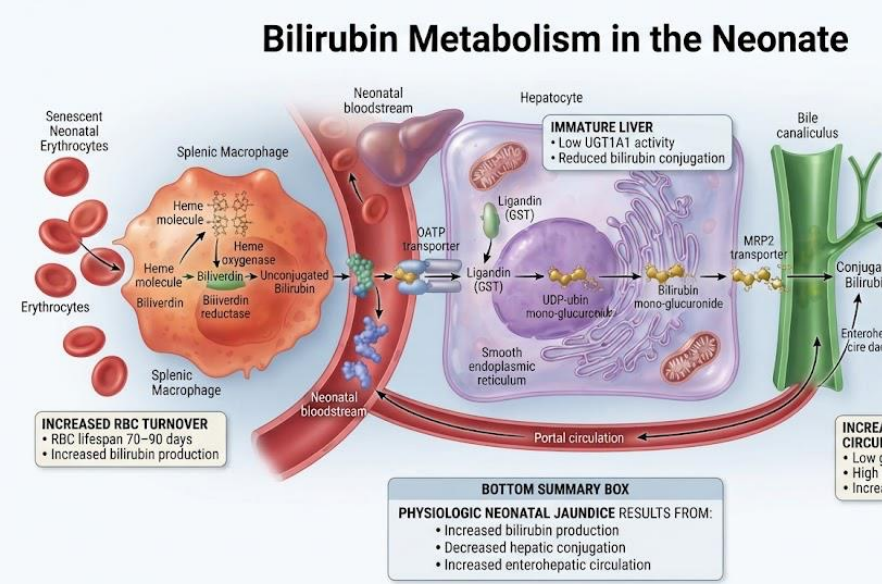
Incidence of kernicterus is roughly **1 per 100,000** live births. Near-total elimination of severe outcomes achieved through universal screening.

The LMIC Reality

Incidence spikes to 25–38 cases per 100,000. Globally, severe jaundice accounts for ~1,008 deaths per 100,000 live births, heavily concentrated in Sub-Saharan Africa.

The Core Inequity

The biological vulnerability of the neonate is universal; the mortality rate is entirely systemic.



① PRODUCTION

RBC
Senescent / haemolysed red cell

▼

HAEM
Released from haemoglobin

▼

BILIVERDIN
haem oxygenase → + CO (1:1)

▼

UNCONJUGATED BILIRUBIN
biliverdin reductase

Neonate makes 2–3× more bilirubin per kg than an adult

② TRANSPORT & CONJUGATION

BOUND TO ALBUMIN
the free (unbound) fraction is the toxic one

▼

HEPATIC UPTAKE
facilitated diffusion; binds ligandin (SLCO1B1 variants impair this)

▼

CONJUGATION
UGT1A1 + glucuronic acid → mono/di-glucuronide

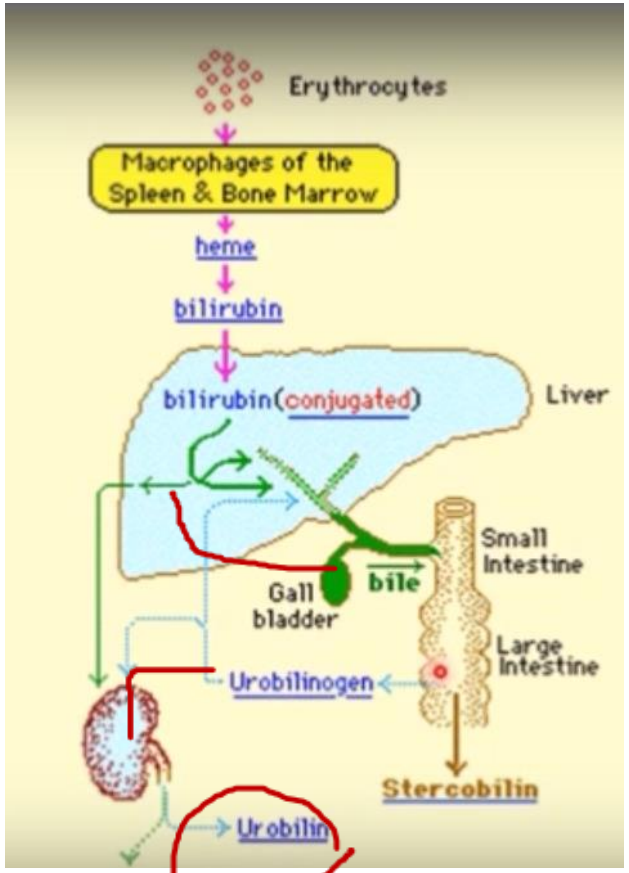
▼

EXCRETED INTO BILE
via MRP2

UGT1A1 activity at birth ≈ 1% of adult levels

After Fig. 72.1, Avery's Diseases of the Newborn, 11th ed. (Golden & Watchko).

Bilirubin metabolism In adult



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

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

BILIRUBIN METABOLISM IN NEONATE

From Intestine to Stercobilirubin & Urobilinogen with Enterohepatic Circulation

- Conjugated bilirubin (water soluble)
- Unconjugated bilirubin (lipid soluble)

Unconjugated bilirubin (Albumin-bound)

LIVER Uptake Conjugation (UGT1A1)

Conjugated bilirubin (bilirubin diglucuronide) Excreted in bile

GALLBLADDER Storage Concentrated bile

DUODENUM Release with bile after feeding

INTESTINE (Colon)

Excreted in feces

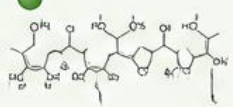
Neonate factors

- Increased RBC turnover
- Immature UGT1A1
- High intestinal β-glucuronidase
- Increased enterohepatic circulation

⇒ Higher risk of jaundice

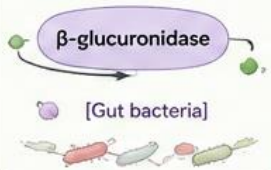
INTESTINAL PHASE – DECONJUGATION & CONVERSION

1. Conjugated bilirubin in intestine
(Bilirubin diglucuronide)

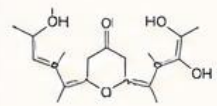


(Glucuronic acid)$_2$

2. Deconjugation by β-glucuronidase
(from intestinal bacteria)
Releases glucuronic acid



3. Unconjugated bilirubin
(Lipid soluble)



4. Reductive reactions (by gut bacteria)

Reduction
↓
Bilirubin
↓
Mesobilirubinogen
↓
Urobilinogen

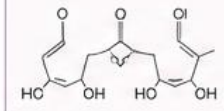
5. Fates of Urobilinogen

Oxidation (major route)
(Urobilinogen oxidized by intestinal bacteria)
↓
Stercobilin
↓
Stercobilirubin
(Brown color of stool)

Reduction (minor route)
↓
Urobilinogen
(Absorbed)

Excreted in feces

Stercobilirubin (major pigment)



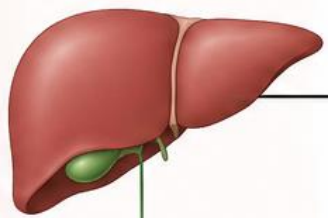
6. Absorption of urobilinogen (minor portion)

Into portal vein

ENTEROHEPATIC CIRCULATION

7. Reuptake by liver

- Urobilinogen taken up by hepatocytes
- May be re-conjugated to bilirubin diglucuronide
- Excreted again in bile

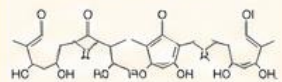


Re-excreted in bile

8. Systemic escape (if liver capacity exceeded)

- Urobilinogen enters systemic circulation
- Filtered by kidneys
- Excreted in urine

Urobilin
(oxidized in urine)
Yellow color of urine



Pigments

- **Stercobilirubin** → Brown (feces)
- **Urobilin** → Yellow (urine)

Key Points in Neonates

- High β-glucuronidase activity → more deconjugation of bilirubin in intestine
- Increased enterohepatic circulation → more bilirubin returns to liver
- Immature liver → less efficient clearance → higher unconjugated bilirubin in blood

UGT1A1: UDP-glucuronosyltransferase 1A1 | **β-glucuronidase:** Enzyme that removes glucuronic acid from conjugated bilirubin
RBC: Red blood cell

THE PATHWAY

Bilirubin metabolism — from red cell to stool

① PRODUCTION

RBC
Senescent / haemolysed red cell

▼

HAEM
Released from haemoglobin

▼

BILIVERDIN
haem oxygenase → + CO (1:1)

▼

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biliverdin reductase

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the free (unbound) fraction is the toxic one

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HEPATIC UPTAKE
facilitated diffusion; binds ligandin (SLCO1B1 variants impair this)

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▼

EXCRETED INTO BILE
via MRP2

UGT1A1 activity at birth ≈ 1% of adult levels

③ THE GUT — AND THE LOOP

CONJUGATED BILIRUBIN IN GUT
water-soluble, excretable

▼ ▼

EXCRETED
in stool
needs feeding & stooling

DECONJUGATED
β-glucuronidase
reabsorbed → back to liver

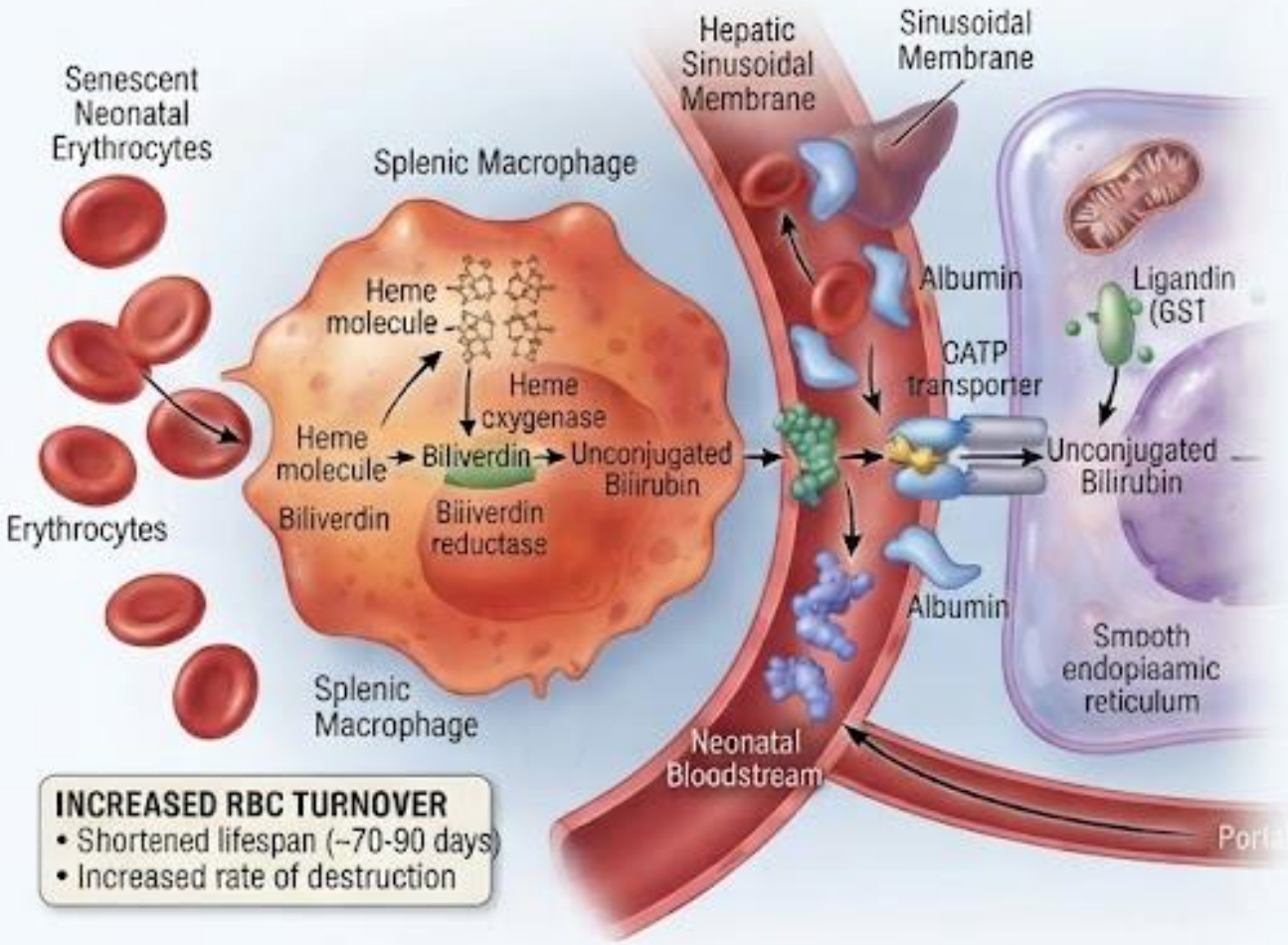
↩ ENTEROHEPATIC CIRCULATION

The neonate's gut is sterile, alkaline and rich in β-glucuronidase — so it recycles bilirubin instead of losing it.

Poor feeding → less stool → more recycling

After Fig. 72.1, Avery's Diseases of the Newborn, 11th ed. (Golden & Watchko).

MECHANISM: INCREASED NEONATAL RBC TURNOVER



CAUSES OF INCREASED RBC TURNOVER IN NEONATES

CATEGORY	SPECIFIC CAUSES
Hemolytic Disorders	Hereditary Spherocytosis
	G6PD Deficiency
	Pyruvate Kinase Deficiency
	Thalassemia (e.g., alpha-thalassemia)
	ABO Incompatibility
Immune-Mediated	Rh Disease (Rh Incompatibility)
	Minor Blood Group Incompatibility
Infections	Congenital Infections (TORCH)
	Sepsis
Other Factors	Polycythemia
	Enclosed Hemorrhage (e.g., Cephalohematoma, Bruising)
	Infant of a Diabetic Mother
	Vitamin K Deficiency (rarely, severe)

CLINICAL SIGNIFICANCE

Increased RBC turnover leads to a higher load of Unconjugated Bilirubin, overwhelming the neonata liver's immature conjugation capacity (UGT1A1) and resulting in neonatal jaundice.

THE PATHWAY

Bilirubin metabolism — follow the molecule

1 Heme breakdown

Senescent RBCs → heme.
Heme oxygenase → biliverdin + CO

2 Unconjugated bilirubin

Biliverdin reductase → bilirubin.
Fat-soluble, cannot be excreted

3 Albumin transport

Bound to albumin in blood —
the “shuttle bus” to the liver

4 Hepatic uptake

Taken up by hepatocyte;
bound to ligandin

5 Conjugation — UGT1A1

Glucuronic acid added →
water-soluble, excretable

6 Excretion + gut

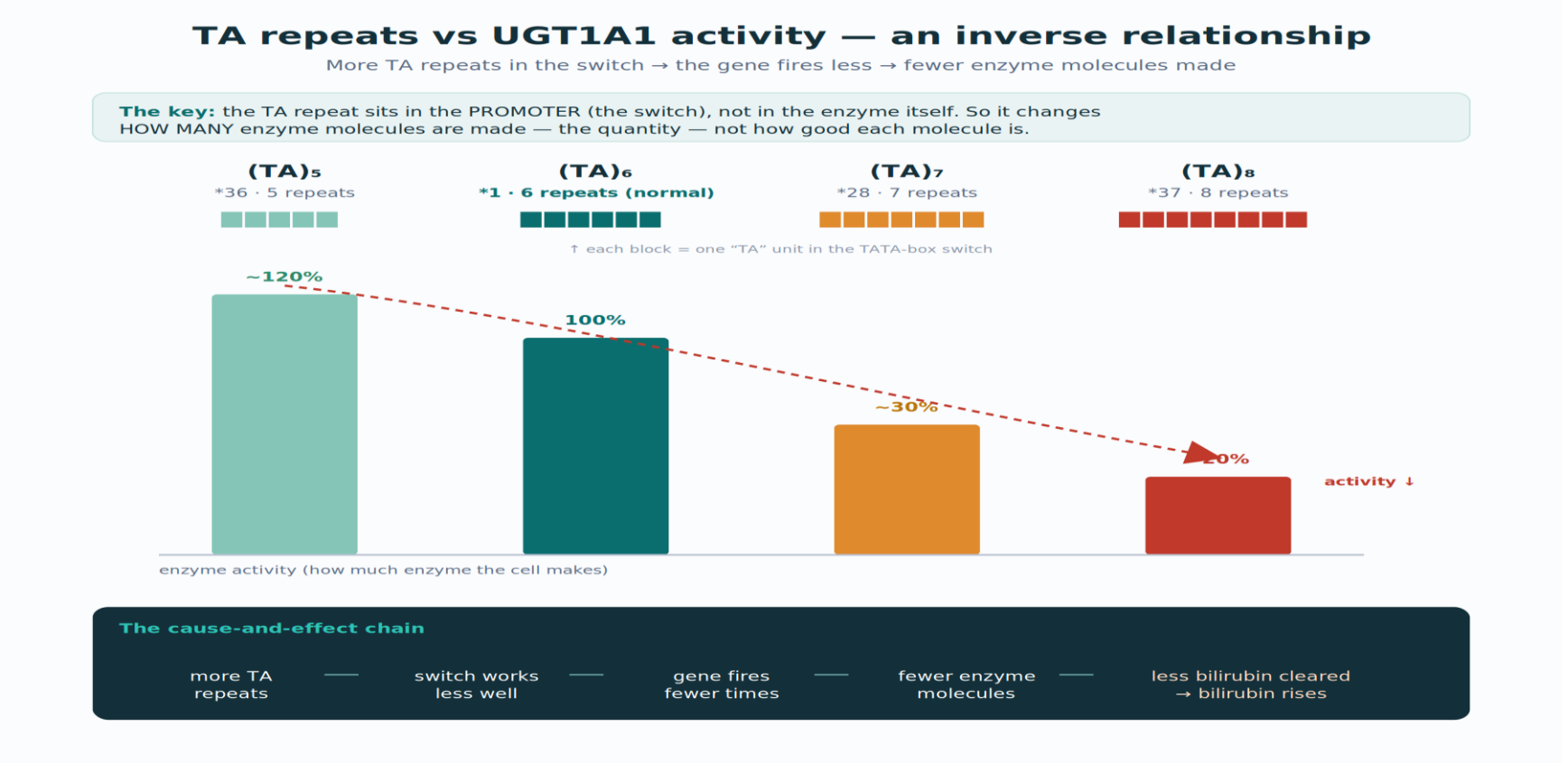
Bile → gut → stercobilin.
Some deconjugated & reabsorbed

KEY LOOP β-glucuronidase in the gut deconjugates bilirubin, which is reabsorbed back to blood = **enterohepatic circulation** — central to neonatal & breast-milk jaundice.

THE KEY RELATIONSHIP

TA repeats vs UGT1A1 activity

The key: the TA repeat sits in the **promoter (the switch), not in the enzyme** — so it changes **how many enzyme molecules are made (quantity)**, not how good each one is.



Inverse relationship: more repeats → lower activity. $(TA)_5 > (TA)_6 > (TA)_7 > (TA)_8$

The “perfect storm”: make more, clear less, recycle more

MAKE MORE

Bilirubin production

- Higher haematocrit at birth

RBC lifespan only ~70–90 d (adult 120)

Production ~2× adult (per kg)

CLEAR LESS

Hepatic conjugation

- UGT1A1 activity ~1% of adult at birth

Matures over the first weeks

Late-preterm = even less capacity

RECYCLE MORE

Enterohepatic circulation

- Sterile gut → little bilirubin→urobilin

High gut β-glucuronidase

Slow feeds / meconium delay = more reabsorption

Bottom line: physiologic jaundice is not a disease — it is the predictable result of normal newborn physiology. Prematurity amplifies all three arms.

Three-hit framework: increased production + immature conjugation + increased enterohepatic reabsorption.

THE FIRST FORK IN THE ROAD

Split the bilirubin before you do anything else

UNCONJUGATED (indirect)

Today's lecture

- Fat-soluble → can cross the blood–brain barrier
- NOT excreted in urine
- Can be neurotoxic → this is the one that causes kernicterus
- Usually physiologic, but always ask: is it pathologic?
- Treated with light, feeding, and (rarely) exchange

CONJUGATED (direct)

Never normal — always pathologic

Direct >1 mg/dL (>17 µmol/L) or >20% of total

- Water-soluble → dark urine, pale stools
- Does NOT cause kernicterus
- Means cholestasis — biliary atresia until proven otherwise
- Phototherapy does not treat it (and risks bronze baby syndrome)
- Urgent: the biliary atresia clock is ticking (Kasai < 60 days)

RULE: Any jaundice persisting beyond 2 weeks (term) or 3 weeks (preterm), or any baby with pale stools/dark urine, gets a **SPLIT bilirubin**. Direct >1 mg/dL (or >20% of total) = cholestasis = refer.

Avery's Ch. 72; NICE CG98 (conjugated fraction → investigate liver disease).

THE FIRST FORK IN THE ROAD

Unconjugated vs conjugated — never confuse them

INDIRECT / UNCONJUGATED

Our focus today

- Fat-soluble; bound to albumin

Can be physiologic OR pathologic

The form that can cross into the brain

Responds to phototherapy & exchange

DIRECT / CONJUGATED

Direct >1 mg/dL (>17 µmol/L) or >20% of total

- Water-soluble

ALWAYS pathologic — never "physiologic"

Think: biliary atresia, infection, metabolic, TPN

Does NOT respond to phototherapy

🚩 **Pale (chalky) stools + dark urine = conjugated jaundice until proven otherwise.** Biliary atresia is time-critical: the Kasai operation works best before 6–8 weeks.

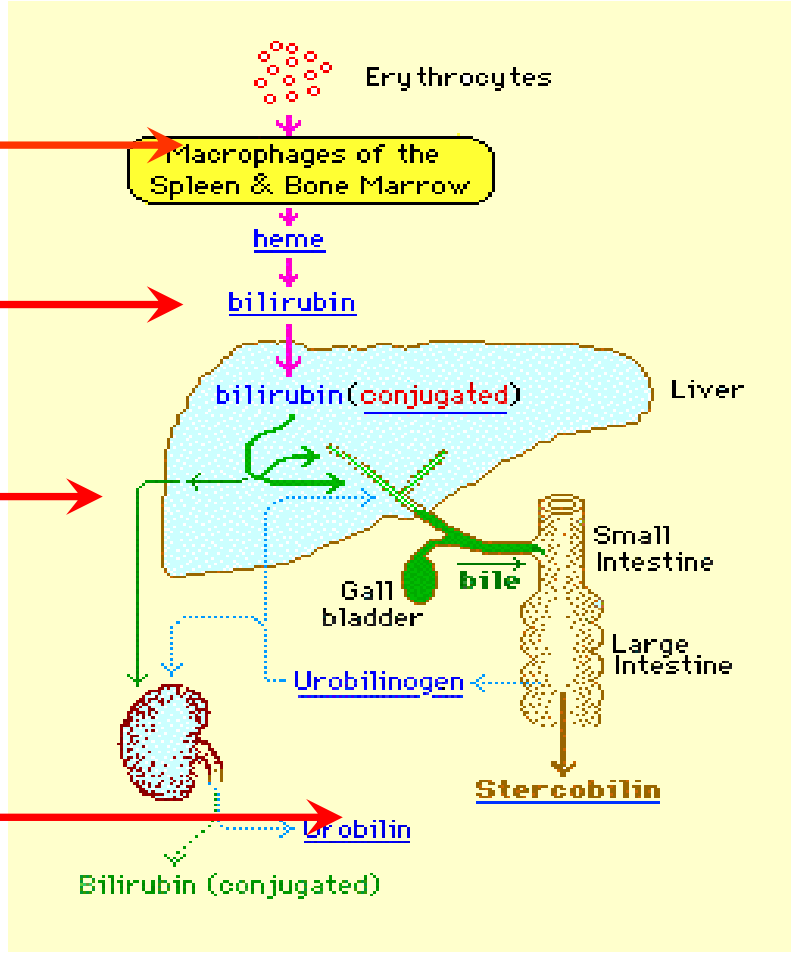
AAP 2022: measure total AND direct bilirubin in prolonged jaundice. NICE: conjugated >25 µmol/L → investigate liver disease.

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)

THE COMMON, BENIGN PATTERN

Physiologic jaundice — what “normal” looks like

ONSET

Appears AFTER 24 h of life

never in the first 24 h

PEAK (TERM)

Day 3–5

then falls

PEAK (PRETERM)

Day 5–7

higher & later

RESOLVES

By ~1–2 weeks

longer if breastfed

RATE OF RISE

Slow & gradual

< the pathologic rate

BABY

Well, feeding, thriving

no other signs

Diagnosis of exclusion: call it physiologic only when timing, rate and a well baby all fit. **Any deviation → treat as pathologic and investigate.**

WHEN JAUNDICE IS A WARNING

Pathologic jaundice — “The 6 Toos”

TOO EARLY

Jaundice in the first 24 h

almost always haemolysis

TOO HIGH

Peak above the treatment threshold

or >425 µmol/L / ~25 mg/dL

TOO FAST

Rising ≥0.3 mg/dL/hour (<24 h)
or ≥0.2 mg/dL/hour (after)
suggests haemolysis

TOO LONG

> 14 d term · > 21 d preterm

→ split bilirubin

TOO SICK

Poor feeding, lethargy, temp instability

think sepsis / ABE

TOO DARK

Conjugated: pale stool, dark urine

biliary obstruction

Mnemonic to keep for life: **Too EARLY · Too HIGH · Too FAST · Too LONG · Too SICK · Too DARK.** Any one “Too” = investigate, don’t reassure.

Rate-of-rise thresholds per CPS 2025. Prolonged-jaundice cut-offs per NICE CG98.

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

A FRAMEWORK YOU CAN'T FORGET

Causes of unconjugated jaundice = the 3 mechanisms

OVERPRODUCTION

"make more"

- Immune haemolysis: ABO, Rh, other

G6PD deficiency, spherocytosis

Cephalohaematoma, bruising

Polycythaemia, sepsis

↓ CONJUGATION

"clear less"

- Prematurity (immature UGT1A1)

Gilbert syndrome

Crigler–Najjar I & II

Hypothyroidism

↑ ENTEROHEPATIC

"recycle more"

- Breast-milk jaundice

Breastfeeding (suboptimal intake)

Bowel obstruction / ileus

Delayed meconium passage

THE OVERPRODUCTION THAT'S DANGEROUS

Haemolytic disease & G6PD — the early, fast risers

ABO incompatibility

- Mother O, baby A or B

Common, usually milder

DAT often weakly positive

1st pregnancy affected

Rh (D) disease

- Mother Rh−, baby Rh+

Severe; worsens each pregnancy

Prevented by anti-D

DAT strongly positive

G6PD deficiency

- X-linked; boys > girls

High in Jordan / Mediterranean

Triggers: fava beans, infection, naphthalene, some drugs

Can be severe in a WELL term baby

Work-up when haemolysis is suspected: blood group + DAT (Coombs), CBC + reticulocytes + blood film, G6PD assay. **In Jordan, screen/consider G6PD in any severe or early jaundice — even a term, well-appearing baby.**

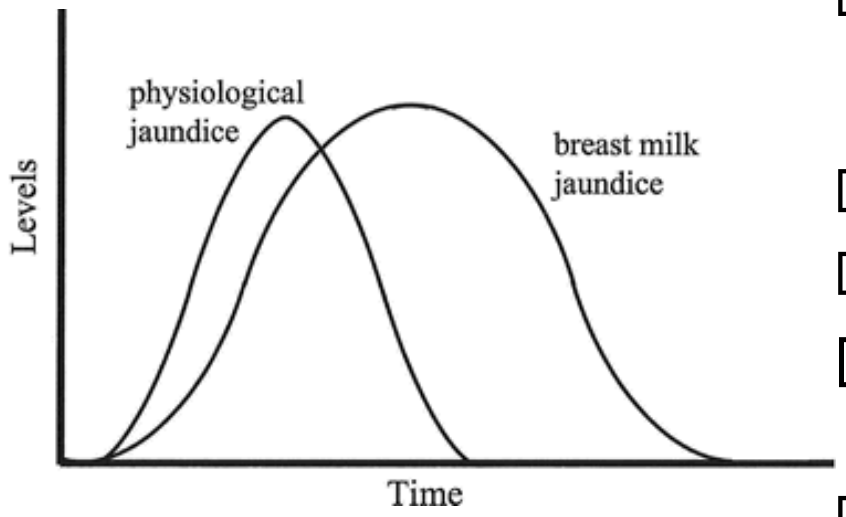
AAP 2022 & CPS 2025: DAT/blood group where maternal antibody screen positive/unknown; G6PD is a neurotoxicity risk factor.

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

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

THE CLASSIC DISTINCTION

Breastfeeding jaundice vs breast-milk jaundice

BREASTFEEDING JAUNDICE

"not enough milk" — a feeding problem

- **Early: days 2–4**

Suboptimal intake → dehydration, weight loss

↑ enterohepatic reabsorption

Fix the FEEDING: support latch, more frequent feeds, lactation help

BREAST-MILK JAUNDICE

milk itself — a well, thriving baby

- **Late: starts day 5–7, can persist 3–12 weeks**

Baby feeding well, gaining weight, thriving

- ❖ Factors in milk
- ❖ ↑ enterohepatic reabsorption
- ❖ Genetic

Do NOT stop breastfeeding — reassure & monitor; exclude other causes if prolonged

Memory hook: BreastFEEDING = too little milk (EARLY). Breast-MILK = the milk itself (LATE & lasting). Breastfeeding is protective overall — support it.

How to assess of neonate at risk of sever hyperbilirubinemia ?

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

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.**

Risk factors: developing it vs brain injury from it

RISK OF SIGNIFICANT HYPERBILIRUBINEMIA

- Lower gestational age (< 38 weeks)

Jaundice in the first 24 h

Predischarge bilirubin near threshold

Haemolysis (ABO/Rh/G6PD), positive DAT

Exclusive/suboptimal breastfeeding, weight loss

Cephalohaematoma / significant bruising

Sibling who needed phototherapy

East-Asian ancestry; maternal diabetes

NEUROTOXICITY RISK FACTORS

- Gestational age < 38 weeks

Albumin < 3.0 g/dL

Isoimmune haemolytic disease (positive DAT)

G6PD deficiency / other haemolysis

Sepsis

Clinical instability in the previous 24 h

These LOWER the treatment thresholds

Neurotoxicity risk factors per AAP 2022 & CPS 2025 — they shift the baby to the lower (risk-factor) threshold curve.

Always do Risk factor

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
Examples: (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.

BEDSIDE ASSESSMENT

Look, but don’t trust your eyes — measure

KRAMER ZONES — cephalocaudal progression

1	Face & neck	~ 5–6 mg/dL
2	Upper trunk	~ 8–10
3	Lower trunk & thighs	~ 12–14
4	Arms & legs	~ 15–18
5	Palms & soles	> 15–20

RULES OF ASSESSMENT

Visual estimation is unreliable
— worse in darker skin & bright light. Never grade severity by eye alone.

Blanch the skin
in good daylight to reveal the underlying colour.

Measure TcB or TSB
in every visibly jaundiced baby; urgently (< 2 h) if jaundiced in the first 24 h.

Plot on hour-specific curves
by gestational age & risk factors — a bare number means nothing.

TcB confirmed with TSB if within 50 µmol/L of threshold or TcB > 250 µmol/L (CPS 2025). Kramer values approximate.

Monitoring

After Birth

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

→ During their Vital signs monitoring

DISCHARGE CRITERIA & PARENTAL EDUCATION

AAP Recommendations | Every Box Must Be Checked Before Safe Discharge

Clinical Discharge Criteria

- ✓ GA ≥ 38 weeks (or extended monitoring if < 38 wks)
- ✓ Vital signs stable ≥ 12 hrs: HR 100–160 · RR < 60 · Temp 36.5–37.5°C
- ✓ Passed at least ONE urine AND ONE stool
- ✓ Two successful breastfeeds or bottle feeds observed
- ✓ Bilirubin risk assessed + plotted on Bhutani nomogram
- ✓ All mandatory screens completed (CCHD · Hearing · Metabolic · Sepsis risk)
- ✓ Hepatitis B vaccine administered (or documented plan)
- ✓ Mother stable + adequate home support confirmed

Parental Education Checklist

- ☑ Signs of illness: fever ≥ 38°C · lethargy · poor feeding · jaundice
- ☑ Safe sleep (ABCs: Alone · Back · Crib firm & flat)
- ☑ Normal voiding & stooling patterns
- ☑ Breastfeeding: latch · frequency · expressing
- ☑ Cord care · bathing instructions · nail care
- ☑ No smoking in home or car
- ☑ Car seat inspection & correct installation
- ☑ When and where to seek urgent help
- ☑ Immunisation schedule (HepB series · vaccines at 2 months)

Minimum Stay: ≥ 24 hrs (WHO · vaginal) | ≥ 48 hrs preferred (AAP) | ≥ 96 hrs (C/S) | Discharge mother + baby TOGETHER

Post-Discharge Follow-Up & Readmission

AAP Periodicity Schedule 2024

- **FOLLOW-UP TIMING:**
  - **Discharged < 48 hours → MUST be evaluated within 48–72 hours after discharge**
  - **Discharged ≥ 48 hours → Should be evaluated within 3–5 days of discharge**
- **Goals of first outpatient visit:**
  - Weight check (confirm ≤ 7–10% loss; ideally regaining)
  - Feeding assessment (latch, frequency, output)
  - Jaundice evaluation (serum bilirubin if clinically jaundiced)
  - Review all newborn screening results
  - Complete parental education, address concerns
- **READMISSION — rates and causes:**
  - ~1–2% of healthy newborns are readmitted within 30 days
  - **#1 cause: Hyperbilirubinaemia / jaundice**
  - #2 cause: Feeding difficulties / excessive weight loss

< 48 hrs	≥ 48 hrs	1–2%	Jaundice
Follow-up: 48–72 hrs	Follow-up: 3–5 days	Re-admission Rate	#1 Cause

TARGETED WORK-UP

Investigations — driven by the clinical picture

ALWAYS / FIRST-LINE

- Total AND direct serum bilirubin

Blood group (mother & baby) + DAT

CBC, reticulocytes, blood film

Packed cell volume

IF HAEMOLYSIS / EARLY

- G6PD assay (essential in our region)

Repeat TSB to define rate of rise

Albumin if severe / near exchange

Sepsis screen if unwell

IF PROLONGED (>2–3 wk)

- Split bilirubin (conjugated?)

Thyroid function (TSH, T4)

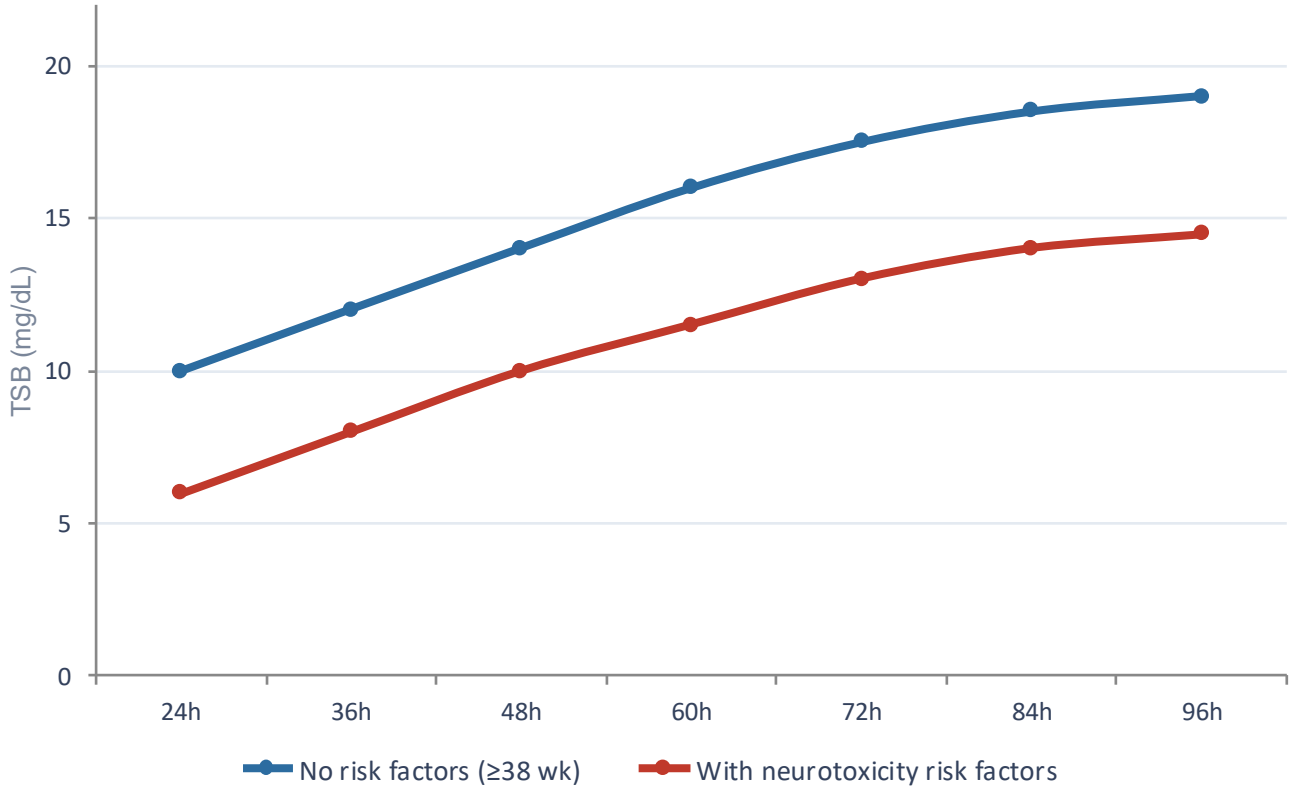
Urine culture / reducing substances

Stool colour, LFTs → liver referral

AAP 2022: measure direct bilirubin in any breastfed infant jaundiced at 3–4 wk / formula-fed at 2 wk. NICE: conjugated >25 µmol/L → liver work-up.

THE MODERN PARADIGM

Universal screening + hour-specific, risk-adjusted thresholds



Schematic — always use the official AAP/CPS/NICE curves for real decisions

Screen everyone

Pre-discharge TcB/TSB at ≥12 h of age, for every newborn

Plot by the hour

Thresholds rise with age in hours — not a single cut-off

Two curves

Risk factors present → use the LOWER threshold line

TSB decides

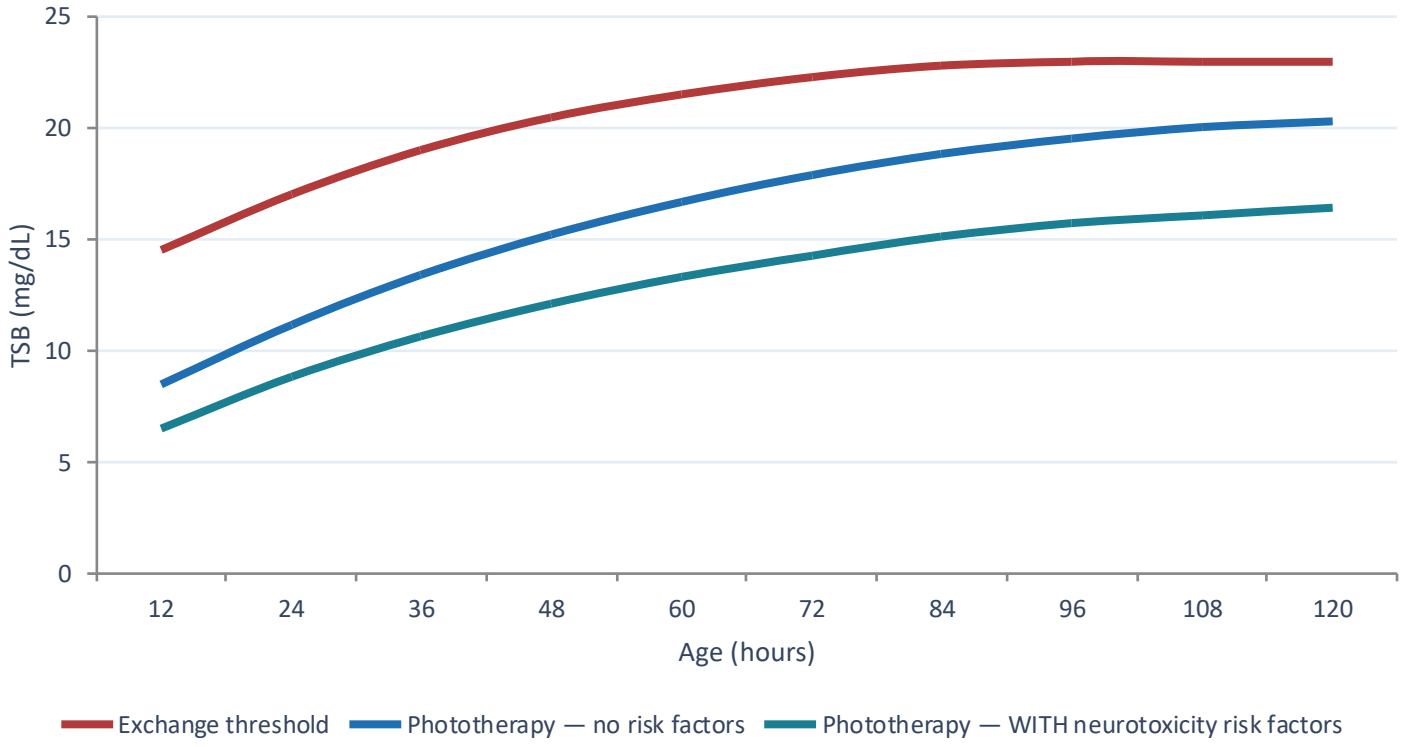
Transcutaneous screens; serum bilirubin treats

PART II

Management

Feed & follow → Phototherapy → Escalate → Exchange

Universal screening + hour-specific thresholds



SCHEMATIC — shape only. Always use the actual AAP 2022 gestational-age-specific curves.

THE THREE INPUTS

1. **Age in HOURS**
2. **Gestational age in WEEKS**
3. **Neurotoxicity risk factors?**

These three give you the threshold. A bilirubin without

SCREENING RULES

- Universal predischarge TcB/TSB for every baby
- Measure a TSB if TcB is within 3.0 mg/dL of threshold, or TcB > 15 mg/dL
- Nobody goes home without a plan

AAP 2022 thresholds as presented in Avery's Ch. 72 (Figs 72.9, 72.11, 72.12).

FIRST-LINE TREATMENT

Phototherapy — how it works & how to do it right

HOW IT WORKS

Blue-green light (~460–490 nm)
converts skin bilirubin into water-soluble photoproducts.

Photoisomerisation → lumirubin
excreted in bile & urine WITHOUT needing conjugation.

Not ultraviolet
— and sunlight is NOT a safe substitute.

Effectiveness ↑ with: shorter wavelength, higher irradiance (intensive ≥ 30 µW/cm²/nm), more skin exposed.

DOING IT WELL

Maximise skin
Nappy only; use intensive/double if needed

Protect the eyes
Opaque eye shields on

Keep feeding
Continue breastfeeding & skin-to-skin; no water/dextrose

Hydration & temp
Monitor weight, output, temperature

Re-check TSB
Within ~12 h; guide by trend vs threshold

AAP 2022 strong recommendation: do NOT give oral water or dextrose to lower bilirubin. Feeding at breast may continue during phototherapy (CPS 2025).

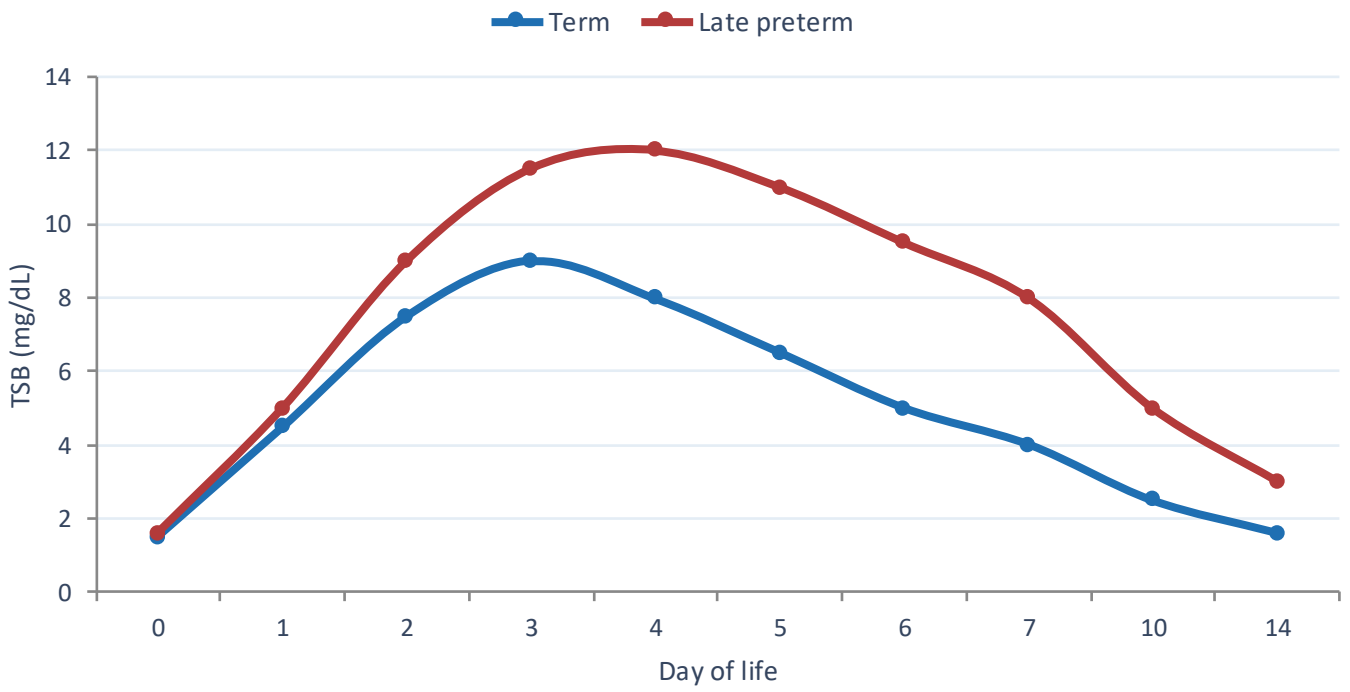
PUT IT TOGETHER

The management plan — a stepwise algorithm

1	**ASSESS & MEASURE**	Every jaundiced baby: history, exam, TcB/TSB. Urgent (<2 h) if jaundiced < 24 h old.
2	**SPLIT & PLOT**	Total + direct bilirubin. Plot TSB on hour/GA/risk-adjusted curve. Direct high → liver work-up.
3	**DECIDE THE RUNG**	Below photo <2mg/dl → optimise feeding + timed follow-up. Approaching → repeat. At threshold → phototherapy.
4	**ESCALATE / EXCHANGE**	In pre-exchange zone → intensive PT, IVF, IVIG, 2-hourly TSB. ABE or ≥ exchange crtetria → exchange.

Always attach a follow-up plan. Early discharge without a timed bilirubin check is how severe jaundice is missed.

Physiologic jaundice — a curve, not a number



Schematic time-course — peaks later and higher in the late preterm, and takes longer to fall

PHYSIOLOGIC — ALL FOUR MUST HOLD

- Appears AFTER 24 hours of age
- Peaks day 3–5 (term), day 4–7 (preterm)
- Resolves by 2 wk (term) / 3 wk (preterm)
- Baby is WELL: feeding, gaining, alert

IF ANY ONE FAILS → PATHOLOGIC

"Physiologic" is a diagnosis of exclusion you may only make in a well baby with a normal trajectory. It is never a reason to skip a bilirubin level in a baby who looks unwell or jaundiced too early.

Curve is schematic (teaching aid) — use hour-specific AAP nomograms for decisions. Avery's Ch. 72.

Escalation of care & exchange transfusion

ESCALATION OF CARE

The pre-exchange safety zone

- **AAP: within 2 mg/dL · CPS: ≤ 1.82 mg/dL (below photo therapy level)**

Start Intensive phototherapy + IV hydration

STAT: TSB + direct, CBC, albumin, type & crossmatch

IVIG 500 mg/kg for isoimmune haemolysis

Repeat TSB every 2 h; transfer to higher care

Escalation-of-care & exchange thresholds per AAP 2022 / CPS 2025. IVIG for isoimmune disease per NICE CG98 & AAP.

NEW — THE NUMBER BEHIND THE NUMBER

ΔTSB: the rate of rise, not just the level

THE DEFINITION

$$\Delta TSB = \frac{TSB_2 - TSB_1}{\text{hours between them}}$$

Expressed in mg/dL per hour. Two timed levels — that is all it takes.

THE HAEMOLYSIS THRESHOLD (AAP 2022 / Avery's Box 72.3)

First 24 hours	**> 0.3 mg/dL / hour**
After 24 hours	**> 0.2 mg/dL / hour**

Exceeding these = suspect HAEMOLYSIS, whatever the absolute level.

WHY A SINGLE BILIRUBIN CAN LIE TO YOU

Two babies at 30 hours of age both have a TSB of 10 mg/dL — comfortably below their phototherapy threshold.

Baby A was 8 mg/dL at 20 hours → ΔTSB = 0.2 mg/dL/h → a physiologic climb. Recheck and follow up.

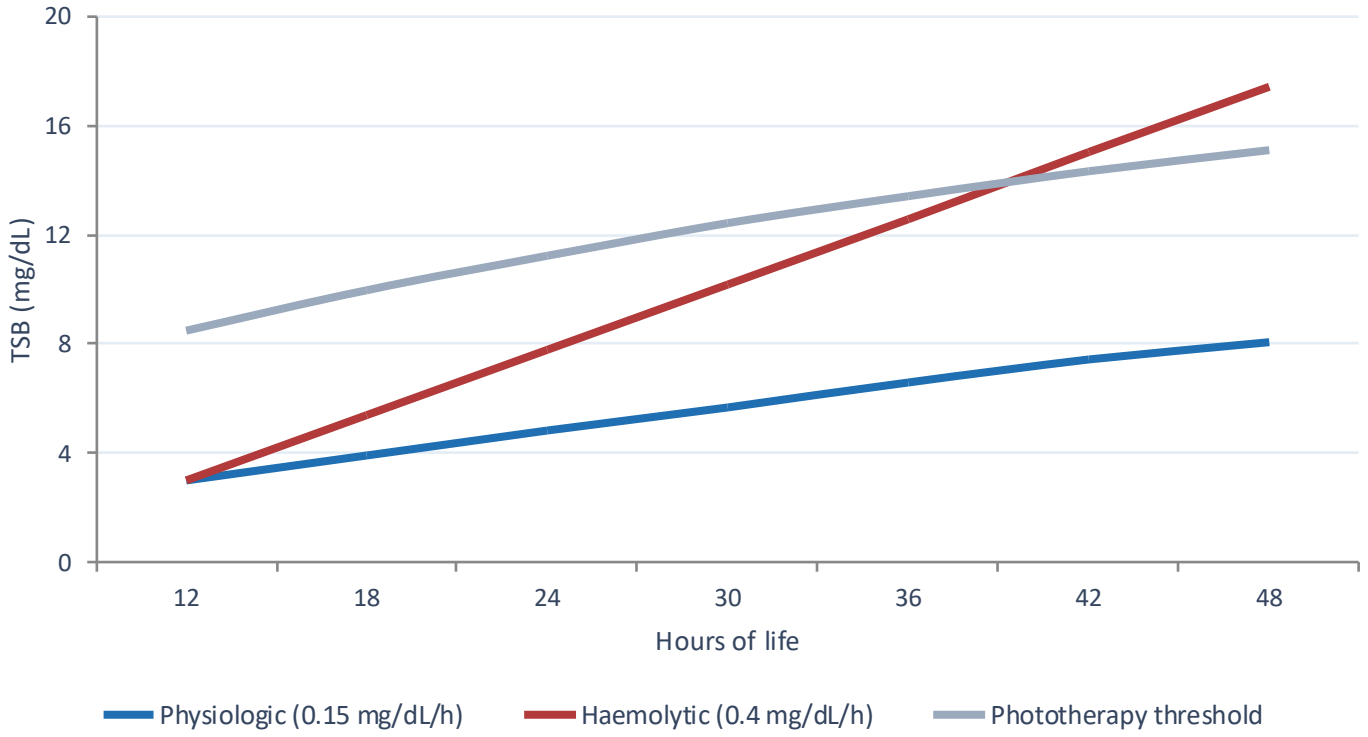
Baby B was 4 mg/dL at 20 hours → ΔTSB = 0.6 mg/dL/h → **haemolysis.** At this rate Baby B crosses the exchange threshold before morning.

Same number. Same hour. Completely different baby. The trajectory told you what the level could not.

Rate-of-rise thresholds: Box 72.3, Avery's Ch. 72 (adapted from AAP 2022).

NEW — PUTTING ΔTSB TO WORK

Using the trajectory at the bedside



The haemolytic baby CROSSES the threshold — the physiologic baby never does. Schematic.

HOW TO MEASURE IT PROPERLY

- Use two TSB values (not TcB) when the rate matters
- Record the exact CLOCK TIME of each sample
- Use the same laboratory / method
- ≥ 4–6 h apart, or sooner if unwell

IF ΔTSB IS HIGH — ACT

- Do NOT discharge
- Haemolysis screen: DAT, groups, FBC, retics, film, G6PD
- Start / intensify phototherapy
- Shorten the recheck interval — think in hours

Threshold line is illustrative — always plot on the actual AAP hour-specific nomogram.

THE WORKHORSE

Phototherapy — how the light actually works

THE MECHANISM

Blue / blue-green light (≈460–490 nm) converts bilirubin in the SKIN into water-soluble **photoisomers** that can be excreted **without needing the liver at all**.

It bypasses the broken step (UGT1A1). That is why it works so fast: photoisomers reach ~10% of TSB within 15 minutes and 20–25% within 2 hours.

THE THREE DIALS OF EFFECTIVENESS

- SPECTRUM — blue/blue-green LEDs are best
- IRRADIANCE — rises steeply as you bring the light CLOSER
- SURFACE AREA — undress the baby; use a light source above and below

PRACTICAL RULES

- Eye protection on; nappy small; maximise exposed skin
- Feeding may continue — breastfeeding does NOT have to stop
- It need not be continuous: brief interruptions for feeds are fine
- Never give water or dextrose to 'flush out' bilirubin

SAFETY & CAVEATS

- Complications are exceptionally rare — do not withhold it
- BRONZE BABY SYNDROME if there is conjugated hyperbilirubinaemia
- A TSB that RISES despite phototherapy = significant haemolysis until proven otherwise

Avery's Ch. 72 — Phototherapy (Golden & Watchko).

Threshold – TSB: how it sets your follow-up

The AAP asks a second subtraction: how far BELOW the phototherapy threshold is this baby? The smaller the gap, the sooner they must be seen again.

THRESHOLD – TSB (mg/dL)	CONTEXT	WHAT YOU DO
0.1 – 1.9	Age < 24 h	Delay discharge. Consider phototherapy; measure TSB in 4–8 h.
0.1 – 1.9	Age > 24 h	Measure TSB in 4–24 h. Delay discharge / consider phototherapy / discharge only with very close follow-up.
2.0 – 3.4	Any age	TSB or TcB in 4–24 h.
3.5 – 5.4	Any age	TSB or TcB in 1–2 days.
5.5 – 6.9	Discharging < 72 h	Follow-up within 2 days; TcB/TSB by clinical judgement.
> 7.0	Discharging < 72 h	Follow-up within 3 days; TcB/TSB by clinical judgement.

Read it as a single sentence: the closer the bilirubin creeps to the line, the shorter the leash. A baby 1 mg/dL below threshold at 20 hours of age does not go home.

Adapted from Fig. 72.9, Avery's Ch. 72 (AAP 2022 discharge/follow-up algorithm).

Escalation of care & exchange transfusion

ESCALATION OF CARE

The pre-exchange safety zone

- **AAP: within 2 mg/dL · CPS: ≤ 1.82 mg/dL L**

  below photo therapy level

Intensive phototherapy + IV hydration

STAT: TSB + direct, CBC, albumin, type & crossmatch

IVIG 500 mg/kg for isoimmune haemolysis

Repeat TSB every 2 h; transfer to higher care

EXCHANGE TRANSFUSION

The last line — rare but life-saving

- **TSB at/above the exchange threshold, OR**

ANY sign of acute bilirubin encephalopathy — regardless of the number

Removes bilirubin & antibody-coated RBCs

Consider bilirubin/albumin ratio in the decision

Risks: catheter, electrolyte shifts, thrombocytopenia — do it in a unit ready for it

Escalation-of-care & exchange thresholds per AAP 2022 / CPS 2025. IVIG for isoimmune disease per NICE CG98 & AAP.

⚑ RED FLAGS ⚑

Jaundice < 24 h old

Assume haemolysis — measure now

Rapidly rising TSB

≥ 5 (µmol/L/h) early / ≥ 3.5 later

Near the exchange line

Escalate; prepare exchange

Signs of ABE

Lethargy, high-pitched cry, arching, poor feeding

Conjugated jaundice

Pale stools, dark urine → biliary atresia

Prolonged jaundice

> 14 d term / > 21 d preterm

Unwell / septic-looking

Temp instability, apnoea, poor tone

Excess weight loss

> 10% → feeding failure & dehydration

UNLEARN THESE

Common myths & pitfalls

MYTH **“I can grade it by eye.”**

FACT Visual estimation is unreliable — always measure & plot.

MYTH **“Put the baby in sunlight.”**

FACT Not reliable or safe; risks burn/dehydration. Use phototherapy.

MYTH **“Stop breastfeeding to fix jaundice.”**

FACT Rarely needed — support feeding; breast-milk jaundice in a well baby is benign.

MYTH **“Give water/dextrose to flush it.”**

FACT AAP: strongly NOT recommended — doesn’t lower bilirubin.

MYTH **“Term & well → can’t be dangerous.”**

FACT G6PD/ABO can cause severe jaundice in a well term baby.

MYTH **“Discharged early = done.”**

FACT No follow-up bilirubin is the classic path to kernicterus.

START WITH A BABY, NOT A NUMBER

Meet Baby Zaid — Day 4 of life

THE STORY

- **Born at 36 weeks (late preterm)**

Exclusively breastfed; latch still being established

Lost 12 % of birth weight

Discharged home at 30 hours of age

Day 4: yellow to the chest, sleepy, feeding poorly

Mother: "Is this the normal newborn yellow… or something serious?"

PAUSE · THINK · PAIR · SHARE

1. What single question about timing would help you most?
2. Which features here worry you — and which reassure you?
3. What is the ONE test that decides everything?
4. Would you treat now, repeat later, or send home?

BACK TO WHERE WE STARTED

Resolving Baby Zaid with our algorithm

ASSESS	36 wk + exclusive breastfeeding + 9% weight loss + lethargy + early discharge = stacked risk. Measure TSB urgently.
PLOT	Plot TSB by hour on the risk-factor (lower) curve — GA <38 wk is itself a neurotoxicity risk factor.
DECIDE	Likely above the risk-adjusted threshold → start intensive phototherapy; correct feeding/hydration; send haemolysis screen incl. G6PD.
SAFETY-NET	Re-check TSB, watch for the pre-exchange zone & any ABE sign; arrange definite follow-up before discharge.

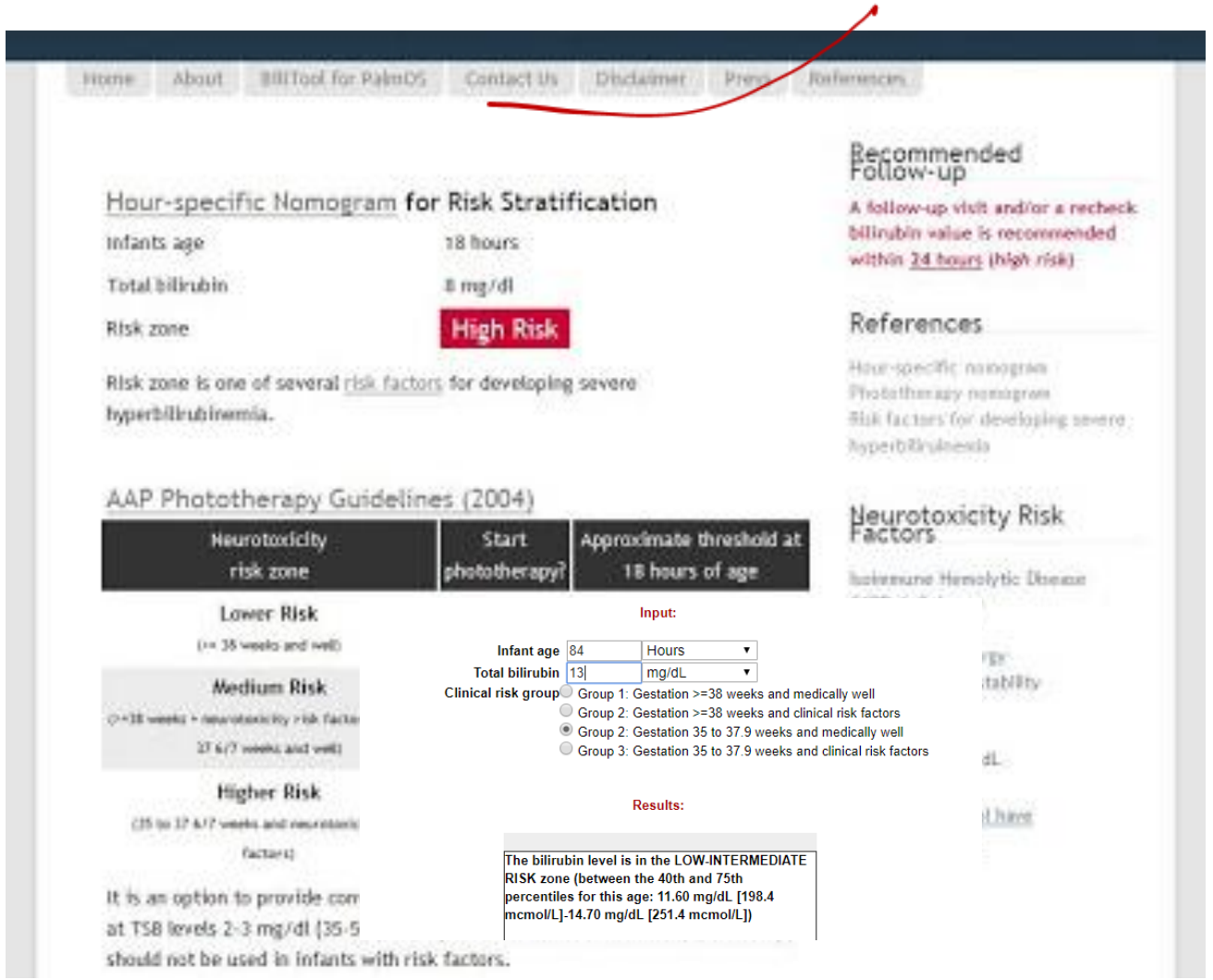
Outcome: treated early, bilirubin falls, breastfeeding continues with support, follow-up secured — kernicterus prevented. That is the whole point.

Useful tools

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**.

You can use Mobile Application to asses risk factors : AAP



A MNEMONIC THAT SAVES BABIES

Pathologic jaundice — “The 6 Toos”

TOO EARLY

Jaundice < 24 hours of age

Haemolysis until proven otherwise. Never physiologic.

TOO HIGH

TSB above the hour-specific threshold

Plot it. Do not eyeball it.

TOO FAST

Rise > 0.3 mg/dL/h (first 24 h)
or > 0.2 mg/dL/h thereafter

The ΔTSB — a haemolysis signature.

TOO LONG

> 2 wk term · > 3 wk preterm

Split the bilirubin. Think cholestasis, hypothyroidism.

TOO SICK

Lethargy, poor feeding, apnoea, temperature instability

Sepsis? Or is this already encephalopathy?

TOO DARK

Dark urine, pale stools

Conjugated. Biliary atresia until excluded.

“Too fast” thresholds from Box 72.3, Avery's Ch. 72 (adapted from AAP 2022).

A FRAMEWORK YOU CAN'T FORGET

Causes = increased load vs decreased clearance

A. INCREASED HEPATIC BILIRUBIN LOAD

Haemolytic — immune (DAT positive)

Rh isoimmunisation · ABO incompatibility · minor blood groups

Haemolytic — enzyme defects

G6PD deficiency · pyruvate kinase deficiency

Haemolytic — membrane defects

Hereditary spherocytosis · elliptocytosis · pyknocytosis

Haemolytic — haemoglobinopathies

α- and γ-thalassaemia

Non-haemolytic load

enterohepatic circulation

B. DECREASED HEPATIC CLEARANCE

Prematurity — including late preterm

The commonest cause of impaired conjugation you will meet

Hormonal

Hypothyroidism · hypopituitarism

Impaired uptake

SLCO1B1 polymorphisms · patent ductus venosus

Conjugation defects — UGT1A1 variants

Crigler–Najjar I (absent) · Crigler–Najjar II (Arias) · Gilbert (UGT1A1*28; UGT1A1*6 in Asians)

Breast-milk feeding · intestinal obstruction, ileus, meconium plug, cystic fibrosis

*Gene–environment interaction: UGT1A1*28 alone may do little — but combined with G6PD deficiency or spherocytosis it markedly increases the risk of SEVERE hyperbilirubinaemia.*

After Box 72.1, Avery's Ch. 72 (Golden & Watchko).

THE MOST DANGEROUS MECHANISM

Haemolysis — and G6PD deficiency in our region

IMMUNE (DAT positive)

- Rh: sensitised mother, severe, often anaemic
- ABO: mother O, baby A or B — commonest
- Minor groups: anti-c, anti-Kell (Kell → anaemia)

ENZYME / MEMBRANE

- G6PD deficiency — X-linked, affects males
- Pyruvate kinase deficiency
- Spherocytosis: ↑MCHC, family history, DAT negative

HOW TO SPOT IT

- Jaundice < 24 h
- ΔTSB > 0.3 mg/dL/h
- Anaemia + reticulocytosis
- Failure to respond to phototherapy

G6PD DEFICIENCY — WHY THIS SLIDE MATTERS MORE IN AMMAN THAN IN AMSTERDAM

Avery's names it directly: *"clinicians everywhere must have a high index of suspicion for G6PD deficiency in neonates whose genetic heritage derives from Africa, the Middle East, the Mediterranean region, and Asia."* It is a leading cause of bilirubin encephalopathy worldwide.

Clinical behaviour: often NO obvious anaemia and NO reticulocytosis. The classic pattern is a sudden, rapid, exponential rise in TSB — sometimes triggered (naphthalene/mothballs, henna, fava beans via breast milk, some drugs). Do not wait for a haemolytic picture to appear.

Avery's Ch. 72 — Key Points and G6PD section.

BACK TO WHERE WE STARTED

Resolving Baby Zaid with our ladder

ASSESS	36 wk + exclusive breastfeeding with poor intake + 9% weight loss + lethargy + early discharge with no predischarge bilirubin. Stacked risk. Measure TSB urgently.
MEASURE	Send TSB now — and a SECOND timed TSB to compute the ΔTSB. Split bilirubin. Mother is group O → send baby's group + DAT.
PLOT	Plot by hour of life on the LOWER curve — GA < 38 wk is itself a neurotoxicity risk factor.
TREAT	Above threshold → intensive phototherapy. Fix the feeding (milk, not water). Correct hydration.
INVESTIGATE	DAT, groups, FBC, retics, film — and G6PD. In Jordan, that assay is first-line, not an afterthought.
SAFETY-NET	Repeat TSB. Watch the ΔTSB and the gap to exchange. He is LETHARGIC — reassess for acute bilirubin encephalopathy now, and escalate if it is present.

Outcome: treated early, bilirubin falls, breastfeeding continues with proper support, follow-up secured — kernicterus prevented. Zaid's story only became a case report if somebody sent him home without a number.

AAP 2022 — early discharge without predischarge bilirubin explicitly not recommended.

Thank YOU

PART THREE

What do we know in Jordan?

Every study on this topic ever published from Jordan — and the questions nobody has answered yet.

THE JORDANIAN EVIDENCE — 1

G6PD deficiency: our single biggest problem

1.44%

G6PD prevalence in screened Jordanian newborns

Males 2.38% · Females 0.36%

≈ 7 : 1 male predominance (X-linked)

JUH · 11,128 newborns screened · 2016–2020

38.1%

of ALL exchange transfusions in northern Jordan were caused by G6PD deficiency (alone or with ABO)

The single commonest cause — ahead of ABO and Rh

Irbid · 336 neonates, 386 exchanges · 6 years

A LESSON IN EPIDEMIOLOGY

1996 cord-blood study (Irbid, n=181): G6PD in 12% of males.

2022 screening study (Amman, n=11,128): 2.38% of males.

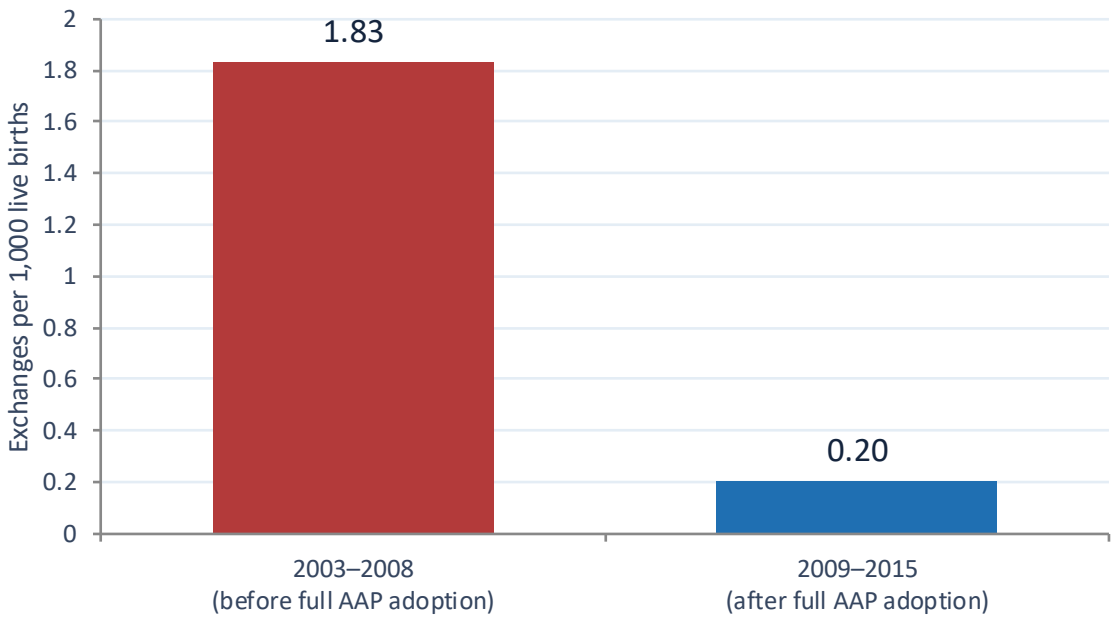
This is NOT a real fall. It reflects different assays, definitions and sampling. Ask this of every prevalence figure you read.

WHAT THIS MEANS FOR YOU ON THE WARD

G6PD deficiency is not a footnote in Jordan — it is the leading cause of exchange transfusion we have measured. **Jordan University Hospital screens every newborn for G6PD, and that programme significantly reduced pathological hyperbilirubinaemia and exchange transfusion in deficient babies.** Send the assay early. Counsel every family about triggers — naphthalene (mothballs), fava beans, henna, and certain drugs.

Al-Lawama M, …, Badran E, et al. JPNIM. 2022;11(1):e110120. · Abu-Ekteish F, et al. Ann Trop Paediatr. 2000;20(1):57–60. · Talafih K, et al. J Obstet Gynaecol Res. 1996;22(5):417–20.

Adopting the guideline changed outcomes — here



38 exchanges / 20,730 births → 7 exchanges / 35,041 births P < 0.0001

WHAT CHANGED AT JUH (end of 2008)

- Full adoption of the AAP threshold nomogram (replacing a fixed 20 mg/dL exchange level)
- 360° intensive phototherapy cradle (2009)
- Structured IVIG use for DAT-positive haemolytic disease

WHO WAS BEING EXCHANGED? (n = 45)

Non-haemolytic causes (26) OUTNUMBERED haemolytic (15).

Late prematurity alone = 9 cases (~20%). Sepsis 6. Dehydration 2.

Peak bilirubin > 20 mg/dL in 78%. Chronic neurological sequelae in 3 of 25 followed > 12 months (12%).

Al-Lawama M, Al-Rimawi E, Al-Shibi R, Badran E. J Blood Med. 2018;9:61–66. (Jordan University Hospital, 2003–2015.)

THE JORDANIAN EVIDENCE — 3

How we actually practise — and what drives jaundice here

THE PRACTICE GAP (northern Jordan, 416 infants ≥ 35 wk)

100% received phototherapy…

50% …but only half actually MET the AAP phototherapy threshold → over-treatment

~50% of infants who MET the exchange criterion never received one → under-treatment

We light up babies who don't need it — and fail to exchange babies who do.

RISK FACTORS IN JORDANIAN BABIES (case-control, n = 312)

ABO incompatibility — adjusted OR 3.59 (95% CI 1.35–9.58)

Fewer daily feeds (P < 0.001)

Prematurity < 37 weeks (P = 0.02)

Caesarean delivery · lower maternal education

Note: feeding METHOD (breast vs bottle) was not significant — feeding

THE BACKGROUND: CONSANGUINITY

About 35% of marriages in Jordan are consanguineous, and first-cousin marriage accounts for roughly 23% of all marriages. **This is the mechanistic backdrop to our burden of recessive and X-linked haemolytic disease** — G6PD deficiency, thalassaemia, membrane defects — and it is why a family history matters so much more here than in the textbooks you are reading.

Khassawneh M, et al. Res Rep Neonatol. 2013;3:27–31. · Karasneh R, Khader Y, et al. Br J Midwifery. 2024. · Islam MM. J Biosoc Sci. 2017 (consanguinity).

What Jordan still does not know

These are not rhetorical questions. Each one is an unpublished study waiting for somebody in this room.

NO national guideline

Jordan has no national clinical guideline and no Ministry of Health universal bilirubin-screening policy. Jordanian authors state plainly that national guidelines "do not exist" — clinicians rely on the AAP graphs.

NO readmission data

No Jordanian study of readmission for jaundice, or of early-discharge practice — despite early discharge being the classic route to severe hyperbilirubinaemia.

NO population incidence

We have no population-level incidence of neonatal jaundice in Jordan. Published figures (10.7% of NICU admissions; 20.9% of admissions in one northern series) are ADMISSION-based, not community rates.

NO local TcB nomogram

No published Jordanian validation of transcutaneous bilirubinometry or a local hour-specific nomogram, though JUH began universal predischarge TcB screening around 2016.

NO kernicterus rate

No Jordanian incidence of kernicterus or acute bilirubin encephalopathy has ever been published. The closest datapoint is 3 of 25 exchanged infants (12%) with chronic neurological sequelae at JUH.

NO genetic data

No Jordanian neonatal study has quantified the contribution of UGT1A1 (Gilbert) variants or hereditary spherocytosis — despite our consanguinity rate.

Meanwhile, practise as if the guideline existed: predischarge bilirubin on every baby · plot it by the hour · screen for G6PD · give every family a follow-up date.

Khassawneh M, et al. 2013; Karasneh R, Khader Y, et al. 2024; Al-Lawama & Badran, J Blood Med 2018. Gaps verified as of July 2026 — absence of a published study is not proof none exists.

IF YOU REMEMBER NOTHING ELSE

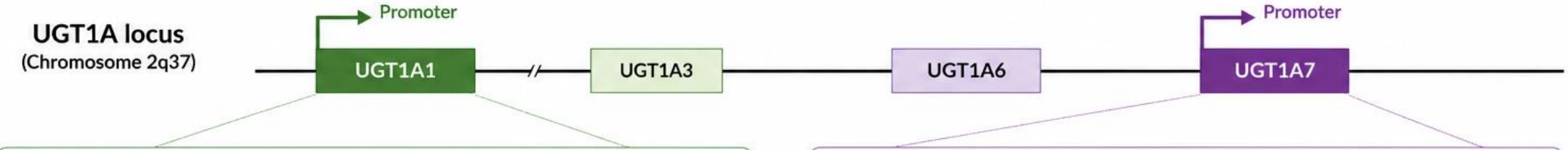
1. Jaundice is usually benign — but you must actively prove it, in every baby.
2. MAKE MORE · CLEAR LESS · RECYCLE MORE explains all of it.
3. A bilirubin without an AGE IN HOURS is uninterpretable.
4. The ΔTSB matters as much as the TSB. > 0.3 mg/dL/h in the first day = haemolysis.
5. Neurotoxicity risk factors LOWER the threshold. Prematurity counts twice.
6. No baby goes home without a bilirubin and a follow-up plan.

Kernicterus is not a disease of ignorance. It is a disease of missed follow-up.

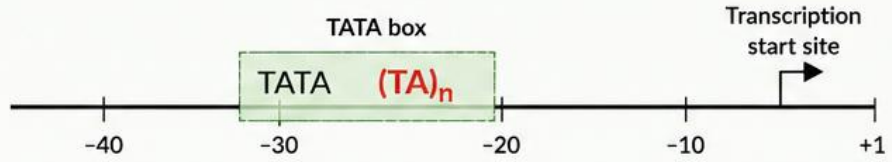
Case synthesis — AAP 2022 thresholds; G6PD priority per Al-Lawama, Badran et al., JPNIM 2022.

How TA Repeat Variation in the TATA Box Affects UGT1A1 and UGT1A7 Expression

The number of TA repeats in the TATA box of each gene's promoter affects how strongly the gene is transcribed.
More TA repeats → stronger promoter → higher gene expression.



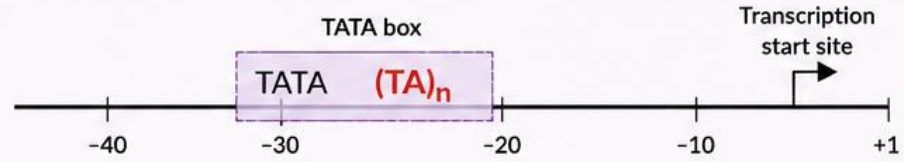
UGT1A1 Promoter – TATA Box $(TA)_n$



TA Repeats (n)	TATA Box Sequence (example)	Effect on UGT1A1 Promoter Activity (Expression)
6 TA repeats (normal)	TATA TATA TATA TATA TATA TATA TATA	Strong promoter High UGT1A1 expression (normal bilirubin conjugation)
5 TA repeats (–1 TA)	TATA TATA TATA TATA TATA TATA	Weaker promoter Reduced UGT1A1 expression (risk of hyperbilirubinemia)
7 TA repeats (+1 TA)	TATA TATA TATA TATA TATA TATA TATA TATA	Stronger promoter Higher UGT1A1 expression (increased activity)

Changes in the TA repeat number in the TATA box of UGT1A1 directly alter promoter strength and gene expression.

UGT1A7 Promoter – TATA Box $(TA)_n$



TA Repeats (n)	TATA Box Sequence (example)	Effect on UGT1A7 Promoter Activity (Expression)
6 TA repeats (normal)	TATA TATA TATA TATA TATA TATA TATA	Strong promoter High UGT1A7 expression (normal activity)
5 TA repeats (–1 TA)	TATA TATA TATA TATA TATA TATA	Weaker promoter Reduced UGT1A7 expression (lower activity)
7 TA repeats (+1 TA)	TATA TATA TATA TATA TATA TATA TATA TATA	Stronger promoter Higher UGT1A7 expression (increased activity)

Changes in the TA repeat number in the TATA box of UGT1A7 directly alter promoter strength and gene expression.

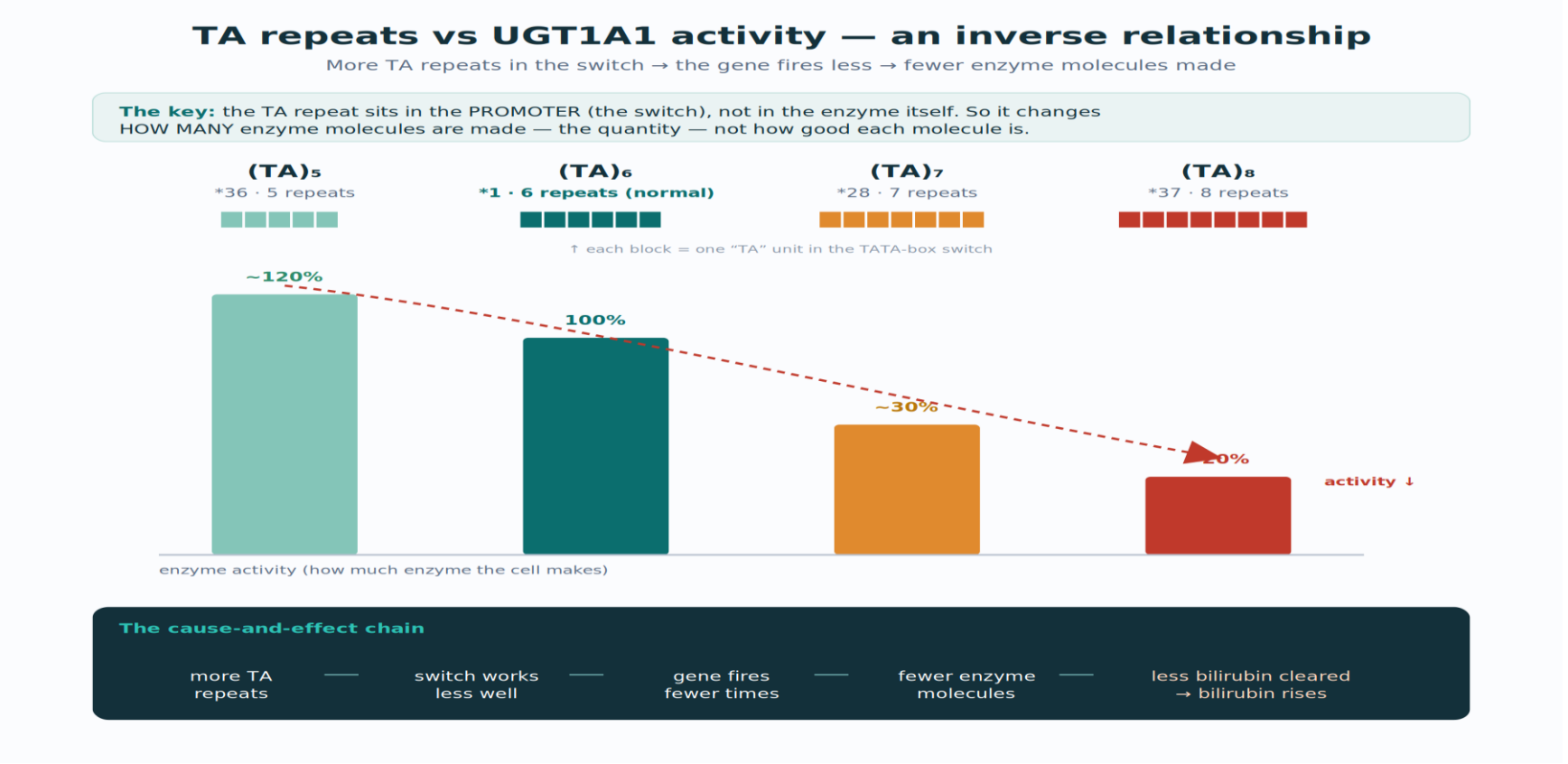
Key Point:
Although UGT1A1 and UGT1A7 are different genes in the same locus, variation in the TA repeat number within each gene's TATA box independently modulates their promoter strength and expression levels.

Legend
$(TA)_n$: Number of TA repeats
+1 : Transcription start site
– : Base pairs upstream (5')

THE KEY RELATIONSHIP

TA repeats vs UGT1A1 activity

The key: the TA repeat sits in the **promoter (the switch), not in the enzyme** — so it changes **how many enzyme molecules are made (quantity)**, not how good each one is.



Inverse relationship: more repeats → lower activity. $(TA)_5 > (TA)_6 > (TA)_7 > (TA)_8$

WHY & HOW

Why more repeats means less enzyme

Why the switch weakens

The TATA box is a **landing pad** where the transcription machinery docks before copying the gene. It has an **ideal size**. Every extra "TA" makes the pad the wrong length, so the machinery docks and fires less efficiently.

Quantity vs quality — two ways to end up with less working enzyme

*28 (TA repeat, in the promoter)

A **quantity** problem: the enzyme is **normal**, the cell just makes **fewer copies** of it. (Common in MENA & Europe.)

*6 (letter change, inside the exon)

A **quality** problem: a **faulty enzyme** is built — a swapped amino acid lowers each molecule's function. (Common in East Asia.)

Both roads end at "less working enzyme" — for opposite reasons.

HOW COMMON IS IT — WITH REFERENCES

UGT1A1 *28 (TA7) frequency across populations

Values = ***28 (TA7) allele frequency** — the share of chromosomes carrying the extra TA repeat. Middle East / North Africa in focus.

Population	Country	*28 (TA7)	Reference (author, year)
Jordanian-Arabs	Jordan	~30% *	*Abudahab et al., 2019*
Circassians	Jordan	~30% *	*Abudahab et al., 2019*
Chechens	Jordan	~30% *	*Abudahab et al., 2019*
Saudis	Saudi Arabia	25.7%	*Alkharfy et al., 2013*
Kuwaitis	Kuwait	~25% *†	*Gulf regional estimate (cf. Saudi)*
North Africans	Tunisia	~25–30% *†	*Regional (cf. Egypt, Premawardhena 2003)*
Egyptians	Egypt	26.0%	*Premawardhena et al., 2003*
Lebanese	Lebanon	35.7%	*Premawardhena et al., 2003*
Yemenites	Yemen	25.4%	*Premawardhena et al., 2003*
Europeans / USA	Europe · USA	38.7%	*Beutler et al., 1998*
African-Americans	USA	38.0%	*compiled in Alkharfy et al., 2013*
East Asians	Japan·Korea·China	13–16%	*compiled in Alkharfy et al., 2013*

** approximate. † no dedicated *28 cohort located — regional estimate. MENA values are broadly intermediate (~¼–⅓), similar to Europe and clearly above East Asia.*

EFFECT ON CANCER

Why UGT1A1 *28 matters in cancer

1 · Chemotherapy toxicity (the big one)

Irinotecan (colorectal & other cancers) is converted to **SN-38** — 100–1000× more potent. **UGT1A1 detoxifies SN-38.**

***28/*28 → ~70% less enzyme → SN-38 builds up → toxicity.**

50% **grade-4 neutropenia in *28/*28**
vs 12.5% carriers · 0% normal (irinotecan 350 mg/m²)

Also higher risk of severe diarrhea, hospitalization and dose delays.

Dosing guidance for *28/*28

FDA label: reduce starting dose by ≥1 level.
DPWG (NL): start at 70% of standard dose.
RNPGx (FR): high dose (≥240 mg/m²) contra-indicated.

2 · Cancer risk (a modifier — evidence mixed)

Besides drugs, UGT1A1 also clears **estrogens** and detoxifies dietary/environmental **carcinogens**. Lower activity may raise lifetime exposure.

- **Breast cancer —** studied as a risk modifier, especially in women with higher estrogen exposure; meta-analyses show a small, inconsistent effect.
- **Colorectal cancer —** explored for both risk and irinotecan response; the strong, proven link is the drug-toxicity one.
- **Other tumours —** reported for ovarian, lung and others — associations remain weak and unconfirmed.

Bottom line: the clinically actionable effect is irinotecan dosing, not a proven cancer-causing role.

Sources: FDA irinotecan label; DPWG 2014; RNPGx 2017; breast-cancer meta-analyses (Breast Cancer Res Treat).

International evidence base

- Golden WC, Watchko JF. Neonatal Hyperbilirubinemia and Kernicterus. In: Avery's Diseases of the Newborn. 11th ed. Elsevier; 2024: Ch. 72, pp. 1045–1066. [primary source for this lecture]
- Kemper AR, Newman TB, Slaughter JL, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics. 2022;150(3):e2022058859.
- Ng E, Altit G, Joynt C, Radziminski N, Narvey M; Canadian Paediatric Society, Fetus and Newborn Committee. Detection and management of hyperbilirubinemia in term and late preterm newborns (≥35 weeks). 2025.
- NICE. Jaundice in newborn babies under 28 days (CG98). London: NICE; 2010, amended 2023.
- Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics. 1999;103:6–14.
- Alangari A, et al. Epidemiology of Glucose-6-Phosphate Dehydrogenase Deficiency in Arab Countries: Insights from a Systematic Review. J Clin Med. 2023;12(20):6648. [regional context]

Unit conversion used throughout: mg/dL = µmol/L ÷ 17.1 (e.g. 425 µmol/L ≈ 25 mg/dL)

Evidence base

- Kemper AR, Newman TB, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics. 2022;150(3):e2022058859.

American Academy of Pediatrics. Technical Report & FAQ on the 2022 Hyperbilirubinemia Guideline. aap.org (accessed 2026).

Ng E, Altit G, Joynt C, Radziminski N, Narvey M; Canadian Paediatric Society, Fetus and Newborn Committee. Detection and management of hyperbilirubinemia in term and late preterm newborns (≥35 weeks). 2025. cps.ca.

NICE. Jaundice in newborn babies under 28 days (CG98). 2010, amended 2023. nice.org.uk/guidance/cg98.

Bhutani VK, et al. Predischarge hour-specific bilirubin nomogram for risk stratification. (Foundational screening evidence.)

Recent implementation studies (2024–2026) confirming the 2022 thresholds reduce phototherapy use without increasing readmission or kernicterus.

The Jordanian literature

- Al-Lawama M, Al-Rimawi E, Al-Shibi R, Badran E. Adoption of the AAP neonatal hyperbilirubinemia guidelines and its effect on blood exchange transfusion rate in a tertiary care center in Amman, Jordan. J Blood Med. 2018;9:61–66.
- Al-Lawama M, Ghanem N, Arabiat E, … Badran E, et al. Prevalence of glucose-6-phosphate dehydrogenase deficiency and the potential of neonatal complication prevention. J Pediatr Neonat Individ Med. 2022;11(1):e110120.
- Al-Lawama M, Badran E, Elrimawi A, et al. Intravenous immunoglobulins as adjunct treatment to phototherapy in isoimmune hemolytic disease of the newborn: a retrospective case-control study. J Clin Med Res. 2019;11(11):760–763.
- Abu-Ekteish F, Daoud A, Rimawi H, Kakish K, Abu-Heija A. Neonatal exchange transfusion: a Jordanian experience. Ann Trop Paediatr. 2000;20(1):57–60.
- Khassawneh M, Rubaie Z, Khashashneh I, Makhlouf F, Alkafajei A. Adherence with American Academy of Pediatrics guidelines when managing neonatal jaundice in Jordan. Res Rep Neonatol. 2013;3:27–31.
- Karasneh R, Khader Y, et al. Maternal and neonatal factors associated with neonatal jaundice in Jordan: a case-control study. Br J Midwifery. 2024.
- Talafih K, Hunaiti AA, Gharaibeh N, Gharaibeh M, Jaradat S. The prevalence of hemoglobin S and G6PD deficiency in Jordanian newborn. J Obstet Gynaecol Res. 1996;22(5):417–420.
- Islam MM. Consanguineous marriage in Jordan: an update. J Biosoc Sci. 2017.
- Batieha AM, Khader YS, … Badran EF, et al. Level, causes and risk factors of neonatal mortality in Jordan: results of a national prospective study. Matern Child Health J. 2016;20(5):1061–1071.

TO BE ADDED: *the recent "Beyond Yellow" paper — citation not yet verified. Please supply the DOI/reference and it will be inserted here and cited on the relevant slides.*

Self Study

Ophthalmologic Problem In neonates

Case based study

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

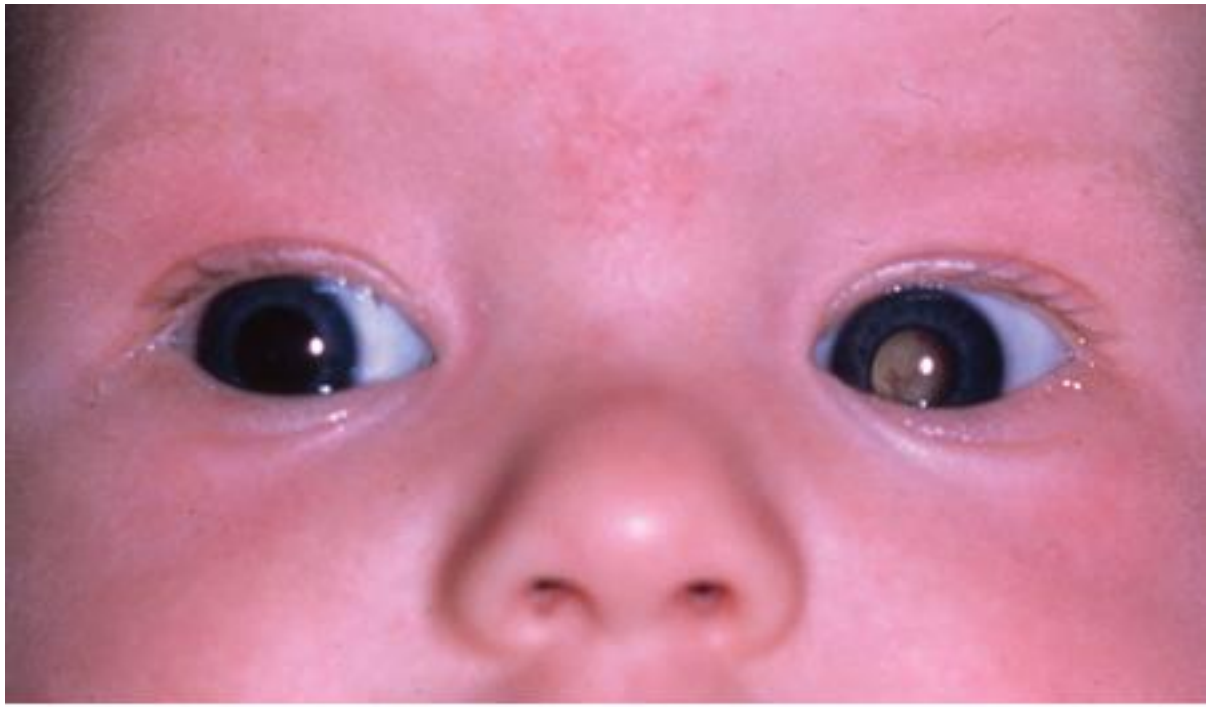
Learning Objectives

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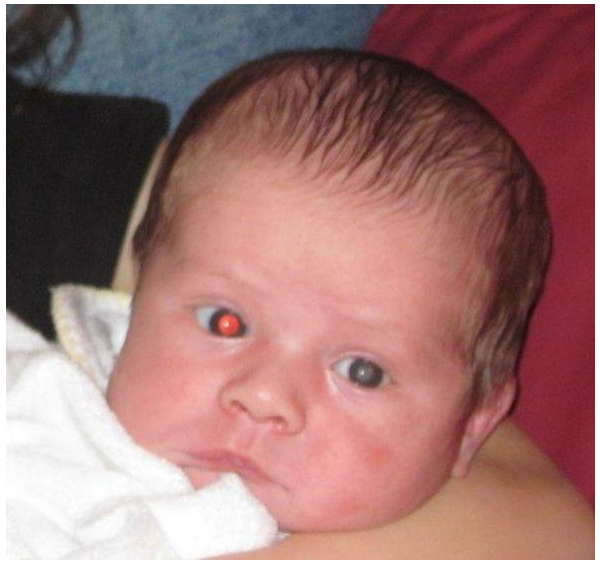
Source: Lueder GT: *Pediatric Practice Ophthalmology:*
www.accesspediatrics.com



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

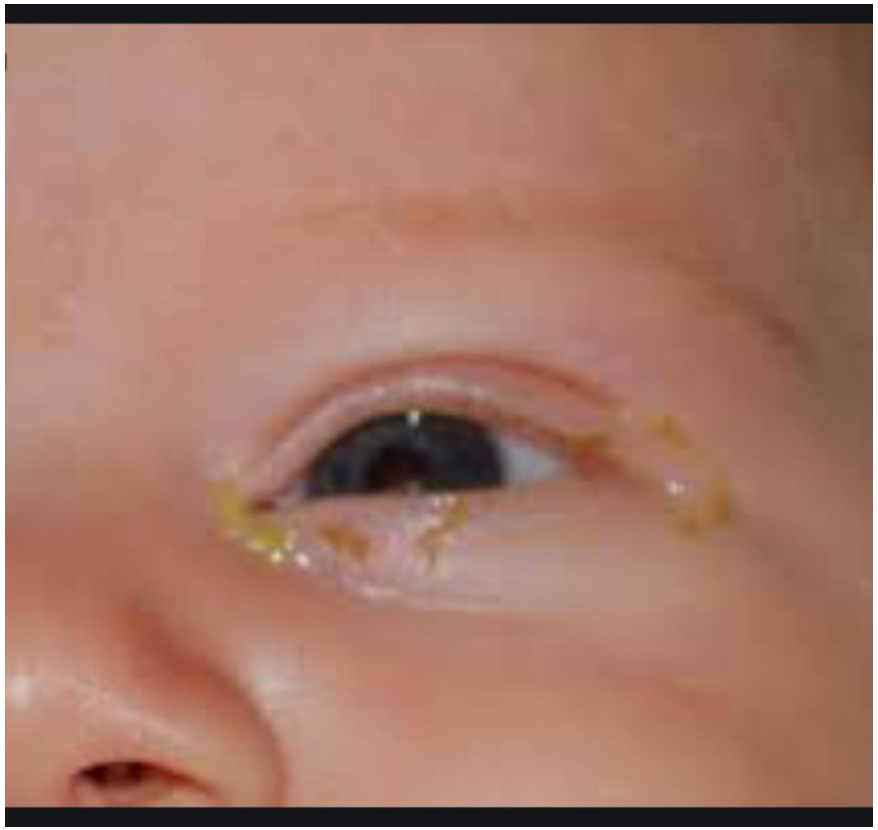
- Duration: 1 wk
- Type of discharge: Mucoid
- Uni/Bilateral: Unilateral
- Eye redness: NO
- Course: Constant

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

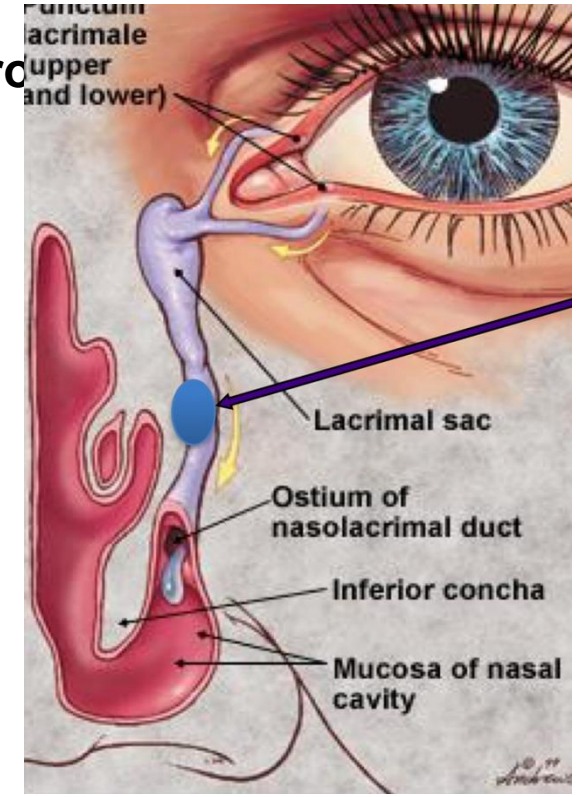


The parents would like to ask why is this pro

The pathogenesis of CNLDO :

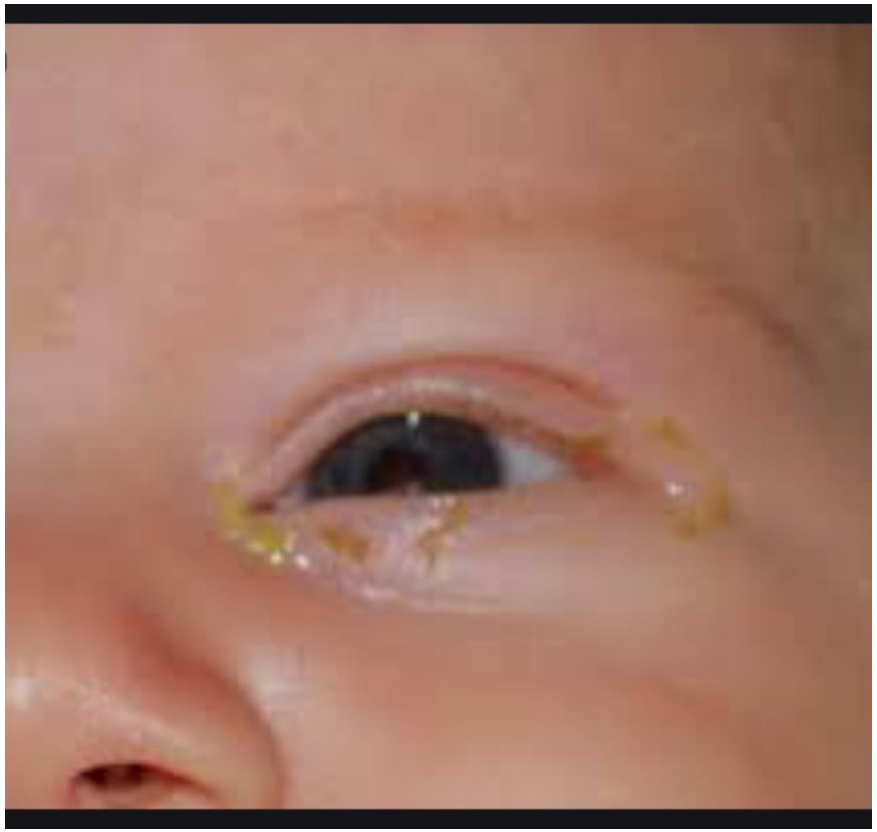
- lies in a mechanical obstruction

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

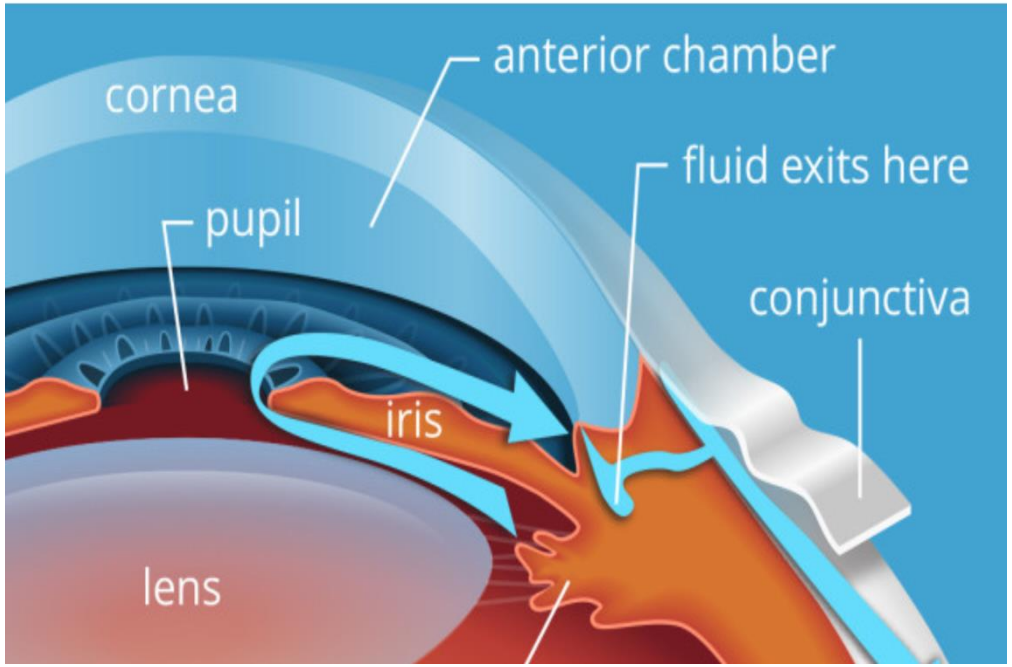
PRIMARY CONGENITAL GLAUCOMAS (PGG)

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

that prevent adequate drainage of aqueous humor,

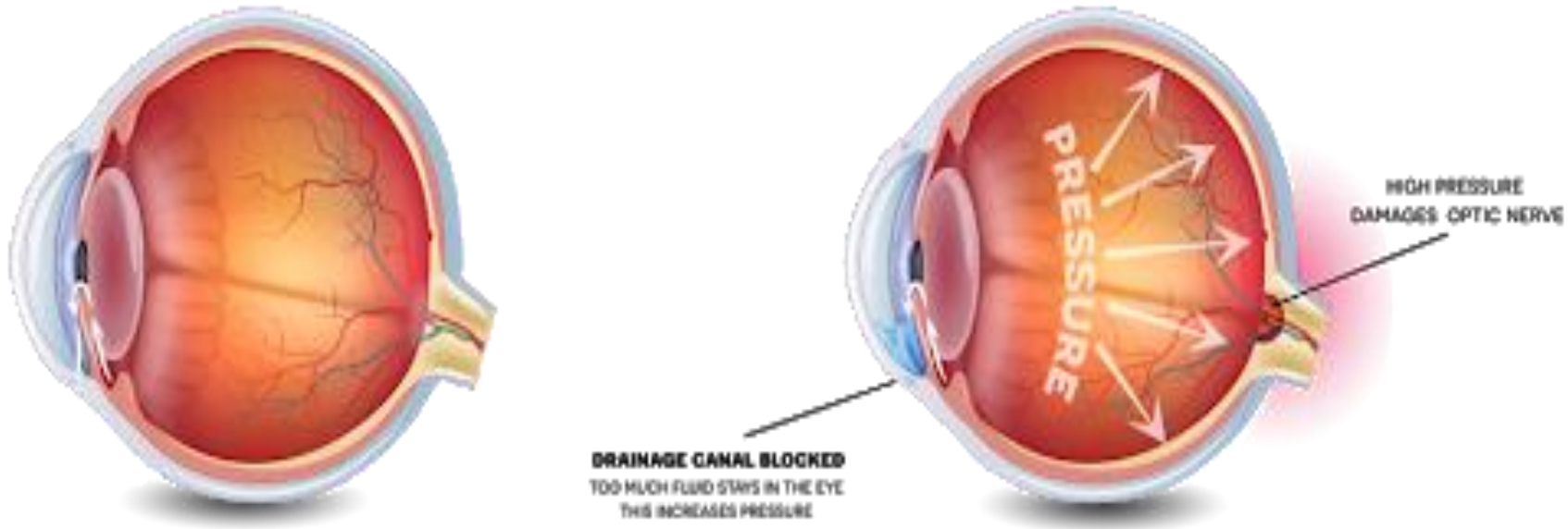
resulting in elevated intraocular pressure (IOP)

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



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

GLAUCOMA

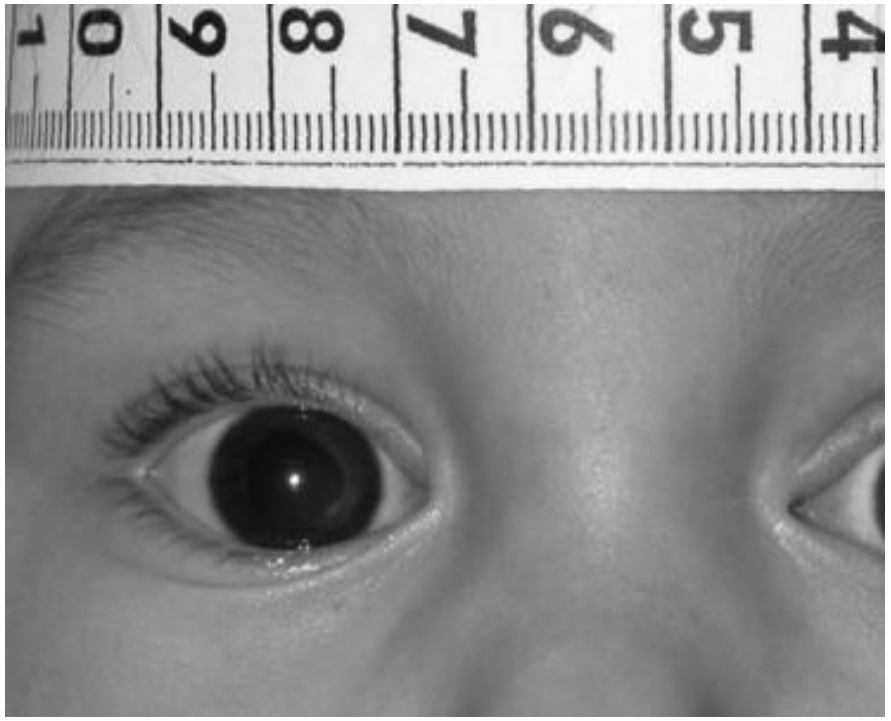


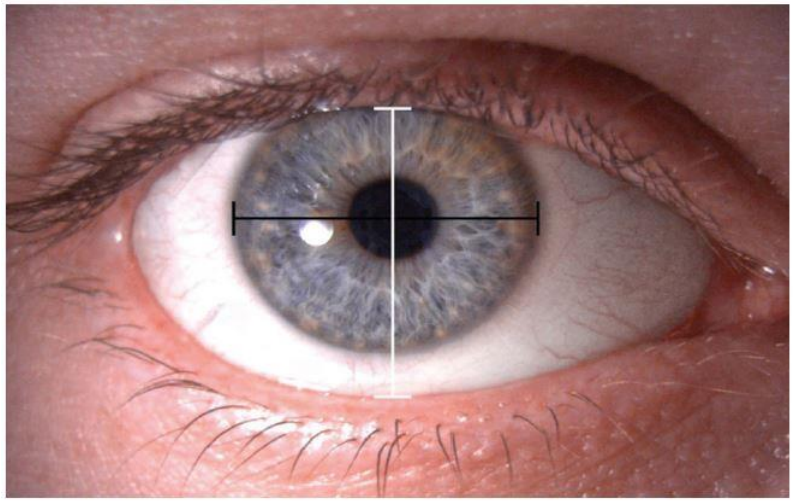
NORMAL EYE

GLAUCOMA

Symptoms of congenital glaucoma

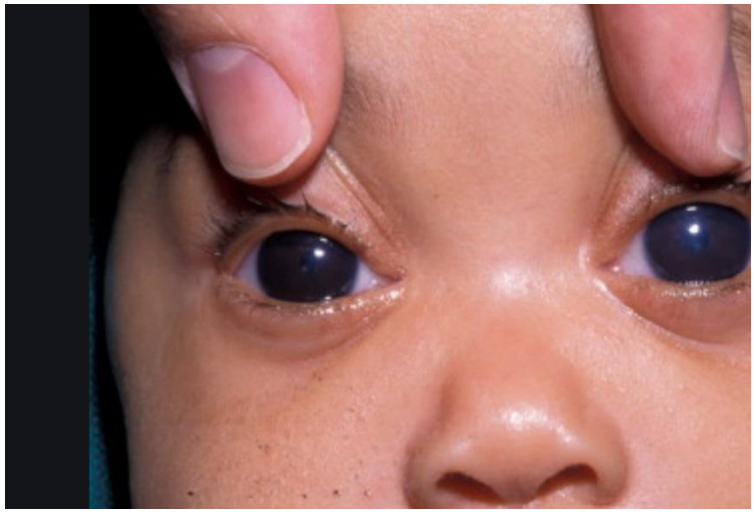
normal horizontal **corneal** diameter is 10.5 mm





Symptoms of congenital glaucoma

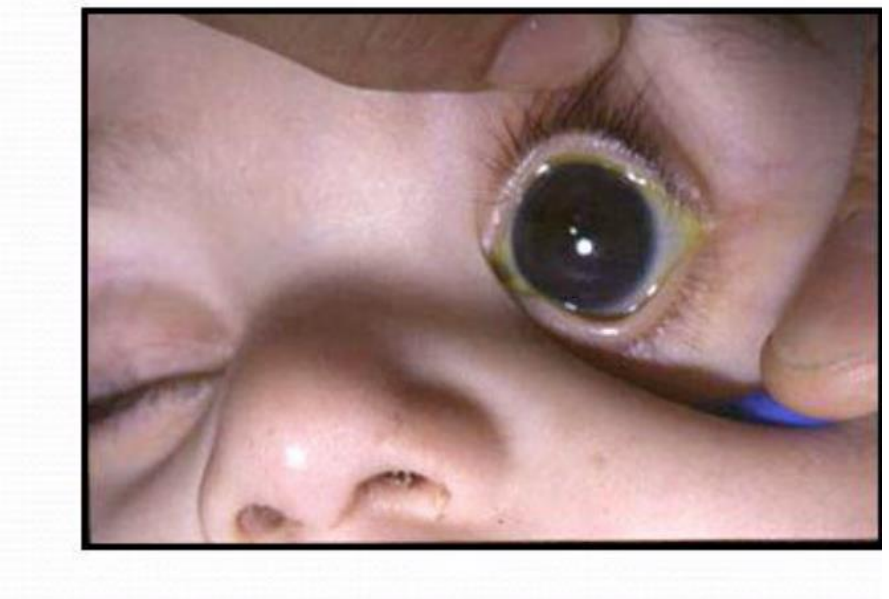
measurements greater than 12 mm are highly indicative of glaucoma.



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

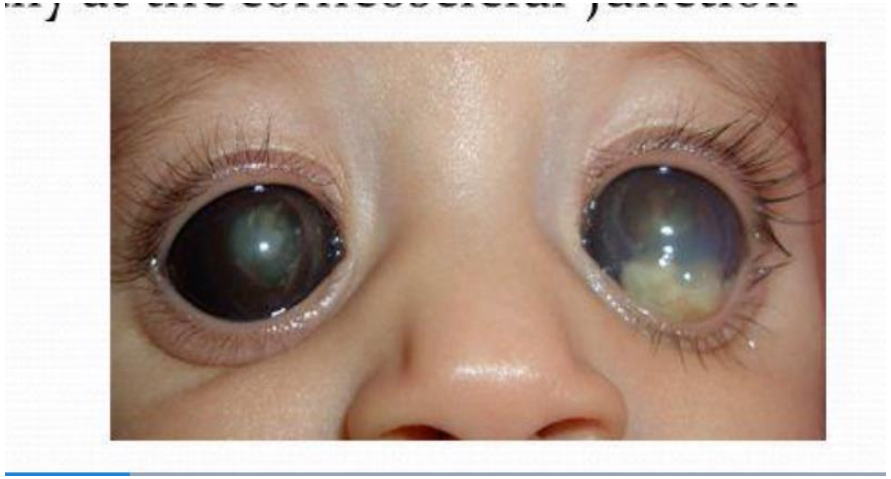
symptoms of congenital glaucoma

- 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)

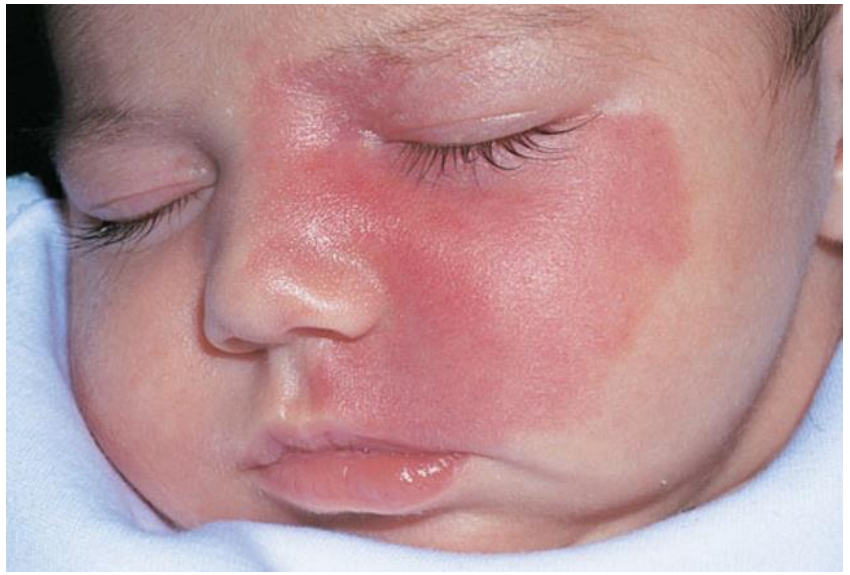
CAN BE :

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

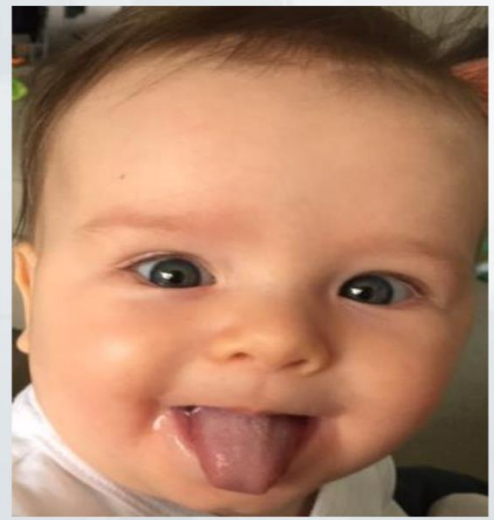
- During 2 weeks Neonatal visit
- Parents noticed that their baby has **squint**
  - They said it is (**intermittent** side ways)
- His history and **Physical exam is unremarkable**
- He was **healthy**
- **Red reflex** were **n**ormal and symmetrical corneal reflex

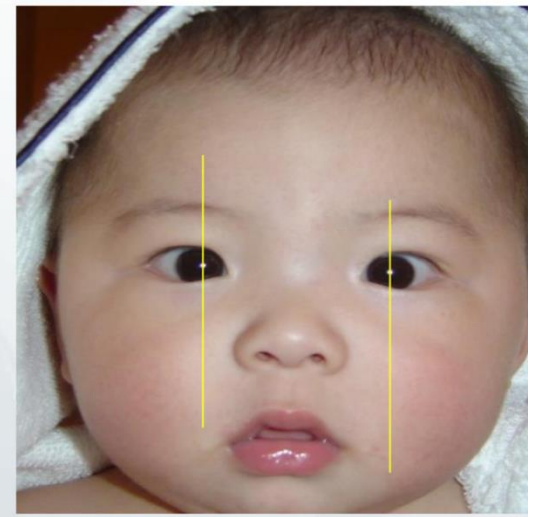
Strabismus – “squint that goes away”

Transient neonatal strabismus

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

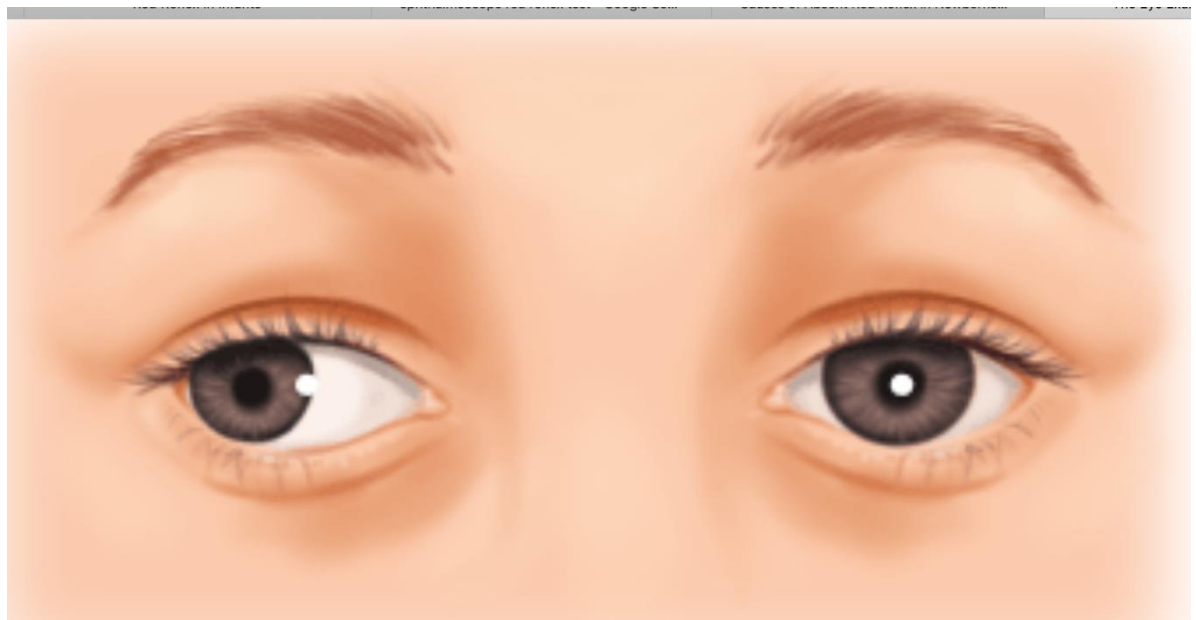
Pseudo-strabismus: Optical Illusion





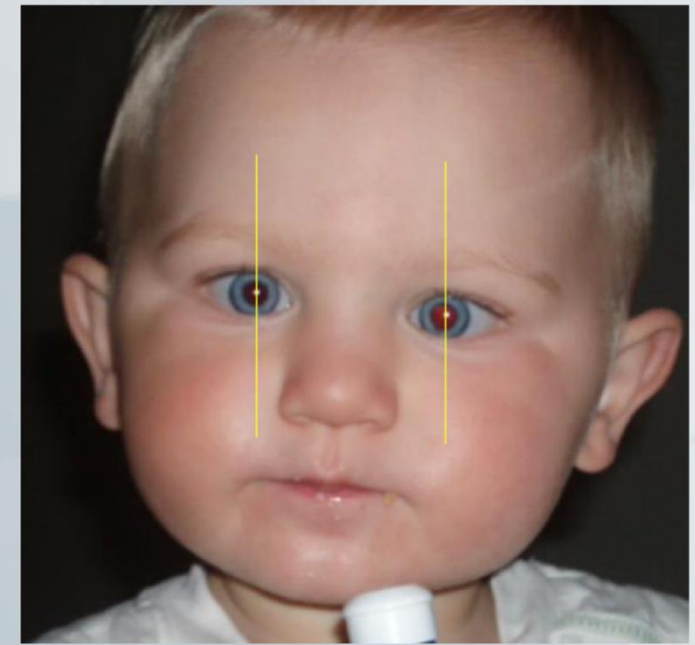
- Wide nasal fold/bridge of nose
- Intermittent – looking sideways
- “see both ears”
- Corneal light reflex - symmetry

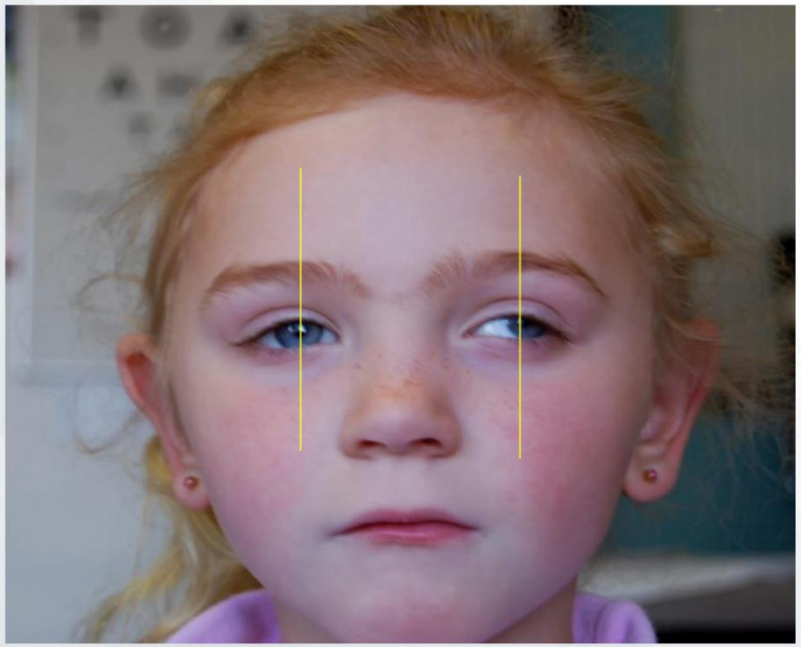
[1]Horwood A. 1993, JAAPOS; [2]Sondhi N. et al. 1988 JAAPOS



Asymmetrical pupillary reflex

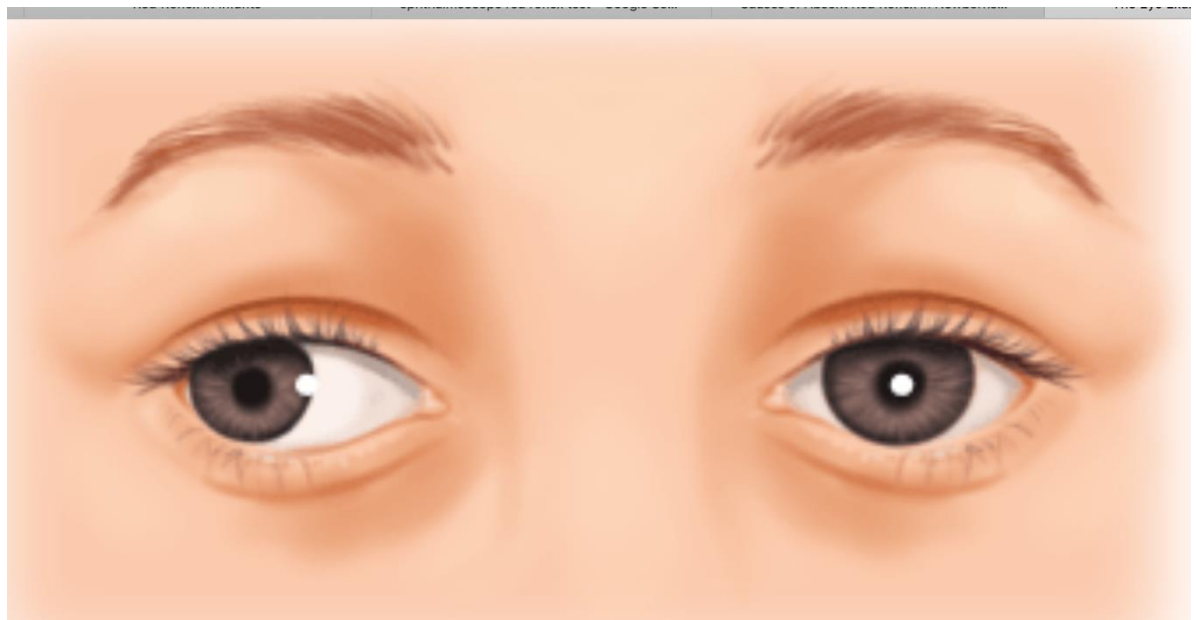
True strabismus – variable direction, size and frequency





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

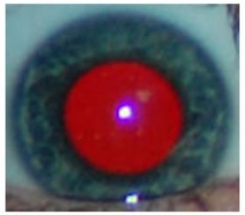
Why IT is important

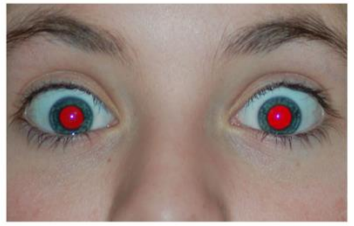
Red reflex

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

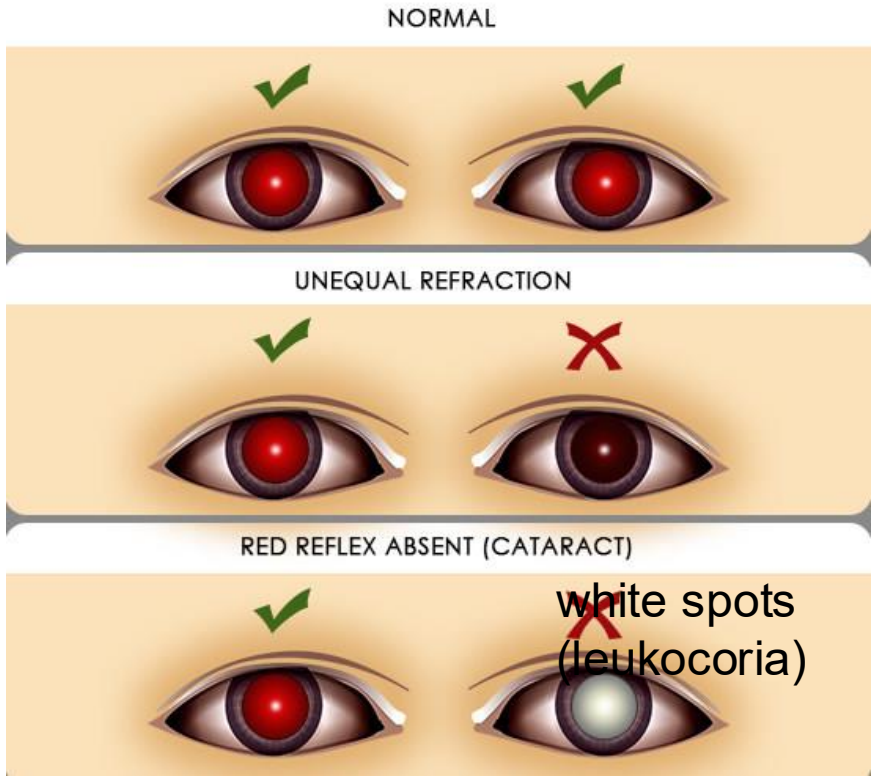




Red reflex should be equal in both eyes

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.

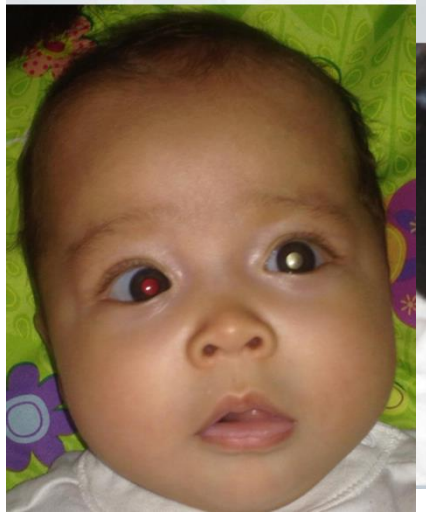
Interruption of Abnormal red reflex

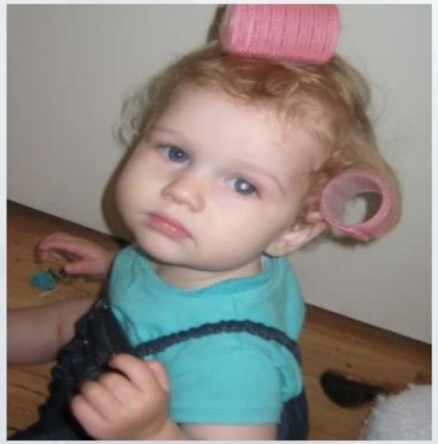


Leukocoria

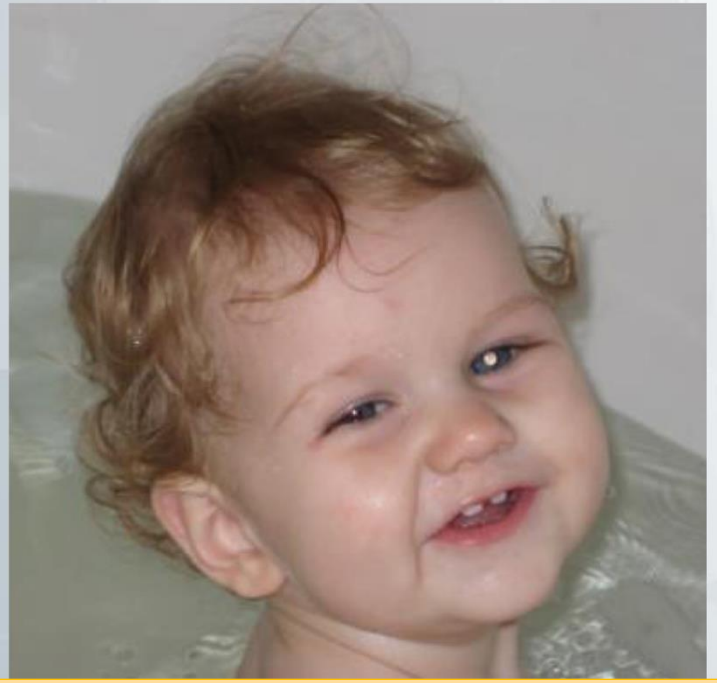
Strabismus may be early signs

"Leuko" – white
"Coria" – pupil



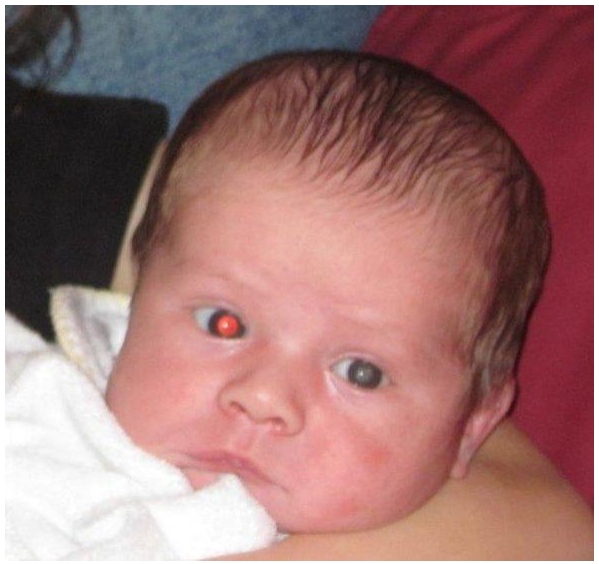


“Isn’t it just the camera flash?”



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

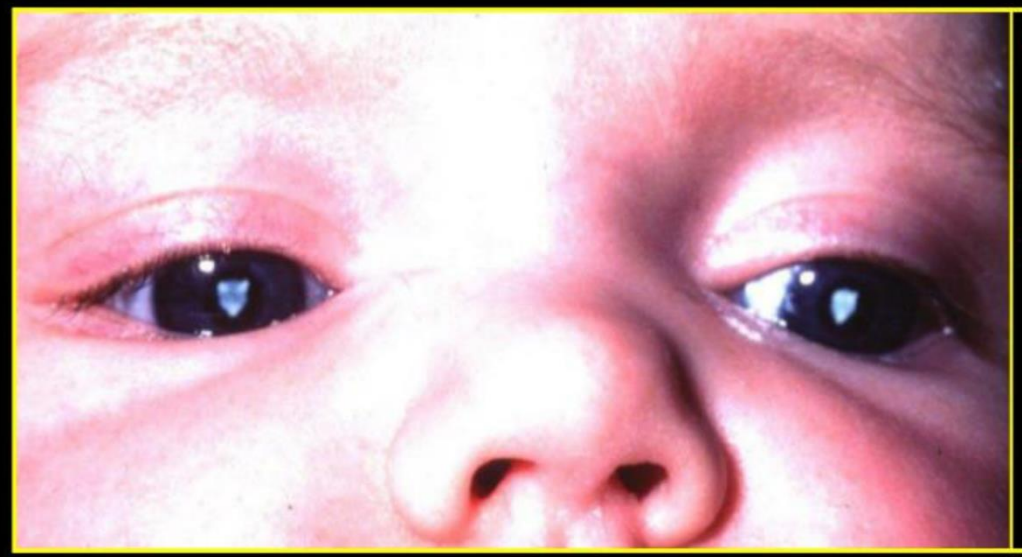
Systemic association

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

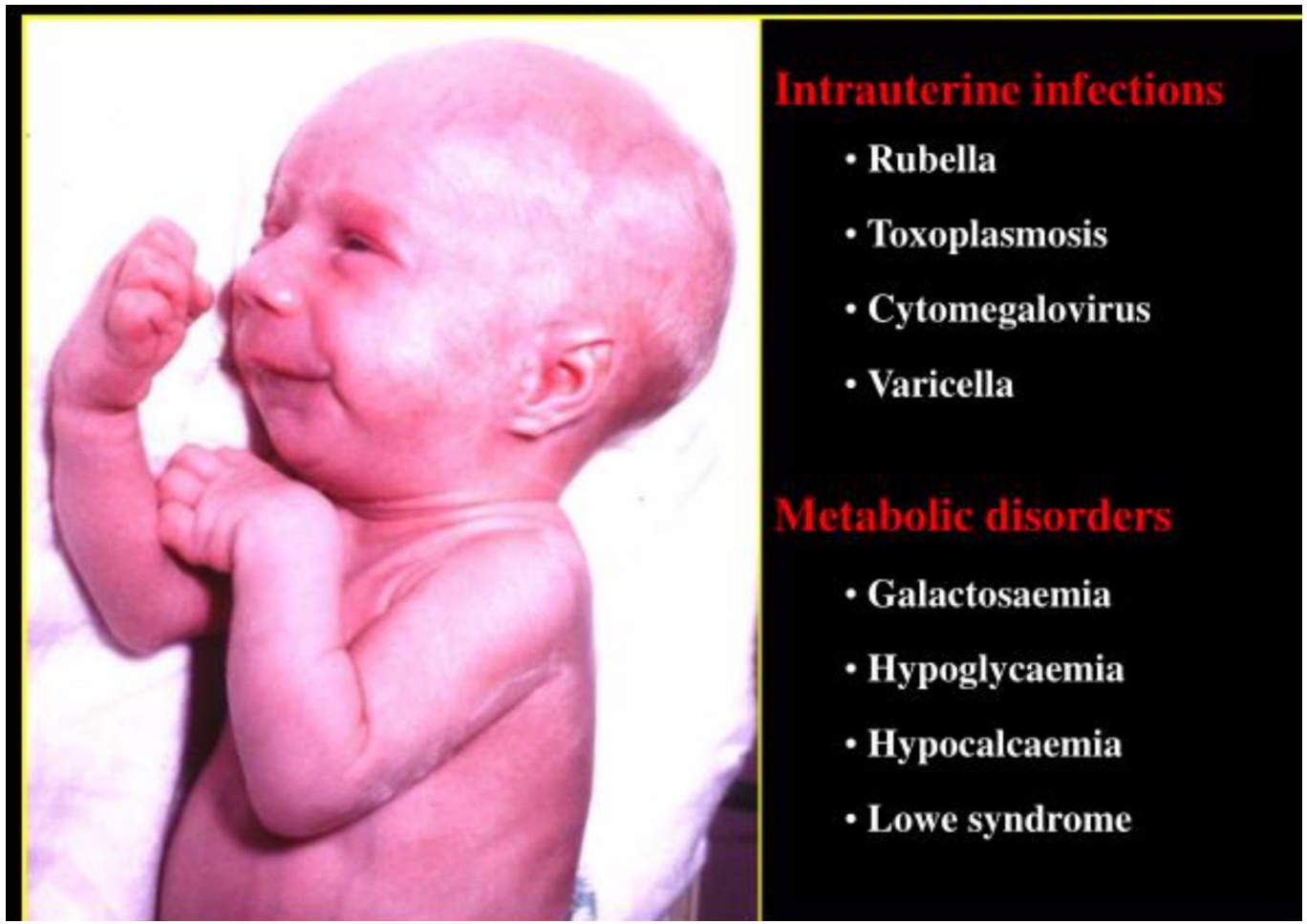


Hereditary
(usually dominant)

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