

Kernicterus

Definition: Permanent neurologic impairment secondary to bilirubin toxicity

Pathologic findings:

- Staining and necrosis of neurons in the basal ganglia, hippocampal cortex, subthalamic nuclei, and cerebellum.
- Followed by gliosis of these areas if patient survives.
- Cerebral cortex is generally spared.

Kernicterus

Clinical presentation (term infants): Rapidly progressive and worsening encephalopathy

- Phase 1> Poor suck, hypotonia, depressed sensorium.
- Phase 2> Fever and hypertonia (may progress to frank opisthotonos).
- Phase 3> Less hypertonia, high-pitched cry, poor feeding, hearing and visual abnormalities, athetosis.

Progresses over 24 hours!! 50% mortality

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Clinical presentation (term infants): Long-term survivors

Choreoathetoid cerebral palsy, sensorineural hearing loss, an upward gaze palsy, mental retardation (some).

Sequelae may also develop in neonates who have never manifested clinical signs of bilirubin encephalopathy in the newborn period.

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Clinical presentation (preterm infants):

- Less stereotyped > ill-appearing infant only.
- CNS staining not (necessarily) indicative of kernicterus.
- 100% mortality.

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Reasons why bilirubin may enter brain:

1. Excess bilirubin production which overwhelms albumin and other blood buffering capacity.
2. Alteration in albumin binding.
3. Increased CNS permeability > disruption of BBB (hypoxemia, meningitis/sepsis).

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Unconjugated bilirubin > nonpolar, lipophilic, binds to albumin in plasma (and RBC/platelet membranes and β -globulin); free U-bili normally soluble at $\sim 1 \mu\text{M}$ --> when binding capacity exceeded, free U-bili in plasma rises

One molecule of albumin binds 2 molecules bilirubin (1st is more tightly bound); at 1:1 molar ratio, 1 g albumin binds 8.4 mg bilirubin:

<u>serum alb</u>	<u>max binding capacity (1, 2 sites)</u>	
4.0 g/dl	33.6 mg/dl	77.2 mg/dl
3.5	29.4	58.5
3.0	25.2	50.4
2.5	21.0	42.0

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Other factors which decrease U-bili binding to albumin:

1. Free fatty acids (sepsis, IV lipid emulsions)
2. Sulfa drugs (e.g., Bactrim)
3. Indomethacin
4. Ampicillin
5. ?pH

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In situ metabolism as potential cause (?):

HO-1 and HO-2 (heme oxygenase enzymes > heme --> biliverdin) and biliverdin reductase (biliverdin --> bilirubin) present and active in brain. Formed bilirubin rapidly cleared from brain by bilirubin oxidase.

Enzymes are developmentally regulated.

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How does bilirubin cause brain damage? Unknown.

Possible “mechanisms”:

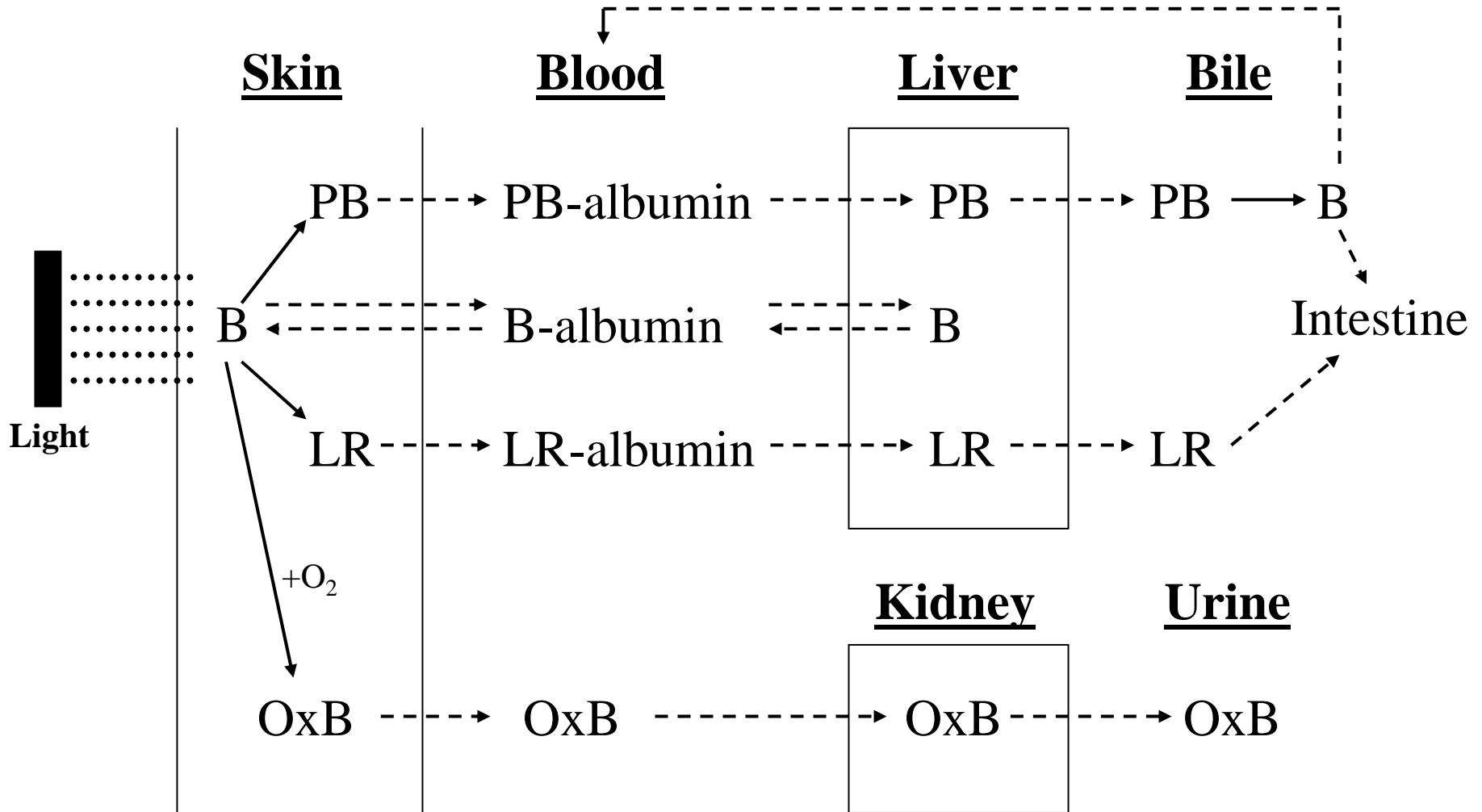
1. Passage thru lipid bilayer into cells and causes damage.
2. Not bilirubin itself, but rather CO (formed in equimolar amounts via HO).

Phototherapy

- Reduces or blunts the rise of U-bili regardless of maturity, presence or absence of hemolysis, or degree of skin pigmentation.
- No (reported) serious side effects, despite extensive use in U.S. and Europe; no (known) adverse outcomes.
- Demonstrated to reduce the need for exchange blood transfusions.
- *Mechanisms*>
 1. Geometric photoisomerization (Z-->E isomer; E isomer more soluble and can be excreted by liver into bile without need for conjugation).
 2. Intramolecular cyclization (bilirubin-->lumirubin)
 3. Oxidized byproducts (minor)

Phototherapy

•Mechanisms, cont>



Phototherapy

Technique>

- *Wavelengths (to induce photoisomerization):*
 - Bilirubin absorption between 420-500 nm (blue range);
 - Maximum: 460 (B-albumin), 440 (free B);
 - [Daylight 550-600 max]
 - Special blue lamps 420-480 peaks (but can't assess skin color and causes vertigo and nausea in caregivers)
- *Energy (or irradiance) ($\mu\text{W}/\text{cm}^2/\text{nm}$):*
 - Measured with photometer (“bili-meter”)
 - Minimum = $5 \mu\text{W}/\text{cm}^2/\text{nm}$
 - Maximum (saturation point) = $11 \mu\text{W}/\text{cm}^2/\text{nm}$
 - Remember--> $I \sim 1/\text{distance}^2$

Phototherapy

Technique, cont.>

- *Surface area:*

The greater the surface area, the greater the effectiveness. Additional lights (double PT) NOT for increased I, but for increased surface area exposure.

White blanket around baby may reflect light onto relatively underexposed areas.

- *Fiberoptic phototherapy (“bili-blankets”):*

Halogen lamp-->fiberoptic bundle to a blanket.

(The AAP does NOT endorse home phototherapy)

- *“Off-time”:*

Intermittent breaks (feeds, bathing, etc.) OK since skin bilirubin pool takes 1-3 hours to restore.

Phototherapy

Complications>

1. Retinal degeneration (animal studies after prolonged use).
2. Increased insensible water loss (increased ~20-25%).
3. Increased GI fluid loss (stools looser and more frequent).
4. Bronze baby syndrome> occurs with conjugated hyper-bili or with cholestasis.