TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER™

Hyperbilirubinemia and Kernicterus

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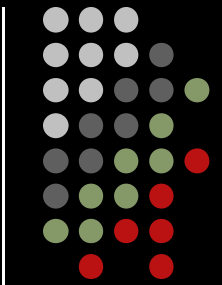
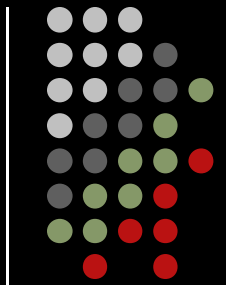
Hyperbilirubinemia



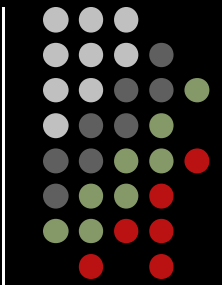
- Most common clinical condition requiring evaluation and treatment in the NB
- Most common cause of readmission in the 1st week
- Generally a benign transitional phenomenon
- May pose a direct threat of brain damage
- May evolve into kernicterus

Kernicterus



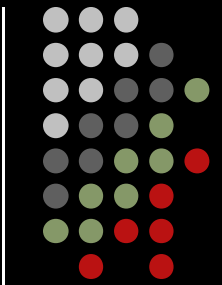
1. Choreoathetoid cerebral palsy
2. High-frequency central neural hearing loss
3. Palsy of vertical gaze
4. Dental enamel hypoplasia (result of bilirubin-induced cell toxicity)

Kernicterus



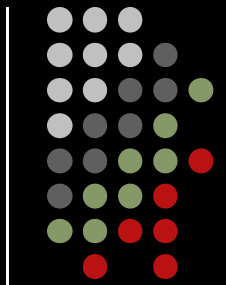
- Originally described in NB with Rh hemolytic disease
- Recently reported in healthy term and late preterm
- Reported in breast-fed infants w/out hemolysis
- Most prevalent risk factor is late preterm

Late Preterm Infant



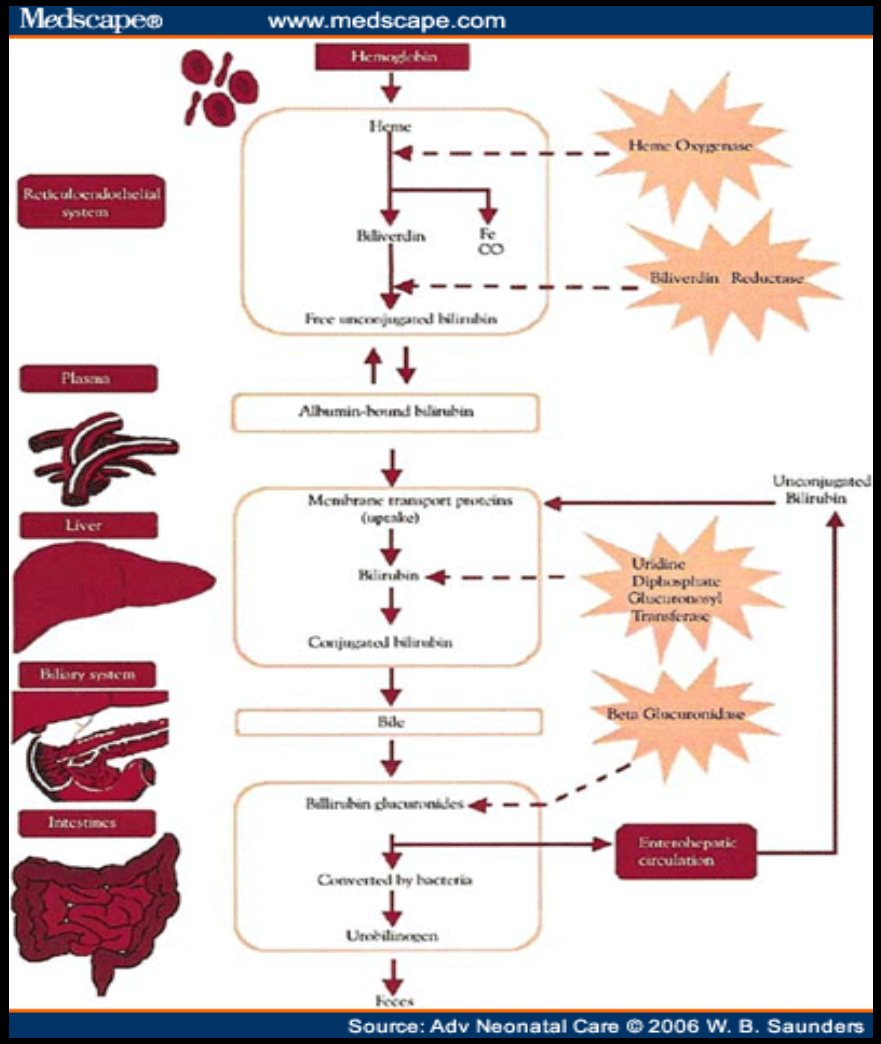
- Relatively immature in their capacity to handle unconjugated bilirubin
- Hyperbilirubinemia is more prevalent, pronounced and protracted
- Eightfold increased risk of developing TSB > 20 mg/dl (5.2%) compared to term (0.7%)

Pathobiology

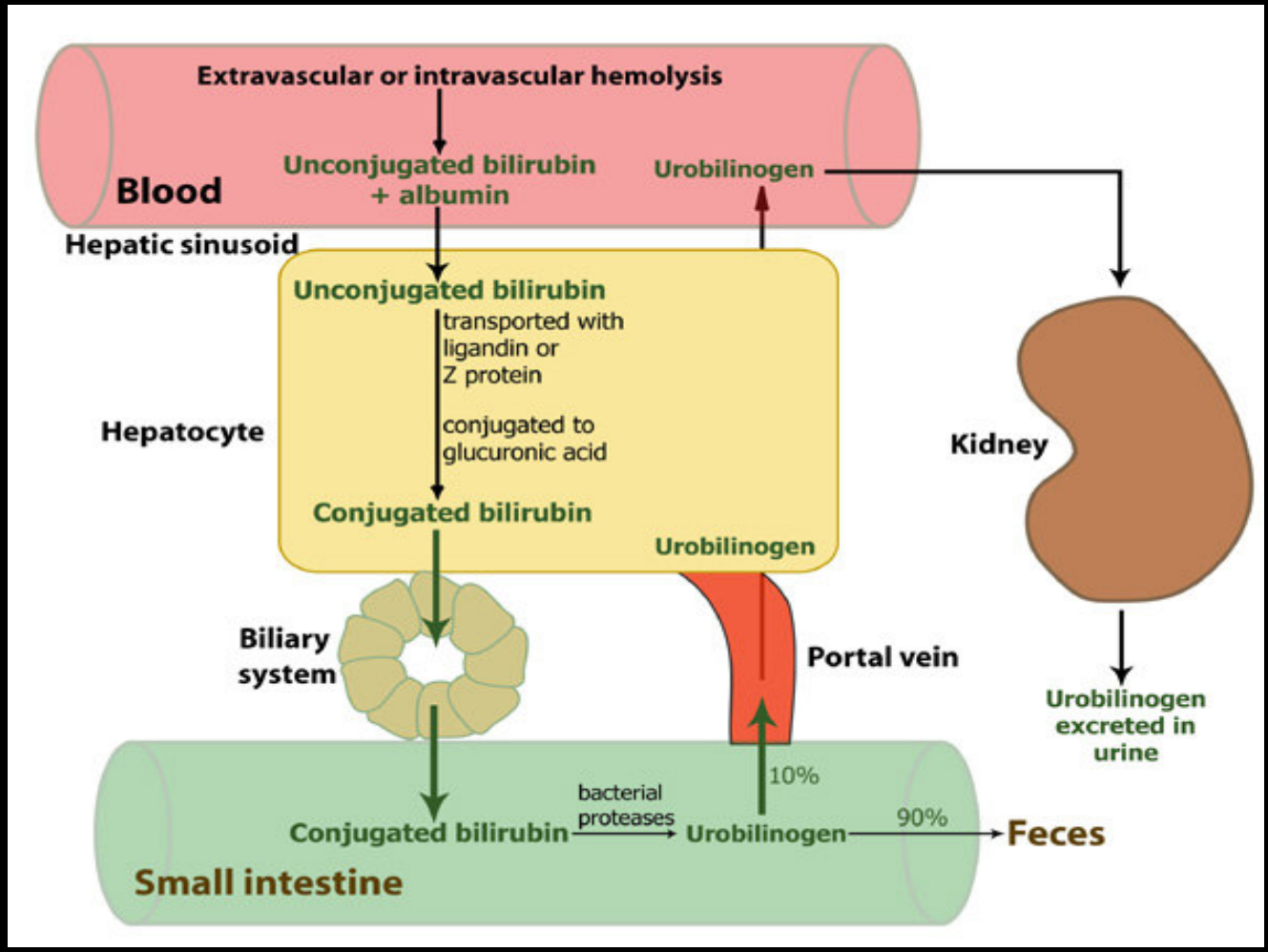


- Increased bilirubin load in the hepatocyte
- Decreased erythrocyte survival
- Increased erythrocyte volume
- Increased enterohepatic circulation
- Decreased hepatic uptake from plasma
- Defective bilirubin conjugation

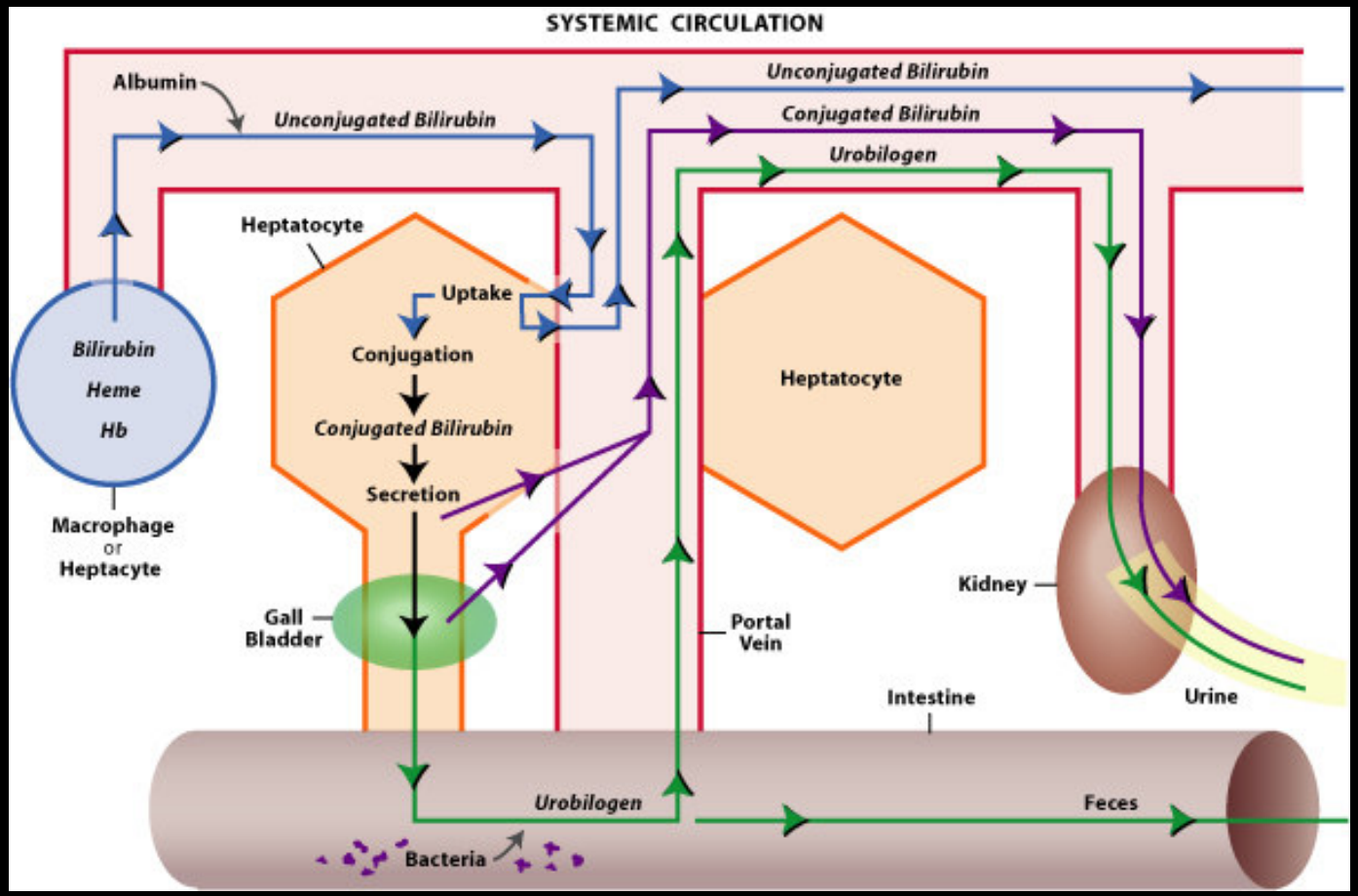
Bilirubin Metabolism



Bilirubin Metabolism



Bilirubin Metabolism

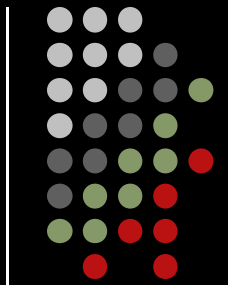


How bilirubin Damages the Brain

- Determinants of neuronal injury by bilirubin

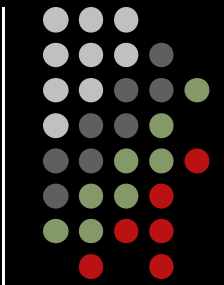
1. Concentration of unconjugated bilirubin
2. Free bilirubin
3. Concentration of serum albumin
4. Ability to bind UCB
5. Concentration of hydrogen ion
6. Neuronal susceptibility

Intracellular Calcium Homeostasis



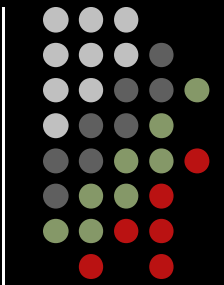
- Bilirubin acts by impairing intracellular Ca+
- Ca+ is the principal mechanism of neuronal cell death and neuronal excitability
- Decreased CaMKII activity is a feature of neuronal toxicity and ischemia
- Bilirubin decrease CBP's in the CNS

MRP1



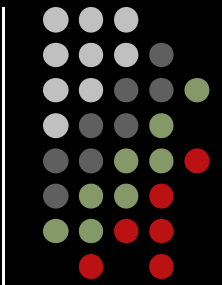
- Bilirubin is removed from cells by way of multidrug resistance-associated protein 1
- MRP1 transports bilirubin w/ an affinity 10 x greater than other substrates
- Represents a mechanism by which bilirubin is removed from CNS into the bloodstream

Apoptosis



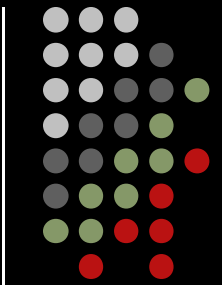
- Bf concentration as low as 160 nM can induce apoptosis
- Bilirubin triggers release of cytochrome c from mytochondria w/ caspase activation
- Apoptotic changes are found in the basal ganglia

Mechanisms for CNS injury



- Diminish serum bilirubin binding capacity
- Enhanced permeability to unconjugated bilirubin influx
- Immaturity of neuronal protective mechanisms

Neuropathology of Kernicterus



- Movement disorders → lesions in the basal ganglia (globus pallidus/subthalamic nucleus)
- Auditory dysfunction → lesions of the auditory brainstem nuclei
- Oculomotor impairment → damage to brainstem ocular nuclei

Bilirubin Toxicity

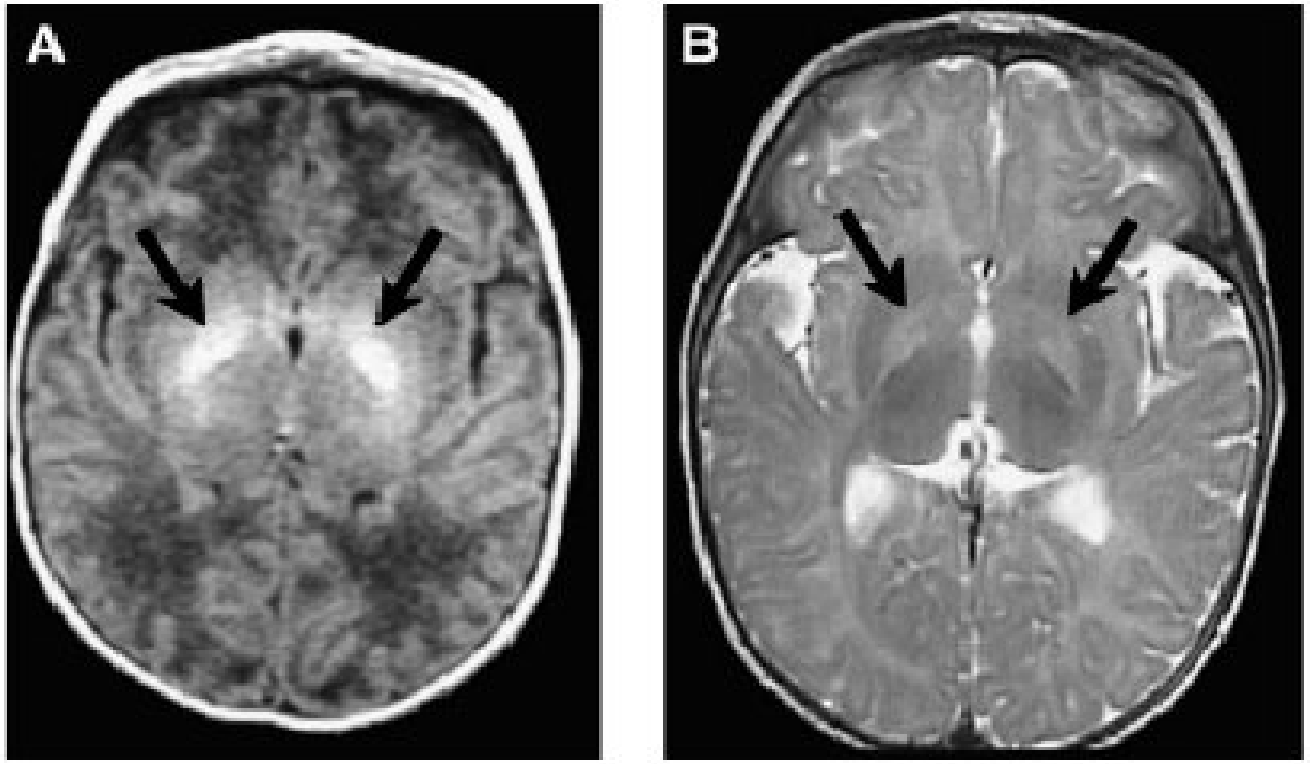
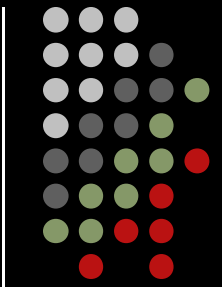


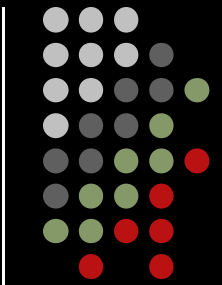
Fig. 1. Axial MRI scans showing bilateral hyperintense lesions in the globus pallidus in axial projections (*arrows*). (*A*) T1-weighted axial image of a 6-day-old, 37-week gestation boy with peak total bilirubin of 34.6 mg/dL. At age 7, this child was highly intelligent but moderately to severely disabled with dystonic, athetoid kernicteric CP; he ambulates with a walker. (*From* Shapiro SM,

Auditory Neuropathy/Dyssynchrony



- Presence of normal OAEs and the absence of ABRs
- Affects 1 in 400 newborns
- AN/AD associated with hearing loss and deafness
- 68% have a complicated perinatal course
- 30% have no identifiable risk factors
- Hyperbilirubinemia/prematurity >50% of patients

Disorders of Movement and Tone



- Dystonia: Excessive/sustained contractions of opposing muscles
- Incoordination of sucking, swallowing, GI and oculomotor motility disturbances
- Autopsy in humans showed extensive neuronal loss in GPi and GPe

Neuroimaging

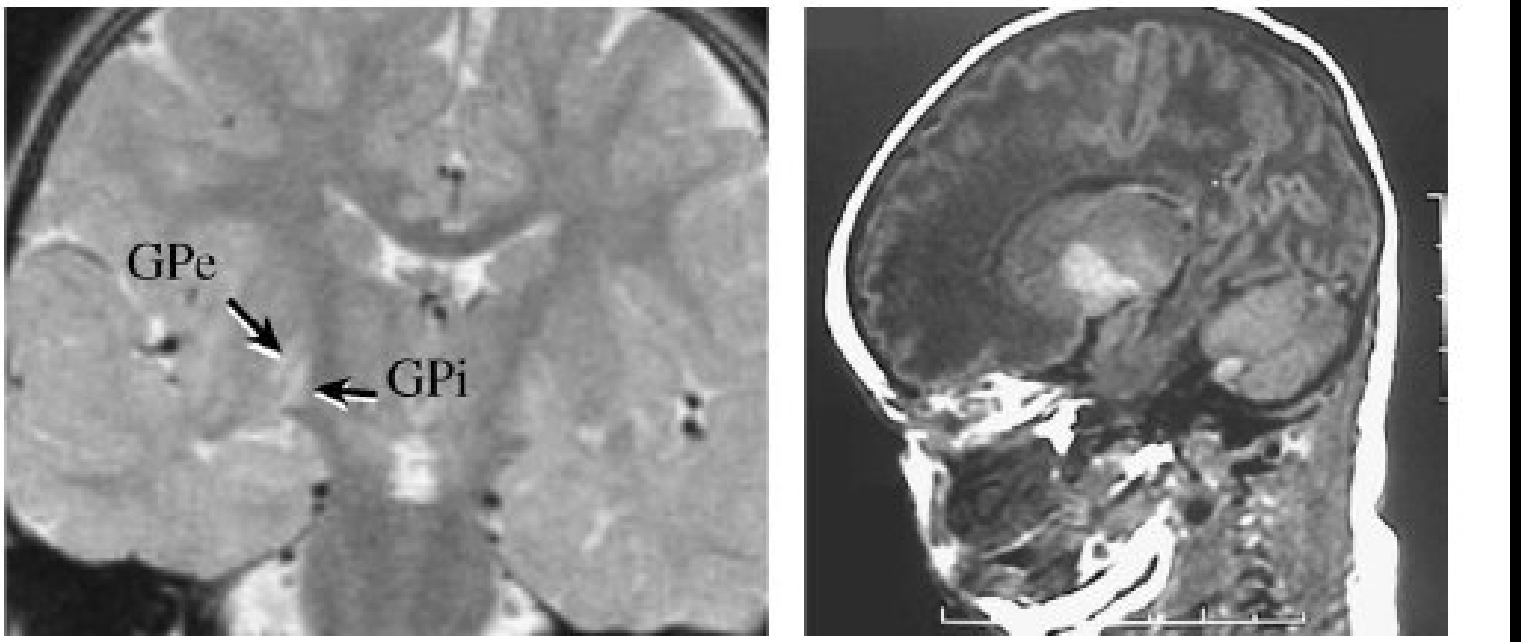


Fig. 2. T2-weighted MRI from a 1-Tesla magnet showing increased signal in coronal (*left*) and sagittal (*right*) views. Note the GPe and GPi can be distinguished in the coronal view.

Clinical Syndromes of Kernicterus

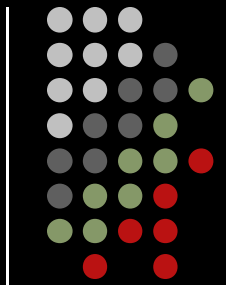
- Produces selective damage of the CNS

Classic Tetrad

1. Athetoid CP
2. Deafness or hearing loss
3. Impairment of upward gaze
4. Enamel dysplasia of primary teeth

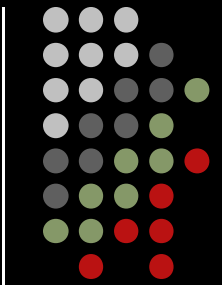
- GI problems suck/swallowing disturbances reflux and constipation

Toxicity Symptomatology



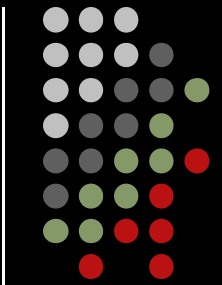
- Begins with: Lethargy and decreased feeding
- Progresses: Variable tone (hypo/hypertonia), high-pitched cry, opisthotonus, impairment of upward gaze (setting sun sign) fever, seizures and death
- Lab: Absent or abnormal ABRs
- MRI: Bilateral hypertense lesions in the GP
- Exchange transfusion may reverse toxicity

Mistakes in Treatment



- No knowledge of the distance of the lights
- Oral feedings promote bilirubin excretion
- Belief that bili level cannot be that high
- Other investigations lead to delays in treatment
- Babies w/ very high TSB and conjugated bili are not treated due to fear of bronze baby
- Discontinuation of therapy due to life-threatening conditions
- Too late to treat

New Definitions of Kernicterus



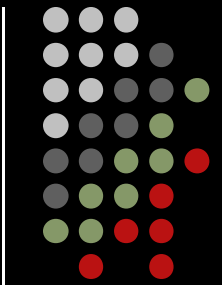
- Clinical symptoms by severity

1. Mild
2. Moderate
3. Severe

- By localization

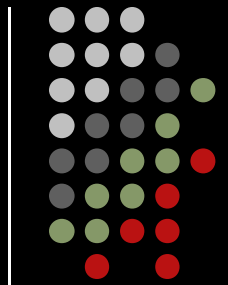
1. Isolated
2. Mixed
3. classic

Severity



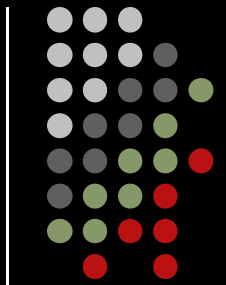
- Mild: Remain high functioning, little to no functional disability, subtle movement disorders and muscle cramps
- Moderate: Prominent dystonia, athetoid movements but able to talk, feed and ambulate unassisted with poor stability.
- Severe: Disabling dystonia, non ambulatory, dysarthric or do not speak and auditory dysfunction or deafness

Associated Risk Factors



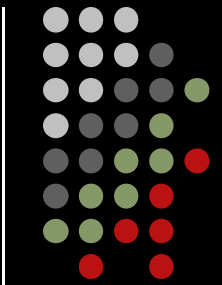
- Breast milk feeding
- Large for gestational age
- Male sex
- Glucose-6-phosphate dehydrogenase deficiency and breast feeding

Breast Feeding



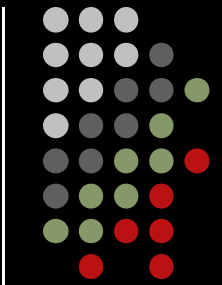
- Breast-fed infants are at higher risk for severe hyperbilirubinemia
- Suboptimal feeding plays an important role
- Enterohepatic circulation accounts for 50% of hepatic bilirubin load in neonates
- Hepatic immaturity
- Breast milk feeds far outweigh the related risk of hyperbilirubinemia

Large for Gestational Age



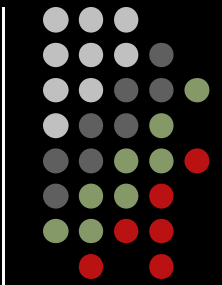
- 1/3 of infants with kernicterus are LGA
- Birth-related risks include: Oxytocin induction, vacuum or forceps delivery and cutaneous bruising
- No specific mechanisms were identified

Male Sex



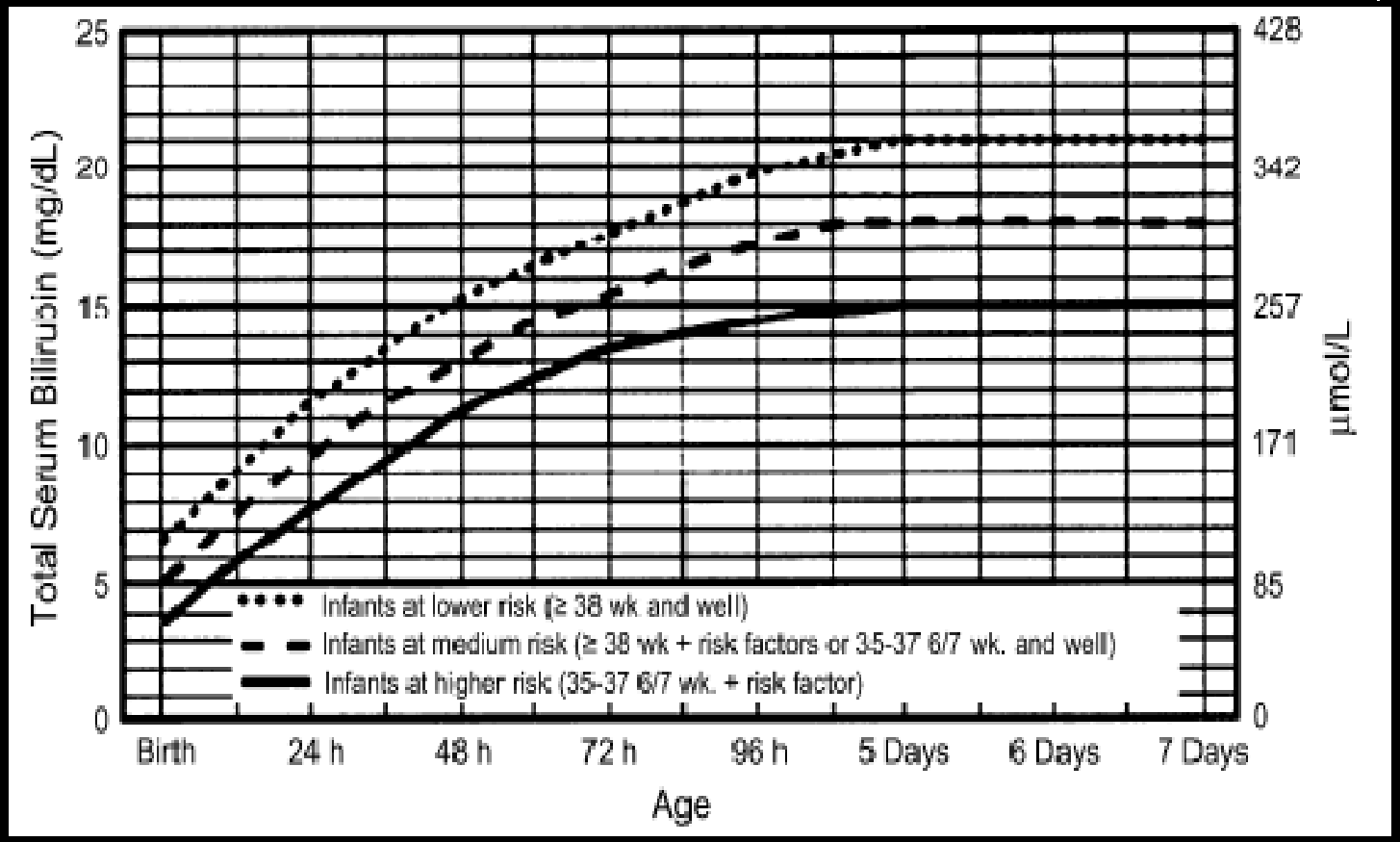
- Males have > bilirubin levels than females
- Gilbert's syndrome is two-fold higher in males
- Increased male susceptibility to bilirubin-induced damage
- BBB permeability to unbound bilirubin
- Neuronal plasma membrane bilirubin passage
- CNS bilirubin binding, metabolism or clearence

Diagnosis

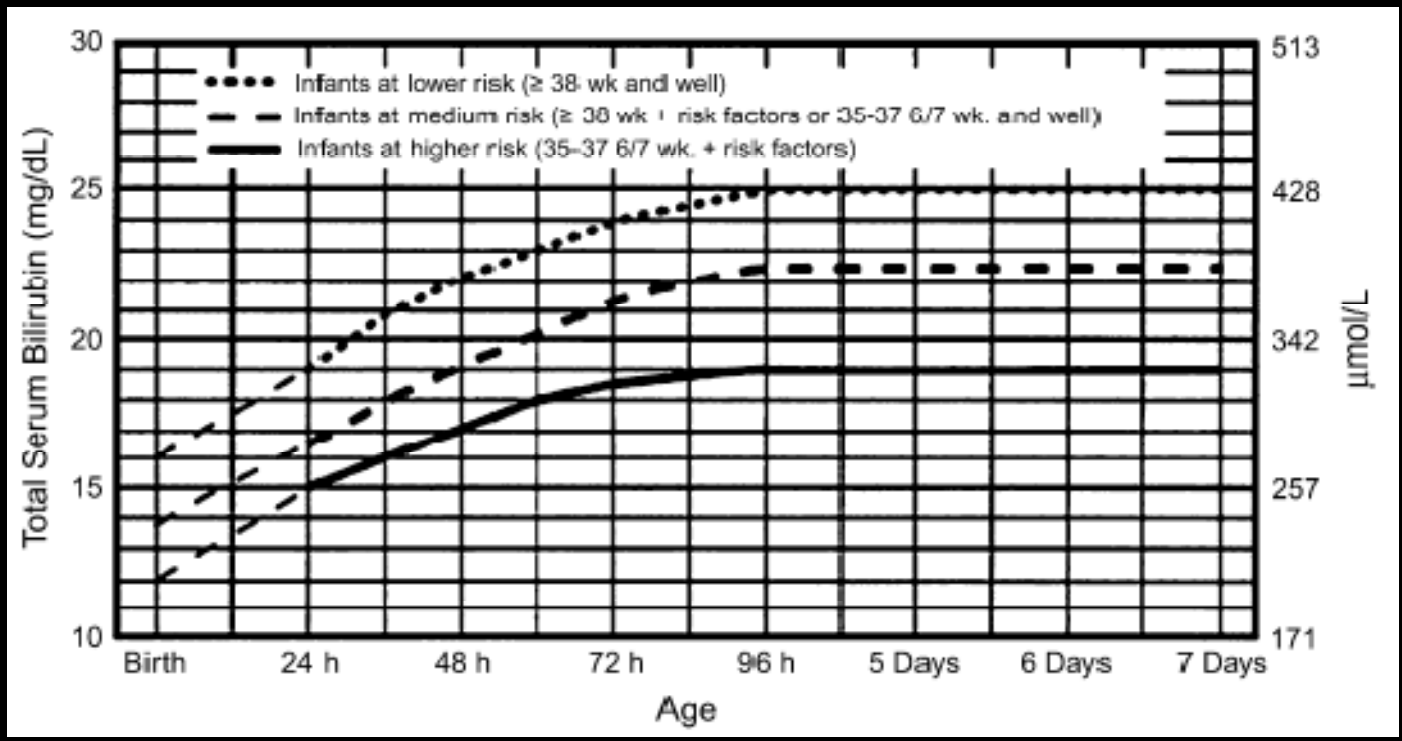


- History of jaundice
- Physical examination: Athetosis, dystonia, fixed postures, spasticity, incoordination
- Laboratory test
- ABRs : absent or abnormal with an increase in conduction time
- OAEs : initially normal may disappear w/ time
- MRI : abnormal GP w/out other abnormalities normal MRI does not exclude the diagnosis

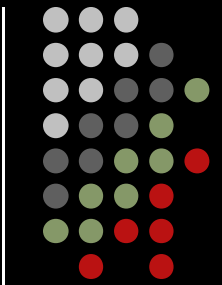
Treatment Guidelines



Exchange Transfusion



Treatment



- Physical, occupational and speech therapy
- Medical : to improve dystonia → Baclofen, GI problems should be evaluated with BS as well as supplemental feeding
- Surgical: Gastrostomy tubes, Nissen to treat GER, cochlear implantation for AN/AD and deafness

References

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