Kernicterus: A Preventable Neonatal Brain Injury

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Key Words: kernicterus, bilirubin induced neurologic dysfunction, neonatal hyperbilirubinemia, newborn jaundice

Summary
Kernicterus, one of the most easily preventable causes of brain injury from severe neonatal jaundice, has re-emerged in the United States and other nations with well developed healthcare systems as a public and societal health concern. Kernicterus, in its usually recognized form, causes devastating disabilities including athetoid cerebral palsy (CP) and speech and hearing impairment. It represents the severe manifestation of bilirubin induced neurologic dysfunction (BIND) syndrome. This condition not only ranks amongst the highest cost per new case (according to the Center of Disease Control’s Financial Burden of Disability study in 1992), but also results in profound and uncompromising grief for the family and loss to siblings of healthy, talkative playmates. And for the child with kernicterus (usually remarkably intelligent, but trapped in an uncontrollable body), grief and frustration are enormous. In 2001 national healthcare organizations, including Centers for Disease Control (CDC), the Joint Commission for the Accreditation of Healthcare Organizations (JACHO) and the American Academy of Pediatrics (AAP) issued alerts to all accredited hospitals and public health professionals in the United States and affiliated organizations that all healthy infants are at potential risk of kernicterus if their newborn jaundice is unmonitored and inadequately treated. Evidentiary analysis of 125 cases, from an informal Pilot Kernicterus Registry, documents that unmonitored or inadequately treated severe hyperbilirubinemia results in kernicterus in otherwise healthy term and near term infants. On the basis of this empirical evidence, the lapses in care and root causes have been associated with the occurrence of kernicterus in these infants. The re-emergence of kernicterus in the United States is the result of interacting phenomena including a) early hospital discharge (before extent of jaundice is known and signs of impending brain damage have appeared); b) lack of adequate concern for the risks of severe jaundice in healthy term and near term newborns; c) an increase in breast feeding without adequate instruction, monitoring and support; d) medical care cost constraints leading to early discharge with loss of supervision; e) paucity of educational materials to enable parents to participate in safeguarding their newborns; and f) limitations within the healthcare systems to provide continuity of care. The current resources for clinical interventions that can drastically and efficiently reduce the increased bilirubin load, intensive phototherapy and exchange transfusions, are available for use in those infants with excessive hyperbilirubinemia. However, these interventions leave a very narrow margin of safety for babies who have rapid or unrecognized increases in their bilirubin load. Because most babies are discharged before the hyperbilirubinemia reaches its peak during the first week of life, preventive and system-based strategies offer a safer, kinder and gentler means to prevent BIND including kernicterus.

Introduction
Kernicterus incidence has not been measured as a clinical or public health index even though it has long been recognized as the pathologic sequela of severe hyperbilirubinemia. Although the condition is uncommon, the consequences are tragic, especially when it affects otherwise healthy term and near term infants. Kernicterus has become uncommon because of effective screening for and prevention of Rh incompatibility, a historically important cause, and the accessibility of phototherapy to treat hyperbilirubinemia due to increased production and/or decreased elimination of bilirubin. Furthermore, adherence by clinicians to the guidelines from the American Academy of Pediatrics (AAP) concerning management of neonatal jaundice was expected to eliminate severe hyperbilirubinemia and prevent kernicterus. Little contemporary information is available on the incidence or prevalence of kernicterus or its consequences. However, anecdotal cases continued to be seen by practicing pediatricians and neurologists and cumulative occurrence is not recorded as a matter of public record or medical literature. That kernicterus occurs in otherwise healthy infants is evident from 125 cases of infants who had been discharged as healthy from their birthing hospitals and who were voluntarily reported to the Pilot Kernicterus Registry from 1992 to 2002. However, no cases of kernicterus in infants with cerebral palsy were found in the retrospective database of the Northern California Kaiser Permanente Medical Care Program (KPMCP) during a similar time period (1991 to

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Vad är skillnaden mellan en radiolog, röntgen Tekniker, och X-ray-tekniker?
In addition, among 111,009 infants in the KPMCP database, 11 (0.01%) developed total serum bilirubin (TSB) levels ≥30mg/dL (when measured), and none apparently developed kernicterus. On the other hand, a Danish population-based study reports 6 cases of kernicterus over a duration of 5 years for an estimated incidence of 1:38,000 well-babies cared for in Danish nurseries.

Pediatricians who have managed babies with neonatal hyperbilirubinemia that progress to acute or chronic bilirubin encephalopathy often feel stigmatized and are disinclined to report, discuss, review or publish their experience. Thus, the scope of the true incidences of overt kernicterus as well as possible "subtle" neurological deficits cannot be ascertained without an innovative and non-adversarial investigative approach. There is a societal expectation to provide a universally available safe birthing experience that includes a safe experience with newborn jaundice. Thus, kernicterus (or a TSB level >30 mg/dL) is now considered a "never-event" by the public health community.

This review focuses on the clinical definitions of BIND, its relationship with hyperbilirubinemia, bilirubin/albmin ratio and with a specific focus on G6PD deficiency-related neonatal hyperbilirubinemia. In addition, the article briefly addresses the role of a systems strategy for a safer experience with newborn jaundice and the potential role of chemoprevention.

A. Bilirubin Induced Neurologic Dysfunction

1. Determinants of Neuronal Injury by Bilirubin

The risk of neuronal injury by bilirubin is primarily determined by the concentration of unbound or "free" unconjugated bilirubin (Bf) and hydrogen ion (pH) in blood. Bf can be measured indirectly or estimated by calculating the molar ratio of total serum bilirubin (TSB) to albumin. Bilirubin enters brain tissue as Bf when the blood binding capacity is exceeded, or when other displacing substances, such as sulphonamides, compete for bilirubin binding sites on albumin. Other important risk factors for kernicterus relate to neuronal susceptibility, including gestational age, infection or sepsis, and hemolysis, especially Rh disease. Sepsis or other neonatal inflammatory conditions and prematurity may decrease the bilirubin binding affinity of albumin.

Even though a "safe" level of bilirubin has not yet been determined, most of the circulatory bilirubin is bound to albumin which acts as a “neuro-protective”. The blood-brain-barrier has long been considered to play a role in protection of the brain from bilirubin toxicity, and its disruption produces diffuse yellow staining but not the specific pattern of kernicterus. Whether the blood brain barrier acts as a pump through ATP-dependent export by transporter molecules to remove Bf from the brain and maintain the concentration gradient of bilirubin from plasma to CSF has yet to be determined, though ATP-dependent export by transporter molecules has been suggested.

Another important determinant of toxicity is neuronal susceptibility. Shapiro et al examined cerebella of jaundiced Gunn rats made toxic at various developmental ages and found that neurons undergoing differentiation at the time of exposure were the most susceptible to cell death, while those that were slightly more or less mature showed only transient changes or seemed to be much less sensitive. This supported the presence of a critical or sensitive period when elevated bilirubin could be most toxic to neuronal development.

Bilirubin can cause neuronal necrosis, and there is now good evidence in vitro that it induces apoptosis, which supports in vivo observations in older literature showing neuroanatomical changes consistent with apoptosis. Evidence also suggests that bilirubin interferes with intracellular calcium homeostasis by altering function and expression of calcium/calmodulin kinase II, by selectively decreasing calcium binding proteins in susceptible brainstem areas and increasing intracellular calcium in cultured neurons, and by sensitizing the cell to other injuries or triggering apoptosis. Bilirubin may also kill cells by causing neuronal hyperexcitability perhaps via excitatory amino acid neurotoxicity, or it may have other membrane of neurotransmitter effects. Finally, it may act by interfering with mitochondrial respiration and energy production, perhaps as an oxidant injury.

Overall, it is hypothesized that bilirubin damages brain tissue cells via necrosis and apoptosis, either alone or in combination, in a neuro-anatomical distribution dependent on the amount, duration, and the developmental timing of exposure of sensitive brain tissue to free bilirubin. With this perspective, the neuroanatomical and clinical expression of injury is likely to be complex with different patterns of damage and a range of clinical expression. Different patterns of expression may relate to 1) the amount of, and duration of exposure to free bilirubin (high level, short duration exposure not necessarily the same as lower level, long duration exposure), 2) the susceptibility of the developing CNS, 3) the relative amount of necrosis vs. apoptosis produced, and 4) whether surviving neurons will be functionally normal or more susceptible to other stressors either at the time of hyperbilirubinemia or afterwards.

2. Neuropathology of Kernicterus

Kernicterus causes selective yellow staining in the basal
ganglia, especially the globus pallidus and subthalamic nucleus. Brainstem nuclei, especially the auditory (cochlear nucleus, inferior colliculus, superior olivary complex), oculomotor and vestibular nuclei are especially vulnerable. Other vulnerable areas include the cerebellum, Purkinje cells, and the hippocampus (especially the CA2 sector). The basal ganglia are associated with the movement disorders of dystonia, athetosis and choreoathetosis. Abnormalities of the auditory brainstem nuclei are associated with deafness, hearing loss, and a recently described entity known as auditory neuropathy. Abnormalities of the brainstem oculomotor nuclei are associated with strabismus and gaze palsies, especially paresis of upgaze. In the auditory system, bilirubin does not appear to affect either inner or outer hair cells, but appears to be toxic to cell bodies of the auditory nerve in the spiral ganglia. Brainstem auditory nuclei and not the pathways are particularly susceptible. The optimum means of assessment is neuro-physiological since this component of the auditory system cannot be imaged. Neuro-physiological assessment involves the evaluation of the mechanical structure of the inner ear by otoacoustic emissions (OAE), and the outer hair cells (inner ear) by cochlear microphonic responses (CM). In infants with kernicterus, these are both normal. Sensori-neural assessment requires the testing of auditory brainstem response (ABR) or brainstem auditory evoked potential (BAEP). In bilirubin-related injury, it is absent or abnormal and reflects damage to the auditory nerve (wave I) as well as the auditory brainstem nuclei (waves III and V).

The basal ganglia lesions can be imaged with magnetic resonance imaging (MRI), the signature of which is bilateral damage of the globus pallidus. The subthalamic nuclei can sometimes be seen and are characteristically affected. Disordered outputs from the basal ganglia are possibly responsible for the dyskinetic movements. The MRI evidence of kernicterus is distinct from that of hypoxia-ischemia; in the latter, the thalamus, cortex and peri-ventricular white matter are involved; while, the caudate nuclei and putamen are not affected in kernicterus.

3. Clinical Definitions of Bilirubin Induced Neurologic Dysfunction

Kernicterus has usually referred to the post-mortem evidence of icteric (yellow) staining of the basal ganglia and lesions of the extra-pyramidal nervous system. The Pilot Registry has offered formal clinical definitions of BIND and Kernicterus (Table I). The spectrum of acute and chronic manifestations of BIND varies from the acute stage bilirubin encephalopathy to those of chronic sequelae such as isolated auditory neuropathy (a form of

<table>
<thead>
<tr>
<th>Severity Score Mental Status</th>
<th>Date/ Time</th>
<th>Date/ Time</th>
<th>Date/ Time</th>
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<tbody>
<tr>
<td>None 0</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild 1</td>
<td>Sleepy, poor feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate 2</td>
<td>Lethargic, Irritable</td>
<td></td>
<td></td>
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<tr>
<td>Severe 3</td>
<td>Semicoma, Seizures Coma</td>
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<tr>
<th>Severity Score Muscle Tone</th>
<th>Date/ Time</th>
<th>Date/ Time</th>
<th>Date/ Time</th>
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<tbody>
<tr>
<td>None 0</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild 1</td>
<td>Neck Stiffness, Mild hyper-hypotonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate 2</td>
<td>Arching neck, retrocolis, Arching trunk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe 3</td>
<td>Bowing of trunk Opisthotonus</td>
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<tr>
<th>Severity Score Cry pattern</th>
<th>Date/ Time</th>
<th>Date/ Time</th>
<th>Date/ Time</th>
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<tbody>
<tr>
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<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild 1</td>
<td>High pitched</td>
<td></td>
<td></td>
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<tr>
<td>Moderate 2</td>
<td>Shril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe 3</td>
<td>Inconsolable</td>
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Total BIND Score

Nurse/MD signature

Score of 7 to 9: represent severe acute bilirubin encephalopathy; urgent interventions are recommended to possibly minimize further brain injury.
Scores of 4 to 6: Represent moderate acute bilirubin encephalopathy and is likely to be reversible with urgent bilirubin reduction.
Scores of 1 to 3: Represent mild acute bilirubin encephalopathy and are usually reversible with urgent bilirubin reduction strategies. An abnormal ABR or “referred” automated ABR would indicative of BIND would be suggestive of moderate to severe ABE.
Table III: Clinical classification of Kernicterus (as proposed by Shapiro SM)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Classic Kernicterus</td>
<td>Have 3 classic signs of kernicterus including: 1) Auditory (AN, hearing loss), 2) Motor (hyperkinetic dystonia or athetosis, choreoathetosis, “athetoid” CP), 3) oculomotor disorder esp. impairment of upgaze, 4) dental enamel dysplasia.</td>
</tr>
<tr>
<td>Mixed Kernicterus or BIND</td>
<td>Auditory predominant: moderate of severe AN ± hearing loss with mild motor symptoms (hypotonia, mildly delayed walking, slightly abnormal muscle tone), normal or slightly abnormal GP (Signals) or MRI</td>
</tr>
<tr>
<td>Isolated Kernicterus or BIND</td>
<td>Has signs and symptoms limited to only one system, either the auditory or motor system. Most cases of isolated kernicterus have turned out to be not strictly isolated, but have findings in another system on close examination.</td>
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<tr>
<th>Location</th>
<th>Clinical</th>
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<tr>
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Table IV: Clinical definitions of Kernicterus severity

<table>
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<tr>
<th>Signs</th>
<th>Neuromotor</th>
<th>Oculomotor</th>
<th>Dental</th>
<th>ABR</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal [with onset of dentition]</td>
<td>Sensori-neural hearing loss</td>
<td>Abnormal [if available]</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>All four abnormal signs are present and/or abnormal MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Abnormal</td>
<td>Any two of these three abnormal are present</td>
<td></td>
<td>If unavailable</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Any two of these four signs are abnormal</td>
<td></td>
<td></td>
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sensorineural hearing loss), and chronic bilirubin encephalopathy of both neuromotor and auditory damage (kernicterus). Though not yet proven, some experts believe that there may be more neurological manifestations of BIND including subtle basal ganglia and central processing disorders. The effect of even moderate increases in TSB levels on early development remains a source of controversy, especially because some clinical manifestations are reversible upon reduction of the TSB concentration.

a. Acute Bilirubin Encephalopathy (ABE) The actual incidence of ABE is not known because (a) there have been no longitudinal surveillance studies of the condition, (b) there is limited awareness and recognition of this diagnosis in healthy babies and (c) the diagnosis is usually not coded on discharge summaries (Table II). However, recent case reports and registries suggest that kernicterus has re-emerged as a public health problem after years of near extinction. The introduction in the 1960’s of Rhogam to prevent Rh sensitization and Rhogam to prevent Rh sensitization and
erythroblastosis, and exchange transfusion and phototherapy to treat hyperbilirubinemia, virtually eradicated kernicterus, which had accounted for 6% of all cases of cerebral palsy seen in large clinics in the early 1950’s. Thus, for the 20 years prior to 1991, there were no published reports of kernicterus in healthy full term infants. The recent cases, during the early and mid 1990s, coincided with trends towards earlier post-partum discharge (before jaundice is clinically evident or reaches its peak) and decreased concern about the toxic potential of bilirubin. The most troubling feature of these reports was that, contrary to popular belief, many of the affected infants had been otherwise well, term newborns without evidence of hemolytic disease.6,30

**Clinical Signs**

The classic signs of acute bilirubin encephalopathy in the severely hyperbilirubinemic term infants include increasing hypertonia, especially of extensor muscles, with retrocolis, opisthotonus, in association with varying degrees of drowsiness, poor feeding, hypotonia, and alternating tone. The early presenting signs and symptoms of ABE can be described in terms of the infant’s mental status, muscle tone, and cry; these progress as the injury worsens (Table III). Because an accurate and reliable scoring system is needed to characterize the phases and progression of ABE and to determine prognosis, this schema for grading the severity of ABE has been developed as a clinical tool (Table IV).31

The presenting signs of ABE are subtle, non-specific and should be elicited by direct questioning from parent of a severely hyperbilirubinemic neonate. During this phase early and prompt interventions can prevent chronic kernicteric sequelae.32 BIND abnormalities with progression to scores between 4 and 6 are often reversible with timely interventions. These signs include early hypertonia and retrocolis, which increase in severity and are usually accompanied by a shrill cry, an unexplained irritability alternate with increasing lethargy. Advanced signs are marked by cessation of feeding, bicycling movements, inconsolable irritability and crying, possible seizures, fever and coma. These are late findings and ominous predictors of the likelihood of severe kernicteric sequelae, even with intensive treatment. Acute stage mortality is due to respiratory failure and progressive coma or intractable seizures. Rate of progression of clinical signs depends on the rate of bilirubin rise, duration of hyperbilirubinemia, host-susceptibility and presence of co-morbidities.

**b. Post-Icteric Sequelae: Chronic Bilirubin Encephalopathy**

Chronic, irreversible bilirubin encephalopathy has variable presentations and may include extra-pyridminal movement disorders (dystonia and athetosis), gaze abnormalities (especially upward gaze-figure 1), auditory disturbances (especially sensori-neural hearing loss with central processing disorders and / or auditory neuropathy), and enamel dysplasia of the deciduous teeth.1,3 Cognitive deficits are unusual but described as being occasionally present and in the retarded range in earlier reports. Such estimates probably reflected, for the most part, an inability to accurately assess intelligence in children with hearing, communication and coordination problems. The neuromotor manifestations of extra-pyramidal damage are present in almost all cases, but occasionally are apparent only with repeated attempts at skilled movements.

**B. Relationship of Total Serum Bilirubin Level to Occurrence of ABE**

There are no randomized clinical trials that demonstrate a specific bilirubin level will or will not cause neuro-toxic damage. The critical TSB level in any healthy baby is likely to be influenced by postnatal age, maturity within the range of term gestational age, duration of hyperbilirubinemia and rate-of-TSB rise. Presence of co-morbidities such as near-term gestation (35 to <38 weeks gestation), hypoalbuminemia, disruption of the blood-brain barrier (asphyxia or trauma), hemolysis (intravascular or extravascular), factors that interfere with albumin binding of bilirubin, infection, and hypoglycemia predispose a newborn to BIND at lower TSB values. A number of investigators, as noted by Poland, have presented evidence that unbound or “free bilirubin” is an appropriate predictor of neurotoxicity.33 At present there are no commercial assays for albumin binding reserve or unbound bilirubin in the US. Preliminary US and Japanese studies have suggested that levels >0.86 microg/dL of unbound bilirubin are associated with an increasing risk of BIND.34-36
The only prospective study that has shown an association between TSB levels and occurrence of ABE is that reported by Mollison and Cutbush in a 1954 follow-up report of babies with hyperbilirubinemia and hypoalbuminemia due to Rh hemolytic disease. These data are from over four decades ago and the sample size is small (n=60) and applicable to babies with severe hemolytic disease. However, an incremental relationship of kernicterus to increasing levels of TSB >19 mg/dl is apparent. Currently most US nurseries discharge babies without screening for hemolysis other than Rh disease. Though hemolysis screening could be helpful, babies with pre-discharge high-risk hyperbilirubinemia (>75th percentile for age in hours) are as likely to have impaired bilirubin clearance due to confounding genetic polymorphisms in the glucuronyl transferase gene and / or delayed maturation of the otherwise normal glucuronyl transferase enzyme system. In the Pilot Kernicterus Registry, the causes for kernicterus were attributed to three equivalent categories (one-third each): hemolytic disorders (mostly ABO isoimmunization), G6PD deficiency (associated with both hemolysis and impaired bilirubin conjugation) and idiopathic causes (presumably due to delayed or impaired function of the glucuronyl transferase enzyme system) coupled with breast-feeding and inadequate nutritional intake. In such newborns with TSB levels >75th percentile a rate of TSB rise >0.20 mg/dl/hr will exceed the peak rate of rise observed at the 95th percentile track on the bilirubin nomogram and increase the bilirubin load. At these rates of rise, the bilirubin load will increase to severe hyperbilirubinemia and risk for BIND.

C. Relationship of Bilirubin to Albumin and Risk of ABE
Albumin concentration is a powerful neuro-protective agent as well as a major determinant of both bilirubin toxicity and level of unbound bilirubin in excessively jaundiced babies. The integrity of binding (below the 1:1 molar ratio) is compromised in a newborn because newborn albumin has a poor binding ability compared to adult albumin. It is further compromised if a) albumin binding affinity is markedly decreased with concurrent prematurity, sickness or acidosis; b) protein bound drugs compete for albumin binding sites. It is further compromised for postnatal age < 72 hours, and if the serum albumin level is lower than expected. In severely hyperbilirubinemic but otherwise healthy newborns (TSB levels >95th percentile and over 72 hours age) the bilirubin to albumin ratio is a useful tool to define one’s “worry” and potential risk for BIND.

For practical purposes, the B: A ratio can be expressed in terms of mg of bilirubin to grams of albumin. A bilirubin to albumin ratio of 7.0 in mg to grams corresponds to a bilirubin to albumin molar ratio of 0.80. Exposure to bilirubin/albumin ratios of >7.0 (mg to gram) carry a clear risk of irreversible neurotoxicity, especially if such exposure is prolonged. Available clinical and experimental data suggests that B: A ratios of >5.3 and <7.0 mg/g (molar ratios of bilirubin to albumin >0.63 and <0.80) are generally associated with reversible abnormalities of auditory brainstem responses. In a term newborn with subtle signs of BIND these B: A ratio values can be reassuring as long as the bilirubin load is vigorously reduced and signs of progression are closely monitored.

D. G-6-PD deficiency, Neonatal Hyperbilirubinemia and Kernicterus
G-6-PD deficiency is one of the commonest enzyme deficiencies in humans and can present with hemolytic crises in children and adults (favism) who ingest fava beans or have exposure to stress of oxidants, drugs,
infections and other chemical triggers.\textsuperscript{36} G-6-PD deficiency is also associated with neonatal hyperbilirubinemia though favism is unusual in infants. The association with severe neonatal hyperbilirubinemia with its potentially devastating complication of kernicterus was made in Greece soon after recognition of G-6-PD deficiency as an entity and has subsequently been reported from many geographic areas in which G-6-PD deficiency is found.\textsuperscript{47} The incidence of neonatal hyperbilirubinemia has repeatedly been shown to be several-fold greater in G-6-PD deficient populations than in the G-6-PD normal population.\textsuperscript{48,49} However, this incidence is not constant and varies in different communities and geographic areas and is related to numerous mutations. Functional severe mutations may cause hemolysis in the absence of stress. Different mutations are characteristic of Asian, African, Southern Europe populations. Gourley linked neonatal jaundice with Gilbert syndrome. Neonates with the GS polymorphism have an increased rate of TSB rise in the first two days after birth and a predisposition to prolonged or severe neonatal hyperbilirubinemia in infants with G-6-PD deficiency or co-inherited with hematological abnormalities: a) beta-thalassemia, b) hereditary spherocytosis and certain forms of ABO incompatibility.\textsuperscript{50,51} Kaplan et al have observed that infants with G-6-PD deficiency do not have an increased incidence of hyperbilirubinemia (compared to G-6-PD normals) unless they also carry the UGT1A1 promoter polymorphism. Homozygotes have significantly higher TSB levels than hemizygotes.\textsuperscript{52}

Two clinical manifestations of G-6-PD deficiency and neonatal hyperbilirubinemia are described in clinical practice: 1) severe jaundice resulting from acute hemolysis, similar to favism; 2) jaundice and hyperbilirubinemia of more gradual but progressive onset. The frequency of either manifestation is not well documented.

1. \textit{Acute and severe jaundice} accompanied by sudden-onset of hemolysis is unusual in neonates. In some cases a known trigger of hemolysis can be identified and results in rapidly rising serum total bilirubin (TSB) levels. Maternal ingestion of fava beans can cause severe intrauterine hemolysis presumably by transplacental transmission of the fava metabolites. In other cases transmission of metabolites to the nursing infant via breast milk has been suggested. However, severe hemolytic episodes can occur even when all known offenders are scrupulously avoided. It is possible that as yet unidentified chemical offenders may be included in the vast array of cleaning or other household materials available. Beutler has emphasized infection as a possible inducer of hemolysis. These severe hemolytic episodes [with clinical evidence of hemolysis] can be unpredictable and there is frequently no warning that acute hemolysis is about to occur. This form of G-6-PD deficiency associated neonatal hyperbilirubinemia may not be completely amenable to prediction of hyperbilirubinemia or prevention of kernicterus.\textsuperscript{53,54}

2. \textit{Gradual onset jaundice with progressive neonatal hyperbilirubinemia}. In contradistinction to the above, significantly more G-6-PD deficient neonates develop hyperbilirubinemia compared with controls. Gradual onset jaundice with progressive neonatal hyperbilirubinemia can be severe and is associated with a slower increase in TSB concentrations than in those with acute hemolysis. With intensive, modern day phototherapy exchange transfusion is rarely necessary with this variant of the hyperbilirubinemia. As these babies are usually treated aggressively, the natural history of the hyperbilirubinemia and consequently the potential of extreme hyperbilirubinemia and the risk of kernicterus are unknown in this subgroup. There is some evidence that this form of jaundice has its origins in utero: TSB values sampled immediately after birth were higher than in controls and correlated with both third day TSB values as well as with those who subsequently developed hyperbilirubinemia, defined as TSB value >15.0 mg/dL. Also, blood carboxyhemoglobin and end tidal carbon monoxide and representative of hemolysis, were higher in G-6-PD deficient neonates than in controls shortly after birth. The pathogenesis of hyperbilirubinemia in G-6-PD deficient neonates appears to be different from G-6-PD normal counterparts, greater emphasis being laid on the role of bilirubin conjugation defects. Also important in understanding of the pathogenesis hyperbilirubinemia is the concept that the TSB at any point in time represents bilirubin production on the one hand, and its elimination from the body, on the other. As long as equilibrium between these processes is maintained, TSB concentrations should not exceed the physiologic range. However, should bilirubin production exceed the body’s capacity to eliminate it, hyperbilirubinemia may develop. Severe hemolysis is not essential to the mechanism of hyperbilirubinemia: moderately increased heme catabolism in the face of diminished bilirubin conjugation may be sufficient to tip the balance. Because increased hemolysis does not appear to play a major role in the patho-physiology of hyperbilirubinemia, diminished bilirubin conjugation has been emphasized by some as an important factor [see Figure 2]. The current literature suggests that insufficiency of bilirubin conjugation is the mechanism of neonatal hyperbilirubinemia in infants with G-6-PD deficiency.\textsuperscript{55-57} Pre-discharge hour-specific bilirubin screening can identify many G-6-PD deficient neonates at high risk for developing hyperbilirubinemia and facilitate discharge and follow-up planning. Of those G-6-PD deficient neonates with pre-discharge TSB value <50\textsuperscript{th} percentile on the hour-specific nomogram, the incidence of developing a TSB >15.0 mg/dL was very
low, but increased progressively as pre-discharge TSB values increased from the 50th to >90th percentile. Additional population-based data are needed to better describe and understand the predictive role of pre-discharge hyperbilirubinemia as well as the natural history of hyperbilirubinemia in both homozygous and heterozygous neonates with G-6-PD deficiency. 58

E. A systems-approach for a safer management of newborn jaundice

The rationale to update “bilirubin guidelines” such as the 1994 AAP guidelines59 are based on new data related to newborn safety, that jaundice is an unreliable indicator for severity of hyperbilirubinemia, the predictive abilities of pre-discharge screening for subsequent severe hyperbilirubinemia is weak and there is a need for lowered bilirubin level thresholds for interventions.60-62 These studies have provided an opportunity for restructuring to a more physician friendly instrument and enhancing its acceptance for wider implementation. The purpose of the guidelines is to ensure that clear criteria for patient safety, family centeredness, and precise, practical, user-friendly, preventive approaches and for timely interventions, are met.63 Barriers to seamless transition from birth to home have been recognized to compound the risk for hyperbilirubinemia. 64-66 Four clinical entities that add to inefficient continuity of care include 1) early discharge (<72 hours age) without timely follow-up, 2) inadequate lactation support, 3) undue reliance on the visual assessment of jaundice to initiate evaluation, and 4) lack of data to define persistence of jaundice, including the potential for unrecognized cholestatic jaundice.

1. Early discharge and multiple providers at multiple sites (problems with “hand-off”). Early discharge shifted the locus of care from the hospital to home and created a need for post discharge observation, a change in venue for patient and family education, and gaps in communication. Furthermore, follow-up appointments after hospital discharge are often scheduled after the anticipated peak of serum bilirubin concentration. Systems are limited to facilitate sharing of clinical data among multiple clinical providers at multiple sites such as between the birth hospital and the paediatric office. New parents may have difficulty arranging for a clinician to check their child after discharge. Flawed interactions between many different parties perpetuate the problems. To ensure a safe first week after birth for all newborns requires broad changes in the processes of care.

2. Inefficient lactation counseling. A clinical diagnosis of jaundice may lead to disruption of breastfeeding rather than implementation of steps that would enhance breast milk intake. Although breast milk is the most appropriate feeding for newborns, exclusive breast feeding, especially if it is not going well, is a major risk factor for hyperbilirubinemia. However, no quantitative data are available to document either the incidence of lactation failure leading to adverse hyperbilirubinemia outcomes or the incidence of lactation disruption associated with management of hyperbilirubinemia.

3. Undue reliance on visual assessment of jaundice. The AAP guideline cautions on the reliance of visual estimation of jaundice. However, the inaccuracy of visual assessment of jaundice may not be widely appreciated.

4. Persistent hyperbilirubinemia. The incidence of persistent indirect hyperbilirubinemia (age >2 weeks), especially in breastfed infants, and its possible sequelae are not known. In addition, clinical distinction of benign persistent jaundice from cholestasis is often difficult. Cholestasis, which occurs in approximately 1:2500 live births, can be a manifestation of more than 70 different diseases, biliary atresia being the most common.67,68 Factors contributing to delayed referral of infants with biliary atresia include lack of follow-up of neonatal jaundice and misdiagnosis of breast milk jaundice. Early diagnosis of biliary atresia is crucial for a successful surgical outcome but has no linkage with kernicterus. It is to be noted the 2004 AAP guidelines strongly recommends that a clinician should not subtract the direct bilirubin value from the total serum bilirubin value for clinical decisions, especially for administration of phototherapy or exchange transfusion.69

Since clear evidence for a course of action has been absent, we have recommended an approach that guarantees patient safety pending the “gathering” of evidence. Structural changes that would facilitate such a system-based approach should include a) pre-discharge bilirubin management; b) follow-up bilirubin management; and, c) lactational support and nutritional management. Currently there are two major pre-discharge screening strategies that are amenable to a system-based approach: i) pre-discharge total serum bilirubin screening and ii) a scoring system based on clinical risk factors. With either approach there should be no room for error and a wide margin of safety to prevent the need for a “crash cart” approach for babies with excessive hyperbilirubinemia. On the basis of available evidence, we should screen all babies for hyperbilirubinemia for targeted follow-up that is based on an hour-specific TSB measured for risk assessment. In addition, we should provide focused universal education with an emphasis on supporting adequate lactational nutrition to decrease severe hyperbilirubinemia and thus prevent kernicterus.70

F. Role of Chemoprevention

Chemoprevention of hyperbilirubinemia by pharmacological agents to effectively reduce adverse bilirubin loads has been studied for several years and recently reviewed by Dennergy.71 The proven available options for pharmacotherapy include drug-induced acceleration of bilirubin excretion (such as use of
Phenobarbital and alteration of bilirubin production by synthetic heme analogues that act as competitive inhibitors for heme catabolism (such as tin mesoporphyrin). In view of patient safety concerns from unmonitored adverse effects related to severe hyperbilirubinemia, the role of chemoprevention in infants at risk for severe hyperbilirubinemia is being investigated. Phenobarbital increases hepatic clearance and excretion, and may be administered prenatally.\textsuperscript{71,72} It is effective when administered 1 week prior to delivery and when given to newborn infants. However, this intervention has limited or no clinical effect when administered to infants ≤32 weeks of gestation and has now been shown to be ineffective when given prior to 12 hours of age. The adverse effects of this therapy are of concern. These are sedation, risk of hemorrhagic disease, and potential for addiction. This drug has a slow onset of effect (usually several days) and a long duration of action (one to two weeks) after its discontinuation. In addition, its confounding effects on other hormones and concerns of drug safety have limited the clinical value of phenobarbital as a chemopreventive agent for newborn jaundice.

Newer chemopreventive strategies have included investigations of a number of synthetic heme analogues that are protoporphyrin derivatives of tin, zinc, manganese, chromium, and cobalt.\textsuperscript{73} Overall, metalloporphyrins (MePs) reduce bilirubin production, can be phototoxic and may increase transcription of HO-1, the inducible HO isozyme. Effective development of this class of compounds has been in the direction of products that are less phototoxic and are stronger inhibitors of heme oxygenase. A number of MePs have been evaluated experimentally with variations of the pertinent metal (such as tin, zinc, chromium) and porphyrin (protoporphyrin, mesoporphyrin, bisglycol porphyrin, etc). Our understanding of the molecular basis of heme oxygenase inhibition is evolving as new heme oxygenase isoenzymes are characterized in different organs. The significance of prolonged and potent, long-lasting inhibition of heme oxygenase needs to be differentiated from a single, acute and transient inhibition. The inherent appeal of naturally occurring molecules, such as zinc, has been questioned by the finding of deleterious effects on rabbit bone marrow erythroid and myeloid cells and by lethal consequences of chromium mesoporphyrin injection in animals. Thus far, the stannic porphyrins, in particular tin protoporphyrin and tin mesoporphyrin have been extensively investigated and found to be safe and effective in preclinical studies. With the successful completion of nearly two decades of extensive clinical pharmacological and toxicological studies, as recently summarized by Kappas,\textsuperscript{74} stannate, an effective MeP, has demonstrated its therapeutic ability to safely reduce bilirubin production through competitive inhibition of heme oxygenase, the rate-limiting enzyme in heme catabolic sequence. Its chemopreventive role is being investigated and evaluated in infants at risk for severe hyperbilirubinemia.

Other strategies that warrant further investigations and clinical trials are use of agents that interrupt the enterohepatic circulation and bilirubin accumulation from the continued action of beta-glucuronidase. Chemoprevention with use of casein supplements\textsuperscript{75} or other agents such as L-aspartic acid could decrease intestinal reabsorption of bilirubin and may have a potential clinical role.\textsuperscript{76}

G. Global Perspective of Jaundice and Kernicterus.

Kernicterus is still thought of by many as a condition that occurs primarily in underdeveloped countries. As the JCAHO root cause list suggests, the safety net protecting newborns has significant deficits. Most families learn about potential problems related to newborn care during childbirth education classes. Unfortunately, the lack of concern about jaundice among health care providers has led to a major lacuna in childbirth education curricula.\textsuperscript{77} The teaching and discussion of jaundice, impact of early discharge, and breast-feeding have been minimal or non-existent. The role of family and community in prevention of BIND and Kernicterus is an integral component of any public health strategy.\textsuperscript{78} Since this condition is not yet a “notifiable” disease, there is an urgent need for a tightening of the “safety net” and reaching all families and health-care workers to supplement existing information and expedite change in current practices for assessing and effectively treating hyperbilirubinemia. Kernicterus is frequent and less preventable in countries with poor access to healthcare (for example: South Asia, and Africa), those with high-risk populations (Middle-East, as well as North African and South African nations) and countries who are rapidly improving their healthcare systems to contemporary standards (Eastern Europe and Latin America).

In conclusion, Kernicterus ranks as a major cause for infant mortality and morbidity in developing countries but not considered as serious as birth asphyxia, sepsis, malnutrition and prematurity. However, it is the only neonatal condition for which safe, inexpensive and effective clinical strategies are easily available. Cost-effective bilirubin reduction strategies such as promotion of breast feeding, universal availability of safe and effective phototherapy as well as chemoprevention need to be targeted to infants at risk while ensuring patient safety and universal access. Global eradication of kernicterus, through a national public health agenda, is feasible and practical. It is essential to a society that aspires for every family and their newborn to have a safer experience with newborn jaundice.

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