Editorial

For a Safer Outcome with Newborn Jaundice

The current increase in reports of kernicterus re-emergence in the past decade in babies discharged otherwise as healthy from United States hospitals represents a crisis of credibility(1-3). As pediatricians, committed to reducing infant mortality and morbidity, we bear an immense responsibility to the society when we discharge a newborn infant to home after birthing. Our clinical evaluation, risk assessment and counseling should anticipate adverse contingencies that may occur in the post-discharge setting, especially during the first week after birth. Among several preventable devastating illnesses during the first month after birth, adverse outcomes attributed to hyperbilirubinemia have been the most tragic due to our effective ability to prevent and treat excessive hyperbilirubinemia (4). The resurgence of kernicterus in several countries has led to a societal demand for patient safety and to the calls for a public health policy to reduce adverse outcomes and provide safer choices. For example, often families face a difficult emergency decision and consent for an exchange transfusion to reduce an excessive bilirubin load or treat acute bilirubin encephalopathy. Our review of lapses in care and root causes serve as the empiric evidence to model a practical, family-centered, system-based approach to monitor and manage hyperbilirubinemia to prevent acute stage kernicterus and the clinical spectrum of bilirubin-induced neurologic dysfunction (1,5,6).

Kernicterus is a "Never Event": Public health concerns of re-emergence of kernicterus have led to re-examination of our clinical approach as well as communications with families of jaundiced newborns that have evolved over the past two decades (*Table I*). The "kinder, gentler approach" to manage jaundice was pioneered by Newman and Maisels in the early 1990s(7). This concept was a clinical response to vigintiphobia" (fear of 20 mg/dl of bilirubin). Demystificaton of this 'fear' was necessary as it came about in an era when exchange transfusion with fresh blood was the only available effective intensive intervention. The resulting data about babies with elevated bilirubin levels led to questioning with regard to the concern of bilirubin neurotoxicity as a realistic problem in healthy infants(8,9). Critical review revealed essentially no evidence of adverse effects of bilirubin on IQ, neurologic examination, or hearing. They concluded that investigation and treatment of normal infants with jaundice was expensive and potentially harmful. This absence of evidence (following a diligent search by these authors) warranted a questioning of the risk of over-treatment. Components of the "kinder, gentler" approach were adopted by the American Academy of Pediatrics (AAP) Practice Parameter for "Management of Jaundice in the Term Newborn" during an era when intensive phototherapy was available as an effective intensive intervention for severe hyperbilirubinemia(4). However, concerns of a possible increase in kernicterus were raised by other bilirubin "experts" upon the adoption of these consensus-based recommendations because no mechanism had been proposed to evaluate their safety and efficacy. In a response to these concerns, Newman and Maisels(7) agreed that new recommendations should be

studied before being accepted as a new "standard of care", and that the evidence on which we based our recommendations is not sufficient to generate "a new standard of care for jaundiced infants," but that "we believe…. our recommendations are more consistent with the available (imperfect) data than the previous recommendations were." Now, national surveillance for kernicterus or its surrogate indices (bilirubin levels above 20 mg/dL before 72 hours age and over 25 mg/dL beyond 72 hours age) are being considered (10) because kernicterus due to newborn jaundice is now deemed a "Never-Event" in the USA(11).

Newborn jaundice and neonatal hyperbilirubinemia is common, usually benign and resolves with supervision of appropriate nutritional intake. These clinical manifestations are the result of an abrupt cessation of bilirubin elimination from the placenta and associated with specific deficiency of hepatic bilirubin uptake, intracellular transport and bilirubin glucoronyl-transferase activity. This is exacerbated by the fact that bilirubin production, secondary to heme catabolism is two to three-fold that of an adult. The jaundice can progress to severe hyperbilirubinemia as predicted on a validated nomogram(12) with total serum bilirubin (TSB) levels >95th percentile for age in hours in about 8 to 11% of healthy newborn infants. In some cases, newborns discharged as healthy have succumbed to serious and often irreversible post-icteric sequelae of increased bilirubin. Presence of co-morbidities of maternal factors such as: maternal diabetes, breast-feeding, mode of delivery; or, neonatal factors such as: prematurity (<38 weeks of gestation), hypoalbuminemia, hemolysis, G6PD deficiency, inborn errors of metabolism, polycythemia, bruising, ethnicity and familial factors affect the vulnerability of the infant to hyperbilirubinemia(4).

Pre-discharge Risk-assessment for Severe Hyperbilirubinemia: Pre-discharge TSB levels or transcutaneous (TcB) levels have been demonstrated to be the most predictive and useful in defining risk as well as targeting follow-up the at-risk neonate so as to prevent subsequent severe hyperbilirubinemia. Such levels can easily be compared to those shown on the aforementioned nomogram to place the baby in an appropriate risk category. For example, most term and near-term infants who have TSB levels >75th percentile have a 3-fold likelihood of developing TSB >95th percentile during the first week after birth(12). A TSB measurement at any given age represents the composite of bilirubin production and enterohepatic re-absorption minus that eliminated from the body. Following the abrupt cessation of placental elimination at birth, it takes several hours before the neonatal ability to initiate an elimination process is manifested. This interval usually takes 3 to 5 days such that hyperbilirubinemia peaks during this age period. However, earlier measurements of TSB can be predictive of severe hyperbilirubinemia regardless of its cause. The predictive window usually commences beyond 12 hours age (ideally when measured after 18 to 24 hours age). Cord TSB measurements have shown that values >2.2 mg/dL are >95th percentile. However, the predictive ability of TSB prior to 12 hours age have not been useful with poor sensitivity and specificity to warrant prediction or intervention(13). Once infants manifest an outcome of severe hyperbilirubinemia, there are two widely used treatment options (*a*) facilitation of bilirubin excretion through the use of alternative pathways (such as phototherapy), (*b*) mechanical removal of bilirubin through an exchange transfusion. Both of these modalities are effective but need to be administered in a timely manner and mandate universal follow-up. In a recent update, the AAP has

recommended a systems-approach for pre-discharge risk assessment– by clinical risk factor scoring or bilirubin screening–such that infants at risk for severe or extreme hyperbilirubinemia may be targeted for post-discharge follow-up(14).

Chemoprevention of hyperbilirubinemia by pharmacological agents to effectively reduce adverse bilirubin loads has been studied for several years and recently reviewed by Dennery(15). 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 chemo-prevention in infants at risk for severe hyperbilirubinemia is being investigated. In this issue, Arya *et al.* describe their observations following a well-designed prospective randomized masked clinical trial(16). The absence of an effective response relates to both the ability to define an at-risk population and the postnatal pharmacokinetics of Phenobarbital. This drug increases hepatic clearance and excretion, and may be administered prenatally. 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 now shown to be ineffective

TABLE I–*Reemergence of Kernicterus (Voluntarily Reported to the Pilot Kernicterus Registry) as Clinical and Public Health Concern. (Epidemiological Incidence of Kernicterus is Unknown Because it is Not a Reportable Condition and the Clinical Diagnosis are Often Delayed or Avoided Because of Medico-Legal Concerns).*

Years of reports	Number of cases reported	Average cases per year	Increase in cases per year	Prevalent health care practice
1953 - 1962*	15	1.5	+ 0.6	Use of exchange transfusion for TSB levels >20 mg/dL
1963 - 1972*	17	1.7	+ 0.8	Phototherapy introduced
Index decade (lowest number of kernicterus cases)				Aggressive phototherapy to prevent progression of TSB from 15 to 20 mg/dL so as to prevent an exchange transfusion.
1973 - 1982	1	0.9	0	
1983 - 1985	3	1.0	+ 0.1	Vingitophobia questioned
1986 - 1988	7	2.3	+ 2.2	Evidence of bilirubin neurotoxicity sought in healthy babies
1989 - 1992	23	5.7	+ 5.6	Kinder, Gentler approach to newborn jaundice recommended
1993 - 1994	24	8.0	+ 7.1	Practice guidelines consensus developed
1995 - 1996	19	8.5	+ 7.6	AAP Practice Guidelines recommended
1999 - 2000	19	8.5	+ 7.6	Kernicterus reemergence reported
2001 - 2002	15	7.5	+ 6.9	Clinical and public health concerns raised
2001-to date	AAP and others recommend a systems-approach to manage newborn jaundice (1,2,3,5,6,14)			

* as reported in the medical literature (13).

when given prior to 12 hours age. The adverse effects of this therapy are also of concern. These are–sedation, risk of hemorrhagic disease, and is potentially addictive. However, it has slow onset of effect (usually several days) and a long duration of action (one to two weeks) after its discontinuation. This drug also has confounding effects on other hormonal synthesis and balance. It is for these concerns of safety that the drug has not achieved clinical value or recognition as a chemopreventive agent.

Newer chemopreventive strategies of neonatal jaundice have included investigations of a number of synthetic heme analogues that are protoporphyrin derivatives of tin, zinc, manganese, chromium, and cobalt(17). 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 sought for less phototoxic and 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 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 to be safe and effective in preclinical studies. With the successful

TABLE II–*Steps For a Safer Outcome With Newborn Jaundice in Otherwise Healthy Infants.*

Steps for a safer outcome	Proposed action strategies
Level of concern	Health and societal education for risks of adverse outcomes due to unmonitored or untreated newborn jaundice
Upon visual concern for jaundice	Unfettered access for nurses / clinicians to measure TcB/TSB levels
Lactational support	Early and on-site lactational instructions for effective intake for all at-risk infants defined by clinical maternal and neonatal factors for hyperbilirubinemia (see text)
Estimate of severity risk	Screen on all infants prior to discharge from birthing hospital and plot the TcB/TSB on a hour-specific bilirubin nomogram
Target follow-up of at-risk infants	Track TcB/TSB on the hour-specific bilirubin nomogram
Timely intervention for severe shyperbilirubinemia	Educate clinicians and "first contact" clinician regarding clinical sign of cute bilirubin encephalopathy
Surveillance of “close-calls”:	Institutional and peer review of care to provided to infants with TSB levels > 25 mg/dL (beyond 72 hours age).

Based on lessons learned from the Pilot Kernicterus Registry(1).

completion of nearly two decades of extensive clinical pharmacological and toxicological studies, as recently summarized by Kappas and Alexander(17,18), 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 entero-hepatic circulation and bilirubin accumulation from the continued action of beta-glucoronidase. Chemoprevention with use of casein supplements or other agents such as L-aspartic acid could decrease intestinal reabsorption of bilirubin and may have a potential clinical role(19).

In conclusion, any approach to manage newborn jaundice, in infants discharged as healthy after birthing, needs to be rigorous, preventive, more broadly based but easier to implement and monitor (*Table II*). The actual risk of unmonitored neonatal jaundice is not known(13). Unfortunately, even in the USA, jaundice may be inadequately or ineffectively monitored, with disastrous results of continued mortality and morbidity of a small but very important number (yet to be determined incidence) of otherwise healthy and precious infants. A system-based approach that is based on the best available evidence to date is efficient, less costly, safer and (most importantly) credible for all newborns. It will require prospective public health validation during its implementation phase. As caring clinicians, our moral and duty-bound responsibilities require us to truthfully communicate with families during the first week and month after birth the safety concerns of all relevant risks(20). In the current era, our reassurance for safety has to be based only on impeccable evidence for patient safety from both severe jaundice and chemo-preventive agents. We as a society have the intellectual capacity and resources to do so. Until, we obtain such evidence; we cannot shield ourselves by comfort of inaccurate numbers, assumptions and statistics (or their lack). With availability of credible evidence, we have the capacity to explain the meaning of risk to practicing clinicians who have the talent to translate their applicability to individual families. In the meantime, let us heed our errors and ignorance and implement a "*kinder, gentler and safer*" strategy.

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