

Management of neonatal hyperbilirubinemia

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In the late 1980s, the question whether bilirubin damaged the brain of healthy infants was unanswered. The absence of documented evidence influenced the formulation of the 1994 consensus-based guidelines for the management of jaundice. Though there has been no formal outcome evaluation of the impact of these guidelines, evidence of bilirubin-related brain damage has been reported in infants with kernicterus discharged as healthy from well baby nurseries through voluntary reports to the informal Pilot Kernicterus Registry.

Do these and other cases indicate a re-emergence of kernicterus in the US? Do we know the risk of clinically monitored jaundice and the current prevalence of kernicterus and can we define the risk for occurrence of kernicterus? As these questions were addressed, lapses in care were identified and attributed as root causes of kernicterus in an era when there should be no barriers

to safe and effective bilirubin-reduction strategies. Of these barriers, lack of continuity of medical supervision during the first week after birth emerges as an underlying concern.

Are there sequelae of severe or prolonged moderate hyperbilirubinemia in the absence of recognized acute bilirubin encephalopathy? More importantly, can we define a bilirubin level that is safe? The updated 2004 AAP guidelines attempt to address these questions and recommend, by consensus, a systems approach which, if implemented by all birthing institutions, should prevent virtually all cases of kernicterus in term and near-term infants. Pending formal evidentiary basis for this preventive strategy, these clinical cases of kernicterus remind us of a need to be vigilant.

Introduction

In October 1994 the Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia

of the American Academy of Pediatrics (AAP) published a practice parameter dealing with the management of hyperbilirubinemia in the healthy term newborn [1]. Ten years later the updated clinical practice guideline [2] represents a consensus of the committee charged by the AAP with a careful review of the evidence and the literature [3].

Concerns about the re-emergence of kernicterus from both the public health community and advocates led to alerts and the declaration of kernicterus as a “never-event” [4, 5, 6, 7]. In light of these events, practicing clinicians face a number of unresolved questions in their daily clinical practice.

Answers to some of these questions are not easily forthcoming because of inadequate evidence-based data, and clinicians will need to rely on clinical experience and continued “worry” [8]. It is evident that clinical decisions will need to be governed by concerns for patient safety and long-term well-being [9].

Does bilirubin damage the brain of healthy infants?

Prior to publication of the 1994 AAP recommendations, the pediatric literature was notable for several articles on a kinder, gentler, demedicalized management of neonatal hyperbilirubinemia because of the apparent “lack of evidence” of bilirubin neurotoxicity in term, apparently healthy babies cared for in the well baby nurseries of the US, Canada and Europe from the 1960s to early 1980s.

It has been claimed that “most studies have failed to substantiate significant association between a specific level of total serum bilirubin (TSB) during ‘non hemolytic’ hyperbilirubinemia in term newborns and subsequent IQ or serious neurologic abnormality (including hearing deficits)” [1].

These recommendations were accepted and placed in practice even though there was a recognition that some studies had detected differences in outcome associated with TSB levels in these low-risk babies [8,

10, 11]. Documented cases of classic kernicterus in infants discharged as healthy from their birth hospitals now confirm that bilirubin can indeed be neurotoxic [9, 12, 13].

Is there a re-emergence of kernicterus in the US?

The 125 cases reported from the Pilot Kernicterus Registry are evidence of shortcomings of the current management of newborn jaundice [11, 12, 13]. One year after publication of the Newman and Maisels articles (1989 and 1990) on the relationship of bilirubin and brain damage in healthy term infants [14, 15] and seven years after the widely quoted Vigintiphobia article [16], the first of reports of kernicterus in term healthy newborns appeared [8].

“Management of Jaundice in the Term Newborn: a Kinder, Gentler Approach” was introduced in 1992 [17], and in 1994 the first AAP Practice Parameter for “Management of Jaundice in the Term Newborn” was published in Pediatrics [1]. Invited commentaries on the “Kinder, Gentler Approach” by other bilirubin “experts” were also published in the same issue [18].

In several of these, concerns were raised that adoption of “consensus-based” recommendations without further scrutiny might lead to an increase in kernicterus and that no mechanism had been proposed to evaluate their safety and efficacy in this newborn population cared for in an era of shortened hospital stays, cost containment and advocacy of breastfeeding.

In response to these commentaries [19] Newman and Maisels 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, [...] we believe however that our recommendations are more consistent with the available (imperfect) data than the previous recommendations were. [...]”

We join Drs. Cashore and Wennberg in encouraging

groups like the American Academy of Pediatrics to develop their own practice guidelines, and that, as Dr. Wennberg suggests, whatever guidelines are developed, outcome evaluation [...] should [...] be an important step in the process. In the meantime, we believe the kinder, gentler approach to the jaundiced infant is also the more prudent."

The frequency of voluntary reports of kernicterus over the past five decades is compiled in **TABLE I**, and the pattern of reports is juxtaposed with prevalent clinical practice. Despite publication of the 1994 AAP guideline for the management of hyperbilirubinemia and the availability of effective strategies to reduce TSB, kernicterus has continued to occur. Systems to monitor the incidence of severe hyperbilirubinemia, kernicterus and other adverse outcomes attributed to newborn jaundice were not put in place.

What has been the outcome evaluation of the 1994 AAP guidelines?

No formal evaluation of the impact of this "Kinder, Gentler" approach to jaundice management in the

general population of newborns was initiated by the public health community. However, Drs Brown and Johnson did initiate an informal voluntary registry of cases at the 1992 Kernicterus Symposium (Pediatric Academic Societies).

Report and analysis of cases on healthy term and near-term infants who sustained kernicteric damage (contributed by colleagues and parents from a broad geographic area) during the period in question have been presented and recorded [9, 12, 13]. Evidence from this convenient sample argues strongly for urgent changes to ensure safer newborn care (for the family and the clinician) as well as the need to establish a formal surveillance for bilirubin-related adverse outcomes.

What is the current prevalence of kernicterus?

The actual risk of unmonitored and untreated neonatal jaundice is not known. In the US and elsewhere, jaundice may be inadequately or ineffectively monitored, with disastrous results of continued mortality and morbidity of a small but very important number of otherwise healthy and precious infants.

Years of reports	Cases voluntarily reported	Average cases per year	Magnitude of change per year	Prevalent healthcare practices for management of jaundice
1953-62	15	1.5	+ 0.6	Use of exchange transfusion for TSB levels >20 mg/dL
1963-72	17	1.7	+ 0.8	Phototherapy introduced
1973-82	1	0.9	0	Phototherapy to prevent progression of TSB from 15 to 20 mg/dL so as to prevent need for an exchange transfusion
1983-85	5	1.7	+ 0.8	Vigintiphobia questioned
1986-88	15	5	+ 4.1	Evidence for bilirubin toxicity sought in reports of kernicterus in healthy babies
1989-91	18	6	+ 5.1	Kinder, Gentler Approach recommended
1992-94	29	10	+ 9.1	AAP Practice Guidelines in development
1995-97	32	11	+ 10.1	Ongoing implementation and distribution of 1994 AAP Practice Guidelines
1998-01	34	8.5	+ 7.6	Increasing awareness of the re-emergence of kernicterus in USA
2002-04	26	8.7	+ 7.8	JCAHO and CDC Alerts and AAP Update: Re-emergence of kernicterus

TABLE I: Reports of kernicterus in the world literature (1953 to 2004)

Unfortunately, these attitudes are not limited to the US but have been exported to Europe as evident from a recent report of kernicterus in Denmark [20]. Ebbesen provided the first factual evidence of kernicterus incidence in the 21st century in the universally available phototherapy era. His report documents six cases over a five-year period for an estimated incidence of 1:38,000 well babies cared for in Danish nurseries.

This observation is consistent with the preliminary US data that estimates an incidence of kernicterus at 1:27,000 well babies discharged in a healthcare system that provides universal access to phototherapy and exchange transfusion [21].

What is the risk of clinically monitored jaundice?

Clinical reports from large population groups cared for by a health system in a multicenter study provide an insight to the incidence of severe hyperbilirubinemia in newborns with screening and treatment at clinician discretion. In this regard it is important to point out the significance as well as the qualifications and limitations of Newman's study in the "captive" populations of newborns in a mature HMO (Health Management Organization) [22].

Follow-up of these newborns after hospital discharge was an established (and enforced) policy, in addition to general adherence to AAP guidelines for phototherapy. The incidence reported for bilirubin levels of 25 mg/dL (427 $\mu\text{mol/L}$) or above in spite of these conditions (1:700 infants) excluded infants with early onset jaundice who were treated before hospital discharge.

These data are consistent with the 1:625 incidence observed by the Collaborative Perinatal Project in the late 1960s [23]. Not addressed in such studies is the incidence of severe hyperbilirubinemia in the population at large, without the intervention of phototherapy or absence of standard of prenatal and perinatal care available in developed countries with regard to infection and Rh disease surveillance.

The approach to safely manage newborn hyperbilirubinemia needs to be more rigorous, more broadly based and easier to implement and monitor. A system-based approach that is based on universal predischARGE bilirubin screening and the best available evidence to date that is efficient, less costly and (most importantly) safer for all newborns [12, 13, 24, 25, 26].

What defines the risk for occurrence of kernicterus?

Investigators have unsuccessfully attempted to correlate the occurrence of kernicterus to a specific or threshold total serum bilirubin level. These have included the diagnostic criterion of a serum bilirubin level above 30 mg/dL (513 $\mu\text{mol/L}$). The bilirubin level criterion has limited but useful evidentiary basis; a significant number of infants with such severe levels of hyperbilirubinemia have been known to escape neurologic injury with prompt interventions [27].

Bilirubin biology strongly argues for use of unbound bilirubin, in a hyperbilirubinemic infant, as a more precise index of toxicity [28]. An increased T-2 weighted signal in the globus pallidus (by MRI – Magnetic Resonance Image) now provides for an objective and distinct evidence of an earlier bilirubin-induced injury [29, 30].

Precise diagnostic criteria for both acute and chronic injury have yet to be defined in a prospective study. Clinical manifestations of both acute bilirubin encephalopathy in jaundiced newborns (irrespective of specific TSB levels) and chronic kernicterus in term and near-term infants are classic and have been described extensively.

These constellations of signs are as diagnostic as clinical signs used for diagnosis of retinopathy of prematurity (now extinct in term newborns). Both require early clinical recognition and acute intervention but are best prevented. Several infants, reported from the Registry, with unequivocal acute-stage kernicterus who received aggressive treatment with intensive phototherapy, exchange transfusion and sometimes serum albumin infusions, appeared to have escaped irreversible bilirubin brain damage [12, 13].

With regard to the suggestion that a specific “high” TSB level be required for a diagnosis of bilirubin encephalopathy, it is important to note that the median TSB level in the reported cases was above 35 mg/dL (598 μ mol/L), but that some babies with TSB levels below 30 mg/dL (513 μ mol/L) prior to age 72 hours and below 25 mg/dL between ages 36 to 48 hours were at risk as compared to babies with higher TSB levels at a later age.

This observation may reflect measured changes in albumin bilirubin binding affinity with postnatal age, and known changes in blood brain barrier function and vascular and blood gas equilibrium in the first 24 to 36 hours after birth [12].

Are there sequelae of severe or prolonged moderate hyperbilirubinemia in the absence of recognized acute bilirubin encephalopathy?

Characterization of neurologic damage as “subtle” or “minor” makes use of subjective adjectives. In their article, Soorani-Lunsing et al prospectively observed the association of an increase in minor neurologic dysfunction throughout the first year of life (study limited to the first year) to the degree of hyperbilirubinemia (233 to 444 μ mol/L) that appears to have a dose-response relationship [31].

The recurrent question asked, “are moderate degrees of hyperbilirubinemia [...] really safe for the brain” has yet to be answered. The relevance of “subtle” or “minor” neurologic abnormalities is of prime clinical importance for practicing pediatricians. If pertinent and preventable, this question, at the very least, should be prioritized for research and either proven or disproven.

Examples listed by Soorani-Lunsing et al include abnormal postural behavior, high-frequency tremors, and deviancies in muscle tone regulation at ages 3 and 12 months that have been reported to progress beyond puberty to muscle tone dysregulation, choreiform dyskinesia, manipulative disability and coordination problems [31-34].

In the classical study of the Collaborative Perinatal

Project conducted in the prephototherapy era of 1960s, the “minor” deficits that were investigated included gait abnormalities, awkwardness, tremors and exaggerated extrapyramidal reflexes. Identification of these deficits requires diligent and painstaking neurological examinations that are often not feasible in a busy pediatric practice [14, 15, 23].

Physical signs, probably “minor” to the practicing clinician, may have a profound personal impact on the child and family. In an era when pediatricians hope to enhance academic and athletic abilities of children, it should be our mandate to address this question of a “safe” bilirubin level by a meticulous, deliberate and scientific investigation. Pioneering research of the cellular mechanisms of bilirubin neurotoxicity will hopefully lead to a better understanding [34 -38].

Can we define a bilirubin level that is safe?

The need for ongoing re-evaluation of clinical practice is rooted in a search for a safer approach to manage newborn hyperbilirubinemia in changing healthcare ecosystems [12, 26, 39].

Consensus and evidence-based data indicate that **a)** kernicterus, based on a standardized definition, can almost always be prevented in term healthy infants; **b)** until we know the risk of unmonitored and untreated hyperbilirubinemia, a systems approach would be safer; and **c)** there is a need to define “safe” levels of bilirubin in healthy and sick infants.

Pediatricians who have managed babies with hyperbilirubinemia that progress to clinical signs of either acute or chronic bilirubin encephalopathy often feel regret and personal vulnerability and therefore are reluctant to discuss, review or publish their experiences. Hence, the scope of the true incidence of overt kernicterus as well as potential “subtle” neurologic deficits cannot be ascertained without a formal, broad-based research agenda.

These issues are further confounded in sick infants in whom the role of bilirubin binding and unbound

bilirubin is even more essential in defining the risk of injury. Our experience with universal predischarge bilirubin screening in the well baby nursery suggests that hour-specific TSB levels <40th percentile appear to be safe in terms of the magnitude of hyperbilirubinemia and the potential risk for subsequent adverse outcome when routine follow-up is provided.

Can we prevent kernicterus by a practical approach?

Continuing occurrences of neonatal mortality and morbidity due to kernicterus have led to a question of patient safety in the management of newborn jaundice [13, 40]. Every one of the cases reported from the Registry, including the fatalities, could have been prevented by the systems approach, based on the Hour-specific Bilirubin Nomogram suggested in our papers [12, 13, 24].

It needs to be emphasized that the approach we suggest has, in pilot studies, been highly effective in reducing the incidence of severe and dangerous hyperbilirubinemia and the need for exchange transfusion, without an increase in costs.

This is the case when viewed in terms of hospital readmissions for excessive hyperbilirubinemia or against the background of costs of caring for children with handicapping kernicteric disabilities. The new 2004 AAP guidelines do not offer new treatment options for hyperbilirubinemia but focus on prevention of severe hyperbilirubinemia and emphasize patient safety; **TABLE II** compares the major differences between the 1994 and current guidelines.

As the 2004 guidelines are implemented, success for the stated goals, reduction in the incidence of severe hyperbilirubinemia and possibly kernicterus, should be demonstrable.

Clinical Practice	1994 AAP Guidelines	2004 AAP Guidelines
Approach	Practitioner-driven	Systems approach
Breastfeeding	Acceptable interruption of breastfeeding	Promotes breastfeeding and lactation support
Gestational Age	Care outlined by term gestation	Care for infants >35 weeks of gestation
Jaundice	Evaluation based on recognition of jaundice	Limitations of jaundice defined and emphasized
Total Serum Bilirubin	Day-specific values	Hour-specific plotted on the nomogram
Tc Bilirubin	Limited accuracy in infants of color	Newer technologies available
Bilirubin: Albumin	Biological role identified	Recommended for clinical use
Interventions	Intensive phototherapy and exchange transfusion thresholds defined	TSB thresholds for intervention adjusted for gestational age and risk factors. Immunoglobulin (IVIG recommended)
Predischarge Risk assessment	(not defined)	Predischarge TSB and/or clinical risk factors risk assessment recommended for all infants
Postdischarge Follow-up	Recommended at clinical discretion	Mandatory follow-up for all infants (at age 3 to 5 days)

TABLE II: 2004 AAP guidelines to manage hyperbilirubinemia: changes in clinical practice

A need for vigilance

The need for changes in the 1994 practice guidelines has been due to an increased awareness that kernicterus can occur in infants cared for in the well baby nurseries. Regardless of the cause for jaundice, the potential risk of unrecognized, unmonitored, untreated severe hyperbilirubinemia has raised concerns for patient safety.

Because kernicterus is preventable but not treatable, and because early and intermediate stages of acute bilirubin encephalopathy may be reversible with prompt and effective bilirubin reduction strategies, our focus needs to shift to a preventive approach, it is in this context that we advocate the universal application of principles enunciated by the Institute of Medicine [41] for patient centeredness, patient safety, timeliness of care and use of effective interventions to prevent kernicterus.

The goal of contemporary society has been best enunciated by the public health community: *"One case of kernicterus is one too many; we can prevent them all"*. Future evidence of adverse effects of either undertreatment or overtreatment of hyperbilirubinemia should continue to impact clinical practice.

A laudable effort by the AAP to monitor and facilitate the implementation of the guidelines offers a promise for continued vigilance [42]. As we pediatricians balance evidence-based medicine with patient safety, let us be truly prudent and protective of all newborn entrusted to our care.

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