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REVIEW ARTICLE

The Neurological Sequelae of Neonatal Hyperbilirubinemia: Definitions, Diagnosis and Treatment of the Kernicterus Spectrum Disorders (KSDs)

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Abstract: ***Background*:** Despite its lengthy history, the study of jaundice, hyperbilirubinemia and kernicterus suffers from a lack of clarity and consistency in the key terms used to describe both the clinical and pathophysiological nature of these conditions. For example, the term Bilirubin-induced Neurological Dysfunction (BIND) has been used to refer to all neurological sequelae caused by exposure to high levels of bilirubin, to only mild neurological sequelae, or to scoring systems that quantitate the progressive stages of Acute Bilirubin Encephalopathy (ABE).

***Objective*:** We seek to clarify and simplify terminology by introducing, defining, and proposing new terms and diagnostic criteria for kernicterus.

***Methods*:** We propose a systematic nomenclature based on pathophysiological and clinical criteria, presenting a logical argument for each term. Acknowledging observations that kernicterus is symptomatically broad and diverse, we propose the use of the overarching term Kernicterus Spectrum Disorders (KSDs) to encompass all the neurological sequelae of bilirubin neurotoxicity including Acute Bilirubin Neurotoxicity (ABE). We further suggest subclassification of KSDs based on the principal disabling features of kernicterus (motor, auditory). Finally, we suggest the term subtle KSD to designate a child with a history of significant bilirubin neurotoxicity with mild or subtle developmental delays.

***Results and Conclusion*:** We conclude with a brief description of the limited treatments currently available for KSD, thereby underscoring the importance of further research. We believe that adopting a systematic nomenclature for the spectrum of clinical consequences of hyperbilirubinemia will help unify the field and promote more effective research in both prevention and treatment of KSDs.

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1. INTRODUCTION

Avoiding neurological damage is the driving force behind understanding, screening, preventing and treating neonatal hyperbilirubinemia. A significant issue within this field is the lack of clarity with regards to the terminology used to describe the conditions associated with bilirubin-induced neurological damage. In this article, we seek to clarify and simplify this terminology by introducing and defining the term Kernicterus Spectrum Disorder (KSD) and then proposing diagnostic criteria for the KSDs. Finally, we will conclude with a discussion of treatment of the KSDs.

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It is important to acknowledge in this article that we do not address hyperbilirubinemia per se. As far as brain damage and neurological sequelae are concerned, neither high Total Serum Bilirubin (TSB) nor high serum Unconjugated Bilirubin (UCB) are the relevant neurotoxic agents. While they certainly are very important risk factors, the neurotoxic agent is clearly free unconjugated bilirubin (Bf, a.k.a. unbound bilirubin) in the Central Nervous System (CNS) [1-4]. Ahlfors has recently summarized efforts to improve the prediction of CNS Bf exposure using TSB and a panel of plasma based albumin-bilirubin binding tests [5].

The severity of the neurodevelopmental outcome in relation to the CNS Bf exposure is modified by factors such as the maturation of the CNS at time of exposure, hemolysis, bilirubin conjugation and elimination, inflammation, acido-

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sis, and mitochondrial and oxidative function, plus perhaps some as yet undetermined genetic factors. The risk of KSDs is assessed acutely by neurophysiological tests such as the auditory brainstem response (ABR, a.k.a. brainstem auditory evoked response) and imaging techniques such as Magnetic Resonance Imaging (MRI). In addition, genetic pathways that determine the relative susceptibility to bilirubin neurotoxicity are hypothesized to be important [6, 7]. Standard nomenclature and diagnostic criteria for KSDs are needed to create consistent outcome measures that can be used to assess the effectiveness of preventative strategies and treatments, and ultimately lead to greater precision in determining the risk of neurological damage from neonatal hyperbilirubinemia.

2. NOMENCLATURE AND DEFINITIONS

We believe that consistent precise nomenclature and standardization of diagnostic criteria will lead to better communication, better outcome measures and better understanding of the risks of neonatal hyperbilirubinemia. These improvements will ultimately lead to both better prevention strategies and treatment of KSDs.

Traditionally, the term kernicterus meant the pathological finding of yellow staining (icterus) of the deep nuclei or "kernel" of the brain. However, improvements in methods such as neuroimaging have allowed for the visualization of abnormalities of specific basal ganglia structures *e.g*., the globus pallidus and subthalamic nucleus. Improvements in imaging, along with other laboratory tests *e.g*., ABR, and clinical signs of Acute Bilirubin Encephalopathy (ABE) [8] have resulted in the ability to confirm a diagnosis of kernicterus without the pathological evidence provided at autopsy.

The use of overlapping terminology such as bilirubin neurotoxicity, ABE, Chronic Bilirubin Encephalopathy (CBE), kernicterus, and Bilirubin-induced Neurological Dysfunction (BIND) [9-12] can lead to confusion. A prime example is seen in the usage of BIND. One might assume that the term BIND would refer to any and all neurological conditions caused by exposure to high levels of bilirubin and in fact it has been used in this manner [3, 9-14]. However, BIND is also commonly used to designate only individuals with relatively mild neurological damage due to bilirubin *i.e*., subtle kernicterus. For completeness, BIND also refers to a scoring system that characterizes quantitatively the progressive stages of ABE [15, 16]. Likewise, the term kernicterus, often used to refer to patients with severe dysfunction, can also be reserved for those individuals with isolated motor or auditory dysfunction [10, 11]. Adding to the confusion is whether the term chronic bilirubin encephalopathy should be used interchangeably with kernicterus.

We propose the use of the overarching term *Kernicterus Spectrum Disorders (KSDs)* to encompass all the neurological sequelae of bilirubin neurotoxicity. We believe that the adoption of KSD is warranted because it incorporates the classically used terminology of kernicterus with the idea that those affected by bilirubin neurological injury represent a diverse spectrum of disorders in both the type and severity of damage.

We believe that to have consistency in the literature, especially in outcome studies, the largely synonymous terms BIND and chronic bilirubin encephalopathy should be abandoned in favor of the singular term KSD. We suggest that when referring to a subset of the spectrum, modifier terms such as mild, moderate and severe can be used with KSD. In conjunction with these severity modifiers, the subtype modifiers auditory, motor and classical kernicterus should also be used to indicate auditory-predominant, motor-predominant and both auditory and motor dysfunction, respectively. It is important to emphasize that this nomenclature represents a significant change from what was previously proposed by many researchers in the field, including one of the authors of this paper (SMS, see for example [10]).

Finally, use of the modifier terms "acute" and "chronic" need to be reviewed. Traditionally, these temporal modifiers are used in conjunction with the term "bilirubin encephalopathy" to differentiate between the initial "acute" signs that can occur at the time of injury, for example high-pitched cry and opisthotonus, and the long term "chronic" symptoms that can develop after the initial injury. Acute signs, as the term implies, are only seen for a short time. Furthermore, they do not necessarily predict outcome. In this context, the term Acute Bilirubin Encephalopathy (ABE) appropriately describes the signs associated with bilirubin neurotoxicity at the time of the exposure. Indeed, the illness is acute and the hyperbilirubinemia is the etiology of the encephalopathy. The appropriateness of the term ABE is in contrast to the use of the term chronic bilirubin encephalopathy. The latter implies an encephalopathy secondary to continued bilirubin exposure, which is almost never the case[1]. The damage is a static one caused by hyperbilirubinemia that has since resolved. Chronic bilirubin encephalopathy refers to the long-term consequences of an acute but resolved process. This is analogous to the use of the terms hypoxic-ischemic encephalopathy and cerebral palsy. Hypoxic-ischemic encephalopathy refers to an acute injury to the brain caused by ischemia, while cerebral palsy refers to the long-term consequences of the ischemic injury. Thus, we propose that the term acute bilirubin encephalopathy should only be used to designate the acute phase of bilirubin encephalopathy and that the term chronic bilirubin encephalopathy be abandoned in favor of KSD.

As an example of this designation system a patient with KSD could be described as having severe motor kernicterus or moderate auditory kernicterus or compound diagnoses such as mild motor, severe auditory kernicterus. Incorporating a single terminology along with a standardized set of modifiers to describe the different subtypes and their severity will significantly reduce confusion for researchers, providers, families and affected individuals as well as improve the overall comparability of future research studies.

The challenge going forward will be to develop an acceptable set of guidelines to define the different levels of severity for both motor and auditory sequelae. In Table **1**, we

[1] With the possible exception of Crigler-Najjar syndrome, which causes prolonged, life-long unconjugated hyperbilirubinemia that if inadequately treated may cause repeated episodes of bilirubin neurotoxicity. However, even in this condition, the neurological sequelae may result from repeated discrete episodes of bilirubin neurotoxcitiy which cause first ABE and subsequently kernicterus.

Table 1. Proposed kernicterus spectrum disorder nomeclature (A) and guidelines for determination of severity (B).

A. Kernicterus Spectrum Disorder Subtypes.

	Auditory - None	**Auditory - Mild**	**Auditory - Moderate**	**Auditory - Severe**
Motor - None	None	Mild Auditory	Moderate Auditory	Severe Auditory
Motor - Mild	Mild Motor	Mild Motor and Auditory	Mild Motor, Moderate Auditory	Mild Motor, Severe Auditory
Motor - Moderate	Moderate Motor	Moderate Motor, Mild Auditory	Moderate Motor and Auditory	Moderate Motor, Severe Auditory
Motor - Severe	Severe Motor	Severe Motor, Mild Auditory	Severe Motor, Moderate Auditory	Severe Motor and Auditory

B. Kernicterus Spectrum Disorder Severity

	Auditory Kernicterus	**Motor Kernicterus**
None	No auditory symptoms	No motor symptoms
Mild	Mild ANSD ABR abnormal but present, may normalize with time) or CAPD ± mild hearing loss; normal or mildly delayed speech	Mild abnormal muscle tone ± writhing movements (athetosis); mild gross motor delays *e.g.* walking; ambulates well, speech is intelligible
Moderate	ANSD with absent or persistent abnormal ABR, mild/moderate hearing loss, may fluctuate; speech delayed or absent	Moderate abnormal muscle tone ± writhing movements, "athetoid" CP; ambulates with or without assistance with abnormal gait with abnormal tone and postures of the hands and feet.
Severe	ANSD with absent ABR, severe-to-profound hearing loss/deafness	Severely abnormal tone ± writhing movements, athetoid CP; unable to ambulate, feed self, sign, speak; often with episodes of severe increased tone and muscle cramps

Abbreviations: ANSD: Auditory Neuropathy Spectrum Disorder; ABR: Auditory Brainstem Response; CAPD: Central Auditory Processing Disorder; CP: Cerebral Palsy; KSD: Kernicterus Spectrum Disorder.

suggest the following guidelines to describe the different levels of severity for both motor and auditory sequelae. The severity of auditory KSD is determined by the amount and persistence of Auditory Neuropathy Spectrum Disorders (ANSDs), Central Auditory Processing Disturbance (CAPD) and hearing loss, and the amount of hearing loss. The term Auditory Neuropathy Spectrum Disorder (ANSD) was coined at a consensus meeting in Lake Como, Italy in 2008[2]. ANSDs are assessed by abnormal or absent ABRs with normal or giant cochlear microphonic responses (CMs) with or without normal Otoacoustic Emissions (OAEs).

We note that there is some debate in the audiology literature regarding the nomenclature and classification of ANSD. The discussion mainly concerns the term "neuropathy", which refers to an abnormality of a peripheral nerve. At issue here is that there is no all-encompassing term that includes injury to both peripheral and central nerves and their central pathways [17, 18]. For example, the primary afferent bipolar auditory neurons originate in the cochlea (inner ear), traverse the peripheral and central auditory portion of the (VIIIth) cranial nerve, enter the central nervous system in the brainstem (pons) and synapse at the ventral and dorsal cochlear nuclei. Kernicterus clearly affects brainstem auditory nuclei (cochlear nucleus, superior olivary complex, medial nucleus of the trapezoid, lateral lemniscus and inferior colliculus) [19] and evidence from the Gunn rat animal model suggests that kernicterus likely also affects the peripheral auditory nerve as well, especially the large myelinated fibers that underlie neural synchrony [20]. Kraus, in a 2014 editorial [21] now considers auditory neuropathy as a spectrum encompassing several pathologies, including disorders of the brainstem, auditory nerve, and ribbon synapses that promote rapid neurotransmitter release and sustained signal transmission [22, 23]. In our opinion, the auditory findings in KSD meet the functional definition of ANSD and this controversy as it relates to ANSD nomenclature is semantic and not germane to our classification of KSD.

Another audiological discussion is whether ANSD should be classified as a central auditory processing disorder (APD) or should be categorized separately. The American Speech Language Hearing Association characterizes auditory Processing Disorders (APD), a.k.a. Central Auditory Processing Disorders (CAPD) as central nervous system auditory deficits that are not the result of other higher-order cognitive, language, or related disorder such as autism, intellectual disabilities, attention deficits, or similar impairments [24].

We agree with Kraus' editorial [21] that ANSD is a specific type of APD. Thus, we consider the auditory pathology associated with KSD an ANSD, using the functional definition of ANSD absent or abnormal ABRs with presence of CMs ± OAEs, and it is also a type of APD under the biological umbrella of neural synchrony [21]

In our experience with ANSD associated with KSD, OAEs are present initially but may disappear with time in the

[2] Hayes D, Sininger Y, Starr A, *et al.. Guidelines for Identification and Management of Infants and Young Children with Auditory Neuropathy Spectrum Disorder;* 2008. Available at: www.thechildrenshospital.org/conditions/speech/danielscenter/ANSD-Guidelines.aspx. Accessed December, 2016.

first year of life, whereas CMs are always present. Thus, abnormal or absent ABRs with the presence of CMs establish the functional diagnosis of ANSD, whereas abnormal or absent ABRs with normal OAEs is consistent with the diagnosis of ANSD, but abnormal or absent ABRs with absent OAEs does not distinguish between ANSD and Sensorineural Hearing Loss (SNHL). Abnormal but not absent ABRs associated with ANSD in KSD are characterized by the presence of wave I (from the auditory nerve) with the absence of waves III (from the cochlear nuclei in the pons) and V (from the lateral lemniscus fiber tract of the midbrain as it enters the inferior colliculus). Furthermore, children with KSD may also have concomitant SNHL, and severe ANSD may be confused with SNHL.

Similarly, the severity of motor KSD is determined by the amount and severity of dystonia and athetosis, and the limitations of voluntary movements. For example, under this scheme, children with dystonia and athetosis who ambulate with an abnormal gait with or without a walker and can feed themselves are described as moderate motor KSD, whereas non-ambulatory children without the ability to ambulate, feed themselves and with severe restriction of voluntary movement are referred to as severe. The most severe motor KSD includes children without voluntary movements unable to speak, with very limited communication (*via* assistive technologies), dystonic crises and status dystonicus. These children are virtually locked in. Finally, we suggest the adoption of the term Bilirubin Neurotoxicity (BNTx) to describe central nervous system toxicity caused by exposure to excessive amounts of unbound unconjugated bilirubin.

It is important to recognize that we purposefully restrict the variables in this classification scheme to the major clinical feature of KSD. Classical kernicterus is traditionally described as including the following clinical features: motor impairments (dystonia, athetosis), auditory impairments (ANSD ± sensorineural hearing loss), oculomotor pareses (especially paresis of vertical upward gaze), and dental enamel dysplasia of the deciduous teeth. We consider that motor and auditory disabilities are the most significant and easily quantifiable clinical features and are therefore used in this classification. Oculomotor dysfunction can be difficult to evaluate on examination, especially in infants and younger children, and dental enamel dysplasia is variably present, and invariably not present when permanent dentition appears.

2.1. Subtle Kernicterus

Whereas classical kernicterus is well described, subtle KSDs are not. These may exist as a constellation of subtle neurodevelopmental disabilities without the classical findings of kernicterus. We believe that subtle KSDs are neurodevelopmental disabilities that, after careful evaluation and exclusion of other possibilities, appear to be due to bilirubin neurotoxicity [10, 11]. The diagnosis of subtle KSD might include individuals with otherwise unexplained neurodevelopmental disabilities with a history of excessive hyperbilirubinemia and previous signs of acute bilirubin encephalopathy. Also at risk for subtle KSD are individuals with less severe hyperbilirubinemia and other risk factors that favor the formation of unbound bilirubin and/or its movement into tissue. These factors include but are not limited to displacers of bilirubin from albumin, acidosis, hypoalbuminemia and albumin that ineffectively binds bilirubin such as occurs in sepsis, inflammation and extreme prematurity [25]. In this regard, because of extreme differences in neuronal maturation at the time of bilirubin neurotoxicity, the neurologic sequelae of KSD may be different in premature neonates. The localization of damage may occur in areas or pathways that are not usually associated with KSDs and may be characterized by less severe injury including isolated hearing loss not meeting ANSD criteria and motor involvement so mild as to be virtually unrecognizable except under the broad descriptive terms of being "awkward" and "clumsy" [31]. Subtle KSD may also associate with conditions related to the findings of classical kernicterus, such as auditory imperception, aphasia and other neurodevelopmental disorders (*e.g.* central auditory processing disorders, sensory and sensorimotor integration disorders, hypotonia, ataxia or clumsiness).

2.2. Kernicterus Spectrum Disorder Plus

Some children who meet diagnostic criteria for kernicterus have additional neurological findings that are not usually seen as the result of bilirubin neurotoxicity. We refer to these cases of concomitant KSD and other neurological conditions as KSD plus (KSD+) to imply that these individuals have KSDs plus some other condition. For example, spasticity *i.e.*, velocity dependent hypertonia, is not a neurological sequela of bilirubin neurotoxicity. The finding of spasticity suggests either alternate etiologies or concurrent neurological conditions, such as hypoxic-ischemic injury in addition to KSD. Other tip-offs that the encephalopathy is not due to bilirubin neurotoxicity include microcephaly, onset of signs before a significant rise in serum bilirubin levels and MRI abnormalities not typically seen in KSD (*e.g.*, lesions of the cerebral cortex, thalamus, caudate, putamen, periventricular leukomalacia, or ventriculomegaly). Cases of concomitant KSD with these other signs indicate kernicterus plus some other neurological disorder, thereafter referred to as KSD+.

2.3. KSD Associated Findings

KSD associated findings are common in children with severe KSD. These include:

1. *Gastroesophageal reflux* (GER) with emesis, which can be quite severe.
2. *Sleep disorders*. We have noted the nearly universal problem of sleep disorders including frequent nighttime awakenings and difficulty in maintaining sleep in our patients with KSDs. Initially, we thought these were due to normal sleep arousals followed by dystonic posturing in children with kernicterus, but more recent work in animals and adults with Parkinson's disease implicates the role of the globus pallidus in maintaining sleep and for the control of sleep and wakefulness. [26-28].
3. *Failure to thrive* from a combination of dysphasia and uncoordinated swallowing plus an increased caloric needs from dystonia.

4. *Status dystonicus*, episodes of severe and prolonged dystonia termed status dystonicus often trigged by intercurrent illness or pain.

5. *Neuro-orthopedic conditions* from dystonia including scoliosis and hip dysplasia.

6. *Seizures*. Generalized seizures may occur during acute bilirubin encephalopathy but do not usually persist after the acute phase is over and abnormalities on electroencephalogram (EEG) have normalized. Antiseizure medication can usually be tapered and stopped. However, it is the authors' experience that there may be an overall increase in seizures in children with kernicterus. This increase may be as high as 10%, in contrast to the 0.3-0.5% prevalence of epilepsy in the children living in developed countries [29]. It should be noted that pathologically, bilirubin neurotoxicity does not affect the neocortex although with severe acute bilirubin encephalopathy, there may be either cortical or subcortical neuronal dysfunction occurring secondarily, perhaps due to secondary cerebrovascular effects in critically ill neonates [30, 31]. In addition, the hippocampus is largely spared with exception of the CA-2 region. Furthermore, episodes of dystonic activity and hyperactivity can easily be confused with tonic-clonic seizures, especially as dystonic episodes may be associated with loss of consciousness complicating the semiology. Dystonic spells can readily be distinguished from seizures by recording with video EEG during the episodes. A preliminary analysis of retrospective data from the kernicterus registry of 125 patients found 41 (33%) diagnosed clinically with neonatal seizures or suspected seizures with information available in 31 infants. Of these, 9 (29%) showed electrographic seizures and 10 (32%) had epileptogenic activity; of the 20 of 41 with follow-up data, 10 developed chronic seizures. Thus, 29 of 125 patients (23%) had EEG evidence of epileptogenic activity, and 10 of 125 (8%) developed epilepsy [32].

2.4. Diagnostic Toolkits for Kernicterus Spectrum Disorders (KSDs)

The diagnosis of kernicterus, especially as used in the medical literature, is all too often vague, nonspecific and poorly defined. If we look at the broad-spectrum of kernicterus disorders as defined in KSDs, it is likely that kernicterus and the effects of bilirubin neurotoxicity may be significantly underreported. Diagnostic criteria for kernicterus have not been established. Shapiro previously proposed a set of criteria to facilitate kernicterus diagnosis [11, 12]. In this paper we review and expand on this classification, further characterizing kernicterus by subtypes. To that end, we have developed a Kernicterus Diagnostic Toolkit (KDT) for providers, researchers and families. The goal of this classification is to determine the likelihood of a KSD, *i.e*., that a neurodevelopmental disorder is due to bilirubin neurotoxicity (Fig. **1**), and to determine its severity and KSD sub-type (Fig. **2**).

These toolkits are designed to assess the probability, severity and type of a KSD with a reasonable amount of certainty (*i.e*., no evidence of kernicterus, possible kernicterus, probable kernicterus and definite kernicterus), to categorize kernicterus according to type (*i.e*., motor-predominant, auditory-predominant and classical) and severity (mild, moderate and severe). Each toolkit returns a numbered score designed to provide an objective and quantifiable measure that will be comparable across assessors. These toolkits are designed to be tested and validated. Since KSDs in prematurely born infants may differ from those in term and near-term infants, these toolkits were designed to be used in individuals born at greater than or equal to 35 weeks gestational age, and not designed to be used to assess individuals who were more prematurely born.

We propose validating these toolkits to standardize the diagnosis and classification of KSDs in hopes that a standard diagnostic algorithm will be useful to families, providers and researchers. Validation will be accomplished by comparing the results of the toolkits to evaluations of children with kernicterus conducted by experts in neurology and neurodevelopmental disabilities, with the additional support of laboratory studies including MRI and audiological evaluations for ANSD. We hypothesize that the KSD Toolkits will reliably correlate with the diagnoses and classifications of expert providers; will allow kernicterus to be diagnosed earlier, more precisely and more consistently than is current practice; and will be useful for families to determine when to seek help regarding their child's diagnosis and treatment. We also hope that this toolkit can be validated and used to collect novel epidemiological data about the KSDs, information about the satisfaction of families and individuals with current treatments, and form the basis of a Kernicterus Spectrum Disorder Registry as well as future comparative effectiveness treatment trial for these disorders.

2.5. The Bilirubin Induced Neurological Dysfunction (BIND) Scale

The BIND scale was developed to quantitatively assess acute bilirubin encephalopathy in the neonatal period. It was originally proposed as a scale from 0-9 where zero is normal and nine is the most abnormal [15]. During the creation of the original BIND scale, there was discussion whether to include laboratory tests such as a characteristically abnormal ABR or MRI, or even the abnormal cry since one could not always assess cry if a child was intubated. Therefore, the original BIND scale was a compromise between the practical and ideal; designed to be useful for a wide audience (as, for example the Apgar score might be more predictive if it included blood gases, but then it would not be universally applicable). The BIND scale has since been modified by others for use in specific situations. For example, a modified BIND scale was evaluated in Nigeria [16] to predict the development and severity of acute bilirubin encephalopathy in resource-limited settings and as a tool in population studies of low- and middle income countries to estimate the magnitude of ABE-related morbidity and mortality. While the BIND scale has proven to be a useful scale for quantitatively characterizing ABE, its utility in predicting KSD outcomes is not as strong. In contrast, KSD Toolkits will be used to assess bilirubin-induced damage after the initial insult. In addition, the KSD toolkits will likely be better suited to developed countries where

KERNICTERUS SPECTRUM DISORDER (KSD) DIAGNOSTIC TOOLKIT ONE: LIKELIHOOD (OR PROBABILITY)

Diagnostic Tool Kit for families or caregivers to determine if an individual has kernicterus.

Child's Name: (Last, First, Middle)	☐ **Male** ☐ **Female**	**Birth Date:**
Parent or Guardian Name: (Last, First)	**Phone Number:**	
Home Address:		**Date Survey Completed:**

DIRECTIONS: *Please choose the score option (0, 1, 2 or 3) that best fits the child's symptoms.*

		SCORE	Your Score
What was the highest bilirubin level recorded?			
	Highest bilirubin level was less than 15 mg/dL	**0**	
	Highest bilirubin level was between 15 to less than 30 mg/dL; or bilirubin never measured but child thought to be extremely jaundiced by provider or family	**1**	
	Highest bilirubin level was greater than 30 and less than 45 mg/dL	**2**	
	Highest bilirubin level was greater than 45 mg/dL	**3**	(0, 1, 2, or 3)
What are the newborn risk factors?			**Your Score**
	None	**0**	
	Suspected infection, Rh Disease, "sick", premature less than 35 weeks gestation	**1**	
	Proven viral or bacterial infections, NEC (necrotizing enterocolitis, *air in the abdomen*), or acidosis (high blood acid level, pH <7.2)	**2**	(0, 1, or 2)
What were the results of the newborn neonatal exam?			**Your Score**
	Normal	**0**	
	Mild acute bilirubin encephalopathy *Lethargy, sleepiness, low or high muscle tone, ±high pitched abnormal cry*	**1**	
	Severe acute bilirubin encephalopathy *Arching of neck and back (opisthotonus), setting sun sign (seeing the "white of the eyes below the eyelids), sometimes with a scared looking face, unexplained fever*	**2**	(0, 1, or 2)
What were the results at your last follow-up exam?			**Your Score**
	Normal	**0**	
	Mild Dystonia *Setting sun sign ± mild abnormal increase or variably increased or decreased muscle tone (dystonia) ± excessive abnormal movements*	**1**	
	Moderate/Severe Dystonia *Severe dystonia, setting sun sign ± excessive abnormal movements*	**2**	(0, 1, or 2)
When the teeth erupted, how was the enamel?			**Your Score**
	Normal	**0**	
	Enamel Dysplasia *Abnormal dental enamel (dysplasia) of the baby teeth (not the permanent teeth) ± flaking or chipping of the enamel of the baby teeth*	**1**	(0 or 1)
What were the results of testing for Auditory Neuropathy Spectrum Disorder (ANSD)?			**Your Score**
	Normal, no ANSD.	**0**	
	Mild *auditory brainstem response (ABR) abnormal but present*	**1**	
	Moderate/Severe *Absent auditory brainstem response (ABR) ± acts deaf*	**2**	(0, 1, or 2)
What were the results of the MRI (Magnetic Resonance Imaging)?			**Your Score**
	Normal	**0**	
	Probable abnormal MRI abnormal *globus pallidus (GP) ± hyperintensity of subthalamic nuclei (STN) on both sides without other abnormalities*	**1**	
	Definite abnormal MRI GP±STN *Abnormal hyperintensity of the globus pallidus (GP) bilaterally ± hyperintensity of subthalamic nuclei (STN) without significant involvement of other structures.*	**2**	(0, 1, or 2)
		Add Your Score Column for Total Score:	

How To Interpret Your Results:	**Interpretation:**	**Total Score:**
	Definite Kernicterus	**10 - 14**
	Probable Kernicterus	**6 - 9**
	Possible Kernicterus	**3 - 5**
	Not Kernicterus	**0 - 2**

Fig. (1). Kernicterus diagnostic toolkit: Likelihood of a kernicterus spectrum disorder (KSD) in individuals born ≥ 35 weeks gestational age.

resources are not an issue and test results, such as ABR and MRI, are usually available for review.

3. TREATMENT OF KERNICTERUS SPECTRUM DISORDERS

In this section, we review the range of treatments offered for KSD. KSD classically presents with motor abnormalities consisting of a dystonic, athetoid, often intractable movement disorder, a combination of appendicular hypertonia and truncal hypotonia, and impaired auditory function with or without hearing loss consistent with an auditory neuropathy [10]. Other associated signs, including dental enamel hypoplasia and oculomotor impairment are not typical targets of treatment and, as such, will not be discussed in this section. It is worth noting that, in as much as can be assessed, children with classic kernicterus appear to have relatively normal intellect [33] and, with appropriate assistive technologies, are capable of age appropriate learning.

3.1. Treatment of Auditory Signs and ANSD

The auditory signs of children with KSDs are primarily due to ANSD with or without concomitant sensorineural

KERNICTERUS SPECTRUM DISORDER (KSD) DIAGNOSTIC TOOLKIT TWO: SEVERITY AND TYPE

Diagnostic ToolKit for families or caregivers to determine severity and type of kernicterus.

Child's Name: (Last, First, Middle)	☐ **Male** ☐ **Female**	**Birth Date:**
Parent or Guardian Name: (Last, First)	**Phone Number:**	
Home Address:		**Date Survey Completed:**

DIRECTIONS: *Please choose the score option (0, 1, 2, or 3) that best fits the child's symptoms.*

How would you describe the auditory symptoms?		**SCORE**	**Your Score**
None	No auditory symptoms	**0**	
Mild	Mild ANSD (*Auditory Neuropathy Spectrum Disorder*; ABR (*Auditory Brainstem Response*) abnormal but present, may normalize with time), or CAPD (*Central Auditory Processing Disorder*) ± mild hearing loss; normal or mildly delayed speech	**1**	
Moderate	ANSD (*Auditory Neuropathy Spectrum Disorder*) with absent or persistent abnormal ABR, mild/moderate hearing loss, may fluctuate; speech delayed or absent	**2**	
Severe	ANSD (*Auditory Neuropathy Spectrum Disorder*) with absent ABR, severe-to-profound hearing loss/deafness	**3**	(0, 1, 2, or 3)
How would you describe the motor symptoms?			**Your Score**
None	No motor symptoms	**0**	
Mild	Mild abnormal muscle tone ± writhing movements (athetosis); mild gross motor delays e.g. walking; ambulates well, speech is intelligible	**1**	
Moderate	Moderate abnormal muscle tone ± writhing movements, "athetoid" CP (*cerebral palsy*); ambulates with or without assistance with abnormal gait with abnormal tone and postures of the hands and feet.	**2**	
Severe	Severely abnormal tone ± writhing movements, athetoid CP (*cerebral palsy*); unable to ambulate, feed self, sign, speak; often with episodes of severe increased tone and muscle cramps	**3**	(0, 1, 2, or 3)
		Your Auditory Score:	
		Your Motor Score:	

How To Interpret Your Results: *Circle the KSD subtypes based on the above scores and find the intersection of the two subtypes on the graph below.*		**Auditory - None**	**Auditory - Mild**	**Auditory - Moderate**	**Auditory - Severe**
		Score 0	*Score 1*	*Score 2*	*Score 3*
Motor - None	*Score 0*	None	Mild Auditory	Moderate Auditory	Severe Auditory
Motor - Mild	*Score 1*	Mild Motor	Mild Motor and Auditory	Mild Motor, Moderate Auditory	Mild Motor, Severe Auditory
Motor - Moderate	*Score 2*	Moderate Motor	Moderate Motor, Mild Auditory	Moderate Motor and Auditory	Moderate Motor, Severe Auditory
Motor - Severe	*Score 3*	Severe Motor	Severe Motor, Mild Auditory	Severe Motor, Moderate Auditory	Severe Motor and Auditory

Fig. (2). Kernicterus diagnostic toolkit: Severity and subtype of kernicterus spectrum disorder (KSD) in individuals born ≥ 35 weeks gestational age.

hearing loss [34]. ANSD, defined as abnormal or absent auditory evoked potentials[3] in the presence of normal or giant cochlear microphonic responses. Note that ANSD is not synonymous with hearing loss but an abnormal processing and dys-synchronization of the auditory signal, which may or may not be associated with hearing loss. Treating ANSD in KSD is essentially the same as treating ANSD from other etiologies, except we suggest children with coexistent severe movement disorders, *i.e.*, those with both severe motor and auditory kernicterus, should not be taught sign language as their primary method of communication for the obvious reason that they will not be able to effectively communicate through sign language due to their motor disability.

Initial treatment of ANSD consists of the use of cued speech to help a child distinguish different phonemes of lan-

[3] These terms are synonymous or nearly synonymous: auditory brainstem response (ABR), brainstem auditory evoked potential (BAEP), brainstem auditory evoked response (BAER).

guage in order to develop normal receptive language [35]. A trial of hearing aids at low intensity can be attempted, though ANSD is not synonymous with hearing loss and hearing aids at higher intensity may damage normal peripheral auditory hair cells. In cases of severe ANSD producing deafness or significant delays, absence of receptive and expressive language development or with absent ABR's (± the presence of ABR wave I), cochlear implantation is often helpful [36]. Clinical experience continues to show that children with ANSD secondary to KSDs do extremely well with cochlear implantation. In those with milder ANSD, such as abnormal ABR waves or a high threshold for the ABR in the presence of normal cochlear microphonic responses or otoacoustic emissions, the role of cochlear implantation is more controversial. To further complicate the decision to treat with cochlear implantation, some children with kernicterus with repeatedly absent ABRs in infancy and decreased responses to sound may go on to develop normal hearing and language without intervention [37].

3.2. Treatment of Motor Signs and Dystonia

The movement disorders of kernicterus are felt to be secondary to the injuries sustained by the basal ganglia (globus pallidus and subthalamic nucleus), resulting in an overflow of neural activity from the basal ganglia. Therefore, most therapies are directed at modulating various components of the basal ganglia circuitry. In moderate to severe motor predominant kernicterus the dystonia can be very difficult to treat. Therapies such as physical and occupational therapy and speech therapy can be helpful. It is important to emphasize that patients with kernicterus are not spastic and thus, treatments used for spasticity are generally not effective in these patients and could even be detrimental (examples of ineffective procedures include dorsal rhyzotomies and orthopedic procedures targeting tendon lengthening).

3.3. Pharmacological treatments

Similarly to ANSD, the pharmacological treatment of dystonias and hypertonia in KSD are derived from treatments used for these symptoms in children and adults without kernicterus. The list below is by no means exhaustive and is presented in an order reflecting the strength of evidence for such treatments in secondary dystonias.

3.3.1. Trihexyphenidyl

Anticholinergic medications have a long history in the pharmacotherapy of dystonia [38]. Trihexyphenidyl, a muscarinic antagonist, is the best studied of these medications in the treatment of dystonia. The mechanism of action of trihexyphenidyl remains to be determined. Cholinergic projections in the CNS tend to targeted deep gray nuclei including several components of the basal ganglia. Furthermore, in the basal ganglia they project onto muscarinic receptors that are tonically activated [39]. There are several lines of evidence that muscarinic receptors segregate with dopamine receptors in the basal ganglia and thereby modulate the overall outflow activity. It is thought that by inhibiting the tonically active cholinergic projections onto the basal ganglia one restores some element of balance between the dopaminergic and cholinergic input and thus reduces the dystonia [40]. Yet, the evidence for the use of trihexyphenidyl in kernicterus is limited. Sanger *et al*. published a prospective study of 23 children with secondary dystonia treated with trihexyphenidyl [41]. While there seemed to be an improvement in some of the children, the benefit was only seen after prolonged treatment (no benefits at 9 weeks but improved at 15 weeks). Furthermore, the children with hyperkinetic movement disorders associated with the dystonia actually worsened. This is important as many children with kernicterus often have an athetoid hyperkinetic disorder. It is also worth noting that in this study there was only one child with kernicterus and that this child did not show any improvement. Yet, we have been impressed anecdotally with a few cases of KSD infants who have been treated effectively with trihexyphenidyl. We conclude that carefully selected children with classical kernicterus may benefit from a trial of trihexyphenidyl. If given, trihexyphenidyl should be continued for at least three months before concluding that there is no benefit.

3.3.2. Oral Baclofen

Oral baclofen, a $GABA_B$ receptor agonist may also be helpful [42]. Jankovic, in the review just cited, states that in children it has been reported to be especially helpful in the treatment of dystonic gait and may be used as an adjunctive to trihexyphenidyl. However, oral baclofen may worsen truncal hypotonia, and this can be a significant limitation in patients with severe KDS who rely on truncal tone for head control and/or ambulation.

3.3.3. Intrathecal Baclofen Pump

One of the major limitations of oral baclofen is its limited ability to cross the blood-brain-barrier [43]. This requires large doses of the medication to attain a clinically significant effect, with the result that the side effects are exaggerated as well. Thus, when oral baclofen treatment is ineffective, intrathecal baclofen is a viable alternative. With direct delivery of baclofen *via* an implanted pump and a catheter into the subarachnoid space, intrathecal baclofen bypasses the blood-brain barrier and is delivered directly to the cerebral spinal fluid. Albright *et al*. reported treatment benefit in a trial of 86 patients, ages 3 to 42 years old, with generalized dystonia refractory to other medications, who were managed with intrathecal baclofen [43]. The dystonia was secondary to cerebral palsy in 71% of the patients. Overall, 86% of the patients saw an improvement in quality of life. It is worth noting that some authors have advocated cervical placement of the catheter (C1-4) [44] to improve delivery of baclofen to the spinal cord and spinal nerves of the upper extremities, or even intraventricular infusions for generalized dystonias [45] to deliver baclofen directly to the brain. While these results are encouraging it is not clear that they apply to kernicterus. To date there has been no report of intrathecal baclofen in patients with kernicterus. However, our clinical experience is that intrathecal baclofen is often an effective treatment for severe dystonia in individuals with kernicterus.

3.3.4. Other Medications

Benzodiazepines, through modulation of $GABA_A$ receptors, have long been used in the treatment of dystonia, most notably for the management of status dystonicus [46]. However,

the evidence supporting their use in the management of dystonia remains scanty and the side effect profile of many of the benzodiazepines, including sedation and sialorrhea, limit their usefulness. Other medications such as carbamazepine, oxcarbazepine and gabapentin have been tried as well. However, they were shown to be of no clinical value in primary dystonias [47]. Case reports and case series have shown some benefits in secondary dystonias. Blakeley and Jankovic reported a case series of 17 patients with symptomatic (known etiology) focal paroxysmal dyskinesias [48]. In this study, drugs found to be effective included clonazepam, carbamazepine, gabapentin and tetrabenazine. Interestingly, of the two patients with kernicterus, one was unresponsive to any treatment while the other responded to trihexyphenidyl [48].

3.4. Botulinum Toxin Injection

The use of boltulinum toxin in the treatment of focal dystonias is well established. In one long-term cohort study of 89 patients with focal dystonias treated for an average of 18 years, botulinum toxin injections were shown to provide sustained symptomatic improvements, although the patients typically required higher doses of the toxin with continued use [49]. Despite the prolonged and higher dose treatment, only 19% of the patients experienced side effects and those were well tolerated for the most part. It is important to recognize that in patients with KSD focal dystonias can be disabling and the judicious use of botulinum toxin can provide significant relief.

3.5. Deep Brain Stimulation

In 2003 the FDA granted a Humanitarian Device Exemption for Medtronic® Deep Brain Stimulation (DBS) device implantation in children at least seven years old with dystonia. The procedure has proven very successful in children with primary dystonias. Additional evidence is accumulating for the treatment of secondary dystonias. In 2009 Katsakiori *et al.* published a prospective study of eight adult patients with secondary dystonias who received DBS [50]. The patients had an average improvement of 30 to 40% in the measurements of standard scales of dystonia. All but one of the patients were implanted in the globus pallidus pars interna. Even more encouraging was a study done in 2009 of 13 adults with cerebral palsy with dystonia-choreoathetosis who were implanted in the sub-thalamic nucleus [51]. The authors found that the patients had a 20% improvement in the Burke-Fahn-Marsden dystonia scale after one year of therapy. This study is especially encouraging in that the choreoathetoid dystonia is reminiscent of the symptoms experienced by patients with kernicterus. Our clinical experience is that children with severe classical and motor kernicterus may obtain benefits with DBS in bilateral globus pallidus pars interna implantation with variable improvements in resting tone, abnormal overflow movements, and sleep, and possibly preventing orthopedic complications *e.g.*, hip dislocations or scoliosis. These early successes with DBS provide hope that advances in determining new lead locations and stimulus parameters may result in significantly more functional improvements in voluntary movements.

3.6. Stem Cell Therapy

Stem cell transplantation for disorders similar to kernicterus has been best studied in cerebral palsy. To date no study has found conclusive evidence that stem cell therapy has a clinical role in the treatment of cerebral palsy [52]. Several laboratories have protocols to assess the feasibility of stem cell transplantation in animal models of kernicterus (personal communication). The results, while promising, are still preliminary and much more work will be needed before these techniques are ready for human testing. The authors are aware of several families who have had stem cells transplanted *via* intravenous injections of autologous umbilical cord derived stem cells. Anecdotally, some of the families have felt that this was beneficial. However, it is difficult to assess the benefit of these procedures, they tend to be quite expensive, the treatment often requires international travel, and there is likely to be a robust placebo effect.

CONCLUSION

The study of hyperbilirubinemia in infants has been ongoing for close to 70 years (with the first major breakthroughs in the 1940s and 1950s in understanding the pathophysiology of hemolytic diseases of the newborn). During this period multiple terms have been intermittently used to describe multiple aspects of the pathophysiology and clinical consequences of bilirubin toxicity. In some cases similar terms have been used to describe two or even three completely different processes (see for example the use of BIND). We believe that it is important for the field as a whole to adopt a proper nomenclature. This will facilitate both the treatment of acute bilirubin encephalopathy and its clinical outcome, kernicterus. We propose the term kernicterus spectrum disorder to describe the range of bilirubin induced neurological sequelae and their spectrum of severity. We further present a simple system to subclassify the various clinical forms of KSDs and we propose the term subtle KSDs to describe children with neurodevelopmental disabilities that, after careful evaluation and exclusion of other possibilities, appear to be due to bilirubin neurotoxicity. It is our hope that this standardization of terminology will lead to a more accurate characterization of the consequences, incidence and prevalence of bilirubin-induced brain damage. This work should help establish more consistent outcome measures to assess the results of prevention and treatment efforts.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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