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Review

Neonatal hyperbilirubinemia: a critical appraisal of current guidelines and evidence

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Abstract

The neurological damage of neonatal hyperbilirubinemia is often seen in developed countries as a remnant of a long gone past before the introduction of effective phototherapy and exchange transfusion. However, several reports in the past two decades from the United States have led to the institution of a Kernicterus National Registry. Similar reports from all over Western Europe have forced the pediatric national societies to issue specific guidelines on the clinical management of neonatal hyperbilirubinemia. The present paper reviews the highlights and pitfalls of the documents from Australia, Canada, New Zealand, India, Israel, Spain, Norway and South Africa.

Keywords

Hyperbilirubinemia, neonate, guidelines.

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Introduction

The resurgence of neonatal bilirubin encephalopathy in developed countries has driven new research interest in what has long been considered a solved problem. At the same time, since kernicterus is thought to be a totally preventable problem, a considerable amount of litigation has arisen on the topic. In the United States, hyperbilirubinemia is second only to delivery room issues for court claims number related to neonatal health [1].

In order both to guide clinical conduct and to prevent court litigation, many national pediatric societies have issued their recommendations on how to recognize and treat clinically significant neonatal hyperbilirubinemia. This paper shortly reviews the advantages and the shortcomings of guidelines on neonatal hyperbilirubinemia and the evidence on this topic.

The official documents from the United States [2], United Kingdom [3], Canada, Australia, New Zealand India, Israel, Spain, South Africa and Norway were taken as references of guidelines.

Definition of significant neonatal hyperbilirubinemia

In general, a clinical guideline can be produced if:

- a negative outcome is clearly identified;
- risk factors for the negative outcome can be objectively defined;
- an effective treatment is available;
- a follow-up program can be put in place.

In the case of neonatal jaundice, the negative event of kernicterus is exceedingly rare to be chosen as the target of clinical guidelines. Some national statements (including those from the UK, Canada and India) do not quote kernicterus as the specific outcome to be prevented. Most recommendations indeed use surrogate measures such as Acute Bilirubin Encephalopathy (ABE) or the more ambiguous "severe hyperbilirubinemia". Beside a poor intrinsic clinical significance, the latter is widely defined across different countries. While Canada and Norway have chosen a total serum bilirubin (TSB) of 20 mg/dl, Israeli guidelines have an higher threshold set at 25 mg/dl. Rather than an absolute concentration, the American Academy of Pediatrics (AAP) and the Indian guidelines prefer to define severe hyperbilirubinemia as a TSB over 95th percentile of a specific, hour-based nomogram. UK and Australian recommendations have different TSB percentiles based on gestational age. Severe hyperbilirubinemia is quoted in the Spanish guidelines but its definition is not clear.

Universal screening of neonatal hyperbilirubinemia

Universal screening of neonatal hyperbilirubinemia is suggested by almost all national guidelines with the remarkable exception of the British NICE document. The strategy of AAP guidelines includes universal bilirubin screening before hospital discharge and planning of a tailored follow-up. In order to properly assess the risk of significant hyperbilirubinaemia, the AAP recommends to measure either the serum bilirubin with a spectrophotometric method (TSB) or the transcutaneous bilirubin (TcB); both values should be plotted on an appropriate nomogram that takes birthweight, post-natal age and a list of risk factors (hemolysis of any etiology; G6PD deficiency, asphyxia, septicaemia, acidosis) into account [2].The hour-specific evaluation of total serum bilirubin (TSB) and predischarge risk assessment by using the predictive nomogram developed by Bhutani et al. has been proved effective in predicting severe hyperbilirubinemia [4]. Nevertheless, the use of Bhutani nomogram as a screening tool has been questioned by some authors for his reliability on different populations and some methodological issues were arisen: follow-up bilirubin levels were not performed in more than 75% of study participants; the nomogram was generated in a retrospective study and not verified prospectively; it included infants from a single urban Pennsylvania hospital, so that the demographic, racial, genetic and environmental features of that particular sample may not adequately represent other newborn populations [5]. To overcome these limits, Romagnoli et al., developed an hour-specific, percentile based nomogram using serial measurements of TSB in a cohort of healthy full term neonates and verified prospectively its predictive ability to identify newborn at risk for significant hyperbilirubinaemia (defined as TSB > 17 mg/dl or need for phototherapy) in a multicenter study involving a large neonatal Italian population. The sensitivity of this nomogram of the 50th percentile to predict significant hyperbilirubinaemia was 100% between 49 and 96 hours, while it was affected by

one false negative result before 48 hours of age. Using the 75th percentile as risk discriminator they obtained 88% of sensitivity between 24 and 48 hours and 95.7% of sensitivity between 49 and 72 hours (one false negative result). The false negative between 49 and 72 hours was a preterm infant who had his TSB measurement at 70 hours of age and subsequently needed phototherapy because he reached a TSB value of 16 mg/dl. The authors suggested that a risk assessment strategy combining the pre-discharge bilirubin risk zone and some clinical factor (such as gestational age) could have a better overall predictive accuracy than a strategy using pre-discharge bilirubin risk zone by itself [5].

The same list of risk factors for neonatal hyperbilirubinemia appears both in the AAP (gestational age, breast feeding, weight loss, bruising, hemolysis, previous sibling receiving phototherapy) and in the British National Institute of Health and Clinical Excellence (NICE) documents. The list is generally different for other geographic locations and it is noteworthy the Indian case where sepsis is mentioned as an independent risk factor for neonatal hyperbilirubinemia.

Transcutaneous bilirubin as screening for hyperbilirubinemia

Measurements of transcutaneous bilirubin (TcB) are widely accepted as a pain saving alternative to TSB with no risk of heel infection, blood sparing for the babies and time sparing for the nurses, at least in low risk situations [6]. It is however surprising that documents from Spain or New Zealand have not yet found a place in their guidelines for this well proved and reliable technology.

TcB is a powerful tool to clinically screen neonatal hyperbilirubinaemia in particular for the widespread practice of early postnatal discharge, although several issues remain open. Several TcB devices have been individually validated versus spectrophotometric or high pressure liquid chromatography (HPLC) determination of TSB, in term or late preterm neonates. The first generation of bilirubinometers showed an accuracy strongly limited by skin pigmentation. More recently, a new generation of bilirubinometers has overcome the problem. At present, the most widely used devices are BiliCheck® and JM-103®. Whatever the device, transcutaneous bilirubinometry measures bilirubin in the subcutaneous tissue and therefore TcB, though significantly correlated to serum bilirubin is not the same thing. The available literature demonstrates an excellent linear correlation between TSB and TcB for these two devices in term and late preterm neonates. In particular JM-103® and BiliCheck® reach almost a 100% sensitivity to predict hyperbilirubinaemia up to a TcB value of 11 mg/dl [4, 5]. It is therefore often recommended to perform a TSB when TcB is higher than 11 mg/dl [6]. De Luca et al., in a systematic review of population differences and analysis of bilirubin kinetics, confirmed that hyperbilirubinaemia trends and kinetics are different among ethnic groups [7]; furthermore skin pigmentation could be a limit for the accuracy of TcB, at least for the older generation of transcutaneous bilirubinometer. Though the majority of published studies validated TcB meters on Caucasian neonates, some authors investigated these technologies also on mostly homogeneous populations of Asian, African and Hispanic infants. Sanpavat et al. [8] compared BiliCheck® vs JM-103® on Thai neonates and found similar correlation of the two devices with TSB but a better accuracy for JM-103®. Engle et al. (9) showed a lower sensitivity of BiliCheck® on Hispanic compared with non-Hispanic neonates; in order to have an almost 100% sensitivity in predicting a TSB > 10 mg/dl and < 15 mg/dl, a TcB cut off of 8 and 9 mg/dl had to be chosen. This was probably due to the higher incidence of hyperbilirubinaemia in the Hispanic population and to the tendency of TcB to underestimate TSB. In African-American infants, the correlation between BiliChek TcB and HPLC measurements of the TSB was as good as in Caucasian infants [10]. To provide useful clinical information, our group compared the performance of the three most widespread transcutaneous bilirubinometers on a Caucasian and African population of term and late pre-term neonates. We also provided the first direct comparison of Bilicheck® and JM-103® in a mixed African and Caucasian population, as previous authors investigated these technologies on Asian or Caucasian infants. A Caucasian and African population of 289 neonates was enrolled with a gestational age ranging from 35 to 41 weeks; birth weight ranging from 1,800 to 4,350 grams; hours of life ranging from 4 to 424. In the total study population correlation analysis using Pearson coefficients showed good results for Bilicheck®

(r = 0.86) and JM-103® (r = 0.85) but poor for BiliMed® (r = 0.70). Similar results were found for the African neonates subgroup. Bilicheck® and JM-103® had a greater area under the curve than BiliMed® when TSB = 14 mg/dl was chosen as a threshold value both for the total study population and the non-Caucasian subgroup; we concluded that Bilicheck® and JM-103®, but not BiliMed®, are equally reliable screening tools for hyperbilirubinemia in our Caucasian and African neonatal population. Moreover, the three devices had a tendency to overestimation on higher end of the tested concentration range. Although this may be *per se* protective against the clinical damage of hyperbilirubinemia, one would expect that newer technologies will be more accurate therefore extending the concentration range where a TSB determination can be spared [11].

In the last years different percentile based, TcB nomograms have been published for Caucasian, Asian and Hispanic population to identify the natural course of TcB levels in these different ethnic groups during the first days of life in healthyterm and near-term neonates [12-15].

Maisels et al. published a nomogram based on 3,984 healthy North American neonates (GA ≥ 35 weeks) from 6 to 96 h of age using the JM-103®; they found that infants requiring additional monitoring were those whose TcB concentrations were ≥ 95th percentile, i.e., those whose TcB is increasing at a rate > 0.22 mg/dl/h in the first 24 hours, > 0.15 mg/dl/h between 24 and 48 h, or > 0.06 mg/dl/h after 48 h. Furthermore, combining pre-discharge TcB levels with two clinical risk factors such as gestational age and exclusive breastfeeding, significantly improved the prediction of subsequent hyperbilirubinaemia [15].

Recently, Fouzas et al. provided data on the natural course of TcB levels for the first 120 postnatal hours and presented a percentile-based TcB nomogram designated for noninvasive and hour-specific evaluation of neonatal hyperbilirubinemia in healthy term and near-term Caucasian neonates. TcB values before the initiation of phototherapy were used. During the first 24 hours of life, the 5th percentile TcB curve from neonates who required phototherapy was constantly below the 75th percentile TcB curve from those who did not require phototherapy, resulting in a substantial overlap of TcB values between neonates requiring and not requiring phototherapy in the first 24 hours. This overlap, although gradually ameliorated, is also present up to 36 hours of life, whilst considering the 95th percentile of neonates not requiring phothotherapy, this overlaps with neonates requiring phothotherapy until 60 hours of life. After this time point, the 5th-percentile TcB curve from neonates who required phototherapy exceeds the 95th-percentile TcB curve of the nomogram [12]. Almost at the same time, Dalal et al. showed that a single TcB measurement at 30 to 48 hours of age predicts subsequent hyperbilirubinemia with a high degree of accuracy for term and late preterm neonates [16]. Recently, an hour-specific nomogram for the Italian population was developed; the 75th percentile of this TcB nomogram used as a cut off value efficiently excludes any subsequent severe hyperbilirubinaemia beyond 48 h of life [17].

About the use of transcutaneous bilirubinometer in preterm infants, few data are available on very preterm neonates. Schmidt et al. [18] demonstrated a sensitivity > 90% using a cut off of 6 mg/dl of TcB to predict a TSB > 8 mg/dl in preterm > 29 wk of GA but the sensitivity decreased for preterm < 29 wk of GA. A study on 340 Italian preterm infants between 30 and 36 weeks showed that BiliCheck® has a good reliability although not as good as in healthy term babies, and its tendency to overestimate suggests its use only for screening purposes. The authors, considering the whole time for serum bilirubin measurement, showed that transcutaneous bilirubinometry is a faster but more expensive technique with a cost of about 5 euro/measurement. Nevertheless, using BiliCheck® as a screening device they could safely avoid 58-79% of blood samples and this would allow a cost reduction of 1,555-2,120 euro/year [19].

Transcutaneous bilirubinometry in term and late preterm infants seems "to have useful diagnostic accuracy when used as a mass-screening device. It can help establish a risk estimate and answer the question: – Should I worry about this infant? –. If this is the way one practices, then this might be the right job for the tool" [20].

Practically, TcB can be used as a screening of hyperbilirubinemia in at term and late preterm neonates:

- performing a TcB determination after 36 hours of life;
- testing TSB when TcB > 75th on the hour-specific nomogram for TcB;
- testing TSB when TcB > 11 mg/dl;
- considering risk factors especially if TcB

is between 40 and 75th, i.e. gestational age less than 37 wk, exclusive breast feeding, increasing of TcB more than 0.15 mg/dl/h between 24-48 h and 0.06 mg/dl/h after 48 h if multiple determinations are performed;
- establishing an appropriate follow up if needed [2, 3].

Treatment of neonatal hyperbilirubinemia

The milestones of treatment of neonatal hyperbilirubinemia are: phototherapy, immunoglobulins for isoimmune haemolytic disease (Rh and AB0 haemolytic disease) and exchange transfusion.

Phototherapy is definitively effective for neonatal hyperbilirubinemia and the mainstay of treatment in all major national documents. However, a closer comparative review shows significant differences in the thresholds for starting and discontinuing the treatment. This is clear from **Fig. 1**, where most national societies prove to be more conservative than the AAP (except the Norwegian guidelines) when considering treatment of their late preterm infants. All figures have no scientific rationale to support them.

The AAP recommends that phothoterapy should be intensive i.e. with a irradiance > 30 $\mu W \cdot cm^{-2} \cdot nm^{-1}$ within the 460 to 490 nm waveband irradiated by fluorescent tube, special blu or the newer LED phothoterapy devices. The AAP recommends to expose maximal skin area, an urgent or "crash-cart" intervention for excessive hyperbilirubinemia, to briefly interrupt for feeding, parental bonding, nursing care, to integrate breast feeding with formula if excessive loss of weight or signs of dehydration occur or to administer i.v. infusion if necessary, to measure periodically rate of response in bilirubin load reduction, to discontinue at desired bilirubin threshold and to be aware of possible rebound [21].

De Carvalho et al. studied a cohort of 116 newborn infants with severe nonhaemolytic hyperbilirubinaemia (TSB ≥ 20 mg⁄dl). All patients were treated with intensive phototherapy. Mean initial TSB concentration was 22.4 ± 2.4 mg⁄dl. Per cent decreases in TSB after 2, 4, 6, 12, 18 and 24 h of phototherapy were 9.4%, 16%, 23%, 40%, 44% and 50%, respectively. No infant was treated with exchange transfusion. Brainstem evoked response audiometry (BAER) was performed in 100% of the patients, and in three of them, this

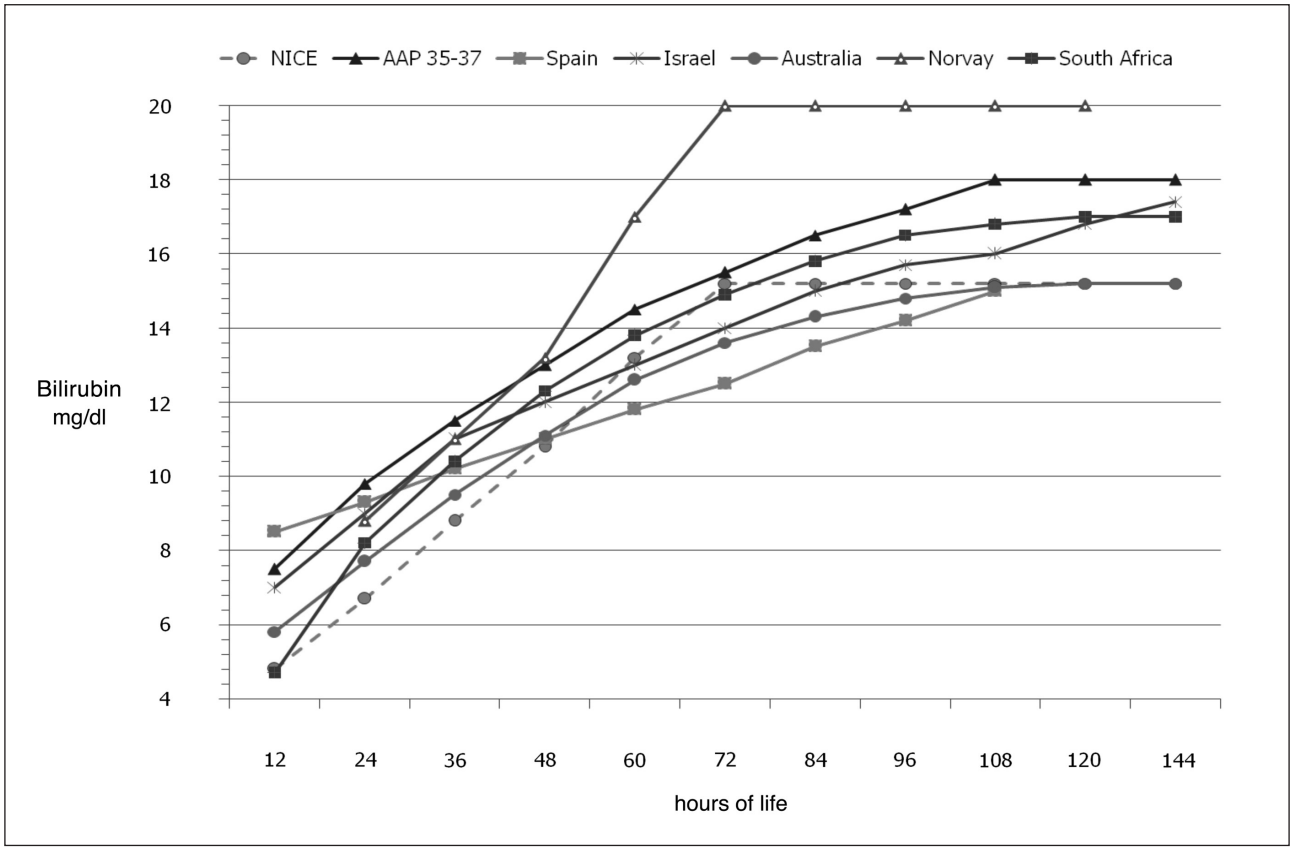

Figure 1. Phototherapy thresholds according to different national guidelines.

examination was abnormal. However, when repeated 3 months later, these BAER examinations were normal. Neurological examination was normal in all patients. This study shows that intensive phototherapy is a valid approach that significantly reduces TSB in nonhaemolytic severe hyperbilirubinemia and decreases the need for exchange transfusion [22].

Looking at international guidelines for treatment of hyperbilirubinemia in preterm and very preterm neonates, this issue is particularly unclear. There are no uniform guidelines regarding the management of hyperbilirubinaemia in preterm infants, although the high frequency of jaundice in these patients and the higher risk for cerebral impairment of such premature babies.

The variability of irradiance used and the lack of documented irradiance are the critical point of the studies on phothotherapy in particular for preterm.

In fact, Morris et al. to understand whether aggressive phototherapy could prevent neurotoxic effects of bilirubin infants in extremely low birth weight (1,000 g or less) randomly assigned 1,974 infants with extremely low birth weight at 12 to 36 hours of age to undergo either aggressive or conservative phototherapy. The result was that aggressive phototherapy did not significantly reduce the rate of death or neurodevelopmental impairment. The rate of neurodevelopmental impairment alone was significantly reduced with aggressive phototherapy but this reduction may be offset by an increase in mortality among infants weighing 501 to 750 g at birth.

The main controversies on this large RCT trial lay in the wide target irradiance used (between 15 to 40 μW per square centimeter per nanometer of wavelength) and the unlimited variability of the brand and number of phototherapy lights, administration of fluids, feedings, and other interventions that were chosen at the discretion of the caregivers [23].

To assess the current practices existing in Italy for the management of jaundice in preterm infants as a preliminary achievement to a call for national guidelines and establishment of a kernicterus registry, Dani et al., send a questionnaire to the 109 level III neonatal units in Italy to ascertain existing guidelines for total bilirubin monitoring and treatment of hyperbilirubinaemia in preterm infants and occurrence of kernicterus. There was a 61% response rate. Eighty-five per cent of responding units had either written guidelines coming from different literature sources or locally developed. The monitoring of bilirubin varied greatly in timing before, during and after jaundice development. Phototherapy and exchange transfusion were given to 56.0 ± 21.0% and 0.2 ± 0.4% of admitted preterm infants in participating centres. Five cases of kernicterus in preterm infants and eleven cases in term infants were documented over the last 10 years. The results of this research shows that the management of hyperbilirubinaemia in preterm infants is not uniform in Italy and would benefit from shared national guidelines together with the establishment of a kernicterus registry to guide therapy [24].

Phototherapy could have side effects as interfering with mother-newborn bonding, alteration of temperature, fluid and electrolytes balance, circadian rhythm disorder and the bronze baby syndrome. All of these can be resolved with prompt monitoring and intervention [25]. More attention is paid in recent years on long term effects of phototherapy. Csoma et al. enrolled 59 monozygotic and dizygotic twins in a cross-sectional study. One of the twin members received neonatal blue light phototherapy and the other did not; neonatal blue light phototherapy was associated with a significantly higher prevalence of both cutaneous and uveal melanocytic nevi. No association was found between the examined gene polymorphisms and the number of pigmented alterations in the examined study group [26]. To date there is no evidence that phototherapy increases incidence of melanoma and carcinoma of the skin [25] but additional in vivo and in vitro studies are necessary on potential long-term adverse effects of phototherapy.

Final considerations

What is the explanation of such a variation in handling the basic features of a universal problem like neonatal jaundice? The answer is in the method. According to the Institute of Medicine [27], a multidisciplinary team systematically evaluating the available scientific evidence is required to produce evidence-based guidelines. Most if not all the examined national documents fail to demonstrate this critical process. Health care professionals other than neonatologists do not seem to have been involved in the analysis. Yet, neonatal nurses, pediatric hepatologists and basic scientists would have been of great help contributing with a different perspective. On the other hand, good quality clinical evidence in the field of neonatal

hyperbilirubinemia is simply lacking, as recently underlined by Diijk and Huzelbos [28]. More clinical and basic research is needed. The true detrimental effects of bilirubin on neonatal health may currently be still unrecognized. Targets other than the CNS may have a greater relevance for bilirubin toxicity than previously thought [29, 30]. Also, the permeability effect of bilirubin on both cerebral microvasculature [31] and intestinal epithelium [32] might cast new light on how we think of bilirubin toxicity itself. These are a few examples of looking at an old issue from a broader perspective, the only reasonable way to give solid answers to neverending problems.

Declaration of interest

No conflicts of interest exist.

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