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An evidence-based view on hyperbilirubinaemia

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ABSTRACT

Introduction: We conducted a review of the evidence which contributes to the current care of jaundiced newborn infants.

Methods: Literature was searched for reviews and randomized controlled trials (RCTs).

Results: Six Cochrane reviews and eight other reviews and eighteen recent RCTs are discussed.

Conclusions: Many children still suffer life-long consequences of severe hyperbilirubinaemia, which could almost always have been prevented relatively easily. Up to date, guidelines summarizing the available evidence into unambiguous recommendations are needed to guide healthcare professionals in the prevention, diagnosis and treatment for infants with hyperbilirubinaemia.

INTRODUCTION

There is a long-lasting relationship between hyperbilirubinaemia and evidence-based medicine (EBM). Clinical studies have been conducted since the first phototherapy (PT) trial in 1958 by Cremer et al. (1) at virtually all levels of evidence. At the first level, several Cochrane and other systematic reviews have analyzed a variety of bilirubin-related issues. At the second level, one of the first large, randomized controlled trials in neonatology was conducted to evaluate the safety of PT (2). At the next level, observational studies

Abbreviations

AAP, American Academy of Pediatrics; AHRQ, Agency for Healthcare Research and Quality; B/A ratio, bilirubin/albumin ratio; BW, birth weight; EBM, evidence-based medicine; ELBW, extremely low birth weight; ET, exchange transfusion; GA, gestational age; G6PD-def, glucose-6-phosphate-dehydrogenase deficiency; ICTRP, International Clinical Trial Registry Platform; IVIG, intravenous immunoglobulin; IQR, interquartile range; LED, light-emitting diode; NCC-WCH, National Collaborating Centre for Women's and Children's Health; NICE, National Institute for Health and Clinical Experience; NICHD, National Institute of Child Health and Human Development; PT, phototherapy; RCT, randomized controlled trial; SNHL, sensorineural hearing loss; TcB, transcutaneous bilirubin; TSB, total serum bilirubin; UDPGT, uridine diphosphate glucuronosyltransferase.

Key Notes

World wide, many children still suffer life-long consequences of severe hyperbilirubinaemia, which could almost always have been prevented relatively easily.

High-quality studies are needed to provide evidence supporting the management of hyperbilirubinaemia.

Up to date guidelines summarizing the available evidence into unambiguous recommendations are needed to guide all healthcare professionals in the prevention, diagnosis and treatment for infants with hyperbilirubinaemia.

analyzed a variety of clinically relevant topics and several cohort studies, including registries, reported on the incidence of hyperbilirubinaemia and kernicterus. At the last, but not the least level, all paediatricians and neonatologists have their expert opinions on almost all matters concerning the management of hyperbilirubinaemia. Despite extensive research, the majority of diagnostic and therapeutic handling of jaundiced newborn infants seems to be based on rather low levels of evidence, e.g., evidence on risk factors and treatment thresholds in term and – even more valid – in preterm infants. Yet, the management of hyperbilirubinaemia is part of routine care in paediatrics, and it appears that management is mostly sufficient considering the rather low incidences of acute and chronic bilirubin encephalopathy in the developed countries. In the developing countries, however, these incidences are much higher. At the same time, it should be considered that the potentially life-long negative health effects are, at least in theory, preventable. In this article, we provide a comprehensive review of the highest levels of recent evidence that has contributed to the current care of jaundiced infants.

METHODS

We searched the literature for Cochrane reviews, other systematic reviews and randomized controlled trials (RCT) in the Cochrane Database (Cochrane: http://www2.cochrane.org/reviews/), Medline Database (Medline: http://www.ncbi.nlm.nih.gov/pubmed/) and in the clinical trial registries (Clinicaltrials.gov: http://clinicaltrials.gov/) and ICTRP [International clinical trial registry platform (ICTRP): http://apps.who.int/trialsearch/)]. The search terms we used were neonatal jaundice, hyperbilirubinaemia, kernicterus and bilirubin in combination with child, newborn or infant. For recent RCTs, we limited our search – for reasons of space – to articles published from 2008 up to and including 2010.

We did not appraise the articles systematically. This review must, therefore, be regarded as an evidence-based view on hyperbilirubinaemia and not as a systematic review.

RESULTS

Reviews

Cochrane reviews

Six Cochrane reviews (3–8) were published on the efficacy of treatment strategies for unconjugated hyperbilirubinaemia. Table 1 shows the characteristics of these reviews including the conclusions. Only the effectiveness of fibre optic PT (3) is supported by sufficient data and is therefore beneficial to the treatment for jaundiced neonates although it is less effective than conventional overhead PT. Metalloporphyrins (4) may be beneficial, but more long-term data are needed to establish its safety. Therapeutic use of IVIG (5) may reduce the need for ETs in infants with blood group incompatibility, and a single volume ET (6) may be sufficient for the treatment for severe hyperbilirubinaemia. Phenobarbitone (7) and intravenous nutrition (8) cannot be recommended, because to date, no quality RCTs have been conducted.

Other systematic reviews

Evans (9) reviewed the evidence on the efficacy of various treatments for hyperbilirubinaemia: ET, PT in the hospital and at home, and albumin infusion. Although no recent data from RCTs support the effectiveness of ET, there is consensus that it is effective in reducing TSB and in preventing bilirubin neurotoxicity. Therefore, it is categorized as likely beneficial. The conclusion on hospital PT is similar to the Cochrane review of 2001 (3): PT is categorized as beneficial. No results of RCTs on albumin infusion or on home PT were found. In addition, the effectiveness of tin-mesoporphyrin was categorized as unknown although one review and five RCTs showed that bilirubin levels and duration of PT are reduced, but long-term follow-up has not yet been studied sufficiently.

Hulzebos et al. (10) reviewed the usefulness of the bilirubin/albumin (B/A) ratio for predicting bilirubin-induced neurotoxicity in preterm infants. No prospective clinical trials exist that studied bilirubin-induced neurotoxicity in relation to the B/A ratio. Six cohort studies evaluated the B/A ratio in preterm infants. Four studies reported stronger correlations between parameters of bilirubin neurotoxicity with the B/A ratio compared to TSB. The authors conclude that the concurrent use of B/A ratio and TSB in the management of hyperbilirubinaemia should be evidenced by a RCT, which has recently been conducted in the Netherlands (ISRCTN 74465643).

Trikalinos (11) and Ip et al. (12) systematically reviewed the evidence for the effectiveness of strategies to prevent chronic bilirubin encephalopathy. Based on the eleven studies included, the combination of risk factors assessment and early TSB measurement is probably better in predicting clinically significant hyperbilirubinaemia than using either one of the strategies alone. Implementing this strategy increased the proportions of newborns treated with PT, while the readmission rate for hyperbilirubinaemia was reduced. No study addressed the effectiveness of risk factors and/or TSB measurements to reduce the incidence of kernicterus.

De Luca et al. (13) systematically reviewed the available nomograms of transcutaneous (TcB) measurements in full-term or near-term neonates across populations with different risk factors. Four studies were included with more than 8000 patients, and mean TcB levels over time for European, Hispanic, Thai and North American newborns were presented. A formula was calculated to describe the rate of the rise of TcB levels needed to cross percentile curves and to indicate the risk of developing severe hyperbilirubinaemia.

Chavla et al. (14) performed a systematic review and meta-analysis to evaluate the role of phenobarbitone in the management of hyperbilirubinaemia in preterm infants. Three RCTs, with altogether 594 children, were included and analyzed. Phenobarbitone reduced peak TSB levels (with a mean of 30 μmol/L), reduced the duration of PT

Table 1 Cochrane reviews on hyperbilirubinaemia

Year (ref) Topic	Number of included RCTs	Number of included patients	Main outcome measures study group vs. control group	Conclusion
2007 (7) Phenobarbitone	0	0		No evidence on efficacy and safety
2006 (6) Single vs. double volume exchange transfusion	1	20 term infants with ABO incompatibility	*Single vs. double ET volume*: similar reduction in TSB: WMD −13 μmol/L (95% CI, −46 to 20 μmol/L)	Insufficient evidence to change current practice of double volume ET
2003 (4) Metalloporphyrins	3	170 near-term infants (GA: 35–41 weeks) with hyperbilirubinaemia	*Metalloporphyrins vs. no treatment*: less need for PT: RR 0.04 (95% CI, 0.00–0.72), less severe hyperbilirubinaemia: RR 0.04 (95% CI, 0.00–0.72), no effect on rash: RR 0.58 (95% CI, 0.08–4.1). No ETs in either group	Metalloporphyrins may reduce TSB levels and need for PT, but long-term effects are unknown. Insufficient data to recommend as routine treatment.
2003 (8) Intravenous nutrition	0	0		No evidence on efficacy and safety
2002 (5) Immunoglobulins	3	189 full-term and preterm infants with AB0 or Rh incompatibility	*Immunoglobulins vs. no treatment:* reduction in number of ETs: RR 0.28 (95% CI, 0.17–0.47)	Immunoglobulins may reduce need for ET, but insufficient data to recommend as routine treatment in infants with isoimmune haemolytic jaundice.
2001 (3) Fibre optic PT	24	1753 term (GA > 36 weeks and/or BW > 2500g) and preterm infants (GA < 36–37 weeks and/or BW < 2000–2500 g)	*Fibre optic PT vs. no treatment*: greater reduction in TSB at 24 h: WMD −10.7% (95% CI, −18.1 to −3.3) *Fibre optic PT vs. conventional PT*: smaller reduction in TSB at 24 h: WMD 3.6% (95% CI, 1.3–5.9), increased use of additional PT: RR 1.7 (95% CI, 1.2–2.4), non-significant increase in ET: RR 1.62 (95% CI, 0.38–6.9) *Fibre optic PT vs. conventional PT in preterm infants*: similar reduction in TSB at 24 h: WMD 1.7% (95% CI, −2.7–6.1), similar duration of PT: WMD 2 h (95% CI, −3.5–7.5) *Fibre optic PT + conventional PT vs. conventional PT*: shorter duration of PT: WMD −12.5 h. (95% CI, −16 to −9 h), trend to greater reduction in TSB: WMD −3.2% (95% CI, −17–10.8)	Fibre optic PT seems safe, but is less effective in term infants, and equally effective in preterm infants when compared to conventional PT. A combination of fibre optic PT and conventional PT is more effective than conventional PT alone.

RCT, randomized controlled trial; GA, gestational age, TSB, total serum bilirubin (μmol/L; 1mg/dL = 17.1μmol/L) ; WMD, weighted mean difference; ET, exchange transfusion; PT, phototherapy; RR, relative risk 95% CI, 95% confidence interval.

(with a mean of 15 h) and reduced the need for PT and/or ET. The authors concluded that although further trials are warranted to evaluate safety and neurodevelopmental outcome, the beneficial effects of phenobarbitone could be relevant in resource-restricted settings where the availability of PT devices and ET equipment is limited.

Long et al. (15) presented a systematic review about genetic polymorphisms of one crucial gene involved in bilirubin metabolism: uridine diphosphate glucuronosyltransferase 1A1 (*UDPGT 1A1*). Eighteen case–control studies from six countries with a total of 1214 patients with hyperbilirubinaemia and 2131 control infants were included in the meta-analysis. *UGT1A1 211G>A* mutation is associated with neonatal hyperbilirubinaemia in Asians (OR, 2.45; 95% CI, 2.10–2.84), but not in Caucasians (OR, 1.54; 95% CI, 0.87–2.75).

Reviews for the purpose of guideline development

Two extensive reviews were conducted for the purpose of guideline development. The Agency for Healthcare Research and Quality (AHRQ) reviewed the literature in 2002 (16) at the request of the American Academy of Pediatrics (AAP) on which the 2004 AAP guideline on the management of hyperbilirubinaemia (17) is based. The National Collaborating Centre for Women's and Children's Health (NCC-WCH) conducted an extensive review (Clinical Guideline Neonatal jaundice, http://www.nice.org.uk/CG98), upon which the 2010 NICE guideline 'Neonatal jaundice' (18) is based.

Both reviews studied the relationship between hyperbilirubinaemia and adverse outcomes and modifying variables, risk factors for the development of hyperbilirubinaemia, the effectiveness of predicting strategies, the

accuracy of transcutaneous bilirubin measurements and the efficacy of treatments. Although there is no strong evidence, beside the kernicterus registries, on the relationship between hyperbilirubinaemia and adverse outcomes, both guidelines agree that children with bilirubin levels above 340 μmol/L should be treated. Both reviews conclude that the combination of early bilirubin measurements and clinical risk factor assessment is a strong predictor for hyperbilirubinaemia, despite the lack of evidence that this strategy reduces adverse outcome (kernicterus). The AAP recommends predischarge bilirubin measurements in all children, while the NICE does not. Therefore, the Bhutani – risk-zones nomogram of the AAP – is not included in the NICE guideline. The AAP guideline update (19) lists eight 'important risk factors', whereas NICE found sufficient evidence for only four risk factors: jaundice in the first 24 h of life, gestational age of <38 weeks, sibling with neonatal jaundice and/or exclusively breastfeeding. Additional risk factors listed by the AAP – but not NICE guideline – are predischarge TSB or TcB above high-intermediate threshold, isoimmune of other haemolytic disease, cephalohematoma or bruising and east-Asian race.

Both reviews concluded that transcutaneous bilirubin measurements are accurate and can reduce the need for blood sampling. The NICE guideline recommends to measure a TSB if TcB > 250 μmol/L (and not to use TcB measurement before 24 h of life, in preterm infants and during phototherapy), whereas the AAP reported in an update (19) several considerations, but no unambiguous recommendations. Although the treatment thresholds for term and near-term infants are more or less similar in both guidelines, the application of the treatment threshold graphs is not the same. The AAP included neurotoxicity risk factors that lower treatment thresholds, while the NICE does not account for extra risk factors. NICE included (consensus based) treatment thresholds graphs for preterm infants, while the AAP does not yet contain these.

Both reviews agree on the effectiveness of treatment. Phototherapy is safe and reduces the need for exchange transfusions, but evidence that outcome is improved is lacking. Exchange transfusions lower TSB values, but the conducted RCTs have not shown improved long-term outcomes.

Randomized Controlled Trials from 2008 up to and including 2010.

The 2008 NICHD PT trial (20) compared aggressive PT with conservative PT in 1974 preterm infants < 1000 g with a composite endpoint of death or neurodevelopmental impairment. The infants in the aggressive group received prophylactic PT. The infants in the conservative group were treated with PT at predefined TSB thresholds (500–750 g: 136 μmol/L and 750–1000 g: 170 μmol/L). Mean peak TSB levels were lower in infants treated with aggressive PT (120 vs. 168 μmol/L, aggressive vs. conservative PT, respectively). Aggressive PT does not reduce the rate of death or neurodevelopmental impairment, nor death alone. By contrast, neurodevelopmental impairment is lower in the infants that received the aggressive treatment. In the subgroup of infants with BW between 500 and 750 g, aggressive PT results in a nearly significant higher death rate (39% vs. 34%, RR 1.13, 95% CI 0.96–1.34), while profound neurodevelopmental impairment was reduced significantly from 14% to 10% (RR 0.67, 95% CI 0.46–0.98).

In Table 2, we summarize the other recent RCTs (21–37), i.e., the RCTs published between 2008 up to and including 2010. These studies focussed on diagnostic aspects such as TcB measurements (21,22) as well as treatment strategies including PT (23–30), prebiotics (31) or pharmacological treatment, i.e., treatment with drugs (32–35) and Chinese herbs (36,37). It is interesting to note that increasingly these clinical trials are being conducted in non-Western countries.

DISCUSSION

Sister Ward's observation in 1956 that sun light bleached the yellow skin of jaundiced infants, the subsequent introduction of phototherapy (38) and the introduction of anti D/Rhesus immunoglobulin have substantially reduced the incidence of severe hyperbilirubinaemia and kernicterus. Nevertheless, severe hyperbilirubinaemia remains a frequently encountered clinical problem and although relatively rare, chronic bilirubin encephalopathy still occurs all over the world (39). In the developed countries, the major cause seems to be system failure of the complex healthcare organizations, while in the developing countries, limited resources seem to contribute (40).

Early identification of infants at risk of developing hyperbilirubinaemia remains of key importance to prevent severe hyperbilirubinaemia. The majority of infants with kernicterus appears to be 'healthy' and breastfed (16). This implies that risk assessment strategies should include 'healthy' newborn infants and should not be restricted to certain subgroups only. Studies evaluating the effectiveness of preventive strategies aiming at the reduction in the incidence of kernicterus seem impossible owing to its low incidence. Therefore, only studies that evaluate the possibility of preventing high TSB levels are feasible. The combination of risk factor assessment and early TSB measurements has shown the highest predictive value for subsequent hyperbilirubinaemia (12). Experts in the USA recommended predischarge bilirubin screening for all infants. The US Preventive Services Task Forces, however, stated that there is insufficient evidence that this strategy reduces the incidence of kernicterus to put this into practice and did not accept universal screening recommendation (41). There is good evidence, however, that universal screening reduces the risk of subsequent severe hyperbilirubinaemia (42–44).

In future, advances in the development of transcutaneous bilimeters may further increase the feasibility of universal bilirubin screening programmes. Many studies have shown that transcutaneous bilirubin measurements can be accurate and that the need for blood sampling can be reduced. Regrettably, not all instruments are equally accurate and TSB levels are generally underestimated, especially in the higher ranges. Transcutaneous measurements should,

Table 2 Recent (from 2008 up to and including 2010) randomized controlled trials on hyperbilirubinaemia

Topic	Year	1st Author (ref) Country	Number of patients	Main outcome measures Study group vs. control group	Conclusion
TcB	2009	Mishra (21) India	617 healthy near-term and full-term infants	*TcB vs. visual estimation of jaundice*: reduced need for blood sampling: 17.5% vs. 26.4%, p = 0.08	TcB measurements effectively reduce the need for blood sampling for TSB measurements
TcB	2008	De Luca (22) Italy	686 healthy near-term and full-term infants	*TcB with BiliCheck vs. TcB with BiliMed*: better correlation with TSB: r = 0.75 vs. 0.45, less variability −87.2–63.3 μmol/L vs. −97.5–121.4 μmol/L	BiliCheck is more accurate than BiliMed. BiliMed underestimates TSB in the higher ranges
PT	2010	Kumar (23) India	272 healthy near-term and full-term infants	*LED PT vs. conventional PT:* similar reduction in TSB: 3.2 ± 2.2 vs. 3.2 ± 2.4 12 μmol/L/h; p = 0.78 and similar median duration of PT: 26 h IQR 22–36 vs. 25 h IQR 22–36 h, p = 0.44	LED PT is as effective as conventional PT in reducing TSB and duration of PT
PT	2010	Tayman (24) Turkey	242 healthy near-term and full-term infants	*Overhead vs. underneath LED*: with similar irradiance of 30μW/cm^2/nm greater reduction in TSB: 3.8 ± 1 vs. 3.1 ± 12 μmol/L/h, p = 0.01 and shorter duration of PT: 30 ± 11.6 vs. 34 ± 12.3 h, p = 0.04	Overhead LED PT is more effective in reducing TSB and duration of PT than LED PT from underneath
PT	2010	Donneborg (25) Denmark	112 healthy full-term and preterm infants with PT	*Turning infant vs. supine position*: similar reduction in TSB after in 24 h of 49% (95% CI, 47–51) vs. 50% (95% CI, 47–53)	Turning the infant during PT is as effective as PT in supine position; turning is unnecessary
PT	2009	Sivanandan (26) India	84 healthy full-term infants	*Reflecting material + PT vs. PT only:* marginal increase in irradiance level of 16μW/cm^2/per 50 nm, similar duration of PT: 23.3 ± 12.9 h vs. 24.9 ± 15.4 h, p = 0.6, similar reduction in TSB in 24 h 39 ± 56 vs. 34 ± 63 μmol/L, p = 0.65	Reflecting material increases irradiance, but is not more effective in reducing TSB and duration of PT
PT	2009	Silva (27) Chile	77 healthy full-term infants	*Double vs. single PT*: trend towards greater reduction in TSB after 24 h: 87 ± 37μmol/L vs. 73 ± 36 μmol/L p = 0.18	Double PT is slightly more effective in reducing TSB than single PT
PT	2009	Naderi (28) Iran	40 healthy full-term infants	*Triple vs. double PT*: similar TSB after 24 h PT: 185 ± 17 vs. 175 ± 34 μmol/L, p = 0.37, similar duration of hospitalization: 42 ± 18 vs. 35 ± 17 h, p = 0.21	Triple PT is as effective as double PT in reducing TSB and duration of hospitalization
PT	2009	Saeidi* (29) Iran	100 full-term infants with PT and BF	*Extra IV fluid vs. Breast-feeding only*: greater reduction rate of TSB after 24 h: 6.5 vs. 4.9 μmol/L/h, p = 0.04	The combination of IV fluid and breastfeeding during PT is more effective in reducing TSB than PT alone
PT	2008	Boonyairittipong (30) Thailand	60 healthy full-term infants	*Double vs. single intensive PT*: greater reduction in TSB after 24 h: 92 ± 34 vs. 60 ± 58 μmol/L, p < 0.001	Double intensive PT is more effective in reducing TSB than single intensive PT
Pharmacol	2009	Bisceglia (31) Italy	69 healthy full-term infants	*Prebiotics vs. placebo*: lower TcB from 72 h onwards: 93 ± 27 vs. 120 ± 42 μmol/L, p < 0.05 and more stools/day: 3.4 ± 0.0.9 vs. 1.7 ± 0.9, p < 0.05	Prebiotics added to formula feeding results in more stools and lower TcB levels in healthy infants with moderate hyperbilirubinaemia
Pharmacol	2009	Jaikrishan (32) India	97 healthy near-term infants with PT	*Gemfibrozol vs. placebo*: similar peak TSB: 268 ± 46 vs. 277 ± 39 μmol/L and similar duration of PT: 40 h, IQR 30–60 h vs. 36, IQR 19–55 h, p = 0.13	Gemfibrozol is not effective in reducing TSB and duration of PT
Pharmacol	2009	Sakha (33) Iran	68 healthy late-preterm infants with PT	*Clofibrate vs. placebo*: lower TSB after 48 h: 137 ± 23 vs. 189 ± 49 μmol/L, p = 0.02 and shorter duration of PT: 64 ± 12 vs. 88 ± 30 h, p < 0.001	Clofibrate is effective in reducing TSB and duration of PT
Pharmacol	2008	Zahedpasha (34) Iran	40 full-term infants with G6PD def with PT	*Clofibrate vs. PT*: lower TSB after 48 h: 172 ± 41 vs. 194 ± 41μmol/L, p = 0.03 and higher discharge rate after 48 h: 33 vs. 5%, p = 0.03	Clofibrate is effective in reducing TSB and duration of PT and hospitalization in infants with G6PD deficiency
Pharmacol	2008	Shanian (35) Iran	50 full-term infants TSB > ET	*Pre-ET albumin vs. no treatment*: lower TSB 6 h after ET: 136 ± 26 vs. 274 ± 36 μmol/L p < 0.001, shorter duration of PT: 8.6 ± 2.4 vs. 25 ± 8.2 h, p < 0.001, and less frequent a second ET: 0 vs. 4 infants	Pre-ET albumin infusion is effective in reducing TSB, duration of PT and need for a second ET
Pharmacol	2008	Chen* (36) China	242 healthy preterm infants	*Yinzhihuang oral liquid vs. no treatment*: significant differences in TcB after 24 h, detailed information not specified	Yinzhihuang oral liquid seems to decrease the incidence of pathological jaundice

Table 2 (Continued)

Topic	Year	1st Author (ref) Country	Number of patients	Main outcome measures Study group vs. control group	Conclusion
Pharmacol	2008	Qiu (37) China	138 infants	*Colonic Taihuang vs. no treatment*: increase in frequency of stools: 4.0 ± 1.3 vs. 2.0 ± 1.1, greater reduction in TSB: 31.5 ± 10.1 vs. 23.3 ± 8.3 μmol/L and shorter duration of hyperbilirubinaemia: 5.6 ± 3.5 vs. 7.8 ± 4.1 days	Colonic Taihuang is effective in reducing TSB

TcB, transcutaneous bilirubin; TSB, total serum bilirubin; PT, phototherapy; Pharmacol, pharmacological study; LED, light-emitting diode; IV, intravenous; ET, exchange transfusion. Data are presented in mean ± SD, or median and IQR, inter quartile ranges.
*Only English abstract available. TSB levels are expressed in μmol/L: 1 mg/dL = 17.1μmol/L

therefore, be interpreted with caution and specific transcutaneous bilirubin nomograms must be developed in large populations of newborns (13). The algorithms of the bilimeters, which convert the colour of skin into a bilirubin value, have improved over time. Recent studies showed that the rate of the rise of bilirubin can be calculated from serial measurements which, in turn, can be used to predict hyperbilirubinaemia and identify those children that will probably need to be treated for hyperbilirubinaemia (11).

Several important issues in the treatment for hyperbilirubinaemia have been evaluated in Cochrane reviews (Table 1). However, the clinical relevance may be limited because quite strict inclusion criteria were applied, and consequently, only small numbers of RCTs with small numbers of subjects were included, with the exception of the fibre optic phototherapy review. The conclusions drawn by the reviewers are also rather conservative. For instance; metalloporphyrines reduce the need for PT with a RR of 0.04 (95% CI 0.00–0.72), which is a highly significant reduction. Nevertheless, it is concluded that metalloporphyrines *may* reduce TSB levels and the need for PT (4). Reviews are by nature always a little behind in time because high level evidence trials need to be presented and reviewed first before being incorporated into Cochrane reviews. Most of the reviews listed in Table 1, however, have not been updated very recently, which also limits the clinical value.

The mainstay of hyperbilirubinaemia treatment is PT. Although many studies have proven that PT is effective in reducing bilirubin levels and preventing ET, no evidence is available to prove that PT actually improves neurological outcome in infants with hyperbilirubinaemia. As a result of ethical considerations, prospective trials comparing PT to 'placebo' are no longer feasible. What we do know, however, is that PT is relatively safe and effective in reducing TSB levels. This is evidenced by the dramatic reduction in the number of ETs (45). The number needed to treat, however, varies considerably across different subgroups (from 10 to 3000 infants treated with PT to prevent one ET) (46). NB: in some clinical trials in developing countries, the proportion of children that undergo ET remains alarmingly high (47).

Evans (9) noted that ETs are likely to be beneficial based on their findings that there are no prospective RCTs that support the effectiveness of ETs in reducing outcome. There are indeed no recent RCTs but Mollison and Walker (48) reported a RCT in 1952, before the PT-era, showing a significant reduction in mortality after exchange transfusions vs. single blood transfusion in haemolytic disease of the newborn.

Recent trials showed that probably the new generation of LED PT devices is as effective as tube lights, and they produce less heat (23,24). Overhead PT LED is probably more effective than PT with a blanket from underneath (24). The irradiance levels of the PT devices should be checked regularly. The recommended minimal irradiance levels are 8–12 $\mu W/cm^2/nm$ for PT and at least 30 $\mu W/cm^2/nm$ for intensive PT (45).

When to start PT remains uncertain, both in full-term and near-term infants as in early- and late-preterm infants. The recent NICHD aggressive vs. conservative PT trial (20) probably generated more questions than answers. For the larger infants (750–1000 g), aggressive PT may be preferred because neurodevelopmental benefits are found without adverse effects. It is far more difficult to draw conclusions for the smallest infants because even though aggressive PT is associated with neurodevelopmental benefits, mortality may be increased. Apparently, it is difficult to find the right balance in the management of hyperbilirubinaemia in these smallest infants. We speculate that PT should not be applied prophylactically to all ELBW infants, but rather that it be individualized to maintain relatively low TSB levels.

Pharmacotherapy in case of hyperbilirubinaemia plays only a modest role in the developed countries. In resource-restricted settings, however, where PT units and ET equipment are limited and power supply may be erratic, pharmacotherapy could become much more relevant. Clofibrates, phenobarbital and metalloporphyrins, bile salts and bilirubin oxidase are promising candidates (49). In this respect, the trials with a variety of Chinese herb-derived drugs are interesting. Molecular mechanisms have been unravelled to a certain extent (50), and several trials have demonstrated the ability of specific herbs to reduce TSB levels, but safety and long-term consequences have not yet been studied sufficiently.

It is of great importance that the available evidence is summarized into guidelines containing clear and unambiguous recommendations; a logical link between evidence and recommendations should be aimed at. Moreover, guidelines

should be freely available for all healthcare professionals involved into perinatal care (in hospital but also at home) Therefore, the guidelines should be adapted and disseminated among all healthcare professionals who care for newborn infants. In the Netherlands, the AAP guideline was adapted to this situation in which perinatal care takes also place at home where several healthcare professionals participate in the prevention and early recognition of hyperbilirubinaemia (51). The recommendations were rephrased using the 5W's method: Who does What to Whom, When and in What way. Additional tools, such as tables, graphs/algorithms, summary boxes and information for the parents were added and put on the world wide web (http://www.babyzietgeel.nl) meaning 'baby looks yellow' (Babyzietgeel: http://www.babyzietgeel.nl/).

CONCLUSIONS

Over the last decades, epidemiology, prevention, diagnosis and treatment for hyperbilirubinaemia have been studied and reviewed extensively. These studies provide data with a variety of levels of evidence to caregivers involved in the management of jaundiced newborn infants. Although many issues concerning hyperbilirubinaemia were elucidated, which led to the improved management of jaundiced infants, many unresolved issues remain and they require more detailed study. These include the role of genetics and environmental factors that may influence the vulnerability to developing kernicterus. Other areas of interest are safe treatment thresholds for preterm infants and the pharmacological treatment for jaundiced infants.

World wide, many children still suffer life-long consequences of severe hyperbilirubinaemia: an event that could almost always have been prevented relatively easily. In the developed countries, the major cause for kernicterus seems to be system failure of the complex healthcare organizations, while in the developing countries, limited resources seem to contribute. Risk factor assessment and predischarge measurement of transcutaneous bilirubin appear to be effective screening methods and could effectively reduce blood sampling. Phototherapy remains the cornerstone of treatment, despite extensive research on novel treatment modalities for unconjugated hyperbilirubinaemia. It is of great importance that the available evidence is summarized into guidelines containing clear and unambiguous recommendations for the prevention, diagnosis and treatment for hyperbilirubinaemia for all healthcare professionals who care for newborn infants.

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CONFLICT OF INTEREST

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