Phototherapy is commonly used for neonatal jaundice but greater control is needed to avoid toxicity in the most vulnerable infants

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Short title: **Phototherapy for neonatal jaundice**

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Abbreviations: AGA, Appropriate for gestational age; GA, gestational age, IVH, Intraventricular haemorrhage; IVIG, Intravenous immune globulin; LGA, Large for gestational age; NICU, neonatal intensive care unit; SGA - small for gestational age; TSB - total serum bilirubin.

FINANCE

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ABSTRACT

Aim: Limited information is available about how guidelines on phototherapy for neonatal jaundice are applied in practice and toxicity is a concern. We studied the use of phototherapy in relation to birth weight and gestational age (GA) in Norwegian neonatal intensive care units (NICUs).

Methods: The study population was all 5,382 infants admitted to the 21 NICUs in Norway between 1 September 2013 and 31 August 2014. Data were recorded daily in the Norwegian Neonatal Network database and anonymised data on patient characteristics, diagnoses, duration, the ages at the start and discontinuation of phototherapy were analysed.

Results: More than a quarter (26.6%) of all infants admitted to Norwegian NICUs during the study period received phototherapy. The use of phototherapy was inversely related to GA and birth weight. More than 80% of the preterm infants under 28 weeks of GA received phototherapy. The duration was significantly longer in the lowest birth weight and GA groups and decreased with increasing birth weight and GA.

Conclusion: Phototherapy is proved to be a strong candidate for the most common therapeutic modality in NICU infants. However, in light of reported toxicity in the smallest, most vulnerable infants, we recommend increased emphasis on quality control.

Keywords: Clinical guidelines, Hyperbilirubinaemia; Neonatal intensive care unit; Neonatal jaundice; Phototherapy.

Key notes

- We studied the use of phototherapy in relation to birth weight and gestational age (GA) in Norwegian neonatal intensive care units (NICUs).
- More than one-quarter (26.6%) of the 5,382 infants admitted to the NICUs in Norway over a one-year period received phototherapy and this exceeded 80% in preterm infants under 28 weeks of GA.

- Increased emphasis on quality control is needed to avoid toxicity in the smallest, most vulnerable infants.

INTRODUCTION

Neonatal jaundice may be the most commonly observed transitional process in newborn infants and it is usually treated with phototherapy, which is non-invasive, easy to apply and generally considered innocuous. Phototherapy leads to the formation of water-soluble bilirubin photoisomers that can be excreted in urine and bile without the need for conjugation, thereby reducing total serum bilirubin (TSB) (1). Ideally, effective phototherapy should be safe (2) and it has long been considered harmless (3).

However, a large multicentre randomised controlled trial, where premature neonates received either aggressive or conservative phototherapy (4), showed a significantly increased relative risk of death (1.19) in the aggressively treated group, if they were mechanically ventilated and had a birth weight of 501-750g (5). The term aggressive implied starting treatment at relatively low TSB levels. The use and dosage of phototherapy varies considerably (6-8) and these variations may partly be related to patient characteristics, the presence of complicating factors and other illnesses. In addition, variations in the use of phototherapy appear to be related to local procedures and treatment traditions (6,9).
In Norway, national consensus-based guidelines for managing neonatal jaundice have been in place since 2006 (10). All NICUs in Norway are connected to the Norwegian Neonatal Network, a national medical quality registry that records diagnoses and on-going clinical activities for all admitted infants on a daily basis. The aim of this national study was to prospectively examine the occurrence and duration of phototherapy for neonatal jaundice in relation to birth weight and gestational age (GA) in Norwegian NICUs over a one-year period.

MATERIALS AND METHODS

Population

The study was performed in all 21 Norwegian NICUs from 1 September 2013 to 31 August 2014 under the auspices of the Norwegian Neonatal Network. The study group comprised all infants with hyperbilirubinaemia who needed phototherapy according to the national guidelines (10) and all other infants admitted to Norwegian NICUs during the same period provided the controls. We formed the

Norwegian NICU Phototherapy Study Group with collaborators in each NICU (Appendix 1), who were responsible for the quality control of the daily electronic data registration in the Norwegian Neonatal Network database.

Variables from the Norwegian Neonatal Network

This study recorded data on gender, GA, birth weight and growth status, total number of hours receiving phototherapy, postnatal age at the start and end of treatment, diagnoses, use of immunoglobulin and exchange transfusion. Phototherapy was initiated, continued and discontinued according to the Norwegian guidelines' chart (10). These guidelines suggest starting phototherapy when a TSB value plots above the intervention line for the infant's birth weight and age in hours and stopping when TSB is 20 µmol/L (~1.2 mg/dL) or more below the intervention line.

Our other paper in this issue of *Acta Paediatrica* reports details on local practice patterns, including among others phototherapy devices and irradiance measurements (11).

Total serum bilirubin measurements

TSB was measured according to the clinical procedures in each NICU and this was typically in a central laboratory or by CO-oximetry / multiple wavelength spectrophotometry on a blood gas machine. All clinical laboratories in Norway participate in a nationwide quality assurance system for analyses, including TSB. TSB was either measured based on clinical indications, to follow up previously elevated values or on-going phototherapy, or as a by-product of a multichannel analysis in a blood gas machine. Transcutaneous bilirubin measurements were only used as a screening tool to determine the need for a blood test.

Ethical considerations

The study was reviewed by the South East Regional Committee for Medical and Health Research Ethics and they considered this to be a quality control study that did not need consent from the individuals in the database or their proxies (2013/287). Accordingly, the study was subsequently reviewed and approved by the Data Protection Officer at Oslo University Hospital (2013/17162).

Data handling and statistics

The statistical analyses were performed using SPSS version 22 (IBM, New York, USA) and SAS version 9.4 (SAS Institute Inc, North Carolina, USA). Categorical data are presented as frequencies with percentages and continuous data are presented as means with standard deviations (SDs), as well as medians, minimum and maximum values. Outcomes were compared across the groups of patients by estimating linear mixed models for continuous variables using the SAS MIXED procedure and generalised linear models using the SAS GLIMMIX procedure for categorical variables. The random effects for hospitals included in the models correctly adjusted the estimates for possible within-hospital cluster effects. Results with p values of < 0.05 were considered statistically significant.

RESULTS

From 1 September 2013 to 31 August 2014, 5,382 infants were admitted to the 21 NICUs in Norway and these represented 9% of the total population of newborn infants (n=60,031). Of these, 1,429 (26.6%) received phototherapy (Table 1), but only 283 were admitted with neonatal jaundice as a primary diagnosis. In 83 infants the duration of phototherapy was not recorded, possibly due to miscoding, and they were not included in our analyses. There was no significant difference between males and females, with regard to receiving or not receiving phototherapy ($p = 0.378$). The use of phototherapy was inversely related to GA and birth weight ($p<0.001$) and more than 80% of the infants born at less than 28 weeks of GA received phototherapy (Table 1). The control group comprised the 3,953 (73.4%) infants who did not receive phototherapy.

Initiation and duration of phototherapy

The duration of phototherapy was significantly longer in the lowest birth weight and GA groups and decreased with increasing birth weight ($p< 0.001$) (Table 2) and GA ($p<0.001$) (Table 3). The age at the start of the first phototherapy treatment was lowest in premature infants and increased significantly with increasing birth weight ($p<0.001$), (Table 2) and GA ($p<0.001$) (Table 3). In addition, the smallest, most immature infants were significantly older when phototherapy was discontinued than the larger, more mature infants (Tables 2 and 3). The duration of phototherapy in patients who started phototherapy during the first three days of life was significantly longer than those who started

phototherapy after the third day of life (Table 4). Initiation of phototherapy at less than three days of age was significantly more common in the low versus higher birth weight groups (Table 4), (p=0.007 for trend).

Phototherapy use relative to growth status

Of all the 5,382 infants who were hospitalised, 1,122 (20.8%) infants were small for gestational age (SGA), 3,814 (70.8%) were appropriate for gestational age (AGA) and 446 (8.2%) were large for gestational age (LGA). There was a statistically significant difference between the incidence of phototherapy in those who were SGA (33.0%), AGA (26.1%) and LGA (13.9%) ($p < 0.001$) (Table 1).

Diagnoses associated with phototherapy

In the total population, the presence of intraventricular haemorrhage (IVH) was significantly positively associated with the need for phototherapy ($p < 0.001$). However, IVH was negatively associated with phototherapy in the group with a birth weight of less than 1,000g ($p =0.003$). Significantly fewer infants with a diagnosis of infection received phototherapy than non-infected infants (19.1 versus 27.7%, $p<0.001$). However, further analyses showed that this was entirely due to the group with a birth weight of more than 2,500g. The need for phototherapy was significantly lower in infants born to diabetic mothers compared to those whose mothers did not have diabetes (16.8 versus 26.9%, $p<0.001$).

Blood group incompatibilities, intravenous immune globulin and exchange transfusion

Hyperbilirubinaemia due to blood group incompatibility was diagnosed in 150 neonates. Of these, 92 had blood group incompatibility as their principal admission diagnosis. Of the 150, 128 (85.3%) received phototherapy, including 22 who received both phototherapy and intravenous immune globulin (IVIG). Only six infants received IVIG without phototherapy. The remaining 16 infants with blood group incompatibilities did not receive IVIG or phototherapy. Exchange transfusion was performed in six patients, including one who also received IVIG.

Kernicterus

During the study year one case of kernicterus was reported and the details of this case have previously been published (12).

DISCUSSION

Neonatal jaundice is a very common reason for diagnostic work-ups and therapeutic interventions in the newborn period, but there appears to be a lack of studies that describe the epidemiology of such therapy in NICUs. The present national study prospectively recorded the selected circumstances surrounding the use of phototherapy in all infants hospitalised in Norwegian NICUs over a one-year period and appears to have been the first study with such a comprehensive scope. This paper primarily focuses on describing the epidemiology of phototherapy use in NICUs. Other details regarding practice patterns are reported in our other paper in this issue of *Acta Paediatrica* (11).

The proportion of NICU infants who received phototherapy

More than one in four infants admitted to Norwegian NICUs received phototherapy during their hospital stay. Of these 1,429 infants, only 283 (19.8%) had a jaundice-related diagnosis as the principal reason for NICU admission. Thus, jaundice often complicates NICU stays and demands treatment. The Norwegian guidelines (10), like many others, suggest therapeutic interventions at lower TSB levels when an infant is sick. Healthy term and near-term infants who require phototherapy are allowed to remain in the maternity unit in most Norwegian hospitals. We were not able to collect data about such phototherapy use outside the NICUs.

Mukherjee et al have presented retrospective data from two US NICUs from 2009-2015 and report that 81% of the 2,023 NICU infants born at less than 35 weeks of GA received phototherapy. Our data cannot be directly compared to this study because they did not included term and near-term infants, who were less likely to need phototherapy. However, we can estimate that 55% of the group that was comparable to the infants in our study received phototherapy (Table 1). Three different guidelines were used during Mukherjee et al's study, with an increasing proportion of infants needing phototherapy following each change (13). Thus, the impact of guidelines was clearly shown.

Gender differences

There was no gender difference in the need for phototherapy among our NICU infants (Table 1). This was compatible with data from other studies (4,13,14), but they included infants not admitted to NICUs (14) or were limited to selected NICU infants (4,13). However, one American population-based study reported that significantly more boys qualified for phototherapy according to the American Academy of Pediatrics guidelines (15). Boys were also disproportionately represented in our Norwegian NICU population (56.4%). Whether this could translate into a overall gender difference in phototherapy needs among Norwegian neonates could not be assessed, due to lack of data on the maternity population of newborn infants.

Need for phototherapy according to prematurity and birth weight

In our study, most of the smallest and most immature infants, more than 80%, received phototherapy and the need for phototherapy decreased with increasing GA. Thus, 12.5% of all newborn infants with a GA of 37 weeks or more received phototherapy and this was higher than the 3.1% found in a healthy low-risk population of term and near-term Norwegian newborn infants (16). This suggests that concurrent illness and, or, more pronounced jaundice contributed significantly to the phototherapy need in our NICU population at this age. Prophylactic phototherapy, as that term is commonly understood, is not recommended in our guidelines (10). However, in common with the 2004 American Academy of Pediatrics' guidelines (2), the Norwegian graph starts at relatively low TSB values at birth, increasing to a higher plateau value at three to four days of age. This approach is applied to even to the most immature infants.

As with all other bilirubin guidelines, the levels of TSB at which intervention is recommended are the results of expert opinion (10). Nevertheless, as phototherapy is recommended from 100 μmol/L (6 mg/dL) in a 24-hour-old infant weighing less than 1,000g and from 125 μmol/L (7.3 mg/dL) in a 24-hour-old 1,000-1,500g birth weight infant, etc, it is not surprising that many of the smallest infants receive phototherapy. Recommendations from a group of American experts on managing jaundice in preterm infants (17) suggested intervening at the same bilirubin level during the first days of life. Thus, during the first two days of life, phototherapy in the smallest premature infants may start at

lower TSB levels in Norway than in the US and the proportion of premature infants receiving early therapy could be higher in Norwegian NICUs than if the US expert recommendations (17) had been applied. However, because suggested intervention levels after the first two to three days of life in the smallest infants are higher in Norwegian guidelines (10) than those suggested by US experts (17) it is conceivable that the overall percentage receiving phototherapy may in fact be lower. This was strongly suggested by preliminary data from two US NICUs (13), where 88% of infants with a GA of less than 28 weeks received phototherapy, compared to 82.4% in our study. This difference was much more pronounced at a higher GA. Thus, 91% of US 28 to less than 32 weeks GA infants received phototherapy, versus 62.6% in our 28 to less than 33 weeks GA infants.

Duration of phototherapy

The fact that more than 80% of the extremely low birth weight infants in our study received phototherapy would not concern us if we could be certain that phototherapy was innocuous (3). However, literature ranging from 1992-2012 suggests that phototherapy may not be as harmless as we think (4,5,18). Of particular concern is the reanalysis of data of almost 2,000 premature infants from the Neonatal Research Network (5), which found increased mortality in mechanically ventilated infants with a birth weight of 750g who had been treated with aggressive phototherapy. The levels of irradiance were not varied as part of that study design and the term aggressive referred to initiation of phototherapy at lower levels of TSB. Consequently, aggressively treated infants received phototherapy for significantly longer than infants whose treatment started at higher TSB levels (88 hours versus 35 hours) (4). In our study the mean duration of phototherapy for infants weighing less than 1,000g was 39 hours, similar to the conservatively treated group in the original paper from the Neonatal Research Network study (4), on which the later re-analysis (5) was based.

The duration of phototherapy in our study was inversely related to GA and birth weight. Mukherjee et al (13) reported that the mean duration of phototherapy in premature infants born at less than 28 weeks was 73 hours and that it increased from 49-82 hours from the first to the last of the three study periods. This compared to a mean of 37 hours in our study (Table 3). Our other paper in this issue of *Acta Paediatrica* (11) shows that there was a considerable variation in phototherapy durations between

NICUs. This suggests that there is potential for further reductions in light exposure, if more attention is paid to local practice patterns, which was a point that was also made by Mukherjee et al (13). Other differences in local practice patterns that might have an impact on duration, such as different phototherapy units and light sources, are further discussed in our other paper in this issue of *Acta Paediatrica* (11).

The average duration of phototherapy in this study were a mean ± SD of 21.0 ± 17.0 and median of 17.0 hours in term infants and a mean ± SD of 29.2 ± 21.9 and median of 22.5 hours in late preterm infants (Table 3). These durations were quite short in view of the fact that these were NICU patients and could not be regarded as healthy. In a study that compared light emitting diode and conventional phototherapy in healthy term and late preterm infants, Kumar et al reported a median duration of 26 and 25 hours, respectively (19). Sachdeva et al reported mean durations of 24 hours and 30 hours, respectively, for intermittent and continuous phototherapy in healthy term and late preterm infants (20), using the American Academy of Pediatrics' phototherapy guidelines (2).

Limited data is available on the expected duration of phototherapy in preterm infants. Tan (21) reported around 28-53 hours in term and preterm infants, using the same intervention limits for both groups. Romagnoli et al (22) found that the mean duration of phototherapy varied between 75.1 hours in preterm infants of up to 30 weeks of GA treated with fluorescent phototherapy from above, plus a fiber optic blanket from below, to 94.5 hours for infants just treated with a fiber optic blanket. Romagnoli notably reported that phototherapy was started in all infants when TSB exceeded 6 mg/dL (103 μmol/L) (22), a considerably lower intervention limit than suggested by our national guidelines, which range from 130-200 μmol/L at a mean starting age of at least three days . Lasky et al (23) reported on a two-centre randomised study of brainstem auditory evoked response latencies in preterm infants with 501-1,000g birth weights, who were randomly allocated to conservative or aggressive phototherapy, as defined in the National Institute of Child Health and Human Development Network study (4). The reported duration of phototherapy varied widely from a mean of 16 hours in the conservatively treated 751-1,000 g infants in one centre to a mean of 178 hours in the aggressively treated 501-750g infants in the other centre. In our study, the mean duration of 38.8 hours for infants

weighing less than 1,000g at birth was at the lower end of the range reported by Lasky et al (23) and our variations were much narrower. However, our data were comparable with Morris et al (4), who reported a mean duration of phototherapy of 35 hours in their conservatively treated infants born weighting less than 1,000g.

Age at initiation of phototherapy

The age at initiation of phototherapy may depend on several factors and this makes comparisons between studies challenging. Lower intervention levels for the smallest, most immature, infants mean that these levels are reached sooner after birth. Our study showed that, on average, infants with birth weights of less than 1,000g started phototherapy on the second day of life, with a mean of 1.8 days (Table 2). On average, all the other groups started phototherapy on the third day of life, with a significant trend towards a later starting time for the more mature infants (Table 2). Due to the immaturity of their bilirubin metabolism, the smallest infants were started on phototherapy early and received it for longer than the more mature infants (Table 4). Because the typical course of physiologic jaundice peaks around days two to four, infants who only start phototherapy after the normal peak has passed are likely to demonstrate a more rapid response. Conversely, those who need phototherapy during the period when TB normally rises cannot be expected to show the same rapid response. Given this multifactorial background, published data on starting times for phototherapy will depend on both the characteristics of study population and on the chosen intervention levels. Tan (21, 24) reported that most infants only started phototherapy on days four and five, while in Seidman et al's (25) study of healthy term infants, the mean starting age was 47 hours. Romagnoli et al (22) described a mean starting age of 38-39 hours in preterm infants of less than 30 week of GA, a number that was very close to our observations for infants born at less than 1,000g (Table 2). Djokomulanto et al (26) studied healthy term newborn infants in need of phototherapy according to Malaysian criteria, starting on the fifth day of life. Martins et al (27) compared different light sources in preterm infants at a mean GA of 33-34 weeks and reported that they started phototherapy at between 65-71 hours, close to the timing of the first phototherapy in our comparable group of infants.

Phototherapy use relative to growth status

The growth status of an infant appears to influence the occurrence of neonatal jaundice, and, therefore presumably the likelihood of needing phototherapy. However, this seems to be primarily related to maternal diabetes. Peevy et al described an increased incidence of neonatal jaundice in LGA, but not AGA, infants who were born to diabetic mothers (28). Jährig et al found increased neonatal jaundice in AGA and LGA infants born to diabetic mothers, but noted that it was more pronounced in LGA infants (29). On the other hand, Gyurkovits et al studied non-diabetic macrosomic infants with birth weights of at least 4,000g and found that the incidence of neonatal jaundice was significantly lower in those infants than in the control group, where the birth weights ranged from 2,500-3,999g. (30). This appeared to be compatible with the lower need for phototherapy in our LGA infants (Table 1).

Friedman et al found that hyperbilirubinaemia was lower in premature infants who were SGA than AGA and speculated that hepatic glucuronyl transferase was prematurely induced due to intrauterine stress (31). Our findings seem to show the opposite, that SGA infants received phototherapy significantly more often than AGA and LGA infants (Table 1). However, this was likely to be a by-product of the way the Norwegian guidelines were designed and not a reflection of differences in bilirubin metabolism per se. Thus, intervention categories are by birth weight, not GA. As a consequence, SGA infants may be treated at lower TSB levels than AGA infants of similar maturity, while, conversely, LGA infants may only be treated at higher TSB levels. Therefore, we analysed term infants separately, defined as more than 37 weeks of GA with birth weights of more than 2,500g, with respect to the impact of growth status on the need for phototherapy, as the intervention limits for these infants were the same. This analysis confirmed that growth status per se did not significantly influence the need for phototherapy (data not shown).

Diagnoses associated with phototherapy

Not surprisingly, most infants with a diagnosis of blood group isoimmunisation received phototherapy (85.3%). The high need for phototherapy in infants with IVH (60.5%) was also expected, as any sequestered blood will contribute to increased bilirubin production. Therefore, the negative association between IVH in infants born at less than 1,000g and phototherapy is difficult to explain. However, Amato et al described a similar finding of less jaundice in infants less than 1,500g birth weight with

IVH (32). On the other hand, Epstein et al described the expected the relationship between IVH and jaundice in infants weighing less than 1,000g at birth, although they did not study phototherapy (33).

Infection is commonly described in the literature, both as a risk factor for neonatal jaundice and as an additional risk for bilirubin encephalopathy when neonatal jaundice and infection occur at the same time. Our finding that significantly fewer infants with a diagnosis of infection needed phototherapy than the overall NICU population does not necessarily contradict this. Thus, one could speculate that the stress of an infection might stimulate bilirubin metabolism. It is also possible that the negative association we found may have been an epiphenomenon related to other characteristics of the NICU population.

IVIG and exchange transfusion

IVIG seems to have largely replaced exchange transfusion in those infants whose TSB rise cannot be controlled by phototherapy Our study found that 28 of the 39 infants in our total cohort who received IVIG had a diagnosis of blood group incompatibility and these figures included 25 of the 30 who received IVIG on the first day of life. Such early use is indicative of the recommended way to use IVIG in Norwegian guidelines, namely as a way to stave off impending exchange transfusion. This is indicative of the recommended way to use IVIG in Norwegian guidelines, namely as a way to stave off impending exchange transfusion. Indeed, some of the apparent discrepancies between those studies that found IVIG to be a helpful strategy in blood group isoimmunisation (34,35) and those who have failed to find any benefit (36,37), may have been because IVIG was used as either a rescue treatment or prophylaxis. Because most infants with blood group isoimmunisation can be handled well with just intensive phototherapy, as shown in our study, a study of prophylaxis will lose statistical power by treating many who do not need IVIG. On the other hand, rescue strategies, specifically target those infants who would otherwise have received an exchange transfusion.

An exchange transfusion is effective in preventing kernicterus, but it is an invasive procedure with significant risks, including catheter related complications, infections, necrotising entercolitis, thrombocytopenia, apnoea, bradycardia, hypocalcaemia and even death (38,39). Older studies show

that exchange transfusion rates were as high as 6% in infants already receiving phototherapy (39) and 22.1% in infants with severe hyperbilirubinaemia, defined as a TSB of more than 425 µmol/L (40).

Our data show that exchange transfusion has become extremely rare in Norway and this is probably due to the use of effective and intensive phototherapy, in some cases combined with IVIG. Six exchange transfusions in a birth population of around 60,000 means that only 0.01% of all Norwegian newborn infants were subjected to this procedure. Clearly, the opportunities for learning this procedure, as well as maintaining skill levels, are non-existent for most residents and attending physicians. Others have also documented a steep decline in the number of exchange transfusions, as low as 0.05% (41).

Kernicterus

Kernicterus is exceedingly rare in Norway and our follow-up survey of all paediatric department chairs in Norway showed that from 2006, when the current guidelines were introduced, to 2015 no further cases of kernicterus had been diagnosed. With an annual birth rate of ±60,000, this translates into one case of kernicterus per 600,000 births, which is lower than any other reported national data to the best of our knowledge.

We speculate that this fortunate situation is due to a system that specifies that following up jaundice in the first two weeks of life is the sole responsibility of the birth hospital. The case that occurred during the study period was due to a failure in the post-discharge follow up, as parents were referred to their local well-baby clinic rather than being taken care of at the birth hospital (12).

Strengths and weaknesses

The strengths of this study were the prospective design, which included all the NICUs in Norway, the large number of patients and the use of a national quality registry that recorded the clinical activities for all admitted infants on a daily basis. Although the results relate to Norwegian infants, it is likely that they could be generalised to similar settings. Ethnicity was not recorded in the database and variations based on this factor could not be captured. Registration at multiple locations and by multiple healthcare personnel may have introduced bias, but the presence of uniform guidelines and the

presence of study group members in each NICU should have minimised this effect. Data from infants receiving phototherapy on maternity wards, but technically considered NICU admissions, were included from two smaller NICUs. These data could not be filtered out during the analysis, but given the small number of infants involved, these are unlikely to have influenced the overall results.

CONCLUSIONS

Phototherapy is a strong candidate for the most common therapeutic modality in NICU infants, as it was given to more than 25 % of the infants admitted to Norwegian NICUs during the study period. The use and duration of phototherapy was significantly higher in infants with a low GA and birth weight. In view of the reports of toxicity in the smallest, most vulnerable infants (4,5), we recommend increased emphasis on quality control. The duration of phototherapy varied widely between NICUs. Details on the impact of these variations are presented in our other paper in this issue of *Acta Paediatrica* (11).

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