







Severe neonatal hyperbilirubinaemia: lessons learnt from a national perinatal audit

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ABSTRACT

Objectives To describe characteristics of neonates with severe neonatal hyperbilirubinaemia (SNH) and to gain more insight in improvable factors that may have contributed to the development of SNH.

Design and setting Descriptive study, based on national Dutch perinatal audit data on SNH from 2017 to 2019.

Patients Neonates, born ≥ 35 weeks of gestation and without antenatally known severe blood group incompatibility, who developed hyperbilirubinaemia above the exchange transfusion threshold.

Main outcome measures Characteristics of neonates having SNH and corresponding improvable factors.

Results During the 3-year period, 109 neonates met the eligibility criteria. ABO antagonism was the most frequent cause (43%). All neonates received intensive phototherapy and 30 neonates (28%) received an exchange transfusion. Improvable factors were mainly related to lack of knowledge, poor adherence to the national hyperbilirubinaemia guideline, and to incomplete documentation and insufficient communication of the a priori hyperbilirubinaemia risk assessment among healthcare providers. A priori risk assessment, a key recommendation in the national hyperbilirubinaemia guideline, was documented in only six neonates (6%).

Conclusions SNH remains a serious threat to neonatal health in the Netherlands. ABO antagonism frequently underlies SNH. Lack of compliance to the national guideline including insufficient a priori hyperbilirubinaemia risk assessment, and communication among healthcare providers are important improvable factors. Implementation of universal bilirubin screening and better documentation of the risk of hyperbilirubinaemia may enhance early recognition of potentially dangerous neonatal jaundice.

INTRODUCTION

Severe neonatal hyperbilirubinaemia (SNH) is a known adverse outcome of the biological phenomenon of elevated unconjugated bilirubin levels during the first days after birth. If SNH is left untreated, it may result in acute bilirubin encephalopathy (ABE) and may ultimately evolve further into kernicterus spectrum disorder (KSD).¹ Successful implementation of hyperbilirubinaemia management guidelines including universal or selective screening strategies, or a priori risk assessment and close follow-up is key to reduce SNH.^{2,3} A systems-based approach, such as a perinatal audit, is recommended to facilitate guideline implementation and change practice

What is already known on this topic?

- Neonatal hyperbilirubinaemia is a physiological phenomenon, but a small proportion of neonates may develop severe hyperbilirubinaemia.
- A priori risk assessment for severe neonatal hyperbilirubinaemia is incorporated in management guidelines and may reduce the risk hereof.
- Late recognition of potentially severe hyperbilirubinaemia delays treatment, exposing neonates unnecessarily to hazardous levels of bilirubin.

What this study adds?

- Perinatal audit meetings on severe neonatal hyperbilirubinaemia identify patient characteristics and improvable factors, and facilitate corresponding improvement actions.
- Key recommendations of the national guideline, including a priori risk assessment, were hardly adhered to, and this was often not reported as improvable factor.
- Risk assessment in medical records and universal transcutaneous bilirubin screening should be incorporated in the national guideline to facilitate early recognition of severe neonatal hyperbilirubinaemia.

to ensure that SNH and imminent KSD are 'never-events'.⁴ Unfortunately, SNH remains a global burden.^{5,6} In the Netherlands, most neonates with SNH are born in a hospital, then discharged early, and subsequently readmitted from home (online supplemental text box 1).⁶ The widespread reliance on visual jaundice assessment to identify potential SNH among neonates cared for at home may, among other factors, contribute to the persistent occurrence of SNH (box 1).

Perinatal audits and hyperbilirubinaemia registries can be useful tools to improve the quality of perinatal care by identifying improvable factors and subsequently, formulating improvement actions by plan-do-check-act cycles. Results have already informed revision of the national guidelines and through doing so, will optimise future quality of care.^{7,8} Auditing case histories of neonates with SNH may help to identify whether care was given

Box 1 Jaundice assessment in the Netherlands

The Dutch neonatal hyperbilirubinaemia guideline recommends documenting an a priori risk assessment for the development of hyperbilirubinaemia in every neonate before discharge from the hospital or primary care birth facility.¹⁵ This a priori risk assessment is based on several risk factors, that is, blood group antagonism; other haemolytic diseases; gestational age <38 weeks; (cephalic) haematomas; exclusive breast feeding; siblings who received phototherapy (PT); large for gestational age associated with maternal diabetes and East-Asian descent. The complete list of risk factors is freely available on www.babyzietgeel.nl (in Dutch). Neonates identified with an increased risk of developing hyperbilirubinaemia should be monitored more closely by all involved healthcare professionals. Hence, it is of utmost importance that this risk assessment, one of the key recommendations of the national guideline, is documented clearly and communicated properly between different healthcare professionals. Visual assessment of neonatal jaundice is one of the daily checks performed by the maternity care assistant (MCA).³¹ Universal transcutaneous bilirubin or total serum bilirubin (TSB) screening is, in contrast to other countries, not the current practice in the Netherlands. If an MCA suspects hyperbilirubinaemia, the MCA is expected to inform the community midwife. The community midwife may decide to quantify TSB. A blood sample is then taken by the community midwife or a specialised home service, and sent to a laboratory. TSB test results are assessed by a laboratory specialist who informs the community midwife. If TSB exceeds the PT threshold (according to the Dutch nomogram, which is based on those of the American Academy of Pediatrics),¹² the neonate will be admitted to the hospital for treatment after consultation of a paediatrician. The Dutch hyperbilirubinaemia management guideline contains a flow chart on early recognition of hyperbilirubinaemia, including monitoring of high-risk neonates (flow chart 1 of the guideline).¹⁵

according to the national hyperbilirubinaemia guideline or not. The aim of this study was to gain more insight in improvable factors that contributed to SNH. We hypothesised that we would learn lessons from perinatal audits to improve diagnosis and quality of care for future neonates with imminent SNH.

METHODS**Design**

A descriptive study based on the national Perinatal Audit Assistant (PAA) database was conducted over a 3-year period (2017–2019).

Setting

SNH was one of the preset themes of the nationwide perinatal audit from 1 January 2017 until 31 December 2019.^{9 10} A case report is reviewed by the involved healthcare professionals during the audit meeting, and improvable factors are identified and improvement actions according to the plan–do–check–act cycle are initiated (online supplemental text box 2). An improvable factor is defined as care that deviates from professional requirements of standard care, national guidelines, or local protocols and that may negatively influence the outcome.¹¹

Patients

Neonates were eligible for audit meetings on SNH if they:

- ▶ Were born ≥ 35 weeks of gestation.
- ▶ Had SNH, that is, a peak total serum bilirubin (TSB) level higher than the exchange transfusion (ET) threshold according to postnatal age and risk factors.¹²

Neonates were not eligible for audit meetings on SNH if they:

- ▶ Had hyperbilirubinaemia caused by antenatally known severe blood group incompatibility as defined by the national guideline.¹³
- ▶ Had a conjugated bilirubin level $> 10 \mu\text{mol/L}$ ($> 0.58 \text{ mg/dL}$) or $> 20\%$ of TSB.

Variables, data collection and statistical analysis

All variables (online supplemental table 1) were retrieved from the PAA database and exported to IBM SPSS Statistics (V.25.0.0.1; IBM). Characteristics and improvable factors are summarised using descriptive statistics. Median and IQR are shown for continuous, not normally distributed data. If the postnatal age of peak TSB was unknown, we assumed that peak TSB was reached at start of ET or, if no ET was performed, at start of phototherapy (PT). Missing data are presented in the Results section.

RESULTS

From 2017 to 2019, 507 perinatal audit meetings were convened. In total, 115 neonates with SNH were registered. Six cases were excluded from further analysis because they did not meet eligibility criteria. In total, 109 cases were used for further analysis (figure 1).

The total number of live-born neonates with a gestational age $\geq 35+0$ weeks in the Netherlands during the 3-year study period was 475 901.¹⁴ Accordingly, the incidence of SNH was 22.9 per 100 000 live-born neonates with a gestational age of 35 weeks or more.

Baseline characteristics

Table 1 shows the baseline characteristics of included neonates: 44 females and 65 males. Median gestational age was 38 weeks and 3 days (IQR 37+5–40+0). Median birth weight was 3300 g (IQR 3000–3723). Most neonates were born vaginally and had blood group O, Rh D-positive mothers. In seven neonates (6%), no maternity care was provided.

A priori risk assessment of hyperbilirubinaemia

Table 2 shows risk factors in neonates with SNH, listed as the a priori risk factors for developing SNH in the national guideline.¹⁵ Approximately half of the neonates had blood group antagonism (defined as incompatible blood groups, with or without positive direct antiglobulin test), predominantly ABO, and most were breast fed. A priori hyperbilirubinaemia risk assessment was documented properly in the medical records of only six neonates (6%).

Hyperbilirubinaemia characteristics

Visual jaundice was noted for the first time at a median postnatal age of 42 hours (IQR 25–66; table 3). Most neonates (76%) were (re)admitted from primary care after in-hospital birth and early discharge. The majority of neonates (67%) had a peak TSB level between 350 and 499 $\mu\text{mol/L}$. All neonates received intensive PT and 30 neonates (28%) received one or more ETs at a median age of 55 hours (IQR 36–96). Nine neonates (9%) with peak TSB levels between 466 and 717 $\mu\text{mol/L}$ had symptoms of ABE. Out of five neonates with clear symptoms of ABE, four

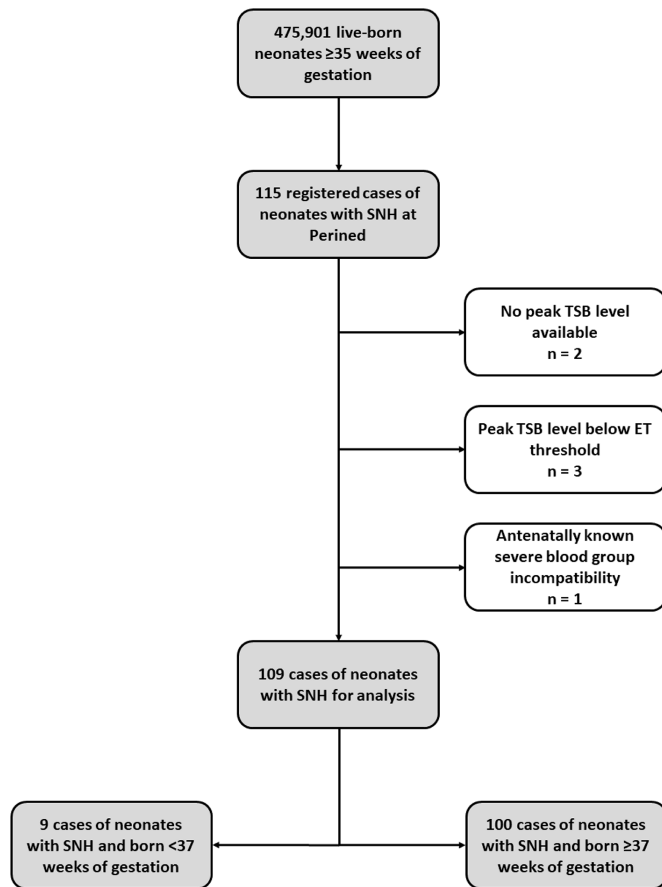


Figure 1 Flow chart of cases. ET, exchange transfusion; SNH, severe neonatal hyperbilirubinaemia; TSB, total serum bilirubin. Flow chart made by first author (BAMvdG).

neonates received an ET. Among the four neonates with mild symptoms of ABE, one neonate received an ET. ABO antagonism was the most common underlying cause of SNH (43%). Another important cause of SNH was dehydration (19%), defined as weight loss >7%. Eight (12%) out of 67 neonates who received an (automated) auditory brainstem response test had an abnormal result. An MRI was performed in 10 neonates, of which five (50%) had abnormalities (online supplemental table 2). Five term-born neonates (5%) with peak TSB levels between 467 and 717 $\mu\text{mol/L}$ had chronic bilirubin encephalopathy. Among the six excluded neonates, none received an ET, and MRI or (automated) auditory brainstem response test was not performed. Clinical follow-up was performed in three neonates out of these six neonates: two were normal and one had mild abnormalities. It was unclear whether this was related to chronic bilirubin encephalopathy.

Improvable factors

The PAA database included 147 improvable factors related to SNH (table 4). In 33 neonates, no improvable factors related to SNH were formulated.

In total, 37 improvable factors (25%) were related to communication, 71 (48%) were related to knowledge deficits, which include mainly deviation from the national guideline ($n=56$).¹⁵ Twenty-three improvable factors (16%) were assessed as related to organisation of care.

Improvable factors represent a range of difficulties in observation and communication by both maternity care assistants (MCAs)

Table 1 Baseline characteristics

	Total (n=109)
Gestational age in weeks+days	38+3 (37+5–40+0)
<36 weeks	1 (1)
36–36+6 weeks	8 (7)
≥37 weeks	100 (92)
Female/male	44/65 (40/60)
Birth weight in grams	3300 (3000–3723)
Place of birth	
Home	9 (8)
PCBC	10 (9)
Hospital, under supervision of community midwife	54 (50)
Hospital, medical indication	35 (32)
Unknown	1 (1)
Type of delivery	
Vaginal	98 (90)
Instrumental	8 (7)
C-section	3 (3)
Mother	
Parity	
Nulliparous	54 (50)
Multiparous	55 (50)
ABO blood group O	75 (69)
Rh D negative	16 (15)
Caucasian ethnicity	55 (51)
Unknown	1 (1)

Data are displayed as numbers (percentages) or medians (IQR). Due to rounding of percentages, some percentages may add up to 101%.

PCBC, primary care birth centre.

Table 2 A priori risk factors for hyperbilirubinaemia

	Total (n=109)
Risk assessment	
Documented	6 (6)
Not documented	90 (83)
Unknown	12 (11)
Missing	1 (1)
Gestational age	
<38 weeks	36 (33)
≥38 weeks	73 (67)
ABO antagonism	47 (43)
No DAT test performed	2 (2)
Rh disease	3 (3)
Type of feeding	
Breast feeding*	94 (86)
Exclusive formula feeding	15 (14)
Family history	
Having a multiparous mother and sibling(s) with hyperbilirubinaemia necessitating PT	23 (42)
Unknown	1 (1)
Missing	1 (1)
LGA after maternal diabetes ³²	3 (3)

Data are displayed as numbers (percentages). Due to rounding of percentages, some percentages may add up to 101%.

*Breast feeding is defined as mothers who intended to give breast feeding. Consequently, this group may also include neonates who were fed with a combination of breast feeding and formula feeding, or who were temporarily formula fed.

DAT, direct antiglobulin test; LGA, large for gestational age (birth weight ≥ 90); PT, phototherapy.

Table 3 Hyperbilirubinaemia characteristics

	Total (n=109)
Postnatal age in hours at first notion of jaundice*	42 (25–66)
Jaundice first recognised by†	
MCA	34 (31)
Community midwife	49 (45)
Nurse in hospital	16 (15)
Paediatrician	7 (6)
Parents	5 (4)
Unknown or missing	23 (23)
Encephalopathy	
Acute symptoms	9 (8)
Chronic symptoms	5 (5)
Peak TSB level	
<275 µmol/L	1 (1)
275–349 µmol/L	15 (14)
350–424 µmol/L	36 (33)
425–499 µmol/L	37 (34)
500–574 µmol/L	14 (13)
≥575 µmol/L	6 (6)
Age at peak TSB level in hours	84 (48–111)
Admitted from primary care	83 (76)
Treatment	
PT	109 (100)
ET	30 (28)
Postnatal age in hours at:	
Start PT	77 (43–111)
Only PT (n=79)	92 (52–118)
PT and ET (n=30)	43 (27–90)
ET (n=30)	55 (36–96)
Presumed cause of hyperbilirubinaemia‡	
ABO antagonism	47 (43)
Of which DAT positive	27 (57)
Rh disease	3 (3)
Of which DAT positive	3 (100)
Haemolytic anaemia	8 (7)
Related to prematurity	9 (8)
Dehydration	21 (19)
Of which breast fed	21 (100)
Birth trauma	1 (1)
Related to instrumental delivery	4 (4)
Congenital hypothyroidism	1 (1)
Neonatal infection	2 (2)
(Suspicion of) inborn error of metabolism	2 (2)
Related to maternal diabetes	1 (1)
Delayed meconium passage	1 (1)
No cause identified	16 (15)
Missing	1 (1)

Data are displayed as numbers (percentages) or medians (IQR).

Acute bilirubin encephalopathy is defined by internationally recognised criteria.¹ Chronic bilirubin encephalopathy is defined as neurological abnormalities at follow-up and an MRI of the brain with abnormalities.

ABO antagonism is defined as incompatibility of ABO blood groups.

Haemolytic anaemia is defined as hyperbilirubinaemia and evidence of haemolysis. This includes inherited erythrocyte cell membrane defects (eg, spherocytosis, elliptocytosis), erythrocyte enzyme deficiencies (eg, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency), and ABO or Rh disease combined with anaemia.

Prematurity was defined as born before 37 complete weeks of gestation with a gestational age based on early ultrasonography.

Dehydration was defined as weight loss >7%.

*Postnatal age at first notion of jaundice is missing in five neonates.

†Multiple answers possible.

DAT, direct antiglobulin test; ET, exchange transfusion; MCA, maternity care assistant; PT, phototherapy; TSB, total serum bilirubin.

Table 4 Improvable factors

	Total (n=147)
Improvable factors per case	1 (0–2)
Type of improvable factor*	
Communication	37 (25)
Insufficient communication	27 (18)
Insufficient documentation of PAA database variables	10 (7)
Knowledge deficit	71 (48)
Deviation from standard care	3 (2)
Deviation from national guideline neonatal hyperbilirubinaemia ¹⁵	56 (38)
Deviation from local guidelines	4 (3)
Other	8 (5)
Organisation of care	23 (16)
Delay	10 (7)
Organisational problems	11 (7)
Insufficient testing	2 (1)
Other†	18 (12)
Category missing	8 (5)

Data are displayed as numbers (percentages) or medians (IQR).

Some problems regarding delayed recognition of jaundice (eg, if parents considered their neonate jaundiced, but no action was taken) were categorised in this category as well.

*Multiple options per improvable factor possible.

†Improvable factors in this category included not having transcutaneous bilirubinometry, but also discrepancy in postnatal age calculation.

PAA, Perinatal Audit Assistant.

and community midwives, for example, severity of jaundice was underestimated; no follow-up was provided in severe jaundice; neonates were not always assessed by the community midwife if an MCA reported severe jaundice; or the MCA did not mention the risks of SNH and urgent reasons for parents to ask for help outside working hours of the MCA. In 8 out of 23 neonates having visual jaundice within 24 hours after birth, this was not communicated to the community midwife or the community midwife was not aware of the urgent need for TSB quantification.

A priori hyperbilirubinaemia risk assessment was not documented in 90 neonates (table 2), this was recorded as an improvable factor in only 24 cases. Lacking medical history regarding hyperbilirubinaemia of siblings was reported as an improvable factor in 5 neonates, but occurred in 23 cases.

The process of TSB quantification itself led to delays of at least several hours in diagnosis of SNH. Sixteen improvable factors in the category organisation of care refer to a delay between quantification of TSB and report of the result. Nine improvable factors mention a delay in referral to the hospital or in start of treatment after report of the TSB result. Delays mainly occurred if the blood draw for TSB quantification was done at home. Other delays occurred when the urgency of hospital admission was not clear to the community midwife or to the parents. Also, delays happened after admission, for example, TSB results remained unnoticed or blood for ET was not ordered.

DISCUSSION

This study describes patient characteristics of 109 (near) term neonates who suffered from SNH and associated improvable factors as identified by perinatal audits. The incidence of SNH was 22.9 per 100 000 live-born neonates. In total, 8% of neonates had symptoms of ABE and ET was performed in 28%. At least five children developed chronic bilirubin encephalopathy. The main identified cause was ABO antagonism, of whom 57% had a positive direct

Box 2 Overview of recommendations

Communication and knowledge

- ▶ Implement universal transcutaneous bilirubin screening at a predefined time and act upon outcome of this screening.
- ▶ Facilitate documentation and communication of a priori risk assessment for hyperbilirubinaemia. For example, incorporate a standard sentence in the (electronic) medical records that indicates whether the a priori risk of developing neonatal hyperbilirubinaemia is normal or increased.
- ▶ Healthcare providers should accept and agree on local standard operating procedures regarding neonatal jaundice in primary care. These standard operating procedures should, among others, include responsibilities and timelines for the process of recognition of jaundice, total serum bilirubin quantification, obtaining the total serum bilirubin result and hospital admission.
- ▶ Define severe neonatal hyperbilirubinaemia as an event in which improvable factors should always be identified and reviewed in a multidisciplinary setting at a preset moment. The paediatrician should hold responsibility for this process.

antiglobulin test. Improvable factors revealed during audit meetings were mainly related to lack of compliance to the national guideline. This may reflect a knowledge deficit in the large majority perinatal healthcare professionals. Although a priori hyperbilirubinaemia risk assessment was very rarely documented, this was mostly not mentioned as improvable factor. Difficulties in communication and observation, and delay in TSB quantification were also frequently identified as improvable factors.

To the best of our knowledge, the Netherlands is the first country with a nationwide perinatal audit regarding neonatal hyperbilirubinaemia. The improvable factors that have been formulated in the audit meetings offer opportunities for improvement actions regarding timely recognition, diagnosis and treatment of SNH. We consider the results of this study generalisable to other countries as well. Despite the different approaches in various countries to identify neonates at risk of developing severe hyperbilirubinaemia, timely detection of jaundiced neonates who need treatment remains a global deficit in all care practices.^{5 8 16}

The perinatal audit database is not a formal registry, and as such, under-reporting is likely. Unfortunately, follow-up on improvement actions was not documented, and definitions of diagnoses and many laboratory tests were not recorded in the PAA database. Using International Classification of Disease (ICD) codes and addition of few more obligatory characteristics will probably increase the appropriateness of this database for future studies.¹⁷ Inherent to the retrospective nature of the analyses, some data were missing.

It appeared that fewer neonates in our study were born after instrumental delivery or a C-section than nationally (3% vs 15%–16%).¹⁴ In line with previous studies, there was a slight male preponderance in neonates with SNH (60% vs 51% nationally), and an over-representation of neonates with a non-Caucasian mother: 48% in our study vs 13% nationally.^{6 14 18–20} Seven mothers did not receive maternity care, of whom six were non-Caucasian. Lack of maternity care and the perceived difficulty of visual assessment of jaundice in non-white neonates may delay timely recognition of SNH.²¹ Additionally, ABO blood group frequencies and incompatibilities, and other haemolytic diseases differ between ethnic groups.²²

Our findings indicate that the a priori risk assessment for hyperbilirubinaemia is hardly ever documented in the medical records of neonates with SNH. Since 2008, a priori risk assessments, including documentation and communication, and close monitoring of neonates, are key recommendations in the Dutch management guideline on hyperbilirubinaemia.¹⁵ Our data indicate that this recommendation of the national guideline is not known or not adopted in clinical practice in 94% of the reported SNH cases. This concerning high percentage needs more extensive root cause analyses and consequently targeted implementation strategies. A long interval between the first notion of jaundice and initiation of treatment was observed in analogy to data from Rennie *et al* who examined claims involving neonatal jaundice.²⁰ Visual inspection of jaundice is neither objective, nor accurate.^{23–26} Additionally, and especially in the home setting, it may take several hours before TSB test result is obtained. Other potential explanations for the delay may be a wait-and-see approach and underestimation of the severity of hyperbilirubinaemia and its potential consequences in otherwise healthy neonates, which has also been shown in a nationwide survey among MCAs.²⁷ ET was performed in only 28% of the neonates, whereas all neonates had a TSB level above ET threshold. This may be declared by the time needed to prepare an ET and the TSB reduction of TSB by intensive PT.

Improvable factors were registered in 76 neonates (70%). Remarkably, the lack of the a priori risk assessment of SNH was mostly not even documented as improvable factor. This may indicate a widespread lack of awareness, or lack of acknowledgement, of the importance of the a priori risk assessment or a knowledge deficit on this specific recommendation. This is important because universal bilirubin screening was not adopted in the Dutch 2008 guideline, since it was assumed that well-organised follow-up in the Dutch perinatal care system would guarantee the early recognition of imminent severe hyperbilirubinaemia.¹⁵

Deviation from guidelines seems a perennial issue. Alkén *et al* showed that non-adherence resulted in kernicterus, whereas this could have been avoided in 11 neonates.¹⁹ The importance of adherence to guidelines is underlined by Canadian data. Sgro *et al* showed a reduction in incidence rates of SNH after implementation of a national hyperbilirubinaemia guideline.²⁸

Additional examination and long-term follow-up were not performed in a substantial proportion of the neonates in our study. Whereas one might consider this as substandard care, recommendations on follow-up investigation after SNH are not part of the current guideline.¹⁵

We recommend, according to guidelines in other countries and advocated by other researchers, adding universal bilirubin screening using transcutaneous bilirubin or TSB measurement to the a priori risk assessment in the upcoming update of the next national guideline.^{29 30} This may also shorten the time interval between first notion of jaundice and start of treatment. Another possible improvement action is the incorporation of a standard sentence in the (electronic) medical records that indicates whether the risk of developing hyperbilirubinaemia is normal or increased. Difficulties in communication between healthcare professionals and delays in the process of TSB quantification should be obviated by clear standard operating procedures in the local obstetric care networks and adequate adherence to these procedures. SNH should remain an event in which improvable factors are identified and improvement actions are formulated in a multidisciplinary setting, for example, during a complication or critical incident review meeting.

Future research should focus on novel, preferably accessible and non-invasive, approaches for early identification of jaundice and underlying mechanisms regarding improvable factors.

CONCLUSIONS

Although SNH is largely preventable, it is still present in the Netherlands. Perinatal audit meetings are important to help identify improvable factors and formulate improvement actions (box 2). Our data indicate that timely recognition—including universal bilirubin screening, improving knowledge, communication, acceptance and compliance to hyperbilirubinaemia guidelines—may reduce the occurrence of SNH.

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