

Unchanged incidence of necrotising enterocolitis in a tertiary neonatal department

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ABSTRACT

INTRODUCTION: At the Department of Neonatology at Rigshospitalet, Copenhagen, Denmark, decades of extensive use of mother's milk and human donor milk should theoretically limit the incidence of necrotising enterocolitis (NEC) among very low birth weight infants. The aim of this study was to determine our local incidence of NEC from 1996 to 2009.

METHODS: The data in departmental clinical database containing information about admissions in the 1996-2009 period was compared with data in the Danish Patient Registry. Inconsistencies were resolved by reviewing the clinical records. The population of interest was infants inborn at Rigshospitalet with an age of 0-1 days on admission.

RESULTS: A total of 8,893 infants were included in the study and 1,843 (20.7%) weighed less than 1,500 g at birth. NEC occurred in 111 of these (6.0%). The incidence ranged from 20.5% in the 500-599 g birth-weight group to 0.5% in the 1,200-1,299 g birth-weight group. There was no trend over time in the incidence of NEC ($b = -0.02/\text{year}$ (95% confidence interval: $-0.59; 0.55$, $p = 0.98$) and no evidence of a higher frequency of NEC in certain months or certain seasons ($p = 0.52$ and $p = 0.32$).

CONCLUSION: Our incidence of NEC was close to average compared with incidences reported in international literature. There was no suggestion of an epidemic cause or that the incidence was decreasing. Considering the impact of NEC on the individual infant, it is important to keep searching for new ways to reduce the problem.

FUNDING: not relevant.

TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency.

Necrotising enterocolitis (NEC) is an ischaemic and inflammatory disease mostly seen in very low birth weight (VLBW) infants. It is the most serious gastrointestinal complication to prematurity, and the associated mortality is high [1-3]. The incidence varies among hospitals. There have been suggestions of seasonality or periodicity of the incidence of NEC and even reports of clusters [4-7].

At the Department of Neonatology in Rigshospitalet (RH), Copenhagen, a tertiary centre, decades of extensive use of mother's milk and human donor milk should theoretically limit the incidence of NEC among the VLBW

infants [8, 9]. The aim of this study was to determine our local incidence of NEC from 1996-2009 and to compare it to the published literature. Furthermore, we wanted to examine if the incidence remained stable over time or showed any evidence of periodicity.

METHODS

Material

We conducted a retrospective study based on data from the departmental clinical database (Neobase) in which 43 variables of hospitalised infants are registered at discharge. We linked these data to administrative data as well as the International Classification of Diseases, 10th edition (ICD-10) diagnoses reported to the Danish Patient Registry. The population of interest was infants inborn at RH with an age of 0-1 days on admission. We hereby excluded readmissions and patients admitted from other hospitals. The period from 1 January 1996 to 31 December 2009 was analysed. There are 6,000 births at RH every year, and 1,000 of these are referred because of high-risk pregnancy. This figure includes all pregnancies at risk of extremely preterm birth in Eastern Denmark. Over the period in question, this referral practice has gradually become more effective.

Feeding practices at the department

At RH, mothers of preterm infants have always been encouraged to express breastmilk and to breastfeed, and a recent study found that 88% of preterms received only or partly mother's milk at discharge from RH in the 2000-2010 period [10]. During the period, donor milk was given to VLBW infants as a supplement to mother's milk for the first 14 days. The current practice is to supplement with donor milk in infants with a gestational age of less than 32 weeks until 35 weeks of corrected gestational age.

Necrotising enterocolitis classifications

Infants were given discharge diagnoses according to the ICD-10 and codes according to the national Neobase coding system. No criteria have been specified for the ICD-10 code DP779 (*necrotising enterocolitis in the newborn*). The coding of NEC in the Neobase is graded from 0 to 3, but does not match Bell's stages [11]. NEC 0 is given when there has been no clinical suspicion or treat-

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 TABLE 1

Codes for necrotizing enterocolitis in inborn infants admitted to the Department of Neonatology at Rigshospitalet 1996-2009. The values are n.

ICD-10 code ^a	NEC grade ^b				Invalid	Missing code	Total
	0	1	2	3 ^c			
DP779	6	27	40	66 (53)	1	0	140
No DP779	8,655	58	13	6 (5)	15	6	8,753
Total	8,661	85	53	72	16	6	8,893

ICD = International Classification of Diseases; NEC = necrotizing enterocolitis.

a) For NEC reported to the Danish Patient Register.

b) In the departmental clinical database.

c) (Infants with ICD-10 codes for abdominal surgery).

ment of NEC. *NEC 1* is given when there was clinical suspicion of NEC and conservative treatment with antibiotics and withholding of feeds was provided. *NEC 2* is given when there were sonographical or radiological signs of NEC. *NEC 3* is given when the criteria of *NEC 1* or *NEC 2* were met and the infant received surgery for NEC. There is no distinction between NEC and focal intestinal perforation in this classification. As the classification *NEC 1* is based solely on clinical suspicion, only infants with the codes of *NEC 2* and *NEC 3* were included as NEC cases in this study. In order to reduce the effect of coding errors, we compared the codes given to the infant in the Neobase (*NEC 0-3*) with the ICD-10 diagnosis (presence of the diagnosis DP77.9 = necrotising enterocolitis in newborn) and with the codes used for abdominal surgery (KJF = surgery in the small or large intestines, KJA = surgery in the abdominal wall, peritoneum, mesentery or omentum, or KJD = surgery in the stomach or duodenum). If we found inconsistencies in the codes, AHN made a review of the infant's admission in order to determine to which Neobase category (0-3) the infant belonged. Inconsistencies included the following types a) discrepancy between the NEC codes in the Neobase and ICD-10 code, b) codes for NEC in the Neobase outside the range 0 to 3, or c) inconsistency between the NEC code in the Neobase and the surgery codes. The review included looking through the infant's medical record, prescription of antibiotics (metronidazole), descriptions of abdominal radiographs or surgery. A paediatric surgeon was consulted if surgical descriptions were ambiguous. In total, 121 clinical records had inconsistencies; 118 were reviewed, while three could not be found.

Statistics

The trend of the incidence over the 13-year-period was tested by linear regression. Auto-correlation and Spearman's test were used to investigate whether there was a significant correlation between the numbers of NEC

cases from one month and the following month. To investigate if there were significant differences in the incidence of NEC across the 12 months of the year or in the four seasons (Mar-May, Jun-Aug, Sep-Nov, Dec-Feb), the chi-squared test with Yates' correction was used. A p-value of 0.05 or below was considered significant. Furthermore, multiple binary logistic regression was done, using NEC as the dependent variable and gestational age, birth weight and year of birth as independent variables.

Trial registration: The study was approved by the Danish Data Protection Agency.

RESULTS

Incidence of necrotising enterocolitis in very low birth weight infants

There were 14,769 admissions at the Department of Neonatology at RH from 1 January 1996 to 31 December 2009. A total of 8,893 infants were included in this study (inborn and admitted to the Department of Neonatology at age 0-1 days). Of these infants, 140 had the ICD-10 code DP77.9 and 210 infants had the codes 1, 2 or 3 in Neobase (**Table 1**). After reviewing a total of 118 medical records with discrepancies, 125 (1.4%) infants of the 8,893 in the study population were classified as having had NEC grade 2 or 3 (grade 1 = 71, grade 2 = 54, grade 3 = 71). Of the 8,893 infants, 1,843 (20.7%) weighed less than 1,500 g at birth (VLBW). NEC occurred in 111 (6.0%) of these infants, meaning that 88.8% of infants with NEC were VLBW.

Because of the referral pattern to the tertiary perinatal centre at RH, a relatively large proportion of infants had a birth weight below 1,000 g. The incidence of NEC in the VLBW infants ranged from 20.5% in the 500-599 g birth weight group to 0.5% in the 1,200-1,299 g group (**Figure 1**).

Within the VLBW group, the mean birth weight decreased by 9.8 g/year ($p < 0.001$) and the mean gestational age by 0.4 days/year ($p < 0.001$).

Periodicity and seasonality

We observed no trend over time in the incidence of NEC ($b = -0.02/\text{year}$ with 95% confidence interval: $-0.59; 0.55$, $p = 0.98$). This result was not changed by multiple logistic regression including birth weight and gestational age ($p = 0.29$). No evidence of a higher frequency in certain months or certain seasons ($p = 0.52$ and $p = 0.32$) was observed. **Figure 2** shows that there were 0-4 infants with NEC per month in the years 1996-2009. We rarely saw more than two incidents in one month, and most often there was only one or none. The autocorrelation coefficient was 0.026 ($p = 0.743$); hence no trend towards a month with many cases of NEC followed by

another month of many cases was seen, i.e. no evidence of periodicity.

DISCUSSION

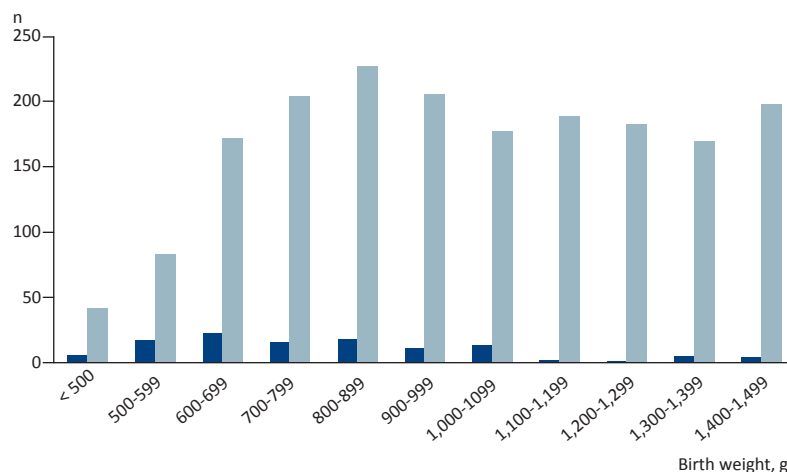
We looked at admissions through 14 years and cross-validated several sources of information. In all cases of disagreement, we reviewed the clinical records, radiographs, and surgeon's reports to validate the diagnosis of NEC. Many of the inconsistencies between coding systems appeared to be the result of simple forgetfulness. Cases with inconsistencies between coding systems were also the cases in which the diagnosis of NEC seemed most difficult to make. This makes our study more than a registry study.

A weakness of our study is that the incidence of NEC depends on the birth weight distribution. The unit provides almost all intensive care for new born infants in the eastern part of Denmark; and extremely preterm infants and other high risk pregnancies are transferred in utero, whereas infants with a gestational age above 28 weeks without special risk factors are born and cared for in local hospitals. This is reflected in the distribution of birth weight in the VLBW group (Figure 1). Our population featured approximately the same number of infants in each weight category above 800 g, whereas the normal birth weight distribution is steadily declining towards the lowest weights. This is important since the incidence of NEC was dramatically higher in infants with a birth weight below 1,000 g than in infants with a birth weight above 1,000 g.

Although highly statistically significant, the decrease in mean birth weight and gestational age during the period was not large enough to influence the change in the rate of NEC over time in our cohort, but it should be taken into consideration when comparing cohorts. For example, American studies have reported high NEC incidences of 10.1% [12] and 8.0% [13], whereas studies from Japan report incidences down to 1.6% [14] (Table 2). In the American studies, infants who were transferred to the specialised centres within 72 hours of birth

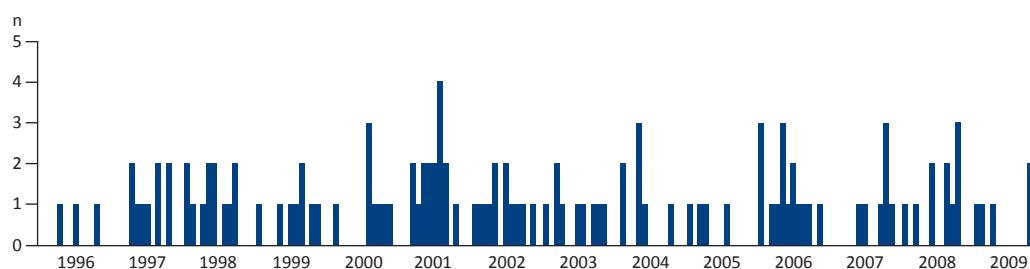
FIGURE 1

The number of very low birth weight infants with necrotizing enterocolitis grade 2 or 3 (■) and the total number of very low birth weight infants (■) in the 1996-2009 cohort divided by birth weight. The birth weight distribution deviates from that in the total birth cohort because of the referral pattern to the Department of Neonatology at Rigshospitalet, Copenhagen.



[12] and within 14 days of birth [13] were included, meaning that a higher proportion of the included infants were at risk of developing NEC, which could partly explain the higher incidence. On the other hand, these studies had a higher proportion of infants with higher birth weights within the VLBW group than our study. The very low incidence of NEC in Japan [14] was based on data from a database that included infants admitted to tertiary neonatal centres and excluded infants with known congenital anomalies or who were moribund at the time of birth. The article compares the Japanese cohort to a Canadian cohort (NEC incidence of 5.9%). The Japanese cohort might include more mature infants than the Canadian since birth weight is generally lower in Japan, but even if there are demographic differences between the Japanese and the Canadian (and Danish) infants, it is unlikely that there is no real difference in NEC

FIGURE 2



Monthly number of very low birth weight infants with necrotizing enterocolitis (NEC) grade 2 or 3 from 1 January 1996 to 31 December 2009 at the Department of Neonatology, Rigshospitalet, Copenhagen.

 TABLE 2

The incidence of necrotizing enterocolitis in very low birth weight infants admitted to tertiary neonatal units in different countries.

Reference	NEC cases/ population, n	Incidence, % (95% CI)
USA, 1991 [12]	269/2681	10.0 (8.9-11.3)
USA, 1995 [13]	144/1804	8.0 (6.7-9.4)
Canada, 2004 [15]	238/3628	6.6 (5.8-7.4)
Italy, 2008 [16]	62/2035	3.1 (2.3-3.9)
Finland, 2010 [17]	61/1900	3.2 (2.5-4.1)
Canada, 2012 [14]	315/5341	5.9 (5.3-6.5)
Japan, 2012 [14]	153/9812	1.6 (1.4-1.8)

CI = confidence interval; NEC = necrotizing enterocolitis.

incidence between countries. A recent national registry study from Sweden reported an incidence of NEC of 2.6% in all VLBW infants born in Sweden in the years 1987-2009 [5]. This incidence is not directly comparable with the incidences discussed above because it is based on a "normal" birth weight distribution, i.e. it is not affected by referral patterns to tertiary centres.

The rate of NEC is also seen to vary within countries. In the US, the incidence ranged from 3.9% to 22.4% among different centres [12], and Canadian and Italian studies also reported large differences among participating centers [15, 16].

In a previous report of NEC incidence in Denmark, the study population was infants younger than three months admitted to a neonatal department in Western Denmark between 1982 and 1991 [18]. All clinical records of infants with the diagnosis enterocolitis necroticans, enterocolitis acuta, perforation intestinum or peritonitis acuta were reviewed and classified according to Bell's staging. The average incidence was 1.2 per 10,000 live births with regional differences (ranging between 0.3 and 3.8). The incidence was increasing over the period. Surprisingly, only 54% of NEC cases were seen in infants below 1,500 g. If assumed that 1% of infants had birth weights below 1,500 g, the incidence of NEC was 0.6% among VLBW infants, which is very low compared with the studies cited above.

This low incidence of NEC reported in Western Denmark where practices are roughly the same as in Eastern Denmark (extensive use of mother's milk and human milk banks) brings us back to the topic of classification as briefly mentioned above. Are the differences we see nationally and internationally as large as reported or is part of the problem that NEC is a difficult diagnosis to make and the extent of the disease even more difficult to grade? Each hospital has different diagnostic strategies, which may bias comparison between sites, whereas investigating trends over time in each site could be more reliable.

Our classification is roughly comparable to Bell's stages 2 and 3 although we required radiological evidence for grade 2, and we included focal intestinal perforation (FIP) in our grade 3. It has become increasingly common to distinguish this condition from NEC [19], and our incidence would have been lower if cases of FIP were excluded. Retrospective classification is less than optimal, but even in prospective studies may raise questions about classification of relatively subtle clinical signs or evaluation of X-rays. Even classification based on the surgeon's observations during surgery or the pathologist's assessment of excised tissue can be considered a subject of discussion. It has been argued that NEC should be divided into multiple subgroups in order to understand the disease completely [20]. In the future, it may be beneficial to develop a simple way to diagnose and classify NEC in order to make good, reproducible epidemiological studies of the disease.

CONCLUSION

The incidence of NEC at the tertiary Department of Neonatology at RH was close to the average of what is reported in the international literature. This is surprising considering the extensive use of maternal and human donor milk in our clinic, which should theoretically protect against NEC. Our material showed neither signs of periodicity nor seasonality, and the incidence was stable over the 14-year-period. Hence, there was no suggestion of an epidemic cause or that the incidence was decreasing. In view of the clinical impact of NEC on the individual infant, it is important to keep searching for new ways to reduce the problem.

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