**Necrotizing enterocolitis and focal intestinal perforation in neonatal intensive care units in the state of Baden-Württemberg, Germany**

Thomas Böhler, Ingo Bruder, Peter Ruet, Jörg Arand, Manfred Teufel, Matthias Mohrmann, Roland Hentschel

1 Medical Service of Statutory Health Insurance in Baden-Württemberg, Karlsruhe; 2 Regional Office for Quality Assurance in Hospitals, Hospital Federation Baden-Württemberg, Stuttgart; 3 Children's Hospital, SLK-Klinikum, Heilbronn; 4 Department of Neonatology, Children's Hospital, University of Tübingen, Tübingen; 5 Children's Hospital, Böblingen; 6 Medical Service of Statutory Health Insurance in Baden-Württemberg, Lahr; 7 Department of Neonatology, Children's Hospital, University of Freiburg, Freiburg, Germany.

**Abstract**

In preterm infants with very low birth weight (VLBW) <1500 g the most important acquired intestinal diseases are necrotising enterocolitis (NEC) and focal intestinal perforation (FIP). We analyzed data of the neonatology module of national external comparative quality assurance for inpatients in the state of Baden-Württemberg, Germany. Between 2010 and 2012, 59 of 3549 VLBW infants developed FIP (1.7%), 128 of them NEC (3.6%). In approximately 3% of infants with BW<1000 g FIP was diagnosed, which was nearly 9 times more often than in infants with BW between 1250 and 1499 g (FIP frequency 0.36%). NEC frequency increased with decreasing BW and was more than 10 times higher in the smallest infants (BW<750 g: 7.87%) compared to those with BW between 1250 and 1499 g (0.72%). The BW limit of 1250 g differentiates between groups of patients with distinguished risks for NEC and FIP.

**Introduction**

In its recently updated directive of quality assurance in the care of term and preterm newborn infants, the Federal Joint Commission (Gemeinsamer Bundesausschuss, G-BA), determines that a level 1 perinatal center (PNC) – offering the highest level of perinatal care in Germany – has to guarantee both the presence of appropriate structures for immediate surgical treatment of preterm infants with a birth weight (BW) <1250 g, and the availability of qualified surgeons for these patients. Patients with a BW of 1250 g and above (i.e., those usually treated in level 2 PNC) may be transferred to PNC level 1 with on-site pediatric surgery in case of need.

Necrotising enterocolitis (NEC) and focal (syn. idiopathic or spontaneous) intestinal perforation (FIP) are the most important acquired intestinal diseases in preterm infants with very low birth weight <1500 g (VLBW). In preterm NEC, feeding difficulties, bacterial overgrowth, ileus and compromise of innate intestinal defenses may cause inflammation in intestinal villi and ischemia. Most infants with FIP are extremely premature, develop gastrointestinal symptoms during their first week of life, and show rapid progress towards serious life-threatening illness. Infants with NEC may be older and more mature at birth, but NEC and FIP may be clinically indistinguishable and definitive diagnosis often requires intervention of a pediatric surgeon.

In Germany, information on the epidemiology of NEC is collected and analyzed in yearly databases in the state of Baden-Württemberg in the neonatal dataset. Data from hospitals in the state of Baden-Württemberg, Germany, which were submitted to the regional office for quality assurance in hospitals (GeQiK®) for the years 2010, 2011, and 2012, were analyzed. The numbers of infants with FIP were extracted from the neonatology module of EsQS (neonatal dataset) using the documentation of each patient’s diagnoses at the time of hospital discharge or death (ICD-10-GM: P78.0). The number of infants with surgically treated FIP were extracted from each patient’s list of diagnoses of surgery (5 surgical interventions with their main diagnosis can be documented per stage in the hospital).

The numbers of infants with NEC were extracted from the documentation of diagnoses at the time of hospital discharge or death (ICD-10-GM: P77) and/or the documentation of NEC stage II and above according to the modified Bell’s classification in the neonatal dataset.11

**Materials and Methods**

Data from hospitals in the state of Baden-Württemberg, Germany, which were submitted to the regional office for quality assurance in hospitals (GeQiK®) for the years 2010, 2011, and 2012, were analyzed. The numbers of infants with FIP were extracted from the neonatology module of EsQS (neonatal dataset) using the documentation of each patient’s diagnoses at the time of hospital discharge or death (ICD-10-GM: P78.0). The number of infants with surgically treated FIP were extracted from each patient’s list of diagnoses of surgery (5 surgical interventions with their main diagnosis can be documented per stage in the hospital).
The numbers of infants with surgically treated NEC were extracted from the neonatal dataset using the item *NEC treated surgically*. For both FIP and NEC, numbers of patients undergoing inter-hospital transfer were derived from data sets giving the key 06 (= transfer to another hospital), while numbers of deaths were calculated from data sets giving the key 07 (= death), according to pre-defined reasons for hospital discharge. All patient data were analyzed after stratification according to birth weight in intervals of 250 g. Minimum, maximum and mean values of disease frequencies and the respective coefficients of variation were calculated using MS Excel 2010.

**Results**

Table 1 shows data from newborn infants treated in hospitals in Baden-Württemberg in the years 2010 to 2012. In 3549 VLBW infants, 57 cases (1.7%) of FIP and 128 cases (3.6%) of NEC were documented. The rate of acquired intestinal disease was higher in infants with a BW <1250 g (n=2439; FIP: n=55 (2.3%); NEC: n=120 (4.9%)) than in infants with a BW from 1250 to 1499 g (n=1110; FIP: n=4 (0.36%); NEC: n=8 (0.72%)). Approximately half of the infants with FIP and/or NEC were treated surgically. Among those VLBW infants with acquired intestinal disease who were not operated, 6 of 17 infants diagnosed with FIP and 9 of 45 infants diagnosed with NEC died.

Figure 1 illustrates the differences in frequencies of FIP and NEC between different BW strata for both diseases separately. In the years 2010 to 2012, FIP was diagnosed on average in 1 out of 60 VLBW infants, while 1 out of 28 developed NEC. The frequency of FIP was similar in all infants with a BW <1000 g (approximately 3%) but was nearly 9 times higher than in infants with a BW between 1250 and 1499 g (0.36%). The frequency of NEC increased with decreasing BW and was more than 10 times higher in infants with BW <750 g (73%) than in infants with BW >1499 g (2.3%).

**Table 1. Occurrence of neonatal focal intestinal perforation (FIP) and necrotizing enterocolitis (NEC) in hospitals in Baden-Württemberg during the years 2010 to 2012. Please note that the neonatal dataset does not allow combined patient follow-up after inter-hospital transfer; there may be both underreporting and overreporting of FIP and NEC (and related procedures).**

| Birth weight | <750 g | 750 to 999 g | 1000 to 1249 g | 1250 to 1499 g | <1500 g | ≥1500 g | Total |
|--------------|--------|-------------|---------------|--------------|--------|--------|-------|
| Total number of admissions | 762 | 802 | 875 | 1110 | 3549 | 30,595 | 34,144 |
| FIP: diagnosis documented at discharge (ICD-10-GM: P78.0) | 23 | 25 | 7 | 4 | 59 | 16 | 75 |
| FIP with surgical procedure | 12 | 11 | 2 | 1 | 26 | 7 | 33 |
| FIP with surgical procedure thereof referral from other hospital | 4 | 5 | 1 | 1 | 11 | 3 | 14 |
| FIP without surgical procedure | 6 | 7 | 2 | 2 | 17 | 2 | 19 |
| FIP without surgical procedure thereof transferred to another hospital | 1 | 5 | 2 | 1 | 9 | 2 | 11 |
| FIP without surgical procedure thereof deceased | 3 | 2 | 0 | 1 | 6 | 0 | 6 |
| NEC stage ≥2 documented in data set or diagnosis documented at discharge (ICD-10-GM: P77) | 60 | 40 | 20 | 8 | 128 | 53 | 181 |
| NEC treated with surgery | 30 | 24 | 12 | 4 | 70 | 12 | 82 |
| NEC with surgical procedure not specific for NEC | 7 | 4 | 1 | 0 | 12 | 9 | 21 |
| NEC without surgical procedure | 23 | 12 | 6 | 4 | 45 | 31 | 76 |
| NEC without surgical procedure thereof deceased | 7 | 1 | 1 | 0 | 9 | 1 | 10 |

ICD-10-GM, International classification of diseases-10, German modified.
higher in the smallest infants (BW<750 g: 7.87%) compared to those with a BW between 1250 and 1499 g (0.72%). In infants with a BW between 1000 and 1249 g, the frequency of NEC (2.29%) was more than three times higher and the frequency of FIP (0.80%) more than two times higher than in those with a BW between 1250 and 1499 g.

In Figure 2 the frequencies of acquired intestinal diseases in VLBW infants with a BW<1250 g are shown for 37 hospitals which had submitted at least one relevant dataset regarding FIP and/or NEC to GeQiK® during the years 2010, 2011, or 2012. Hospital volume, i.e., the total number of infants with a BW<1250 g treated in that hospital is depicted on the X-axis. Disease frequency normalized by its respective regional average per 100 infants with a BW<1250 g is plotted on the Y-axis. Figure 2A shows the variations in frequencies of FIP between hospitals. Absolute FIP frequencies varied from 0 to 6.5%, the empirical coefficient of variation was 1.3315. The highest frequency amounted to 2.9 times the average regional FIP rate of 2.3% (55 cases in 2439 infants). Normalized FIP frequencies did not significantly correlate with hospital volume.

Figure 2B shows the variations in frequencies of NEC between hospitals. Absolute NEC frequencies varied from 0 to 12.1%, the empirical coefficient of variation was 1.1218. The highest frequency amounted to 2.5 times the average regional NEC rate of 4.9% (120 cases in 2439 infants). Normalized NEC frequencies also did not significantly correlate with hospital volume.

Discussion and Conclusions

This is the first population-based analysis of the epidemiology of acquired intestinal disease of preterm infants in hospitals in Baden-Württemberg. Our data show that – during the years 2010 to 2012 – the most frequent surgical emergencies in VLBW infants, NEK and FIP were diagnosed more often in infants with a BW<1250 g compared to those with a higher BW. The rule imposed by the G-BA, that PNC level 1 have to guarantee appropriate structures for immediate surgical treatment including the availability of qualified surgeons for these patients, can thus be based on external evidence: the BW limit of 1250 g, which distinguishes PNC 1 and PNC 2 (Supplementary Table 1), also differentiates groups of patients with clearly distinguished risks for NEC and FIP and different requirements for surgical interventions.

NEC is thought to represent the most frequent emergency in neonatology caused by intestinal disease and it is commonly assumed that emergencies such as intestinal perforation due to FIP and NEC need immediate intervention by a qualified surgeon. Shorter intervals between the first symptoms, diagnosis, and surgical repair may improve survival, may reduce the need for complex surgical interventions, and may lead to less long-term morbidity, e.g., short bowel syndrome. Early consultation of the neonatologist and the pediatric surgeon may not necessarily result in more surgery; rather, it may result in prolongation of conservative treatment and watchful waiting without missing the appropriate time for surgery. Recently, Linge et al. have shown that not every preterm infant with gastrointestinal symptoms has FIP or NEC or requires surgery. In 7.9 to 10.8% VLBW infants with BW<1000 g FIP or NEC were diagnosed, but approximately twice that number had shown symptoms which were indicative of these diseases. Thus, 1 in 5 preterm infants with BW<1000 g may need consultation with pediatric surgeons during early stages of acquired gastrointestinal disease. Appropriate structures needed to effectively treat these patients on-site may comprise an operation...
theatre whose room temperature can be raised to 28°C,1 warming mattress and overhead heat radiator suitable for VLBW, special equipment for anesthesiologists and special surgical instruments, as well as the availability of anesthesiologists experienced in peri- and intraoperative handling of VLBW.14

Our data are in accordance with reports in the literature. Sankaran et al.8 found that NEC incidence in Canada decreased with increasing BW: among infants with a BW between 501 and 1000 g the incidence was 11.2%, compared to 4.3% in infants with a BW between 1001 and 1500 g, and below 2% in infants with a BW above 1500 g. The risk to acquire NEC was nearly doubled in infants with a gestational age <28 weeks compared to those aged 28 weeks and above (odds ratio 1.9; 95% confidence interval 1.4 to 2.7). The data set of the national German reference center for surveillance of nosocomial infection in the years 2008 to 2012 yields a cumulative 5-year NEC incidence of 6% in infants with a BW <500 g (83/1313), of 4.8% in infants with a BW from 500 to 999 g (640/13,220), and of 1.3% in infants with a BW from 1000 to 1499 g (259/20,716).15 Thus, both nationally and internationally, published NEC rates are comparable to our data.

To our knowledge, no population-based studies of the epidemiology of FIP in preterm infants have been performed in Germany. Eicher et al.16 reported in a single center study on 28 out of 280 preterm infants with a BW <1000 g who underwent surgery for acquired intestinal disease between 2002 and 2007 (19 with FIP, 9 with NEC). In an observational study from Japan, Okuyama et al.7 reported on 39 VLBW infants who underwent laparotomy during previous 20 years; 19 of them had NEC, and 8 had FIP. Eicher et al.16 comment on their FIP rate (6.6%) in inborn preterm infants <1000 g BW, which is increased compared to international data, that there may be more awareness regarding the distinction of NEC and FIP, leading to a perceived increase in FIP frequency in more recent studies.

Frequencies of FIP and NEC differ between the NICUs in Baden-Württemberg and range from no cases at all to 2.5 times the regional mean for NEC and 2.9 times the regional mean for FIP. The coefficients of variation of the frequencies of these diagnoses between the hospitals are rather low.17 Variability may be explained by i) difficulties in clinical differential diagnosis without surgical intervention,13 ii) differences in preventive strategies such as infant feeding regimes,18 or the use of probiotics.19 However, our study is limited by general data quality of the neonatal dataset including the problem of small numbers.20 In addition, a NICU without on-site availability of pediatric surgeons may transfer infants to PNC with such a service before a definitive diagnosis is made. Thus, diagnoses may be missed after transfer of a patient to another hospital (underreporting) and in units with low patient volume the frequency of FIP and NEC may be underestimated, or a patient may be included in 2 data sets (overreporting).

Hunter et al.7 noticed that, during the past 20 years, there was no significant improvement in mortality and morbidity of VLBW infants related to acquired gastrointestinal disease despite the general progress in neonatal intensive care. Overall improvements in treatment outcome of VLBW infants may require a better understanding of pathogenesis, prevention, and treatment of these diseases. At the moment, possible next steps in quality assurance in neonatal wards in Baden-Württemberg may therefore consist in a structured dialogue with the contributing hospitals about differences in the strategies they adopt to prevent NEC and FIP based on an epidemiologic analysis over a period of 5 years.

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