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Risk factors associated with surgical FIP and NEC in premature newborns.

Kapapa M[1*], Hahne J[2], Serra A[1]

[1]Department of Pediatric Surgery, University Medical Centre Ulm, Eythstrasse, Germany

[2]Department of Pediatric and Adolescent Medicine, University Medical Centre Ulm, Eythstrasse, Germany

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Abstract

Background: Necrotizing Entero Colitis (NEC) and Focal Intestinal Perforation (FIP) affect almost exclusively preterm babies <1500 g and the incidence ranges up to 15% and gut perforation in NEC (NECp) strongly affects clinical outcome and mortality. Aiming to understand the mechanism underlying the disease prenatal and birth risk factors, pregnancy age, gender, birth weight, postnatal complications like PDA, or coagulation disorder and drug administration (antibiotics, indomethacin), mechanical ventilation or parenteral nutrition had to be considered to induce NEC, NECp or FIP.

Methods: This is a retrospective, single-centre review including preterm newborn with NEC, NECp or FIP in a period of 10 years, including all preterm with diagnosed NEC, NECp and FIP born before the 37th Gestational Week (GW) and excluding children with NEC, NECp or FIP born after the 37th GW, as well as premature babies without NEC, NECp or FIP. All data were obtained through the analyses of maternal and NICU medical records. During the survey period 27.414 deliveries occurred in this centre, therewith 76 affected preterm were included in our cohort.

Results: Premature mortality risk was significantly higher in male than in female with NEC and NECp (p=0.040). A coagulation disorder (p=0.018) as well as insulin substitution (p=0.008) were significantly more frequent in NECp and FIP. FIP preterm received significantly more antibiotics (p=0.009) and glucose (p=0.021) than NEC preterm. NECp preterm were more frequently administered surfactant (p=0.018), needed longer respiratory support (p=0.034), were more often intubated (p=0.022) and had longer additional oxygen supply (p=0.013) than NEC or FIP. FIP and NECp preterm received more often fresh frozen plasma (p=0.031) and were significantly longer parenteral fed (p=0.035). Minimizing preterm stress by implementation a standardized "minimal handling" protocol by nurses and doctors reduced significantly the number of NECp (p<0.001).

Conclusion: Early detection and appropriate therapy for NEC, NECp or FIP particularly in early stages of disease help to reduce mortality. Stress decrease *via* a standardized "minimal handling" protocol could be practiced everywhere regardless of the geographical location and equipment of the neonatal intensive care unit.

Keywords: Early neonatal period, Focal intestinal perforation, Necrotizing enter colitis, Risk factors.

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Introduction

NEC, NECp and FIP are severe diseases that primarily affect preterm with extremely low birth weight [1]. NEC is the most common and frequently lethal surgical emergency of the gastrointestinal tract with an incidence up to 15% in preterm <1500 g [2]. Degrees of severity are classified in BELL criteria [3] and around 20% develop multiple gut perforations [4] with mortality rates up to 70% [5]. The aetiology is still mainly unknown. Viral or bacterial infections [6] as well as previous damage of the intestinal wall due to reduced perfusion [7], hypoxemia, initiating of feeding [8], intestinal microbiota [9] or toxic contaminants have been suggested resulting in peritonitis and sepsis [10]. Besides clinical experience, the diagnosis of suspect preterm requires good monitoring and careful observation [11]. The BELL criteria are neither specific nor obligatory, including bilious or bloody enteric, frequent vomiting, bloody stools, as well as bloated, rigid and oedematous abdomen.

In advanced stages, signs of sepsis are mandatory [10]. Furthermore, a correct differentiation between FIP and NECp is often difficult. In FIP the inflammation is limited to a small area with a milder systemic inflammatory reaction, occurring mostly in severe immature babies already in the first days of life [12]. The observation of free intra-abdominal air as seen in abdominal x-rays, does not allow differentiating if the intestinal perforation was caused by FIP or NECp. To better understand underlying mechanisms involved in the pathogenesis of NEC and FIP, we aimed to verify possible postnatal risk factors which may help differentiate the 3 conditions. Therefore, our study has three objectives: 1) To evaluate postnatal risk factors in the affected children; 2) To optimize the diagnosis using the

knowledge of risk factors associated to the clinical findings classified in the BELL criteria and 3) To estimate factors that had protective effects on rate of bowel perforation.

Methods

Design

This study was designed as a retrospective single-centre review including preterm newborns with NEC, NECp or FIP. The study period comprised the interval between 01.01.2004 until 31.12.2014. The ethics committee of the university of Ulm approved the project (No. 13/15). All data were obtained through the analyses of maternal and NICU medical records.

Inclusion criteria

All preterm with diagnosed NEC, NECp and FIP born before the 37th gestational week during the study period were included.

Exclusion criteria

Children with NEC, NECp or FIP born after the 37th gestational week, as well as premature babies before the 37th gestational week without any of the 3 above mentioned conditions were excluded.

Patients and surveyed subjects

A database of the preterm children was created based on the International Classification of Diseases (ICD-9 and ICD-10). The diagnostic codes P07.3 (premature babies), P77 (necrotizing enterocolitis) and P78.0 (bowel perforation in neonatal period) were used. During the survey period 27.414 deliveries occurred, therewith 76 affected preterm were included in our cohort.

Data Collection

Maternal prenatal and infantile postnatal records were evaluated, assessing and collecting data on incidence, gender distribution and mortality; gestational age, weight and height at birth and postnatal management including complications, surfactant application, mechanical ventilation and oxygen supply, medicament therapies and form of nutrition. Additionally, the beginning of symptoms basis of BELL criteria was either registered or inferred for definition of the timeline of disease progress.

Statistics

The recorded data were initially analyzed with descriptive methods and clearly outlined. The mean, standard deviation, median and range were reported in the case of quantitative parameters, absolute and relative frequencies for the qualitative parameters. Exploratory tests between interesting subsets were selected based on the underlying parameters. When analyzing frequencies, the chi-square test and fisher's exact test were used. The t-test and the Kruskal-Wallis test were used in the study of continuous variables. Given the size of the subsets, the t-test and non-parametric tests such as Mann-Whitney test, Wilcoxon and Kruskal-Wallis were performed in addition to ANOVA, including post-hoc testing. Ordered logistic regressions for univariate and multivariate group differences and analyses of covariance were performed. Significance was established as $p \leq 0.05$. All statistical tests were analyzed using the IBM SPSS software, version 26 (IBM, Illinois, USA).

Results

Risk factors of prematurity

During the study period a total of 27.414 children were born in our tertiary hospital; 51.3% were males (n=14.065; prevalence 0.51) and 48.7% females (n=13.348; prevalence 0.48). Age, birth weight and height showed no significant difference in these groups. Seventy-six (n=76) preterm (64.5% male (n=49) and 35.5% female (n=27)), were included. The incidence was as follows: 35.5% NEC (n=27; 0.09%; 0.98/10,000), 48.7% NECp (n=37; 0.13%; 1.35/10,000) and 15.8% FIP (n=12; 0.4%; 0.44/10,000). Interestingly, in the period of 2004-2009 in all groups the number of affected children was significantly higher, than in the period of 2010-2014 (p=0.049); in subgroup of NECp the decrease of incidence was also statistically significant (p<0.001).

The overall mortality was 18.5% in NEC (n=5), 29.7% in NECp (n=11) and 0.0% in FIP children. In 2 patients (12.5%) the cause of death could not be undoubtedly assigned to either group, therefore these children were excluded from the analysis. The overall mortality was 29.7% (males n=16; 87.5% and females n=14; 12.5%). There was no significant association between mortality and either age at birth, birth size and weight, postnatal complications, and postnatal respiratory effort. Gender association was found; significantly more males died in our cohort (p=0.040) (Table 1).

Risk Factors	NEC (n=27;%) Mean ± SD; Range	FIP (n=12;%) Mean ± SD; Range	NECp (n=37;%) Mean ± SD; Range	X^2- value	p-value
Pregnancy week	27 (100%); 26.9 ± 2.8; 22-31	12 (100%); 25.6 ± 2.3; 22-30	37 (100%); 26.2 ± 3.3; 23-36		0.448
Birth weight (g)	27 (100%); 902.0 ± 395; 290-1720	12 (100%); 782.0 ± 264; 420-1400	37 (100%); 862 ± 471; 230-2650		0.709
Height (cm)	26 (96.3%); 34.7 ± 4.9; 22-44	11 (91,7%); 33.5 ± 3.6; 28-37.5	34 (91.9%); 34 ± 4.7; 26-48		0.891

BELL classification					
Ia/b	2 (7.4%)	No data	2 (5.4%)		
II a/b	19 (70.4%)		3 (8.1%)	38.565	<0.001
III a/b	6 (22.2%)		32 (84.5%)		
Gender					
Male	17 (63%)	9 (75%)	23 (62.2%)	0.694	0.707
Female	10 (37%)	3 (25%)	14 (37.8%)		
Mortality	5 (18.5%)	0 (0.0%)	11 (29.7%)	4.98	0.083
Gender mortality	Male 14 (87.5%)	Female 2 (12.5%)		4.691	0.04

Table 1. Preterm risk factors in NEC, NECp and FIP.

Postnatal risk factors

Complications: Congenital infections (NECp in 81.1% <NEC 81.5% <FIP 100%) were some of the most frequent complications observed. A nosocomial infection was significantly more present in FIP/NECp when compared to NEC (p=0.044). Postnatal hypotension was significantly more frequent in NEC/NECp compared to FIP (p=0.012). Conversely, a Persistent Ductus Arteriosus (PDA) was significantly more frequent in FIP (n=10; 83.3%; p=0.031) than in NECp (70.3%, n=26) or NEC (44.4%, n=12). Additionally, PDAs were also significantly more frequent when comparing both NECp/FIP against NEC alone (p=0.015). Coagulation disorders were present in 27.6% and significantly more often in FIP/NECp *vs.* NEC (p=0.018). The need for re-intubation (p=0.049) and for re-use of continuous positive airway pressure (CPAP; p=0.001) was significantly higher in FIP (n=11; 91.7%) compared to NEC/NECp (Table 2).

Postnatal Factors	**NEC (n=27;%)**	**FIP (**n=12;%)	**NECp (n=37;%)**	**NEC** *vs.* **FIP** *vs.* **NECp (X^2)**	**p-value**	**Perforation** *vs.* **no perforation**(X 2)	**p-value**	**NEC/NECp** *vs.* **FIP (X^2)**	**p-value**
Postnatal complications									
Co-natal infections	21 (77.7%)	12 (100%)	30 (81.0%)	3.061	0.216	0.773	0.526	2.94	0.113
Bradycardia	12 (44.4%)	7 (58.3%)	19 (51.3%)	0.694	0.707	0.517	0.632	0.396	0.754
Nosocomial infections	14 (51.8%)	10 (83.3%)	27 (72.9%)	4.855	0.088	4.414	0.044	1.7	0.317
Postnatal Hypotension	18 (66.6%)	10 (83.3%)	27 (72.9%)	1.167	0.558	0.681	0.433	0.857	0.492
Hypotension at birth	10 (37.0%)	9 (74.9%)	12 (32.4%)	7.042	0.03	0.244	0.808	6.905	0.012
Apnea-bradycardia syndrome	24 (88.8%)	12 (100%)	29 (78.3%)	3.805	0.149	0.383	0.737	2.412	0.195
PDA	12 (44.4%)	10 (83.3%)	26 (70.2%)	6.967	0.031	6.303	0.015	2.493	0.192
Glucose utilization-trouble	5 (18.5%)	5 (41.5%)	15 (40.5%)	3.926	0.14	3.921	0.073	0.497	0.515
Coagulation disorder	3 (11.1%)	4 (33.3%)	14 (37.8%)	5.808	0.055	5.716	0.018	0.232	0.727
Resuscitation	1 (3.7%)	1 (8.3%)	6 (16.2%)	2.668	0.263	2.07	0.247	0.073	1
Vaccination	14 (51.8%)	11 (91.6%)	22 (59.4%)	5.754	0.056	1.771	0.222	5.371	0.024
Re- Intubation	14 (51.8%)	11 (91.6%)	25 (67.5%)	5.953	0.051	3.614	0.078	4.24	0.049
Re- CPAP	8 (29.6%)	11 (91.6%)	14 (37.8%)	13.929	0.001	3.242	0.093	13.501	<0.001

Postnatal drug administration									
Indomethacin	12 (44.4%)	10 (83.3%)	21 (56.7%)	5.155	0.077	2.51	0.148	4.152	0.058
Ibuprofen	4 (14.8%)	1 (8.3%)	2 (5.4%)	1.666	0.435	1.573	0.238	0.013	1
Glucocorticoids	8 (29.6%)	5 (41.5%)	13 (35.1%)	0.562	0.755	0.39	0.618	0.352	0.741
Vasopressors	15 (62.9%)	9 (74.9%)	27 (72.9%)	2.548	0.28	2.531	0.132	0.402	0.74
Insulin	6 (22.2%)	7 (58.3%)	20 (54.0%)	7.728	0.021	7.66	0.008	1.29	0.345
Caffeine	17 (62.9%)	5 (41.5%)	15 (40.5%)	3.422	0.181	3.418	0.093	0.281	0.756
Theophylline	16 (59.2%)	5 (41.5%)	14 (37.8%)	2.993	0.224	2.94	0.099	0.11	1,000
Morphine	11 (40.7%)	8 (66.6%)	22 (59.4%)	3.129	0.209	2.94	0.099	0.928	0,367
Antibiotics	20 (74.0%)	12 (100%)	12 (32.4%)	4.481	0.106	3.236	0.101	2.672	0.009
Antifungals	16 (59.2%)	4 (33.3%)	18 (48.6%)	2.286	0.319	1.436	0,338	1.538	0.346
Packed red blood cells	14 (51.8%)	9 (74.9%)	27 (72.9%)	3.631	0.163	3.614	0.078	0.537	0.529
Fresh frozen plasma	3 (11.1%)	4 (33.3%)	13 (35.1%)	5.008	0.082	4.993	0.031	0.362	0.722
Phenobarbital	16 (59.2%)	10 (83.3%)	25 (67.5%)	4.004	0.135	2.972	0.147	2.345	0.191
Iron drops	23 (85.1%)	12 (100%)	34 (91.8%)	2.285	0.319	1.573	0.238	1.446	0.588

Table 2. Postnatal factors in NEC, NECp and FIP.

Drug therapy

The use of Indomethacin due to PDAs was higher in NECp/NEC compared to FIP alone, although this difference was barely non-significant (p=0.058). FIP preterm were significantly more often treated with insulin (p=0.021) due to glucose metabolism dysfunction than NEC and NECp; additionally, the use of insulin was significantly higher in FIP and NECp compared to NEC (p=0.008). Antibiotic treatment was significantly more frequent in NEC and NECp preterm than in FIP (p=0.009) and the duration was significantly longer in FIP (p=0.009; median 6.17 days) compared to NECp (median 4.52 days) or NEC (median 3.24 days).

These differences were also observed even when analysing FIP/NECp *vs.* NEC (p=0.014) and NEC/NECp *vs.* FIP (p=0.011). Packed red blood cells were used more frequent (p=0.078) in FIP/NECp *vs.* NEC as well as Fresh Frozen Plasma (FFP) (p=0.031) was necessary in 95.2%. The amount of inotropic medication used both within the NEC, NECp and FIP group and in comparison, with each other, does not differ significantly (p=0.280) this also applies to the frequency of inotropic medication administration (p=0.720; data not shown) (Table 2).

Prematurity-specific therapies

Idiopathic respiratory distress syndrome is attributed to surfactant-factor deficiency in preterm infants therefore surfactant therapy was performed in NECp significantly more often (2.67 times; p=0.018), than in NEC (1.59 times) or FIP (2.0 times). Postnatal oxygen therapy was necessary in 93.4% (n=71) and was maintained in NECp significantly longer (73.79 days; n=33; 89.2%; p=0.013), then in FIP (51.3 days; n=12; 100%) or NEC (32.86 days; n=26; 96.4%). In 97.3% of all preterm a form of respiratory support was necessary for an average of 45.58 days (0-193 days) and in 75% an additional endotracheal intubation, this significantly more often in NECp (p=0.022).

NECp children required significantly longer mechanical ventilation with an average of 56.38 days (0-193 days; p=0.034) than FIP (48.55 days, 13-90) and NEC (30.19 days, 0-120). We assess the BELL criteria immediately after clinical signs appear and documented them continuously. The clinical symptoms of NEC as classified in BELL criteria started in FIP significantly earlier with onset on average after 8.6days of life, compared to NECp (14.1 days) and NEC (23.7 days) (p=0.022). All children were operated within 6 hours of the diagnosis of perforation.

The beginning of enteral nutrition *via* nasogastric tube showed no significant differences among the groups, and in 96% the enteral nutrition was carried out with infant formula supplemented by breast milk in 42.7% of the patients. An overlap of parenteral and enteral nutrition was present in 100%, FIP and NECp preterm were significantly longer fed partially parenteral (p=0.035; median 42.7 days), then NEC (median 30.8 days) (Table 3).

Therapy duration	NEC (n=27; mean, range or %)	FIP (n=12; mean, range or %)	NECp (n=37; mean, range or %)	p-value
Antibiotics (d)	3.24 (0-6)	6.17 (3-14)	4.52 (1-14)	0.009
Surfactant application (times)	1.69 (1-3)	2 (1-3)	2.57 (1-5)	0.018
Ventilation (d)	30.19 (0-120)	48.55 (13-90)	56.38 (0-193)	0.034
Oxygen supply (d)	32.86 (1-120)	73.79 (4-229)	51.3 (5-89)	0.013
Intubation (d)	20.94 (1-93)	26.90 (5-53)	47.79 (2-193)	0.022
Begin of symptoms/ orientated at BELL Criteria (d)	14.14 (4-58)	8.58 (4-22)	23.74 (4-71)	0.001
Nutrition *via* nasogastric tube after surgery (d)	68.5 (37-136)	60.3 (15-119)	68.0 (4-131)	0.857
Nutrition breast milk after surgery (n)	13 (48.1%)	7 (58.3%)	13 (36.1%)	0.35
Nutrition breast milk postnatal (n)	13 (48.1%)	7 (58.3%)	12 (33.3%)	0.224
Nutrition formula milk after surgery (n)	25 (92.6%)	12 (100%)	36 (97.3%)	0.079
Nutrition formula milk postnatally (n)	25 (92.6%)	12 (100%)	35 (94.6%)	0.483
Partially parenteral feeding (d) perforation *vs.* no perforation	30.8 (26-64)	42.7 (26-107)	42.7 (14-172)	0.035
Total duration stay on NICU (d)	42.58 (2-103)	62.08 (16-117)	49.5 (1-172)	0.456

Table 3. Therapies after birth in NEC, NECp and FIP preterm.

Lastly, we could confirm that the minimization of preterm stress by the implementation a standardized "minimal handling" protocol by nurses and doctors in the year reduced significantly the number of NECp ($p<0.001$). This is the most likely explanation for the decrease in the number of NEC, NECp and FIP cases in the 2004-2009 period compared to the period of 2010-2014 ($p=0.049$) and clearly demonstrates the utmost importance of the "minimal handling" in premature babies.

Relative risk for perforation and for mortality

The odds ratio for the here analyzed variables for the occurrence of intestinal perforation in preterm are listed in Table 4. The relative risk for a perforation is higher with additional coagulation disorders (4.645-fold), after FFP administration (4.250-fold), insulin therapy (4.295-fold), antibiotic therapy (3.080-fold), PDA persistence (3.462-fold), Re-intubation (2.4571-fold) or Re-CPAP (2.474-fold), packed red blood cell transfusion (2.571-fold), abdominal surgery (2.250-fold) and after indomethacin treatment (2.153-fold). Similarly, the probabilities for mortality in association with all the studied variables are listed in Table 4. The relative risk for mortality was higher in accordance to gender (5.000-fold higher for males) and 4.565-fold higher in children after abdominal surgery. Interestingly, connate infections yielded no higher risk for mortality (Table 4).

Factor	Relative Risk	Significance	Lower estimate	Higher estimate
Relative risk for perforation				
Coagulation disorder	4.645	0.018	1.224	17.623
Insulin	4.295	0.008	1.477	12.495
FFP	4.25	0.031	1.117	16.176
Antibiotics	3.88	0.101	0.871	10.896
PDA	3.462	0.015	1.287	9.308
Indomethacin	2.953	0.148	0.828	5.599
Re-Intubation	2.571	0.078	0.959	6.892

Surgery	2.25	<0.001	1.476	3.43
Packed red blood cells	2.571	0.078	0.959	6.892
Re-CPAP	2.474	0.093	0.912	6.712
Indomethacin	2.153	0.148	0.828	5.599
Vaccination	1.915	0.222	0.731	5.014
Mortality	1.274	0.775	0.391	4.196
Insulin	1.25	0.208	0.806	1.938
Gender	1.107	1	0.416	2.944
Relative risk for mortality				
Gender	5	0.04	1.042	23.985
Abdominal surgery	4.565	0.17	0.553	37.685
Connately infection	0.524	0.454	0.139	2.012

Table 4. Relative risk for perforation and for mortality (95%CI).

Discussion

Preterm risk factors

Survival rates of preterm have been steadily improving due to better medical care [13], which paradoxically resulted in an increase of incidence for NEC and NECp [14]. However, we observed a decrease, especially for NECp and FIP <1000 g birth weight [15]. Despite improvements in NICU management, the mortality from NEC is still high and increases significantly after surgical treatment [16], especially in males [17]. The mortality rate of FIP is generally lower, up to 26%, regardless if surgery is performed or not [18]. In our cohort, the mortality rate with 29.7% for NECp was fortunately low when compared to others like Shah et al. None of our FIP children died, perhaps due to the fact that they were less critically-ill compared to NEC or NECp and due to a good interdisciplinary NICU management with early diagnosis and adequate management.

Our findings that male preterm were affected by NEC and NECp two times and FIP three times more frequently than female preterm were also observed by Fisher et al. [18], but different to Pandey et al. who could not find any gender association [19]. One possible explanation for gender mortality difference could be dissimilar gut microbiome in male compared to female preterm in the first 20 days of life, which could result in case of translocation of bacteria to faster perforation and fulminant sepsis with severe peritonitis [20]. We could also confirm that with decreasing gestational age and birth weight the risk for NEC, NECp and FIP increases [14]; additionally, we could also show that FIP preterm are born earlier than NEC and NECp like elsewhere describe. Pandey et al. found lower body weight in FIP and <1500 g for NEC and NECp, which we have also observed.

Minimal handling protocol

Using a minimal handling protocol as part of the daily care of premature infants reduces stress and showed significant influence dropping perforated NEC rates in preterm and therefore decreases mortality in our cohort. This stress relieving effect was described for intracranial haemorrhage by Schmid et al. [21] but not yet for perforated NEC.

Postnatal factors

Postnatal complications: Prematurity is considered to be the most important risk factor for NEC and FIP development, but other factors are strongly suspected to influence their development. One of them is a haemodynamically-relevant PDA which plays a key role in intestinal perforation. A reduced blood flow and intestinal perfusion, caused by PDA, may lead to a disturbance of the mucosal barrier, which subsequently evolves to intestinal wall ischemia and bowel perforation [22]. Sharma et al. found that FIP preterm are more affected than NEC and NECp, a finding which we can corroborate. Additionally, in over 30% of NEC cases a PDA is present and these neonates are more likely to undergo abdominal surgery and even the conservative therapy for PDAs may play an important role in the development of NEC [23].

Co-natal infections as well as nosocomial infections represent a great risk for postnatal complications as demonstrated by our findings and those of Ramasethu et al. [24]. Ramasethu could show an increased risk for invasive procedures and surgeries, central line associated bloodstream infections and translocation of pathogenic bacteria across the epithelial barrier in preterm caused by less diverse gut microbiome harbor. We found significantly more often a coagulation disorder and postnatal hypotension in NECp and FIP, which has not been observed in other series such as those from Sharma et al. [17]. A possible explanation for this is a dramatic drop of platelets through destruction caused by peritonitis or sepsis after bowel perforation. NEC preterm received several platelet transfusions to treat bleeding, hypovolemia and severe thrombocytopenia

this could play a direct or indirect part in the pathogenesis of bowel mucosal injury [25].

Postnatal drug therapy: A PDA and its therapy may be responsible for inducing bowel perforation in preterm [26], yet there is no consensus to date on both. The most frequent drugs used for attempting a PDA closure are indomethacin or ibuprofen, and Gulack et al. found no significant difference in closure rate between these two drugs [27], while Khuwuthyakorn et al. could show that indomethacin was more effective [28]. Chan et al. showed a significant increase of intestinal perforation in NEC after treatment with ibuprofen [23], while Gephart et al. described a significantly reduced risk of NEC after PDA treatment with ibuprofen and not indomethacin, which seemed to be more frequently associated with bowel perforation. We agree with the latter data. Additionally, an early postnatal antibiotic therapy is an important risk factor for the development of NEC or death [29].

We can also fully support this aspect because it is well known, that empiric antibiotic use was associated to lower bacterial diversity in the gut microbiome and increased colonization with potentially germs in preterm infants [24]. Interestingly, in our cohort prematures with FIP and NECp were significantly more likely to have received insulin for therapy of postnatal glucose metabolism disorders than NEC. We can therefore support that insulin may be a risk factor for the development of a FIP or a perforation in general as shown by Decaro et al. [30]. The cause is probably not solely due to administration of insulin, but is part of a complex interplay of increased stress (caused by sepsis), with the resultant increased blood sugar level, which is treated with insulin as therapy.

The exact time point of perforation was understandably not exactly known, so insulin could be a trigger or a was administered close around this time point of interest. The administration of FFP or packed red blood cells, especially in preterm, can lead to haemolysis, which can result to a clinical deterioration and should always be weighed strictly with the risks [31]. Stritzke et al. found a transfusion-associated necrotising enterocolitis in neonates [32]. We have observed a significant association of FFP administration and bowel perforation, which does suggest a correlation which still needs to be further elucidated. We could not show any connection of the amount or frequency of inotropic drugs administration on increased risk for gut perforation, but Aziz et al. showed that higher vasoactive-inotropic scores were directly associated with mortality in extremely premature infants.

Postnatal medical therapy: A duration of an antibiotic therapy ≤ 10 days leads to a three-fold increase of NEC and NECp in preterm [33]. An explanation could be that long-lasting antibiotic therapy destroys the protective intestinal flora and leads to overgrowth of potentially pathogenic germs. Therefore, an accurate risk-benefit assessment is important and any antibiotic therapy should be terminated as soon as possible. Nosocomial infections also play an essential role and were present in our series in FIP>NECp>NEC, which were to our knowledge for the first time compared against each other. The role of these infections has already been demonstrated by Sharma et al. [17], who also suggested that the infections have an additionally deleterious effect resulting in perforation.

Gephart et al. demonstrated that mechanical and bag-mask ventilation are significant risk factors for development of NEC and NECp [34]. We partially agree with these authors, however in our series it was not the need for respiratory support alone but rather the duration of the mechanical ventilation the most important risk factor for NECp and FIP preterm. Markel et al. support this result, suggesting that the bacterial colonization of the respiratory tract is a possible cause sepsis-associated NEC as well as Oxygen application [35]. We observed that the need for oxygen per se was not the risk but rather we found significant differences among the groups in terms of the duration of O2 therapy (NECp>FIP>NEC). The necessity of oxygen suggests a hypoxic metabolic situation and the consequent hypoxemia leads to intestinal ischaemia and inflammatory response [36], which a clear risk factor for FIP leads to local intestinal hypoperfusion and perforation [37].

Early beginning of enteral feeding with breast milk and a short duration of parenteral nutrition reduces significantly the risk for NEC, NECp or FIP. We completely support these findings, yet Viswanathan et al. found that a protocol for slow feedings reduces significantly the incidence of NEC and combined NEC/death in “micropremies” (<1000 g) [34]. Juhl et al. found that the 1978 BELL staging system is still up-to-date and well suited to classify NEC [35], a conclusion we can corroborate. Using BELL criteria for an earlier suspicion and diagnosis of NEC or FIP resulting in a faster management and better outcome [36]. After implementing a NICU “minimal handling”-management in preterm the incidence of NEC and FIP decreased, especially NECp dropped down significantly [21].

Relative risk for perforation and for mortality

We have observed a 5–fold higher risk for mortality in male preterm NEC patients as compared to females. This seems to be a particular consequence of the disease per se, as several studies from different countries like China and Korea have shown no difference in the mortality between preterm males and females [37]. One possible explanation is a growing understanding of how sex differences in disease prevalence, manifestation, and response to treatment are rooted in the genetic differences between males and females, based on a fundamental difference in chromosome complement. Since in males the X-chromosome carries only maternal imprints, the epigenetic modifications in the expression of genes may influence the response to several diseases including NEC. In females the presence of both maternal and paternal imprints may result in a protective effect in face of a severe disease such as NEC [38].

Conclusion

We have shown that the optimization of intensive therapy is not associated with an increase in the incidence of NEC, NECp or FIP. We conclude that minimal handling management

minimized stress to preterm regarding the number of NEC, NECp and FIP. The standard use of breast milk for nutrition was firmly established later in our cohort and therefore does not play a major role in this positive development. The amount and frequency of inotropic drugs used for circulatory support have no negative influence in terms of increased risk of NEC, NECp and FIP. In premature infants the duration of mechanical ventilation should be kept as short as possible, as we have shown that the length of ventilation time correlates with the number of NECp and FIP.

Furthermore, we were able to show that additional factors like re-intubation and CPAP-therapy, or Insulin therapy or FFP administration are associated with NEC or FIP in our children, in addition to the well-known and established risk factors like prematurity, gender, hypotension or coagulation disorder. This knowledge is quite most important for the quick recognition and management of preterm affected by NEC, NECp or FIP, in addition to the knowledge of maternal risks factors and clinical symptoms according to BELL Criteria. The consequent determination of the sum of "cumulative" risk factors will warrant a better and faster identification of preterm with higher risk for the development of NEC and FIP. Due to the often-protracted impairments of the children, regular monitoring of the neurological development and precise assessment of food intake and tolerance are important for the long-term follow-up in order to correctly assess the individual quality of life in the long term.

List of Abbreviations

FIP: Focal Intestinal Perforation; NEC: Necrotizing Enterocolitis without Perforation; NECP: Necrotizing Enterocolitis with Perforation; NICU: Neonatal Intensive Care Unit.

Trial registration: The ethics committee of the University of Ulm approved the project (No. 13/15).

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval and consent to participate

Parents have given their written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol has been approved by the research institute`s committee on human research. The local ethics committee of the University Hospital Ulm approved this study (No. 13/15).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

MK organized the study, performed the clinical examinations and was a major contributor in writing the manuscript. JH contacted the parents, organized the database and analyzed the data. AS supervised the project and interpreted the patient data. All authors read and approved the final manuscript.

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*Correspondence to:

Melanie K

Department of Surgery, University of Ulm Medical Centre

Eythstrasse 24, 89075 Ulm,

Germany

E-mail: melanie.kapapa@uniklinik-ulm.de