

# Clinical Spectrum and Outcomes of Neonatal Necrotizing Enterocolitis

PRZEMYSŁAW GAŁĄZKA<sup>1,2</sup>, MAGDALENA CHRZANOWSKA<sup>1</sup> and JAN STYCZYŃSKI<sup>2</sup>

<sup>1</sup>*Department of General and Oncological Surgery for Children and Adolescents Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum, Bydgoszcz, Poland;*  
<sup>2</sup>*Department of Pediatric Hematology and Oncology, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum, Bydgoszcz, Poland*

**Abstract.** *Background/Aim: The objective of the study was analysis of risk factors associated with outcome of necrotizing enterocolitis (NEC) in infants in a single-center study. Patients and Methods: All consecutive infants hospitalized for NEC over a period of 6 years were retrospectively analyzed for clinical course, infections, treatment and outcome. Results: Out of 76 patients, surgical management was applied in 56 (53 exploratory laparotomy, three initial peritoneal drain placement) and in 20 there was only a conservative approach. Segmental intestinal resection was performed in 41 patients. Survival from NEC in our cohort was 79%. We found that independent adverse risk factors of outcome of newborns and infants with NEC were gut perforation, infection, abdominal wall erythema, and development of acute kidney injury. Conclusion: We underline the value of both surgical and conservative approach with careful management in this cohort of patients.*

Necrotizing enterocolitis (NEC) is a complex predominantly intestinal inflammatory disorder affecting preterm infants, and the major cause of morbidity and mortality in this age group. It is one of the most common gastrointestinal (GI) emergencies in the neonatal period. NEC has multifactorial etiology and is characterized by a variable degree of intestinal gangrene. Population-based studies have estimated the

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*Correspondence to:* Przemysław Gałązka, MD, Ph.D., Department of General and Oncological Surgery for Children and Adolescents, Jurasz University Hospital, Nicolaus Copernicus University Toruń, Collegium Medicum, ul. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland. Tel.: +48 525854015, Fax: +48 525854093, e-mail: galazkaprzemek@hotmail.com

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incidence of NEC between 0.72-1.8 per 1,000 live births (1). Most neonates diagnosed with NEC are at the age of less than 32 weeks of gestation, particularly in the case of extremely low birth weight infants weighing less than 1,000 g, while a decline in incidence occurs after 35 weeks of gestation (2).

Well-known risk factors for development of NEC include prematurity and bacterial colonization of the gastrointestinal tract (3, 4). With increasing survival of extremely premature infants, the number of neonates at risk for developing NEC continues to rise. Clinical features of NEC include the presence of physiological and metabolic instability, abdominal distention, and feeding intolerance (5). Disease severity is characterized by clinical and radiographic findings, known as the Bell staging system (6).

The objective of this study was the analysis of the clinical course and risk factors for outcomes of infants with NEC in a single-center study.

## Patients and Methods

*Design of the study.* A total of 76 consecutive infants including 43 (56.6%) males, and 33 (43.4%) females with NEC hospitalized at the Department over a period of 6 years were retrospectively analyzed for clinical course, infections, treatment and outcome. The study was approved by Collegium Medicum in Bydgoszcz Bioethical Committee No 465/2011.

*NEC diagnosis and classification.* NEC was diagnosed on the basis of clinical, laboratory (*e.g.* white blood cell count, neutrophil count, platelet count, blood gas balance, C-reactive protein) and radiological (*e.g.* ultrasound, X-ray) signs and symptoms. Patients admitted to the Department were treated surgically or conservatively. Surgical treatment was based on laparotomy or peritoneal drainage. The newborns were classified according to Bell's (6-8) or modified Tepas criteria (9). NEC classification in Bell's criteria with Walsh-Kliegman modification (6-8) included three stages: Stage I: suspicion of NEC (A, occult GI bleeding; B, GI bleeding); stage II: diagnosed NEC (A, mild; B, intermediate); stage III: advanced NEC (A, without perforation; B, with perforation). Additionally, we classified patients with NEC according to Tepas criteria of NEC natural history

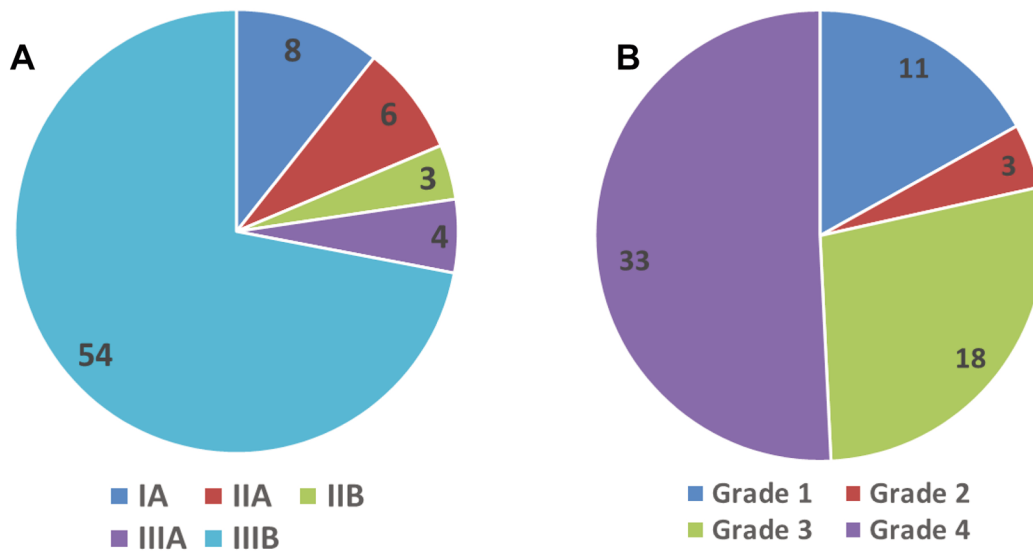


Figure 1. Frequency distribution of patients according to Bell's classification (6-8) (A) and modified Tepas classification (9) (B).

(9) with our own modification, which included four grades: Grade 1: no necrosis, no perforation; grade 2: perforation but without metabolic or hematologic derangements; grade 3: severe clinical symptoms with coexisting metabolic and hematological derangements (thrombocytopenia, neutropenia, left shift of segmented neutrophils, metabolic acidosis, hyponatremia, bacteremia, or hypotension) together with free intraperitoneal air; grade 4: severe clinical symptoms with coexisting metabolic and hematological derangements, without free intraperitoneal air.

**Statistical analysis.** Categorical variables were compared by the chi-square test or Fisher exact test, with odds ratio (OR) and 95% confidence interval (95% CI); and non-categorical variables by the Mann-Whitney test. The primary endpoint of the study was overall survival (OS). The survival curves were determined by the Kaplan–Meier method and compared with log-rank test. Risk factors analysis for surgical treatment were in univariate analysis were by uni- and multivariate logistic regression. Risk factor analysis for survival was performed using a univariate Cox model. Factors significant in univariate model were analyzed in multivariate Cox model. The results of the multivariate analysis are presented by hazard ratio (HR) with a 95% CI. A value of  $p < 0.05$  was considered statistically significant. The analysis was performed using the statistical package SPSS 25.0 (IBM, Armonk, NY, USA).

## Results

**Demographics.** The median gestational birth age was 29 weeks (range=23-41 weeks), median weight 1095 g (range=570-4,620 g), median Apgar score 5 (range=1-10), and median age at admission 12 days (range=1-3 days). The distribution of patients according to Bell's and modified Tepas classifications are shown in Figure 1.

**Microbial colonization.** On admission, colonization was diagnosed in 53 patients, including bacterial etiology in 52 patients (Gram-positive in 35, and Gram-negative in 17), and fungal etiology in eight patients. Gram-positive strains detected included: methicillin-resistant coagulase-negative *Staphylococcus* in nine, *Staphylococcus aureus* in four, *Staphylococcus spp* in eight, *Staphylococcus epidermidis* in two, *Staphylococcus haemolyticus* in seven, *Streptococcus pneumoniae* in one, *Streptococcus viridans* in two, *Enterococcus faecalis* in seven, and *Enterococcus faecium* in seven. Gram-negative strains included: *Klebsiella pneumoniae* in five, *Klebsiella oxytoca* in four, *Escherichia coli* in 14, *Enterobacter cloacae* in three, *Serratia marcescens* in one, *Citrobacter spp* in two, *Corynebacterium spp* in two, *Pseudomonas aeruginosa* in one, *Acinetobacter baumannii* in 2, and *Stenotrophomonas maltophilia* in four. Fungal colonization included: *Candida albicans* in six, *Candida guilliermondii* in one, and *Candida faringe* in one.

**Infectious complications.** Infections developed in 51 patients, including sepsis in 48 patients, microbiologically documented infection in 28 patients, and clinically documented infection in 21 patients. Bacterial etiology of infection was diagnosed in 26 patients (Gram-positive in 14, and Gram-negative in 12), and fungal infection in seven patients. Infection with Gram-positive strains included: *Staphylococcus epidermidis* in nine, *Staphylococcus haemolyticus* in three, *Streptococcus pneumoniae* in one, and *Enterococcus faecium* in one. Infection with Gram-negative strains included: *Klebsiella pneumoniae* in two, *Escherichia coli* in four, *Enterobacter cloacae* in two, *Aeromonas spp* in one, *Acinetobacter baumannii* in two, and

Table I. Univariate analysis of risk factors for overall survival of infants with necrotizing enterocolitis at day 60 after admission to hospital.

Parameter	Subgroup	N	Kaplan–Meier analysis		Univariate Cox analysis	
			Survival	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Classification by Bell*	Stage I-II	17	0.94±0.06	0.082	1	
	Stage III	58	0.74±0.06		5.0 (0.6-38)	0.118
Classification by Tepas**	Grade 1-2	34	0.97±0.03	<b>&lt;0.001</b>	1	
	Grade 3-4	41	0.63±0.07		15 (2.0-90)	<b>0.008</b>
Gestational age	≥30 Weeks	41	0.88±0.05	<b>0.042</b>	1	
	<30 Weeks	35	0.69±0.08		2.8 (1.0-8.2)	0.053
Birth weight	≥1,000 g	43	0.84±0.06	0.266	1	
	<1,000 g	33	0.69±0.08		1.7 (0.6-4.7)	0.273
Apgar score	≥5	38	0.87±0.06	0.088	1	
	<5	38	0.71±0.07		2.4 (0.8-7.1)	0.099
Age at admission	≥14 Days	32	0.84±0.06	0.337	1	
	<14 Days	44	0.75±0.06		1.6 (0.6-4.8)	0.343
Colonization	No	23	0.85±0.05		1	
	Yes	53	0.65±0.09	<b>0.044</b>	2.6 (1.0-7.0)	0.054
Bacterial colonization	No	33	0.86±0.05		1	
	Yes	43	0.70±0.08	0.078	2.4 (0.9-6.6)	0.088
Bacterial colonization Gram+	No	41	0.89±0.05	0.053	1	
	Yes	35	0.71±0.07		2.9 (0.9-9.0)	0.065
Infection	No	25	0.96±0.04	<b>0.015</b>	1	
	Yes	51	0.71±0.06		8.3 (1.1-62)	<b>0.041</b>
Sepsis	No	28	0.89±0.06	0.104	1	
	Yes	48	0.73±0.06		2.7 (0.8-9.5)	0.119
Clinically documented infection	No	55	0.88±0.05	<b>0.002</b>	1	
	Yes	21	0.57±0.11		4.1 (1.6-11.5)	<b>0.005</b>
Carbapenem use	No	27	0.96±0.04	<b>0.007</b>	1	
	Yes	49	0.69±0.07		9.7 (1.3-71)	<b>0.028</b>
Glycopeptide use	No	23	0.96±0.04	<b>0.023</b>	1	
	Yes	53	0.72±0.06		7.4 (1.0-54)	0.053
Netilmicin use	No	63	0.75±0.06	0.052	27 (0.1->100)	0.225
	Yes	13	1.00		1	
Gastrointestinal hemorrhage	No	57	0.84±0.05	<b>0.019</b>	1	
	Yes	18	0.61±0.11		3.2 (1.2-8.1)	<b>0.026</b>
Septic shock	No	34	0.91±0.05	<b>0.014</b>	1	
	Yes	41	0.68±0.07		4.3 (1.2-14)	<b>0.024</b>
Acidosis	No	30	0.93±0.05	0.010	1	
	Yes	44	0.68±0.07		5.6 (1.3-24)	<b>0.023</b>
Abdominal wall erythema	No	47	0.89±0.05	<b>0.004</b>	1	
	Yes	28	0.61±0.09		4.2 (1.4-12)	<b>0.008</b>
Platelet count	≥150×10 <sup>6</sup> /l	32	0.88±0.06	0.092	1	
	<150×10 <sup>6</sup> /l	43	0.72±0.07		2.5 (0.8-7.6)	0.105
White blood cell count	<15×10 <sup>6</sup> /l	49	0.84±0.05	0.102	1	
	≥15×10 <sup>6</sup> /l	25	0.68±0.09		2.3 (0.8-5.7)	0.112
Intra-abdominal fluid	No	26	0.92±0.05	<b>0.034</b>	1	
	Yes	49	0.71±0.06		4.4 (1.0-18)	0.052
Perforation	No	28	0.96±0.04	<b>0.005</b>	1	
	Yes	48	0.69±0.07		10.2 (1.4-76)	<b>0.024</b>
Complications	No	30	1.00	<b>&lt;0.001</b>	1	
	Yes	46	0.65±0.07		52 (0.9->100)	0.056
Acute kidney injury	No	63	0.92±0.03	<b>&lt;0.001</b>	1	
	Yes	13	0.15±0.10		24 (8-71)	<b>&lt;0.001</b>
Age at discharge	≥36 Days	38	0.90±0.05	<b>0.017</b>	1	
	<36 Days	38	0.68±0.07		3.6 (1.2-11)	<b>0.025</b>
Length of stay	≥20 Days	36	0.89±0.05	<b>0.029</b>	1	
	<20 Days	40	0.70±0.07		3.2 (1.1-10)	<b>0.040</b>

\*According to (6-8). \*\*According to (9). Statistically significant *p*-values are shown in bold.

Table II. Multivariate analysis of risk factors for overall survival.

Parameter	Factor present	Kaplan–Meier analysis		Multivariate Cox analysis	
		Survival	p-Value	HR (95% CI)	p-Value
Infection	No	0.96±0.04	<b>0.015</b>	1	
	Yes	0.71±0.06		11 (1.1->100)	<b>0.044</b>
Gastrointestinal hemorrhage	No	0.84±0.05	<b>0.019</b>	1	
	Yes	0.61±0.11		2.5 (0.4-13)	0.296
Acidosis	No	0.93±0.05	<b>0.010</b>	1	
	Yes	0.68±0.07		1.8 (0.3-21)	0.543
Abdominal wall erythema	No	0.89±0.05	<b>0.004</b>	1	
	Yes	0.61±0.09		5.4 (1.4-21)	<b>0.014</b>
Intra-abdominal fluid	No	0.92±0.05	<b>0.034</b>	1	
	Yes	0.71±0.06		1.4 (0.1-12)	0.623
Perforation	No	0.96±0.04	<b>0.005</b>	1	
	Yes	0.69±0.07		18 (1.6->100)	<b>0.020</b>
Acute kidney injury	No	0.92±0.03	<b>&lt;0.001</b>	1	
	Yes	0.15±0.10		25 (4.1->100)	<b>&lt;0.001</b>

CI: Confidence interval; HR: hazard ratio. Statistically significant p-values are shown in bold.

*Stenotrophomonas maltophilia* in two. Infections with fungi included: *Candida albicans* in five, *Candida guilliermondii* in one, *Candida faringe* in one, and *Candida pellicula* in one.

**Surgical treatment.** Out of 76 patients, 56 were treated surgically (53 exploratory laparoscopy, three peritoneal drain placement) and 20 conservatively only. Intestine resection with concomitant creation of enterostomy was performed in 41 patients, at a median of 12 days (range=1-45 day). Median length of resected intestine was 10 cm (range=3-72 cm). significantly risk factors for surgical treatment in univariate analysis were: Grade 3-4 in modified Tepas classification (HR=5.0, 95% CI=1.6-16,  $p=0.006$ ), stage III in classification by Bell (HR=28, 95% CI=6.9->100,  $p<0.001$ ), and perforation (HR=9.9, 95% CI=3.0-32,  $p<0.001$ ), while birth weight <1,000 g was a factor reducing the decision on surgical treatment (HR=0.20, 95% CI=0.1-0.7,  $p=0.007$ ). The only risk factor remaining significant for surgical treatment in multivariate analysis was stage III in classification by Bell (HR=40, 95% CI=7.4->100,  $p<0.001$ ).

**Antibiotic utilization.** All patients were treated with antibiotics, including: meropenem in 39, imipenem in 13 (carbapenems in 49), vancomycin in 45, teicoplanin in 8, linezolid in one, piperacillin-tazobactam in 12, cephalosporines III/IV generation in 10 (ceftazidime in eight, ceftriaxone in two, cefepime in one), metronidazole in 60, amikacin in 13, netilmicin in 13, gentamicin in one, amoxicillin with clavulanate in 12, cefuroxime in one, cefoperazon with sulbactam in three, ciprofloxacin in three, ampicillin in two, and colistin in two. Overall, 66 patients were administered

antifungals, including fluconazole in 61, amphotericin B in three, voriconazole in one, and anidulafungin in one.

*Univariate analysis of risk factors for overall survival.*

Overall, 16 (21%) patients died, at a median of 16 days (range=1-35 days) after admission to the Department. In univariate analysis, the following risk factors significantly contributed to adverse outcome: Grade 3/4 in modified Tepas classification, infection, use of carbapenems, use of glycopeptides, GI hemorrhage, septic shock, acidosis, abdominal wall erythema, intestine perforation, acute kidney injury, age at discharge less than 36 days, and length of hospital stay less than 20 days (Table I).

Apart from the parameters shown in Table I, also sex, mode of delivery (cesarean section), fungal colonization, Gram-negative bacterial colonization, microbiologically documented infections, specific bacterial strain, other laboratory and radiographic findings, as well as the use of any other antibiotic, had no influence on survival.

*Multivariate analysis of risk factors for OS.*

The following independent factors, significant in univariate Cox analysis were included in the multivariate analysis: Infection, clinically documented infection, GI hemorrhage. septic shock, acidosis, abdominal wall erythema, intra-abdominal fluid, perforation, and acute kidney injury (Table II, Figure 2). On the other hand, the following factors were considered dependent on others: Modified Tepas classification, carbapenem use, age at discharge, and length of stay.

Four independent factors significantly increased the risk of death due to NEC: Gut perforation, infection, abdominal wall erythema, and the development of acute kidney injury.

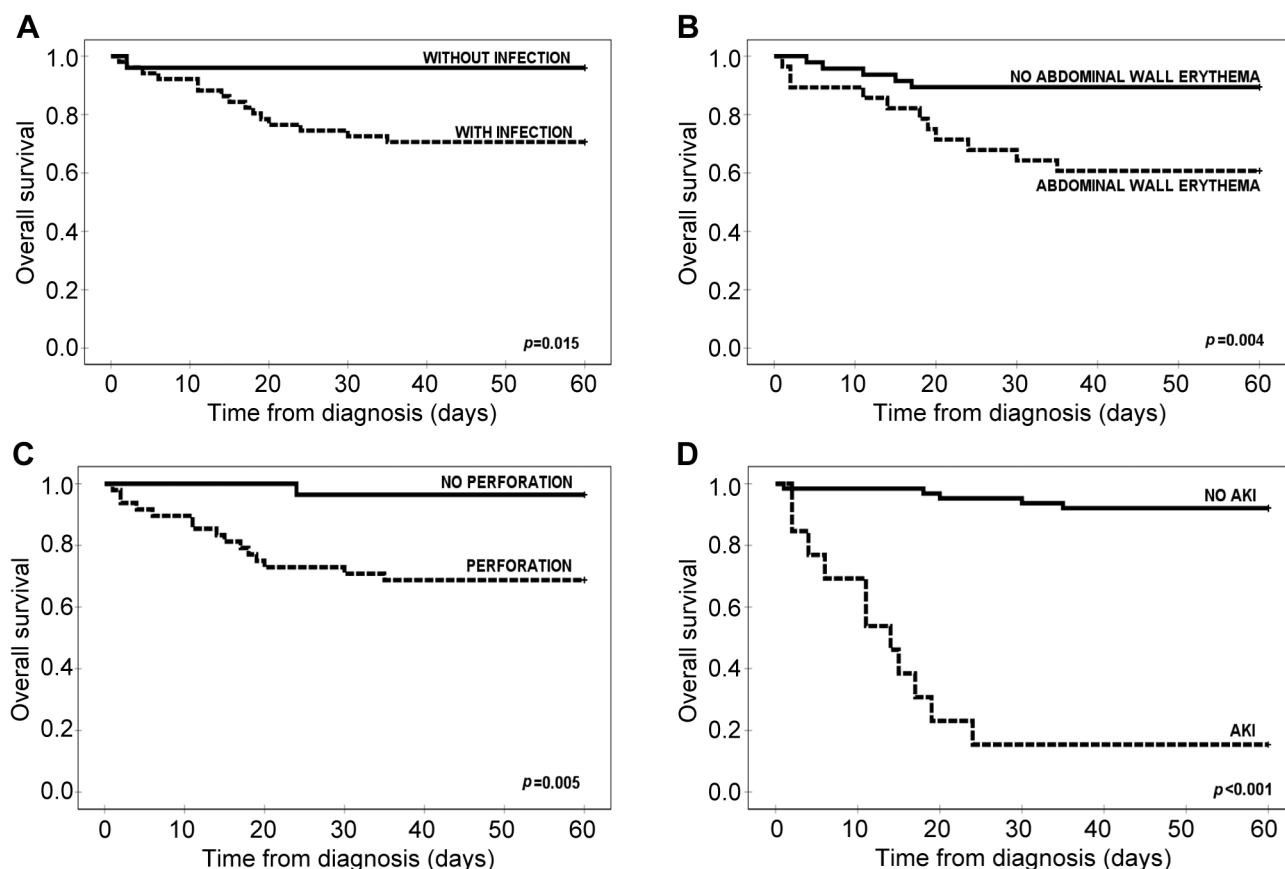


Figure 2. Overall survival with respect to concomitant infection (A), abdominal wall erythema (B), perforation (C) and acute kidney injury (AKI) (D).

## Discussion

The major finding of this study was determination of four independent adverse risk factors for outcome of newborns and infants with NEC, namely gut perforation, infection, abdominal wall erythema, and development of acute kidney injury.

Most patients included in the study were treated surgically either by exploratory laparotomy or with peritoneal drainage. In multivariate analysis, we showed that stage III in classification by Bell including perforation was the strongest factor influencing the decision of surgical treatment, while birth weight <1,000 g was the factor determining an initial conservative approach. Lower birth weight is a well-known factor associated with a higher frequency and greater severity of disease (10, 11).

A number of laboratory and radiographic parameters confirmed adverse values of parameters assessing clinical status, and those confirming gut perforation have the highest value in selection of therapeutic approach and outcome of NEC. Obviously, a newborn's death due to NEC is

associated with severe clinical signs, laboratory parameters (leukocytosis, high level of C-reactive protein, metabolic acidosis) and radiological signs (no gas in the digestive tract). Perforation of the GI tract is usually followed by metabolic acidosis and typical radiological signs (free echogenic fluid in peritoneum and free gas in the abdomen). The same symptoms might develop in the case of post-surgical complications, such as acute kidney injury, which is frequently associated with the severity of enterocolitis (12). We also found that abdominal wall erythema was a relatively frequent symptom in our cohort, and had an adverse prognostic value. This phenomenon is rarely described in the literature, and it might be included in symptoms of abdominal distension (13).

In our cohort, a classic surgical treatment of NEC was applied: Resection of the necrotic bowel segment together with temporary proximal enterostomy creation. Nowadays several options for surgical treatment are proposed, depending mainly on the extent of necrosis and the patient's general status (14, 15). In an experimental model, it has been shown that laparoscopy has acceptable levels of agreement with laparotomy



in NEC lesions of both the colon and the small intestine (16). There is still an open question of the use of minimally invasive surgery in neonates and small infants (14-16).

We previously showed that in case of congenital abdominal cystic lesions, a laparoscopically assisted minimal-access approach resulted in minimal risk of complications and complete recovery in all patients (17). On the other hand, a completely different approach was necessary for patients with Hirschsprung's disease (18).

This study has some limitations. Apart from its retrospective design and long-term inclusion as a single-center study, we also did not analyze factors which may have contributed to the development of NEC, including the general care of newborns, such as antenatal corticosteroid use, delayed enteral feeding, human milk feeding, and pre- or probiotic administration (19). On the other hand, we analyzed a large number of risk factors, including clinical classifications, clinical signs and symptoms, laboratory and imaging parameters both in diagnosis of NEC and in the selection of treatment approach; however, no other independent factors were found which contributed to OS. The use of specific antibiotics, including carbapenems and glycopeptides, was bound to worsen survival, however, this was because of severe infection which required these 'reference' antibiotics and not any negative impact of the antibiotics themselves.

In conclusion, survival from NEC in our cohort was 79%. We found that independent adverse risk factors of outcome of NEC in newborns and infants were gut perforation, systemic infection, abdominal wall erythema, and the development of acute kidney injury. We underline the value of both surgical and conservative approach with careful management in this cohort of patients. The role of minimally invasive surgery in NEC might be a question of future research.

## Conflicts of Interest

The Authors have no conflicts of interest to disclose in regard to this study.

## Authors' Contributions

PG: Concept/design, data analysis/interpretation, writing article; PG, MC, and JS: data collection, data analysis/interpretation; PG and JS: critical revision of article, approval of article.

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