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Necrotizing Enterocolitis following Gastroschisis Repair: An Update

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Abstract

Purpose:

Necrotizing enterocolitis (NEC) is a known complication of gastroschisis with an incidence above the expected rate in the neonatal population. While many physicians today are aware of this association, the last publication to explore this association in detail and identify possible risk factors of NEC in gastroschisis patients was published over twenty years ago. From our large database of patients with gastroschisis managed by a single group of pediatric surgeons, we reviewed our experience and the recent literature to update what is known about gastroschisis and NEC.

Methods:

From 2001 to 2017, a gastroschisis registry was maintained. Data from 218 gastroschisis patients were reviewed. Patient demographics and hospital course were reviewed. Patients with confirmed NEC were compared to those without NEC.

Results:

Two hundred eighteen patients were born with gastroschisis during the time frame of this study. We observed a 5% rate (11 of 218) of NEC. Five patients (45%) developed recurring NEC and 4 patients (36%) were readmitted for NEC development following initial discharge. Variables associated with NEC included low gestational age ($P=0.016$) and low birth weight ($P=0.003$). Patients born prior to 37 weeks gestation had a 4.8 times greater risk of developing NEC than those born at term. Rates of IUGR were not statistically different between NEC and non-NEC patients. The method of delivery (cesarean vs vaginal), use of a silo, and form of nutrition were not significantly associated with NEC development.

Conclusions:

The overall incidence of NEC has decreased compared to earlier reports. NEC does complicate the hospital course for patients, significantly increasing duration of in-hospital treatment. NEC in gastroschisis differs in comparison to traditional NEC, presenting later in life. Risk factors identified include low gestational age and low birth weight. Avoiding elective preterm deliveries may decrease the rate of NEC in gastroschisis.

Keywords

gastroschisis

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Necrotizing Enterocolitis Following Gastroschisis Repair: An Update

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Abstract

Introduction: Necrotizing enterocolitis (NEC) is a known complication of gastroschisis with an incidence above the expected rate in the neonatal population. While many physicians today are aware of this association, the last publication to explore this association in detail and identify possible risk factors of NEC in gastroschisis patients was published over twenty years ago. From our large database of patients with gastroschisis, managed by a single group of pediatric surgeons, we reviewed our experience and the recent literature to update what is known about gastroschisis and NEC.

Methods: From 2001 to 2017, a gastroschisis registry was maintained. Data from 218 gastroschisis patients were reviewed. Patient demographics and hospital course were reviewed. Patients with confirmed NEC were compared to those without NEC.

Results: Two hundred eighteen patients were born with gastroschisis during the time frame of this study. We observed a 5% rate (11 of 218) of NEC. Five patients (45%) developed recurring NEC and 4 patients (36%) were readmitted for NEC development following initial discharge. Variables associated with NEC included low gestational age (P=0.016) and low birth weight (P=0.003). Patients born prior to 37 weeks gestation had a 4.8 times greater risk of developing NEC than those born at term. Rates of intrauterine growth restriction (IUGR) were not statistically different between NEC and non-NEC patients. The method of delivery (cesarean vs vaginal), use of a silo, and form of nutrition were not significantly associated with NEC development.

Conclusions: The overall incidence of NEC, based on our data, has decreased compared to earlier reports. NEC does complicate the hospital course for patients, significantly increasing duration of in-hospital treatment. NEC in gastroschisis differs in comparison to traditional NEC, presenting later in life. Risk factors identified include low gestational age and low birth weight. Avoiding elective pre-term deliveries may decrease the rate of NEC in gastroschisis.

Introduction

Gastroschisis is a congenital right-sided paraumbilical defect allowing protrusion of intestines and other abdominal viscera out of the abdominal cavity, occurring in approximately 1 in 4000 live births¹ and has increased by about 6% every two years for reasons unknown.² Necrotizing enterocolitis (NEC) is a bacterial infection of the intestine, primarily observed in pre-term and small for gestational age (SGA) babies.³ The reported rate of necrotizing enterocolitis in gastroschisis patients has been quite variable in previous studies.⁴⁻¹⁶ While many physicians today are aware of the association of NEC in gastroschisis patients, the last publication to explore this association in detail and identify possible risk factors of NEC in gastroschisis patients was published over twenty years ago.⁴ We examined our experience with gastroschisis to identify risk factors for necrotizing enterocolitis in this patient population.

Materials and Methods

Patient Population and Data Collection:

From 2001 to 2017, a gastroschisis registry was prospectively maintained at Children's Hospital and Medical Center, the University of Nebraska Medical Center, and Creighton University Medical Center (Omaha, NE). Patient demographics, surgical details, postoperative infections and complications, and length of stay were reviewed. Patients with confirmed NEC were compared to those without NEC. This study was approved by the University of Nebraska Medical Center- Joint Pediatric Institutional Review Board (#445-09-EP).

Definitions: The diagnosis of necrotizing enterocolitis was made using Bell's classification of radiographic and clinical findings (Table 1). Clinical findings of NEC included abdominal distention, hematochezia, and hemodynamic instability. Radiographic findings included pneumatosis intestinalis and portal venous gas. Prematurity was defined as a gestational age less than 37 weeks. Intrauterine growth restriction (IUGR) was defined as a birth weight at or below the 10th percentile for gestational age.

Table 1.

Modified Bell's Criteria were utilized to assist with staging NEC in our study.

Stage	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA Suspected	Temp instability Apnea Bradycardia Lethargy	Gastric retention Abd distention Emesis Heme + stool	Mild ileus Intestinal dilation	NPO Abx x3 days
IB Suspected	Same as IA	Grossly bloody stool	Same as IA	Same as IA
IIA	Same as IA	Same as IB + Absent bowel sounds ± abdominal tenderness	Intestinal dilation Ileus Pneumatosis intestinalis	NPO Abx x 7-10 days
IIB	Same as IA + Metabolic acidosis Thrombocytopenia	Same as IIA + Abdominal tenderness ± abdominal cellulitis or RLQ mass	Same as IIA + ascites	NPO Abx x 14 days
IIIA Intact bowel	Same as IIB + Hypotension Bradycardia Severe apnea DIC neutropenia	Same as IIB + Peritonitis Abdominal distention	Same as IIB	NPO Abx x 14 days Fluid resuscitation Inotropic support Ventilator therapy Paracentesis
IIIB Perforated bowel	Same as IIIA	Same as IIIA	Same as IIIA + Pneumoperitoneum	Same as IIIA + Surgery

Statistical Analysis: Results were expressed as mean±SD or median and interquartile range as appropriate. Relative risks were also assessed. Analysis was performed using the Mann-Whitney test for continuous data and the Fisher's exact test for categorical data. A p-value of less than 0.05 was considered statistically significant.

Results

Two hundred eighteen patients were born with gastroschisis during the time frame of this study. The average gestational age was 35.7 weeks with the average birth weight of 2455 grams. One hundred forty-six (67%) were born via cesarean section. Thirty-three percent (71 of 218) of patients were carried to term with the remaining patients delivered prior to 37 weeks gestation. Patients were kept on the ventilator for an average of 5.6 days (median=2). Silos were used on 45% (98 of 218) of patients for an average of 7.2 days. The average length of stay was 55.2 days (median=36.5) (Table 2).

We observed a 5% rate (11 of 218) of NEC. Five patients (45% of NEC patients) developed recurring NEC and 4 patients (36% of NEC patients) were re-admitted for NEC development following initial discharge (Tables 3 & 4). Variables associated with NEC included low gestational age (34.3 weeks vs 35.8 weeks, P=0.016) and low birth weight (P=0.003). Patients born prior to 37 weeks gestation had a 4.8 times greater risk of developing NEC than those born at term. Rates of IUGR were not statistically different between NEC and non-NEC patients. The method of delivery (cesarean vs vaginal), use of a silo, and form of nutrition were not significantly associated with NEC development. NEC developed on a median of 65 days of life. Infants who developed

Table 2.

Demographics of the total patient population identify an average population of late pre-term infants with a higher-than-normal rate of IUGR.

N=218	Mean ±SD or number (%) or range
Sex	55% Male 45% Female
Gestational age	35.69± 2.00 weeks Range: 28-40weeks
Carried to term	32.6%
Spontaneous labor	46%
Birth weight	2455.0 ± 531.8g Range: 1120-4200g
IUGR Rate	18.4% IUGR
Type of delivery	67% Cesarean 33% Vaginal

NEC stayed a median of 69 days longer than patients who did not develop NEC (104 days vs 35 days, P=0.014) (Tables 3 & 4).

Discussion

The incidence of gastroschisis is roughly 1 in 4,000 live births and appears to increase with a 6% rise every two years for reasons unknown.^{1,2,17-21} Worldwide, the survival rate of infants born with gastroschisis has also improved greatly.^{22,23} One of the known complications of gastroschisis is necrotizing enterocolitis. Although numerous reports of gastroschisis have identified the rate of NEC in gastroschisis, the last series to discuss this complication in detail was published over twenty years ago.^{1-2,4-6,9,11-16,24} From our series of patients with gastroschisis, we reviewed our experience and the recent literature to update what is known about gastroschisis and NEC.

NEC is primarily a disease of very low birth weight, pre-term infants, affecting 10% of infants born weighing less than 1500 grams and resulting in high rates of morbidity and mortality in neonatal intensive care units.^{12,25} Traditional NEC occurs by the second or third week of life.²⁶⁻²⁸ NEC in gastroschisis presents less traditionally. Gastroschisis patients

were diagnosed with NEC much later, with a median day of diagnosis of 65 days of life. Additionally, patients that developed NEC generally weighed more than 1500 grams. Necrotizing enterocolitis is typically treated with gut rest, antibiotics, and, if needed, surgery. Similar methods of treatment were seen in our NEC patients.

Among our NEC patients, only one (9%) required surgical intervention. Our high rate of successful conservative management is unique in comparison to the general neonatal NEC population, which typically requires much higher rates of surgical intervention.²⁶⁻²⁸ Fullerton et al observed a 24% (49 of 204) rate of surgical intervention among gastroschisis patients with NEC.¹² Fullerton et al identified a higher mortality rate among surgical NEC patients compared to those conservatively managed (12.2% vs 3.9%). These findings suggest a different, less severe clinical course of NEC in gastroschisis compared to NEC among very low birth weight neonates. Fullerton et al suggested this fact supports the view that NEC is an "umbrella diagnosis" representing variant underlying pathologies, stating prevention and treatment must be tailored on a patient-to-patient basis. Our study also experienced only one mortality, unlike the high mortality

Table 3.

Gastroschisis patients who developed necrotizing enterocolitis were compared to gastroschisis patients who did not develop necrotizing enterocolitis and data were compared using the Mann-Whitney test for continuous data and the Fisher's Exact test for categorical data.

	NEC Group n=11	Non-NEC Group n=207	P
Sex			0.352
Male	8 (73%)	112 (54%)	
Female	3 (27%)	95 (46%)	
Gestational age	34.3 ± 2.00 weeks	35.8 weeks	0.016
Birth weight	1955 ± 299.0g (1451 to 2435g)	2479 ± 422.2g (1120 to 4200)	0.003
IUGR	4 (36%)	36 (17.4%)	0.121
Delivery Method			1.000
Cesarean Section	7 (64%)	138 (67%)	
Vaginal Delivery	4 (36%)	69 (33%)	
Spontaneous Labor	36% Yes	46% Yes	0.758
Carried to term			0.108
Yes	1 (9%)	70 (34%)	
No	10 (91%)	137 (66%)	
Silo			0.228
Yes	7 (64%)	91 (44%)	
No	4 (36%)	116 (56%)	
Mean Length Range	5.9 ± 2.0 days (2-8 days)	7.3 ± 3.1 days (3-15d)	0.130
Ventilator Days	2 (Q1, Q3= 2, 6)	2 (Q1, Q3= 1, 6)	0.544
Length of Stay	104 days (Q1, Q3= 56, 114)	35 days (Q1, Q3= 26, 56)	0.014

Table 4.

Data on demographics and management of each patient who later developed necrotizing enterocolitis area included below.

Demographics							Diagnosis and Treatment				
EGA (weeks)	Birth Weight (g)	Silo?	DOL Diagnosed (days)	Post Closure Day	LOS (days)	How diagnosed	Bell's Stage	Antibiotics Prescribed	Length Antibiotics Prescribed	Surgery	
1	35	2160	Yes	94	88	80	Bloody stool Pneumatosis Temp. instability Bradycardia Dilated bowel loops	II a	Ampicillin, Gentamicin, Flagyl	8d	
2	32	1780	Yes	63	58	54	Pneumatosis Distended bowel Portal Air Bloody stool Abdominal distension	II a	Ampicillin, Gentamicin, Clendamyacin	8d	
3	36	1724	Yes	54 & 75	47 & 68	114	Pneumatosis Distended bowel Portal Air Ascites	III a	Zosyn, Gentamicin Gentamicin, Zosyn, Flagyl	10d 10 d	
4	37	2435	No	40	40	114	Abdominal distension Portal venous gas Fluid collection	III a	Vancomycin, Gentamicin, Zosyn	14d, 11d, 14d	Yes
5	36	2160	Yes	69 & 87	61 & 79	145	Pneumatosis Bloody stool Distended Bowel	II a	Zosyn Zosyn, Gentamicin, Flagyl	7d 7d, 7d, 7+10 d	
6	35	2255	No	73	73	25	Pneumatosis Bloody stool Intestinal ischemia	II a	Ampicillin, Gentamicin, Flagyl	14d	
7	31	1451	Yes	15	13	199	Pneumatosis Temp. instability Loose stool Lethargy	II b	Gentamicin, Zosyn, Vancomycin	21d, 3d, 9d	
8	34	1990	Yes	42, 62, & 76	35, 55, & 69	104	Pneumatosis Temp. instability Lethargy Abdominal distension Bilious emesis	II a	Zosyn Vancomycin, Zosyn	11d 7d	
9	36	2390	Yes	65 & 79	59 & 73	107	Feeding intolerance Pneumatosis Bloody stool	II a	Zosyn	10d, 7d	
10	31	1700	No	52 & 76	52 & 76	36	Pneumatosis Abdominal distension Hematochezia	II a	Flagyl Zosyn	7d 10d	
11	34	1900	No	41	41	58	Pneumatosis Temp. instability Lethargy	II a	Zosyn Vancomycin	7d	
Mean	34	1990		62.5	58.1	89.8					

rate seen in pre-term infants with NEC and gastroschisis in prior studies.⁸

The last study to explore the association of NEC and gastroschisis in detail was Oldham's study, published over 20 years ago.⁴ Compared to his study, we experienced a relatively low rate of NEC (18.5% vs 5%, 10/54 vs 11/218, respectively). An additional 13 patients in the former study had soft signs of NEC, making the difference even greater. Mortality in Oldham's series was 20% overall compared to the single death in our series. These differences are likely due to advances in perinatal, neonatal, and surgical care of this

complicated patient population. Further, our current series carefully reviewed each NEC case and assigned a Bell's stage to ensure the accuracy of diagnosis. Our rate of NEC in this study was comparable to that rate found in several more recent studies, ranging from 0-15%⁵⁻¹⁶ (Table 5).

Patients in Oldham's study were diagnosed with NEC on an average of 52 days of life, comparable to our study (62.5 days, median 65 days). Both studies documented that patients were readmitted due to development of NEC (Oldham: 3/10, Current Study: 4/11). Fifty-four percent (29 of 54) of patients

in Oldham's study vs. 55% (120/218) in our study underwent primary closures of their abdominal wall defect. Both reported recurring NEC (Oldham: 38%, Current Study: 45%).⁴

Lao et al looked at 2490 gastroschisis patients, with a NEC rate of 5%, which is comparable to our experience (5%).⁴ The median length of stay in Lao's study was 35 days, as opposed to our 104 day median length of stay. Forty percent of NEC patients were born prior to 37 weeks gestation in Lao's study, while the number climbed to 91% in our study. Lao et al identified potential modifiable factors

impacting mortality to include large bowel resection and the presence of bacterial sepsis, both factors associated with NEC. The clinical impact of NEC is consistent in both studies, emphasizing the importance of identifying modifiable factors to reduce the incidence of NEC.

Older reports of gastroschisis have suggested early delivery may be associated with better outcomes.²⁹⁻³¹ This remains controversial. More recent studies show worse outcomes with early delivery, including an increased risk of infectious complications³² and poorer long-term neurodevelopmental outcomes.³³ Maramreddy et al found gastroschisis patients delivered prior to 37 weeks gestation had a 14 times greater risk of morbidities than patients carried to term.⁶ Soares et al also did not support pre-term delivery of fetuses with gastroschisis, finding no benefit to achieving full feeds faster.¹ Huang et al found that gastroschisis pregnancies carried to term led to earlier defect closures, and shorter times to full feeds, suggesting that the benefits of early delivery cannot be substantiated.³⁴ Gorra et al found that pre-term gastroschisis patients experienced poorer developmental outcomes.³³ Pre-term, low birth weight infants have been identified as being at increased risk of infection.³² Patients who developed NEC were on average 1.5 weeks younger at birth and weighed 484 grams less. Infants not carried to term were found to be 4.8 times more likely to develop NEC than infants carried to term. This raises concern about an increased risk of NEC with scheduled pre-term delivery of patients with gastroschisis.

Prior publications have identified the protective nature of human breast milk against late onset sepsis, NEC, and death.^{9,35-36} The etiology of this may be associated with more swift weight gain and reduced feeding intolerance associated with breastfed infants. Unlike these studies, our study found no statistically significant difference in the rate of NEC due to form of nutrition. The practice of initiating trophic feeds within the first 72 hours may also promote digestive tolerance, allowing faster volume increases and helps the neonate achieve full feeds earlier.³⁷

The gastroschisis patients whom develop NEC tend to have a much more complicated medical course, resulting in a longer length of stay on average. NEC can also occur after discharge home, requiring readmission of 4 of our patients. Because NEC presents itself very differently in the gastroschisis population as compared to the general neonatal population, it is vital for neonatologists, surgeons, and general pediatricians to remain vigilant to

Table 5.

Literature review of relevant studies reviewing this topic are summarized below.

Author	Date	Patients	NEC Patients	Rate of NEC	Conclusion
Oldham	1988	54	10	18.5%	High incidence of NEC: 30% readmitted for NEC (3 of 10)
Jayanthi	1998	54	8	15%	Unpasteurized, expressed breast milk may protect from NEC
Snyder	1999	185	8	4%	Increased mortality seen in NEC patients (3 of 8)
Eggick	2006	66	6	9%	No difference seen between NEC and No-NEC patients in regards to birth weight or gestational age
Charlesworth	2007	110	7	6.36%	NEC was more frequent in pre-term (P=0.13) and infants larger than 2kg (P=0.15)
Maramreddy	2009	36	3	8.3%	No NEC found in term infants
Lao	2010	2490	127	5.1%	5% NEC according to PHIS database
Kassa	2011	79	0	0%	No NEC observed
Overcash	2014	191	2	1%	Early gestational age was only variable to predict adverse outcomes
De Buys	2015	68	5	7.4%	Database mortality rate of 12%
Fullerton	2017	4420	204	4.6%	3.9% death rate among NEC patients 49 surgical NEC cases (12.2% mortality among surgical cases)
Gupta	2017	682	26	3.8%	NEC risk associated with outborn status, admission after 2009, and CLABSI
Current Study	2017	218	9	4.1%	NEC more common in small, pre-term infants: 44% readmitted for NEC (4 of 11)

the possibility of acute illness outside of the setting of a patient's initial hospitalization for gastroschisis repair. For those gastroschisis patients who do experience NEC as a complication, conservative management is more frequently successful as compared to NEC in the general neonatal population

Conclusion

The overall incidence of NEC has decreased compared to earlier reports. NEC does not complicate the hospital course for patients, significantly increasing duration of in-hospital treatment. NEC in gastroschisis differs in comparison to traditional NEC, by presenting later in life. Risk factors identified for NEC in gastroschisis include low gestational age and low birth weight. Avoiding elective pre-term deliveries may decrease the rate of NEC in gastroschisis. ■

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