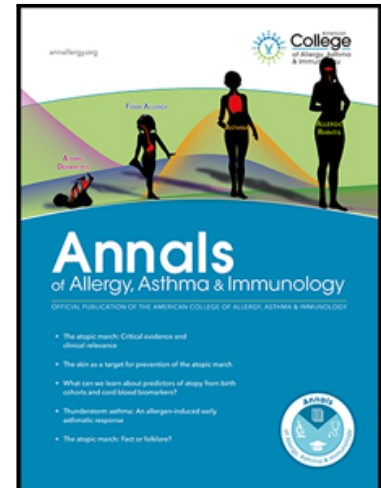


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Differentiation of food protein-induced enterocolitis syndrome misleading to necrotizing enterocolitis

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Hye Ran Yang: designing the study, interpreting data, drafting the manuscript, giving final approval of the version to be published

Conflict in Interest

The authors declare no conflicts of interest

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Clinical Trial Registration

This study was approved by the Institutional Review Board(IRB)/ethics committee of Seoul National University Bundang Hospital(SNUBH) (No. B-2006-616-107). Also the IRB/ethics committee of the SNUBH has waived informed consent for this study.

Keywords

Enterocolitis, Necrotizing; Food protein-induced enterocolitis syndrome; Preterm infant; Birth of Full-term infant

Abbreviations/Acronyms

Food protein-induced enterocolitis syndrome; FPIES

Necrotizing enterocolitis; NEC

Gastrointestinal; GI

Immunoglobulin E; IgE

Seoul National University Bundang Hospital; SNUBH

Pneumatosis intestinalis; PI

Gestational age; GA

Oral food challenge; OFC

Institutional Review Board; IRB

Whole blood cell; WBC

Nil per os; NPO

Background: Food protein-induced enterocolitis syndrome (FPIES) is a rare non-IgE-mediated food allergy with necrotizing enterocolitis (NEC)-like symptoms, but requires differential diagnosis, as treatments differ.

Objective: This study aimed to evaluate the clinical, laboratory, and radiological findings that differentiate FPIES from NEC in preterm and term infants.

Methods: Clinical features, comorbidities, laboratory and radiological findings of neonates with presumed NEC were reviewed retrospectively and compared between FPIES and NEC in preterm and term infants who were admitted to the neonatal intensive care unit at Seoul National University Bundang Hospital between May 2003 and February 2020.

Results: 10 of 150 (6.7%) preterm and 17 of 38 (44.7%) term infants with presumed NEC were confirmed to have FPIES; the remainder had NEC by modified Bell's criteria. Demographics and comorbidities were similar between these groups. Symptoms such as hematochezia, shock, leukocytosis, peripheral eosinophilia, and feeding of extensively hydrolyzed milk formula or elemental formula after discharge were significantly different between the two groups in term infants ($P < 0.05$), but not in preterm infants. On abdominal ultrasonography, pneumatosis intestinalis was more common among preterm FPIES (44.4%) than NEC cases (21.6%) ($P = 0.044$). Among preterm infants, 4 FPIES (40%) and 25 NEC (17.9%) cases required surgery ($P = 0.102$).

Conclusion: Differentiating FPIES in neonates with a suspicion of NEC is important, as dietary elimination of the triggering milk protein can be recommended instead of prolonged fasting and antibiotic treatment, indicated for NEC, in both term and preterm infants.

INTRODUCTION

Necrotizing enterocolitis (NEC) is the most common life-threatening condition of the gastrointestinal (GI) tract in neonates, with a mortality rate of 20%–30%.¹ The etiology of NEC is diverse and multifactorial. Although its specific cause is uncertain, immaturity of the GI tract and systemic immunity are significant factors²⁻⁴, implying that characteristics of NEC in preterm and full-term infants would differ.⁵

Food protein-induced enterocolitis syndrome (FPIES) is a rare non-immunoglobulin E (IgE)-mediated food allergy that is clinically diagnosed based on the GI and systemic symptoms that develop after exposure to a specific food allergen, which improve with dietary elimination of the triggering food.⁶⁻⁸ Severe symptoms commonly result in a misdiagnosis of sepsis.⁹

Given the similarity between the clinical manifestations of FPIES and NEC in the neonatal period, these conditions are difficult to distinguish in practice.⁹ Therefore, if not suspected by clinicians, FPIES could be misdiagnosed as NEC, leading to unnecessarily prolonged antibiotic use or fasting, and persistent symptoms that are refractory to treatment.¹⁰ Nevertheless, few studies have reported on the differentiation of FPIES from NEC in full-term and preterm neonates.

In the present study, we aimed to evaluate the proportion of FPIES among full-term or preterm neonates initially diagnosed with NEC and compare the demographic and clinical features, underlying comorbidities, laboratory and radiological findings, and clinical outcomes that help differentiate FPIES from NEC in preterm and term infants.

METHODS

Subjects and diagnosis of NEC

Initially, 232 infants (53 term and 179 preterm infants) who were admitted to the neonatal intensive care unit at Seoul National University Bundang Hospital (SNUBH) between May 2003 and February 2020 were diagnosed with NEC.

Diagnosis and staging of NEC were based on the modified Bell's criteria for NEC; 1) systemic signs, including apnea, lethargy, temperature instability, bradycardia, hypotension, metabolic acidosis, thrombocytopenia, neutropenia, and disseminated intravascular coagulation; 2) intestinal signs, including abdominal distention, elevated pre-gastric residuals, absent bowel sounds, abdominal tenderness, and cellulitis; and 3) radiological signs, including ileus, intestinal dilation, pneumatosis intestinalis (PI), portal vein gas, ascites, and pneumoperitoneum.¹⁰ Infants who were transferred to other hospitals (n = 18), those who were diagnosed with NEC > 30 days after birth (n = 14), and those with congenital GI tract anomalies (n = 12) were excluded (Fig. 1). Finally, a total of 188 NEC cases were included in this study (Fig. 1).

Patients who were initially diagnosed with NEC were considered to have “presumed NEC” and were categorized according to gestational age (GA) as follows; 1) full-term infants born after 37 weeks of GA (n = 38) and 2) preterm infants born before 37 weeks of GA (n = 150). Data on demographic factors, GA, perinatal history, family history of allergy, age at diagnosis, clinical symptoms and signs related to NEC or FPIES, comorbidities, clinical course and outcome, type of feeding, and laboratory and radiological findings were retrospectively reviewed from medical records. The following comorbidities previously known as NEC risk factors were reviewed^{5, 11, 12}; 1) congenital heart diseases, including patent ductus arteriosus; 2) acute gastroenteritis, proven through tests for stool microorganisms; 3) birth asphyxia, with Apgar score < 7 at 5 minutes after birth; 4) respiratory distress syndrome, requiring

assisted mechanical ventilation with or without surfactant replacement therapy; 5) transient tachypnea of newborn; 6) pneumothorax; 7) pulmonary hypertension; 8) sepsis or shock, applied antibiotics with hemodynamic instability, with or without proven culture and strong suspicion of sepsis; 9) hypoglycemia (glucose level: < 40 mg/dL) at birth; 10) polycythemia with hematocrit > 65%; and 11) seizures.

Laboratory tests and radiological investigation

Laboratory tests, including those for complete blood cell count with differential count, and highly sensitive C-reactive protein were reviewed retrospectively.

Findings of simple abdominal radiography, including cross-table lateral view and abdominal ultrasonography performed by pediatric radiologists, were reviewed in all enrolled patients and described as either “normal” or “abnormal,” including intestinal dilatation, ileus, PI, ascites, and pneumoperitoneum.¹⁰

Diagnosis of FPIES

The International Consensus Guideline for the Diagnosis and Management of FPIES was used for the diagnosis of FPIES, requiring the fulfillment of the major criterion and three or more minor criteria.⁹ The major criterion was vomiting 1–4 h after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms.⁹ The minor criteria included the following nine clinical features: a second episode of repetitive vomiting after eating the same suspect food, repetitive vomiting episodes 1–4 h after eating a different food, extreme lethargy, marked pallor with any suspicious reaction, need for emergency department visit, need for intravenous fluid support, diarrhea within 24 h, hypotension, and hypothermia.⁹

In this study, FPIES was suspected among neonates with presumed NEC who met the

above diagnostic criteria and the final diagnosis of FPIES was made based on the oral food challenge (OFC) test or positive findings clinically corresponding to OFC by pediatric gastroenterologists and neonatologists. As for the OFC test protocol in suspected patients, oral trophic feeding was initiated with cow's milk 10 ml, containing 0.14~0.15 g of cow's milk protein per kilogram of body weight according to the International consensus guidelines of OFC protocol,^{9,13,14} which described the administration of challenge food at a dose of 0.06 to 0.6 g per kilogram of body weight.⁹ In addition, it was confirmed that clinical symptoms were completely resolved and did not recur when extensively hydrolyzed hypoallergenic formula or elemental formula was administered to neonates diagnosed with FPIES according to the OFC test.

Statistical analyses

All statistical analyses were performed using SPSS Statistics (version 22.0; IBM Corporation, New York, NY). Continuous variables, described as median (range), were analyzed using the Mann–Whitney test. Categorical variables, described as numbers (%), were analyzed using Fisher's exact test. In all statistical analyses, statistical significance was set at $p < 0.05$.

This study was approved by the Institutional Review Board (IRB) / ethics committee of the SNUBH (No. B-2006-616-107). The IRB/ethics committee of the SNUBH has waived informed consent for this study. This study was performed in accordance with the Declaration of Helsinki and the approved guidelines and regulations.

RESULTS

Patient characteristics

A total of 188 neonates initially diagnosed with NEC were recruited retrospectively by a review of medical records and were categorized as full-term ($n = 38$) and preterm ($n = 150$) infants. The differences in basic clinical characteristics are described in Table 1. Among infants with presumed NEC, FPIES was diagnosed using an OFC test ⁹ in 17 of 38 (44.7%) term infants and 10 of 150 (6.7%) preterm infants.

Basic clinical characteristics and comorbidities

Basic demographics and comorbidities, which are risk factors for NEC in term infants, were not significantly different between the FPIES and NEC groups in both term and preterm infants (Table 2).

Clinical manifestations, laboratory findings, and radiological findings

A comparison of the clinical symptoms as well as the laboratory and radiological findings between the FPIES and NEC groups in term and preterm infants is shown in Table 3.

Regarding clinical manifestations in term infants with presumed NEC, hematochezia was more frequent in the FPIES group than in the NEC group ($P = 0.004$). Shock was also significantly more frequent in the FPIES group than in the NEC group ($P = 0.023$) among term infants (Table 3). The whole blood cell (WBC) count and eosinophil percentage were significantly different between the FPIES and NEC groups (Table 3). Radiological findings were similar between the FPIES and NEC groups in term neonates (Table 3).

In preterm infants with presumed NEC, no statistically significant differences in clinical symptoms and laboratory findings between the FPIES and NEC groups were found (Table 3). However, among preterm infants, among radiological findings, PI was significantly more

frequent in the FPIES group than in the NEC group ($P = 0.044$), while ileus was more frequent in the NEC group than in the FPIES group ($P = 0.159$). Additionally, radiological findings of intestinal perforation were observed in a number of NEC cases, but not in FPIES cases among preterm infants (Table 3).

Clinical outcomes

Regarding clinical outcomes of term neonates initially diagnosed with presumed NEC, no perforation or operation cases were reported in the FPIES group, whereas one (4.8%) perforation case and two (9.5%) bowel resection cases were reported in the NEC group of term infants ($P = 0.492$).

In term infants, the type of feeding at the time of discharge was determined as extensively hydrolyzed hypoallergenic milk formula in 6 (35.3%) infants, elemental formula in 10 (58.8%) infants, and maternal dietary elimination along with breastfeeding in one (5.9%) infant in the FPIES group. Among term infants with NEC, cow's milk formula was used in 8 (42.1%) infants, extensively hydrolyzed hypoallergenic formula was used in 3 (15.8%) infants, and maternal dietary elimination with breast milk was used in only one (5.3%) infant; elemental formula was not used in any infant ($P < 0.001$; Table 3). Among preterm infants with FPIES, extensively hydrolyzed hypoallergenic and elemental formula were used in 3 (30%) and 6 (60%) infants, respectively. Among preterm infants with NEC, 79 (64.8%) infants received cow's milk formula and 32 (26.2%) infants received breast milk ($P < 0.001$) (Table 3).

DISCUSSION

To date, no study has investigated the proportion of FPIES in neonates who were initially presumed to have NEC. In addition, the prevalence of FPIES involving cow's milk is

uncertain, with one single-center study reporting it to be 0.34%.⁷ Nevertheless, some reports indicate that the incidence of FPIES has recently increased.^{15, 16} Here, we determined the proportion of FPIES among term and preterm neonates who were initially suspected of having NEC in a single-center study. In our study, FPIES was diagnosed in 14.4% of infants with presumed NEC. Subgroup analysis showed that 44.7% of term and 6.7% of preterm infants with presumed NEC were diagnosed with FPIES. The number of NEC cases was clearly higher in preterm infants than in term infants, as reported previously.^{17, 18} Our results indicate that there may be a markedly higher proportion of FPIES cases than expected, particularly among full-term neonates with presumed NEC. Under clinical suspicion of FPIES as a possible differential diagnosis, definite diagnoses of FPIES may increase accordingly.

Prematurity is the main risk factor for developing NEC, and many other risk factors can be present in preterm infants. In our study, although the difference between FPIES and NEC was not statistically significant in terms of demographics and comorbidities, the onset age in preterm neonates with NEC was relatively younger than that in preterm neonates with FPIES. Notably, four preterm neonates who were finally diagnosed with FPIES developed cow's milk protein allergy, including IgE mediated and non-IgE mediated allergy, after bowel resection due to NEC^{19, 20}; hence, the age of onset of FPIES was relatively older than that of NEC in preterm infants.

FPIES may present with GI symptoms, such as repetitive vomiting, decreased activity, pallor, watery or bloody diarrhea, and hemodynamic instability, all of which also occur in NEC.⁹ On comparison of the clinical manifestations of NEC and FPIES in the present study, hematochezia and shock were more frequently observed in the FPIES group than in the NEC group among full-term infants, but clinical symptoms were similar between groups among preterm infants.

Although laboratory findings are not essential for FPIES diagnosis, leukocytosis is accompanied by eosinophilia and thrombocytosis in FPIES.²¹ In our study, leukocytosis and increased eosinophil percentage without peripheral eosinophilia were noted in full-term neonates with FPIES, consistent with previous findings, while thrombocytosis did not reveal statistically significant difference in this study.¹ In contrast, in preterm infants, there were no statistically significant differences in laboratory findings between the two groups. This may be because FPIES may occur secondary to NEC in preterm infants.

According to a recent study, typical abdominal ultrasound features of NEC were observed in patients with FPIES.²² In our study, there were no significant differences in radiological findings between FPIES and NEC in term infants, whereas PI was more commonly present in the FPIES group than in the NEC group among preterm infants. In contrast, ileus was more frequent in the NEC group than in the FPIES group among preterm patients, and radiological evidence of intestinal perforation was present only in preterm patients with NEC, but not in preterm patients with FPIES. Although PI is known as a typical radiologic finding of NEC, it could also be shown in cases with FPIES in our study as similar to the results from a recent study.²² Therefore, clinical findings and disease course may also be important in diagnosing FPIES beyond the presence of PI on abdominal ultrasound. Additionally, even in term infants, perforation was noted in only one case in the NEC group; there was no case of perforation in the FPIES group. This may be because there were relatively more severe cases at risk of intestinal perforation among NEC patients than in milk allergy cases.

For clinical outcomes, since there was no perforation, surgery was not necessary in either term or preterm infants with FPIES, as reported previously.²³ In 4 preterm neonates in the FPIES group who underwent abdominal surgery because of NEC or meconium plug syndrome, bowel resection was followed by the development of FPIES. Several previous studies suggested that the risk of food allergy, whether IgE mediated or non-IgE mediated,

may increase because of the exposure of undigested food protein in neonatal short bowel syndrome.²⁴⁻²⁶ Likewise, it can be assumed that FPIES might also develop after massive bowel resection in the present study. Further study is needed in the future that can prove the relationship between bowel resection and food sensitization in neonatal patients.

Although there were no significant differences in the duration of nil per os (NPO), this period was relatively longer in preterm FPIES than in preterm NEC neonates in our study. When NEC is suspected, NPO and antibiotics are empirically implemented as treatments. However, without clinical recognition of FPIES as a possible diagnosis, repetitive symptoms can occur in infants with FPIES with the re-introduction of formula feeding and may result in treatment failure and recurrence of disease, although this can be an unintentional OFC test diagnosing FPIES in practice.¹⁰ This may explain why the NPO duration was longer in preterm patients with milk protein allergy than in those with NEC in our study.

In general, treatment of FPIES involves the dietary elimination of triggering food.⁹ In neonates, as cow's milk protein is a major allergen, dietary recommendations usually include switching to hypoallergenic or elemental formula or breast milk with maternal dietary elimination. In this study, all FPIES patients avoided the cow's milk formula after final diagnosis; one of the three dietary strategies described above was used instead. In both term and preterm infants, elemental formula feeding, followed by hypoallergenic formula feeding, were mainly advised in the FPIES group. In contrast, in the NEC groups, cow's milk formula or breastfeeding was used in most term and preterm infants. The hypoallergenic formula was used only in a small proportion of patients, and no patient with NEC was fed with the elemental formula in our study.

Although FPIES is a non-IgE-mediated food allergy, some patients can have comorbidities related to atopic diseases such as eczema and food IgE sensitization.⁹ In previous studies, IgE-mediated food allergy was noted in 2–12% of FPIES patients.^{15, 16, 27} Therefore, further

studies may be needed on the differences in IgE sensitization to cow's milk protein between NEC and FPIES in preterm and term infants and risk factors for IgE sensitization and cross-reactivity to dietary proteins during long-term follow-up after the onset of FPIES.

Our study has some limitations. First, this study was designed and performed as a retrospective, single-center study. Second, because FPIES was diagnosed in a small portion of neonates with presumed NEC, the size of the FPIES groups was relatively smaller than that of the NEC groups. Nevertheless, there have been no studies on the proportion of FPIES in presumed NEC or a comparison of demographic, clinical, laboratory, and radiological findings and clinical outcomes of FPIES and NEC in term and preterm neonates. The results of our study may be valuable in differentiating FPIES from NEC in practice to avoid misdiagnosis and improper management.

In conclusion, differentiating FPIES from NEC in neonates with NEC showing an atypical clinical course despite proper management is necessary. Hematochezia and shock, along with laboratory findings of leukocytosis and elevated eosinophil levels, may assist in diagnosing FPIES rather than NEC in term infants. Furthermore, it should be emphasized that radiological findings of intramural gas in preterm infants with repetitive GI symptoms after the beginning of feeding might also indicate FPIES. With awareness of FPIES as a possible differential diagnosis, an accurate diagnosis of FPIES as milk protein allergy can be made. Because NEC is the most common life-threatening condition of the GI tract in neonates, concern for NEC should be prioritized. However FPIES should be on differential diagnosis in presence of recurrent GI symptoms despite appropriate NEC treatment, such as dietary elimination of triggering milk protein. In such circumstances, unnecessary and prolonged therapeutic fasting and use of antibiotics can be avoided if FPIES is diagnosed as suspected by the clinician.

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Table 1. Basal clinical characteristics of the study subjects with presumed NEC

Variable	Term presumed NEC* (n = 38)	Preterm presumed NEC* (n = 150)	p value
Male, n (%)	17 (44.7)	78 (52.0)	0.470
GA at birth, week (median [range])	38.7 (37.0–41.0)	29.0 (23.14–36.9)	< 0.001
Age at diagnosis, day (median [range])	8 (1–30)	15 (1–62)	0.019
Body weight at birth, g (median [range])	3,200 (1,902–3,950)	1,125 (430–3,315)	< 0.001
Vaginal delivery, n (%)	18 (50.0)	33 (22.0)	0.001
Comorbidity, n (%)			
Low birth weight (< 1,500 g)	2 (5.3)	144 (96.0)	< 0.001
Congenital heart disease	4 (10.5)	83 (55.3)	< 0.001
Acute gastroenteritis	4 (10.5)	14 (9.4)	0.765
Birth asphyxia	5 (13.2)	99 (66.0)	< 0.001
Respiratory distress	2 (5.3)	120 (80.0)	< 0.001
Transient tachypnea of newborn	1 (2.7)	1 (0.7)	0.364
Pneumothorax	0 (0.0)	6 (4.0)	0.603
Pulmonary hypertension	1 (2.7)	21 (14.0)	0.052
Sepsis or shock	1 (2.7)	32 (21.3)	0.007
Hypoglycemia	1 (2.7)	13 (8.7)	0.308
Polycythemia	0 (0.0)	4 (2.7)	0.584
Seizure	3 (7.9)	10 (6.7)	0.728
Finally diagnosed as FPIES, n (%)	17 (44.7)	10 (6.7%)	< 0.001

Data are expressed as number (%) for numeric parameters and median (range) for continuous parameters.

Continuous variables were analyzed using the Mann–Whitney test, and categorical variables were analyzed using Fisher’s exact test.

Statistical significance was set at $p < 0.05$.

*Neonates who were initially presumed to have necrotizing enterocolitis based on the modified Bell’s criteria,

NEC, necrotizing enterocolitis; GA, gestational age; FPIES, food protein-induced enterocolitis syndrome

Table 2. Comparison of demographics and comorbidities between the FPIES group and the NEC group in term and preterm infants initially diagnosed with presumed necrotizing enterocolitis

Variable	Term			Preterm		
	FPIES (n = 17)	NEC (n = 21)	<i>p</i> value	FPIES (n = 10)	NEC (n = 140)	<i>p</i> value
Male, n (%)	7 (41.2)	11 (52.4)	0.752	6 (60.0)	72 (51.4)	0.747
GA, week (median [range])	39.1 (37.0–40.6)	38.8 (37.0–41.0)	0.525	32.1 (25.9–34.7)	28.9 (23.1–26.9)	0.190
Age at diagnosis, day [median (range)]	9 (2–30)	6 (1–28)	0.152	17.5 (7–29)	15 (1–62)	0.860
Body weight, g (median [range])	3,200 (2,250–3,950)	3,040 (1,902–3,720)	0.144	1,425 (620–2,450)	1,115 (430–3,315)	0.340
Vaginal delivery, n (%)	10 (62.5)	8 (40.0)	0.315	0 (0.0)	33 (23.6)	0.118
Comorbidity, n (%)						
LBW (<1,500 g)	0 (0.0)	2 (9.5)	0.492	10 (100.0)	134 (95.7)	1.000
CHD	1 (5.9)	3 (14.3)	0.613	6 (60.0)	77 (55.0)	1.000
Acute gastroenteritis	3 (17.6)	1 (4.8)	0.307	0 (0.0)	14 (10.0)	1.000
Birth asphyxia	2 (11.8)	3 (14.3)	1.000	5 (50.0)	94 (67.1)	0.309
Respiratory distress	2 (11.8)	0 (0.0)	0.193	6 (60.0)	114 (81.4)	0.114
TTN	0 (0.0)	1 (4.8)	1.000	0 (0.0)	1 (0.7)	1.000
Pneumothorax	0 (0.0)	0 (0.0)	1.000	0 (0.0)	6 (4.3)	1.000
Pulmonary hypertension	1 (5.9)	0 (0.0)	0.447	1 (10.0)	20 (14.3)	1.000
Sepsis or shock	0 (0.0)	1 (4.8)	1.000	4 (40.0)	28 (20.0)	0.222
Hypoglycemia	0 (0.0)	1 (4.8)	1.000	0 (0.0)	13 (9.3)	0.602
Polycythemia	0 (0.0)	0 (0.0)	1.000	0 (0.0)	4 (2.9)	1.000
Seizure	1 (5.9)	2 (9.5)	1.000	0 (0.0)	10 (7.1)	1.000

Data are expressed as number (%) for numeric parameters and median (range) for continuous parameters.

Continuous variables were analyzed using the Mann–Whitney test, and categorical variables were analyzed using Fisher’s exact test. Statistical significance was set at $p < 0.05$.

FPIES, food protein-induced enterocolitis syndrome; GA, gestational age; LBW, low birth weight; CHD, congenital heart disease; TTN, transient tachypnea of newborn

Table 3. Comparison of clinical features, laboratory findings, radiologic findings, and outcomes between the FPIES group and the NEC group in term and preterm infants with presumed NEC

Variable	Term				Preterm			
	Total (n = 38)	FPIES (n = 17)	NEC (n = 21)	p value	Total (n = 150)	FPIES (n = 10)	NEC (n = 140)	p value
Symptom, n (%)								
Hematochezia	26 (68.4)	16 (94.0)	10 (47.6)	0.004	73 (48.7)	8 (80.0)	65 (46.4)	0.052
Vomiting	19 (50.0)	9 (52.9)	10 (47.6)	1.000	45 (30.0)	2 (20.0)	43 (30.7)	0.724
Abdominal distention	13 (34.2)	6 (35.3)	7 (33.3)	1.000	104 (69.3)	4 (40.0)	100 (71.4)	0.069
Shock	10 (26.3)	8 (47.1)	2 (9.5)	0.023	56 (37.3)	5 (50.0)	51 (36.4)	0.502
Laboratory finding, median (range)								
Hemoglobin (g/dL)	15.4 (10.7–19.3)	15.4 (10.7–18.6)	15.5 (12.2–19.3)	0.056	12.3 (7.4–20.0)	12.4 (9.6–15.5)	12.3 (7.4–20.0)	0.142
WBC (/μL)	11,360 (5,600–23,250)	14,770 (9,300–22,860)	10,300 (5,600–23,250)	0.048	9,870 (1,470–52,850)	10,730 (2,760–22,180)	9,850 (1,470–52,850)	0.869
Platelet (/μL)	314,000 (135 k–384 k)	319,000 (222 k–478 k)	289,000 (135 k–519 k)	0.121	257,000 (6 k–770 k)	299,500 (77 k–511 k)	257,000 (6 k–770 k)	0.436
ANC (/μL)	5,657.5 (1,529–19,065)	6,972.0 (2,663–13,739)	4,426.5 (1,529–19,065)	0.377	4,330.0 (221–34,353)	3,839.0 (524–14,861)	4,330.0 (221–34,353)	0.243
Eosinophil (%)	3.2 (0–9.2)	4.35 (1.2–8.6)	2 (0–9.2)	0.016	2.2 (0–25.1)	2.15 (0–8.0)	2.2 (0–25.1)	0.893
hsCRP (mg/dL)	0.1 (0.01–3.91)	0.1 (0.09–3.91)	0.1 (0.01–0.77)	0.352	0.2 (0.01–20.94)	0.1 (0.08–20.94)	0.2 (0.01–15.70)	0.477
Radiological finding, n (%)				0.944				
Normal	8 (21.6)	3 (18.8)	5 (23.8)	0.080	36 (24.3)	3 (30.0)	33 (23.7)	0.083
Ileus	21 (56.8)	10 (62.5)	11 (52.4)	1.000	67 (45.3)	2 (20.0)	65 (46.8)	0.159
Pneumatosis intestinalis	7 (18.9)	3 (18.8)	4 (19.0)	0.078	34 (23.0)	4 (40.0)	30 (21.6)	0.044
Perforation	1 (2.7)	0 (0.0)	1 (4.8)	<0.001	11 (7.4)	0 (0.0)	11 (7.9)	<0.001
NEC grading, n (%)				0.298				
1a	16 (42.1)	5 (29.4)	11 (52.4)		50 (33.3)	1 (10.0)	49 (35.0)	

1b	10 (26.3)	5 (29.4)	5 (23.8)		37 (24.7)	3 (30.0)	34 (24.3)	
2a	9 (23.7)	5 (29.4)	4 (19.0)		24 (16.0)	2 (20.0)	22 (15.7)	
2b	2 (5.3)	2 (11.8)	0 (0.0)		14 (9.3)	3 (30.0)	11 (7.9)	
3a	0 (0.0)	0 (0.0)	0 (0.0)		7 (4.7)	1 (10.0)	7 (5.0)	
3b	1 (2.6)	0 (0.0)	1 (4.8)		18 (12.0)	0 (0.0)	17 (21.1)	
Outcome								
NPO duration (day)	3 (0-14)	3 (0-8)	3 (1-14)	0.774	5 (0-35)	8 (3-35)	4 (0-21)	0.089
Operation	2 (5.3)	0 (0.0)	2 (9.5)	0.492	29 (19.3)	4 (40.0)	25 (17.9)	0.102
Survival	37 (100.0)	17 (100.0)	21 (100.0)	1.000	133 (88.7)	9 (90.0)	124 (88.6)	0.890
Type of feeding at the time of discharge				< 0.001				< 0.001
Cow's milk formula	8 (22.8)	0 (0.0)	8 (42.1)		79 (60.8)	0 (0.0)	79 (64.8)	
Extensively hydrolyzed hypoallergenic formula	9 (25.0)	6 (35.3)	3 (15.8)		7 (5.4)	3 (30.0)	4 (3.3)	
Elemental formula	10 (27.8)	10 (58.8)	0 (0.0)		8 (6.2)	6 (60.0)	2 (1.6)	
Breast milk feeding	7 (19.4)	0 (0.0)	7 (36.8)		33 (25.4)	0 (0.0)	32 (26.2)	
Maternal dietary elimination	2 (5.6)	1 (5.9)	1 (5.3)		3 (2.3)	1 (10.0)	3 (2.5)	

Data are expressed as number (%) for numeric parameters and median (range) for continuous parameters.

Continuous variables were analyzed using the Mann-Whitney test, and categorical variables were analyzed using Fisher's exact test.

Statistical significance was set at $p < 0.05$.

FPIES, food protein-induced enterocolitis syndrome; WBC, white blood cell; ANC, absolute neutrophil count; hsCRP, highly sensitive C-reactive protein; NEC, necrotizing enterocolitis; NPO, nil per os

Figure Legend

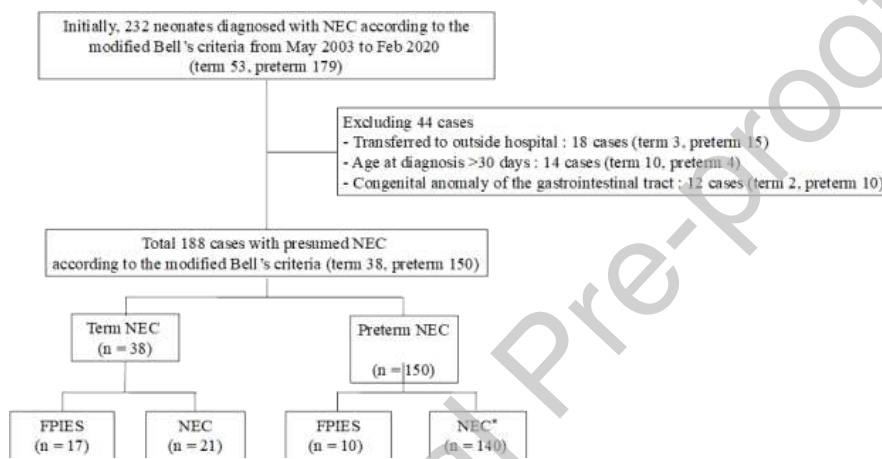


Fig. 1. Process of inclusion and exclusion of cases

*Patients who were initially diagnosed with presumed necrotizing enterocolitis (NEC) were classified into the food protein induced enterocolitis syndrome (FPIES) group and the NEC group according to the International guidelines for diagnosing FPIES.