



## Understanding of Clinical Presentation, Timing of Presentation and the Outcome in the Development of Necrotizing Enterocolitis

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### Abstract

**Background:** *Necrotizing Enterocolitis (NEC) remains as the disease with significant morbidity and mortality in preterm infants. The lack of universally reliable diagnostic criteria makes it difficult to establish the diagnosis. By understanding the clinical presentation and timing of presentation in the development of NEC, it will help in the management of the disease, thus contributing in the outcome of the disease. Incomplete knowledge regarding NEC impedes the diagnosis and treatment of patients with the disease.*

**Objective:** *This study was initiated to give a better understanding regarding the clinical features and onset of NEC in neonatal, to evaluate the correlation of clinical presentation, timing of development and the outcome of the disease among Chinese infants in Suzhou.*

**Methods:** *This non-interventional, retrospective study was conducted at Children Hospital of Soochow University including infants admitted to the Neonatal Department during 5 years period, from June 2010 to June 2015, diagnosed with Necrotizing Enterocolitis. Data used in this study were collected from the hospital database. Cases with confirmed diagnosis of Necrotizing Enterocolitis (based on Bell staging) were evaluated. Cross tabulation, chi square and regression analysis test were used to find the correlation and  $P < 0.05$  was considered to be the statistically significant value.*

**Results:** *A total of 100 infants (N=100) included in this study, 61% were male and 39 % were female. As expected preterm is highly associated with the development of NEC, but the more premature the infant the later will be the time presentation. Early-onset NEC infants had lower incidence of respiratory distress syndrome. Early identification and better understanding of clinical features of NEC in neonatal may reduce the incidence and improve the outcome in NEC. Further studies are required to understand the etiology of this disease process.*

**Conclusion:** *1) Despite improvements in neonatal intensive care, NEC remains a critical disease in preterm infants and confers many serious complications and mortality. 2) Preterm newborns are highly associated with the development of NEC. 3) The more premature the infant, the later will be the onset of the disease. 4) Early-onset NEC infants had lower incidence of respiratory distress syndrome. 5) Proposition that in preterm infants clinical presentation of NEC differs from that in term infants has been made, in which term infants is associated more with underlying congenital conditions (e.g congenital heart disease) 6) Clear diagnostic criteria need to be used consistently to differentiate between NEC and other entities.*

**Keywords:** *Necrotizing Enterocolitis / Clinical Presentation / Neonatal / Timing / Outcome.*

### INTRODUCTION

Necrotising enterocolitis (NEC) is an acquired gastrointestinal disease associated with significant morbidity and mortality in preterm infants. The

more premature and lower birth weight, the higher mortality and increased risk of serious abnormal condition, resulted from the disease. Its incidence ranged between 6% and 7% in recent multicentre studies of low birth weight infants, although with

variations among hospitals. The overall mortality rate is 20% to 40%, depending on the disease severity and need for surgical intervention, and NEC associated with complications, including intestinal strictures, short bowel syndrome and increased risk of neurodevelopmental delay. Unfortunately, the number of diagnosed cases of NEC has not decreased with advancements in neonatal care; in fact, it is projected to increase because of improved survival rate of the most premature infants, thereby creating a need of a better understanding on the clinical presentation and onset on the development of the disease to create an effective preventive strategies for a better outcome of the disease.

NEC is defined as an inflammatory intestinal disorder predominantly occurs in premature infants, especially those with birth weight less than 1000g and born prior to 28 weeks' gestation, characterized by variable damage to the intestinal tract, ranging from mucosal injury to full-thickness necrosis and perforation. The clinical features of NEC varies among abdominal distension, emesis, lethargy, apnoea, bradycardia and bloody stools. The laboratory assessment may reveal neutrophilia or neutropenia, anemia, electrolyte imbalances including hyponatremia, metabolic acidosis, glucose instability, elevated C - reactive protein and thrombocytopenia. When the disease is severe, it can lead to respiratory failure and cardiovascular instability.

A staging system for NEC developed by Bell and colleagues in 1978 and later revised can be used to determine the severity of the disease and guide the treatment. Stage I includes nonspecific abdominal symptoms and systemic signs of infection. Stage II pertains to a more advanced disease with continued nonspecific symptoms combined with radiographic findings including pneumatosis intestinalis. Stage III is the most severe stage and is associated with intestinal perforation, peritonitis, and increased mortality. Radiographic manifestations of NEC include pneumatosis intestinalis, portal venous gas, and pneumoperitoneum.

The pathogenesis of NEC is complex and

multifactorial, thus remains incompletely understood. Defining and predicting the incidence of Neonatal NEC is difficult but important. This retrospective study is aimed to a better understanding of clinical presentation of neonatal NEC, timing of presentation and the suspected outcome on the development of Neonatal NEC, so it can be diagnosed as early as possible and be treated and prevented accordingly. In this study we used Children's Hospital of Soochow University's database of admitted infants diagnosed with NEC in 5 years period (June 2010 to June 2015), then analysed it to estimate the correlation between clinical presentation of the development of NEC, timing of presentation and the outcome.

The clinical presentation of NEC includes nonspecific aspects of the history, such as vomiting, diarrhea, feeding intolerance and high gastric residuals following feeding. More specific GI tract symptoms include abdominal distention and occult blood in the stools.

With disease progression, abdominal tenderness, abdominal wall edema, dilated loop of bowel may develop. Systemic signs such as apnea, bradycardia, and shocks are indicators of physiologic instability. The overall mortality for NEC ranges from 20-40% but approaches 100% in infants with the most severe form of the disease. Because NEC afflicts 2-5% of all NICU admissions and causes serious morbidity, NEC continues to impose a heavy burden on neonatal population

## 1. MATERIALS AND METHODS

### 1.1 Study Design

A non-interventional, retrospective study was carried out to estimate and get a better understanding in the clinical presentation in development of NEC in neonatal. The data used in the study was retrospectively collected and recorded from the hospital database. Medical history of 100 infants with confirmed diagnosis of NEC, admitted to the Children Hospital Affiliated to Soochow University, from June 2010 to June 2015 were evaluated.

### 1.2 Patient Selection

Infants that are selected for this study were patients of Neonatal Department of Children Hospital Affiliated with Soochow University with confirmed diagnosis of Necrotizing Enterocolitis. The diagnosis of NEC was defined according to the Bell staging criteria based on clinical features and radiological evidence. The gestational age at birth as assessed. Neonates dying the first day of life, born less than 23 week's Gestational Age and those with any immunodeficiency disease, inherited metabolic disorder, and major gastrointestinal malformations were excluded. The data analysed not included information of the nutritional treatment received by individual infants. All neonates were uniformly managed as per standard neonatal intensive care unit (NICU) guidelines.

### 1.3 Study Assessments

A thorough evaluation on each of the medical history was done to understand the base line characteristics of the patients and features of clinical presentation in the development of NEC in all the participating subjects. The baseline characteristics that is considered in this study were gestational age, gender, birthweight, twin gestation and delivery method. The clinical presentation presumed to be associated NEC were: blood in stool, abdominal distention, fever, vomiting, feeding intolerance, radiological changes, small for gestational age (<10<sup>th</sup> centile for the given GA week and sex), meconium aspiration syndrome, presence of congenital heart disease, neonatal anemia, sepsis, apnea, respiratory distress syndrome, postnatal asphyxia, and IUGR.

The time of diagnosis of NEC (in days) was documented in all of the infants to determine the early and late onset of NEC. The histogram of the time to onset of NEC suggested a bimodal distribution with the first peak around at the first 8 days of age and the second peak after the 19 days of age. The least overlap between the 2 distributions was noted to be at day 14. Based on this, the timing of appearance is divided into two

different group, early onset <14 days and late onset  $\geq$  14 days. The course in the hospital and progress were monitored and immediate outcome at discharge was recorded in the medical history of participating infants.

### 1.4 Statistical Analysis

All the medical records of infants that are included in the study were reviewed, collecting the variables of interest for this study in Microsoft Excel format. Data were analysed using the statistical software SPSS 17. The description of qualitative data was carried out as absolute frequencies and percentages, and quantitative data as mean, median, standard deviation and range, according to data distribution. Summary tables as well as descriptive statistics were calculated for the entire parameters of interest. For categorical tables, percentage distributions and frequency were also analysed. Cross tab, chi-square and regression analysis was used to define correlation with statistical significance measured at  $P < 0.05$

## 2. RESULTS

### 2.1 Basic Characteristics

Total of 100 infants (N=100) with confirmed diagnosis of NEC were enrolled from patients that were admitted in the Children Hospital Affiliated with Soochow University during the period of June 2010 to June 2015. Male (61%) was the majority gender of patient concluded in this study. 43 patients presented with LBW, 19 with VLBW and 6 with ELBW; 2161g was the mean and 2030g was the median for the birthweight. Majority of the infants diagnosed with NEC (68%) was a preterm baby, 16% was an early term, leaving the rest with full term (12%) and late term (4%). This study also shows that 15% of the study participants was a twin gestation and small majority of infants presented with NEC had vaginal delivery.

### 2.2 Clinical Presentation

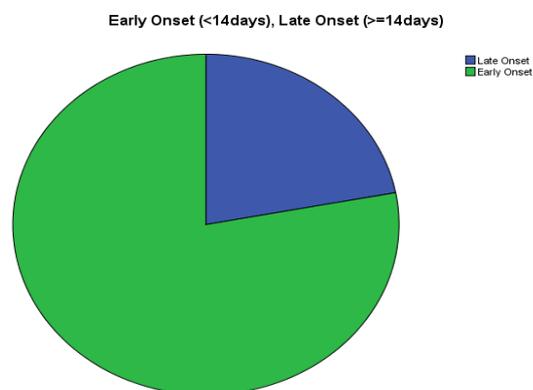
The major clinical features that is related to the development of NEC in this study were bloody stools, abdominal distension, vomiting and fever.

Among the NEC patients, there are 28 (28%) patients with abdominal distension, 24(24%) have bloody stools and 15(15%) that experiences vomiting. While 10 patients have symptoms of feeding intolerance. In addition to the previous clinical presentation, 11% of the patients are presented with Radiographic changes (e.g. thickened bowel walls, dilated bowel loops, a paucity of bowel gas)

According to the finding of this study, other than gastrointestinal sign, patients with NEC also present systemic signs include lethargy (11%), increased episodes of apnea (6%), postnatal asphyxia (31%), temperature instability (22%), RDS (28%) and sepsis (25%). That are 32 patients with abnormal laboratory tests that shows presence of neonatal anemia (32%). Among 100 patients evaluated in this study there are 15 patients, 11 patients and 1 patient associated with the presentation of congenital heart disease, small for gestational age and IUGR respectively.

### 2.3 Timing of Presentation

The earliest recorded for the time of presentation was on the first day of life, the latest was on the 73<sup>rd</sup> days of life, with the mean of 9<sup>th</sup> days of life. Early onset of NEC presentation occupies 78% of the case evaluated in this study. This study suggests that the most infant who develop NEC are premature, but also suggests that the more premature the infant, the later will be the onset of the disease.



**FIG.1** Time of presentation of clinical manifestation in the development of NEC, dividing it into two groups, Early Onset (<14days)

and Late Onset (≥14 days)

### 2.4 Outcome

In this study, the outcome of NEC in the study population is categorized by three different group. There are 31 patients (31%) with voluntary discharge which explains number of patients who requested for voluntary discharge before completing the whole course of treatment provided by the hospital, or to patients who were referred to another hospital for further treatment. There are 65 patients (65%) with hospital discharge which means these patients were being dismissed by the hospital with a good prognosis and 4 (4%) patients who died during the course of the treatment. The duration of hospital stays of each infants participated in this study was also recorded and shows mean value of 29.5 days.

### 3. DISCUSSION

NEC is defined as an inflammatory intestinal disorder predominantly occurs in premature infants, especially those with birth weight less than 1000g and born prior to 28 weeks' gestation, characterized by variable damage to the intestinal tract, ranging from mucosal injury to full-thickness necrosis and perforation. Despite considerable research, preventive strategies have remained elusive for several decades, reflecting the lack of a clear delineation of what constitutes the diagnosis of classic NEC. Thus, the term "necrotizing enterocolitis" often reflects a spectrum of intestinal conditions that differ with respect to pathogenesis and strategies required for prevention and treatment.

Infants that are selected for this study were patients of Neonatal Department of Children Hospital Affiliated with Soochow University with confirmed diagnosis of Necrotizing Enterocolitis. The diagnosis of NEC was defined according to the Bell staging criteria based on clinical features and radiological evidence (FIG. 2). The data analysed not included information of the nutritional treatment received by individual infants. All neonates were uniformly managed as per standard neonatal intensive care unit (NICU) guidelines.

Stage	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, hemepositive stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics x 3 days
IB Suspected	Same as above	Grossly bloody stool	Same as above	Same as IA
IIA Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibiotics x 7 to 10 days
IIB Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites	NPO, antibiotics x 14 days
IIIA Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, Disseminated Intravascular Coagulation (DIC), and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites	NPO, antibiotics x 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis

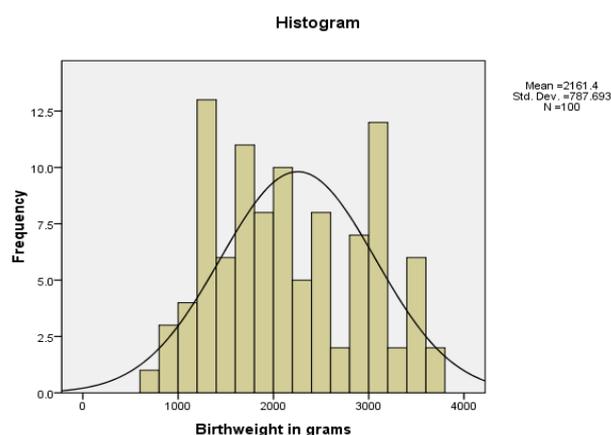
**FIG.2** Bell Staging for the diagnosis of Necrotizing Enterocolitis

In this study, a total of 100 infants (N=100) with confirmed diagnosis of NEC were enrolled from patients that were admitted in the Children Hospital Affiliated with Soochow University during the period of June 2010 to June 2015.

**3.1 Basic characteristics:**

The evaluation of basic characteristics of the patients included in this study shows that the infants presented with the diagnosis of NEC were more likely to be male (61%). This is consistent with earlier studies that also found more affected males, but the association between gender and NEC has not been found. There are 43 patients presented with LBW, 19 with VLBW and 6 with ELBW; 2161g was the mean and 2030g was the median for the birthweight of this study participants (presented in Figure 3). Majority of the infants diagnosed with NEC (68%) was a preterm baby, 16% was an early term, leaving the rest with full term (12%) and late term (4%).

Figure 4 sets out the percentage of gestational age in four category (preterm, early term, full term and late term). As expected, the frequency was higher at low GA. Immaturities, as well as reduced ability to self-regulation are important etiopathogenic factors that explain why NEC is disease that affect more frequently premature babies. NEC in early and full term neonates differs from that seen in preterm and is usually associated with underlying congenital conditions, e.g congenital heart diseases, predisposing to intestinal hypoperfusion via the diving seal reflex (reflex with circulatory shunting to selectively perfuse the vital organs at the expense of other “non-vital” ones, such as intestine)



**FIG. 3** Percentage of the BW of the infants with confirmed diagnosis of NEC in the 5 years period (June 2010 – June 2015)



**FIG. 4** PREMATURITY AND NEC. Percentage of gestational age distribution on infants with confirmed diagnosis of NEC in the 5 years period (June 2010 – June 2015)

This study shows that small majority of infants presented with NEC had normal delivery (58%). According to Maayan-Metzger et al., epidural anaesthesia could cause a transient drop of blood pressure, which then possibly compromising placental blood supply and fetal circulation. In addition to this, two other studies showed an increased risk for NEC after vaginal delivery. According to the recent research, mode of delivery is one of the most important determinants of the infantile gut microbiota; caesarean section is associated with lower numbers of bifidobacteria and bacteroides and higher number of *Clostridium difficile*.

### 3.2 Clinical Features

#### 3.2.1 Gastrointestinal presentation

The clinical presentation of NEC can range from non-specific signs that progress insidiously over several days to a fulminant onset of gastrointestinal signs, multi organ dysfunction and shock over a few hours. Almost all VLBW infants have intermittent gastrointestinal symptoms, such as abdominal distension, bloody stools, and feeding intolerance, that may cause concern, but most do not have NEC. Gastrointestinal immaturity impairs intestinal motility and decreases nutritional absorption. Impaired intestinal motility prevents movement of substrate through the intestine, resulting in stasis and possible bacterial overgrowth. Impaired nutritional absorption may result in carbohydrate fermentation with subsequent gaseous intestinal distension and damage to the fragile intestinal epithelium as well as bacterial invasion of the intestinal wall. Among the study population, there are 28 (28%) patients with abdominal distension, 24(24%) have bloody stools and 15(15%) that experiences vomiting. This result show a similar finding with numerous study that has been done. In this study majority of VLBW infants with confirmed diagnosis of NEC shows abdominal distension (21.4% N=6).

#### 3.2.2 Systemic Presentation

This study shows that are 25 infants presented

with sepsis (25%). The presence of sepsis caused by CNS has been specifically addressed, since some studies have shown its relationship with NEC, possibly through cytotoxic toxins, such as delta toxin, that directly damage intestinal mucosa. There were 32 infants presented with the diagnosis of neonatal anemia. This study did not enable us to discern if the affected patients were sicker or had a higher incidence of anemia. Some authors have found that lower hematocrit levels and PRBC transfusion were independent and statistically significant associated factors for NEC. The proportion of CHD in infants with NEC was low and non-significant, as well as the number of infants presented with IUGR. After studying neonates with CHD that developed NEC, McElhinney et al. concluded that reduced mesenteric perfusion was the main cause, although various other etiologic factors play a part. Although the data for the relationship between IUGR and NEC did not reach statistical significance in this study, the association between IUGR and NEC was observed and described in other studies. Conditions associated with decreased placental blood flow, leading to chronic intrauterine hypoxia and growth restriction, may compromise intestinal blood flow to the fetus and thus predispose to NEC.

#### 3.3 Time of Presentation

In this study, the earliest recorded for the time of presentation was on the first day of life with the mean of 9<sup>th</sup> days of life. This study found that majority age of onset ranges from 1-3 days of life (49%), which is similar with previous study that has been done. In more mature neonates, the disease mainly occurs in the first week after birth (16.7 % in early term and 14.1% in the full term patients). The term neonate who is immediately affected postnatally is found likely to be systematically ill with other predisposing conditions, such as birth asphyxia, respiratory distress, congenital heart disease, or metabolic abnormalities, or has a history of abnormal fetal growth pattern. Specific signs that may be part of the history include abdominal distention, passage

of blood per rectum, abdominal radiographs that reveal dilated loops of bowel, and other signs of systemic infection. Premature babies are at risk for developing NEC for several weeks after birth. Presenting clinical features may include subtle signs of feeding intolerance and subtle systemic signs. Signs of feeding intolerance can include abdominal distention, increased gastric residuals and occasionally vomiting. Systemic symptoms can insidiously progress to include nonspecific signs and symptoms, such as apnea and bradycardia and lethargy, among the primary manifestation(s). With the early onset of the disease, the clinical signs may be mild; whereas infants with the fulminant disease can present with severe clinical abnormalities. This study shows Early-onset NEC infants had lower frequency of respiratory distress syndrome. Approximately one third of the subjects in this study (32%) shows presentation of neonatal anemia. Yet, it was not statistically significant ( $P>0.05$ ), similar staging of NEC severity regardless of anemia.

According to regression analysis, taking all clinical features into consideration as independent variables, the severity of NEC a dependent variable, it was observed that the basic characteristics of preterm and male gender; as well as clinical presentation of abdominal distension and sepsis had significant estimation of coefficient in the model. This indicates the fact that the influence of preterm, gender, abdominal distension and sepsis to the diagnosis of NEC is significant, where the relationship is positive.

### 3.4 Outcome of the Disease

This study found that birth weight and gestational age correlate well to the outcome, of without leaving the fact that other factors can influence the clinical course in neonates. Majority of the patients (84%) are managed medically, leaving 16% of the study population requiring surgical treatment. There are 4 patients who died during the course of the treatment, all of which had early onset of NEC.

According to the Chi-square test and cross-table test, it was observed that the P value for time of

presentation and the outcome of the disease development were all larger than 0.05 indicating that the time of presentation and the disease outcome are not independent significantly at level of 0.05. The results identified the fact that there might be no correlation between time of presentation (onset) and the outcome.

### 4. SUMMARY

From this study it can be concluded that:

- 1) Despite improvements in neonatal intensive care, NEC remains a critical disease in preterm infants and confers many serious complications and mortality.
- 2) Preterm newborns are highly associated with the development of NEC.
- 3) The more premature the infant, the later will be the onset of the disease.
- 4) Early-onset NEC infants had lower incidence of respiratory distress syndrome.
- 5) Proposition that in preterm infants clinical presentation of NEC differs from that in term infants has been made, in which term infants is associated more with underlying congenital conditions (e.g congenital heart disease)
- 6) Clear diagnostic criteria need to be used consistently to differentiate between NEC and other entities.

### 5. LIMITATIONS

This study is subject to some limitations inherent to retrospective study. The limitation includes absence of control group and total reliance on patient medical records, which were obtained by different individuals from June 2010 to June 2015. This study strictly evaluating the non-nutritional potential risk factor in study evaluation, therefore the results may not cover the overall potential factors that may affect the development of NEC in neonatal. Last, study subjects are infants admitted in Neonatal Department in one hospital, so that the result might not reflect the whole Chinese population. Further studies, either retrospective with larger sample size or prospective are needed.

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