

## Seasonal variation in the incidence of necrotizing enterocolitis

Charles L. Snyder · Matt Hall · Vidya Sharma ·  
Shawn D. St. Peter

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### Abstract

**Background** Necrotizing enterocolitis (NEC) has been reported to occur in a sporadic manner and in clusters of cases. We hypothesized that variations in the incidence of NEC were random, without clustering. In order to define the pattern of NEC in the United States, we analyzed the Pediatric Health Information System (PHIS) database to evaluate whether NEC cases are distributed randomly or exhibit temporal clustering or periodicity.

**Methods** After obtaining IRB approval, we queried the PHIS database for all patients with NEC (ICD-9 code of 777.5) over a 13-year period. Sixteen children's hospitals were studied, and individual institutional and aggregate data were reviewed. Fisher's Kappa and Bartlett's Kolmogorov–Smirnov tests were used to identify periodicity.

**Results** During the study interval, there were 2,93,076 neonatal admissions, and 4,559 (1.6%) infants were diagnosed with NEC. Statistical analysis demonstrates a periodicity of 6 months in the occurrence of NEC. Fisher's Kappa was 16.924 and Bartlett's Kolmogorov–Smirnov was 0.281, which translates to a *P* value of <0.0001.

**Conclusions** On the basis of a national database analysis it appears a temporally non-random distribution of NEC cases does exist.

**Keywords** Necrotizing enterocolitis · Epidemiology · Seasonality · Incidence

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C. L. Snyder (✉) · V. Sharma · S. D. St. Peter  
The Children's Mercy Hospital, Kansas City, USA  
e-mail: clsnyder@gmail.com

M. Hall  
Child Health Corporation of America, Shawnee Mission,  
Kansas, USA

### Introduction

Necrotizing enterocolitis (NEC) is the most common surgical emergency in newborns. Its incidence is estimated to be about 3 per 1,000 live births, with a tenfold increase in low birth weight infants. NEC accounts for approximately 5% of all neonatal intensive care unit admissions (NICU) [1–4]. Data from the National Institute of Child Health and Human Development Neonatal Research Network have demonstrated a 7% incidence of NEC in all newborns under 1,500 g [2].

Most cases occur in a sporadic or endemic pattern; when the disease occurs in clusters, the question of epidemic NEC arises. Seasonality has been reported suggesting the presence of epidemics [5, 6]. In an attempt to uncover non-random patterns in density of NEC cases, we reviewed data from the Pediatric Health Information System (PHIS) which has not been previously employed to address this issue.

### Methods

After obtaining IRB approval (#07 07-107X), we queried the PHIS database. The PHIS database is maintained by the Child Health Corporation of America (Shawnee Mission, KS, USA) and includes demographic, diagnostic, and charge data for freestanding, noncompeting, children's hospitals. The PHIS includes both diagnoses and procedures coded using *the International Classification of Diseases, Ninth Revision* (ICD-9). We identified cases of NEC over a 13-year interval (1992–2005) utilizing the ICD-9 code (777.5). The PHIS database includes for 35 freestanding children's hospitals. Complete data for the study interval were available from 16 hospitals, which were used for the analysis. Their locations are listed in Table 1.

**Table 1** Analysis of NEC incidence by institution. Variability in the temporal clustering by individual institutions is shown, with significant periodicity indicated in the second column

| Location           | <i>P</i> value |
|--------------------|----------------|
| San Diego, CA      | 0.9501         |
| Dayton, OH         | 0.9418         |
| Denver, CO         | 0.8705         |
| Orange County, CA  | 0.7813         |
| Little Rock, AR    | 0.4796         |
| Chicago, IL        | 0.4008         |
| Akron, OH          | 0.3848         |
| Corpus Christi, TX | 0.2588         |
| Pittsburgh, PA     | 0.1574         |
| Memphis, TN        | 0.1501         |
| Columbus, OH       | 0.0131         |
| Miami, FL          | 0.0018         |
| Norfolk, VA        | 0.0015         |
| Kansas City, MO    | 0.0015         |
| Madera, CA         | 0.0004         |
| St. Petersburg, FL | <0.0001        |

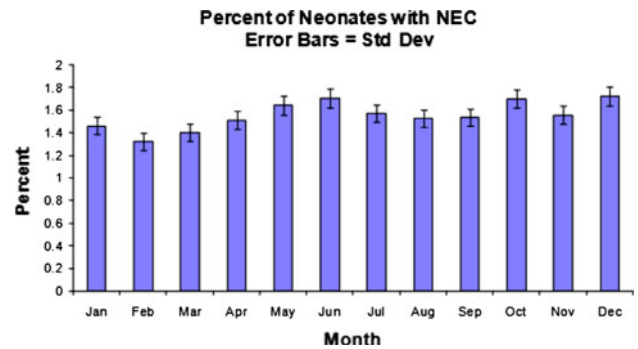
Statistical analysis of the incidence of NEC over time for all patients as a whole, as well as for individual institutions was performed. Fisher's Kappa (White Noise Test) and Bartlett's Kolmogorov–Smirnov (K–S) were used to identify periodicity in the data. These tests utilize the frequency and interval between cases in a time series to detect the presence or absence of statistically significant seasonality. The Fisher's Kappa compares the largest periodogram ordinate by the mean of all ordinates. Bartlett's K–S test compares the normalized cumulative periodogram of the series to the cumulative distribution function of uniform random variable. They are used together as Fisher's Kappa is better for a single sinusoid buried in a random pattern while Bartlett's may detect more general departures from white noise.

## Results

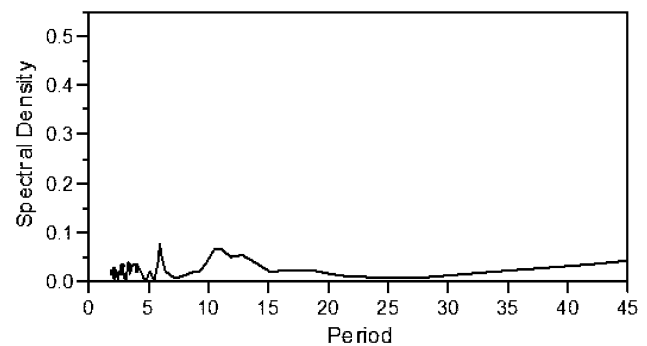
There were 2,93,076 neonatal admissions and 4,559 (1.6%) infants were diagnosed with NEC. The relative percentages of NEC cases per month are displayed in Fig. 1. Data are based on the admission date.

The spectral density of incidence of cases shows a periodicity of 6 months in the data with peaks at 6 and 12 months (Fig. 2).

The Fisher's Kappa was 16.924 and Bartlett's Kolmogorov–Smirnov was 0.281, which was highly significant ( $P < 0.0001$ ). Variability in the clustering within time series from each individual institution is listed in Table 1.



**Fig. 1** The monthly incidence of NEC over the study interval by percent of admissions with NEC



**Fig. 2** Spectral density graph demonstrating peaks at 6 and 12 months. The 6-month periodicity was statistically significant with probability of random distribution being  $6.38 \times 10^{-7}$

## Discussion

A tendency to perceive random events as non-random is a well-recognized phenomenon in human cognition [7]. The result can be the perception of patterns that may not exist. The commonly employed phrase in clinical care, “these cases come in threes” may be a product of this natural tendency. The possibility of patterns in the incidence of NEC is of particular interest because NEC represents a clinical picture of symptoms and pathologic findings for which we are still devoid of insight regarding the precise etiology. Evidences in support of epidemics include lack of correlation of NEC incidence with patient load [8]. Others have reported monthly variation in the incidence of NEC [5, 6], including an analysis of Kids' Inpatient Database for the year 2000 which documented the percentage of NEC admission per month as low as 7.1% in January and as high as 10% in July [5]. Similar monthly variations were identified in our study (Fig. 1).

The results of this study identify with some certainty that within the time-interval series on a national level, a non-random pattern exists. The exact reason remains conjecture but may allude to the influence of infectious etiology. An increased incidence of NEC related to bacterial

colonization has been reported, with isolation of *Escherichia coli* and *Klebsiella pneumoniae* from upper and lower gastrointestinal sources [9]. Many authors have described epidemics of NEC related to specific pathogens [10–13]. Others have reported epidemics for which no infectious agent can be identified [14]. However, these are all within a single unit or area which would be expected for clusters in which the bacterium is suspected, or a particular local emerging strain is horizontally transferred throughout the unit by caregivers. Our findings are unlikely to be explained by a bacterial influence, given the wide regional hospital representation. While older data had found temporal and geographic clustering of NEC cases over a 5-year interval in the 1970s, this was coincident with acute gastrointestinal illness in NICU personnel and resolved with increased infection-control measures [15]. Similarly, one report documented a significantly lower incidence of NEC during a 2-month interval in which gowns were worn over street clothes by staff and visitors to the NICU [16]. Infection control measures are an unlikely explanation for what is seen in this contemporary data set given the strict infection control regulations enforced in most nurseries.

Aside from infection control policies, other practice habits have been implicated in NEC clustering, including transfusion practices and feeding techniques [13, 17, 18]. It has been shown that feedings were advanced more rapidly in epidemic NEC cases versus controls, suggesting that feeding regimens may have contributed to clustering of cases. Not only would such practice habits be unlikely to explain patterns in the national data set used here (because of NICU variations), but most nurseries are also well aware of these concerns and have protocols in place for feeding at risk infants. While one may interpret Table 1 as support for local practice habits—since some institutions have detectable periodicity and others do not—this fact is misleading. The individual institutional periodicity is shown to demonstrate how the national data translates to each unit; however, the tools utilized evaluate the pattern as a sequence of intervals between cases. Therefore, a few institutions with no periodicity may demonstrate dramatic periodicity when the sequences are overlapped, which is the reason that aggregate findings are more important than variability within each institution.

As opposed to a bacterial source, a viral influence on the incidence of NEC would be more plausible. There is a well-known seasonality for many common viral infections which occur at a national level. Many viruses have been associated with outbreaks of NEC, including echovirus type [19, 22], coronavirus [20], rotavirus [21], and coxsackievirus [22]. Viral infection may not cause NEC, but can cause a clinical picture indistinguishable from NEC and thus would be included in the database employed. However, one would not expect viruses to affect only

premature infants and thus a viral influence would theoretically result in more term infants with NEC. Correspondingly, infants affected by epidemic NEC were found to have higher birth weights and Apgar scores, fewer perinatal complications, later onset, and better outcome in a retrospective case-controlled study [10].

The pathogenesis of the clinical entity known as NEC is undoubtedly multifactorial. Therefore, it would be unlikely that a single pathway accounts for the overall pattern seen in this study. However, it would be quite plausible that an infectious etiology results in an increased number of cases superimposed on the random baseline pattern of NEC, creating the non-random pattern we detected. Of the infectious etiologies, a viral source would be more likely than bacterial as discussed above. While the seasonal viral fluctuations are typically respiratory and not enteric, the seasonal impact of viruses on NEC may be a consequence of direct enteric infection. These seasonal illnesses may influence the overall health of infants and mothers secondarily altering the incidence of NEC, particularly considering the fact that NEC appears to be an opportunistic process most commonly occurring in the weakest patients.

There is debate in the statistical community on the relative merits of using tests for time series as we have done. An alternate approach, collapsing months across years and then performing a statistical analysis can be utilized as well. The time series approach is currently considered more robust since it takes full advantage of longitudinal data.

Limitations of this study include those intrinsic to large database analysis. There may be variations in the diagnostic criteria between hospitals. Some patients with gastrointestinal illness from other causes, rather than true necrotizing enterocolitis, may be erroneously included. As an example the database does not distinguish between isolated ileal perforation and NEC which are clinically distinct disease states.

While we must continue clinical and basic science research to provide answers in the prevention and treatment of this devastating disease, the data herein demonstrate that a non-random distribution in the incidence of NEC currently exists.

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