HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2012 February 01.

Published in final edited form as:

J Perinatol. 2011 August ; 31(8): 519–523. doi:10.1038/jp.2010.193.

The Age of Necrotizing Enterocolitis Onset: An Application of Sartwell's Incubation Period Model

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Abstract

Objectives—Model age of necrotizing enterocolitis (NEC) onset applying Sartwell's model of incubation periods, and examine its relationship to gestational age (GA).

Study design—Retrospective chart review of St. Louis Children's Hospital neonates diagnosed with NEC (≥ Bell's stage II) from 2004 to 2008, inclusive.

Results—The relationship between age of NEC (N=84 cases) onset and GA best fits a non-linear model, with infants ≤ 28 weeks having a disproportionately longer time to onset than older GA groups and explained 50.3% of the variability in age of NEC onset. Additional clinical variables provided no improvement in explaining age of NEC onset. Application of Sartwell's model to age of NEC onset proved a good fit, when birth is used as the common exposure episode, and age is the equivalent of the incubation period.

Conclusion—The relationship between day of NEC diagnosis and GA is non-linear, with lower GA infants having disproportionately longer time to onset. Despite these GA differences, the fit to Sartwell's model for incubation periods model is consistent with NEC being a consequence of an event that occurs at or soon after birth.

Keywords

premature morbidity; intestinal injury; newborn

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Financial Disclosure: No financial relationships relevant to this article to disclose

Conflict of Interest

The authors declare no conflict of interest.

Introduction

Necrotizing enterocolitis (NEC) is a serious necro-inflammatory injury of the distal small bowel and proximal colon that predominantly affects premature infants. The highest frequency of NEC is in very low birth weight (VLBW) infants, i.e., those born weighing less than or equal to 1500 grams, ranging from 5 to 12% in most studies [1–3]. Overall NEC mortality remains at 15%, and approaches 30% [1, 4] for VLBW [5, 6] infants.

Many environmental and host factors have been implicated in the pathogenesis of NEC. However, the processes leading to NEC remains unknown. It remains unclear whether NEC results for a singular inciting "event", or from sequential post-natal exposures. In the 1950s, Sartwell reported that incubation periods for infections, in which victims had single known exposures, followed log normal distributions, while those caused by sequential exposures did not [7, 8]. This model has since been applied to a variety of infectious diseases, as well as to complex and genetic disorders [9–16]. Diseases with well defined exposures or clearly defined genetic etiologies fit log normal distributions in terms of time to onset (following exposure or birth), while those with ill defined etiologies or caused by sequential environmental influences do not [9–12]. In this study, we asked if the age of diagnosis for NEC fits a model consistent with a common time window of exposure, or one more strongly influenced by varied postnatal environmental factors.

Methods

Washington University Human Resources Protection Office approved this retrospective study. We analyzed the charts of all infants diagnosed with NEC (International Classification of Diseases, 9th Revision, Clinical Modification code 777.5) at St. Louis Children's Hospital, who were discharged between January 2004 and January 2008. The day of NEC diagnosis was defined as the first day of clinical findings consistent with Bell's staging, confirmed by radiologic evidence of NEC. Only patients who fulfilled the Modified Bell's Stage II [17] clinical and radiological findings (pneumatosis intestinalis, portal vein gas) or III (stage II plus presence of pneumoperitoneum) were included. We excluded patients with Bell's stage I, as well as patients with spontaneous intestinal perforation (SIP) using guidelines from Gordon [18], patients transferred to St. Louis Children's Hospital with a pre-existing diagnosis of NEC for whom radiographs and clinical data were unavailable, and patients with severe congenital or chromosomal abnormalities. We extracted gestational age at birth, gender, race, birth weight, parity, route of delivery, Apgar scores, Bell's Staging, surgical intervention for NEC (laparotomy and abdominal drainage), and hospitalization outcome (died from any cause, or discharged alive) from the medical record.

We tested the distribution for age of NEC diagnosis for normality, and strongly rejected this distribution pattern (Shapiro-Wilk test $p < 0.0001$). Therefore, we used the nonparametric Kruskal-Wallis and Mann-Whitney tests to test differences between median day of onset among gestational age groups. Scatter plots and measures of correlation (Pearson's correlation for linear correlation) were used to portray the relationship between gestational age and day of NEC diagnosis. Day of NEC onset was log transformed and did not strongly reject normality testing ($p > 0.02$). Sartwell's model was applied to NEC using the log

transformed time interval from birth to day of NEC onset as the “incubation period”. The frequencies for the age of NEC diagnosis were grouped in time intervals (days) and the cumulative frequencies and corresponding percentages determined. Data were plotted as cumulative percentages against log time [(7)]. The “estimated median” is the point of 50% cumulative frequency when plotting log time against cumulative frequency. The “dispersion factor” is a coefficient which, when multiplied or divided by the estimated median incubation period, provides the endpoints of an incubation interval containing an estimated 68% of the observations [(7)]. It provides an estimate of dispersion independent of the length of incubation, allowing comparison between diseases, or in this study, gestational age groups. All analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

Results

During the four-year study period, 180 infants at our institution had an ICD-9 diagnosis of NEC (code 777.5), corresponding to 5.1% of NICU admissions in this interval. Ninety-six were excluded from our study because they had a major congenital anomaly (N=32), lack of confirmatory radiographic/clinical data prior to transfer (N=42), or Bell’s Stage I or SIP (N=22), leaving 84 infants for analysis (Figure 1). Characteristics of groups by gestational age are provided in Table 1. Among these 84 infants with NEC, no gender imbalance was seen, and frequencies of multiple gestation and delivery route reflected those of our NICU population. African – American infants with NEC were over-represented in all gestational age categories except infants 25 to 26 weeks gestation compared to our NICU population (45% African - American) in all gestational age groups (Table 1).

Across the entire study population, there was a substantial negative linear correlation between age of NEC onset and gestational age at birth ($r=-0.647$, Figure 2). In the linear model gestational age accounts for 41.8% of the variability in age of NEC onset ($r^2=0.418$). Fit was diminished when birth weight rather than gestational age was used ($r=-0.539$, $p<0.001$, data not shown), accounting for 29.1% of the variability in age of NEC onset. Fit improved using a nonlinear model of 1/(gestational age), increasing the proportion of variance explained to 46.4%. When both 1/(gestational age) and gestational age are included in the model the proportion of variance explained rose to 50.3% providing a significant improvement in fit ($p=0.0134$). The addition of birth weight, gender, race, multiple gestations and delivery route and 5 minute Apgar score did not substantively add to the explanation of age of NEC onset variance. The improvement using the factor 1/ (gestational age) reflects the disproportionately greater delay in onset in infants with earlier gestational ages. This non-linear relationship between gestational age and age of NEC onset is evident in Figure 3. The median day of diagnosis was significantly later for the group consisting of infants with <29 weeks of gestation at birth (14 – 27.5 days), compared to older infants (6 – 8 days), (Figure 3 for significance testing). Additionally, the interval change in the days to diagnosis of NEC between gestational age categories did not change linearly with gestational age. For each 2 week increase in GA, the interval decrease from the previous gestational age category for age of diagnosis varied between 9 days at the lowest GA group to 0 days at the highest GA group (Figure 3).

Because testing of the distribution for age of NEC diagnosis rejected the hypothesis of a normal distribution, times were log transformed. The resulting data better fit a log normal distribution, and Sartwell's model was applied to NEC using age of NEC diagnosis as the candidate "incubation period." A plot of the cumulative distributions for log normal days to NEC onset (Figure 4) illustrates the overall good fit of Sartwell's model, comparable to the fit of examples in his seminal paper [7]. This visual assessment is supported by formal statistical goodness-of-fit tests (e.g. Shapiro-Wilk test $p > 0.05$). Further, Sartwell's "estimated medians" closely matched the actual sample gestational category medians. The dispersion factor, a measure of variation independent of the magnitude of the incubation time (see Methods), was 2.62 for the entire cohort (Table 1), indicating that the range of days of diagnosis of NEC encompassing 68% of cases on either side of the estimated median is from 3.0 to 20.8 days. For infants ≤ 28 weeks this range expanded to 9 to 37 days. Although the model fit the data well, Figure 4 demonstrates non-random deviation from the model prediction. Specifically, the cumulative percentages for earlier onset (lower log normal days of diagnosis) were consistently less than predicted for the entire cohort as well as within gestational age categories (data not shown).

Overall, 51.2% of the patients included in the analysis underwent NEC-related surgical intervention. Mortality across all gestational ages was 23.8%, ranging from zero in infants >30 weeks GA to >60% in infants <25 weeks GA (Table 1). Mortality in infants undergoing surgical intervention across gestational ages was ≥40%.

Discussion

This is the first study to apply Sartwell's modeling for incubation periods to NEC. We demonstrate that the age of NEC onset fits Sartwell's log normal model of incubation periods. Incubation periods fitting Sartwell's model imply a single identifiable factor or point exposure that initiates a chain of events leading to illness [7, 19]. For NEC, the incubation period is age of NEC onset, with birth as the point of exposure.

Such a good fit suggests that an event at or soon after birth could be necessary, though perhaps not sufficient, for the development of this devastating disorder. Birth as an important event in NEC development is not a new concept, given its absence *in utero*, but the log normal occurrence of age of NEC diagnosis does suggest that the day of diagnosis of NEC is less affected by exposure to environmental factors within the NICU than the process of parturition and introduction to extra-uterine life. These distributions, while not negating the roles of other precipitating co-factors, do compel us to scrutinize biologic processes that begin in the immediate neonatal period as the controlling driver of NEC.

What could be such an early postnatal precipitant of NEC? Recent hypotheses implicate bacterial colonization [18, 20–22] in the development of NEC. The fetal intestine is sterile *in utero* [23, 24] with colonization beginning only after birth. If bacterial colonization at or soon after following birth is analogous to exposure to infectious agents that cause various illnesses in Sartwell's model, then a log normal model regardless of gestational age would result, as we demonstrate. However, we also must account for what appears to be non-random deviation from the model prediction. Whether lower than predicted rates of

occurrence in early days of life are related to temporary protection from initial antibiotic exposures, or other yet-to-be discerned variables, is not now clear. It is plausible that varying degrees of intestinal tract development, related to in utero development, could account for some of the differences for time to NEC development between gestational age categories. This again highlights the likely interaction between events that begin in parturition, and that continue post-natally.

This also is the first study of NEC to model the effect of gestation on age of onset. While an inverse relationship between gestational age and day of NEC diagnosis has been previously reported [25–28], ours is the first description and quantification of its non-linear nature. (Figures 2 and 3). By including the disproportionately longer age to onset for infants at very early gestational ages (1/gestational age) we were able to account for 50% of the variability in age of NEC onset. This degree of contribution from a single factor is somewhat unusual within complicated biologic systems, particularly the complex preterm infant. Gestational age has typically accounted for 30% or less of variation evident in other common preterm morbidities, including neurodevelopmental outcomes [29, 30]. The importance of gestation age to timing of onset again points to an interaction between events related to birth, and stage of intestinal development.

The NEC rate reported in this study (5.1%) resembles recent studies [2, 3, 31]. Also, the mortality rates of 23.8% for all children with NEC, and ≥ 40% for patients ≤28 weeks of gestational age, are similar to previous series [6, 27, 32–34], and confirm the described inverse relationship between NEC mortality and gestational age [3, 31, 35]. These high mortality rates highlight the lack of progress made over this time interval in treating this devastating disease.

We wish to note several limitations of this study. First, we used day of NEC diagnosis as the end of the incubation period, but it is possible that the radiographic manifestations required for inclusion in the study represent a pathologic process that began earlier, so our estimates of age of onset are therefore inaccurate. However, in the absence of an identifiable herald sign of NEC that more precisely represents its onset, we and others are necessarily obligated to use the date of the radiographic abnormality as the most defensible and definable point of NEC onset. Second its retrospective nature limits our ability to account for potential variables that could have impacted age of onset, beyond gestational age.

In conclusion, Sartwell's model, when applied to NEC, demonstrates log normality across all gestational age groups. The adherence of age of NEC onset to this model of incubation periods further supports a theory of NEC causation that is strongly influenced by a point exposure, in this case birth. The incubation period appears to start at or soon after birth, quite likely from a point source acquisition of sensitizing microbes. Gestational age differences in response to birth are evident as indicated by the continued correlation between GA and age of diagnosis of NEC. But birth, regardless of gestational age, and not subsequently occurring events, appear to be most critical event in terms of starting the clock that leads to NEC.

Acknowledgements

Ms. González-Rivera was supported by the Doris Duke Clinical Research Foundation. Dr Warner received support from the Children's Discovery Institute MD II-2009-201. Drs. Tarr and Warner were partially supported by UH2 AI083265 and DDRCC grant 5P30 DK052574 to Washington University Digestive Diseases Research Core Center. Drs. Warner and Hamvas received support from the Washington University Institute for Clinical and Translational Studies (UL1 RR024992). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Dr. Culverhouse is partially supported by the National Institute of General Medical Sciences (K25 GM69590).

We wish to thank the late Dr. David Alling for his insight and wisdom regarding incubation period distributions, and Beth Wolf, Gina Meyers, Amy Distler, and Christine Musser for assistance with manuscript preparation.

Abbreviations

NICU	neonatal intensive care unit
NEC	necrotizing enterocolitis
GA	gestational age
VLBW	very low birth weight
SLCH	St. Louis Children's Hospital
SIP	spontaneous intestinal perforation

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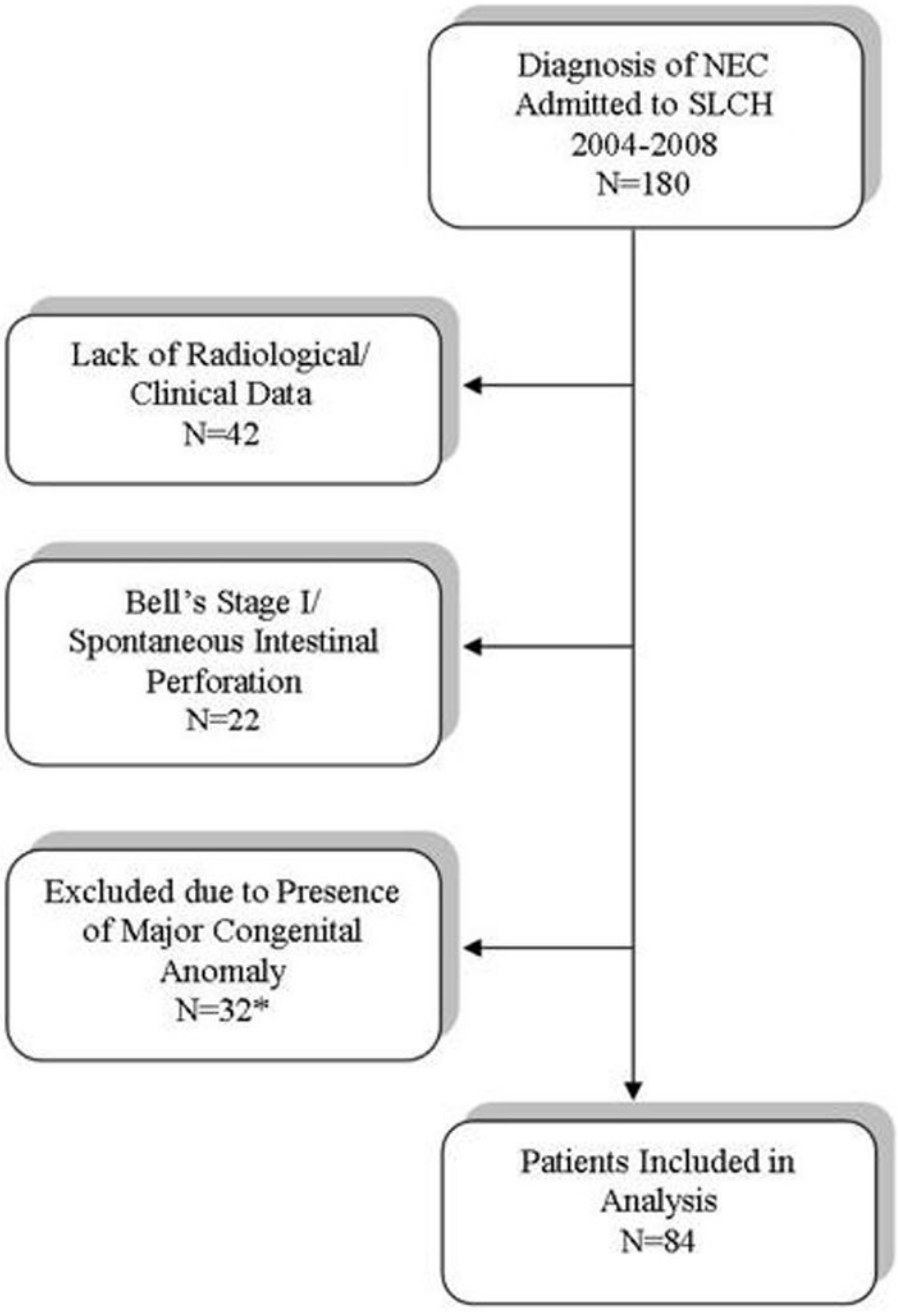


Figure 1. Distribution of patients included and excluded from analysis for this study

*Gastrointestinal malformations: gastroschisis (N=11), microcolon (N=1), Hirshsprung's Disease (N=1) intestinal atresia with perforation (N=2); cardiac anomalies: dextrocardia (N=1), hypoplastic right or left ventricle (N=5), transposition of great vessels (N=4), truncus arteriosus (N=1), tetralogy of Fallot (N=1), aortic coarctation (N=2), total anomalous venous return (N=1); renal anomalies: renal agenesis (N=1); chromosomal anomalies: Down syndrome (N=1).

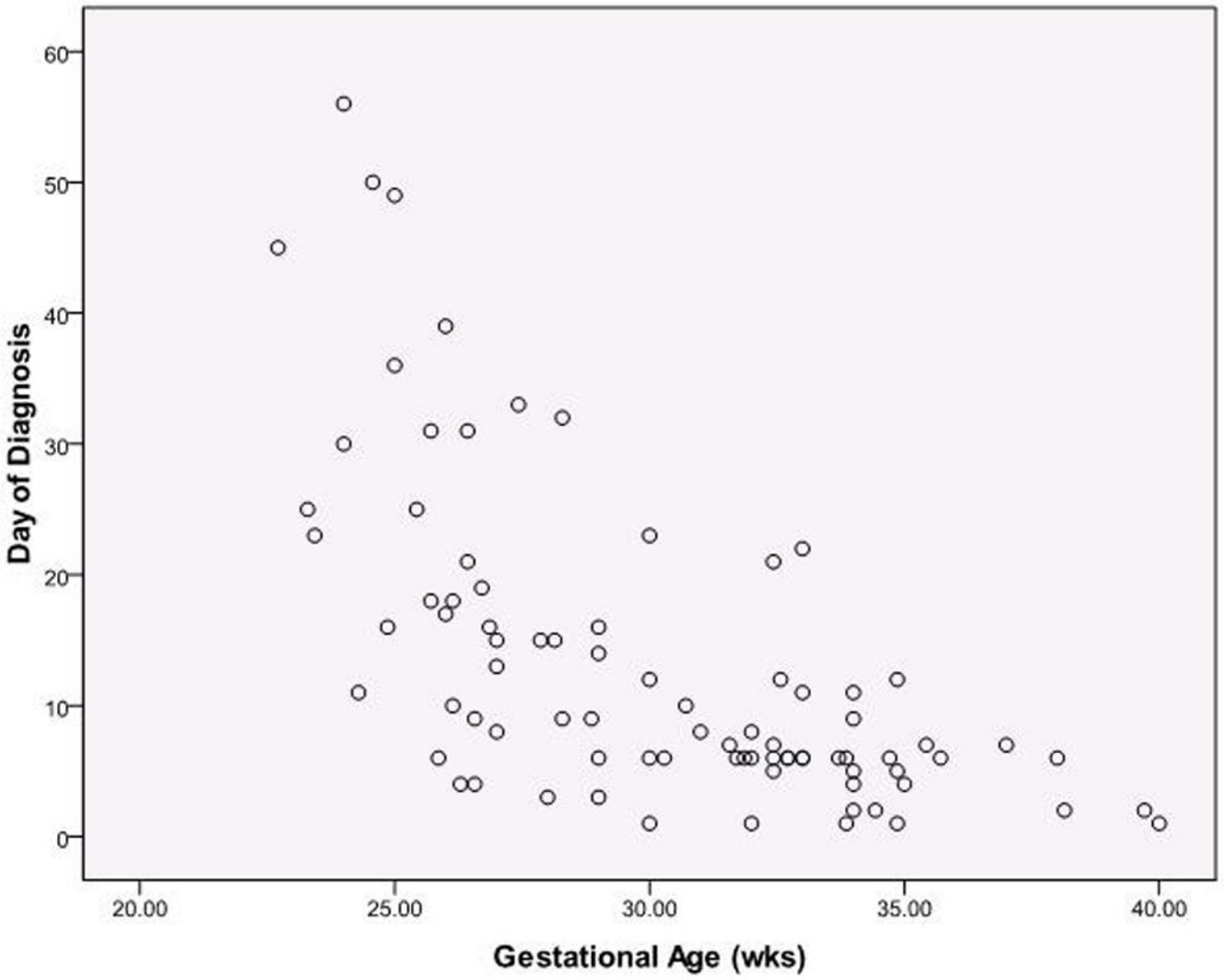
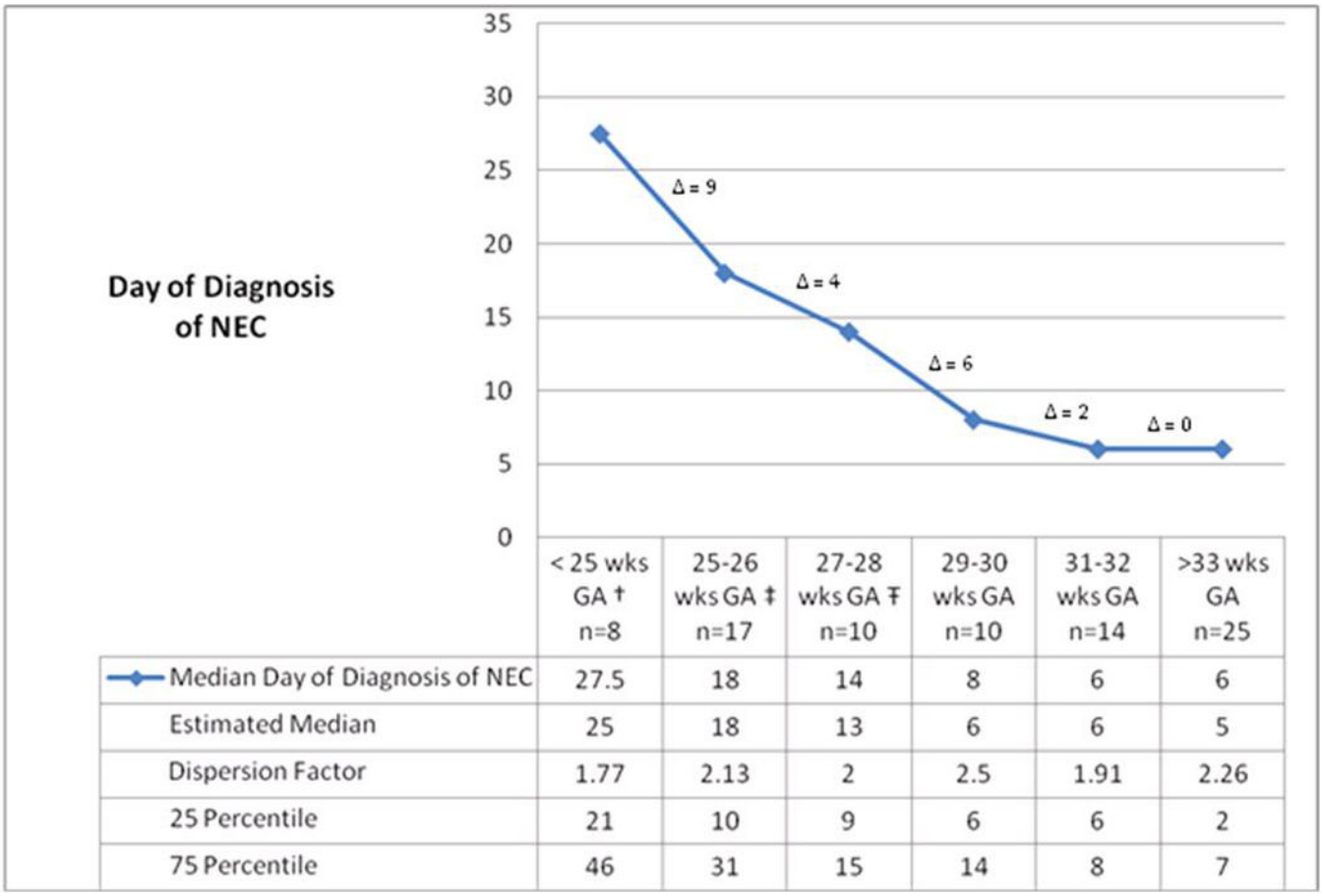


Figure 2. Inverse relationships between gestational ages and ages of diagnosis of NEC

Scatter plot for all subjects. N= 84. The regression model including GA and 1/(GA) explains 50.3% of variation in day of diagnosis and significantly improved fit (p=0.0134).



	< 25 wks GA † n=8	25-26 wks GA ‡ n=17	27-28 wks GA ∓ n=10	29-30 wks GA n=10	31-32 wks GA n=14	>33 wks GA n=25
Median Day of Diagnosis of NEC	27.5	18	14	8	6	6
Estimated Median	25	18	13	6	6	5
Dispersion Factor	1.77	2.13	2	2.5	1.91	2.26
25 Percentile	21	10	9	6	6	2
75 Percentile	46	31	15	14	8	7

Figure 3. Median age of diagnosis of NEC according to gestational age group

† Median day of diagnosis of NEC for group < 25 weeks GA is significantly different from each group ≥ 27 weeks GA ($p < 0.05$ for all)

‡ Median day of diagnosis of NEC for 25–26 weeks GA is significantly different from each group ≥ 29 weeks GA, ($p < 0.05$ for all)

∓ Median day of diagnosis of NEC for 27–28 weeks GA group significantly different from < 25 weeks GA and each group ≥ 31 weeks GA ($p < 0.05$ for all)

Δ= difference in median age of diagnosis of NEC between gestational age groups.

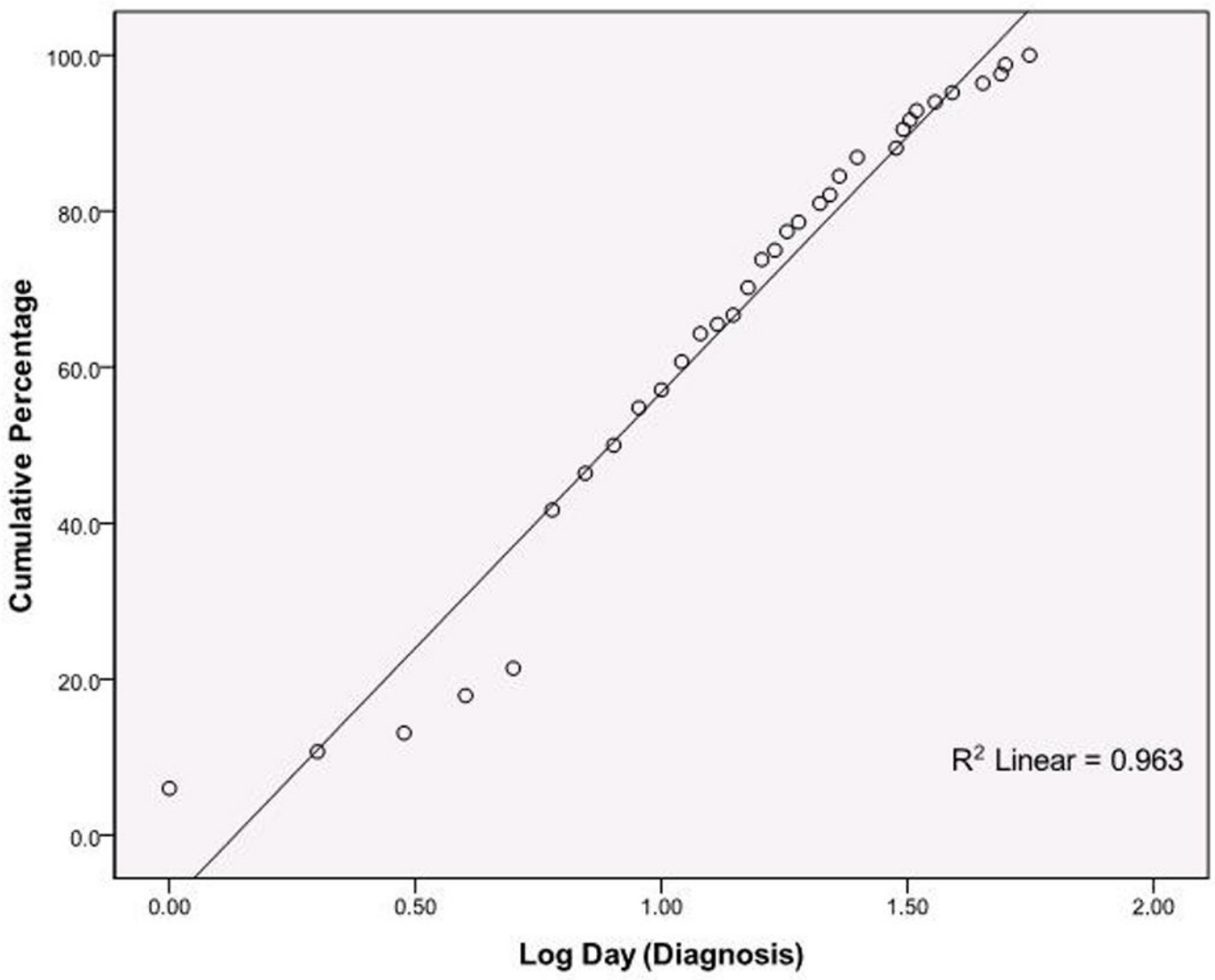


Figure 4. Application of Sartwell's log normal model: Cumulative distribution for log normal distribution of age of NEC diagnosis[10]

The y axis represents cumulative percentages of cases; the x axis represents the time scale, expressed as $\log_{10}$ values. Each point represents all the NEC cases presenting at the given time point. These are plotted by the cumulative percentage they represent (y axis). N=84, Shapiro-Wilk test $p > 0.05$ indicating significant fit to predicted log normal distribution.

Table 1

Demographic Varibales by Gestational Age

	Gestational Age (weeks)					
	<25	**25–26**	**27–28**	**29–30**	**31–32**	**33–40**
N	8	17	10	10	14	25
Race						
% White	37.5	64.7	30	40	42.9	36
% African -American	62.5	29.4	50	60	50	64
%other	0	5.9	20	0	7.1	0
Gender (% male)	37.5	47.1	50	40	64.3	56
Delivery (% cesarean)	62.5	58.8	50	60	42.9	44
Multiple Gestation (%)	0	47.1	20	10	28.6	4
Median Apgar Score (5 min)	7	6	8	8	9	9
Bell's Staging (% Stage III)	50	35.3	20	21.4	21.4	16
Surgery (%)	75	52.9	70	60	35.1	28
Surgical Mortality (%)	50	41.1	40	100	NA	NA
Total Mortality (%)	62.5	52.9	40	20	0	0