Effect of Deregionalized Care on Mortality in Very Low-Birth-Weight Infants With Necrotizing Enterocolitis

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IMPORTANCE There has been a significant expansion in the number of low-level and midlevel neonatal intensive care units (NICUs) in recent decades. Infants with necrotizing enterocolitis represent a high-risk subgroup of the very low-birth-weight (VLBW) (<1500 g) population that would benefit from focused regionalization.

OBJECTIVES To describe the current trend toward deregionalization and to test the hypothesis that infants with necrotizing enterocolitis represent a particularly high-risk subgroup of the VLBW population that would benefit from early identification, increased intensity of early management, and possible targeted triage to tertiary hospitals.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted of NICUs in California. We used data collected by the California Perinatal Quality Care Collaborative from 2005 to 2011 to assess mortality rates among a population-based sample of 30,566 VLBW infants, 1879 with necrotizing enterocolitis, according to the level of care and VLBW case volume at the hospital of birth.

EXPOSURES Level and volume of neonatal intensive care at the hospital of birth.

MAIN OUTCOMES AND MEASURES In-hospital mortality.

RESULTS There was a persistent trend toward deregionalization during the study period and mortality rates varied according to the level of care. High-level, high-volume (level IIIB with >100 VLBW cases per year and level IIIC) hospitals achieved the lowest risk-adjusted mortality. Infants with necrotizing enterocolitis born into midlevel hospitals (low-volume level IIIB and level IIIA NICUs) had odds of death ranging from 1.42 (95% CI, 1.08-1.87) to 1.51 (95% CI, 1.05-2.15, respectively). In the final year of the study, just 28.6% of the infants with necrotizing enterocolitis were born into high-level, high-volume hospitals. For infants born into lower level centers, transfer to a higher level of care frequently occurred well into the third week of life.

CONCLUSIONS AND RELEVANCE These findings represent an immediate opportunity for local quality improvement initiatives and potential impetus for the regionalization of important NICU resources.
The past 4 decades represent a dynamic period in perinatal health care. In parallel with improvement in the survival of preterm infants, there was a transition from systematic regionalization in the 1970s to a period of deregionalization as neonatal intensive care technologies became more widely available. This paradigm shift led to an expansion in the number of low-level and midlevel neonatal intensive care units (NICUs) with an associated increase in the proportion of the preterm population born into nontertiary hospitals during the 1990s.

In 2011, the Toward Improving the Outcome of Pregnancy III: Enhancing Perinatal Health Through Quality, Safety and Performance Initiatives report emphasized the need for quality improvement initiatives and the focused regionalization of perinatal care. Important to achieving these goals is the early identification and targeted management of diseases that affect high-risk patient subgroups. Necrotizing enterocolitis (NEC), one such disease, is a leading cause of morbidity and mortality among preterm infants, affecting approximately 7% of very low-birth-weight (VLBW) (<1500 g) newborns. Necrotizing enterocolitis is an acquired disease that typically presents after the first week of life, suggesting a potential window of opportunity for intervention. Progressive disease occurs in approximately half of all affected infants with mortality rates exceeding 30% in those requiring an emergency operation. Non-specific presenting symptoms lead to delayed diagnosis and late transfer to higher levels of care.

Given that the management of NEC relies heavily on a multidisciplinary approach involving neonatologists, pediatric radiologists, and surgeons, it is increasingly important to understand the relationship between level of care and NEC outcomes in an era of deregionalization. Furthermore, institutional surgical capabilities contribute in large part to the American Academy of Pediatrics (AAP) neonatal level of care definitions. Necrotizing enterocolitis is thus well suited to serve as the substrate for a focused evaluation of the effect of deregionalization on disease-specific neonatal mortality.

We assessed the outcomes for VLBW infants born in California from 2005 to 2011. Our aims were to describe the current trend toward deregionalization and to test the hypothesis that infants with NEC represent a particularly high-risk subgroup of the VLBW population that would benefit from early identification, increased intensity of early management, and possible targeted triage to tertiary hospitals. Such findings would represent an immediate opportunity for quality improvement initiatives at the institutional level and broader motivation for the regionalization of vital neonatal care resources.

Methods

We performed a retrospective cohort study using data collected by the California Perinatal Quality Care Collaborative (CPQCC) from 2005 to 2011. This study was conducted under institutional review board waiver granted by the Stanford University Panel on Medical Human Subjects. More than 90% of all perinatal facilities in California submit detailed clinical data to the CPQCC, enabling high-integrity data capture for essentially every VLBW encounter. A unique identifier is assigned to each infant permitting longitudinal patient tracking across encounters and between facilities. Our study cohort included all VLBW infants born into a CPQCC-enrolled facility or a collocated facility (born into a separate hospital with an onsite satellite NICU) during the study period.

Level and Volume of Care

Neonatal intensive care units designate a self-reported level of care on an annual basis, with designations corresponding to the period-appropriate 2004 AAP policy statement. A level I facility is a newborn nursery that provides basic neonatal services and is not equipped to care for VLBW infants. Few VLBW deliveries occur in these facilities and typically represent emergency deliveries followed by immediate transfer to institutions that can provide higher levels of care. Such infants were excluded from our analysis. Level II NICUs are specialty centers capable of stabilizing and resuscitating high-risk infants and providing short-term mechanical ventilation. Level III NICUs are subspecialty centers that provide comprehensive neonatal care and are further subdivided into IIIA, IIIB, and IIIC based on the degree of surgical care available. Level IIIA NICUs have only minor surgical capabilities, not including the ability to perform laparotomy or peritoneal drainage for NEC. Level IIIB NICUs provide major surgery, including laparotomy and peritoneal drainage, and level IIIC NICUs provide major surgery with the additional capabilities of extracorporeal membrane oxygenation and cardiopulmonary bypass. These definitions were updated by the AAP in 2012 to include levels I to IV.

Given the annual assignment of the AAP designations and a study period that preceded the AAP update, we applied the 2004 level of care definitions to our analyses.

We calculated the number of NICUs by level of care for each year during the study period, the annual VLBW case volume for each NICU level of care, and the proportion of the VLBW population whose care was initially managed at each level of care, comparing the first year of the study (2005) with the final year of the study (2011). For all analyses, we created 4 distinct categories (levels II, IIIA, IIIB low volume, and IIIB/IIIC high volume). We empirically tested volume and level cutoffs, including the 25th, 50th, and 75th percentiles for volume at each category. The level IIIB NICUs in the 75th percentile for VLBW volume (>100 VLBW infants per year) had patient populations and unadjusted mortality rates similar to those of the IIIC centers and were grouped into the IIIB/IIIC high-volume category for subsequent analyses. This level IIIB/IIIC high-volume categorization, although empirically determined in our analysis, is congruent with the previous report of the VLBW volume-outcome relationship by Phibbs et al.

Study Cohorts

From the population of all VLBW infants born into CPQCC or collocated facilities, we identified those with and those without NEC. The CPQCC labeled VLBW infants as having NEC if they were diagnosed with NEC at operation or at postmortem examination, or if NEC was diagnosed clinically and radiographically according to the following criteria: 1 or more clini-
intestinal findings including bilious gastric aspirate or emesis, abdominal distention, or occult or gross blood in the stool in the absence of an anal fissure, and 1 or more radiographic findings including pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum. Infants who met these criteria, but were found at operation or postmortem examination to have an isolated intestinal perforation, were coded distinctly as having focal gastrointestinal perforation. We excluded infants with this disease process from the NEC group given their trend toward having an earlier presentation of disease, a lower overall mortality rate, and a general belief that focal perforation is a clinical entity distinct from NEC.8

Statistical Analysis
We compared infant and maternal characteristics across NICU levels of care using the χ² test for categorical variables and the Wilcoxon rank sum test for continuous variables with non-normal distributions. We performed multivariable logistic regression using in-hospital mortality as the dependent variable and NICU level of care as the dependent variable. Each infant and maternal covariate was tested independently and was included in the final model because they represent well-described perinatal risk factors. We built final models for the entire VLBW cohort as well as for VLBW infants without and VLBW infants with NEC. Given the inclusion of multiple continuous predictors in the final models, we assessed the goodness of fit according to Hosmer and Lemeshow8 and found an adequate fit for all 3 models (P = .56, P = .41, and P = .47) and receiver operating characteristic area-under-the-curve values of 0.87, 0.89, and 0.67, respectively. Statistical significance was determined by P < .05. All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc.).

Results
Level and Volume of Care
There was an overall increase in the number of NICUs in the CPQCC from 98 in 2005 to 127 in 2011 (Figure 1), a finding representative of the changing NICU landscape in California during that time. The entirety of this growth was attributable to an increase in the number of level II, IIIA, and IIIB NICUs; the number of level IIIC facilities decreased from 17 in 2005 to 15 in 2011. The annual VLBW volumes were larger for higher levels of care, from a median of 43 VLBW infants per year in level II NICUs to a median of 125 infants per year in level IIIC NICUs (Figure 2).

In addition to the growth in the number of low-level and midlevel NICUs, there was an associated change in the distribution of care for both the entire VLBW cohort and the NEC subgroup (Table 1). There was a decrease in the overall percentage of VLBW infants born into and having care initially managed at hospitals providing the highest degree of care (ie, level IIIB/IIIC high-volume NICUs) from 42.5% to 26.5% during the study period, a finding that was replicated in the NEC subgroup. The overall percentage of the study cohort born into and having care initially managed at level IIIA and IIIB low-volume NICUs increased substantially, and the proportion of the study population born into level II centers remained relatively constant throughout the study period.

Study Cohort Characteristics
From approximately 3 million live births in California during the study period, we identified 30566 VLBW infants, of whom 1879 (6.1%) developed NEC. Table 2 details infant and maternal characteristics. The VLBW infants without NEC born into level IIIB/IIIC high-volume NICUs had lower birth weights, were more likely to be less than 32 weeks’ gestational age at birth, and...
and were more likely to have major congenital malformations compared with those born into lower-level centers. Those born into level IIIB/IIIC high-volume NICUs also had lower initial length of stay and the highest rate of acute transfer to a higher level of care (for any medically indicated reason or owing to hospital bed shortage) compared with the unadjusted mortality rates, the VLBW infants with NEC born into level IIIB/IIIC high-volume NICUs. In accordance with the unadjusted mortality rates, the VLBW infants with NEC born into level IIIB/IIIC high-volume NICUs had a 42% to 51% increase in odds of mortality compared with VLBW infants born into level IIIB/IIIC high-volume NICUs.

Multivariable Logistic Regression

After adjusting for multiple infant and maternal characteristics, there was a 21% to 34% and a 21% to 32% increase in the odds of mortality for all VLBW infants and VLBW infants without NEC, respectively, born into level II, IIIA, or IIIB low-volume NICUs compared with those born into level IIIB/IIIC high-volume NICUs; odds ratios are reported in Table 3. This trend was exaggerated for VLBW infants with NEC born into level IIIA or IIIB low-volume NICUs, with a 42% to 51% increase in odds of mortality compared with VLBW infants born into level IIIB/IIIC high-volume NICUs. In accordance with the unadjusted mortality rates, the VLBW infants with NEC born into level II NICUs (those who had the shortest initial length of stay and the highest rate of acute transfer to facilities with a higher level of care) had risk-adjusted mortality rates comparable to those born into level IIIB/IIIC high-volume NICUs.

Sensitivity Analyses

We also performed an analysis limited to patients for whom the diagnosis of NEC was entered into the CPQC database on the initial data sheet obtained at the hospital of birth. This was done to specifically identify the cohort of infants with a confirmed diagnosis of NEC before transfer to another hospital. In this sensitivity analysis, the sample size decreased to approximately 900 infants, but the trends remained as described in the original sample (22%-42% increase in the odds of mortality for those born into level II, IIIA, or IIIB low-volume NICUs vs level IIIB/IIIC high-volume NICUs).
Discussion

Our study demonstrates that the deregionalization of neonatal intensive care continued in California from 2005 to 2011 and that risk-adjusted mortality was higher for VLBW infants born into lower-level, lower-volume centers, an observation consistent with findings from previous decades. Among VLBW infants with NEC, mortality was significantly increased at level IIIA and IIIB low-volume NICUs compared with the mortality for VLBW infants born into level IIIB/IIIC high-volume NICUs. We did not find a significant increase in mortality for those with NEC born into the lowest level of care (level II NICUs). Infants born into level II NICUs had a significantly higher rate of acute transfer and shorter birth hospital length of stay. These findings suggest the existence of effective triage practices for infants with suspected NEC born into low-level centers and an immediate opportunity for quality improvement initiatives at midlevel centers.

Table 2. VLBW Infant Characteristics by Hospital Volume and Level of Care, 2005 to 2011

<table>
<thead>
<tr>
<th>NICU Level of Care Category of Initial Hospitalization</th>
<th>VLBW Infants Without NEC</th>
<th>VLBW Infants With NEC</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td></td>
<td></td>
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<tr>
<td>Male sex, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, g, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appar score ≥7, %</td>
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<td></td>
</tr>
<tr>
<td>Mechanical ventilation &gt;4 h, %</td>
<td></td>
<td></td>
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<tr>
<td>Maternal factors, %</td>
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<tr>
<td>Abbreviations: IQR, interquartile range; LOS, length of stay; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; VLBW, very low birth weight.</td>
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a Level IIIB NICUs with more than 100 VLBW admissions per year were considered high volume and were combined with the level IIIC NICUs to represent the highest-level, highest-volume centers. One hundred VLBW admissions per year represented the 75th percentile for annual volume among level IIIC NICUs. |

b Acute transfer was defined as a transfer to a higher level of care for medical or surgical care not provided at the current center or transfer owing to facility bed limitations. 

c Calculation was median LOS in days at the birth hospital and included only infants undergoing acute transfer.
Table 3. ORs for Mortality by NICU Volume and Level of Care for VLBW Infants in California, 2005-2011*

<table>
<thead>
<tr>
<th>NICU Level and Volume</th>
<th>All VLBW Infants</th>
<th>VLBW Infants Without NEC</th>
<th>VLBW Infants With NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Level II (all volumes)</td>
<td>1.21 (1.04-1.41)</td>
<td>.02</td>
<td>1.21 (1.02-1.43)</td>
</tr>
<tr>
<td>Level IIIA (all volumes)</td>
<td>1.34 (1.17-1.52)</td>
<td>&lt;.001</td>
<td>1.32 (1.14-1.51)</td>
</tr>
<tr>
<td>Level IIIB (low volume)</td>
<td>1.31 (1.19-1.46)</td>
<td>&lt;.001</td>
<td>1.29 (1.15-1.44)</td>
</tr>
<tr>
<td>Level IIIB/IIIC (high volume)</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Abbreviations: NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; OR, odds ratio; VLBW, very low birth weight.

*Model included year of birth, sex, black race, birth weight, gestational age, Apgar scores at 1 and 5 minutes, severity-weighted congenital malformation score, patent ductus arteriosus, antenatal corticosteroid administration, respiratory distress syndrome, mechanical ventilation longer than 4 hours, multiple gestation, and prenatal care as well as maternal hypertension, gestational diabetes, and chorioamnionitis.

In 1976, the initial Toward Improving the Outcome of Pregnancy: Recommendations for the Regional Development of Maternal and Perinatal Health Services report called for the widespread, systematic regionalization of neonatal care facilities in an attempt to match infant needs with level of neonatal care. Initial reports of regionalized perinatal health care systems showed promising results. The process of regionalization in conjunction with the development of antenatal corticosteroid therapy and early postnatal surfactant therapy led to impressive decreases in overall perinatal infant mortality rates. However, the widespread dissemination of these technologies, a surplus of newly trained neonatologists, and emerging market forces driven by a new national reimbursement scheme prompted the subsequent era of deregionalization. This process continues in California today as evidenced by both an increase in the number of low-level and midlevel NICUs and an increase in the proportion of the VLBW population born into and treated within these centers.

After the initial call for regionalization, there were several studies highlighting specific trends that persist in our contemporary cohort. In 1982, Paneth et al described increased mortality for infants weighing 501 to 1250 g when born into midlevel centers compared with those born into the lowest or highest level of care. The authors noted prompt transfer of such infants out of low-level NICUs; however, the midlevel NICUs had longer initial lengths of stay. A subsequent analysis suggested that the lowest-level centers provided poorer intrapartum and early postpartum care, as evidenced by higher mortality rates, but engaged in more appropriate early transfer practices, leading to 28-day mortality rates comparable to those of tertiary NICUs. Conversely, the midlevel NICUs provided appropriate early care but had higher 28-day mortality rates presumably owing to inefficient transfer of high-risk infants. In our cohort we observed notably worse outcomes for VLBW infants with NEC born into midlevel centers (level IIIA and IIIB low-volume NICUs) associated with longer initial lengths of stay, frequently into the third week of life, compared with those born into the lowest (level II NICUs) and highest (level IIIB/IIIC high-volume NICUs) levels of care.

Infants with NEC represent a significant portion of the high-risk NICU population; approximately 13% of all VLBW deaths were associated with NEC in our study population. Along with improvement in the overall survival rates for preterm infants, the incidence of NEC has increased without substantial improvement in NEC-associated mortality rates. Continued improvement in outcomes for these high-risk infants therefore depends on either eliminating existing deficiencies across levels of care or improving the triage of high-risk newborns to tertiary centers earlier in the course of the disease. During the present study period, 3106 VLBW infants were born into level II NICUs. Improved adherence to the AAP guidelines with respect to prenatal triage of preterm deliveries will lead to improved outcomes for these infants. Furthermore, our results indicate that the timely transfer of VLBW infants to a level IIIB/IIIC high-volume NICU at the initial clinical concern for NEC may lead to significantly improved outcomes compared with the current practice of transferring infants with advanced NEC when emergency rescue surgery is required.

Given the nature of the data in the present study, we were unable to identify the exact time of disease onset. It is possible that a portion of our study population developed NEC after transfer to a higher level of care. Despite the detail available in the CPQCC data set, we were also unable to identify all potential confounders, such as bacterial sepsis, or the proximal cause of the disparities observed in the overall outcomes. Finally, although the odds of mortality for VLBW infants born into level II NICUs compared with the odds of mortality for those born into level IIIB/IIIC high-volume NICUs were not statistically significant, there was a relatively small number of infants in this category. It is possible that we may not have had the power to detect a significant difference for this comparison.

We speculate that the association described between the NICU level of care and odds of mortality results, at least in part, from the acuity of care provided during the early stages of disease and that early transfer to a higher level of care would mitigate this effect. The management of NEC relies on early recognition followed by aggressive initiation of bowel rest and empirical use of antibiotics. We believe that regionalization would enable the care of most infants to be managed at tertiary facilities with continuous access to specialists crucial to the timely diagnosis and initiation of existing management strategies. On a higher level, regionalization would facilitate more accurate assessment of novel therapies in controlled settings with uniform treatment protocols. We acknowledge that the difficulty in diagnosing NEC implies that regionalized care would require excess triage of several high-risk infants. However, we observed improved outcomes for all VLBW infants born into level IIIB/IIIC high-volume hospitals, indicating that excess triage would carry significant secondary benefits.
Conclusions

Outcomes for VLBW infants continue to be suboptimal when they are not born into high-level, high-volume centers. In a dynamic period of continued deregionalization, the NEC population is a particularly high-risk subgroup of the VLBW population for whom regionalized neonatal intensive care will be beneficial. A conscious refocusing of policy initiatives is required to maximize the quality of care provided to the youngest and most vulnerable members of our society.

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Study concept and design: Kastenberg, Lee, Gould, Sylvester.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Kastenberg, Lee, Sylvester.

Critical revision of the manuscript for important intellectual content: All authors.

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REFERENCES


