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Short-term weight gain velocity in infants with congenital diaphragmatic hernia (CDH)

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ABSTRACT

Background: Appropriate post-natal growth remains a mainstay of therapeutic goals for infants with CDH, with the hypothesis that optimizing linear growth will improve survival through functional improvements in pulmonary hypoplasia. However, descriptions of growth and the effect on survival are limited in affected infants.
Objective: Describe in-hospital weight gain related to survival among infants with CDH.
Design/methods: Children's Hospitals Neonatal Database (CHND) identified infants with CDH born ≥34 weeks' gestation (2010–14). Exclusion criteria were: admission age > 7 days, death/discharge age < 14 days, or surgical CDH repair prior to admission. Weight gain velocity (WGV: g/kg/day) was calculated using an established exponential approximation and the cohort stratified by Q1: <25%ile, Q2–3: 25–75%ile, and Q4: >75%ile. Descriptive measures and unadjusted Kaplan-Meier analyses describe the implications of WGV on mortality/discharge.
Results: In 630 eligible infants, median WGV was 4.6 g/kg/day. After stratification by WGV [Q1: ($n = 156$; <3.1 g/kg/day); Q2–3 ($n = 316$; 3.1–5.9 g/kg/day), and Q4 ($n = 158$, >5.9 g/kg/day)] infants in Q1 had shortest median length of stay, less time on TPN and intervention for gastro-esophageal reflux relative to the other WGV strata ($p < 0.01$ for all). Unadjusted survival estimates revealed that Q1 [hazard ratio (HR) = 9.5, 95% CI: 5.7, 15.8] and Q4 [HR = 2.9, 95% CI: 1.7, 5.1, $p < 0.001$ for both] WGV were strongly associated with NICU mortality relative to Q2–3 WGV.
Conclusion: Variable WGV is evident in infants with CDH. Highest and lowest WGV appear to be related to adverse outcomes. Efforts are needed to develop nutritional strategies targeting optimal growth.

1. Introduction

Congenital diaphragmatic hernia (CDH) occurs in 1:2000 to 1:3000 live births [1,2] and is associated with pulmonary hypoplasia, pulmonary hypertension (PH), LV hypoplasia, respiratory failure, and indeed a 24–40% risk of mortality [3–10]. Additional contributors to mortality include preterm birth (<34 weeks gestation), type of surgical repair, prenatal diagnosis of CDH, and the presence of associated major congenital anomalies (cardiac, genetic syndrome, and other major anomalies) [10,11].

Appropriate post-natal growth remains a mainstay of therapeutic goals for infants with CDH, with the hypothesis that optimizing growth will improve survival through functional improvements in pulmonary hypoplasia. Despite this hypothesis, growth failure has been reported throughout the hospitalization in infants with CDH, with an incidence of 26% at ICU discharge to 38% at hospital discharge [12]. Other reports demonstrate this persistent trend through 6 months and 12 months of age, with growth failure shown in 60% and 20–30% of infants with CDH, respectively [12,13]. In a population of critically ill, mechanically ventilated infants without CDH, suboptimal nutrient intake was

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associated with significant morbidity and mortality [14]. While these studies provide some insight into the frequency of growth failure in infants with CDH, little is known about in-hospital growth velocity and the contribution to adverse outcomes. We hypothesized that greater early post-natal growth velocity would be associated with survival in infants with CDH. In this report, our aim was to describe growth velocity in infants with CDH that survived >14 days.

2. Methods

2.1. Data sources and eligibility criteria

The Children's Hospital Neonatal Database (CHND) captures clinical data on every infant admitted to 28 participating Level IV NICUs [15,16]. The procedures for data abstraction have been previously described [15], and in summary, prospective and ongoing training with clinical definitions, case-based practice, and annual auditing for reliability and validity occur at each participating center.

We identified infants with CDH who were referred to CHND centers in 2010–14. These infants were distinguished from those with pulmonary adenomatoid malformations, sequestrations, lobar emphysema, and other lung malformations.

Infants were excluded if their database records were incomplete, diaphragmatic repair had occurred prior to referral, were previously discharged home prior to admission, or born <34 weeks' gestation. The gestational age exclusion was included because it corresponds to relative contraindications for extracorporeal support (ECMO) and outcomes differ for preterm infants with CDH [10,17]. Also, infants who were admitted after 7 days of life or whose length of stay (LOS) was <14 days were omitted. The latter was applied because infants were not expected to add significant body weight in a period shorter than 14 days, regardless of disease severity. We then trimmed the cohort based on weight-gain velocity (<3rd%ile or >97th%ile) as outlier weight-gain was not a focus of the analysis. Finally, we linked CHND records to administrative data in PHIS, the Pediatric Health Information System, for validation purposes and thus, unlinked records were omitted.

2.2. Outcome(s) measurement

The primary outcome was inpatient weight-gain velocity (WGV) measured from the time of birth to discharge or death. Using patients' recorded weights, WGV was estimated using a validated, exponential method [18,19]; $WGV = [1000 \times \ln(W_n / W_1)] / (D_n - D_1)$ where n denotes the day when the discharge or death weight was recorded and "1" denotes birth weight. Once calculated, the cohort was stratified into three groups based on WGV, Quartile 1 (Q1: WGV < 25%ile), Quartiles 2–3 (Q2–3: WGV 25–75%ile) and Quartile 4 (Q4: WGV > 75%ile).

Using the stratification of Q1, Q2–3, and Q4 of WGV, we describe secondary outcomes among these three groups including mortality, burden of respiratory support, duration of total parenteral nutrition (TPN), central line days, TPN delivery after NICU discharge , route of feedings, mode of feeding (bolus vs continuous), type of feeding tube utilized at discharge, and treatment for gastroesophageal reflux. These analyses were done among survivors to NICU discharge, as applicable. For infants that died, we also report their presumptive cause of death designated by the medical providers.

2.3. Independent variables & data analyses

Infants were described using antenatal, pre-referral or post-admission characteristics. Birth characteristics included gender, gestational age at birth in completed weeks' gestation, associated anomalies as previously described, location of birth, APGAR scores, resuscitative interventions at birth, and small for gestational age (SGA), defined as birth weight less than or equal to the 10th percentile using gender-specific standards [20]. Each parameter was used to describe the eligible infants stratified by WGV. Given their association with prolonged LOS, both the use of ECMO and incident blood stream infections (BSIs) in accordance with National Healthcare Safety Network (NHSN) definitions [21], were reported.

Bivariable analyses were performed to determine which variables were associated with WGV. Student's t-test and χ^2 test of proportions were used, as appropriate, and non-parametric testing was used for variables that demonstrated significant variation from a normal distribution (e.g., gestational age, age at referral). Then, multivariable multinomial regression analyses were used to isolate the factors that were independently associated with WGV. Significant predictors were kept using backward selection until no longer significant with the inclusion of other variables.

In secondary analyses, we re-defined an equation to predict the timing to discharge using a life table/Kaplan-Meier analysis, thus, WGV became a predictor of mortality using LOS as the variable for time after birth. As a secondary analysis, only unadjusted analyses are reported.

Data description and analyses were performed using SAS v9.3 (Cary, NC). Each contributing hospital obtained IRB oversight to participate in the CHND; the Ann & Robert H. Lurie Children's Hospital of Chicago Research Center's Institutional Review Board approved this study (#2011-14673).

3. Results

Information on 1083 infants with CDH were accessed in CHND on 2/01/2015. Infants were omitted based on gestational age < 34 weeks ($n = 77$), admission after 7 days of age ($n = 12$), length of stay < 14 days ($n = 142$), incomplete charts ($n = 98$) or home or repaired prior to admission ($n = 48$). Also, 40 infants were excluded because their growth was <3rd%ile or >97th %ile in WGV and 36 infants' records remained unlinked to the PHIS data to determine hospital LOS. Thus, 630 infants were included in the analysis. 532 infants (84%) survived to discharge, and due to intra- and inter-hospital transfers from the NICU in 52 infants, 480 infants were available for analysis at the time of NICU discharge.

These eligible infants stratified in the following quartiles of WGV: 156 in Q1 (24.8%), 316 in Q2–3 (50.2%) and 158 in Q4 (25.1%; Table 1). 480 infants were discharged home, 102/480 (21.3%) in Q1, 260/480 (54.2%) in Q2–3 and 118/480 (24.6%) in Q4. Overall weight gain velocity was 4.7 g/kg/day (IQR 3.3–5.8) with median WGV of 1.9 g/kg/day in Q1, 4.6 g/kg/day in Q2–3, and 6.8 g/kg/day in Q4 ($p < 0.0001$). In-hospital WGV was similar for survivors and non-survivors (Fig. 1) and did not vary with LOS.

CDH infants in Q1 had a shorter hospital length of stay, were less likely to have an intrathoracic stomach prior to repair, were more likely to have a primary repair of the diaphragm, and had lower respiratory morbidity (Fig. 1). Infants in Q2–3 had a slightly higher gestational age at birth and a significantly lower mortality rate than infants in the other strata. And infants in Q4 were more likely to be born at <37 weeks' gestation, small for gestational age (SGA), and with a lower birth weight and head circumference. No differences were seen between groups regarding age at referral, sex, the presence of anomalies, and multiple gestation. With respect to postnatal factors, assignment of an APGAR <3 at 5 min, admission pH < 7, brain imaging abnormalities, postnatal treatment with steroids, and ECMO use were similar between groups.

Overall weight gain during hospitalization followed a linear pattern over time for both survivors and non-survivors (R-sq. = 0.8843; $R = 0.94$). Overall mortality was 15.6%, and variability in mortality was seen between groups (29.5% in Q1, 7.9% in Q2–3, and 17.1% in Q4; $p < 0.001$). Unadjusted survival estimates revealed that Q1 [hazard ratio (HR) = 9.5, 95% confidence intervals (CI): 5.7, 15.8] and Q4 [HR = 2.9, 95% CI: 1.7, 5.1, $p < 0.001$ for both] WGV were strongly