RESEARCH LETTER

Association of Oxygen Target and Growth Status With Increased Mortality in Small for Gestational Age Infants: Further Analysis of the Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT)\(^1\) compared the effect of oxygen saturation targets on retinopathy of prematurity or death among infants born at 24 to 27 weeks' gestational age. One thousand three hundred sixteen infants were randomized to lower (85%-89%) vs higher (91%-95%) target oxygen saturation. Rates of severe retinopathy of prematurity or death were not different (28.3% and 32.1%, respectively; relative risk with lower target, 0.90; 95% CI, 0.76-1.06; \(P = .21\)). Lower oxygen targets reduced severe retinopathy of prematurity among survivors (8.6% vs 17.9%; relative risk, 0.52; 95% CI, 0.37-0.73; \(P < .001\)). However, an unanticipated and unexplained finding was increased mortality in the lower saturation group (19.9% vs 16.2%; relative risk, 1.27; 95% CI, 1.01-1.60; \(P = .04\)). The study included neurodevelopmental assessment at 2 years of age; at that assessment we noted a disproportionate loss of small for gestational age (SGA) infants. This observation promoted us to assess whether there was an interaction between oxygen target group and growth status.

\section*{Methods}

Methods and outcomes of SUPPORT have been reported previously.\(^1\) The study was approved by the institutional review boards at all participating institutions, and parents gave written informed consent for enrollment prior to delivery. In this post hoc analysis, we compared survival rates and causes between SGA (<10% on the Olsen curves)\(^2\) and appropriate for gestational age (AGA) infants by assigned target saturation groups using Kaplan-Meier survival analyses. We repeated the analyses in the original cohort using Poisson regression in a generalized estimating equations model that controlled for stratification by clinical center, gestational age strata (24 0/7 to 25 6/7 weeks vs 26 0/7 to 27 6/7 weeks), and familial clustering (as multiple births were randomized to the same treatment group) with the addition of a term-testing interaction between the randomized oxygen target group and growth status.

\section*{Results}

Of the 1316 infants enrolled in SUPPORT, 237 infants died (Table). Thirty-seven of 96 SGA infants (38.5%) died, while 200 of 1220 AGA infants (16.4%) died (\(P < .01\)). Mortality did

\begin{table}
\centering
\begin{tabular}{llll}
\hline
\textbf{Table. Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial Population Characteristics and Causes of Death by Growth Status} & & & \\
\hline
\textbf{Population Characteristics} & \textbf{Infants, No./Total No. (\%)} & \textbf{\textit{P} Value for Significance} \\
\hline
Birth weight, mean (SD), g & SGA (\(n = 96\)) & AGA (\(n = 1220\)) & \\
516.3 (89.3) & 854.8 (76.8) & <.001 \\
Gestational age at birth, mean (SD), wk & 26.1 (1.1) & 26.2 (1.1) & .33 \\
Multiple birth & 14/96 (14.6) & 323/1220 (26.5) & .01 \\
Male & 46/96 (47.9) & 666/1220 (54.6) & .21 \\
Race/ethnicity & & & \\
Non-Hispanic black & 38/96 (39.6) & 451/1220 (37.0) & \\
Non-Hispanic white & 46/96 (47.9) & 475/1220 (38.9) & \\
Hispanic & 8/96 (8.3) & 251/1220 (20.6) & \\
Other/unknown & 4/96 (4.2) & 43/1220 (3.5) & \\
Antenatal steroids (any) & 91/96 (94.8) & 1174/1219 (96.3) & .45 \\
Death & & & \\
In the delivery room & 1/96 (1.0) & 5/1220 (0.4) & .38 \\
Prior to discharge & 37 (38.5) & 200 (16.4) & <.01 \\
Causes of death & & & \\
Respiratory distress syndrome & 8 (21.6) & 43 (21.5) & \\
Bronchopulmonary dysplasia & 8 (21.6) & 18 (9) & \\
Intraventricular hemorrhage & 4 (10.8) & 20 (10) & \\
Infection & 2 (5.4) & 42 (21) & \\
Necrotizing enterocolitis or perforation & 6 (13.5) & 38 (19) & \\
Malformation & 1 (2.7) & 12 (6) & \\
Pulmonary hypoplasia & 2 (5.4) & 4 (2) & \\
Other & 7 (18.9) & 23 (13.5) & \\
\hline
\end{tabular}
\end{table}

Abbreviations: AGA, appropriate for gestational age; SGA, small for gestational age.
not differ significantly for AGA infants between both saturation groups (lower target 17.6% vs higher target 15.2%; \( P = .17 \)). In contrast, SGA infants had more than twice the mortality in the lower vs the higher target group (lower target 56.1% vs higher target 25.5%; \( P < .01 \); interaction term \( P = .06 \)) (Figure). Severe retinopathy of prematurity was reduced in the lower saturation group in AGA infants (8.5% vs 16.5%; relative risk 0.55; 95% CI, 0.30-0.78; \( P < .001 \)), with a numerical difference in the SGA survivors that did not reach statistical significance (12.5% vs 35.1%; relative risk 0.59; 95% CI, 0.17-2.07; \( P = .41 \)). The leading causes of death in the AGA infants were respiratory distress syndrome and infection, while the leading causes of death in SGA infants were respiratory distress syndrome and bronchopulmonary dysplasia. There was no difference in mortality from necrotizing enterocolitis (14% SGA vs 16% AGA).

**Discussion** | This post hoc study found evidence of an interaction between SGA infants and lower oxygen targets associated with increased mortality, which, to our knowledge, has not been reported before. Appropriate for gestational age infants did not experience the same mortality in the lower

---

**Figure. Kaplan-Meier Survival Curves for Small and Appropriate for Gestational Age Infants in the Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial by Randomized Oxygen Saturation Strata**

A, Small for gestational age infants randomized to the lower oxygen target (shown in tan) had significantly poorer survival than those randomized to the higher oxygen target (shown in blue). B, Appropriate for gestational age infants had similar mortality between the 2 oxygen strata.
saturation group. It is known that SGA infants have higher mortality and worse outcomes compared with AGA infants of the same gestation.1 Furthermore, growth restriction has been shown to increase the risk of pulmonary hypertension in the setting of bronchopulmonary dysplasia.4-6 These reports mirror our finding of bronchopulmonary dysplasia as a leading mortality cause in the SGA cohort.

We view these analyses as hypothesis generating. These results must be confirmed in other oxygen targetting studies. An important opportunity to do this is in the planned Neonatal Oxygenation Prospective Meta-analysis, which includes data from 4800 infants with a prespecified analysis by growth status. We speculate that SGA infants may experience hypoxia in utero that destabilizes respiratory control or affects pulmonary vascular resistance, increasing vulnerability to lower saturation targets.

Michele C. Walsh, MD, MSc
Juliani M. Di Fiore, BSEE
Richard J. Martin, MD
Marie Gantz, PhD
Waldemar A. Carlo, MD
Neil Finer, MD

Author Affiliations: Department of Pediatrics, University Hospitals Rainbow Babies and Children’s Hospital, Case Western Reserve University, Cleveland, Ohio (Walsh, Di Fiore, Martin); RTI International, Research Triangle Park, North Carolina (Gantz); Department of Pediatrics, University of Alabama, Birmingham (Carlo); Department of Pediatrics, University of California, San Diego (Finer).

Corresponding Author: Michele C. Walsh, MD, MSc, Division of Neonatology, Rainbow Babies and Children’s Hospital, 11100 Euclid Ave, Cleveland, OH 44106-6010 (michele.walsh@uahospitals.org).


Author Contributions: Dr Gantz had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the analyses. Study concept and design: Walsh, Martin, Carlo. Acquisition, analysis, or interpretation of data: Walsh, Di Fiore, Gantz, Carlo, Finer.

Drafting of the manuscript: Walsh, Di Fiore, Martin.

Critical revision of the manuscript for important intellectual content: Di Fiore, Gantz, Carlo, Finer.

Statistical analysis: Walsh, Gantz.

Obtained funding: Walsh, Martin.

Administrative, technical, or material support: Di Fiore, Carlo.

Study supervision: Martin.

Conflict of Interest Disclosures: None reported.

Funding/Support: The National Institutes of Health and the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network provided grant support for the study and supplemental funding via R03HD078528.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: This article represents the views of the authors and does not necessarily represent the views of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network.

Additional Contributions: The members of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network who contributed to this article include Barbara Stoll (Emory University, Atlanta, Georgia), Pablo Sanchez (Nationswide Childrens Hospital, Columbus, Ohio), Kristi Watterberg, (University of New Mexico, Albuquerque), Seetha Shankaran (Wayne State University, Detroit, Michigan), and Rose Higgins (Eunice Kennedy Shriver National Institutes of Child Health and Human Development, Bethesda, Maryland). Data collected at participating sites of the NICHD Neonatal Research Network were transmitted to RTI International, the data coordinating center for the network, which performed the storage, management, and analyses of the data.


Letters

Resource Burden During the 2014 Enterovirus D68 Respiratory Disease Outbreak at Children’s Hospital Colorado: An Unexpected Strain

Enterovirus D68 (EV-D68) is a unique enterovirus that shares biological properties with human rhinoviruses.1 It primarily causes respiratory disease, particularly in children with asthma. Although rarely reported from 1970 to 2005, small clusters of EV-D68 respiratory disease have been increasingly reported since 2008.2-3 From August to November 2014, an outbreak of EV-D68 respiratory disease occurred throughout the United States, with 1153 microbiologically confirmed infections in 49 states.4,5 However, owing to marked underascertainment of cases, the true magnitude and impact of this outbreak are difficult to estimate. The objective of this study is to characterize and quantify the resource burden at a tertiary care children’s hospital during the 2014 EV-D68 respiratory disease outbreak.

Methods | Children’s Hospital Colorado (CHCO) Anschutz Medical Campus is a tertiary care children’s hospital in Aurora, Colorado, operating 444 inpatient beds including 32 pediatric intensive care unit beds, with approximately 17000 inpatient admissions and 70 000 emergency department visits in 2014. Based on epidemiologic data from respiratory virus testing at CHCO, the EV-D68 outbreak period was defined as August 1 through September 30, 2014 (Figure 1).

This is an observational retrospective time series study comparing observed resource utilization during the defined 2014 EV-D68 outbreak period vs expected values forecasted from historical data. Monthly resource utilization data were collected through the CHCO infectious disease data warehouse. Respiratory patient volumes include children with International Classification of Diseases, Ninth Revision codes within major diagnostic category 4 (diseases and disorders of the respiratory system). Days of therapy (DOT) reflect documented administration of a medication or treatment on a calendar day in the electronic medical record. Direct patient care services delivered by respiratory therapists were converted into units of service (UOS) using Children’s Hospital Association Pediatric Analysis and Comparison Tool criteria. This study...