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Reply

To the Editor:

We appreciate the questions raised by Thanh et al about our clinical trial evaluating the safety and efficacy of intravenous umbilical cord blood infusion for the treatment of children with autism spectrum disorder (ASD). We did not target CD34 dosing in this clinical trial because our preclinical studies and early-phase clinical trial data in children with ASD and children with cerebral palsy (CP) did not show any association between improvement and CD34 dosing.

Our data showed that the cell responsible for modulation of neuroinflammation, stimulation of oligodendrocyte proliferation, remyelination, and increasing whole brain connectivity is the CD14+ monocyte in cord blood.[1-4] Cord blood banks do not measure CD14 cell content but do measure total nucleated cells (TNCCs) and CD34. For this reason, selection of cord blood units for the participants with ASD and CP in our clinical trials has been based on TNCC. We are investigating whether infused CD14 cell doses correlate with response but do not have that data at this time.

In our first randomized trial using autologous cord blood in young children with CP, we reported an effective dose threshold of 25 million cells/kg.[5] We saw the same trend in our initial phase I trial in children with ASD.[6] Since that time, we have targeted greater TNCC doses in our trials involving children with CP and have observed a dose effect up to 100 million cells/kg (unpublished data). For our trials with children with ASD, we target a minimal dose of 25 million cells/kg. Although CD34 cell dosing is quantitated in all our trials, we have not seen any relationship between CD34 dose and response. The CD34 doses in the trial reported in *The Journal* are typical of CD34 doses achievable with an unmodified cord blood transplant or cord blood infusion. We are following children in the trial published in *The Journal* for a period of 12 months postinfusion and will be reporting the 12-month outcome data at a later date.

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https://doi.org/10.1016/j.jpeds.2020.11.064

Supported by The Marcus Foundation, Atlanta, GA. G.D. reports technology unrelated to the submitted work that has been licensed and she and Duke University School of Medicine have benefited financially. G.D. has patents 62757234, 62757226, 15141391, and 62470431 pending. J.K. has a patent 62470431 pending and Duke University School of Medicine signed an option agreement with CryoCell International to license the clinical indication in this study.

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Premature congenital heart disease: building a comprehensive database to evaluate risks and guide intervention

To the Editor:

We read with interest the report by Matthiesen et al.[1] This large population based study found a 2-fold increase in incidence of preterm birth in the setting of major congenital heart disease (CHD) and delineated specific subgroups of CHD with even higher adjusted risks (specifically, right ventricular outflow tract obstructions). This study fills a major gap of knowledge with respect to understanding the link between certain CHD lesions and the insults to the fetal environment, and highlights that little is known about the impact of perinatal risk factors on outcomes for this vulnerable preterm population. This is in part due to the recognition that no existing neonatal or cardiac focused database adequately collects the full spectrum of data points (eg, prenatal, perinatal, postnatal, and surgical) critical to perform outcomes research and identify best practices for the neonatal population with CHD. In addition, unique to preterm patients with CHD, postnatal care often requires transfer of patients between neonatal and cardiac units, further impeding comprehensive data collection.

Recent studies have explored the link between maternal disorders and CHD,[2,3] but the majority of contemporary postnatal evidence has focused on the negative associations between CHD mortality and gestational age at birth.[4-6] Despite advances in neonatal, cardiac, and cardiothoracic surgical management that continue to improve morbidity and mortality outcomes for premature infants with CHD, severe neonatal morbidities (eg, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and bronchopulmonary dysplasia) still exist in this population, although true incidence of each varies between studies and by gestational age.[4-6] To fully understand the complex interplay between maternal factors, CHD, and prematurity, and to better identify specific prognostic factors for guiding therapeutic interventions and discerning outcomes, a multicenter neonatal-cardiac database that collects comprehensive prenatal, perinatal, and postnatal data throughout a hospital course is needed specifically for preterm CHD.

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https://doi.org/10.1016/j.jpeds.2020.11.056

The authors declare no conflicts of interest.
Acknowledgments are available at www.jpeds.com.

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Reply

To the Editor:

We thank Chaudhry et al and the Children's Hospital Neonatal Consortium Cardiac Focus Group for the recognition and the interest in our recently published work. Moreover, we thank the authors for raising the important need for databases encompassing prenatal, neonatal, postnatal, and surgical data on patients with congenital heart defects. We agree that such databases are urgently needed to identify and stratify this patient population according to the risk of mortality and short-term complications such as neonatal morbidities, but also long-term complications such as neurodevelopmental disorders. Databases covering data from before to after delivery hold the potential to inform clinical practice and may ultimately provide the stepping-stones for improving outcomes.

Previous studies have indicated that prenatal factors such as fetal growth and maternal medical conditions may impact outcomes in this population.[1-3] Perinatal factors such as timing of delivery and time to neonatal surgery,[4-6] and intraoperative factors such as hematocrit have also been shown to affect outcomes.[7] However, studies have been scarce and many studies have been limited by small sample sizes, and we agree with Chaudhry et al that several gaps in the current knowledge still exist.

In Denmark, the setting of our study, several opportunities to combine individual level prenatal, perinatal, and postnatal data exist. Prenatal and perinatal data have been collected in the Danish Fetal Medicine Database (nationwide since 2011)[8] and the Danish Medical Birth Registry (nationwide since 1973).[9] Neonatal data from all Danish neonatal intensive care units are currently collected in the Danish National Quality Database for Newborns (nationwide since 2016).[10,11] Lifelong follow- up is enabled by multiple sources, including hospital diagnoses and surgical procedures stored in the Danish National Patient Registry (nationwide since 1977)[12]; prescribed medication in the Danish National Prescription Registry (nationwide since 1994)[13]; and vital status in the Civil Registration System (nationwide since 1968).[14]

Acknowledgment

We are indebted to the following institutions that serve the infants and their families, and these institutions also have invested in and continue to participate in the Children's Hospital's Neonatal Database (CHND).

Jeanette Asselin, Beverly Brozanski, David Durand (ex officio), Francine Dykes (ex officio), Jacquelyn Evans (Executive Director), Theresa Grover, Karna Murthy (Chair), Michael Padula, Eugenia Pallotto, Anthony Piazza, Kristina Reber, and Billie Short are members of the Children's Hospitals Neonatal Consortium, Inc. For more information, please contact: support@thechnc.org.

The site sponsors/contributors for the CHND include:

1. AI DuPont Hospital for Children, Wilmington, DE (Kevin Sullivan)
2. All Children's Hospital, St. Petersburg, FL (Victor McKay)
3. American Family Children's Hospital, Madison, WI (Jamie Limjoco)
4. Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL (Karna Murthy, Gustave Falciglia)
5. Arkansas Children's Hospital, Little Rock, AR (Robert Lyle, Becky Rogers)
6. Brenner Children's Hospital, Winston Salem, NC (Cherie Welch)
7. Children's Healthcare of Atlanta, Atlanta, GA (Anthony Piazza)
8. Children's Hospital and Research Center Oakland, Oakland, CA (Priscilla Joe)
9. Children's Hospital Boston, Boston, MA (Anne Hansen)
10. Children's Hospital Colorado, Aurora, CO (Theresa Grover)
11. Children's Hospital of Alabama, Birmingham, AL (Carl Coghill)
12. Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA (Toby Yanowitz)
13. Children's Medical Center, Dallas, TX (Rashmin Savani,)
14. Children's Mercy Hospitals and Clinics, Kansas City, MO (Eugenia Pallotto)
15. Children's National Medical Center, Washington, DC (Billie Short, An Massaro)
16. Children's Healthcare of Atlanta at Scottish Rite (Gregory Sysyn)
17. Children's Hospital Los Angeles, Los Angeles, CA (Rachel Chapman)
18. Children's Hospital of Michigan, Detroit, MI (Girija Natarajan)
19. Children's Hospital of Omaha (Lynne Willett, Nicole Birge)
20. Children's Hospital of Wisconsin, Milwaukee, WI (Michael Uhing, Ankur Datta)
21. Children's Hospital Orange County, Los Angeles, CA (Michel Mikhael)
22. Cincinnati Children's Hospital, Cincinnati, OH (Beth Haberman)
23. Connecticut Children's Hospital, Hartford, CT (Annmarie Golioto)
24. Cook Children's Health Care System, Fort Worth, TX (Annie Chi, Yvette Johnson)
25. Florida Hospital for Children (Rajan Wadhawan)
26. Hospital for Sick Children, Toronto, ON (Kyong-Soon Lee)
27. Le Bonheur Children's Hospital, Memphis, TN (Ajay Talati)
28. Nationwide Children's Hospital, Columbus, OH (Kristina Reber)
29. Primary Children's Medical Center, Salt Lake City, UT (Con Yee Ling)
30. Rady Children's Hospital, San Diego, CA (Mark Speziale, Laurel Moyer)
31. Riley Children's Hospital, Indianapolis, IN (William Engle)
32. Seattle Children's Hospital, Seattle, WA (Elizabeth Jacobsen-Misbe, Robert
33. St. Christopher's Hospital for Children, Philadelphia, PA (Suzanne Touch)
34. St. Louis Children's Hospital, St Louis, MO (Rakesh Rao, Beverly Brozanski)
35. Texas Children's Hospital, Houston, TX (Gautham Suresh)
36. The Children's Hospital of Philadelphia, Philadelphia, PA (Michael Padula, David Munson)