of conditions such as postural orthostatic tachycardia syndrome based on OI and nausea has resulted in a treatable problem in many of these youth.[1] In fact, we have seen the nausea resolve when the OI is treated.[2] Screening for OI can be easily done in the physician's office without the need to expose the child to unnecessary procedures. If there is evidence of OI, the child and family can be advised to follow recommendations for management of OI, the first choice of which is lifestyle modifications, such as increased fluid intake and physical activity.[3]

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S.T. serves as a consultant for Takeda Pharmaceuticals. J.F. serves on the speakers' bureau for Mead Johnson.

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A phase II randomized clinical trial of the safety and efficacy of intravenous umbilical cord blood infusion for treatment of children with autism spectrum disorder

To the Editor:

Dawson et al have drawn attention to the outcomes of umbilical cord blood (UCB) administration for the treatment of 180 children with autism spectrum disorder (ASD).[1] Because there is a substantial interest in stem cell therapy as a potential candidate or therapeutic approach for ASD, these outcomes are noteworthy. The authors provide findings from a large sample size, randomized process with a control group, and processing paradigms, although the results did not support the efficacy of UCB administration. However, several points may influence interpretation of the findings.

First, we note that the authors administrated a relatively low dose of UCB-derived mononuclear cells and CD34+ cells compared with previous studies.[2,3] Other investigators have suggested that the minimum cell dose at which the CD34+ could show influence in nonmalignant diseases is 1.7×10^5 CD34+ cells per kilogram of patient's body weight (PBW).[4] The CD34+ cells in the current studyare 0.3×10^5 cells/kg PBW and 0.7×10^5 cells/kg PBW for autologous UCB and allogeneic UCB, respectively. In addition, intravenous infusion of cells limits delivery, as cells might be trapped in organs such as the lung, heart, liver, or kidney, which in turn reduces therapeutic effects on the brain.[5] Hence, the dosage of UCB may be a reason for the lack of evidence of efficacy. Second, the authors reported the results of a 6-month follow-up; this is a relatively short period to observe the progressive improvement of children with ASD. Previous studies demonstrated improvements observed after 12-month and 18-month follow-up, especially on the Childhood Autism Rating Scale score[3] and the Clinical Global Impression Scale.[6,7]

In summary, the authors' conclusion may be limited within the trial's scope and suggest no significant difference between 2 groups when CD34+ cells were administrated intravenously at the lower dose with a 6-month follow-up. Future research using UCB (high CD34+ cells and multiple doses) via other administration routes should be considered.

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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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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