How can we prevent early death in preterm infants?

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The study by de Almeida et al. is a multi-center prospective cohort study of early (< 6 days of age) intrahospital neonatal deaths of very low birth weight (VLBW) infants from eight tertiary care hospitals in Brazil.[1] It was observed that 16% of the 579 eligible infants died early, and the mortality rate varied from 5-31% between centers. This difference in mortality between centers persisted despite adjustments for illness severity. In addition to center of birth, other variables that were associated with mortality were lower gestational age, absence of maternal hypertension, lower Apgar scores, and presence of respiratory distress syndrome. There are several important strengths and limitations of this analysis and certain useful insights that can be obtained from this report as will be discussed in this commentary.

The strengths of this study include the multi-center nature of the study involving eight tertiary university hospitals from three states, the prospective cohort evaluation, use of an unambiguous "hard" outcome such as mortality, and careful evaluation of illness severity using the Score for Neonatal Acute, Physiology, Perinatal Extension, Version II (SNAPPE-II). A limitation is that the results from these tertiary centers may not be generalizable to peripheral centers which may have worse outcomes for a similar illness severity or to similar tertiary centers in other developing countries wherein the local infrastructure and staff expertise may be different. In addition, despite an adequate sample size for the regression analysis as performed in this study, a detailed

evaluation of factors contributing to intercenter differences in early mortality requires a larger number of analyzed variables and a corresponding increase in sample size.

The variables associated with early neonatal mortality in this study such as center of birth, lower gestational age, absence of maternal hypertension, lower Apgar scores, and presence of respiratory distress syndrome are well known as predictors of mortality and these results may, therefore, be considered as unsurprising. However, important insights into the causes of mortality may be obtained by a closer evaluation of the center variable. The authors are to be commended on their focus on the factors underlying intercenter differences in mortality. As the authors rightly point out, differences in mortality persist even after corrections for differences in neonatal characteristics. Such differences are well known,[2,3] but explanations for these differences have been lacking. The authors show that important differences exist in "evidence-based potentially better practices" such as antenatal steroids, prophylactic surfactant, and active resuscitation between these units, although it is difficult to determine which of these interventions were actually beneficial in this population. It must also be remembered that use of an intervention does not necessarily indicate a "need" for that intervention and that association of a variable with a bad outcome may indicate either that the variable is a marker of outcome (and not a predisposing factor), or is a response of the neonate (or the clinician) to

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a different factor associated with the bad outcome or may possibly indicate involvement of the variable in the causal pathway leading to death. In general, variables contributing to intercenter differences (after correcting for markers of illness severity) can be broadly classified as:

(a) Known and measured variables. These are variables that are known to be associated with outcomes and are commonly measured (e.g. use of antenatal steroids, prophylactic surfactant, use of continuous positive airway pressure, severity of intraventricular hemorrhage, etc.).

(b) Known and unmeasured variables. These are variables that are known to be associated with outcomes but are not commonly measured, either to limit the number of collected variables for purposes of analysis or to limit the cost and labor involved (e.g. tidal volumes, mean airway pressures, blood gas variables, cytokine serum concentrations, magnitude of chorioamnionitis on histology, etc.).

(c) Unknown variables (e.g. unknown markers of illness severity, clinician expertise, experience of nurses, staffing patterns, medicolegal environment, moral and ethical beliefs of caregivers and parents, etc.).

Differences in mortality rate may also be evaluated according to the time of death. It is known that much of the mortality in extremely premature infants occurs in the first few days[4] and different factors contribute to mortality when prediction models are developed for subsequent mortality using only antenatal variables, variables available soon after birth, at 24 hours of age, or at 1 week of age.[5] It will be important to determine whether the intercenter differences in mortality of the preterm infants occur mostly in the delivery room (perhaps due to withholding of therapy), in the first day after birth (perhaps related to ineffective resuscitation), or over the course of the first week (perhaps related to unsuccessful management of respiratory distress syndrome). The contribution of the known measured, known unmeasured, and unknown variables to outcomes may vary by postnatal age and other specific modifying variables.

In the current study,[1] the authors concluded that a significant proportion of the risk factors associated with early neonatal mortality can be modified by interventions and that there is a need to identify possible best practices and adopt them uniformly. However, the major limitation is that these possible best practices are generally limited to the known measured variables, and interventions limited to these practices will need to be rigorously evaluated as to efficacy before being uniformly adopted. Participation in multi-center quality improvement collaborations has been shown to lead to change in care practices and to be associated with improved outcomes.[6] However, Walsh et al.[7] tested whether neonatal intensive care unit (NICU) teams trained in benchmarking and quality improvement would change practices and improve the survival without bronchopulmonary dysplasia (BPD). This study was a cluster-randomized trial of 4,093 inborn infants of birth weight < 1,250 g at 17 centers of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network in the USA. Three centers were identified as the best performers, and the remaining 14 centers were randomized to intervention or control. Outcomes (survival free of BPD) were compared between years 1 and 3. It was observed that intervention centers implemented potentially better practices (e.g. reduced oxygen saturation targets, reduced mechanical ventilation). Despite these changes, rates of survival free of BPD remained similar in intervention and control groups and significantly less than the rate in the best performing centers.[7] Therefore, adoption of potentially better practices does not guarantee an improvement in outcome.

In summary, we know a great deal about the risk factors for death in preterm infants. The current multi-center study confirms that risks factors in the population studied are comparable to those reported in the literature from other populations. While center differences continue to be reported, we do not know why marked center differences in various outcomes persist, even after adjustment for many patient characteristics. It is presumed that these differences are the result of various care practices but it is difficult to identify precisely which combination of practices are "potentially better" and need to be adopted. While there are some proven therapies that should be implemented now, the best approach to reduce most center differences and improve outcomes of preterm infants in many care practices will require well designed studies.

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Childhood quality of life in the changing landscape of pediatric rheumatology

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The last decade has seen dramatic changes in the treatment of children with rheumatic disease. With the introduction of biologic agents into adult and pediatric autoimmunity comes an increasing understanding that patients with these disorders can experience improvement in their quality of life (QOL).

Prior to their introduction, the therapeutic armamentarium was not only limited in its extent and toxicity but also by its efficacy. On the other hand, the available tools assessing outcome were narrowly focused, literally applied from the adult literature, untested and mainly failed to assess the true impact of a therapeutic approach, which ultimately remains the only relevant one, QOL.

The article by Klatchoian et al.[1] from São Paulo, Brazil, which this editorial is dedicated to, examines the validity of a QOL score in a Brazilian population of children with systemic lupus (SLE) and juvenile arthritis (JA).

In the latter population, it has finally been recognized that these diseases can persist into adulthood causing disability, pain, and physical dysfunction.[2,3] Although it was once thought that children with JA outgrow their disease, long-term remission is infrequent, with remission rates (defined as drug-free and asymptomatic for ≥ 2 years) varying greatly among disease subtypes.[4,5] A recent retrospective analysis of 392 patients 8 years of age and older found that the probabilities of remission 10 years after onset were 37, 47, 23, and 6% for patients with systemic-onset, oligoarticular, rheumatoid factor (RF)-negative polyarticular, and RF-positive polyarticular JA, respectively.[4]

A review of several studies in 984 children with JA over a mean of 20.5 years concluded that, at a mean age of 30 years, 47% of these patients still had active arthritis, 46% reported difficulties in daily living, and 22% had undergone JA-related