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Does Early Treatment with Inhaled Budesonide Prevent Death or Bronchopulmonary Dysplasia in Extremely Preterm Infants?

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In a recent randomized trial by Bassler et al.,(1) investigators found no difference in the risk of death or survival with bronchopulmonary dysplasia (BPD) among extremely preterm infants randomized to early prophylactic inhaled budesonide, compared to those randomized to placebo. The trial did find a fairly large decrease in the incidence of survival with BPD among infants randomized to budesonide (risk difference of approximately 10%, corresponding to a number needed to treat (NNT) of 10 (95% CI 6 to 29) to prevent one outcome of BPD among surviving infants). However, the other component of the composite outcome, death, had a relative risk point estimate in the opposite direction leading to an overall negative result of the primary study outcome.

How are we to interpret these findings? As has been suggested by Freemantle et al.,(2) results from trials reporting composite outcomes should focus on the result of the composite outcome itself rather than the individual components. The effects of experimental treatment on individual components of the composite outcome, in this case death and survival with BPD, should be considered as secondary outcomes. One major issue in interpreting composite outcomes arises when the individual components of a composite outcome diverge, which has been noted in other important trials in neonatology, including the aggressive vs. conservative phototherapy(3) and SUPPORT trials.(4) As authors have written with regards to composite outcomes in adult cardiovascular studies,(5) "Higher event rates and larger treatment effects associated with less important components may result in misleading impressions of the impact of treatment." Given the unequal weight many families would give to the components of the primary outcome, with many considering death to be a more important outcome than survival with BPD, caution is appropriate in interpreting the results of this study. However, the possibility that the difference in mortality is due to chance alone should also be acknowledged. Importantly, short-term assessment of lung function in the hospital, measured by the outcome of BPD, can vary significantly from longer-term, patient-centered outcomes, such as assessment of lung health (e.g. wheezing, emergency room or physician visits for breathing problems)(6) as well as more sophisticated measures of lung function into adolescence.(7) Reassuringly, the authors have planned for longer-term

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CONFLICTS OF INTEREST

None

follow-up, allowing for the potential opportunity for additional assessments of pulmonary health to be undertaken.

Questions also remain regarding the effects of early inhaled budesonide on long-term neurodevelopmental outcomes. Of note, the secondary outcome of brain injury, while not statistically different, was higher among budesonide infants (RR 1.25; 95% CI 0.94–1.65), highlighting the importance of the longer-term follow-up at 18–22 months planned by the study investigators.

Although there was a decrease in the incidence of BPD among survivors with early inhaled budesonide treatment, a concurrent increase in death cannot be ruled out. Based on these findings, routine use of early preventive inhaled budesonide cannot be currently recommended in clinical practice and additional studies are needed.

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