Translating Best Evidence into Best Care

EDITOR'S NOTE: Studies for this issue were identified using alerts from *Archives of Disease in Childhood-Education and Practice, Archives of Disease in Childhood-Fetal and Neonatal, Archives of Disease in Childhood, British Medical Journal, Journal of the American Medical Association, New England Journal of Medicine, Pediatric Infectious Disease Journal, Pediatrics, The Journal of Pediatrics, and The Lancet*. Search terms were "paediatrics" [All Fields] OR "pediatrics" [All Fields] OR "pediatrics" [MeSH Terms]. In addition, studies were also identified using PubMed, Clinical Queries. Cleo Pappas, MLIS, Library of the Health Sciences, University of Illinois at Chicago, contributed to the review and selection of this month's abstracts.

—Jordan Hupert, MD

EVIDENCE-BASED MEDICINE PEARL: NUMBER NEEDED TO TREAT (NNT): A clinically valuable statistic, typically obtained from the abstract or the results section of a therapy article, is the NNT, the number of patients one must treat for one patient to derive benefit from the new therapy. The calculation of the NNT is straightforward. First, locate the abstract and/or results section and identify the type of result you consider clinically meaningful. In order to calculate the NNT, the result must be in binary form (eg, percent improved or number improved per total number of patients in that group). If needed, calculate the percent improved in each of the 2 study groups and subtract the percentages. This result is called the absolute risk reduction. The inverse of the absolute risk reduction is the NNT. If the new treatment is more harmful than the control, then the NNT is referred to as the number needed to harm. An example of number needed to harm may be seen in the oxygen saturation article (see piece by Bateman on page 1529 regarding article by Stenson et al; N Engl J Med 2013;368:2094-104). If you prefer to have the calculations (and the 95% CI of the NNT) computed automatically, try the EBM calculator by Dr Alan Schwartz (http://araw.mede.uic.edu/~alansz/tools.html).

—Jordan Hupert, MD

EVIDENCE-BASED MEDICINE LIBRARIAN PEARL: "LIMITS": In the September 2013 issue of *The* Journal (Pappas; J Pediatr 2013;163:922-6, Evidence-Based Librarian Pearl), we discussed methods to expand search results by "pearl culturing" from a single ideal article. We will discuss how to logically limit our search retrieval when our search results are too numerous. PubMed offers search filters (available following the initial search). To view all available filters select the words "show additional filters." To activate a filter, you must highlight it. A checkmark will appear next to it, and the filter, will appear at the top of search results with an exclamation point. Default filters include article types, text availability, publication dates, and species. "Show Additional Filters" will bring up language, sex, subjects, journal categories, ages, and search fields. Employing too many filters may overly restrict your results, resulting in the loss of relevant articles. The species filter distinguishes between human and animal studies. Selecting "human" will eliminate the veterinary literature, as well as animal bench mark research. It will, however, also eliminate articles where the database indexer presumed the human concept to be so apparent as to be unnecessary to include in the indexer list of descriptors. Limiting the search to "English" will eliminate foreign language articles. Age offers a good opportunity to focus on pediatric articles. Selecting "Text Availability" limits your retrieval to only the freely-available segment of the database (20% of PubMed). "Search Fields" offers a wonderful opportunity to limit your retrievals to a specific author, institution, journal, or geographic area. A judicious use of limits can make an unwieldy retrieval both manageable and relevant.

—Cleo Pappas, MLIS

A lower oxygen-saturation target decreases retinopathy of prematurity but increases mortality in premature infants

Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, et al for the BOOST II collaborative group. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* 2013;368:2094-104.

Question Among premature infants < 28 weeks gestation, what is the therapeutic efficacy of a lower oxygen saturation target, compared with a higher target, in reducing the rate of retinopathy of prematurity (ROP)?

Design Randomized controlled trial.

Setting Neonatal intensive care units in the United Kingdom, Australia and New Zealand.

Participants Preterm infants < 28 weeks gestation.

Intervention Infants were assigned to a higher (91%-95% saturation) or lower (85%-89% saturation) target saturation range. Halfway through the trials, the oximeter-calibration algorithm was revised.

Outcomes Rates of ROP and mortality at hospital discharge.

Main results A total of 2448 infants were recruited. Among the 1187 infants whose treatment used the revised oximeter-calibration algorithm, the rate of death was significantly higher in the lower-target group than in the higher-target group (23.1% vs 15.9%, number needed to harm 14; 95% CI 9-37). There was heterogeneity for mortality between the original algorithm and the revised algorithm ($P = .006$) but not for other outcomes. In all 2448 infants, those in the lower-target group for oxygen saturation had a reduced

rate of ROP (10.6% vs 13.5%, number needed to treat 35; 95% CI 18-957) and an increased rate of necrotizing enterocolitis (10.4% vs. 8.0%, number needed to harm 42; 95% CI 22-930). There were no significant between-group differences in rates of other outcomes or adverse events. For the subgroup of infants enrolled after the calibration-algorithm was revised, the mortality rate was significantly increased in infants assigned to the lower saturation range. For the entire cohort of infants, the rate of ROP was significantly reduced in the lower saturation range.

Conclusions Targeting an oxygen saturation range at 85%-89% was associated with an increased risk of death and lower risk of ROP.

Commentary The concept of a "trade-off" between a lower incidence of ROP and increased mortality as the target saturation decreases demands further analysis. Neither BOOST II nor the similarly designed SUPPORT trial[1] reported on the possible effect of covariates such as caffeine exposure or transfusion. Neither study allowed for the possibility that the relationship between ROP susceptibility and oxygen saturation changes as postmenstrual age advances. An unusual aspect of the study design also deserves scrutiny: in contrast to a typical doseresponse investigation in which outcomes are related to fixed therapeutic doses, ranges of physiologic response to widely variable oxygen application defined the intervention arms. Thus, interventions were applied "on average," with overlap ping interventions and spillover outside the target ranges—an extreme example of "intention to treat." We do not know to what extent individuals who experienced death or ROP actually received their intended intervention. Was mortality related to time spent at very low saturations (below 85%), or to the depth or frequency of episodic desaturations? Was ROP related to time spent in the hyperoxemic range (above 95%)? Although the results of a formal meta-analysis including SUPPORT, BOOST II, and the recently published Canadian trial are pending, targeting an oxygen saturation range of 90%-95% for premature infants receiving oxygen is a prudent, albeit provisional, therapeutic goal.[1,2] Meanwhile, these trials need to be explored for their wealth of detailed, patient-specific information that may reveal how patterns of exposure and the influence of covariates relate to the outcomes.

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References

1. Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959-69.
2. Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, et al. Canadian Oxygen Trial (COT) Group. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA 2013;309:2111-20.

On-demand, not scheduled, nebulization (epinephrine or saline) improves important clinical outcomes in hospitalized infants with bronchiolitis

Skjerven HO, Hunderi JO, Brügmann-Pieper SK, Brun AC, Engen H, Eskedal L, et al. Racemic adrenaline and inhalation strategies in acute bronchiolitis. *N Engl J Med*. 2013;368:2286-93.

Question Among infants hospitalized with bronchiolitis, what is the therapeutic efficacy of both nebulized racemic epinephrine and scheduled administration, compared with nebulized saline and on-demand administration, on the length of hospitalization?

Design 2X2 factorial randomized controlled trial.

Setting 8 hospitals in southeastern Norway from January 2010 through May 2011.

Participants Infants < 12 months of age with bronchiolitis and no more than one previous episode of wheezing.

Intervention Racemic epinephrine versus saline and scheduled administration versus on-demand administration in a 2X2 factorial design.

Outcomes The primary outcome was length of hospital stay.

Main Results Length of stay, use of oxygen supplementation, nasogastric-tube feeding, ventilatory support, and relative improvement in the clinical score from baseline (preinhalation) were similar in the infants treated with inhaled racemic adrenaline and those treated with inhaled saline ($P > .1$ for all comparisons). On-demand inhalation, as compared with fixed-schedule inhalation, was associated with a significantly shorter estimated mean length of stay—47.6 hours (95% CI 30.6-64.6) vs 61.3 hours (95% CI 45.4-77.2; $P = .01$)—as well as less use of oxygen supplementation (38.3% of infants vs 48.7%, number needed to treat 8; 95% CI 5-33), less use of ventilatory support (4.0% vs 10.8%, number needed to treat 15; 95% CI 9-58), and fewer inhalation treatments (12.0 vs 17.0, $P < .001$).

Conclusions In the treatment of acute bronchiolitis in infants, inhaled racemic adrenaline is not more effective than inhaled saline. However, the strategy of inhalation on demand appears to be superior to that of inhalation on a fixed schedule.

Commentary The long-lasting claims of efficacy of many interventions for bronchiolitis have been challenged by the growing evidence base from recent large trials.[1] The study by Skjerven et al of hospitalized infants with first- or second-time wheezing, greatly improves the precision of previous meta-analyses.[1,2] The 2 × 2 factorial design tackled two putatively independent comparisons: epinephrine versus saline nebulization and scheduled versus "on demand" administration. Although there was a considerable number