be cognizant of the methodologic weaknesses of this meta-analysis, and researchers should use these weaknesses as lessons to help them design better observational long-term research studies. Only well-designed studies with representative samples will allow us to provide families with evidence-based estimates of cancer in their child. ■

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Prolonged Ductal Patency in Preterm Infants: Does It Matter?

In this volume of *The Journal*, Clyman et al present analysis of data collected in the Patent Ductus Arteriosus: TO LEave it alone or Respond And Treat Early (PDA-TOLERATE) trial, examining the hypothesis that the risk of bronchopulmonary dysplasia (BPD) in infants born before 28 weeks of gestation is linked to interaction between prolonged positive-pressure ventilation and prolonged exposure to a moderate-to-large patent ductus arteriosus (PDA).[1] This study represents the capstone of a triad of recent inquiries into these relationships by Clyman et al.[1-3] Such post hoc analyses are fraught with potential for false discoveries, but these reports are notable not for what they find but for what they do not and, therefore, deserve close attention.

See related article, p 283

The prior 2 reports draw upon data collected prospectively for over 15 years at a single center (University of California San Francisco). The first shows that the risk of death or BPD was greater among infants in whom a moderate-to-large PDA was present for 7 days or more (OR 2.57 vs infants exposed for <7 days; 95% CI 1.71-3.87, $P < .0001$).[2] The rates of the combined outcome (or, conversely, survival without BPD) did not differ among groups with durations of PDA exposure ≥7 days ($P = .66$; **Figure**; available at www.jpeds.com). In the second report, grade 2-3 BPD (defined as requiring nasal cannula flow rates >2 L/minute, noninvasive positive airway pressure, or invasive mechanical ventilation at a postmenstrual age of 36-$^{0}/_{7}$- 36-$^{6}/_{7}$ weeks[4]) was also more likely in infants exposed to moderate-to-large PDA for ≥7 days (OR 5.10; 95% CI 2.58-10.1, $P < .0001$); again, longer exposures (beyond 7 days) were not associated with incremental risk ($P = .67$ by 2-by-3 χ^2).[3] This relationship held only for infants who required invasive ventilation for ≥10 days; among those intubated for <10 days, the risk of grade 2-3 BPD was low and did not significantly increase whether exposed to PDA for <1 week (2%) or for several weeks (6%; $P = .13$).[3] Examination of these relationships in the PDA-TOLERATE cohort confirmed that prolonged exposure to PDA (≥10 days) was associated with increased risk of either any BPD or grade 2-3 BPD only in

BPD	Bronchopulmonary dysplasia
PDA	Patent ductus arteriosus
PDA-TOLERATE	Patent Ductus Arteriosus: TO LEave it alone or Respond And Treat Early

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infants who were intubated for ≥10 days (OR 5.81; 95% CI 1.55-21.6, and 7.23; 1.12-46.4, respectively), but not among those who were intubated for <10 days (OR 0.86; 95% CI 0.22-3.33 and 1.17; 0.17-7.80, respectively). Among infants intubated for ≥10 days, neither the rates of any BPD nor of grade 2-3 BPD differed among groups exposed to PDA for 11-14, 15-20, or ≥20 days ($P = .16$ and .64 by 2-by-3 χ^2, respectively).

Few prior studies have similarly evaluated the relationship between the duration of PDA exposure and BPD. Mirza et al also found that longer exposure to a "significant" PDA is associated with an increased rate of death or BPD (aOR 1.37; 95% CI 1.03-1.82), but did not indicate whether PDA was treated as a bivariate or continuous variable. However, there was no difference in unadjusted risk between infants with PDA for 1-2 weeks (51%) compared with those exposed for >2 weeks (59%; $P = .97$).[5] Schena et al described increased rates of death or BPD with exposures to hemodynamically significant PDA (≥E2, ≥E3, or E4 by McNamara classification[6]) for more than 7 days (unadjusted OR 3.85, 2.18-6.78; 3.45, 1.83-6.50; and 15.1, 1.43-156, respectively). In multivariate analysis, exposure to E2 PDA had no significant impact, but E3-E4 PDA was associated with increased risk (aOR 1.70 per week of exposure, 95% CI 1.09-2.66). Durations of E3-E4 exposures were relatively short and a minority of subjects were exposed to E3-E4 PDA for >7 days (4.8 ± 6.2 days and 38%, respectively, among infants who died or developed BPD); the gradient of risk within subjects with exposures >7 days was not assessed.[7] The results reported in these recent reports are, therefore, both novel and highly informative.

These results have important implications. First, as suggested by Clyman et al, infants who are intubated for <10 days do not need treatment to close a persistently patent ductus, even if it is moderate-to-large.[1] Second, because infants intubated for ≥10 days do not accrue incremental risk of death or BPD with further exposure to a moderate-to-large PDA, there appears to be little, if anything, to be gained from treatment to close the ductus after 10 days of age. Numerous randomized trials and several meta-analyses of early PDA treatment have failed to demonstrate reduction in mortality or BPD[8-16]; early treatment to close the PDA is ineffective, with the exceptions of increased ductal closure (and a resultant decrease in "rescue" treatment or ligation) and possibly reduced severe intraventricular hemorrhage. Although a few individual trials have reported effects on other secondary or post hoc outcomes,[1] only reduction in intraventricular hemorrhage appears to be reproducible (but does not appear to be mediated by PDA closure[17-19]). Because most subjects in these trials were enrolled and randomized in the first 7 days after birth,[16] the potential utility of later treatment has remained largely unexplored. The present data help close that gap. The PDA-TOLERATE data, along with the 2 antecedent papers, indicate that we should not expect benefit from later treatment, as later PDA closure—even among infants receiving prolonged ventilation in the presence of a moderate-to-large PDA—is not associated with incremental risks for BPD, grade 2-3 BPD, or the combined outcome of death or BPD. Neither early nor late treatment obviates these risks.

Another important implication should not be overlooked. The step increases in BPD risk with exposures exceeding 7-10 days indicate that persistence of the PDA is a biomarker for an increased risk of BPD.[1] Absence of a dose-response relationship between duration of ductal patency and risk of BPD beyond that threshold, however, casts doubt on the underlying hypothesis that prolonged exposure to excessive pulmonary blood flow has a causal role in development or progression of BPD. A recent update to the classic Bradford Hill criteria for causality cautioned "While the presence of a dose-response relationship does not always support causality, its absence *when expected* would lead us to doubt causality."[20]

As Altman and Bland have stated, "it is usually reasonable not to accept a new treatment unless there is positive evidence in its favour."[21] Curiously, endorsement of therapies to close the PDA in preterm infants seems to have evolved into the argument that "we don't know that it is not effective, and it makes sense that it might be, so let's just do it." That argument is flawed for several reasons: First, evidence of efficacy (ie, that the patient actually benefits from the treatment) is lacking in this instance. Second, we do know that treatment to close the ductus is ineffective (for achievement of outcomes other than ductal closure itself) in all circumstances for which there are reliable data. Although the available data do not definitively preclude the possibility that treatment to close the PDA may be beneficial in special circumstances, uncertainty around the nature of those specific situations should lead to design and execution of randomized trials to assess the potential for benefit in those situations. Mitra and McNamara have recently provided a thoughtful and comprehensive framework for design of informative trials.[22] Only after such trials demonstrate true utility—defining which outcomes are prevented in which infants by which intervention—should treatment be adopted into clinical practice. Until such evidence is available, we have an obligation to our patients to stop exposing them to therapies that are, at best, unproven, and in most instances, apparently ineffective. Those who wish to continue to do so must shoulder the obligation to provide evidence that supports the efficacy of those practices. ■

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Infant Growth After Maternal Dietary Supplementation Before and During Pregnancy

Of the estimated 140 million infants born each year in the world, approximately 20 million babies are born with a low birth weight (<2500 g),[1] and a partially overlapping 23 million are small for gestational age.[2] Besides having a markedly increased risk of mortality, these small newborns are vulnerable to growth failure, malnutrition, morbidity, and developmental delay in childhood and adverse health consequences in adult life.[3,4] Prevention of fetal growth restriction and low birth weight is therefore considered a public health priority, especially in Sub-Saharan Africa and South Asia, where the incidence is greatest.

See related article, p 199

Because maternal undernutrition is a major risk factor for fetal growth restriction and low birth weight, antenatal dietary supplementation is a logical intervention to prevent these adverse pregnancy outcomes. Birth size can be increased by supplementing maternal diets with micronutrients or more comprehensive products with micro- and macronutrients and energy.[5,6] What has been less clear is whether it is important to start the dietary supplementation before or during pregnancy and whether the possible fetal growth gains in size are preserved after birth. These 2 questions were addressed in the Women First trial, in which nonpregnant women from Democratic Republic of Congo, Guatemala, India, and Pakistan were randomized to receive no supplementation (Arm 3) or dietary supplementation starting either before pregnancy (Arm 1) or at around 11 weeks of gestation (Arm 2) and continuing until delivery. All participants in Arms 1 and 2 received small-quantity, lipid-based nutrient supplements (SQ-LNS, 20 g/d, containing protein, fat, carbohydrates, multiple micronutrients, and 118 kcal energy). Women who became malnourished or failed to gain

LNS Lipid-based nutrient supplements
SQ Small-quantity

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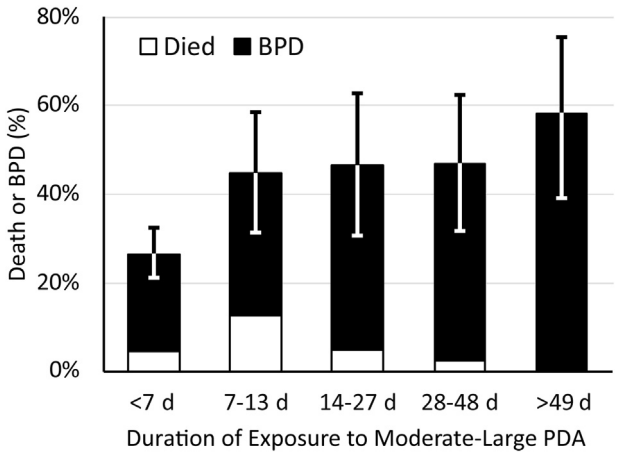

Figure. Duration of exposure to moderate-to-large PDA and risk of death or BPD. Death or BPD was less frequent in infants exposed to PDA for <7 days ($P < .0001$), but did not differ among groups with exposure times >7 days ($P = .66$). Error bars represent 95% CIs for rates of the combined outcome of death or BPD. Data from Clyman RI et al.[2]