

# Inhaled Nitric Oxide for Preterm Infants: What Can Change Our Practice?

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Although little evidence of effect is provided in trials and meta-analyses,<sup>1,2</sup> the use of inhaled nitric oxide (iNO) in preterm infants with hypoxemic respiratory failure persists.<sup>3</sup> This persistent and increasing use of iNO has occurred despite the publication of the National Institutes of Health Consensus Statement and the report from the American Academy of Pediatrics; in both of these, the authors conclude that the evidence does not support the use of iNO in preterm infants with respiratory failure.<sup>4,5</sup> Despite these cautionary guideline statements, almost half of newborn patients administered iNO in the United States are preterm infants.<sup>3</sup>

Finer and Evans<sup>6</sup> argue that this persistent use of iNO in preterm infants is not due to ignorance of the evidence; more likely explanations are that clinicians feel that the evidence is not generalizable to a particular clinical situation or that, despite the evidence, the instinct to attempt to normalize physiology prevails when faced with a hypoxic infant on respiratory support. Perhaps the continued use of iNO in preterm infants is driven by the concern that trials have not adequately identified subgroups of infants who may benefit from treatment. Kinsella et al<sup>7</sup> argue that there is a strong rationale for the use of iNO in infants with persistent pulmonary hypertension of the newborn (PPHN) and that there is a need for more rigorous evaluation of preterm infants with proven persistent pulmonary hypertension. Some room

for clinical discretion is included in the current recommendations, in which it is stated that “there are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which inhaled nitric oxide may have benefits in infants <34 weeks gestation.”<sup>4</sup> Recommendations from the American Heart Association, the American Thoracic Society, and others have strengthened this approach with suggestions that iNO can be beneficial for preterm infants with PPHN.<sup>7–9</sup> Unfortunately, there is little to inform the neonatal community regarding this discretion.

In this issue of *Pediatrics*, Carey et al<sup>10</sup> report on a retrospective cohort of infants born between 22 and 29 weeks’ gestation who received nitric oxide during the first week of life. Although a large proportion of the infants treated with iNO had a clinical diagnosis of PPHN (67%) and almost half had an echocardiographic examination (49%), it is unclear what specific echocardiographic criteria were evaluated before treatment. Because of concern regarding confounding (of baseline characteristics and timing of treatment), the authors used a sequential balanced risk set approach, employing propensity score matching to adjust for covariance imbalance between patients who received iNO during the first 7 days of life and their matched referents. Similar to the individual trials and meta-analyses, the authors report that iNO is not associated with reduced mortality

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among extremely preterm neonates with respiratory distress syndrome, including a subset of these infants with PPHN.

Carey et al<sup>10</sup> provide yet another piece of evidence that iNO is of limited (if any) value in the preterm infant. That said, the off-label use of iNO for preterm infants in hypoxemic respiratory failure will probably persist. If there is continued use of iNO in preterm infants with hypoxic respiratory failure and concern for PPHN, specific study of this population is warranted. In these studies, a pretreatment echocardiographic evaluation would need to be included before random assignment to iNO or standard management. Trial designs could be adaptive in nature, similar to the early trials of extracorporeal membrane oxygenation, in which only the outcome of mortality was evaluated.<sup>11</sup> If, in fact, the therapy appears to be lifesaving, further studies would be warranted to address neurodevelopmental follow-up of this population.

Neonatologists have been “voting with their feet.” A significant number of preterm infants are still treated with iNO despite little evidence of clinical benefit. Many would argue that it is, in fact, an ethical responsibility of clinicians to use all treatments that they feel may be lifesaving. However, iNO is both unproven and expensive and demands further evaluation. Currently, registries of infants

with PPHN are being established by investigators (J.P. Kinsella, MD, personal communication, 2017). This, and the possibility of future adaptive trials, will be the only way to further clarify this clinical conundrum.

#### ABBREVIATIONS

iNO: inhaled nitric oxide  
PPHN: persistent pulmonary hypertension of the newborn

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