In the current issue of the journal, Ellsworth et al report a small but significant increase (from 5.0% to 6.2%) in the off-label use of inhaled nitric oxide (iNO) between 2009 and 2013 in preterm infants born earlier than 30 weeks. This increase occurred in spite of the publication of the iNO Consensus Statement in 2011 and the 2014 report from the American Academy of Pediatrics. Both reports conclude, on the basis of quality evidence, with recommendations against using iNO to reduce mortality and morbidity in preterm infants with respiratory failure. The findings of Ellsworth et al are probably generalizable. They cite a usage rate of 6.9% for a comparable preterm cohort in the Vermont Oxford Network and review of data in the same gestational group from the New South Wales/Australian Capital Territory network (by NE) shows a rate of 7.2%.

So why this continued use of iNO, considering the strength of evidence against using this expensive treatment? There would seem to be 3 possibilities: first and least likely, lack of awareness of the evidence; second and more likely, a view that the evidence is not generalizable to a particular situation; or third and most likely, that, despite the evidence, the neonatal intensivists’ instinct to attempt to normalize physiology prevails when faced with a hypoxic ventilated baby.

We speculate that iNO is being mainly used in 2 clinical scenarios: first, during acute crises of oxygenation in the first week or two of life and, second, in infants with evolving chronic lung disease with suspected or documented pulmonary hypertension. The evidence against using iNO is strongest in the first of these scenarios. Meta-analysis is not perfect and cannot, even through sophisticated statistical manipulation, account for differences in aspects of patient care, unit practices, and individual patient differences. It was for this reason that the individual patient data meta-analysis was facilitated with the cooperation of the iNO trial principal investigators. This also showed no benefits from iNO stratifying for a range of variables, including oxygenation index, making it difficult to argue that the evidence is not generalizable to the sickest infants.

Our speculation would be that usage is being driven mainly by the intensivists’ desire to normalize physiology in critical clinical situations. This would be fine if there were no harms or costs, but there are. Trends to increased adverse outcome are seen in the smallest infants (<1000 g), and the financial costs of this treatment are significant, estimated by Ellsworth et al at $153 million for infants born at <34 weeks in the United States.

iNO has many effects on the lungs, but is mainly used as a pulmonary vasodilator. The premise to evaluate iNO in preterm infants was based on the view that preterm infants in respiratory failure often had unrecognized pulmonary hypertension (PH). It is a shortcoming of the evidence that none of the large trials required ultrasound diagnosis of PH, and thus one cannot determine whether infants with proven PH had a benefit from iNO compared with those who did not. Severe PH
(pulmonary artery pressure [PAP] at or above systemic) is actually not common in the preterm infant, and predominantly right-to-left ductal shunting is rare even in the early postnatal period. Preterm PH is usually secondary to pulmonary parenchymal pathology, and this may explain the limited impact of iNO. However, there are some groups of preterm infants in whom severe PH is almost universal, particularly infants born after prolonged oligohydramnios. It is interesting that it is this group of infants who were the subject of some of the early encouraging observations on preterm iNO usage. Consistent with this, several reports since then (and the authors’ clinical experience) have observed that these infants are often acutely responsive to iNO.

The evidence around the use of iNO in evolving chronic lung disease is less consistent, with the trial of Ballard et al showing a small but significant reduction in chronic lung disease (CLD). However, the recently completed trial “Inhaled Nitric Oxide for the Prevention of Bronchopulmonary Dysplasia in Preterm Infants,” also known as NEWNO, did not duplicate this finding. The study protocol closely followed that of the Ballard et al trial with enrollment of 451 infants weighing <1250 g at birth requiring ventilation and enrolled between days 5 and 14. The study included infants weighing <800 g receiving continuous positive airway pressure. Infants randomized to iNO were treated with 20 ppm for 72 to 96 hours and then 10 ppm until day 10, and then to 5 ppm for a further 14 days even if off respiratory support. The overall results did not demonstrate a reduction in bronchopulmonary dysplasia or survival without bronchopulmonary dysplasia and do not provide support use of iNO for this indication.

What is the best way forward in balancing the need to get evidence into practice while still leaving room for individual clinician judgment? Units can and should develop evidence-based guidelines for the use of iNO for preterm infants. Such guidelines could allow for its use in the presence of severe PH, but such guidelines would not support the use of iNO to treat persistent hypoxemia in the absence of such evidence. It is an issue that there is a lack of consensus as to how to define PH. Almost every infant on high-pressure ventilation will have a PAP above normal. This will often be a physiologic response to high positive intrathoracic pressure. The ultrasound criteria for PH used in the term infant iNO trials were set low and would have included many such infants with physiologic PH. We would propose that thresholds should be set on the basis of ultrasound criteria that would define PAP at or above a normal systemic pressure, so as to encompass only infants with unequivocally pathologic PH.

The proposed guidelines need to leave room for individual clinician judgment but could require parental consent by using a consent document approved by the institutional review board with agreed language before iNO is used. The risk for iNO appears to be highest and efficacy lowest for infants weighing <1000 g at birth, and this could be the first target population of such an approach. There could be a mandated checklist before iNO initiation in such infants that requires optimizing all aspects of care and ensuring adequate diagnostic studies. These approaches would highlight the uncertainty of using iNO in the very preterm infants to physicians and other health care workers, as well as parents. In addition, these measures could be initiated with an audit tool for allowing a monthly review of iNO use and the infants’ outcomes. It would also serve to identify such infants for longer-term follow-up, if they are not already in a known risk group.

More generally, there is a need for specifically focused trials of iNO on preterm infants with evidence of PH, and perhaps other specific conditions, such as prolonged oligohydramnios, to determine if there are conditions in this population for which iNO may improve outcomes. Such trials should have enrollment criteria that will define pathologic PH, as discussed previously. These studies will require significant collaboration and the current information about usage and the associated costs should encourage and stimulate such trials. In addition, a review of a large number of very preterm infants with PH that would include their longer-term neurodevelopmental outcomes would be very helpful, and perhaps a registry of such patients could be developed for this purpose. The existing European Inhaled Nitric Oxide Registry (www.medscinet.net/ino/, iNORegistry@lwh.nhs.uk) may be a useful resource in this endeavor. There would need to be agreed-on diagnostic criteria, and details of the infants’ management, which would facilitate an understanding of the morbidity and mortality of such infants.

In conclusion, the evidence does not justify the current rates of usage of iNO in preterm infants. This treatment is hugely expensive and may be harmful in the smallest infants. There is a need for a local and collective effort to rationalize this usage through development of clinical guidelines and more targeted clinical trials.

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