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Inhaled nitric oxide therapy in neonates and children: reaching a European consensus

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Abstract Inhaled nitric oxide (iNO) was first used in neonatal practice in 1992 and has subsequently been used extensively in the management of neonates and children with cardiorespiratory failure. This paper assesses evidence for the use of iNO in this population as presented to a consensus meeting jointly organised by the European Society of Paediatric and Neonatal Intensive Care, the European Society of Paediatric Research and the European Society of Neonatology. Consensus Guidelines on the Use of iNO in Neonates and Children were produced following discussion of the evidence at the consensus meeting.

Keywords Inhaled nitric oxide · Pulmonary hypertension · Persistent pulmonary hypertension of the newborn · Extracorporeal membrane oxygenation · Vasodilator · Pulmonary

Introduction

Inhaled nitric oxide (iNO) has been used in Europe to treat a variety of conditions in neonates and children since 1992, foremost in persistent pulmonary hypertension of the newborn (PPHN), which has remained a major therapeutic challenge in the NICU [1, 2]. Introduction of iNO into clinical use was virtually unregulated in Europe, where supplies of industrially produced gas were freely available. Subsequently clinical trials have established roles for iNO therapy in the treatment of term neonates with severe respiratory failure and a pharmaceutical quality product has recently become available in Europe and the United States. The high cost of the licensed product, compared to previous industrial supplies, and the narrow scope of the drug's licensed indications suggested to our group that a consensus should be established on the use of iNO therapy in neonates and children covering both its approved and potential indications.

Methods

An Advisory Board was established under the auspices of the European Society of Neonatal and Paediatric Intensive Care to co-ordinate the scientific programme of the meeting. The board consisted of experts with proven scientific or clinical expertise relevant to the clinical use of iNO. The board identified a further panel of experts who were invited to act as section leaders whose role was to review the literature in their designated subject area. Section leaders were asked to produce written summaries of their subject area, which were then circulated to delegates prior to the meeting and which formed the basis of the evidence presented to delegates at the consensus meeting itself.

A further panel of opinion leaders were invited to attend the meeting on the basis of their known interest in the use of iNO or their status as opinion leaders in the field of neonatal and paediatric intensive care. The European Society of Paediatric Research and the European Society of Neonatology were officially represented at the meeting. At the consensus meeting each subject area was presented in summary by the section leader(s), following which open discussion led to the composition of draft consensus statements. These were then edited and re-presented to delegates with further discussion leading to final agreement on the individual consensus statements.

Results

Inhaled nitric oxide in term and near-term neonates

Neonatal hypoxaemia may result from *intra-pulmonary shunting*, from *extra-pulmonary shunting* (so-called PPHN) or from cyanotic congenital heart disease. The presence of interstitial pulmonary infiltrates or a low volume lung (<6–7 ribs) on chest X-ray strongly suggests parenchymal lung disease. Alveolar recruitment has been shown to render babies with severe hypoxaemic respiratory failure responsive to iNO, when they were previously unresponsive [2]. Exogenous surfactant and ventilatory manoeuvres [3] should therefore be deployed to optimise lung volume before iNO is introduced. If cyanosis persists after any necessary lung recruitment manoeuvres have been applied, an echocardiogram should be obtained to confirm or exclude the presence of congenital heart disease or pulmonary hypertension as causes of cyanosis. Inhaled NO is most likely to benefit babies with PPHN with recruited lung volume and is unlikely to benefit babies with cyanotic heart disease.

The recent Cochrane Review was used as a framework in this discussion [4]. The review, last updated in December 2000, included 12 relevant trials in its analysis, all of which used random allocation [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. One further on-going study received limited analysis since, at the time of review, it was on-going and published only as an abstract [16]. A literature search up to October 2003 failed to reveal any new randomised, controlled trials not already included in the Cochrane review.

The limitations of the studies presented within the Cochrane review were highlighted. Of major importance, the entry criteria differed markedly between trials as did dosage and ventilatory strategies, there being a suggestion that high frequency oscillatory ventilation (HFOV) appears beneficial in achieving a response to iNO [10]. Eight of the 12 clinical trials studied the effect of iNO on the overall clinical course of the babies included and, in particular, whether the need for extracorporeal membrane oxygenation (ECMO) was reduced. Only six trials did not allow crossover [6, 7, 8, 11, 12, 13]. Of the six studies which did not allow crossover, three [6, 11, 12] found a statistically significant reduction in the combined outcome of death or requirement for ECMO in the NO group. A meta-analysis of all six studies found that iNO treatment resulted in a reduction in the incidence of death or requirement for ECMO (relative risk 0.65) [4].

Inhaled nitric oxide therefore appears to improve outcome in hypoxaemic term and near-term infants. The improvement is due mainly to a reduction in the need for ECMO, since mortality was not reduced. The two largest studies [6, 11] included infants with congenital diaphragmatic hernia as sub-groups. A separate analysis has been presented from one of these studies [17]. There was no evidence that outcome was improved in these babies through the use of iNO, even if short-term improvements in oxygenation did occur. It is important to note that whilst iNO reduced the need for ECMO, the majority of mature babies in these studies went on to ECMO.

Only one study has considered long-term follow-up as a primary or secondary hypothesis. In this study, the incidence of disability, the incidence of deafness and infant development scores were all similar between tested survivors who received NO and those who did not [18].

The major randomised, controlled trials of iNO in term or near-term babies have used echocardiography to

exclude congenital heart disease as a cause of hypox-aemia prior to exposure to iNO. Babies with such lesions are at best unlikely to benefit from iNO, as cyanosis is due to extra-pulmonary shunting. Inhaled NO exposure may even be harmful in some babies with congenital heart disease, such as those with obstructed total anomalous pulmonary venous drainage or severe left ventricular dysfunction with right-to-left ductal shunting [19], in whom pulmonary arteriolar vasoconstriction may be clinically beneficial by reducing left heart filling.

Dosage and response to inhaled nitric oxide treatment in term and near-term neonates

Decisions regarding continued use of iNO therapy cannot be based on the primary end points used in the pivotal studies, such as reduced mortality or 'avoidance' of ECMO. Instead clinicians must use surrogate physiological end points in order to establish whether an initial test exposure to iNO is effective. Improvement in oxygenation of approximately 20% over baseline values at 30–60 min has been used in many studies as an indicator of early response to iNO including six of the studies in the Cochrane review [5, 6, 7, 9, 11, 12].

Four published studies have reported dose-response data for this group of babies [7, 20, 21, 22]. All four studies suggest that a maximal beneficial effect of iNO is already seen at concentrations of less than 30 ppm. Further increases of iNO (to 80–100 ppm) do not appear to result in further improvement of oxygenation above that achieved at 20–30 ppm. The large NINOS study [11] used initial doses of 20 ppm iNO, but exposed 'partial responders' to 80 ppm. Only 6% of these partial responders were converted to full response by 80 ppm iNO.

In the small study published by Tworetzky et al. a maximum reduction of pulmonary artery pressure was observed at 20 ppm NO, whereas maximal improvement in oxygenation occurred at 5 ppm [23]. Response to the introduction of iNO usually occurs rapidly in 'responders'. Some investigators attribute clinical improvements seen several hours later to iNO administration [24]. However it was the expert group's view that there is a serious danger that babies with very severe hypoxaemia could be harmed if ECMO referral were to be delayed whilst waiting for a 'late' response.

If no substantial effect has been achieved during a trial of iNO, treatment with iNO should be rapidly discontinued or the baby transferred on iNO to a level 3 or tertiary neonatal unit. This should occur as soon as the clinician is convinced that iNO is not inducing a beneficial effect judged by improving oxygenation. The trial to improve oxygenation with NO should not last longer than 4 h. The reason not to prolong NO therapy unnecessarily is that NO synthase is down-regulated, with suppression of endogenous NO production. Down-regulation of endogenous NO synthase by the use of iNO has been suggested [25, 26, 27].

We were unable to identify studies establishing the optimal regime for maintenance of iNO therapy once an initial response has been established. It is, however, logical in clinical practice to seek to minimise iNO exposure by lowering the iNO dose, provided the beneficial effects on oxygenation and general clinical stability are maintained. This approach was described by Kinsella et al. [28] in the early stages of the clinical exploration of iNO therapy and further validated by Clark et al. [6].

Discontinuation and weaning

Some information is available on strategies for weaning patients from iNO as clinical improvement occurs. In a prospective study, Demirakca et al. evaluated the clinical response to iNO in neonates and children with acute respiratory distress syndrome (ARDS) [21]. Attempts to discontinue iNO were made as soon as a stable respiratory status (PEEP<6 cmH$_2$O, inspiration/expiration ratio of 1:2, FiO$_2$ <0.8 and an iNO concentration of 5 ppm) had been achieved. Oxygenation index (OI) values of less than 5 predicted successful withdrawal with a sensitivity of 75%, a specificity of 89%, a positive predicted value of 69% and a negative predictive value of 91% [21].

Aly et al. [29] adopted a weaning strategy for babies with PPHN which included step-wise 5 ppm decrements of iNO doses. Discontinuation of iNO was performed as soon as the patient was stable with an FiO$_2$ less than 0.5. Weaning was successful at the first attempt in 9 out of 16 patients. In the remaining seven neonates, major signs of deterioration (oxygen saturation drop >10% or below 85%) prompted a reinstitution of iNO treatment for 30 min. Subsequently, FiO$_2$ was raised by 0.4 and a successful withdrawal of iNO was then obtained. Interestingly, FiO$_2$ could be returned to the pre-weaning value in a few hours. Sokol et al. [30] noted that significant deterioration of PaO$_2$ occurred in some babies even when weaned from 1 to 0 ppm, suggesting that iNO is physiologically active even at very low concentrations. There may be a role for other vasodilators such as epoprostenol, iloprost, endothelin antagonists or selective phosphodiesterase inhibitors [31] when weaning babies from iNO after treatment courses of sufficient duration to down-regulate NO synthase.

Toxicity

Nitric oxide reacts with oxygen to form nitrogen dioxide (NO$_2$) where the reaction rate is proportional to the square of the NO concentration and directly proportional to the

oxygen concentration. Whilst NO itself is a relatively reactive molecule, NO_2 is demonstrably more reactive and toxic and is a radical (it has an unpaired electron). Due to the fact that NO is usually administered in combination with high inhaled oxygen concentrations and that NO_2 in animal experiments is damaging to the lungs already at low concentrations when administered with other oxidants, the main toxicological concern should be focused on NO_2 exposure and this should be kept to a minimum. In long-term exposure lung damage may occur at 0.5 ppm NO_2 and acute lethal effects are seen from 100 ppm. Human subjects inhaling 2–3 ppm NO_2 for 5 h demonstrated reductions in antioxidant defences and an increase in alveolar permeability [32]. Reactive species such as peroxynitrite formed from NO_2, as well as being implicated in short-term toxicity, have the potential to cause damage to DNA, raising the possibility of mutagenic or carcinogenic effects. However, the concentrations of iNO and NO_2 to which patients are exposed clinically are largely within the permitted limits for occupational exposure [33]. There is as yet no evidence that inhalation of NO has any lasting adverse effects. Long-term follow-up of children exposed to iNO therapy will be required to establish any late adverse effect.

When NO reacts with haemoglobin, methaemoglobin (metHb) is formed. MetHb is not directly toxic, but is unable to carry oxygen. If metHb is allowed to accumulate it can significantly reduce the oxygen-carrying capacity of blood. The monitoring and management of metHb during clinical iNO therapy is discussed below.

Inhalation of NO has been shown by some investigators [34], but not by others [35], to inhibit platelet function. The randomised controlled neonatal trials have, however, not shown any difference in bleeding complications between groups administered iNO or control gas [4].

Delivery and monitoring

Nitric oxide administration systems should deliver constant concentrations of iNO within the respiratory gas mixture independent of ventilator mode or settings, ensure a rapid mixing and minimise contact time between NO and oxygen, thereby reducing the possibility of generating high NO_2 levels [36, 37, 38]. The delivery system should display the pressure within the NO cylinder to permit timely cylinder changes to be undertaken without loss of gas supply. The system should ideally encompass a backup power supply for use in the event of mains failure or during intra-hospital transport. A manual backup or 'hand bagging' facility must be provided for use in the event of ventilator failure or other indications for hand ventilation, as sudden discontinuation of iNO therapy can be life-threatening [36, 37, 39].

The safest approach to iNO delivery is probably to use only pharmaceutical grade NO stored in cylinders and at concentrations and conditions approved by drug regulatory bodies and delivered by devices tested and approved according to the appropriate medical device legislation.

In the clinical setting, measurement of iNO and NO_2 concentrations can be undertaken using chemiluminescence or electrochemical devices. There are a number of practical disadvantages of chemiluminescence analysers in the clinical setting, including their high cost, their need for relatively high sample volumes, noise, their need for regular calibration and their relative inaccuracy in measuring NO_2 due to the "quenching" effect [37]. Electrochemical analysers use two separate fuel cell sensors for NO and for NO_2, placed either in the gas mainstream or side stream of the ventilatory circuit. Electrochemical devices do not underestimate NO_2 levels, are inexpensive, silent, easy to calibrate and require very low gas sample volumes. Most devices are portable. Electrochemical analysers are, however, relatively insensitive (resolution 0.5 ppm) and their measurements may be affected by temperature, pressure, humidity and the presence of other gases in the environment [37]. Although many early studies of iNO delivery systems were constructed by investigators for their own studies, a number of delivery and monitoring systems have been developed for clinical use and are commercially available [39, 40].

Inhaled NO_2 concentrations should be kept to a minimum. Clinical and experimental evidence show that it is possible to administer 20 ppm iNO whilst generating NO_2 concentrations of less than 0.2 ppm [38]. Direct comparisons with tolerable environmental NO_2 concentrations should take into account that the awake person inhaling NO_2 is exposed to at least 50% lower NO_2 concentrations in their trachea due to efficient scavenging of NO_2 in the upper airways.

Nitric oxide has been supplied for clinical use by a number of suppliers as a compressed gas diluted in a balance of nitrogen with final NO concentrations of between 100 and 1000 ppm. The gas is supplied in aluminium cylinders filled to pressures of 150–200 bar. Very concentrated preparations may be difficult to deliver accurately whilst mixtures with low NO concentrations can reduce FiO_2 excessively [41]. The final choice of cylinder NO concentration will, therefore, depend on the characteristics of the delivery system in use and the required FiO_2 and FiNO. The future availability of iNO as a pharmaceutical within Europe may encourage standardisation.

Environmental safety

The US National Institute for Occupational Safety and Health (NIOH) suggest a "Permitted Exposure Limit" for

NO_2 of 5 ppm and NO 25 ppm over an 8-h period for these potentially toxic substances [33]. Several European countries have regulated maximal occupational exposure to 2 ppm NO_2. Extrapolating this to the ICU in which iNO would be administered for a 24-h period, it would be prudent to aim for environmental levels of NO_2 in the ICU below 1.5 ppm. Environmental NO contamination can occur from two sources during iNO administration: dumped waste ventilator gas and accidental leakage of concentrated gas from a delivery system or cylinder. The US Food and Drug Administration state, in their specification for medical delivery of NO, that such delivery "does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required" [42]. A similar ruling is applied by the UK National Health Service, which states that scavenging of waste NO is unnecessary provided that ventilation in the ICU meets required standards [43]. Several studies confirm that this advice is sound [44, 45]. There must, however, be a small risk of high environmental levels occurring from uncontrolled release of a large volume of concentrated gas from a cylinder in the event of a serious error or accident. For this reason, the consensus group suggest that it is reasonable to measure environmental levels of NO_2 continuously.

Transport

In 30–50% of babies given a trial of iNO the therapy does not result in a sustained positive oxygenation response [4]. Most babies who fail to respond to iNO are potential ECMO candidates. Since acute withdrawal of iNO may be associated with severe rebound hypoxaemia, even in babies who apparently respond poorly [46, 47], arrangements must be in place for these babies to be transferred to an ECMO centre without interruption of iNO delivery. Occasionally non-neonates may require transport within or between hospital whilst receiving iNO.

Apart from the ability to deliver iNO safely to the baby during transport, consideration must also be given to safety of the staff and crew within the transport vehicle, and compliance with any regulations governing such use. Kinsella et al. recently reported concentrations of NO and NO_2 in the cabin environment of various transport vehicles during iNO use and confirmed them to be negligible. Furthermore, they calculated the effects of uncontrolled release of a full US D-type NO cylinder containing 350 l NO gas. In this "worst case scenario" environmental NO levels were unlikely to reach dangerous levels (maximum 40 ppm fixed wing aircraft, 34 ppm ground ambulance, 94 ppm small helicopter) [48].

The expert group recommend that equipment for delivery and monitoring of iNO during transport should comply with standards for medical devices and the safety and test requirements of the specific aircraft or other transport vehicle used. Several delivery systems have been used during transport and at least two portable systems are commercially available, one of which is specifically designed as a transport system [48].

Staff training

Clinical use of iNO involves potential hazards for both staff and patients, mainly from the risk of exposure to toxic levels of NO and NO_2, but also issues such as safe handling of gas cylinders. The safe and appropriate use of medical equipment requires adequate preparation and training. Regulatory authorities frequently recommend standards for training in the use of medical equipment, typically stating that training should include both theoretical and practical instruction [49]. US guidelines for neonatal use recommend physician training [50] and some nursing authors have discussed the need for training [51]. It has also been recommended that protocols or guidelines should be compiled by hospitals using iNO, covering all aspects of its use including responsibility for off-label prescription. Such protocols should aim to help staff deliver iNO therapy that is both safe and effective [52].

Use of inhaled nitric oxide in preterm neonates

For the purposes of this paper, 'preterm' neonates are defined as those babies too premature to be considered for ECMO should their condition require it, i.e. babies less than 34 weeks completed gestation [53].

Inhaled NO may improve oxygenation in preterm neonates with hypoxaemic respiratory failure in one of two ways: (1) it may reverse extra-pulmonary shunting by selectively decreasing pulmonary vascular resistance (PVR) and (2) it may reduce intra-pulmonary shunting (and/or V/Q mismatch) by redistributing pulmonary blood flow. The former mechanism is likely to be the most important in infants with primary or secondary PPHN, whereas the latter will be more important in the majority of preterm infants who have parenchymal lung disease as the primary cause of their hypoxaemic respiratory failure.

There are three published, randomised, controlled trials (RCTs) of iNO therapy in preterm infants [14, 54, 55], overviews of which have been reported in the form of two systematic reviews [53, 56]. A total of 207 infants have been studied in these RCTs. Other RCTs (such as the UK INNOVO trial, NICHD Preemie iNO trial and other US trials) are either on-going or have only just completed recruiting and results are not yet available. One small RCT has reported the long-term neurodevelopmental outcome following iNO therapy [57].

A Cochrane Review has summarised the results of the three RCTs in preterm infants [53]. The study of Kinsella

et al. [55] is the single most useful trial in that it recruited neonates with hypoxaemic respiratory failure early in the course of their respiratory disease, the intervention was masked, an important primary outcome (mortality) was chosen, there was no crossover treatment with iNO and infants were carefully evaluated for intraventricular haemorrhage (IVH). There is no evidence of an effect of iNO on mortality or chronic lung disease (CLD) at 36 weeks, or on survival without CLD in preterm infants with hypoxaemic respiratory failure. Doses of between 5–20 ppm iNO appear to be effective in improving arterial oxygenation within the first 2 h of treatment. One study showed a reduction in days of ventilation with 5 ppm iNO in survivors [55] whilst another study reported no difference [14].

Sufficient data are lacking for evaluation of the possible effects of iNO on periventricular haemorrhage or on long-term neurodevelopmental outcome. Thus, with the data currently available, the consensus group do not recommend the routine use of iNO in the preterm infant and strongly recommend its use in this indication only within controlled clinical trials. The use of iNO could, however, be justified as rescue therapy in life-threatening hypoxaemia after lung recruitment has been optimised.

Use of inhaled nitric oxide in paediatric acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) may result from many systemic disease processes, and affects people of all ages. No drug therapy has been found to impact substantially on survival in ALI cases. Inhaled NO has been used in this setting principally because of its effect in improving oxygenation as therapy commences, due to improved ventilation-perfusion matching.

The comments in this section are aimed at guiding the clinical use of iNO in paediatric practice. Recommendations on ALI and ARDS had to be formed on a very limited base of information as, apart from case series and anecdotes about children, almost all data on such clinical use of iNO were only available for adult patient populations. Five randomised controlled trials were evaluated (Dellinger [58], Dobyns [59], Lundin [60], Troncy [61], Michael [62]) in a recent Cochrane review [63] assessing 535 patients, with only one trial focused on children [59]. Inhaled NO had no impact on mortality in trials without crossover (relative risk 0.98, 95% confidence intervals 0.66, 1.44) or with crossover of treatment failures to open-label iNO (RR 1.22, 95% CI 0.65, 2.29). Evidence published in one study demonstrated that iNO resulted in a transient improvement in oxygenation in the first 24 h of treatment: the oxygenation index (OI) showed a mean difference of −3 (95% CI −5.354, −0.646), and PaO_2/FiO_2 ratio and a mean difference of 35 (95% CI

20.236–49.764) [58]. Other clinical indicators of effectiveness, such as duration of hospital and intensive care stay, were inconsistently reported. There were no complications reported to be directly attributable to this treatment.

Based on these data, it appears that iNO has no effect on mortality and only transiently improves oxygenation in ALI/ARDS. There is insufficient data to assess other end points. The authors of the Cochrane review suggest that any further trials of iNO in this indication must stratify for underlying disease, since outcome is thought to be more related to this than to respiratory failure alone.

Use of inhaled nitric oxide in children with cardiac disease

Pulmonary hypertension is an important problem in many children with acquired or congenital heart disease. As a selective pulmonary vasodilator, as in neonatal PPHN, iNO has the potential to improve the management of these patients. Numerous reports of iNO usage in such patients have been published including its use in the assessment of the reversibility of pulmonary hypertension as a diagnostic procedure [64, 65] and in the perioperative management of pulmonary hypertension or RV afterload reduction [66, 67, 68]. Inhaled NO has also been shown to complement standard methods of differentiating reactive from fixed pulmonary vascular disease [64, 65].

Inhaled NO has been shown to be effective in the management of some patients with severe reactive pulmonary hypertensive episodes following cardiac surgery [69, 70]. In these patients, iNO is believed to replace endogenous NO production, which is temporarily impaired due to the effects of cardiopulmonary bypass on the pulmonary endothelium. One randomised, controlled trial [71] reported that the prophylactic administration of 10 ppm iNO was associated with a significant reduction in pulmonary hypertensive events and a reduction in time to meeting extubation criteria. Mortality and length of ICU stay were, however, unaffected. Another similar, but smaller, study failed to demonstrate any benefit from prophylactic iNO [72]. The view of the consensus meeting experts was that data from other clinical trials was required before the routine prophylactic use of iNO could be recommended in children at risk of pulmonary hypertensive events after repair of congenital heart surgery. Inhaled NO has also been shown to improve the haemodynamic status in patients with elevated PVR after the Fontan operation [73] and in those with failing right ventricles [74]. There are no RCT's in this group of patients.

In summary, there are few RCTs on the use of iNO in children with cardiac disease from which to draw evidence-based conclusions. There is insufficient evidence to recommend the routine use of prophylactic

postoperative iNO in congenital heart patients at risk of pulmonary hypertension. The expert group felt that there is, however, sufficient evidence (from large case series) to support a trial of 20 ppm iNO for 10 min, increasing to 40 ppm if no response to the lower dose, in patients with clinically significant pulmonary hypertension complicating their perioperative course. In this setting it is recommended that iNO should only be continued if there is documented evidence of important haemodynamic improvement. After a 30-min trial of iNO at 20 ppm, increasing to 40 ppm, consideration should be given to discontinuing the drug if no clinically significant response has occurred.

Conclusion

These guidelines, "Use of iNO in neonates and children: consensus guidelines from the European Society of Paediatric and Neonatal Intensive Care, the European Society of Paediatric Research and the European Society of Neonatology", (please see ESM), were compiled by a group of practitioners with knowledge of iNO therapy drawn from the majority of European states. The guidelines are designed to allow the safe use of this therapy, within both its permitted and its potential uses. It is hoped that these guidelines will encourage evidence-based practice and further clinical trials on the use of iNO therapy.

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References

1. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, Verter J, Stoll BJ, Lemons JA, Papile LA, Shankaran S, Donovan EF, Oh W, Ehrenkranz RA, Fanaroff AA (2000) Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics 105:14–20

2. Kinsella JP, Abman SH (1996) Clinical pathophysiology of persistent pulmonary hypertension of the newborn and the role of inhaled nitric oxide therapy. J Perinatol 16:S24–27

3. Kinsella JP, Abman SH (2000) Clinical approach to inhaled nitric oxide therapy in the newborn with hypoxemia. J Pediatr 136:717–726

4. Finer NN, Barrington KJ (2000) Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev CD000399

5. Barefield ES, Karle VA, Phillips JB 3rd, Carlo WA (1996) Inhaled nitric oxide in term infants with hypoxemic respiratory failure. J Pediatr 129:279–286

6. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, et al. (2000) Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Engl J Med 342:469–474

7. Davidson D, Barefield ES, Kattwinkel J, Dudell G, Damask M, Straube R, Rhines J, Chang CT (1998) Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study. Pediatrics 101:325–334

8. Christou H, Van Marter LJ, Wessel DL, Allred EN, Kane JW, Thompson JE, Stark AR, Kourembanas S (2000) Inhaled nitric oxide reduces the need for extracorporeal membrane oxygenation in infants with persistent pulmonary hypertension of the newborn. Crit Care Med 28:3722–3727

9. Day RW, Lynch JM, White KS, Ward RM (1996) Acute response to inhaled nitric oxide in newborns with respiratory failure and pulmonary hypertension. Pediatrics 98:698–705

10. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, Redding GJ, de Lemos RA, Sardesai S, McCurnin DC, Moreland SG, Cutter GR, Abman SA (1997) Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 131:55–62

11. The Neonatal Inhaled Nitric Oxide Study Group (NINOS) (1997) Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 336:597–604

12. Roberts JD Jr, Fineman JR, Morin FC 3rd, Shaul PW, Rimar S, Schreiber MD, Polin RA, Zwass MS, Zayek MM, Gross I, Heymann MA, Zapol WM (1997) Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med 336:605–610

13. Wessel DL, Adatia I, Van Marter LJ, Thompson JE, Kane JW, Stark AR, Kourembanas S (1997) Improved oxygenation in a randomized trial of inhaled nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics 100:E7

14. The Franco-Belgium Collaborative NO Trial Group (1999) Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. Lancet 354:1066–1071

15. Cornfield DN, Maynard RC, deRegnier RA, Guiang SF 3rd, Barbato JE, Milla CE (1999) Randomized, controlled trial of low-dose inhaled nitric oxide in the treatment of term and near-term infants with respiratory failure and pulmonary hypertension. Pediatrics 104:1089–1094

16. Sadiq F (1998) Illinois multicenter trial. Treatment of persistent pulmonary hypertension of the newborn with inhaled nitric oxide: a randomised trial. Pediatr Res 43:192A

17. The Neonatal Inhaled Nitric Oxide Study Group (NINOS) (1997) Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia.. Pediatrics 99:838–845

18. The Neonatal Inhaled Nitric Oxide Study Group (NINOS) (2000) Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the neonatal inhaled nitric oxide study group (NINOS). J Pediatr 136:611–617

19. Henrichsen T, Goldman AP, Macrae DJ (1996) Inhaled nitric oxide can cause severe systemic hypotension. J Pediatr 129:183

20. Finer NN, Etches PC, Kamstra B, Tierney AJ, Peliowski A, Ryan CA (1994) Inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation: dose response. J Pediatr 124:302–308

21. Demirakca S, Dotsch J, Knothe C, Magsaam J, Reiter HL, Bauer J, Kuehl PG (1996) Inhaled nitric oxide in neonatal and pediatric acute respiratory distress syndrome: dose response, prolonged inhalation and weaning. Crit Care Med 24:1913–1919

22. Lönnqvist PA, Winberg P, Lundell B, Sellden H, Olsson GL (1994) Inhaled nitric oxide in neonates and children with pulmonary hypertension. Acta Paediatr 83:1132–1136

23. Tworetzky W, Bristow J, Moore P, Brook MM, Segal MR, Brasch RC, Hawgood S, Fineman JR (2001) Inhaled nitric oxide in neonates with persistent pulmonary hypertension. Lancet 357:118–120

24. Goldman AP, Tasker RC, Haworth SG, Sigston PE, Macrae DJ (1996) Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics 98:706–713

25. Dotsch J, Demirakca S, Zepf K, Hanze J, Parida S, Rascher W (2000) Recovery from withdrawal of inhaled nitric oxide and kinetics of nitric oxide-induced inhibition of nitric oxide synthase activity in vitro. Intensive Care Med 26:330–335

26. Black SM, Heidersbach RS, McMullan DM, Bekker JM, Johengen MJ, Fineman JR (1999) Inhaled nitric oxide inhibits NOS activity in lambs: potential mechanism for rebound pulmonary hypertension. Am J Physiol 277:H1849–H1856

27. Petros AJ (1994) Down-regulation of endogenous nitric oxide production after prolonged administration. Lancet 344: 191

28. Kinsella JP, Neish SR, Shaffer E, Abman SH (1992) Low-dose inhalation nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 340: 819–820

29. Aly H, Sahni R, Wung JT (1997) Weaning strategy with inhaled nitric oxide treatment in persistent pulmonary hypertension of the newborn. Arch Dis Child Fetal Neonatal Ed 76:F118–F122

30. Sokol GM, Fineberg NS, Wright LL, Ehrenkranz RA (2001) Changes in arterial oxygen tension when weaning neonates from inhaled nitric oxide. Pediatr Pulmonol 32:14–19

31. Atz AM, Wessel DL (1999) Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. Anesthesiology 91:307–310

32. Rasmussen TR, Kjaergaard SK, Tarp U, Pedersen OF (1992) Delayed effects of NO_2 exposure on alveolar permeability and glutathione peroxidase in healthy humans. Am Rev Respir Dis 146:654–659

33. Anonymous (1988) Recommendations for occupational safety and health standards. MMWR 37:1–29

34. Gries A, Herr A, Motsch J, Holzmann A, Weimann J, Taut F, Erbe N, Bode C, Martin E (2000) Randomized, placebo-controlled, blinded and cross-matched study on the antiplatelet effect of inhaled nitric oxide in healthy volunteers. Thromb Haemost 83:309–315

35. Albert J, Norman M, Wallén NH, Frostell C, Hjemdahl P (1999) Inhaled nitric oxide does not influence bleeding time or platelet function in healthy volunteers. Eur J Clin Invest 29:953–959

36. Miller OI, Celermajer DS, Deanfield JE, Macrae DJ (1994) Guidelines for the safe administration of inhaled nitric oxide. Arch Dis Child 70:F47–F49

37. Francoe M, Troncy E, Blaise G (1998) Inhaled nitric oxide: technical aspects of administration and monitoring. Crit Care Med 26:782–796

38. Schedin U, Frostell CG, Gustafsson LE (1999) Formation of nitrogen dioxide from nitric oxide and their measurement in clinically relevant circumstances. Br J Anaesth 82:182–192

39. Kirmse M, Hess D, FujinoY, Kakmarek RM, Hurford WE (1998) Delivery of inhaled nitric oxide using the INOvent delivery system. Chest 113:1650–1657

40. Stenqvist O, Kjelltoft B, Lundin S (1993) Evaluation of a new system for ventilatory administration of nitric oxide. Acta Anaesth Scand 37:687–691

41. Lindwall R, Frostell, CG, Lönnqvist PA (2002) Delivery characteristics of a combined nitric oxide continuous positive airway pressure system. Paediatr Anaesth 12(6):530–536

42. Anonymous (2000) Classification of nitric oxide administration apparatus, nitric oxide analysers and nitrogen dioxide analysers. H Final Rule. Fed Regist 65:11464–11465

43. Squire S (1996) An effective method of scavenging nitric oxide (with personal communication from NHS Estates). Br J Anaesth 77:432–434

44. Phillips ML, Hall TA, Sekar K, Tomey JL (1999) Assessment of medical personnel exposure to nitrogen oxides during inhaled nitric oxide treatment of neonatal and pediatric patients. Pediatrics 104:1095–1100

45. Goldman AP, Cook PD, Macrae DJ (1995) Exposure of intensive-care staff to nitric oxide and nitrogen dioxide. Lancet 345:199–200

46. Kinsella JP, Neish SR, Ivy DD, Shaffer E, Abman SH (1993) Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. J Pediatr 123:103–108

47. Kinsella JP, Schmidt JM, Griebel J, Abman SH (1995) Inhaled nitric oxide treatment for stabilization and emergency medical transport of critically ill newborns and infants. Pediatrics 95:773–776

48. Kinsella JP, Griebel J, Schmidt JM, Abman SH (2002) Use of inhaled nitric oxide during interhospital transport of newborns with hypoxemic respiratory failure. Pediatrics 109:158–161

49. Anonymous (2000) Equipped to care. The safe use of medical devices in the 21st century. Medical Devices Agency, London

50. Anonymous (1999) Use of inhaled nitric oxide. Pediatrics 106:344–345

51. Noel S (1999) Nitric oxide at work in the intensive care unit; implications for nursing practice. Nurs Crit Care 4:249–255

52. Glynn G (1999) Nitric oxide: a nursing experience. J Neonatal Nurs 5:11–14

53. Barrington KJ, Finer NN (2001) Inhaled nitric oxide for respiratory failure in preterm infants (Cochrane Review). Cochrane Database Syst Rev 4

54. Subhedar NV, Ryan SW, Shaw NJ (1997) Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child 77:F185–F190

55. Kinsella JP, Walsh WF, Bose CL, Gerstmann DR, Labella JJ, Sardesai S, Walsh-Sukys MC, McCaffrey MJ, Cornfield DN, Bhutani VK, Cutter GR, Baier M, Abman SA (1999) Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial. Lancet 354:1061–1065

56. Hoehn T, Krause MF, Buhrer C (2000) Inhaled nitric oxide in premature infants—a meta-analysis. J Perinat Med 28:7–13

57. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV (2001) Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 90:573–576

58. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, Davis K Jr, Hyers TM, Papadakos P (1998) Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Crit Care Med 26:15–23

59. Dobyns EL, Cornfield DN, Anas NG, Fortenberry JD, Tasker RC, Lynch A, Liu P, Eells PL, Griebel J, Baier M, Kinsells JP, Abman SH (1999) Multicenter randomized-controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxaemic respiratory failure. J Pediatr 134:406–412

60. Lundin S, Mang H, Smithies M, Stenqvist O, Frostell C (1999) Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. Intensive Care Med 25:911–919

61. Troncy E, Collet J-P, Shapiro S, Guimond JG, Blair L, Ducruet T, Francoeur M, Scharbonneau M, Blaise G (1998) Inhaled nitric oxide in acute respiratory distress syndrome: A pilot randomized controlled study. Am J Respir Crit Care 157:1483–1488

62. Michael JR, Barton G, Saffle JR, Mone M, Markewitz BA, Hillier K, Elstad MR, Campbell EJ, Troyer BE, Whatley RE, Liou TG, Samuelson WM, Carveth HJ, Hinson DM, Morris SE, Davies BL, Day RW (1998) Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS. Am J Respir Crit Care 157:1372–1380

63. Sokol J, Jacobs SE, Bohn D (2000) Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Cochrane Database Syst Rev CD002787

64. Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ (1993) Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. Circulation 88:2128–2138

65. Adatia I, Perry S, Landzberg M, Moore P, Thompson JE, Wessel DL (1995) Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation. J Am Coll Cardiol 25:1656–1664

66. Roberts JD Jr, Lang P, Bigatello LM, Vlahakes GJ, Zapol WM (1993) Inhaled nitric oxide in congenital heart disease. Circulation 87:447–453

67. Miller OI, Celermajer DS, Deanfield JE, Macrae DJ (1994) Very-low-dose inhaled nitric oxide: a selective pulmonary vasodilator after operations for congenital heart disease. J Thorac Cardiovasc Surg 108:487–494

68. Wessel DL (1993) Inhaled nitric oxide for the treatment of pulmonary hypertension before and after cardiopulmonary bypass. Crit Care Med 21:S344–S345

69. Wessel DL, Adatia I, Thompson JE, Hickey PR (1994) Delivery and monitoring of inhaled nitric oxide in patients with pulmonary hypertension. Crit Care Med 22:930–938

70. Goldman AP, Delius RE, Deanfield JE, Macrae DJ (1995) Nitric oxide is superior to prostacyclin for pulmonary hypertension after cardiac operations. Ann Thorac Surg 60:300–305; discussion 306

71. Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS (2000) Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet 356:1464–1469

72. Day RW, Hawkins JA, McGough EC, Crezee KL, Orsmond GS (2000) Randomized controlled study of inhaled nitric oxide after operation for congenital heart disease. Ann Thorac Surg 69:1907–1912; discussion 1913

73. Goldman AP, Delius RE, Deanfield JE, Miller OI, de Leval MR, Sigston PE, Macrae DJ (1996) Pharmacological control of pulmonary blood flow with inhaled nitric oxide after the fenestrated Fontan operation. Circulation 94 (9 Suppl):II-44–II-48

74. Schulze-Neick I, Bultmann M, Werner H, Gamillscheg A, Vogel M, Berger F, Rossaint R, Hetzer R, Lange PE (1997) Right ventricular function in patients treated with inhaled nitric oxide after cardiac surgery for congenital heart disease in newborns and children. Am J Cardiol 80:360–363