

Increase in the use of inhaled nitric oxide in neonatal intensive care units in England: a retrospective population study

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ABSTRACT

Objective To describe temporal changes in inhaled nitric oxide (iNO) use in English neonatal units between 2010 and 2015.

Design Retrospective analysis using data extracted from the National Neonatal Research Database.

Setting All National Health Service neonatal units in England.

Patients Infants of all gestational ages born 2010–2015 admitted to a neonatal unit and received intensive care.

Main outcome measures Proportion of infants who received iNO; age at initiation and duration of iNO use.

Results 4.9% (6346/129 883) of infants received iNO; 31% (1959/6346) were born <29 weeks, 18% (1152/6346) 29–33 weeks and 51% (3235/6346) >34 weeks of gestation. Between epoch 1 (2010–2011) and epoch 3 (2014–2015), there was (1) an increase in the proportion of infants receiving iNO: <29 weeks (4.9% vs 15.9%); 29–33 weeks (1.1% vs 4.8%); >34 weeks (4.5% vs 5.0%), (2) increase in postnatal age at iNO initiation: <29 weeks 10 days vs 18 days; 29–33 weeks 2 days vs 10 days, (iii) reduction in iNO duration: <29 weeks (3 days vs 2 days); 29–33 weeks (2 days vs 1 day).

Conclusions Between 2010 and 2015, there was an increase in the use of iNO among infants admitted to English neonatal units. This was most notable among the most premature infants with an almost fourfold increase. Given the cost of iNO therapy, limited evidence of efficacy in preterm infants and potential for harm, we suggest that exposure to iNO should be limited, ideally to infants included in research studies (either observational or randomised placebo-controlled trial) or within a protocolised pathway. Development of consensus guidelines may also help standardise practice.

INTRODUCTION

Inhaled nitric oxide (iNO) is widely used in the treatment of hypoxaemic respiratory failure and persistent pulmonary hypertension of the newborn (PPHN). Although a well-established therapy in term and near-term infants with these conditions, the off-label use of iNO in preterm infants <34 weeks of gestation remains controversial. Population-based data indicate that there is wide variation in administration rates among US hospitals, but there are no equivalent data from the UK or mainland Europe.^{1–4} Data from individual centres and multicentre studies suggest that

What is known about the subject?

- Inhaled nitric oxide (iNO) is a well-established and licensed therapy in term and near-term infants with hypoxaemic respiratory failure and pulmonary hypertension.
- Evidence for the safety and efficacy of iNO in preterm infants is lacking.
- iNO use is highly variable internationally; data describing iNO use across neonatal units in the UK are lacking.

What this study adds?

- Use of inhaled nitric oxide (iNO) increased over time from 3.4% (1293/37 885) in 2010–2011 to 6.4% (3112/48 838) in 2014–2015.
- Increase in iNO use is most notable in the most preterm infants born <29 weeks for which there is a paucity of evidence of benefit.
- There is a wide variation in iNO usage between neonatal intensive care units in England.

the use of iNO is increasing,^{2–5} especially in preterm infants, despite the lack of evidence of benefit in this population.

We aimed to describe temporal changes in the use of iNO in neonates admitted to neonatal units in England using national data routinely recorded during clinical care and held in the National Neonatal Research database (NNRD). Our objectives were to (1) describe the proportion and characteristics of preterm and term infants who receive iNO between 2010 and 2015 and (2) determine whether there is variation in iNO use across tertiary level neonatal units and over time between 2010 and 2015.

METHODS

Setting, study design and data source

This retrospective cohort study used routinely recorded, deidentified data held in the



Table 1 Patient demographics and outcomes for infants born less than 29 weeks gestation admitted to neonatal units in England and treated with iNO

	2010–2011	2012–2013	2014–2015
Neonatal admissions requiring ≥ 1 day of intensive care (with and without iNO)	6730	6587	6410
Infants treated with iNO	329 (4.9%*)	611 (9.3%*)	1019 (15.9%*)
Birth weight (g)	790 (65 0,950)	795 (67 0,985)	790 (66 0,985)
Gestational age (weeks)	26 (24, 27)	26 (24, 27)	26 (24, 27)
Male sex	180 (55%)	364 (60%)	553 (54%)
Prolonged rupture of membranes >24 hours†	113 (34.4%)	190 (31.1%)	173 (17.0%)
Surfactant therapy in labour ward or neonatal unit	324 (98.5%)	589 (96.4%)	935 (91.8%)
Initiation of iNO therapy (day)	10 (2,33)	13 (2,46)	18 (3,48)
Duration of iNO therapy (days)	3 (2,5)	2 (1,4)	2 (1,4)
Diagnosis (not mutually exclusive)‡			
<i>Respiratory distress§ syndrome</i>	255 (77.5%)	505 (82.7%)	920 (90.3%)
<i>Pulmonary hypoplasia</i>	30 (9.1%)	40 (6.6%)	49 (4.8%)
<i>Pulmonary hypertension</i>	100 (30.4%)	164 (26.8%)	260 (25.5%)
<i>Congenital pneumonia</i>	2 (0.6%)	2 (0.3%)	10 (1.0%)
<i>Congenital diaphragmatic hernia</i>	0	0	1 (0.1%)
Death among infants who received iNO	143 (43.5%)	224 (36.7%)	242 (23.8%)

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise.

*Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care. All values are given as n, % or median (25th,75th centiles), as appropriate.

†Prolonged rupture of membranes >24 hours uses a combination of discharge diagnoses and recorded duration of rupture of membranes.

‡Extracted codes available in online supplemental file.

§This includes the diagnosis respiratory distress syndrome and signs of respiratory distress of newborn (see online supplemental file 1). iNO, inhaled nitric oxide.

NNRD. The NNRD has complete coverage of infants admitted for neonatal care at a National Health Service neonatal unit in England, Scotland and Wales. The NNRD is formed from data extracted from neonatal electronic health record systems used by health professionals during routine clinical care. A defined data extract comprising approximately 450 items,⁶ the Neonatal Data Set, is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London where data are cleaned and entered into the NNRD. High completeness and accuracy ($>95\%$) of data held in the NNRD have been confirmed by a formal comparison with those recorded in case record forms of a multicentre, randomised placebo-controlled trial (RCT).⁷ Neonatal units in England contributing data to the NNRD consented for their unit data to be included in the study.

Study population and data extraction

We included data from infants who required any neonatal intensive care (defined using British Association of Perinatal Medicine categories of care 2011,⁸ primarily as needing mechanical ventilation or noninvasive ventilation plus parenteral nutrition) over a 6-year period, 01 January 2010 to 31 December 2015 in England. Infants who did not receive intensive care on a neonatal unit or who were not cared completely in units in Wales and Scotland were excluded from the analysis.

We extracted daily variables (receipt of iNO, surfactant), demographic variables (birth weight, sex, gestational age), maternal factors (prolonged rupture of membranes >24 hours), diagnoses and survival to neonatal unit discharge. See online supplemental file 1 for diagnostic codes.

Outcomes

The primary outcome was the rate of iNO use as a proportion of infants who received neonatal intensive care, unit level.

The following secondary outcomes were analysed for infants who received iNO:

- ▶ Timing of iNO initiation (postnatal age in days).
- ▶ Duration of iNO.
- ▶ Diagnoses including respiratory distress syndrome, persistent pulmonary hypertension of the newborn, pulmonary hypoplasia, congenital pneumonia, congenital diaphragmatic hernia, congenital heart disease, meconium aspiration syndrome (among infants ≥ 34 weeks of gestation).
- ▶ Survival to neonatal unit discharge.

Statistical analyses

We describe the cohort at two levels: (1) at the level of the population of infants who received at least 1 day of neonatal intensive care and (2) at the level of the neonatal unit. For all outcomes, separate analyses were

Table 2 Patient demographics and outcomes for infants born 29–33 weeks' admitted to neonatal units in England and treated with iNO

	2010–2011	2012–2013	2014–2015
Neonatal admissions requiring ≥ 1 day of intensive care (with and without iNO)	12 781	13 796	14 556
Infants treated with iNO	144 (1.1%*)	315 (2.3%*)	693 (4.8%*)
Birth weight (g)	1603 (1311,1972)	1500 (1290,1800)	1500* (1256,1800)
Gestational age (weeks)	30 (29,32)	31 (29,32)	31 (30,32)
Male sex	91 (63.2%)	187 (59.4%)	406 (58.6%)
Prolonged rupture of membranes >24 hours§	34 (23.6%)	86 (27.3%)	124 (17.9%)
Surfactant therapy in labour ward or neonatal unit	131 (91.0%)	229 (72.7%)	418 (60.3%)
Initiation of iNO therapy (days)	2 (1,3)	3 (1,20)	10 (2,24)
Duration of iNO therapy (days)	2 (2,4)	1 (1,3)	1 (1,2)
Diagnosis (not mutually exclusive)‡			
<i>Respiratory distress† syndrome</i>	92 (63.9%)	240 (76.2%)	604 (87.2%)
<i>Pulmonary hypoplasia</i>	23 (16.0%)	46 (14.6%)	72 (10.4%)
<i>Pulmonary hypertension</i>	76 (52.8%)	108 (34.3%)	163 (23.5%)
<i>Congenital pneumonia</i>	1 (0.7%)	3 (1.0%)	2 (0.3%)
<i>Congenital diaphragmatic hernia</i>	7 (4.9%)	11 (3.5%)	15 (2.2%)
Death among infants who received iNO	59 (41.0%)	68 (21.6%)	76 (11.0%)

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise.

One baby with a birth weight less than 300 grams was removed from this calculation (n=692).

*Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care. All values are given as n, % or median (25th, 75th centiles) as appropriate.

†This includes the diagnosis respiratory distress syndrome and signs of respiratory distress of newborn (see online supplemental file 1).

‡Extracted codes available in supplementary file.

§Prolonged rupture of membranes >24 hours uses a combination of discharge diagnoses and recorded duration of rupture of membranes. iNO, inhaled nitric oxide.

conducted by a priori defined gestational age bands: (a) extremely preterm (<29 weeks of gestation), (b) moderately preterm (29–33 weeks of gestation) and (c) late preterm/term (>34 weeks of gestation).

Results are presented using medians (interquartile ranges) and percentages for continuous and categorical variables, respectively.

For the neonatal unit-level analysis, we limited this to the 47 tertiary neonatal units in England who have treated five or more infants with nitric oxide. For this analysis, we attributed iNO use to the first unit providing iNO therapy regardless of whether an infant was treated with iNO in more than one neonatal unit. The total number of neonatal units in England during this period decreased from 169 (in 2010–2011) to 161 (in 2014–2015); this reflects the merger or closure of units. Rates of iNO use across tertiary units are presented graphically without comparative testing.

Patient and public involvement

Results will be disseminated to parents, ex-patients and members of the public through the Imperial College Neonatal Data Analysis Unit website, social media and strong links between the authors and parent/patient groups.

RESULTS

During the 6-year study period, 129 883 infants received at least 1 day of intensive care in England; 4.9% (6,346) of these received iNO. Use of iNO increased over time from 3.4% (1293/37 885) in 2010–2011 to 6.4% (3112/48 838) in 2014–2015.

When analysed by gestational age band over the entire study period, 9.9% (1959/19 727) of infants born <29 weeks received iNO; corresponding percentages are 2.8% (1152/41 133) for 29–33 weeks and 4.7% (3235/69 022) for ≥ 34 weeks (tables 1–3). Mortality among iNO-treated infants decreased over time in all gestational age groups.

By gestational age bands

Less than 29 weeks

31% (1959/6346) of infants who received iNO were born <29 weeks of gestation (table 1). Among infants born in the later epoch, a lower proportion had diagnoses of prolonged rupture of membranes or pulmonary hypoplasia recorded and a higher proportion had respiratory distress syndrome (RDS) recorded and received surfactant. (table 1). Of 282 had congenital heart disease; the most common were atrial or ventricular septal defects (67%) (online supplemental table 2).

Table 3 Patient demographics and outcomes for infants born >34 weeks' gestation admitted to neonatal units in England and treated with iNO

	2010–2011	2012–2013	2014–2015
Neonatal admissions requiring ≥ 1 day of intensive care (with and without iNO)	18 374	22 777	27 872
Infants treated with iNO	820 (4.5%*)	1015 (4.5%*)	1400 (5.0%*)
Birth weight (g)	3273 (2840,3665)	3240 (2760,3690)	3220* (2680,3630)
Gestational age (weeks)	40 (38,41)	39 (37,40)	39 (37,40)
Male sex	450 (54.9%)	577 (56.9%)	756 (54.0%)
Prolonged rupture of membranes >24 hours§	82 (10.0%)	92 (9.1%)	68 (4.9%)
Surfactant therapy in labour ward or neonatal unit	532 (64.9%)	613 (60.4%)	713 (50.9%)
Initiation of iNO therapy (days)	2 (1,2)	2 (1,2)	2 (1,2)
Duration of iNO therapy (days)	3 (2,5)	3 (2,5)	2 (1,5)
Diagnosis (not mutually exclusive)‡			
<i>Respiratory distress syndrome</i> †	259 (31.6%)	378 (37.2%)	778 (55.6%)
<i>Pulmonary hypoplasia</i>	61 (7.4%)	67 (6.6%)	101 (7.2%)
<i>Meconium aspiration syndrome</i>	314 (38.3%)	378 (37.2%)	440 (31.4%)
<i>Pulmonary hypertension</i>	598 (72.9%)	703 (69.3%)	885 (63.2%)
<i>Congenital pneumonia</i>	42 (5.1%)	52 (5.1%)	74 (5.3%)
<i>Congenital diaphragmatic hernia</i>	55 (6.7%)	57 (5.6%)	83 (5.9%)
Death among infants who received iNO	165 (20.1%)	160 (15.8%)	212 (15.1%)

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise.

One baby with a birth weight less than 300 grams was removed from this calculation (n=1399).

*Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care. All values are given as n, % or median (25th,75th centiles) as appropriate.

†This includes the diagnosis respiratory distress syndrome and signs of respiratory distress of newborn (see online supplemental file 1).

‡Extracted codes available in online supplemental file.

§Prolonged rupture of membranes >24 hours uses a combination of discharge diagnoses and recorded duration of rupture of membranes. iNO, inhaled nitric oxide.

29–33 weeks

Eighteen per cent (1152/6 346) of infants who received iNO were born at 29–33 weeks of gestation. A lower proportion of infants born in the later epoch had PPHN recorded and a higher proportion had RDS recorded, although surfactant use was lower in the later epoch. In the 2014–2015 epoch, iNO was initiated later and administered for a shorter duration (table 2). Of 264 infants had congenital heart disease; 52% were atrial or ventricular septal defects (online supplemental table 2).

Greater than or equal to 34 weeks

Fifty-one per cent (3235/6346) of infants who received iNO had a gestational age of ≥ 34 weeks at birth. The proportion of these infants who received iNO increased marginally between 2010–2011 and 2014–2015. A lower proportion of these infants born in the later epoch had prolonged rupture of membranes, PPHN or meconium aspiration syndrome; and a higher proportion had RDS recorded and received surfactant. iNO was initiated later and administered for a shorter duration (table 3). Of 616 of these infants who received iNO had congenital heart disease and 41.6% (256/616) were atrial or ventricular septal defects (online supplemental table 2).

Comparison between tertiary units

There was wide variation in the proportion of infants receiving intensive care who also received iNO between the 47 tertiary neonatal intensive care units in England across all gestation groups (figure 1A). This was especially marked among infants <29 weeks of gestation where iNO use varied between 0.7% and 36.5% (figure 1B).

When considering unit-level trends over time, iNO use in >29 week gestation infants increased between 2010–2011 and 2014–2015 in almost all units (figure 1C); however, a more mixed picture was seen in less preterm infants (figure 1D).

DISCUSSION

In this large population-level study, we found that almost 1 in 20 infants who received any period of intensive care at an English neonatal unit were treated with iNO, that this rate almost doubled between 2010–2011 and 2014–2015 and that the temporal increase in iNO use was seen across all gestational ages. The temporal increase was most evident among more preterm infants <34 weeks, in whom the use of iNO increased threefold from 2.4% to 8.2% and where evidence for iNO is most lacking. There was a similar 3–4-fold increase in rates of iNO use for

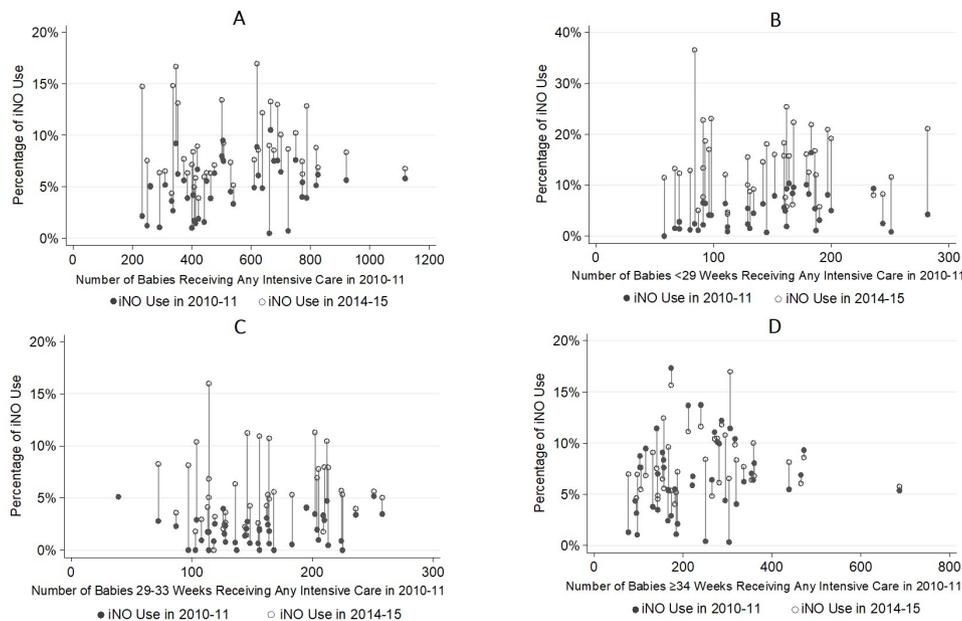


Figure 1 (A) iNO use for tertiary neonatal units for all gestational ages. (B) iNO use for tertiary neonatal units for infants born <29 weeks. (C) iNO use for tertiary neonatal units for infants born 29–33 weeks. (D) iNO use for tertiary units for infants born ≥34 weeks the numbers of infants receiving intensive care for more than one day in 2014–2015 (denominator) are not presented.

infants born <29 weeks and 29–33 weeks, from 4.9% to 15.9% and from 1.1% to 4.8% for infants, respectively. In the most preterm group, an additional 690 infants born <29 gestational weeks were treated with iNO in 2014–2015 compared with 2010–2011.

It is difficult to compare these data with internationally reported iNO usage rates because other studies commonly report rates as a proportion of all neonatal admissions, whereas we report rates as a proportion of infants receiving neonatal intensive care. We used this denominator because of differences in the organisation of neonatal care (use of a networked model of care in the UK results in numerous transfers between neonatal units as part of routine care) and to minimise the impact of variations in practice around admissions of term infants for short periods. Rates of iNO usage in US studies are reported between 0.9% and 1.3%^{2 3} of all neonatal admissions. To our knowledge, this is one of the largest studies of iNO use in neonatal practice; other studies have reported iNO use in various US healthcare organisations (including children’s hospitals) and in all admissions including infants receiving lower acuity categories of neonatal care.^{1 4 9 10}

The Canadian Neonatal Network (CNN) found similar rates (1 in 25; 4.2%) of iNO use among infants born <34 weeks between 2010 and 2013. As different gestational age categories were used, direct comparisons cannot be made, but the use of iNO was broadly similar to the recent UK figures; however, in contrast to the increasing use in the UK, iNO use was stable across the 4 years in the CNN.¹¹

Approximately half of all infants who received iNO in this study were born at <34 weeks of gestation. This is relevant because the licenced indication for iNO limits

treatment to newborn infants ≥34 weeks of gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.¹² This finding is, however, broadly consistent with other studies from the US and Europe, which showed that 40%–46% of all treated infants were <34 weeks of gestation.^{3 13} Treatment rates for preterm infants in this study (5.1% of preterm infants <34 weeks of gestation) were comparable to other studies from the US reporting rates of 2.6% to 7.2% in the same gestation groups,^{1 4 9 10} and in this comparison, the different denominator in US studies is less likely to influence results as the majority of more preterm infants will receive intensive care.

We find that not only is off-label treatment with iNO of preterm infants <34 weeks of gestation widespread but also is increasing—particularly in the most preterm infants. The evidence base supporting routine use in these most preterm infants, both in respect of safety and efficacy, is weakest.^{2–4} Post hoc analyses from a study which randomised 420 neonates born <34 weeks of gestation to placebo or iNO found an apparent increase in mortality and higher rate of intraventricular haemorrhage in infants with a birth weight ≤1000 g.¹⁴

The reason for increasing use of iNO off-label in particular in the most preterm infants is not known but is likely to be multifaceted and reflect the absence of other proven ‘rescue’ cardiorespiratory interventions for these smaller infants with severe hypoxaemic respiratory failure (such as extracorporeal membrane oxygenation) and full reimbursement of off-label iNO use in England. Furthermore, there is some limited evidence for the use of iNO in specific groups of preterm infants including those born following preterm prolonged rupture of membranes and those with echocardiographic criteria



of PPHN physiology, supported by expert opinion and consensus statements.^{15–18} There is growing experience in the use of iNO and the immediate short-term oxygenation response can be gratifying for clinicians and may encourage further use. However, whether the short-term benefit in oxygenation is translated into longer term benefit in preterm infants is unknown and needs further investigation. Moreover, the perception of absence of harm should not be extrapolated from term infants simply because there is a lack of convincing evidence of harm in preterm infants.

Treatment with iNO was started later and duration of treatment was shorter in later epochs, suggesting that preterm infants were more commonly treated outside the acute respiratory phase. Although there is little evidence of efficacy of iNO as rescue therapy in acute respiratory failure or later ventilator-dependent chronic lung disease,^{19,20} we speculate that clinicians might be increasingly willing to use off-label iNO in such circumstances.

This study also demonstrates large variation between English neonatal units in rates of iNO use, in keeping with that reported in recent US studies^{1,10} where a similar degree of variation from 0.4% to 21.9% was seen in iNO use in preterm infants between 13 National Institute of Child Health and Human Development (NICHD) neonatal research network centres. The variation between neonatal units in the US decreased following publication of national guidance.²¹ Such national guidance is not available for the UK but might help standardise practice in this area if it was to be developed.

Overall mortality decreased in iNO-treated infants during the study period. This trend mirrors national data reporting improved survival in extremely preterm infants in England²² over a similar timeframe. The lower mortality seen in later epochs may also reflect a change in case mix as iNO therapy is offered more readily to infants with less severe cardiorespiratory failure. This type of ‘therapeutic creep’ has been described with other neonatal interventions.²³ This study was not designed to analyse changes in outcomes beyond simple descriptive data.

The strengths of this study include the use of a large national data set derived from electronic patient data routinely entered by health professionals at the point of care, which has been shown to be accurate and complete. This contrasts with previous similar reports such as those from the National Institute of Child Health and Development Neonatal Research Network and the Pediatric Medical Group that have focused on admissions to tertiary neonatal units or to a large network of neonatal care providers, respectively.^{3,9} Limitations of this study include that data held in the NNRD are recorded as part of routine clinical care and we cannot exclude the possibility of incomplete or inaccurate data. Also, we did not set out to capture information about neonatal iNO use in other critical care settings, such as paediatric or cardiac intensive care units, and these data would have been excluded from this study. Our study was also not

designed to describe specific aspects of iNO therapy such as indication for use and dosage regimens.

Our study describes the increasing use of iNO, especially in more preterm infants, but was not designed to address the issue of potential benefits and risks of this practice. While iNO might be effective in certain subgroups of preterm infants such as those with pulmonary hypoplasia and/or PPHN physiology, its short-term and long-term safety has not yet been established. Potential concerns include an association between neonatal iNO therapy and pulmonary toxicity, brain injury and an increased risk of childhood cancer.^{24,25} iNO is also one of the most expensive treatments available in neonatal care and there are likely to be resource implications of increasing use. Although there are limited data on costs of iNO therapy in the UK,²⁶ estimates from the USA suggest a cost of approximately US\$125/hour or US\$3000/day.²⁷

In summary, the use of iNO in English neonatal units has almost doubled between 2010 and 2015, with the most notable increase seen in the most premature infants. There was substantial variation in iNO use between units. Approximately half of the treated infants were preterm <34 weeks of gestation in whom iNO was used off-label and without high-quality evidence of efficacy or safety. Given the cost of iNO therapy, limited evidence of efficacy in preterm infants, and potential for harm, we suggest that exposure to iNO should be limited, ideally to infants included in research studies (either observational or RCT) or within a protocolised pathway that permits a short trial of iNO to assess acute oxygenation response. Development of consensus guidelines might also help standardise practice.

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