Cost-effectiveness of inhaled nitric oxide for the management of persistent pulmonary hypertension of the newborn
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared two treatment strategies for persistent pulmonary hypertension of the newborn (PPHN). One strategy was conventional ventilation in the authors' setting, which was not described in full detail in the current study. The other strategy was the addition of inhaled nitric oxide (iNO), a selective pulmonary vasodilator, to the conventional ventilation treatment regimen.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The characteristics of the target population were not described in full detail. The authors used an additional cohort to derive further outcome probabilities. This comprised neonates of greater than 34 weeks' gestation with PPHN who were treated at the neonate intensive care unit (NICU) at the Children's Hospital of Philadelphia (CHOP). Further inclusion or exclusion characteristics were not provided.

Setting
The setting was tertiary care (an NICU). The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1997 and 2000. The primary effectiveness data derived from the cohort of infants were collected between 1991 and 1993 for the conventional treatment cohort and between 1995 and 2002 for the iNO cohort. The costs were derived from sources published in 2002 and were reported for the fiscal year 2001.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies. Where data were not available in the literature, the authors used primary data from the authors' setting.

Link between effectiveness and cost data
In terms of the cohort of infants used to complement the estimation of outcome probabilities, the costing was carried out retrospectively on the same sample of patients.
Study sample
The sample size of the cohort was not determined in the planning phase of the study. In addition, power calculations were not performed retrospectively. The cohort comprised all infants treated for PPHN in the NICU at the CHOP between 1991 and 2002, who were not included in blinded, randomised controlled trials. No infants were reported to have been excluded from the cohort. The cohort comprised 123 infants, of which 32 received conventional ventilation treatment and 91 received the combination of iNO and ventilation treatment.

Study design
The analysis was based on a single-centre cohort study. The duration of follow-up was from birth of the neonates to the end of the initial hospitalisation due to PPHN. The loss to follow-up was not reported, nor was blinding of the outcome assessment.

Analysis of effectiveness
It was not reported whether the analysis was conducted on an intention to treat basis. The primary outcomes used were:

- the probabilities of side effects with and without extracorporeal membrane oxygenation (ECMO);
- the probabilities of major side effects with and without ECMO;
- the survival rates at hospital discharge with major side effects, with and without ECMO;
- the survival rate with minor side effects without ECMO; and
- the survival rates without the need for home medical support with major, minor or no side effects, with and without ECMO.

The birth weight and gestational age were similar between the two groups. Infants who were treated with iNO had a significantly lower 1-minute Apgar score, higher Caesarean section rates and longer time from birth to the decision of ECMO, and more days on ventilator in comparison with the conventional ventilation treatment group. Although the patient groups differed in their baseline characteristics, the authors did not report particular adjustments carried out to account for confounding factors.

Effectiveness results
The results for iNO treatment (conventional treatment) were as follows (the reader is referred to the paper for the 95% confidence intervals).

The probability of side effects was 0.7895 (0.7059) with ECMO and 0.6212 (0.6) without ECMO.

The probability of major side effects was 0.6957 (0.5744) with ECMO and 0.6667 (1) without ECMO.

The survival rate at hospital discharge with major side effects was 0.9444 (0.9444) with ECMO and 0.8333 (0.6667) without ECMO.

The survival rate with minor side effects was 0.9091 without ECMO.

With ECMO, the survival rate without the need for home medical support was 0.25 (0.2222) for major side effects, 0.625 (0.1667) for minor side effects and 0.8571 for no side effects.

Without ECMO, the survival rate without the need for home medical support was 0.3636 (0) for major side effects, 0.9 for minor side effects and 0.9474 (1) for no side effects.

Clinical conclusions
In terms of the survival rates, the addition of iNO seems to have been more effective than the conventional ventilation treatment.

**Modelling**

The authors used a decision analytic model to determine the costs and effectiveness of the two treatment options. The time horizon of the model was one year, while the timeframe of the cohort study was from birth of the neonates to the end of the initial hospitalisation due to PPHN. For the purpose of the model, "death" was defined as any infant that died during the initial hospital visit for PPHN. "Survive with need for home medical support" was defined as any infant necessitating any supplemental medical support (e.g. nasogastric feeding, supplemental oxygen, medication for control of seizures). "Survive without need for home medical support" was defined as any infant that survived after hospital discharge without any supplementary medical or nursing care (except from care routinely administered). Side effects included in the analysis were divided into major and minor. Major side effects were seizures, gastrointestinal or pulmonary haemorrhage, intraventricular haemorrhage, necrotising enterocolitis, and the need to re-administer iNO after it was discontinued. Minor side effects were gastroesophageal reflux disease, infiltrated intravenous catheter necessitating therapy, or blood stream infection without cardiovascular association.

**Outcomes assessed in the review**

The input parameter for both treatment options used in the model was the need for ECMO rescue.

**Study designs and other criteria for inclusion in the review**

The authors mainly included randomised controlled trials in their review. The study population of the studies was restricted to newborns of more than 34 weeks’ gestation who had hypoxic respiratory failure and evidence of pulmonary hypertension, as described in clinical or echocardiographic guidelines.

**Sources searched to identify primary studies**

MEDLINE and PubMed were searched for primary studies.

**Criteria used to ensure the validity of primary studies**

To be included, the studies had to have blinded, randomised assignment to treatment protocol without non-blinded use of iNO for rescue treatment of PPHN.

**Methods used to judge relevance and validity, and for extracting data**

Not reported.

**Number of primary studies included**

Overall, 6 primary studies were included in the review.

**Methods of combining primary studies**

Different results were combined into a point estimate using a Mantel-Haenszel (meta-analysis) method to estimate a combined odds ratio. The results of the meta-analysis were compared with a published meta-analysis (Finer et al. 2001, see ‘Other Publications of Related Interest’ below for bibliographic details).

**Investigation of differences between primary studies**

The authors do not seem to have investigated differences between the primary studies.
Results of the review
The meta-analysis was used to derive point estimates for the risk of ECMO rescue treatment. The need for ECMO rescue was 0.3062 (95% confidence interval, CI: 0.2623 - 0.3529) in the iNO group and 0.5371 (95% CI: 0.4822 - 0.5913) in the conventional treatment group.

Measure of benefits used in the economic analysis
The authors used survival and quality-adjusted life-years (QALYs) for one full year after discharge as the measure of benefit in the economic analysis. They assigned different utility values to each health state. Survival without supplemental medical support was defined as 1 full QALY, while dying before hospital discharge was assigned a utility of 0 QALY. Survival with need for home medical support was associated with a EuroQOL state of “some problems with performing usual activities” and assigned a utility of 0.87 QALY. A group of neonatologists at the CHOP assigned utility values using questions about different types of home medical support.

Direct costs
The direct medical costs included in the analysis were the costs of the hospital room, labour costs (i.e. the physician's, nurse's and respiratory therapist's time), laboratory costs and procedural costs. The laboratory costs were for chest X-ray anteroposterior, chest X-ray anteroposterior/lateral, abdominal ultrasound, complete, abdominal ultrasound limited, magnetic resonance imaging (MRI) head, MRI head without contrast, upper gastrointestinal, head ultrasound, computed tomography (CT) head without contrast, CT head with contrast, CT head with/without contrast, echocardiogram and electroencephalogram. Procedural costs covered transfusion of blood products, artery cannulation, PICC placement, broviac, venous cannulation, umbilical artery catheterisation, umbilical venous catheterisation, chest tube, reintubation, bronchoscopy, brainstem auditory evoked response, evoked potentials, direct laryngoscopy with bronchoscopy, tracheostomy, G-tube, cardiac catheterisation and pH probe. Other costs included the ventilator cost, use of nasal cannula, ECMO supplies, medication costs (using generic costs or cheapest wholesale price), total parenteral nutrition and enteral feedings. The travel costs were also included in the analysis, although the source of these costs was not reported.

With the exception of medication costs, all the unit costs were reported but the quantities of resources used were not. The resources used were derived from the cohort in the authors' setting. All the costs were derived from official published sources and were adjusted to represent 2001 prices. The costs in the base-case analysis were incurred for 1 year, making discounting irrelevant.

Statistical analysis of costs
The authors carried out a nonparametric bootstrap analysis using Stata 7.0 statistical software (College Station, TX) to derive a median estimate and 95% CIs for the costs. A random sample of 123 infants was drawn, with replacement from the pool of 123 infants of the cohort for 2,000 interactions.

Indirect Costs
The costs of lost income due to absence from work were included. The costs and the quantities were not analysed separately. The costs were derived from official published sources and the authors used average hourly wage (Bureau of Labour Statistics). The resources used were derived from the cohort in the authors’ setting. All the costs were adjusted to represent 2001 prices. The costs in the base-case analysis were incurred for 1 year, making discounting unnecessary.

Currency
US dollars ($).

Sensitivity analysis
The authors carried out one-way threshold analyses, varying all the input variables to determine the ones that resulted in a cost-effectiveness ratio of $0/outcome, $50,000/outcome and $100,000/outcome. The ranges used were derived from...
CIs estimated in the bootstrap analysis.

The authors also carried out probabilistic sensitivity analyses, varying all input variables simultaneously using Monte Carlo simulation methods to test the robustness of the results. For those input variables derived by the meta-analysis, the authors used a beta or normal distribution. Uniform distributions were assigned to all other input parameters using a rank ordering of the results of the bootstrap analysis from lowest to highest.

In the sensitivity analysis, the authors extended the time horizon of the model from one year to the average lifetime of 75 years using 5% and 2% annual discount rates.

**Estimated benefits used in the economic analysis**
The conventional ventilation treatment resulted in 0.8954 life-years (LYs) saved for each infant, while the iNO treatment resulted in 0.9297 LYs saved per infant. iNO resulted in 0.0343 additional LYs saved per infant.

The conventional ventilation treatment resulted in 0.8262 QALYs gained for each infant, while the iNO treatment resulted in 0.8861 QALYS gained per infant. iNO resulted in 0.0599 additional QALYs gained per infant.

**Cost results**
Conventional ventilation treatment resulted in a total cost of $40,468 per infant. The equivalent cost for iNO was $41,609.

**Synthesis of costs and benefits**
An incremental analysis was performed. iNO treatment resulted in an incremental cost of $19,022 per QALY gained and $33,234 per LY saved.

The one-way sensitivity analysis demonstrated that the results were robust to variability in the data. The $50,000 per QALY gained threshold was only exceeded by varying the following parameters:

the total cost of the conventional ventilation group in period 1 (time from birth to the decision for ECMO therapy);

the period 2 total costs (time from the decision for ECMO therapy to extubation from mechanical ventilation) in both treatment infants needing ECMO rescue treatment and who survived with major side effects;

the probability of side effects with ECMO in the conventional ventilation group; and

the probability of having major side effects without ECMO in the conventional ventilation group.

Varying the probability of having a major side effect without ECMO in the conventional ventilation group resulted in a threshold of greater than $100,000 per QALY gained.

When applying a 75-year time horizon, the results were improved and iNO resulted in a cost-effectiveness ratio of $976 per QALY gained. These results were robust to variations in the discount rate.

The probabilistic analyses demonstrated that iNO was cost-effective, accounting for a cut-off of $100,000 per QALY gained in 80.9% of the trials. In 35.7% of the trials iNO was found to be more cost-effective than conventional ventilation treatment, while in 3.6% of the trials it was found to be more costly and less effective than conventional treatment.

**Authors' conclusions**
From a societal perspective, inhaled nitric oxide (iNO) was cost-effective but not cost-saving in treating infants with persistent pulmonary neonatal hypertension (PPHN).
CRD COMMENTARY - Selection of comparators
An explicit justification was given for the comparators used. Convention ventilation would seem to represent the commonly used approach in the authors' setting. You should decide if they represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
Although a systematic review of the literature was not undertaken, the authors included only randomised controlled trials in their review, assuring a better quality of the estimates used. Most of the input parameters were derived using primary data obtained from a cohort of patients in the authors' setting. The study sample was representative of the study population and, although the patient groups were shown to differ at analysis, an extensive statistical analysis was undertaken to account for potential confounding factors. Since no power calculations were reported, it was not possible to ascertain whether the results obtained were due to the intervention or to chance. The other estimates were arrived at by the use of meta-analytic techniques. The authors clearly reported the methods used to derive their estimates of effectiveness, but did not adopt a weighting scheme to reflect differences in sample size. However, an appropriate statistical analysis was undertaken to account for potential biases and confounding factors.

Validity of estimate of measure of benefit
The measure of benefit used was the health utility (QALYs), measured over a full year after discharge. The values of an expert group (neonatologists at the CHOP) were used to assign utilities at different health states, while some utilities were derived from published studies.

Validity of estimate of costs
The economic analysis was conducted from a societal perspective. It seems that all the relevant categories of costs have been included. The unit costs were reported (apart for medication costs and productivity losses), thus enhancing the reproducibility of the results to other settings. The quantities of resources used were derived from the cohort of infants in the authors' setting and an appropriate statistical analysis of the quantities was performed. All the cost estimates were derived from published sources. An extensive sensitivity analysis was undertaken to assess the robustness of the estimates used. The time horizon in the base-case analysis was one year and discounting was not necessary. When the time horizon was extended to 75 years, discounting was appropriately conducted. The price year was reported, which will aid any future reflation exercises. The authors consider a strength of their study to be the fact that resources used, rather than the adjustment of charges with cost-to-charge ratios, were used to assess the true costs associated with caring for a neonate.

Other issues
The authors compared their findings with those from other studies which, in general, showed their findings to be in agreement. In terms of the cost estimates, the authors suggested that costs from the CHOP were generalisable to large regional NICUs with ECMO capability (i.e. mostly referring to academic centres), but not to other NICUs across the USA. The authors do not appear to have presented their results selectively. The study enrolled infants of more than 34 weeks' gestation suffering from PPHN and this was reflected in the authors' conclusions. The authors reported further limitations to their study. For example, the long-term costs and benefits of iNO treatment were not estimated. In addition, the authors were unable to calculate the long-term costs and benefits of iNO treatment and the potential immeasurable costs associated with the use of ECMO, such as increased risk of cerebrovascular disease or neurologic deficits.

Implications of the study
The authors did not make explicit recommendations for changes in policy or practice. However, they suggested “given the high costs that an infant with PPHN accrues during his or her hospital stay, efforts should focus on primary prevention of the condition and improved efficiency in the use of iNO in infants with PPHN”. In addition, they stressed the need for further research into specific areas. In particular, costs related to iNO should be investigated further, and future studies should try to take the long-term effects and costs of using iNO and ECMO treatments into consideration.
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**Other publications of related interest**

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