Cost-Effectiveness of Inhaled Nitric Oxide for the Management of Persistent Pulmonary Hypertension of the Newborn

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ABSTRACT. *Objective.* **Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that has become part of the standard management for persistent pulmonary hypertension of the newborn (PPHN). This treatment modality, like many in neonatology, has not been well studied using quantitative economic techniques. The objective of this study was to evaluate the economic impact of adding iNO to the treatment protocol of PPHN for term infants from birth to the time of discharge from their initial hospitalization.**

Methods. **We used decision analysis modeling from a societal perspective to obtain an incremental cost-effectiveness ratio. Outcome probabilities were taken from the medical literature and a cohort of 123 infants who were treated with PPHN at The Children's Hospital of Philadelphia between 1991 and 2002. Costs were estimated from daily resources used by these infants in 2001 dollars. Survival and quality-adjusted life years were used as effectiveness measures. One-way, threshold, and probabilistic sensitivity analyses were performed to assess the robustness of the base-case estimate.**

Results. **The addition of iNO to the treatment regimen of PPHN increased the cost of treating an infant by an average of $1141, primarily from an increased number of mechanical ventilation days. Use of iNO led to 3.4% more lives saved and a 6% increase in the average utility gained per infant. The incremental cost-effectiveness ratio was $33 234 per life saved and $19 022 per quality-adjusted life year gained. The model was robust to changes in outcome probabilities, cost, and utility variables. Only 3.6% of the trials using probabilistic sensitivity analysis found iNO to be more expensive with a worse outcome than conventional therapy alone, whereas 35.7% of the trials found iNO to be cheaper and more effective than conventional treatment alone.**

Conclusions. **iNO is cost-effective but not cost-saving in treating infants with PPHN from a societal perspective. There are critical time points during an infant's hospitalization that could improve the efficiency and consequently the cost of care for this patient population.** ***Pediatrics*** **2004;114:417–426;** ***cost-effectiveness analysis, inhaled nitric oxide, persistent pulmonary hypertension, neonate, decision analysis.***

ABBREVIATIONS. NICU, neonatal intensive care unit; ECMO, extracorporeal membrane oxygenation; PPHN, persistent pulmonary hypertension of the newborn; iNO, inhaled nitric oxide; CHOP, Children's Hospital of Philadelphia; CI, confidence interval; QALY, quality-adjusted life year; CV, conventional ventilation.

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Neonatal intensive care remains an expensive method of caring for neonates, with up to 35% of direct hospital expenditures on infants occurring in neonatal intensive care units (NICUs).[1] This percentage has been rising over the past decade as a result of technologic advances, improved survival of the most premature neonates, and increased number of admissions to NICUs. There has been limited quantitative evidence of the economic effectiveness of technologies involved in neonatal intensive care. Besides 1 economic evaluation of NICU care,[2] such technologies as surfactant replacement therapy,[3,4] erythropoietin treatment,[5] extracorporeal membrane oxygenation (ECMO),[6] and prophylaxis against respiratory syncytial virus[7] have been studied systematically. Other policies, such as guidelines to decrease human immunodeficiency virus transmission[8,9] and the effects of screening guidelines for retinopathy of prematurity,[10] have been studied using decision analysis techniques. Even with these analyses currently published, there have been calls for more rigorous economic research and specific standards before adopting a technologic advancement.[11]

Persistent pulmonary hypertension of the newborn (PPHN) is characterized by elevated pulmonary arterial pressures that lead to hypoxia and respiratory failure. One to 2 term infants per 1000 live births are born with this condition, which has a mortality rate of ~10%. Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that has become the first-line treatment for this condition. ECMO remains the second-line treatment for an infant who fails to improve. Six randomized controlled trials comparing iNO with placebo[12–17] and 1 meta-analysis[18] have shown a decreased risk of death or decreased need for the use of ECMO in infants who have PPHN and receive iNO in addition to standard medical therapy (relative risk: 0.72 by meta-analysis.[18])

In most of the randomized controlled trials, fewer infants in the group randomized to receive iNO required use of ECMO rescue therapy. Thus, it has been hypothesized that the addition of iNO to the management of PPHN should be cost-saving to both the patient and society. However, Jacobs et al[19] found that the addition of iNO actually increased the cost of care, with a cost-effectiveness ratio of $36 613

(1997 Canadian) per life saved. Similar results were seen in a companion study, following 68 infants out to 18 months of age.[20] Because this study was performed on a subgroup of infants in 1 of the 6 randomized trials,[15] this study may have been underpowered.[21] The costs used in this analysis may not represent the costs of using iNO outside a randomized controlled trial; as technologies develop and diffuse into routine practice, they may be used in ways that were not studied by randomized controlled trials—a phenomenon known as treatment expansion.[22,23]

This project, then, was designed to evaluate the impact of the addition of iNO to the management of PPHN from a societal perspective using quantitative decision analysis techniques. Data from all available randomized controlled trials, as well as an 11-year cohort of patients, were incorporated into the study design to broaden the generalizability of the study results and assess the impact of iNO on current usages of the medication. This study was also designed to calculate the costs of care from daily resources used, not charges of care. From these data, quality improvement efforts can be developed to optimize the treatment of these infants.

METHODS

This study used a decision analysis design to perform an incremental cost-effectiveness analysis from a societal perspective, comparing the addition of iNO to the treatment regimen for PPHN with conventional treatment without iNO. The time frame for this study was from birth to the end of the initial hospitalization for PPHN. For this study, "death" was defined as any infant who died during the initial hospitalization for PPHN. "Survive with need for home medical support" was defined as any infant who survived to discharge from the initial hospitalization but required any supplemental medical support such as nasogastric feedings, supplemental oxygen, or medication for control of seizures. "Survive without need for home medical support" was defined as any infant who survived to hospital discharge and required no additional nursing or medical assistance than routinely administered to a newborn child. Side effects were classified into "minor" and "major." "Major side effects" included seizures, gastrointestinal or pulmonary hemorrhage, intraventricular hemorrhage, necrotizing enterocolitis, or the need to re-administer iNO after it was discontinued. Infants who had 3 minor side effects or an air leak or bronchopulmonary dysplasia with 1 other side effect were classified as having major side effects. "Minor side effects" included any other side effect, such as gastroesophageal reflux disease, infiltrated intravenous catheter requiring therapy, or blood stream infection without cardiovascular involvement. There were 4 parts of the study design: 1) the design of the decision tree, 2) the outcome probabilities for each branch of the decision tree, 3) the terminal outcomes for each branch of the tree, and 4) the determination of costs for each branch.

Decision Tree

The decision tree for this study is presented in Fig 1.[24] All hypothetical patients in this model entered the tree at the decision node at the left-hand margin. Infants progressed down only 1 path to hospital discharge at the right-hand margin. Outcome probabilities determined the likelihood that a patient will take one branch or another in the tree at each choice node. Costs were accumulated by the specific path that a patient takes, and the final outcome was determined by the terminal node that a patient reaches at the right-hand margin.

Outcome Probabilities

Outcome probabilities were obtained from data in the medical literature and from a cohort of infants who had PPHN and were treated at The Children's Hospital of Philadelphia (CHOP). Point estimates for the risk of ECMO rescue treatment were determined from a meta-analysis of the available literature. Randomized controlled trials were found using the search terms "inhaled nitric oxide AND neonate AND randomized controlled trials" in both Medline and PubMed. The reference list from each of these studies was examined for other studies not identified by the computerized literature searches. Included studies required a blinded, randomized protocol for assignment of treatment protocol without nonblinded use of iNO for rescue treatment of PPHN. Specific enrollment protocols were limited to newborn infants who were >34 weeks' gestation and had hypoxic respiratory failure and evidence of pulmonary hypertension by reasonable clinical or echocardiographic guidelines. Six studies were included.[12–17] Results from the literature search were combined into a point estimate using a Mantel-Haenszel approach to calculate a combined odds ratio and compared with a previously published meta-analysis.[18] The results of our meta-analysis were identical to the reported study; thus, the reported results were used in the model when appropriate.

Outcome probabilities that could not be estimated from the medical literature were calculated using data from a cohort of neonates who were >34 weeks' gestation and had PPHN managed at the NICU at CHOP between 1991 and 2002. All infants who were not treated with iNO as part of a blinded, randomized, controlled trial were included in this cohort; infants who were treated between January 1, 1991, and March 30, 1993, were part of the conventional treatment cohort; infants who were treated between January 1, 1995, and June 30, 2002, were included in the iNO cohort. After June 30, 2002, community hospitals within the catchment area of CHOP began to acquire iNO to treat infants with PPHN. Thus, the time of referral and the relative severity of infants with PPHN could have changed significantly after this point; therefore, we opted to stop collection of data to limit any time bias associated with this event. The diagnosis of PPHN was documented within the medical record by 1 of 2 methods:

1. Echocardiographic evidence of elevated pulmonary arterial pressures, as defined by the presence of a right-to-left shunt across the ductus arteriosis or patent foramen ovale; estimation of systemic or suprasystemic pulmonary arterial pressures from a tricuspid regurgitation jet; or evidence of right ventricular hypertrophy with aberrant contractility.
2. Clinical evidence of PPHN, as defined by >5% difference in preductal and postductal oxygen saturations for 15 minutes after establishment of adequate ventilation. Adequate ventilation may include >8 ribs expansion on posterior-anterior chest radiograph or a carbon dioxide measurement ≤45 cm H_2O on 1 arterial blood sample. Also, there must be 2 arterial oxygen measurements ≤100 cm H_2O while on 100% oxygen.

After Institutional Review Board approval was obtained from CHOP, 32 infants in the conventional treatment group and 91 infants in the iNO group were identified for the cohort and charts were abstracted. Nonparametric bootstrap analysis was run with 2000 iterations using Stata 7.0 statistical software (College Station, TX) to obtain a median estimate and 95% confidence intervals (CIs) for the outcome probabilities within each time period using data from all 123 infants. Data from the 95% CI were used in the 1-way and probabilistic sensitivity analyses. Appendix A shows the point estimate for each outcome probability included in the decision model and the data used to derive this estimate.

Outcome Statistics

Two effectiveness measures were used in this study. The first measure was survival to hospital discharge. We used this measure to compare the results of this analysis with a previous cost-effectiveness analysis.[19] However, these infants may be discharged from the hospital on supplemental medical support such as nasogastric feedings or supplemental oxygen. The second outcome measure assigned a utility to these outcomes in quality-adjusted life years (QALYs) for 1 full year after discharge. Survival without supplemental medical support was defined as 1 full QALY, and dying before hospital discharge was defined as a utility of 0 QALY. "Survival with need for home medical support" was equated to a EuroQOL state of "some problems with performing usual activities," which has been assigned a utility of 0.87 QALYs in previous work.[25] These assigned utilities were validated by a group of neonatologists at CHOP using questions about various types of home medical support. We chose a 1-year time horizon because of the uncertainty about the relative life expect-

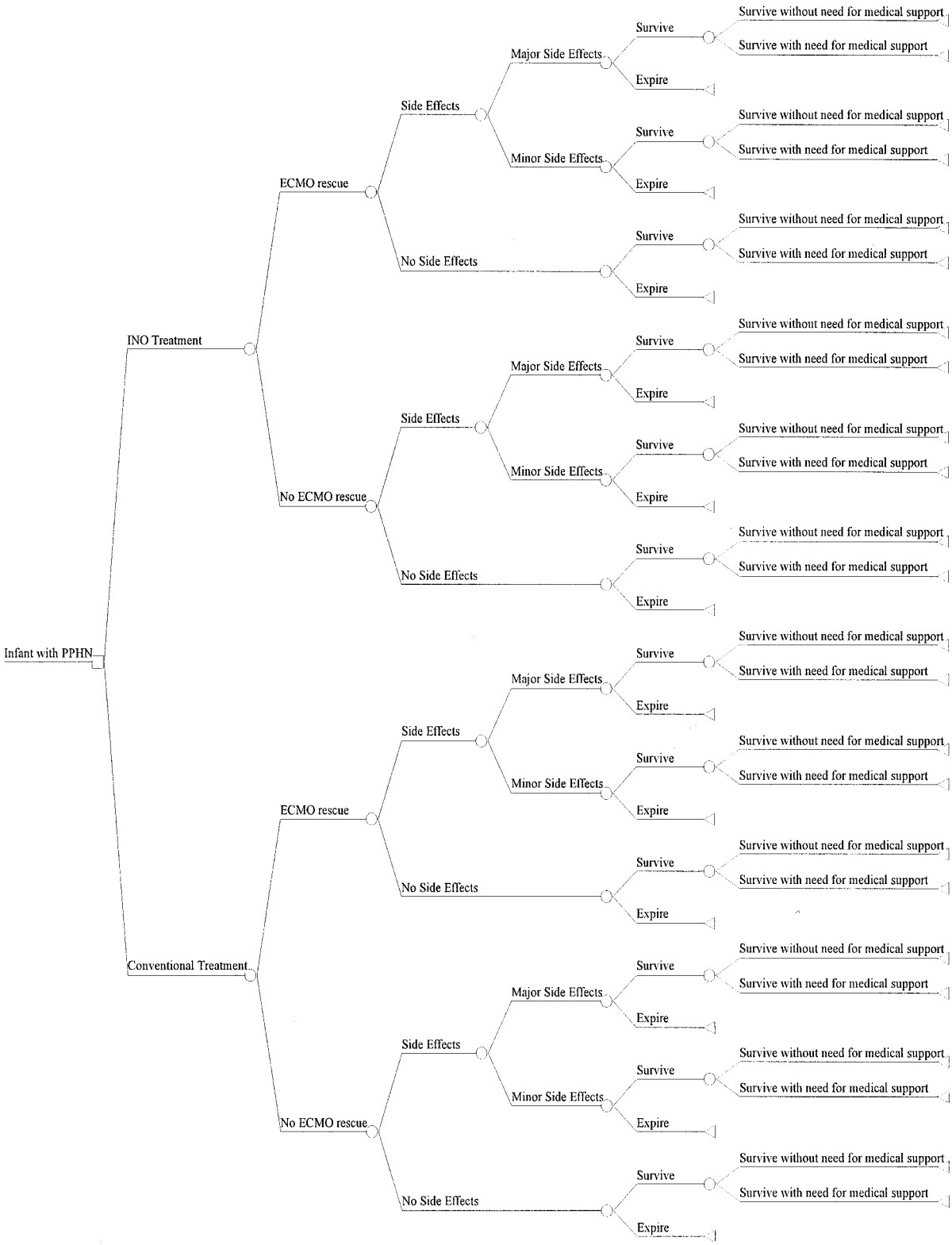

Fig 1. Decision analysis tree. The compared treatment regimens are represented as the branches after the square box on the left margin. Decision nodes are represented as circles. Terminal outcome nodes are represented as triangles on the right margin. Period times are shown at the bottom. Increasing time is denoted by the horizontal axis moving to the right. Period 1 represents the time from birth to the decision for ECMO therapy. To pass into period 2, an infant either needed to receive ECMO treatment or tolerate weaning of support to 70% fraction of inspired oxygen and 10 ppm iNO. Period 2 represents the time from the decision for ECMO therapy to extubation from mechanical ventilation. Period 3 represents the time from extubation to hospital discharge as defined in the text and in Fig 2.

ancies of the children, long-term costs, and long-term benefits of survival. As part of the sensitivity analysis, we also calculated the results of the study using a 75-year time horizon, 2% or 5% yearly discount rate, and a constant utility measure.

Costs

Costs were estimated from a retrospective chart review of the initial hospitalization of all 123 infants in the CHOP cohort. We

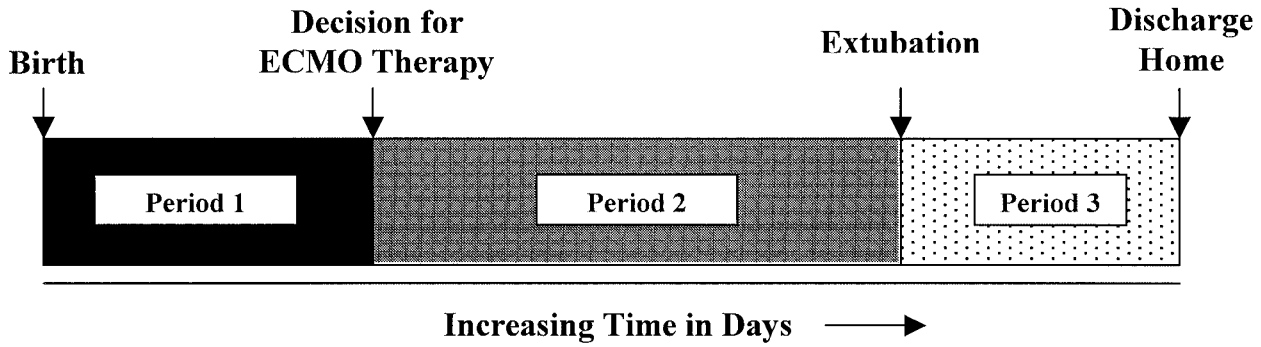

Fig 1. Continued.

abstracted all resources used for each day in the hospital, estimating a base cost for each resource using the medical literature,[26–28] Bureau of Labor Statistics,[29] 2001 Medicare data,[30,31] and the 2001 Red Book of wholesale drug prices.[32] All base costs were adjusted to 2001 dollars using inflation data from the Bureau of Labor Statistics.[33] Appendix B shows the point estimates for costs of each resource area used in the study. For each infant, we calculated a daily cost for each hospitalization day by multiplying the base costs by the resources used on that day.

Costs were then divided into 3 time periods as shown at the bottom of Fig 1. The time from birth to the day of ECMO treatment was designated as period 1 costs. For infants who did not require ECMO rescue treatment, we defined a priori this time period as the time between birth and the day when the infant was treated with a maximum oxygen concentration of 70% and 10 ppm iNO. All infants in our cohort of patients who tolerated this reduction of support were treated without ECMO rescue therapy. Period 2 costs, or ventilated costs, were accumulated from the day of ECMO treatment (or reaching 70% oxygen and 10 ppm iNO) to the day of extubation. This time period is represented on the decision tree as the paths between the side effects node and the terminal outcome nodes. Period 3 costs, or nonventilated costs, were the costs accumulated from the day of extubation to the day of discharge. This time period is represented at the pathways of "survival without need for home medical support" or "survival with need for home medical support." Infants who died during the initial hospitalization accumulated costs only for periods 1 and 2 as appropriate. For infants who were either back-transported (n = 11) or were missing data from the beginning of life, we first calculated the average costs for each day of life of the remaining infants in the cohort. We then input the average cost value for each missing day of data. Finally, for each infant, we added the individual daily costs for each day in periods 1, 2, and 3 to create the representative periods 1, 2, and 3 cost variables.

Nonmedical costs of care were divided into 2 parts. Costs associated with loss of job time were estimated using the average hourly wage from the Bureau of Labor Statistics.[29] Travel costs were calculated by multiplying the distance between the zip code of residence and zip code 19104 (the zip code for CHOP) by $0.36. These costs were added to the daily and period costs for each infant.

Nonparametric bootstrap analysis was performed using Stata 7.0 statistical software (College Station, TX) to obtain a median estimate and 95% CIs for costs within each time period. A random sample of 123 infants was drawn, with replacement, from the pool of 123 available infants for a total of 2000 iterations. The median point was used as the point estimate for each cost variable in the model, whereas the 95% CIs were used as the range of possible values in the 1-way and probabilistic sensitivity analyses. Appendix C shows these estimates for the decision model.

Data Analysis

Data analysis occurred in 2 stages using Data, version 4.0 (TreeAge Software, Williamstown, MA). The initial decision model was analyzed using the variables shown in Appendix A to obtain a base-case estimate of the incremental cost-effectiveness of iNO. The incremental cost-effectiveness ratio was calculated by dividing the difference in costs between the iNO and conventional ventilation (CV) groups by the differences in effectiveness of the 2 groups. We also calculated the net monetary benefit of iNO in this study using a ceiling ratio of $50 000 and $100 000 per unit of effectiveness saved. Net monetary benefits were used to address any possible mathematical inconsistencies that may arise from dividing costs by a very small difference in effectiveness. The ceiling ratio is the threshold used by society to decide whether a technology is cost-effective.[34] A cost-benefit analysis grounded in welfare economic theory, whereby the effectiveness of a therapy is measured in monetary units rather than utility or survival, was not performed because of the difficulty in assigning a monetary benefit to the surviving children.

To account for the uncertainty of these 2 estimates, we performed 1-way, threshold, and probabilistic sensitivity analyses. For the 1-way sensitivity analyses, we varied each variable over a range of values shown in Appendixes A and C to obtain a distribution of possible cost-effectiveness ratios. We identified variables for which the cost-effectiveness ratio crossed predetermined thresholds of $0/outcome, $50 000/outcome, and $100 000/outcome.[35]

To allow all of the probability, outcome, and cost variables to vary simultaneously, we performed a probabilistic sensitivity analysis using Monte Carlo simulation techniques.[36,37] β or normal distributions were calculated for those variables defined in Appendix A by the meta-analysis. Uniform distributions were defined for the other variables using a rank ordering of the results of the bootstrap analysis from lowest to highest. The 2.5th (51st) and 97.5th percentile (1950th) values were used as cutoffs for the uniform distributions input into the model. Before each Monte Carlo simulation of the model, a value for each unknown variable was selected randomly from the defined probability distribution. The simulation was performed using these values, and the cost and effectiveness of the iNO and CV arms were calculated. New

TABLE 1. Demographic Data From the Children's Hospital of Philadelphia Cohort

	iNO Cohort	Conventional Treatment Cohort
N	91	32
Birth weight, g	3410 ± 602	3333 ± 602
Gestational age, wk	39.3 ± 1.7	39.0 ± 1.9
1-Min Apgar	5.1 ± 2.6*	6.5 ± 2.2
5-Min Apgar	7.4 ± 1.8	8.1 ± 1.3
Male gender	55.0%	65.6%
Delivery via cesarean-section	65.9%†	38.7%
Time to arrival at CHOP, median hours (range)	24 (4–100)	21 (5–144)
Period 1 time, median days (range)	4 (1–15)‡	2.5 (1–15)
Time on ventilator, median days (range)	12 (4–80)§	10 (3–39)
Length of stay, median days (range)	24 (1–82)	23 (2–91)

All variables reported as mean ± SD percentage or median and range.
* P = .009 by t test.
† P = .018 by Fisher's exact test.
‡ P = .016 by nonparametric rank sum test.
§ P = .031 by nonparametric rank sum test.

TABLE 2. Base-Case Estimates of Incremental Cost-Effectiveness Ratios

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost-Effectiveness	Incremental Cost-Effectiveness
Utility as the effectiveness measure						
Conventional treatment	$40 468		0.8262		$48 982	
iNO treatment	$41 609	$1141	0.8861	0.0599	$46 956	$19 022 per QALY
Survival as the effectiveness measure						
Conventional treatment	$40 468		0.8954		$45 197	
iNO treatment	$41 609	$1141	0.9297	0.0343	$44 755	$33 234 per survival

With a ceiling ratio of $50 000 or $100 000 per QALY or survival, the net monetary benefit for utility is $1854 or $4849, respectively, and the net monetary benefit for survival is $574 or $2289, respectively.

values were chosen for the next run, and the model was rerun. A total of 2000 iterations of the model were performed with new values for each unknown variable chosen before the run. No changes were made to the value of the unknown variables before an individual patient entered the model. The distribution of values was analyzed for the stability of the base-case results. Previous research suggests that choosing the value for each unknown variable before each run, rather than before each individual patient, will lead to more accurate assessment of the shape of the simulated distribution of cost-effectiveness ratios and conclusions about the superiority of 1 of the arms of the decision tree.[38]

RESULTS

Table 1 shows demographic and clinical data for the 123 infants in the CHOP patient cohort. Birth weight and gestational age were similar between the

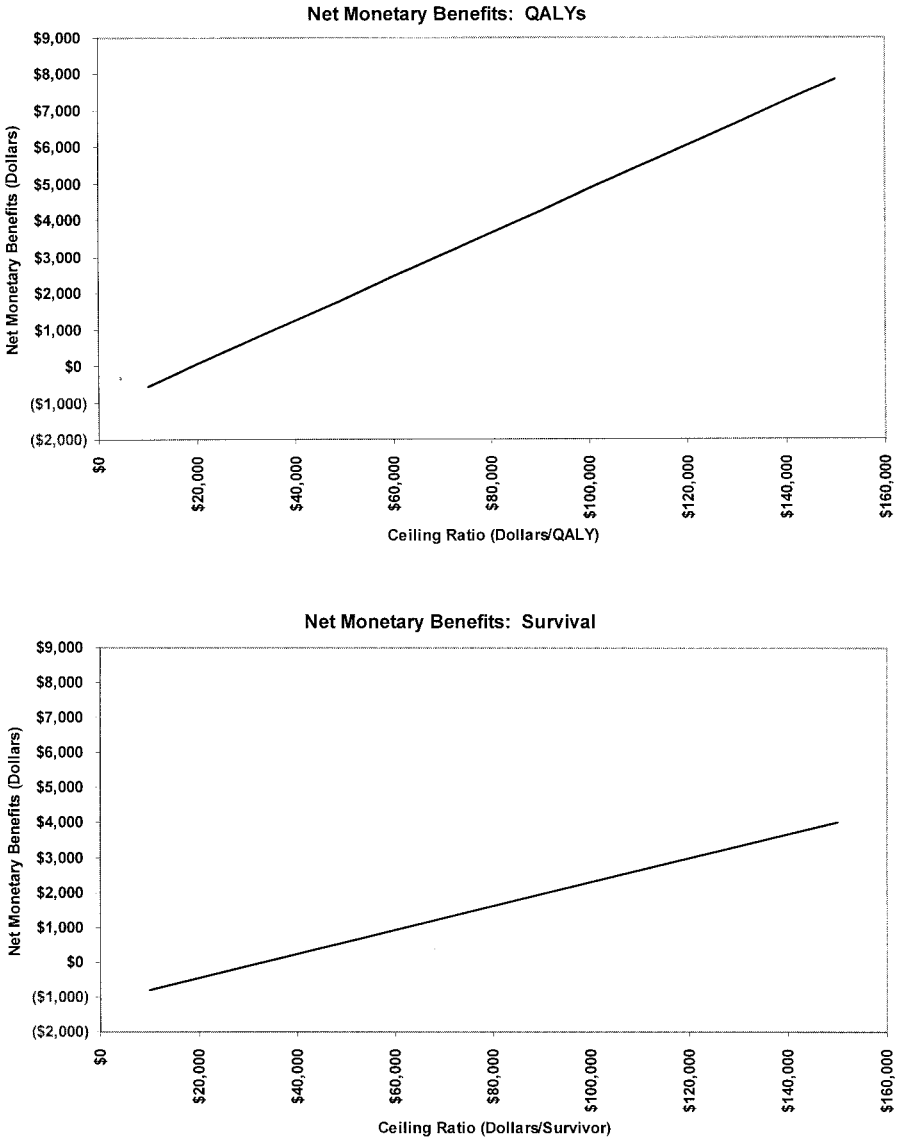

Fig 2. Net monetary benefit curves for base-case model, using survival and QALYs as the outcome measure. Acceptable ceiling ratios (in dollars per survival or dollars per QALY) are noted on the horizontal axis, and net monetary benefits in dollars are plotted on the vertical axis.

2 groups. Infants who were treated with iNO had a significantly lower 1-minute Apgar score, higher cesarean section rates, longer time in period 1, and more days on the ventilator when compared with infants in the CV cohort. Length of stay was similar between the 2 groups of infants.

The results of the base-case analysis are presented in Table 2. The addition of iNO to the treatment regimen for PPHN increased the cost of treating an infant by an average of $1141. Use of iNO led to 3.43% more lives saved and a 6% increase in the average utility gained by an infant. The incremental cost-effectiveness ratio using survival as the outcome was $33 234 per life saved. When utility was used as the effectiveness measure, the incremental cost-effectiveness ratio was $19 022 per QALY gained. Similar results were found when we used net monetary benefits as the outcome measure for different ceiling ratios (Fig 2).

Using utility as the effectiveness measure, the results of the base-case analysis were insensitive to 1-way sensitivity analysis for the range of values shown in Appendixes A and C for each variable. Changes in 92% (34 of 37) of cost variables and 91% (21 of 23) of outcome probabilities kept the incremental cost-effectiveness ratio <$50 000 per QALY. The 5 variables that resulted in an incremental cost-effectiveness ratio >$50 000 per QALY were period 1 costs of the CV group, period 2 costs for both iNO and CV infants who required ECMO rescue treatment and survived with major side effects, the probability of side effects with ECMO in the CV group, and the probability of having a major side effect without ECMO in the CV group. Changes in only 1 variable, the probability of having a major side effect without ECMO in the CV group, resulted in a cost-effectiveness ratio of >$100 000 per QALY. However, this result occurred at a bootstrap-chosen probability of .357, which was at the lowest extreme for this variable in the model. Changes in the assigned utility for "survival with need for home medical support" between 0.5 and 0.99 had little effect on the cost-effectiveness ratio; as the utility came closer to 1 QALY, the cost-effectiveness ratio approached the value obtained when survival was used as the outcome measure.

Extending the time horizon from 1 year after discharge to an average lifetime of 75 years with a 5% yearly discount rate improved the absolute cost-effectiveness ratio of iNO to $976 per QALY. The results were insensitive to changes in the assigned utility for "survival with need for home medical support" from 0 to 0.99, changes in the discount rate to 2% yearly, and changes in the life expectancy of the "survival with need for home medical support" group.

We also identified variables for which 1-way sensitivity analysis resulted in a cost-effectiveness ratio <$0 per QALY. Changes in these variables suggest areas to improve the efficiency of iNO treatment, making it cost saving for society. In the iNO arm of the model, changes in only 2 cost variables (period 2 costs for surviving infants who were treated with ECMO and had major side effects and period 1 costs) and 2 outcome probabilities (need for ECMO and the likelihood of major side effects on ECMO) resulted in a cost-effectiveness ratio of <$0 per QALY. To reach this level of efficiency, only changes in period 1 costs ($11 165 to $10 097, decrease by 9.5%) and need for ECMO treatment (30.62% to 27.1%, decrease by 11.5%) were <15% of the point estimate for these variables.

Probabilistic sensitivity analysis showed that iNO was cost-effective when added to the treatment for PPHN for a cutoff of $100 000 per QALY in 80.9% of the trials. iNO was cheaper and led to an improved outcome 35.7% of the time. Only 3.6% of the trials found iNO to be more expensive with a worse outcome than conventional therapy alone.

The addition of iNO to treat PPHN in term neonates resulted in an increased cost of care, although iNO leads to a substantial reduction in the use of ECMO rescue therapy. iNO leads to significant savings in the 231 patients who would require ECMO treatment without the use of iNO but do not require ECMO with the availability of iNO. These savings total $5 412 826, or $23 432 per infant. However, these savings are offset by the increased cost of treating the 463 infants who would not require ECMO regardless of the availability of iNO (cost increase with iNO of $4 699 825, or $10 151 per infant) or the 306 infants who would require ECMO despite the availability of iNO (cost increase with iNO of $1 850 666, or $6048 per infant). The added costs are the result of increased period 1 costs for infants who require ECMO ($893 048, or 48.3% of the increased cost using iNO) and increased period 2 costs for infants who would not require ECMO ($3 331 831, or 70.9% of the increased cost using iNO).

DISCUSSION

Using decision analysis techniques, the addition of iNO to the treatment regimen of PPHN led to an incremental cost-effectiveness ratio of $19 022 per QALY or $33 234 per life saved when compared with conventional management alone. This ratio was insensitive to changes in the majority of cost, probability, and utility variables within the model. Probabilistic sensitivity analysis showed that only 3.6% of the trials would result in iNO's being more expensive with a worse outcome than conventional therapy alone. A total of 35.7% of the trials found that iNO was cheaper, with improved outcomes, than conventional therapy alone. These results compare favorably to any accepted "cutoff" of $50 000 or $100 000 per outcome.[34]

This study adds to the growing literature of economic evaluations of technologies in neonatology.[2–7] The results of this study compare favorably to the results of these studies, especially with the robustness of the results to 1-way, threshold, and probabilistic sensitivity analyses. Also, by using decision analysis techniques, we were able to incorporate the results of 6 randomized controlled trials[12–18] and observational data from an 11-year cohort of patients at CHOP.

Given the reduction in ECMO use, it is surprising that the use of iNO is not cost saving. Our data

support the results of a previous analysis using different economic techniques[19] and suggest that even highly beneficial treatments may have hidden costs that affect the delivery of care. Use of decision analysis techniques and calculating the daily costs of care for each infant helps to identify variables that most influence the efficiency of care of infants with PPHN. The increased costs of caring for an infant with PPHN on iNO occur during the period between birth and the decision to use ECMO; reducing these costs by 9.5%, or approximately 1 half-day of care, could lead to more efficient treatment of these infants. We also saw that iNO lengthened the ventilator days for infants who would not receive ECMO regardless of the availability of iNO. Data from daily costs, which are not available in many administrative data sets, point out several areas for improved efficiency in the treatment of infants with PPHN.

Cost data represented the resources used rather than the adjustment of charges with cost-to-charge ratios. This method is recommended by the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine.[35] Previous costing studies of premature infants have adjusted the charges accrued by a hospital cost-to-charge ratio typically reported by Medicare.[26,39] Because this ratio is an average of all patients treated at 1 hospital, the cost-to-charge ratio may not represent the adjustment needed for NICU patients. Other studies have used detailed cost-to-charge ratios that identify the necessary adjustments for each cost center within the hospital.[27,28] The advantage to using resources used, rather than charges accrued, is a more accurate assessment of the true costs associated with caring for a neonate—>$41 000 per infant treated for PPHN.

This study used some probability data from the results of 6 randomized controlled trials. These data may not accurately represent current clinical practice; a small number of patients received iNO therapy for >10 days in our cohort. To improve the generalizability of the data, we collected additional detailed data from a large cohort of infants with PPHN at CHOP. Some costs, such as room and travel costs, were estimated using the medical literature and zip codes. The robustness of the model to large changes in the cost variables suggests that these estimates were satisfactory. Cost data were also obtained from a cohort of patients from 1 center in the Eastern United States. Until the past year, use of iNO has been limited to large regional NICUs with ECMO capability. Costs from the CHOP cohort are generalizable to these units because of the inherent similarities of these centers. We will need more investigation into the costs of care as iNO diffuses from these large, predominantly academic centers to other NICUs across the United States. Finally, this study was unable to calculate the long-term costs and benefits of iNO therapy. There may be hidden, unmeasurable costs to the use of ECMO that may not be apparent until many years later, such as an increased risk of cerebrovascular disease or neurologic deficits. Our study was able to quantify the costs and benefits of this treatment that are measurable. Additional studies are needed to identify and quantify these unmeasured costs and benefits of care after discharge from neonatal intensive care.

Using decision analysis techniques, iNO was cost-effective but not cost-saving in treating infants with PPHN from a societal perspective. Data from the total costs and 1-way sensitivity analyses point to the pre-ECMO decision process and treatment of the infant while on mechanical ventilation as areas for improved efficiency of care. Currently, though, there are no algorithms to distinguish among infants who would improve with the use of conventional therapy alone, infants who would require ECMO rescue regardless of management, and infants who would respond to iNO and remain off of ECMO. 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.

Appendix A. Outcome Probabilities Used in Decision Analysis Model (Estimate and 95% CI)

	Estimate	Lower Limit	Higher Limit	Data Source
iNO pathway				
Need for ECMO rescue	0.3062	0.2623	0.3529	refs 12–18 meta-analyses
Side effects on ECMO	0.7895	0.6341	0.9167	Cohort
Chance of major side effects with ECMO	0.6957	0.5	0.8621	Cohort
Survival with major side effects on ECMO	0.9444	0.8	1	Cohort
Survival without need for home medical support with major side effects on ECMO	0.25	0.0588	0.4706	Cohort
Survival without need for home medical support with minor side effects on ECMO	0.625	0.25	1	Cohort
Survival without need for home medical support with no side effects on ECMO	0.8571	0.4444	1	Cohort
Side effects without ECMO	0.6212	0.4918	0.7544	Cohort
Chance of major side effects without ECMO	0.6667	0.5128	0.8125	Cohort
Survival with major side effects without ECMO	0.8333	0.6522	0.96	Cohort
Survival with minor side effects without ECMO	0.9091	0.6667	1	Cohort
Survival without need for home medical support with major side effects without ECMO	0.3636	0.1538	0.6	Cohort
Survival without need for home medical support with minor side effects without ECMO	0.9	0.6667	1	Cohort
Survival without need for home medical support with no side effects without ECMO	0.9474	0.8125	1	Cohort

Continued

Appendix A. Continued

	Estimate	Lower Limit	Higher Limit	Data Source
Conventional treatment pathway				
Need for ECMO rescue	0.5371	0.4822	0.5913	refs 12–18 meta-analyses
Side effects on ECMO	0.7059	0.5	0.8889	Cohort
Chance of major side effects with ECMO	0.5714	0.3077	0.8333	Cohort
Survival with Major side effects with ECMO	0.9444	0.8	1	Cohort
Survival without need for home medical support with major side effects with ECMO	0.2222	0	0.6	Cohort
Survival without need for home medical support with minor side effects with ECMO	0.1667	0	0.6667	Cohort
Side effects without ECMO	0.6	0.3	0.8667	Cohort
Chance of major side effects with ECMO	1	1	1	Cohort
Survival with major side effects without ECMO	0.6667	0.2	1	Cohort
Survival without need for home medical support with major side effects without ECMO	0	0	0	Cohort
Survival without need for home medical support with no side effects without ECMO	1	1	1	Cohort
Utility variables				
Survival without need for home medical support (QALY)	1	1	1	Set by study
Survival with need for home medical support (QALY)	0.87	0.5	0.99	ref 25
Death (QALY)	0	0	0	Set by study

Appendix B. Resource Costs, 2001 Dollars[33]

Resource Area	Cost	Data Source
Room cost, per d	$ 500.00	refs 26–28
Labor costs		
Physician, 1 h of time	$ 61.43	ref 29
Nurse, 1 h of time	$ 21.93	ref 29
Respiratory therapist, 1 h of time	$ 18.66	ref 29
Laboratory costs	Per individual laboratory test	ref 31
Radiology costs		
Chest X-ray, AP	$ 26.06	ref 30
Chest X-ray, AP/lateral	$ 33.67	ref 30
Abdominal X-ray, AP	$ 27.87	ref 30
Abdominal ultrasound, complete	$ 111.86	ref 30
Abdominal ultrasound, limited	$ 81.45	ref 30
MRI head	$ 463.35	ref 30
MRI head without contrast	$ 477.83	ref 30
Upper GI	$ 88.33	ref 30
Head ultrasound	$ 84.71	ref 30
CT head without contrast	$ 212.85	ref 30
CT head with contrast	$ 212.85	ref 30
CT head with/without contrast	$ 318.55	ref 30
Echocardiogram	$ 139.37	ref 30
EEG	$ 167.24	ref 30
Procedure costs		
Transfusion of blood products	$ 36.20	ref 30
Artery cannulation	$ 157.83	ref 30
PICC placement	$ 79.64	ref 30
Broviac, venous cannulation	$ 151.67	ref 30
Umbilical artery catheterization	$ 52.85	ref 30
Umbilical venous catheterization	$ 52.85	ref 30
Chest tube	$ 210.68	ref 30
Reintubation	$ 114.75	ref 30
Bronchoscopy	$ 149.14	ref 30
BAERs	$ 94.84	ref 30
Evoked potentials	$ 55.75	ref 30
Direct laryngoscopy with bronchoscopy	$ 185.34	ref 30
Tracheostomy	$ 114.75	ref 30
G-tube	$ 272.94	ref 30
Cardiac catheterization	$ 124.16	ref 30
pH Probe	$ 187.51	ref 30
Ventilator cost, per d	$ 80.00	Depreciation costs
Use of nasal cannula, per d	$ 20.00	Equipment costs
ECMO supplies	$1000.00	Equipment costs
Medication costs	Per individual medication: generic or cheapest wholesale price	ref 32
TPN	$ 97.09	ref 32
Enteral feedings per d	$ 15.00	Formula costs

AP indicates anteroposterior; MRI, magnetic resonance imaging; GI, gastrointestinal; CT, computed tomography; EEG, electroencephalogram; BAER, brainstem auditory evoked response; TPN, total parenteral nutrition.

Appendix C. Cost Variables Used in Decision Analysis Model (Estimate and 95% CI)

	Estimate	Lower Limit	Higher Limit	Data Source
Period 1				
iNO pathway	$11 165.51	$9976.68	$12 397.54	Cohort
CV pathway	$8247.07	6025.30	10 868.49	Cohort
Period 2				
One-time ECMO procedure costs	$2500.00	$0	$5000.00	Cohort
iNO pathway				
Survival with major side effects with ECMO	$38 326.79	$27 373.92	$50 564.12	Cohort
Survival with minor side effects with ECMO	$20 404.99	$14 842.52	$27 645.53	Cohort
Survival with no side effects with ECMO	$18 850.08	$14 347.56	$24 275.02	Cohort
Survival with major side effects without ECMO	$14 709.22	$10427.00	$20 037.33	Cohort
Survival with minor side effects without ECMO	$11 682.62	$8122.85	$16 716.32	Cohort
Survival with no side effects without ECMO	$8404.46	$5922.66	$11 030.34	Cohort
Death with major side effects with ECMO	$45 371.42	$30 000.00	$50 000.00	Cohort
Death with minor side effects with ECMO	$0	$0	$0	Cohort
Death with no side effects with ECMO	$0	$0	$0	Cohort
Death with major side effects without ECMO	$1372.58	$0	$5490.32	Cohort
Death with minor side effects without ECMO	$0	0	0	Cohort
Death with no side effects without ECMO	$0	0	0	Cohort
CV pathway				
Survival with major side effects with ECMO	$34 310.18	$20 236.96	$49 753.73	Cohort
Survival with minor side effects with ECMO	$24 701.58	$15 778.93	$35 340.21	Cohort
Survival with no side effects with ECMO	$15 209.52	$13 270.15	$17 635.77	Cohort
Survival with major side effects without ECMO	$5247.36	0	$15 059.54	Cohort
Survival with minor side effects without ECMO	$0	0	0	Cohort
Survival with no side effects without ECMO	$3147.19	$619.05	$9183.66	Cohort
Death with major side effects with ECMO	$0	0	0	Cohort
Death with minor side effects with ECMO	$0	0	0	Cohort
Death with no side effects with ECMO	$0	0	0	Cohort
Death with major side effects without ECMO	$0	0	0	Cohort
Death with minor side effects without ECMO	$0	0	0	Cohort
Death with no side effects without ECMO	$0	0	0	Cohort
Period 3				
iNO pathway				
Discharged without need for medical support with major side effects with ECMO	$22 133.71	$15 574.69	$30 024.44	Cohort
Discharged with need for medical support with major side effects with ECMO	$22 970.09	$15 963.68	30 004.24	Cohort
Discharged without need for medical support with minor side effects with ECMO	$13 661.34	$9778.45	$18 260.49	Cohort
Discharged with need for medical support with minor side effects with ECMO	$16 867.77	$14 083.06	$20 658.36	Cohort
Discharged without need for medical support with no side effects with ECMO	$14 707.22	$9633.23	$19 176.51	Cohort
Discharged with need for medical support with no side effects with ECMO	$7616.02	$5000.00	$12 000.00	Cohort
Discharged without need for medical support without major side effects without ECMO	$10 717.31	$7065.56	$16 176.53	Cohort
Discharged with need for medical support without major side effects without ECMO	$18 268.99	$14 062.21	$24 701.57	Cohort
Discharged without need for medical support without minor side effects without ECMO	$9999.62	$7824.17	$12 195.43	Cohort
Discharged with need for medical support without minor side effects without ECMO	$15 846.71	$12 000.00	$20 000.00	Cohort
Discharged without need for medical support without no side effects without ECMO	$8913.77	$7711.24	$10 161.68	Cohort
Discharged with need for medical support without no side effects without ECMO	$15 770.17	$12 000.00	$20 000.00	Cohort
CV pathway				
Discharged without need for medical support with major side effects with ECMO	$18 293.47	$15 536.09	$22 348.06	Cohort
Discharged with need for medical support with major side effects with ECMO	$23 552.71	$11 899.61	$38 321.32	Cohort
Discharged without need for medical support with minor side effects with ECMO	$9626.54	$7000.00	$20 000.00	Cohort
Discharged with need for medical support with minor side effects with ECMO	$23 767.99	$13 392.89	$42 852.11	Cohort
Discharged without need for medical support with no side effects with ECMO	$12 446.82	$8478.62	$14 631.28	Cohort
Discharged with need for medical support with no side effects with ECMO	$18 244.11	$15 847.82	$21 868.26	Cohort
Discharged without need for medical support without major side effects without ECMO	$0	$0	$0	Cohort
Discharged with need for medical support without major side effects without ECMO	$16 855.77	$8245.26	$22 772.98	Cohort

Continued

Appendix C. Continued

	Estimate	Lower Limit	Higher Limit	Data Source
Discharged without need for medical support without minor side effects without ECMO	$0	0	0	Cohort
Discharged with need for medical support without minor side effects without ECMO	$0	0	0	Cohort
Discharged without need for medical support without no side effects without ECMO	$10 208.61	$7210.12	$13 783.32	Cohort
Discharged with need for medical support without no side effects without ECMO	$0	$0	$0	Cohort

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