

A Quality Improvement Initiative to Standardize Use of Inhaled Nitric Oxide in the PICU

Todd J. Karsies, MD*; Laura Evans, RRT-NPS†; Randall Frost, BSBA, BSWE‡; Onsy Ayad, MD*; Richard McClead, MD, MHA§

ABSTRACT

Background: Inhaled nitric oxide (iNO) is a potent pulmonary vasodilator used off-label to treat refractory hypoxemia in the pediatric intensive care unit (PICU). However, clinical practice varies widely, and there is limited evidence to support this expensive therapy. Our objective was to test whether implementation of a clinical guideline for iNO therapy would decrease practice variability, reduce ineffective iNO utilization, and control iNO-related costs. **Methods:** We used quality improvement (QI) methodology to standardize the use of iNO in a single quaternary care PICU (noncardiac). All PICU patients receiving iNO therapy between January 1, 2010, and December 31, 2013, were included. The QI intervention was the development and implementation of a clinical guideline for iNO initiation, continuation, and weaning. iNO use was monitored using statistical process control charts. **Results:** We derived baseline data from 30 preguideline patients (35 separate iNO courses) compared with 33 postguideline patients (36 separate iNO courses). Despite similar baseline characteristics, disease severity, and degree of hypoxemia, postguideline patients had a shorter median [interquartile range (IQR)] duration of iNO therapy than preguideline patients [76 (48–124) hours versus 162 (87–290) hours; $P < 0.0001$]. We have sustained the reduced iNO usage throughout the postguideline period. Postguideline patients also had improved provider documentation and a median iNO cost savings of \$4,600. **Conclusions:** Implementation of iNO usage guidelines was associated with decreased iNO usage and cost of iNO therapy in the PICU. (*Pediatr Qual Saf* 2017;2:e011; doi: 10.1097/pq9.000000000000011; Published online February 27, 2017)

INTRODUCTION

Background Knowledge

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that is approved by the US Food and Drug Administration for the treatment of persistent pulmonary hypertension of the newborn. However, it is used off-label for a variety of conditions in neonates and older children. In the pediatric intensive care unit (PICU), iNO is used to treat acute hypoxemic respiratory failure, mainly due to acute respiratory distress syn-

drome (ARDS). Although several adult and pediatric studies have evaluated iNO use for acute hypoxemic respiratory failure, improved hypoxemia has not clearly translated into improved mortality or morbidity.^{1–8} A recent review of pediatric ARDS included iNO as an unrecommended therapy.⁹ Despite this, iNO continues to be used as rescue therapy in children with refractory hypoxemia. Intensivists are inconsistent in their use of iNO in these patients. Moreover, the cost of iNO therapy can be as much as \$3,000 per day of use.¹⁰



From the *Department of Pediatrics, Pediatric Critical Care Medicine, Nationwide Children's Hospital, Columbus, Ohio; †Department of Respiratory Therapy, Nationwide Children's Hospital, Columbus, Ohio; ‡Department of Quality Improvement Services, Nationwide Children's Hospital, Columbus, Ohio; §Department of Pediatrics, Office of the Chief Medical Officer, Nationwide Children's Hospital, Columbus, Ohio. *Corresponding author. Address: Richard McClead, MD, MHA700 Children's Dr Columbus OH 43205 E-mail: Richard.McClead@nationwidechildrens.org Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CC-BY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

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Local Problem

At Nationwide Children's Hospital (NCH), iNO use has increased annually in the neonatal and pediatric critical care units. From 2009 to 2011, mean (SD) iNO utilization in the PICU increased from 157.3 (± 155.1) hours per patient to 285.6 (± 272.7) hours per patient. Hospital-wide utilization of iNO was projected to exceed 36,000 hours in 2012 at an estimated cost of 2.1 million dollars. Thus, iNO therapy in critically ill patients is an ideal topic for a quality improvement (QI) intervention. The following specific question needs to be addressed: can standardizing iNO therapy reduce ineffective iNO utilization and control costs associated with the care of critically ill patients in a noncardiac population?

METHODS

Ethical Issues

This QI work involved the implementation of consensus-based therapeutic guidelines developed by a multidisciplinary team of clinical experts. Per policy, the project did not qualify as research involving human subjects. Therefore, approval by the Institutional Review Board was not required.

Setting

The PICU at NCH is a quaternary care 30-bed mixed medical/surgical (noncardiac) intensive care unit (ICU). All patients are managed or comanaged by board-certified pediatric intensivists. The PICU provides care to over 2,000 patients annually. Historically, between 12 and 23 patients per year receive iNO therapy.

Intervention/Planning

At the request of NCH executive leadership, we established a multidisciplinary QI team in late 2011. The team consisted of pediatric intensivists, respiratory therapists, and QI experts. The purpose of the QI committee was to develop unit-specific guidelines for iNO use that would result in standardized patient care, reduced ineffective iNO therapy, and decreased overall iNO utilization.

The PICU QI team reviewed the available literature regarding iNO therapy.^{3,11} Lacking clear evidence-based guidelines for the off-label use of iNO, the multidisciplinary team developed consensus-based guidelines that provided indications for initiating iNO therapy, criteria for determining an effective response, and stopping and weaning criteria. The initial iNO guidelines were developed in January 2012 and fully implemented in March 2012. Before implementation, all critical care physicians and respiratory therapists received education regarding the iNO therapy guidelines.

Figure 1 shows a flowchart for the iNO therapy guidelines. Patients with respiratory failure were candidates for iNO therapy when their oxygenation index (OI) exceeded 20 or when noncardiac patients exhibited right ventricular dysfunction or pulmonary hypertension or both. Although physicians dictated all treatment decisions, the respiratory therapists were expected to prompt discussion of the patient's therapy during daily bedside rounds. Physicians were expected to document the reason for starting iNO, the patient's response to treatment, and the daily assessment for weaning of iNO. Chart auditing with physician feedback was performed for iNO use, as well as documentation of treatment expectations.

Data Collection and Definitions

The following data elements were obtained on all patients receiving iNO therapy: demographics, diagnoses, comorbidities, duration of iNO treatment, duration of mechanical ventilation, ICU and hospital length of stay (LOS), oxygenation and ventilation parameters, infection testing results, use of extracorporeal membrane oxygenation (ECMO) or pulmonary vasodilators other than iNO, and mortality. Pa-

tients were categorized by their primary reason for respiratory failure. Patients with a primary pulmonary diagnosis required mechanical ventilation for respiratory pathology (e.g., pneumonia, aspiration, bronchiolitis). Patients were classified as having septic shock if this diagnosis was documented by the attending physician at the time of PICU admission. Patients were considered immunocompromised if they had undergone recent chemotherapy, were neutropenic, or had underlying primary or acquired immunodeficiency.

The severity of hypoxemia was determined using the arterial partial pressure of oxygen to fraction of inspired oxygen ratio (P/F ratio) and OI when arterial blood gas values were available. When arterial blood gas values were not available, the oxygen saturation to the fraction of inspired oxygen ratio (S/F) was used. OI was calculated by multiplying the mean airway pressure (MAP) by the fraction of inspired oxygen and then dividing by the arterial partial pressure of oxygen and multiplying by 100. The severity of illness was determined using the Pediatric Risk of Mortality Score (PRISM III) obtained at the time of ICU admission.¹²

The cost of iNO was calculated using the hourly iNO rate negotiated annually with the iNO manufacturer. The cost of iNO was converted to 2013 US dollars using the online Consumer Price Index inflation calculator (<http://data.bls.gov/cgi-bin/cpicalc.pl>). We also evaluated physician guideline compliance for documentation of indications for starting iNO, response to iNO, and weaning. The intensivists were expected to document OI or S/F ratio criteria for iNO therapy initiation and OI or S/F ratio change for the succeeding iNO response. Also, they were expected to document plans for weaning iNO therapy daily.

After guideline implementation, patients were candidates for iNO therapy if they had an OI > 20 or S/F ratio < 200. A positive response to iNO therapy was determined by an OI decrease of $\geq 10\%$ or S/F ratio increase by $\geq 10\%$.

Data Analysis

Patient characteristics and other group differences between pre- and postguideline implementation were compared using Mann-Whitney (Wilcoxon) test, 2-sample *t* test, or Fisher's exact test as appropriate after transformation to a normal distribution. The LOS and time on mechanical ventilation were analyzed using log-rank test. Duration of iNO therapy for individual patients was evaluated using a statistical process control (SPC) I chart.¹³ Data were subjected to log transformation, and control limits with respect to the normalized data were generated. A reverse transformation was then used to plot the control limits on the original data scale. We also performed a rational subgroup analysis on the data to compare patients who responded to iNO therapy with those who did not.¹³

Multivariate logistic regression was performed to adjust mortality for illness severity and septic shock. Data analysis was performed using JMP for Mac 10 (SAS Institute, Cary, N.C.). A *P* < 0.05 was considered significant for traditional statistical analysis. For SPC charting, standard criteria for adjusting the centerline and control limits were used.¹³

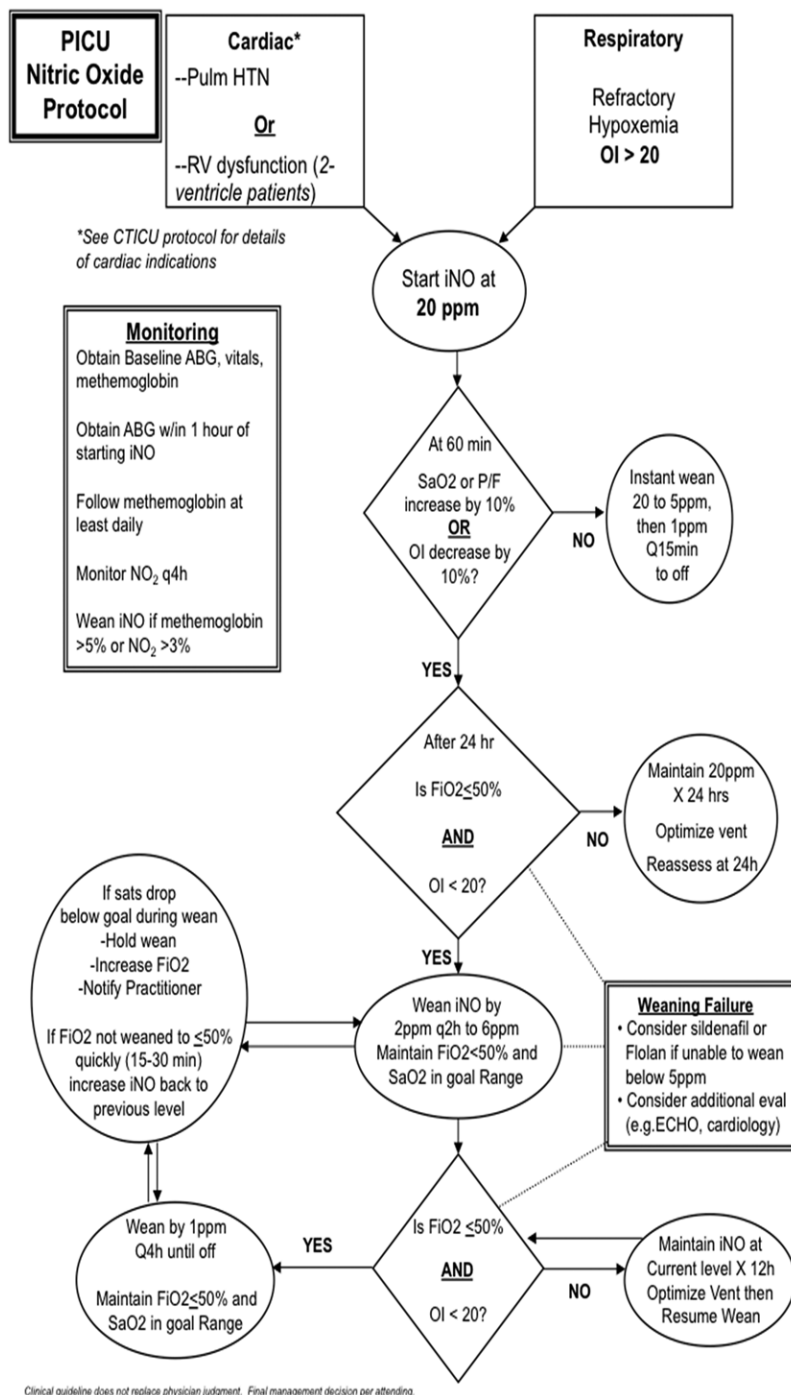


Fig. 1. Nationwide Children’s Hospital PICU iNO treatment guidelines, including criteria for starting, response, and weaning. *Cardiac patients identified with pulmonary hypertension were managed according to a separate protocol described by Simsic et al.¹⁴ P/F ratio is the arterial partial pressure of oxygen to the fraction of inspired oxygen. When arterial blood gases were not available, the S/F ratio or oxygen saturation to fraction of inspired oxygen was used.

RESULTS

Patient Characteristics

From January 1, 2010, until iNO therapy guideline implementation in January 2012, there were 30 patients (35 iNO courses) who served as the baseline population. After guideline implementation through December 2013, there were 33 patients (36 iNO courses).

We saw no significant differences in baseline characteristics (Table 1). There were also no differences in degree of hypoxemia or MAP at the initiation of iNO between groups (Fig. 2). No difference was seen in the time from endotracheal intubation to first iNO initiation [preguideline median of 65 hours (IQR, 6–158) versus postguideline median of 22 hours (IQR, 6–142; $P = 0.51$)].

iNO Use

Postguideline patients had a significant reduction in the duration of iNO therapy (Table 2; Fig. 3). Although both responding and nonresponding patients contributed to this decrease, it was most apparent in nonresponders (see rational subgroup analysis below). Although there was no difference in the number of patients who met starting or response criteria between groups, postguideline patients were significantly more likely to be weaned per criteria than preguideline patients (72% versus 37%; $P = 0.004$).

Table 1. Baseline Characteristics of Patients Treated With iNO Before and After PICU Guideline Implementation

Baseline Characteristics	Preguideline, n = 30	Postguideline, n = 33	P
Age (y)*	2 (0.79–12.5)	4 (0.96–14)	0.51
Male sex	16 (53)	12 (36)	0.21
Primary pulmonary diagnosis	23 (77)	25 (76)	1.0
Septic shock diagnosis	11 (37)	11 (33)	0.8
Initial PRISM III*	11 (7–16)	8 (5–19)	0.34
Pulmonary hypertension	3 (10)	3 (9.1)	1.0
Bronchopulmonary dysplasia	2 (6.7)	3 (9.1)	1.0
Trisomy 21	3 (10)	2 (6.1)	0.66
Congenital heart disease	4 (13)	4 (12)	1.0
Immunocompromised	4 (12)	4 (13)	1.0

Data expressed as n (%), unless otherwise noted.
*Median (IQR).

In addition, postguideline patients were more likely to have appropriate documentation than preguideline patients for iNO start (53% versus 23%; $P = 0.01$), clinical response (78% versus 43%; $P = 0.004$), and weaning (75% versus 46%; $P = 0.02$). In May 2012, there was a statistically significant reduction in iNO usage after guideline implementation (Fig. 4). Twelve of 14 successive points were below the centerline. This special cause variation indicated a change in the process. In response, we lowered the centerline from 196 hours to 120 hours per iNO course. Of note, we have sustained the improvement in iNO utilization through June 2016 with a slight increase in average utilization per patient noted in the second quarter of 2016. However, this increase remains below our original goal of 154 hours per patient. Also, the number of PICU patients treated with iNO each year has increased to 14 in 2014, 20 in 2015, and 14 through the first 6 months of 2016 (see figure, Supplemental Digital Content 1, <http://links.lww.com/PQ9/A2>).

There were 2 significant outliers noted in Fig. 4. Outlier A was a 4-month-old male with bronchopulmonary dysplasia and presented with respiratory failure, shock, and multiorgan failure. He had a combination of pulmonary hypertension and pulmonary vein stenosis. Despite the addition of sildenafil, he continued to have a recurrence of pulmonary hypertension requiring iNO therapy and ultimately died from his multiorgan failure. Outlier B was a 10-year-old

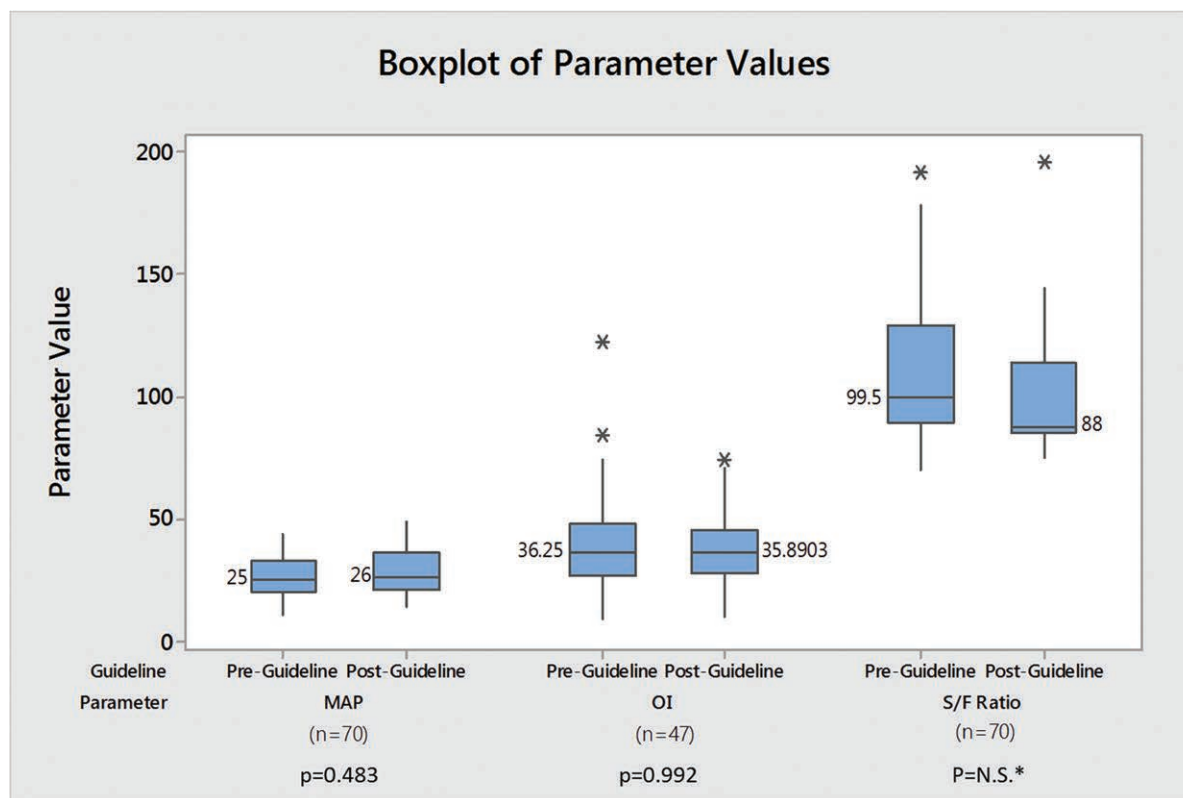


Fig. 2. Boxplot of respiratory parameters pre- and post-iNO guideline implementation: MAP, OI, and S/F. *The actual P value for the pre- and post-S/F ratios was 0.04. However, because the shape of the distributions for the 2 groups are so disparate, the Mann-Whitney test is not appropriate. A variety of transformations were performed in an attempt to normalize the distributions; however, no transformation gave a satisfactory result. (n=) refers to the number of iNO courses.

female with trisomy 21 and obesity. She was admitted with ARDS requiring ECMO support. She also had multiple episodes of severe refractory hypoxemia, both before ECMO and after decannulation, despite treatment with sildenafil and bosentan. She ultimately was discharged from the hospital on home mechanical ventilation after an 8-month stay.

Rational subgroup analysis indicated a decrease in duration of iNO therapy after guideline implementation in both iNO responding and nonresponding patient groups (Fig. 5).

Table 2. Comparison of Outcomes Between Patients Treated With iNO Before and After Guideline Implementation

Outcomes	Preguideline	Postguideline	P
ICU LOS (h)*	443 (324–895)	477 (181–761)	0.08†
Hospital LOS (h)*	726 (447–1,114)	592 (310–1,203)	0.25†
Mechanical ventilation (h)*	359 (283–846)	304 (141–551)	0.03†
Mortality‡	15 (50%)	7 (21%)	0.02§
ECMO‡	6 (20%)	5 (15%)	0.74§
iNO duration (h)			
Per course*	162 (87–290)	76 (48–124)	0.0004
Per patient*	147 (89–283)	75 (45–120)	0.0005
iNO cost (2013 US dollars)			
Per course*	10,385	4,900	0.0005
Per patient*	(5,282–18,642)	(3,106–7,946)	0.0006
	9,452	4,852	0.0006
	(3,863–17,829)	(2,866–7,709)	

*Median (IQR).
 †Log-rank test.
 ‡n (%).
 §Fisher's exact test.
 ||Wilcoxon rank sum test.

The baseline preimplementation average utilization per patient was 181.7 (SD, 151.5) hours with an upper control limit of 550.5 hours. There are only 6 nonresponding patients after guideline implementation. Thus, accurate control limits could not be generated. However, the mean iNO utilization for this group was 44.7 (SD, 32.8) hours. Patients who responded to iNO therapy required an average of 89.3 (SD, 64.3) hours with an upper control limit of 259.3.

Clinical Outcomes and Cost

We observed no significant differences in ICU or hospital LOS between groups (Table 2). Postguideline patients did have a shorter duration of mechanical ventilation (Table 2). Mortality was significantly higher in the preguideline group [odds ratio, 3.76; 95% confidence interval, 1.18–13.47; Table 2]. This mortality difference persisted even when adjusting for PRISM III and diagnosis of septic shock (adjusted odds ratio, 3.73; 95% confidence interval, 1.23–11.1). No difference was seen in the number of patients requiring ECMO support. Postguideline patients also had a lower cost of iNO therapy on a per-course basis as well as per patient (Table 2). Guideline implementation resulted in a median iNO cost savings of \$4,600 (2013 US dollars) per patient (Table 2).

DISCUSSION

Our PICU iNO treatment guideline was associated with a significant reduction in iNO use as well as significant reduction in iNO cost over 24 months after guideline

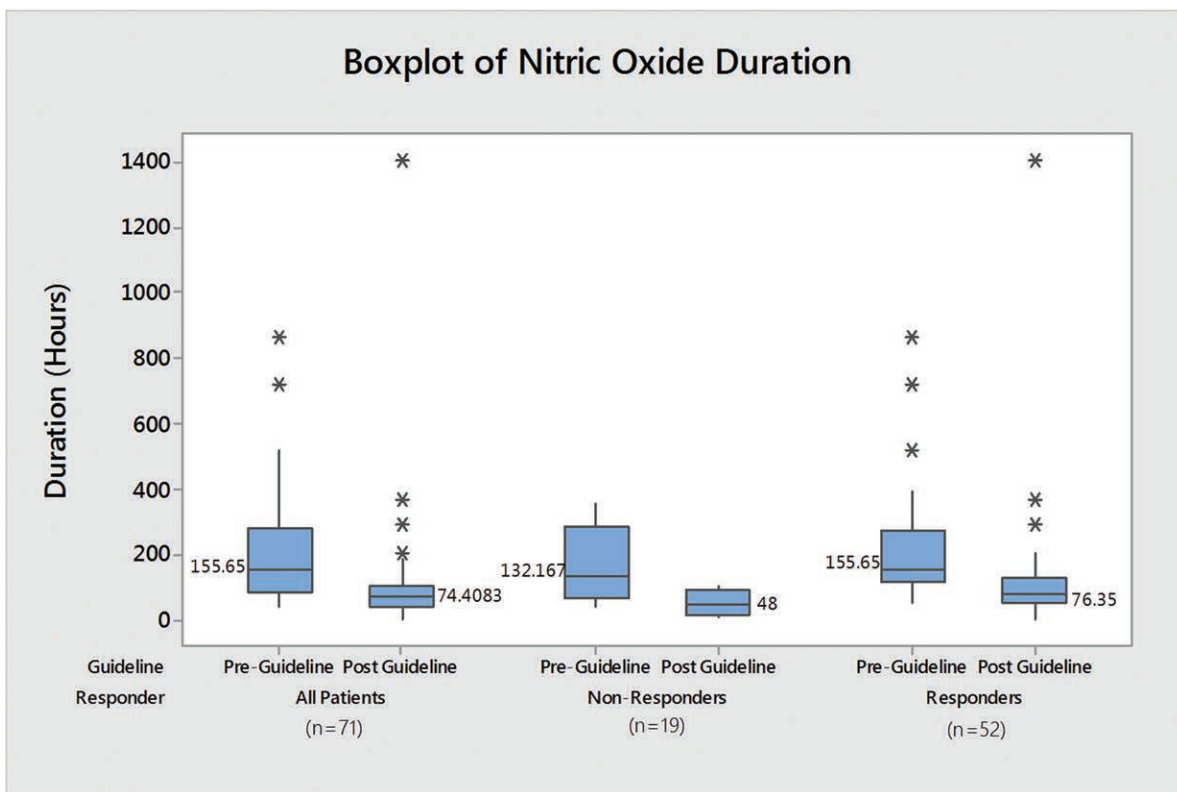
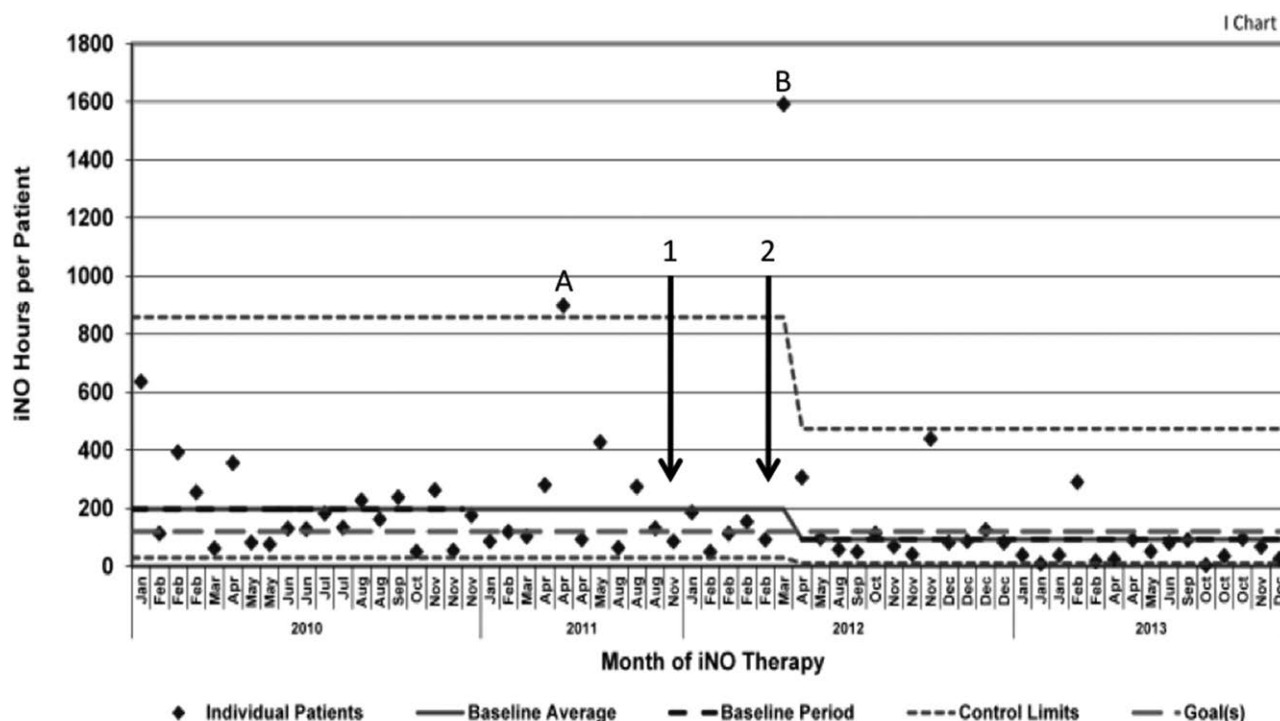


Fig. 3. Boxplot of iNO duration (in hours) for all patients, stratified by response to iNO. (n=) refers to the number of iNO courses.



NOTE: A ln(x) transformation was used to calculate appropriate control limits. These limits may not be equidistant from the centerline.

Fig. 4. SPC I chart demonstrating decreased mean hours of iNO use per patient course after guideline implementation. Each point represents an individual patient course. Time point 1 is when the initial QI committee convened while the guidelines were implemented at time point 2. Points A and B represent significant outliers. Outlier A was a 4-month-old male with respiratory failure, shock, and pulmonary hypertension. He ultimately died from his multiorgan failure. Outlier B was a 10-year-old female with trisomy 21 admitted with ARDS. She ultimately was discharged from the hospital on home mechanical ventilation after an 8-month stay.

implementation. Although iNO is not currently recommended for treatment of hypoxemic respiratory failure, we expect that intensivists will continue to use it as a rescue therapy for refractory hypoxemia. Therefore, utilization of specific treatment guidelines is essential to optimize patient care and decrease costs associated with iNO use.

Although we did demonstrate a significant reduction in iNO use, our guideline compliance was not perfect, suggesting that there may still be room for improvement in patient care. Although the guidelines use OI as a criterion for iNO use, 28% of postguideline patients did not have an arterial blood gas done before iNO initiation. This omission may be due to the rapid acute deterioration in some patients that led to iNO initiation. There still may be room for improving patient selection by increasing the number of patients with OI used to guide the iNO decisions. Guideline modification to include the use of oxygen saturation index could be useful as there has been a trend away from arterial line use in pediatrics. Also, compliance with documentation expectations was not ideal. Just over half of postguideline patients had appropriate documentation for starting iNO. Documentation of response and weaning was better, with at least three-fourths of patients having appropriate documentation for each. We are currently developing strategies such as electronic medical record note templates to improve documentation.

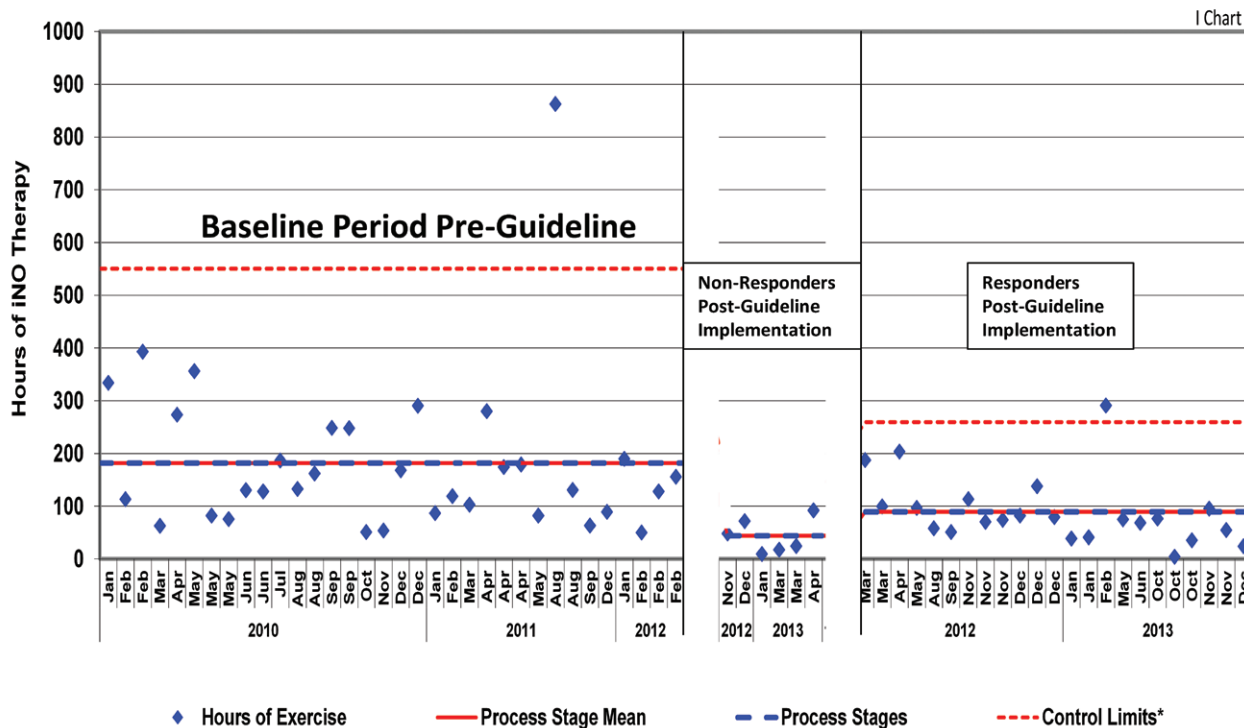
Limitations

There are several limitations of our study. This study was a QI project implemented in a single multidisciplinary (noncardiac) ICU and not a controlled trial. The selection of patients was at the discretion of the attending physician without strict mandatory criteria; other care was also not protocolized and may have varied over time. Therefore, there may be unmeasured confounders that could impact the response to iNO, the duration of iNO therapy, or the clinical outcomes. The intensivist group was unchanged during the study period, making significant practice shifts outside of the guidelines less likely. Of note, we implemented the iNO guidelines in a noncardiac ICU. The utility of these guidelines in our unit should not be generalized to patients treated with iNO for cardiac indications. However, Simsic et al.¹⁴ previously reported guidelines for iNO therapy in our cardiac ICU. Additionally, since this was a single-center study with a small population (total n = 63), the generalizability to a broader population is limited. Our findings, however, are consistent with those seen in both cardiac and mixed ICU populations.^{14,15}

Given the lack of other evidence for the benefits of iNO therapy, there may be a need for a robust randomized controlled trial investigating the effect of iNO on mortality and morbidity outcomes in pediatric severe acute hypoxemic respiratory failure. The largest pediatric study to



Rational Subgroup Analysis of Responders and Non-Responders After iNO Guideline Implementation



* A $\ln(a+bx)$ transform to correct for right skew was used to determine control limits. Limits were then reverse transformed to reflect original data metrics.

Fig. 5. A rational subgroup analysis of the difference in iNO utilization after implementation of the iNO guideline among responding and nonresponding patients. The baseline preimplementation average utilization per patient was 181.7 (SD, 151.5) hours. After guideline implementation, both responding and nonresponding patient groups demonstrated a decrease. The mean iNO utilization for the nonresponder group was 44.7 (SD, 32.8) hours. This decrease reflects the impact of the guideline stopping criteria for nonresponding patients. Patients who responded to iNO therapy required an average of 89.3 (SD, 64.3) hours with an upper control limit of 259.3. (For additional information regarding rational subgroup analysis, please see reference 13, pp. 288–289).

date by Dobyns et al. only included 108 patients and was published over 15 years ago; so it is unlikely to reflect the current lung-protective ventilator strategies that are the hallmark of ARDS respiratory management.³ The recent trial by Bronicki et al. does raise the possibility that iNO may still have a role, provided it is used more efficiently.⁸ A clinical trial utilizing this (or a similar) protocol, as well as lung-protective ventilator strategies, could provide much-needed evidence regarding the best use of iNO in pediatric severe hypoxemic respiratory failure and ARDS. At the very least, a multicentered quality learning collaborative evaluating a standard iNO therapy guideline for critically ill pediatric patients would be of benefit to the PICU community.

CONCLUSIONS

Implementation of iNO treatment guidelines in our PICU was associated with decreased usage and decreased cost of iNO therapy in critically ill children with severe acute hypoxemic respiratory failure. Further research is needed to determine the sustainability of this intervention as well

as to clarify the role of iNO in the treatment of refractory hypoxemia in children.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article. This study was supported by departmental resources. The authors have no conflicts of interest relevant to this article to disclose.

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