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Sildenafil Exposure in the Neonatal Intensive Care Unit

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Abstract

Objective—Pulmonary hypertension causes substantial morbidity and mortality in infants. Although Food and Drug Administration approved to treat pulmonary arterial hypertension in adults, sildenafil is not approved for infants. We sought to describe sildenafil exposure and associated diagnoses and outcomes in infants.

Study Design—Retrospective cohort of neonates discharged from more than 300 neonatal intensive care units from 2001 to 2016.

Results—Sildenafil was administered to 1,336/1,161,808 infants (0.11%; 1.1 per 1,000 infants); 0/35,977 received sildenafil in 2001 versus 151/90,544 (0.17%; 1.7 per 1,000 infants) in 2016. Among infants <32 weeks' gestational age (GA) with enough data to determine respiratory outcome, 666/704 (95%) had bronchopulmonary dysplasia (BPD). Among infants ≥32 weeks GA, 248/455 (55%) had BPD and 76/552 (14%) were diagnosed with meconium aspiration. Overall, 209/921 (23%) died prior to discharge.

Conclusion—The use of sildenafil has increased since 2001. Exposed infants were commonly diagnosed with BPD. Further studies evaluating dosing, safety, and efficacy of sildenafil are needed.

Keywords

premature infant; sildenafil; pulmonary hypertension; bronchopulmonary dysplasia; neonate

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Conflict of Interest

None.

Pulmonary hypertension in preterm and term infants represents a heterogeneous collection of diagnoses that collectively are associated with poor outcomes. Pulmonary hypertension can be idiopathic or related to underlying diagnoses, including congenital heart disease, congenital diaphragmatic hernia, and persistent pulmonary hypertension of the newborn (PPHN) secondary to meconium aspiration syndrome or other hypoxic respiratory failure in term and preterm infants, often with respiratory distress syndrome.^{1–3} Pulmonary hypertension can also occur in premature infants with bronchopulmonary dysplasia (BPD).^{1,2,4–6} Despite new technologies and therapies, such as extracorporeal membrane oxygenation or pulmonary vasodilation medications, the estimated mortality of infants diagnosed with pulmonary hypertension remains at 10 to 20%.^{1,3,4,7–9} Other morbidities associated with pulmonary hypertension include prolonged mechanical ventilation (including high-frequency mechanical ventilation), need for extracorporeal life support, or progression to right heart failure.^{1,3,4,10} Surviving infants may require exogenous oxygen for an extended period of time. To improve these outcomes, providers increasingly turn to drugs approved for the treatment of pulmonary hypertension in adults, such as sildenafil. As a potent inhibitor of type-5 phosphodiesterase, sildenafil produces pulmonary vasodilation by potentiating the effects of endogenous nitric oxide.^{3,9}

Since the U.S. Food and Drug Administration (FDA) approved sildenafil in 2005 for the treatment of pulmonary arterial hypertension in adults, off-label clinical and investigational use of sildenafil in children and infants has anecdotally increased.^{11–13} Although there have been a few smaller trials in infants with PPHN, no large-scale study has provided definitive evidence to support safety and efficacy of sildenafil in infants.^{6,14–22} Moreover, the safety and efficacy of sildenafil in infants with pulmonary hypertension related to causes other than PPHN (i.e., BPD related) are ill defined, with limited studies and case reports to support routine use.^{7,11,13,21,23–30} Reported adverse effects of sildenafil in infants include severe systemic hypotension and increased incidence of retinopathy of prematurity (ROP), but none has been consistently reported.^{13,28,30–39}

In this study, we describe the frequency of use of sildenafil in a large number of neonatal intensive care units (NICUs), the change in prescribing patterns from 2001 to 2016, the diagnoses and interventions associated with sildenafil use, and the occurrence of in-hospital morbidity and mortality.

Methods

We performed a retrospective chart review using a clinical database of infants discharged from 1 of 349 community and tertiary care center NICUs across North America managed by the Pediatrix Medical Group. Data were obtained from an electronic medical record that prospectively captures information including medication information, diagnoses, admission notes, daily progress notes, and discharge notes generated by clinicians. We identified infants 23 weeks' gestational age (GA) at birth discharged from 2001 to 2016 and exposed to sildenafil in the first 180 postnatal days.

We collected demographic data including GA, birth weight, and exposure to antenatal steroids. We collected the postnatal age at the time of sildenafil exposure, duration of

exposure, interventions received during hospitalization, and all diagnoses made during the hospitalization. Interventions of interest included mechanical ventilation as well as any exposure to surfactant or inhaled nitric oxide (iNO). Diagnoses of interest included severe congenital heart disease, congenital diaphragmatic hernia, meconium aspiration syndrome, pulmonary hypertension (encompassing various classifications of pulmonary hypertension, as the database did not differentiate between them), severe ROP, and BPD.

We defined mechanical ventilation as either conventional or high-frequency ventilation. We defined severe congenital heart disease as any diagnosis of tricuspid atresia, tetralogy of Fallot, transposition of the great arteries, hypoplastic right or left heart, Ebstein's anomaly, total anomalous pulmonary venous return, truncus arteriosus, any valvular atresia, atrioventricular septal defect, other single ventricles, or interrupted aortic arch. We defined severe ROP as ROP requiring bevacizumab, laser eye therapy, or cryotherapy. We used a BPD definition that varied with GA. Infants <32 weeks GA were classified as having BPD if they required respiratory support (nasal cannula, continuous positive airway pressure, or mechanical ventilation) or supplemental oxygen continuously from 36^{0/7} to 36^{6/7} weeks postmenstrual age. Infants ≥32 weeks GA were classified as having BPD if they required respiratory support or supplemental oxygen continuously from postnatal days 28 to 34.^{40,41} If an infant was discharged or transferred before the date of evaluation for BPD, then the data were considered "missing" as it could not be accurately determined whether the infant met criteria for BPD. We defined hypotension as the receipt of inotropes including epinephrine, dopamine, dobutamine, and norepinephrine.

Statistical Analysis

We categorized infants by GA into two groups—infants <32 and ≥32 weeks GA at birth—and used contingency table analysis to examine the association between characteristics of the infants and the categorized GA. We used standard summary statistics including counts (percentages) and medians (25th and 75th percentiles) to describe all study variables. For percentages <1%, we translated the count into number per 1,000 infants. We used Cochran-Armitage tests to evaluate trends over time, and chi-square or Wilcoxon's rank-sum tests to compare distributions of study variables across groups. Analyses were conducted using Stata 15.1 (College Station, TX), and we considered a *p*-value <0.05 statistically significant.

Results

Over the 16-year study period, 1,160,796 infants were discharged from NICUs managed by the Pediatrix Medical Group, and sildenafil was administered to 1,336 infants (1.1/1,000 infants). Sildenafil use increased over the study period from 0/35,977 infants in 2001 to 151/90,544 infants (1.7/1,000 infants) in 2016. There was a decrease in the number of infants exposed in 2013 to 123/86,734 infants (1.4/1,000 infants) but use increased again the following year. Peak use was in 2012 with 161/85,922 infants exposed to sildenafil (1.9/1,000 infants) (Fig. 1). The median GA of infants exposed to sildenafil was 28 weeks (25th and 75th percentiles: 25 and 37) with a median birth weight of 929 g (610 and 2,866). Infants ≥25 weeks GA had the highest exposure, with 1.4% exposed (Fig. 2). Of the 1,336 infants exposed to sildenafil, all but 217 infants were diagnosed with pulmonary

hypertension; of those 1,119 infants, 749 had BPD (Table 1). Of the 921 infants exposed to sildenafil for whom mortality outcomes were known, 209 (23%) died prior to discharge.

Infants <32 Weeks' Gestational Age

Of 184,262 infants born <32 weeks GA, 783 (4.2/1,000 infants) were exposed to sildenafil. The median start of sildenafil was at 104 postnatal days (25th and 75th percentiles: 75 and 130). Sildenafil was initiated after 28 postnatal days in 723 (92%) infants (Fig. 3). The median duration of in-hospital sildenafil exposure was 26 days (25th and 75th percentiles: 10 and 51).

Of the 783 infants exposed to sildenafil, 631 (81%) were diagnosed with pulmonary hypertension. Of 704 infants exposed to sildenafil with enough data to determine the respiratory outcome, 666 (95%) infants had BPD (Table 1). Of 783 exposed, 148 (19%) infants were diagnosed with severe ROP, but only 62 of 148 (42%) were diagnosed after sildenafil administration. Altogether, 313 (40%) infants exposed to sildenafil received inotropic support. Also, 279 (36%) infants exposed to sildenafil received iNO during their hospitalization. Death occurred in 135 of 520 (26%) infants prior to discharge from the NICU.

Infants ≥32 Weeks' Gestational Age

Of 976,534 infants born ≥32 weeks GA, 552 (0.5/1,000 infants) were exposed to sildenafil. The median start of sildenafil was at 11 postnatal days (25th and 75th percentiles: 3 and 32). Sildenafil was initiated within the first 7 days of life in 345 (66%) infants (Fig. 3). The median duration of in-hospital sildenafil exposure was 11 days (25th and 75th percentiles: 4 and 20).

Of the 552 infants exposed to sildenafil, 488 (88%) were diagnosed with pulmonary hypertension. Of 455 exposed to sildenafil with enough data to determine the respiratory outcome, 248 (55%) infants had BPD (Table 1). The next most common diagnoses were congenital diaphragmatic hernia (94 [17%] infants) and meconium aspiration syndrome (76 [14%] infants). Altogether, 287 (52%) of infants exposed to sildenafil received inotropic support. Also, 197 (36%) infants exposed to sildenafil received iNO during their hospitalization. Death occurred in 74 of 400 (19%) infants prior to discharge from the NICU.

Discussion

We identified a large group of term and preterm infants exposed to sildenafil. Clinicians' off-label use of sildenafil in this cohort increased more than fivefold since 2005, when sildenafil was first FDA approved for use in adults with pulmonary arterial hypertension. Infants who received sildenafil were most commonly diagnosed with pulmonary hypertension, and preterm infants exposed to sildenafil were frequently diagnosed with BPD. Nearly one quarter (23%) of infants exposed to sildenafil died. Infants born at <32 weeks started sildenafil at a median 104 postnatal days, while infants born at ≥32 weeks started sildenafil at a median 11 postnatal days. This difference may be due to the different pathologies seen in these two groups, which leads to development of pulmonary hypertension at different

postnatal ages. Infants <32 weeks' GA are likely receiving sildenafil for BPD-related pulmonary hypertension, which presents at a later postnatal age; infants ≥32 weeks' GA are likely receiving sildenafil for pulmonary hypertension from different diagnoses, including congenital diaphragmatic hernia or meconium aspiration syndrome, which present at an earlier postnatal age. This is further supported by 95% of infants <32 weeks' GA being diagnosed with BPD, whereas only 55% of infants ≥32 weeks' GA had a BPD diagnosis.

Our data confirm an overall increase in sildenafil use in hospitalized infants, although the overall use of sildenafil remains low. We suspect that in the setting of high morbidity and mortality related to pulmonary hypertension, clinicians may have been hopeful that sildenafil would work similarly in infants to improve outcomes as it does in adults with pulmonary hypertension. Interestingly, the use of sildenafil in Pediatrix NICUs declined from 2012 to 2016, coinciding with the release of an FDA drug safety communication in August 2012. This statement was based off the STARTS-1 and STARTS-2 studies and recommended against the use of sildenafil in children due to concerns for increased morbidity and mortality at high doses in treatment-naïve children.^{11,42,43} However, this study's conclusions may have limited translatability to the NICU population. Disease processes that cause pulmonary hypertension in the neonate are often different from those that cause pulmonary hypertension in older infants and children. Infants in the NICU are also often treated with higher fractions of inspired oxygen, which may upregulate the pulmonary type-5 phosphodiesterase activity and may allow for the use of lower doses of sildenafil.⁴⁴

Neonates with pulmonary arterial hypertension specifically secondary to BPD have poor survival (53% at 2 years).⁴ The most common cause of death in infants with pulmonary hypertension is a pulmonary hypertensive crisis, where pressures in the lungs become so elevated that the heart cannot pump blood to the body. This is seen clinically by poor perfusion and decreasing oxygen saturations. Many medications, including sildenafil, are used in the NICU without a clear understanding of their risk–benefit profile. In infants with pulmonary hypertension, the proposed benefits are lower pulmonary artery pressures and ultimately improved survival.¹ Nevertheless, sildenafil has been associated with ROP and hypotension in neonates and increased mortality at high doses in children older than 1 year.^{38,39,42} Even with these side effects in mind, limited treatment options with their own toxicities and the availability of an oral formulation of sildenafil that can be administered in an outpatient setting make it an appealing option.

The strengths of our study include the large sample size over a 16-year period from many different academic and community NICUs across North America. This study has multiple limitations, including the retrospective nature of the data, lack of data on route of medication administration, lack of specific indication for sildenafil use, and lack of complete mortality data. Clinical diagnoses were assigned at the discretion of the treating physician at each individual site. As normal blood pressure parameters are poorly defined in premature infants, we attempted to capture hypotension by identifying infants exposed to inotropes, which serves as a conservative marker of hypotension as it relies on clinician judgment that an intervention is necessary to correct the blood pressure. Furthermore, we cannot comment on dosing and the effect this may have had on mortality. A comprehensive, ideally

prospective, evaluation of the efficacy and safety of sildenafil in the neonatal population, including its effects on mortality and outcomes of pulmonary hypertension, is warranted.

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References

1. Dhillon R. The management of neonatal pulmonary hypertension. *Arch Dis Child Fetal Neonatal Ed* 2012;97(03):F223–F228 [PubMed: 21278430]
2. Iacovidou N, Syggelou A, Fanos V, Xanthos T. The use of sildenafil in the treatment of persistent pulmonary hypertension of the newborn: a review of the literature. *Curr Pharm Des* 2012;18(21):3034–3045 [PubMed: 22564297]
3. Porta NF, Steinhorn RH. Pulmonary vasodilator therapy in the NICU: inhaled nitric oxide, sildenafil, and other pulmonary vasodilating agents. *Clin Perinatol* 2012;39(01):149–164 [PubMed: 22341543]
4. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007;120(06):1260–1269 [PubMed: 18055675]
5. Trembath A, Laughon MM. Predictors of bronchopulmonary dysplasia. *Clin Perinatol* 2012;39(03):585–601 [PubMed: 22954271]
6. König K, Barfield CP, Guy KJ, Drew SM, Andersen CC. The effect of sildenafil on evolving bronchopulmonary dysplasia in extremely preterm infants: a randomised controlled pilot study. *J Matern Fetal Neonatal Med* 2014;27(05):439–444 [PubMed: 23796045]
7. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. *Pediatrics* 2006;117(04):1077–1083 [PubMed: 16585301]
8. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. *Cochrane Database Syst Rev* 2011;2011(08):CD005494
9. Jain A, McNamara PJ. Persistent pulmonary hypertension of the newborn: Advances in diagnosis and treatment. *Semin Fetal Neonatal Med* 2015;20(04):262–271 [PubMed: 25843770]
10. Goodman G, Perkin RM, Anas NG, Sperling DR, Hicks DA, Rowen M. Pulmonary hypertension in infants with bronchopulmonary dysplasia. *J Pediatr* 1988;112(01):67–72 [PubMed: 3335964]
11. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naïve children with pulmonary arterial hypertension. *Circulation* 2012;125(02):324–334 [PubMed: 22128226]
12. Galiè N, Ghofrani HA, Torbicki A, et al.; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353(20):2148–2157 [PubMed: 16291984]
13. Steinhorn RH, Kinsella JP, Pierce C, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. *J Pediatr* 2009;155(06):841–847 [PubMed: 19836028]

14. Nyp M, Sandritter T, Poppinga N, Simon C, Truog WE. Sildenafil citrate, bronchopulmonary dysplasia and disordered pulmonary gas exchange: any benefits? *J Perinatol* 2012;32(01):64–69 [PubMed: 21941230]
15. Al Omar S, Salama H, Al Hail M, et al. Effect of early adjunctive use of oral sildenafil and inhaled nitric oxide on the outcome of pulmonary hypertension in newborn infants. A feasibility study. *J Neonatal Perinatal Med* 2016;9(03):251–259 [PubMed: 27589542]
16. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. *Cochrane Database Syst Rev* 2017;8:CD005494 [PubMed: 28777888]
17. Perez KM, Laughon M. Sildenafil in term and premature infants: a systematic review. *Clin Ther* 2015;37(11):2598–2607 [PubMed: 26490498]
18. Hilgendorff A, Apitz C, Bonnet D, Hansmann G. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102(Suppl 2):ii49–ii56 [PubMed: 27053698]
19. Tan K, Krishnamurthy MB, O'Heney JL, Paul E, Sehgal A. Sildenafil therapy in bronchopulmonary dysplasia-associated pulmonary hypertension: a retrospective study of efficacy and safety. *Eur J Pediatr* 2015;174(08):1109–1115 [PubMed: 25796626]
20. Trottier-Boucher MN, Lapointe A, Malo J, et al. Sildenafil for the treatment of pulmonary arterial hypertension in infants with bronchopulmonary dysplasia. *Pediatr Cardiol* 2015;36(06):1255–1260 [PubMed: 25824807]
21. Samiee-Zafarghandy S, Smith PB, van den Anker JN. Safety of sildenafil in infants*. *Pediatr Crit Care Med* 2014;15(04):362–368 [PubMed: 24583505]
22. Wardle AJ, Wardle R, Luyt K, Tulloh R. The utility of sildenafil in pulmonary hypertension: a focus on bronchopulmonary dysplasia. *Arch Dis Child* 2013;98(08):613–617 [PubMed: 23625986]
23. Vargas-Origel A, Gómez-Rodríguez G, Aldana-Valenzuela C, Vela-Huerta MM, Alarcón-Santos SB, Amador-Licona N. The use of sildenafil in persistent pulmonary hypertension of the newborn. *Am J Perinatol* 2010;27(03):225–230 [PubMed: 19866403]
24. Caputo S, Furcolo G, Rabuano R, et al. Severe pulmonary arterial hypertension in a very premature baby with bronchopulmonary dysplasia: normalization with long-term sildenafil. *J Cardiovasc Med (Hagerstown)* 2010;11(09):704–706 [PubMed: 19829144]
25. Carroll WD, Dhillon R. Sildenafil as a treatment for pulmonary hypertension. *Arch Dis Child* 2003;88(09):827–828 [PubMed: 12937112]
26. Hon KL, Cheung KL, Siu KL, et al. Oral sildenafil for treatment of severe pulmonary hypertension in an infant. *Biol Neonate* 2005; 88(02):109–112 [PubMed: 15870496]
27. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. *Circulation* 2005;111(24):3274–3280 [PubMed: 15956137]
28. Karatza AA, Bush A, Magee AG. Safety and efficacy of Sildenafil therapy in children with pulmonary hypertension. *Int J Cardiol* 2005;100(02):267–273 [PubMed: 15823634]
29. Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009;154(03):379–384 [PubMed: 18950791]
30. Balasubramanian H, Strunk T, Kohan R. Arterial hypotension and prerenal failure in an extremely preterm infant associated with oral sildenafil. *J Perinatol* 2015;35(06):458–459 [PubMed: 26012476]
31. Fang AY, Guy KJ, König K. The effect of sildenafil on retinopathy of prematurity in very preterm infants. *J Perinatol* 2013;33(03): 218–221 [PubMed: 22766743]
32. Leibovitch L, Matok I, Paret G. Therapeutic applications of sildenafil citrate in the management of paediatric pulmonary hypertension. *Drugs* 2007;67(01):57–73 [PubMed: 17209664]
33. Marsh CS, Marden B, Newsom R. Severe retinopathy of prematurity (ROP) in a premature baby treated with sildenafil acetate (Viagra) for pulmonary hypertension. *Br J Ophthalmol* 2004;88 (02): 306–307 [PubMed: 14736800]
34. Pierce CM, Petros AJ, Fielder AR. No evidence for severe retinopathy of prematurity following sildenafil. *Br J Ophthalmol* 2005; 89(02):250

35. Kehat R, Bonsall DJ, North R, Connors B. Ocular findings of oral sildenafil use in term and near-term neonates. *J AAPOS* 2010;14 (02):159–162 [PubMed: 20199882]
36. Shekerdemian LS, Ravn HB, Penny DJ. Interaction between inhaled nitric oxide and intravenous sildenafil in a porcine model of meconium aspiration syndrome. *Pediatr Res* 2004;55(03): 413–418 [PubMed: 14711900]
37. Kahveci H, Yilmaz O, Avsar UZ, et al. Oral sildenafil and inhaled iloprost in the treatment of pulmonary hypertension of the newborn. *Pediatr Pulmonol* 2014;49(12):1205–1213 [PubMed: 24420987]
38. Limjoco J, Paquette L, Ramanathan R, Seri I, Friedlich P. Changes in mean arterial blood pressure during sildenafil use in neonates with meconium aspiration syndrome or sepsis. *Am J Ther* 2015;22 (02):125–131 [PubMed: 23344111]
39. Samiee-Zafarghandy S, van den Anker JN, Laughon MM, Clark RH, Smith PB, Hornik CP; Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee. Sildenafil and retinopathy of prematurity risk in very low birth weight infants. *J Perinatol* 2016;36(02):137–140 [PubMed: 26491852]
40. Trembath A, Hornik CP, Clark R, Smith PB, Daniels J, Laughon M; Best Pharmaceuticals for Children Act—Pediatric Trials Network. Comparative effectiveness of surfactant preparations in premature infants. *J Pediatr* 2013;163(04):955–960 [PubMed: 23769501]
41. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163(07): 1723–1729 [PubMed: 11401896]
42. FDA Drug Safety Communication. FDA recommends against the use of Revatio (sildenafil) in children with pulmonary hypertension. 8 30, 2012 Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm317123.htm>. Accessed October 10, 2014
43. Barst RJ, Beghetti M, Pulido T, et al.; STARTS-2 Investigators. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. *Circulation* 2014;129(19):1914–1923 [PubMed: 24637559]
44. Farrow KN, Groh BS, Schumacker PT, et al. Hyperoxia increases phosphodiesterase 5 expression and activity in ovine fetal pulmonary artery smooth muscle cells. *Circ Res* 2008;102(02): 226–233 [PubMed: 17991881]

Fig. 1.
Sildenafil exposure by year.

Fig. 2.
Sildenafil exposure stratified by gestational age.

Fig. 3.
Postnatal age at the time of first sildenafil exposure among infants.

Table 1

Demographics and outcomes of infants exposed to sildenafil

	<32 wk <i>N</i> = 783	32 wk <i>N</i> = 552
Male	439 (56)	308 (56)
Antenatal steroids	632 (81)	71 (13)
Median gestational age, wk (IQR)	25 (24, 27)	38 (36, 39)
Median birth weight, g (IQR)	655 (545, 800)	3,015 (2,474, 3,501)
Diagnoses		
Pulmonary hypertension	631 (81)	488 (88)
Meconium aspiration syndrome	0	76 (14)
Congenital diaphragmatic hernia	5 (<1)	94 (17)
Congenital heart disease	18(2)	80 (14)
Bronchopulmonary dysplasia ^a	666 (95)	248 (55)
Interventions		
Mechanical ventilation	760 (97)	484 (88)
Inhaled nitric oxide	279 (36)	197 (36)
Surfactant	265 (34)	84 (15)
Inotropes	313 (40)	287 (52)
Outcome		
Death ^b	135 (26)	74 (19)
Severe retinopathy of prematurity	148 (19)	0

Abbreviation: IQR, interquartile range.

Note: Data are *n* (%), unless otherwise indicated.^aOne hundred and seventy-six infants were transferred to other acute care facilities before bronchopulmonary dysplasia outcome could be determined.^bFour hundred ten infants were transferred to other acute care facilities before mortality outcomes could be determined.