Cardiology in the Young

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Pharmacoepidemiology of combination pulmonary vasodilator therapy in critically ill infants

Karan R. Kumar[1,2], Elizabeth C. Ciociola[3], Kayla R. Skinner[2], Gargi M. Dixit[2], Sunshine Alvarez[2], Elijah K. Benjamin[2], Jeffrey C. Faulkner[2], Rachel G. Greenberg[1,2], Reese H. Clark[4], Daniel K. Benjamin Jr[1,2], Christoph P. Hornik[1,2] and Jan Hau Lee[5,6]

[1]Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; [3]University of North Carolina School of Medicine, Chapel Hill, NC, USA; [4]Pediatrix Center for Research, Education, Quality, and Safety, Sunrise, FL, USA; [5]Children's Intensive Care Unit, KK Women's and Children's Hospital, Singapore, Singapore and [6]Paediatrics Academic Clinical Programme, Duke-NUS School of Medicine, Singapore, Singapore

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Corresponding author:
Karan R. Kumar;
Email: karan.kumar@duke.edu

Abstract

Background: New drugs to target different pathways in pulmonary hypertension has resulted in increased combination therapy, but details of this use in infants are not well described. In this large multicenter database study, we describe the pharmacoepidemiology of combination pulmonary vasodilator therapy in critically ill infants. *Methods:* We identified inborn infants discharged home from a Pediatrix neonatal ICU from 1997 to 2020 exposed to inhaled nitric oxide, sildenafil, epoprostenol, or bosentan for greater than two consecutive days. We compared clinical variables and drug utilisation between infants receiving simultaneous combination and monotherapy. We reported each combination's frequency, timing, and duration and graphically represented drug use over time. *Results:* Of the 7681 infants that met inclusion criteria, 664 (9%) received combination therapy. These infants had a lower median gestational age and birth weight, were more likely to have cardiac and pulmonary anomalies, receive cardiorespiratory support, and had higher in-hospital mortality than those receiving monotherapy. Inhaled nitric oxide and sildenafil were most frequently used, and utilisation of combination and monotherapy for all drugs increased over time. Inhaled nitric oxide and epoprostenol were used in infants with a higher gestational age, earlier postnatal age, and shorter duration than sildenafil and bosentan. Dual therapy with inhaled nitric oxide and sildenafil was the most common combination therapy. *Conclusion:* Our study revealed an increased use of combination pulmonary vasodilator therapy, favouring inhaled nitric oxide and sildenafil, yet with considerable practice variation. Further research is needed to determine the optimal combination, sequence, dosing, and disease-specific indications for combination therapy.

Introduction

Pulmonary hypertension is a major cause of mortality and morbidity, affecting approximately 2 per 1000 live births annually.[1] Mortality approaches 10% for infants with moderate-to-severe disease and increases further in premature infants or those with pre-existing cardiac and pulmonary anomalies.[2] Of infants who survive, at least 25% face significant long-term morbidities such as chronic lung disease and neurodevelopmental impairment.[3] Despite advances in neonatal ventilation strategies and targeted pharmacotherapy over the past three decades, pulmonary hypertension remains a significant problem for critically ill infants accounting for up to 4% of all admissions to tertiary neonatal ICUs.[4]

Pulmonary hypertension in infants is highly heterogeneous due to differences in pathophysiology, clinical presentation, and comorbidities.[5] Despite this, pharmacological treatment has remained largely unchanged.[6] Recently, it has been recognised that treatment approaches should be tailored to the multiple distinct clinical phenotypes of infants with pulmonary hypertension.[7] Additionally, the emergence of novel drugs to target different mechanistic pathways has opened up new treatment options for infants with pulmonary hypertension.[8]

Inhaled nitric oxide and phosphodiesterase inhibitors are the mainstay of contemporary neonatal pulmonary hypertension treatment.[9] At the same time, endothelin receptor antagonists and prostacyclins are increasingly being investigated and used off-label.[9] This has led to a rise in reports of combination therapy for high-risk infants, despite a lack of

pharmacoepidemiology data to help guide treatment decisions and provide prognostic information.[10] Given the severity of outcomes for infants with pulmonary hypertension and the paucity of data on combination therapy, reporting real-world pharmacotherapy treatment strategies in this population is critical. This would aid in identifying the ideal combination or sequence of therapies that would benefit infants with a specific clinical phenotype.

In this study, we used a large multicenter electronic clinical data warehouse to describe the pharmacoepidemiology of critically ill infants requiring combination therapy with pulmonary vasodilators.

Materials and methods

Data source

We collected data from an electronic health record database that prospectively captures information generated by clinicians on infants cared for by the Pediatrix Medical Group in 446 neonatal ICUs in North America from 1997 to 2020. This information is gathered from routine clinical care documentation, including admission notes, daily progress notes, and discharge summaries. The record consists of data on multiple aspects of care, including demographics, maternal history, medications, procedures, laboratory results, and diagnoses. These de-identified data were transferred to the Pediatrix Clinical Data Warehouse for quality improvement and research.[11] This study was approved by the Duke University Institutional Review Board with a waiver of consent.

Study population

We included infants exposed to at least one of inhaled nitric oxide, intravenous or enteral sildenafil, intravenous epoprostenol, or enteral bosentan for greater than two consecutive days to ensure adequate time for simultaneous combination exposure. We excluded infants who were outborn, had missing information on discharge status, and were transferred to another institution at the time of discharge.

Definitions

We defined combination therapy as simultaneous exposure to at least two pulmonary vasodilator medications for greater than two consecutive days at any point during hospitalisation. This criterion was established to distinguish genuine combination therapy from a transition between therapies. We defined monotherapy as exposure to only one pulmonary vasodilator medication at a given time for greater than two successive days during hospitalisation. We defined pulmonary vasodilator use at discharge or death as exposure on the day of or prior to discharge or death, respectively.

We defined infants as having congenital heart disease (CHD) if they had documentation of any major (e.g. tetralogy of fallot, transposition of the great arteries, hypoplastic left heart syndrome, total anomalous pulmonary venous return) and minor heart defects (e.g. atrial septal defect, ventricular septal defect) as a clinical diagnosis in the electronic health record. We defined infants as having a patent ductus arteriosus, persistent pulmonary hypertension of the newborn, or congenital diaphragmatic hernia (CDH) if it was documented as a clinical diagnosis in the electronic health record. We defined lung anomalies as documentation of any of these clinical diagnoses in the electronic health record: cystic lung disease; lobar emphysema; pulmonary agenesis, sequestration, and lung hypoplasia; and surfactant protein abnormalities. We defined bronchopulmonary dysplasia (BPD) as continuous respiratory support (supplemental oxygen, nasal cannula, high-flow nasal cannula, nasal continuous positive airway pressure, conventional mechanical ventilation, or high-frequency ventilation) between 36 0/7 and 36 6/7 weeks postmenstrual age for infants < 32 weeks gestational age or between postnatal age 28 to 34 days for infants ≥ 32 weeks gestational age, as previously reported.[12]

We defined inotrope receipt as postnatal exposure to dobutamine, dopamine, epinephrine, norepinephrine, vasopressin, or milrinone. We defined diuretic receipt as postnatal exposure to acetazolamide, amiloride, bumetanide, chlorothiazide, diazoxide, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, or metolazone. We defined receipt of postnatal steroids as exposure to dexamethasone, hydrocortisone, methylprednisolone, prednisolone, or prednisone.

We defined exposure to extracorporeal membrane oxygenation and the presence of a tracheostomy if it was documented as a procedure in the electronic health record. We defined non-invasive respiratory support as exposure to hood oxygen, nasal cannula, high-flow nasal cannula, or non-invasive positive pressure ventilation. We defined mechanical ventilation as exposure to conventional mechanical ventilation or high-frequency ventilation. We defined ventilator days as the number of days exposed to invasive mechanical ventilation (conventional or high-frequency). We defined oxygen therapy as exposure to a fraction of inspired oxygen content $> 21\%$ and oxygen days as the number of days exposed to a fraction of inspired oxygen content $> 21\%$.

Data collection

We collected the following variables: gestational age, birth weight, small for gestational age status, race/ethnicity, sex, 5 minute Apgar score, type of delivery, inborn status, death status, antenatal steroid exposure, postnatal medications (pulmonary hypertension medications, inotropes, diuretics, postnatal steroids), diagnoses, and cardiorespiratory therapies as defined above.

For each individual and combination use of pulmonary hypertension medication(s), we collected the gestational age; postnatal age and postmenstrual age at first exposure; duration of exposure during hospitalisation; and frequency of use at any time during hospitalisation, at discharge home, and at death during hospitalisation.

Statistical analysis

We used frequencies (with percentages) and medians (with 25^{th} and 75^{th} percentiles) to describe categorical and continuous study variables, respectively. We compared the distribution of clinical variables between infants receiving monotherapy versus combination PH therapy using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Additionally, we reported the following drug utilisation characteristics for each individual and combination pulmonary hypertension medication: gestational age of infants exposed to medication; postnatal age and postmenstrual age at first exposure; duration of exposure; and frequency of use at any time during hospitalisation, at discharge home, and at death during hospitalisation. We graphically represented the progression of individual and combination use over time using line graphs, stacked area graphs, and Alluvial diagrams.[13]

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We conducted three separate subgroup analyses on drug utilisation characteristics by focusing on infants with BPD, CHD, or CDH. Our aim was to identify any specific practice patterns with respect to pulmonary hypertension therapy within these particular subgroups.

We defined statistical significance as a p-value < 0.05. We performed all statistical analyses using Stata 17.0 (StataCorp, College Station, Texas).

Results

Infant characteristics

We identified 7681 infants that met the study inclusion and exclusion criteria (Supplementary Figure S1). These infants had a median gestational age of 31 (25^{th}, 75^{th} percentile: 25, 37) weeks and a median birth weight of 1557 (730, 3033) grams. Of these infants, 2883 (38%) were diagnosed with bronchopulmonary dysplasia, 1144 (15%) had CHD, 4543 (59%) had a patent ductus arteriosus, 5978 (78%) experienced persistent pulmonary hypertension of the newborn, 791 (10%) had at least one lung anomaly, 291 (4%) were born with congenital diaphragmatic hernia, and 3959 (52%) infants were exposed to prenatal steroids. At total of 5836 (76%) infants in our cohort survived to discharge.

Of the infants in our study cohort, 664 (9%) received simultaneous combination therapy at some point during their hospitalisation (Table 1). These infants were smaller and less mature compared to those receiving monotherapy, with a median gestational age of 28 (25, 37) versus 31 (26, 37) weeks ($p < 0.001$) and median birth weight of 1016 (590, 2760) versus 1610 (750, 3055) grams ($p < 0.001$), respectively; and had a higher in-hospital mortality rate [268 (40%) vs. 1577 (22%), $p < 0.001$].

Treatment or support before pulmonary hypertension medication exposure

Before an infant's first pulmonary hypertension medication exposure, 2010 (26%) were exposed to at least one inotrope, 1253 (16%) received at least one diuretic, and 1203 (16%) received postnatal steroids. Mechanical ventilation was required in 4192 (55%) infants, 6794 (88%) needed oxygen therapy with a median fraction of inspired oxygen content of 75% (40, 100), 38 (< 1%) received a tracheostomy, and 19 (< 1%) required extracorporeal membrane oxygenation before the first pulmonary hypertension medication exposure.

Infants receiving combination therapy at any point during their hospitalization were more likelyto be exposed to diuretics and inotropes, require respiratory support with mechanical ventilation for alonger duration and higher number of oxygen days, receive a tracheostomy, and require extracorporealmembrane oxygenation before an infant's first exposure to a pulmonary hypertension medication (Supplementary Table S2).

Pulmonary hypertension medication utilization

Among all infants in the Pediatrix database, the prevalence of exposure to any of the four pulmonary hypertension medications increased from 1997 to 2020 (Figure 1). Inhaled nitric oxide utilisation increased from 0.06% in 1997 to 0.84% in 2020; sildenafil was first used in 2003 and increased in prevalence from 0.01% to 0.16% in 2020; epoprostenol and bosentan were first used in 2005 and both grew in prevalence from < 0.01% to 0.02% in 2020. Similarly, the prevalence of monotherapy and combination therapy increased over time (Figure 1). Monotherapy increased from 0.06% in 1997 to 0.80% in 2020. We did not observe combination therapy until 2003 and utilisation increased from 0.01% to 0.10% in 2020.

The frequency, gestational age of infants exposed, postnatal age and postmenstrual age at first exposure, duration of therapy, and use at discharge or time of death varied among each pulmonary hypertension medication and any combination of the four medications (Table 2 and Supplementary Table S2). Inhaled nitric oxide was administered to 7270 (95%) infants at some point during their hospitalization, followed by sildenafil [1177 (15%)], epoprostenol [95 (1%)], and bosentan [78 (1%)].

Inhaled nitric oxide and epoprostenol were mainly used in the very and late preterm population [median gestational age of 31 (26, 37) and 36 (29, 38) weeks, respectively] at an early median postnatal age [1 (0, 5) and 4 (1, 28) days, respectively] and for a short median duration [6 (4, 10) and 8 (5, 18) days, respectively]. On the other hand, sildenafil and bosentan were mainly used in the extreme and very preterm population [median gestational age of 27 (25, 36) and 26 (24, 32) weeks, respectively] at a much later median postnatal age [59 (13, 108) and 132 (78, 173) days, respectively] and for a longer median duration [28 (12, 66) and 31 (9, 84) days, respectively] (Table 2 and Figure 2).

Inhaled nitric oxide was mainly used as monotherapy [7104 (98%) with any single use vs. 648 (9%) with any combination use]; sildenafil was utilised as both monotherapy and combination therapy [968 (82%) vs. 631 (54%)]; and epoprostenol [18 (19%) vs. 85 (89%)] and bosentan [6 (8%) vs. 76 (97%)] were mainly used as combination therapy (Table 2). A similar pattern was seen for infants who died on pulmonary hypertension therapy [957 (86%) died on monotherapy vs. 150 (14%) died on combination therapy with inhaled nitric oxide; 119 (45%) vs. 147 (55%) with sildenafil; 4 (16%) vs. 21 (84%) with epoprostenol; and 3 (12%) vs. 23 (88%) with bosentan]. Conversely, only a small number of infants [17 (<1%)] were discharged on combination therapy and all were prescribed sildenafil and bosentan.

Dual therapy with inhaled nitric oxide and sildenafil was the most common combination therapy [599 (8%)], followed by triple therapy with inhaled nitric oxide, sildenafil, bosentan [49 (1%)] (Supplementary Table S2). The most common combination therapy that did not include inhaled nitric oxide was dual therapy with sildenafil and bosentan [33 (1%)]. Only 7 (<1%) infants were exposed to quadruple therapy. Most were extremely or very preterm infants [median gestational age of 28 (26, 38) weeks] and received this therapy at a late postnatal age [94 (53, 173) days] and for a very long median duration of 131 (44, 286) days.

There were between 0 and 6 changes to the pulmonary hypertension medication combinations throughout an infant's neonatal ICU hospitalisation, with the initial and final medication(s) routinely differing from each other (Supplementary Figure S2).

In subgroup analysis, we found that: (1) infants with BPD received iNO at an earlier gestational age as compared to all infants in our main analysis [median gestational age of 26 (24, 30) and 31 (26, 37) weeks, respectively] (Supplementary Table S3), (2) infants with CHD received epoprostenol at a later PNA as compared to all infants in our main analysis [median PNA of 20 (4, 138) and 4 (1, 28) days, respectively] (Supplementary Table S4), and (3) all pulmonary hypertensive medications in infants with CDH were used at term or near-term median gestational ages (Supplementary

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Table 1. Infant characteristics

Characteristic	Monotherapy (n = 7017)	Combination therapy (n = 664)	p -Value
Gestational age (weeks)			
≤ 25	1716 (24)	206 (31)	< 0.001
26–28	1200 (17)	128 (19)	
29–32	860 (12)	74 (11)	
33–36	1033 (15)	69 (10)	
≥ 37	2206 (31)	187 (28)	
Birth weight (g)			
< 1000	2573 (37)	327 (49)	<0.001
1000–1499	818 (12)	54 (8)	
1500–2499	959 (14)	82 (12)	
2500–3499	1715 (24)	148 (22)	
≥ 3500	951 (14)	53 (8)	
Race/ethnicity			
White	3270 (47)	276 (42)	0.01
Black	1597 (23)	164 (25)	
Hispanic	1374 (20)	158 (24)	
Other	426 (6)	33 (5)	
5-minute APGAR score			
0–3	793 (11)	65 (10)	0.008
4–6	1945 (28)	221 (33)	
7–10	4096 (58)	361 (54)	
Male sex	4003 (57)	364 (55)	0.31
Cesarean section	5011 (71)	492 (74)	0.15
SGA	1082 (15)	215 (32)	<0.001
Antenatal steroids	3562 (51)	397 (60)	<0.001
PPHN	5375 (77)	603 (91)	<0.001
Congenital diaphragmatic hernia	211 (3)	80 (12)	<0.001
Lung anomalies *	672 (10)	119 (18)	<0.001
Bronchopulmonary dysplasia	2408 (34)	475 (72)	<0.001
Congenital heart disease	986 (14)	158 (24)	<0.001
Patent ductus arteriosus	4046 (58)	497 (75)	<0.001

Variables presented as frequency (%).
PPHN = persistent pulmonary hypertension of the newborn; SGA = small for gestationalage.
* Cystic lung disease; lobar emphysema; pulmonary agenesis, sequestration, & lung hypoplasia.

Table S5). All other drug utilisation characteristics, including duration of use and frequency of use were similar between all infants in the main analysis and infants in each subgroup analysis.

Discussion

In this large multi-center observational study, we described the use of combination pulmonary hypertension drug exposure in a cohort of critically ill infants discharged from the NICU. We found that utilisation of monotherapy and combination treatment for all medications increased over time, with inhaled nitric oxide and sildenafil most used individually and concurrently. Infants exposed to combination therapy were smaller and less mature, had more cardiopulmonary disease, and were more likely to receive cardiorespiratory support than infants receiving only monotherapy. This pattern suggests that infants with greater illness severity were higher utilisers of combination therapy. The drug utilisation characteristics for each combination of medications varied substantially. Most infants experienced numerous changes in their treatment regimen, with initial and final medication combinations frequently differing. These findings suggest a need for more clarity regarding the appropriate combination of

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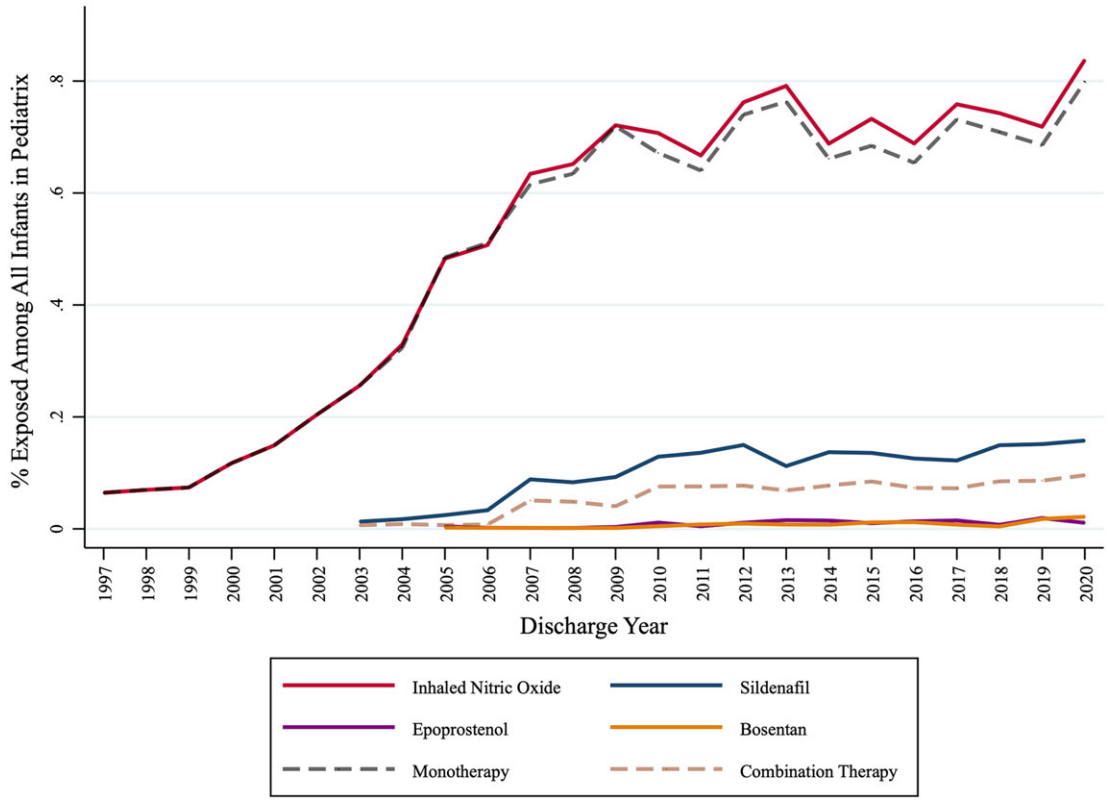

Figure 1. Prevalence of pulmonary hypertension medication exposure by discharge year among all infants in the pediatrix database.

pulmonary hypertension medications, the optimal sequence of their use, and the specific clinical phenotypes for which they should be employed.

The aetiology of pulmonary hypertension in infants is multifactorial, attributable to variations in pathophysiology, clinical presentation, and comorbidities.[5] It can be categorised into numerous types, including but not limited to persistent pulmonary hypertension of the newborn, bronchopulmonary dysplasia-associated pulmonary hypertension, and CHD-associated pulmonary hypertension.[6] Each of these clinical phenotypes can present at different postnatal ages with variable severity and disruptions in pulmonary vascular signalling pathways, which can have distinct implications for clinical management. Remodelling of the pulmonary vasculature in pulmonary hypertension can be attributed to the breakdown of one of the following signalling pathways: nitric oxide-cGMP, prostacyclin-cAMP, and endothelin receptor.[14] The main drugs for pulmonary hypertension aim to address perturbations in these pathways. Inhaled nitric oxide and phosphodiesterase-5 inhibitors, such as sildenafil, increase cGMP levels and cause vasodilation of the pulmonary vasculature. Prostacyclins, such as epoprostenol, initiate vasodilation by increasing cAMP levels and inhibiting pulmonary artery smooth muscle cell proliferation. Endothelin receptor antagonists, such as bosentan, augment pulmonary vasodilation by inhibiting endothelial-mediated vasoconstriction.

Despite these various therapies, only inhaled nitric oxide has gained Food and Drug Administration (FDA) approval as a pulmonary vasodilator in infants. However, this approval is limited to term and near-term infants with persistent pulmonary hypertension of the newborn.[15] Regardless, off-label use of inhaled nitric oxide in infants has become widespread for treating multiple phenotypes of pulmonary hypertension or preventing the development of bronchopulmonary dysplasia.[16] Our findings affirm this use based on the following observations: (1) it was the most commonly administered therapy with 95% of infants receiving it, (2) its use increased almost 15-fold over the past two decades, (3) it was mainly used early and for a short duration, in line with its FDA approved indication, and (4) it was used in a wide range of gestational ages. These characteristics are consistent with prior multicenter epidemiologic evaluations of inhaled nitric oxide in infants.[17]

We found that sildenafil was the second most frequently used pulmonary hypertension therapy, administered to 15% of infants, with a similar increase in utilisation as inhaled nitric oxide during our study. These infants were almost exclusively premature yet usually received sildenafil at near-term or term postmenstrual ages and for a median duration of nearly one month. This is consistent with current recommendations and off-label use of sildenafil as treatment for bronchopulmonary dysplasia-associated pulmonary hypertension and as adjuvant therapy to inhaled nitric oxide in premature infants with persistent pulmonary hypertension of the newborn.[18,19]

Similar to sildenafil, bosentan was solely used in preterm infants, at post-term postmenstrual ages, and for a median duration of approximately one month. This is despite bosentan only being FDA-approved in 2017 for treating specific types of pulmonary hypertension in children > 3 years of age.[20] These characteristics of bosentan use in our cohort are consistent with reports and guidelines mentioning endothelin receptor antagonists as a potentially beneficial therapy for bronchopulmonary dysplasia-associated pulmonary hypertension and late or refractory persistent pulmonary hypertension of the newborn.[21]

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Table 2. Any pulmonary hypertension medication use

Characteristic	iNO (n = 7270)	Sildenafil (n = 1177)	Epoprostenol (n = 95)	Bosentan (n = 78)
Gestational age (weeks)	31 (26, 37)	27 (25, 36)	36 (29, 38)	26 (24, 32)
PNA at first exposure (days)	1 (0, 5)	59 (13, 108)	4 (1, 28)	132 (78, 173)
PMA at first exposure (weeks)	33 (27, 38)	39 (36, 42)	38 (35, 40)	46 (42, 50)
Duration of use (days)	6 (4, 10)	28 (12, 66)	8 (5, 18)	31 (9, 84)
Frequency of use				
Any single use	7104 (98)	968 (82)	18 (19)	6 (8)
Any combination use	648 (9)	631 (54)	85 (89)	76 (97)
At discharge	0 (0)	454 (39)	0 (0)	17 (22)
In isolation	0 (0)	437 (96)	0 (0)	0 (0)
In combination	0 (0)	17 (4)	0 (0)	17 (100)
At death	1107 (15)	266 (23)	25 (26)	26 (33)
In isolation	957 (86)	119 (45)	4 (16)	3 (12)
In combination	150 (14)	147 (55)	21 (84)	23 (88)

Continuousand categorical variables presented as median (25th, 75th percentile) andfrequency (%), respectively.
iNO = inhaled nitric oxide; PNA = postnatal age; PMA = postmenstrual age.

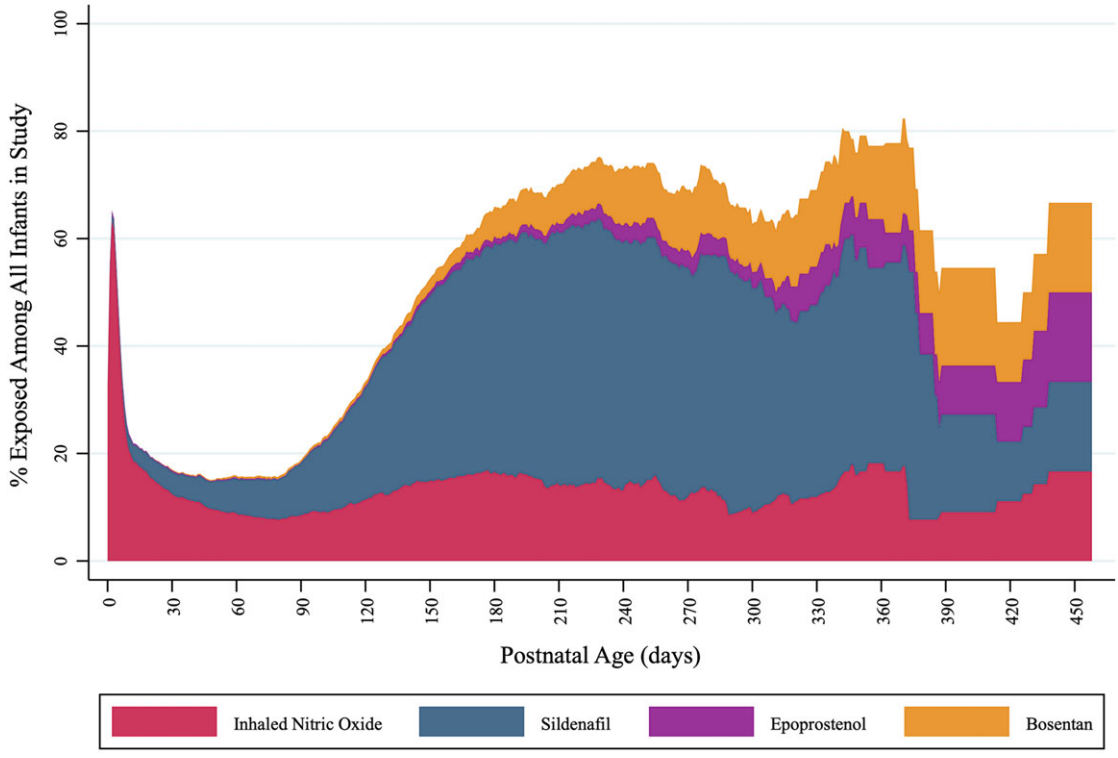

Figure 2. Proportion exposed to pulmonary hypertension medications by postnatal age among all infants included our study.

In our study, epoprostenol had a similar drug utilisation profile to inhaled nitric oxide: early exposure, short duration of therapy, and use in near-term and term infants – characteristics congruent to infants having persistent pulmonary hypertension of the newborn. Although there is limited data about the use of prostacyclin analougs in infants, a handful of reports demonstrate clinical improvements in near-term or term infants with persistent pulmonary hypertension of the newborn.[22] However, there are also several reports showing prostacyclin use for severe bronchopulmonary dysplasia-associated pulmonary hypertension and

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persistent pulmonary hypertension of the newborn that is refractory to other interventions.[23] The characteristics exhibited by these infants do not align with those observed in our cohort receiving epoprostenol monotherapy, emphasising the importance of defining clinical phenotypes that would benefit from each pulmonary hypertension therapy.

Adult guidelines have described clinical phenotypes amenable to specific therapeutic targets at different points along the natural history of pulmonary hypertension.[24] This has led to several studies demonstrating that combination therapy can improve clinical outcomes through additive or synergistic effects.[25] Similar phenotype-driven studies are lacking in infants and children, with only a handful of studies available on combination therapy.[26] This is even though combination therapy has increased 10-fold over the last two decades in our study.

Our study found that concurrent utilisation of inhaled nitric oxide with other pulmonary vasodilators was the most common in hospitalised infants, especially dual or triple therapy with enteral medications such as sildenafil and bosentan. It is important to note that these exposures typically took place at term or post-term postmenstrual ages and for relatively brief periods. This short overlap is common practice in facilitating the weaning of inhaled nitric oxide and transition to enteral medications in critically ill infants.[27]

We also observed that sildenafil was used frequently in combination with drugs other than inhaled nitric oxide, with the most frequent being bosentan. These infants were exclusively premature and received therapy at a later age and longer duration than treatment with sildenafil alone. All infants discharged home on combination therapy in our study received both medications. This was also recently demonstrated in a single-center randomised controlled trial of 40 infants with high-risk pulmonary hypertension receiving dual therapy with sildenafil and bosentan compared to sildenafil alone, which showed decreased pulmonary arterial pressures.[28] This is similarly consistent with adult studies demonstrating that dual therapy with a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist is the most effective and widely utilised combination for pulmonary hypertension.[29]

In our study, both bosentan and epoprostenol were primarily used as combination therapy with other pulmonary vasodilators, yet never together as dual therapy. This is even though combination therapy with prostacyclins and endothelin receptor antagonists has increased in frequency in children and adults.[30] Additionally, we observed that any dual or triple therapy regimen involving epoprostenol occurred early during an infant's hospitalisation and generally for less than one week. There are rare reports of intravenous prostacyclin used in combination therapy in infants with pulmonary hypertension, but all similarly involve early and brief treatment of severe persistent pulmonary hypertension of the newborn.[31] Various factors may contribute to the limited use of concurrent therapy with prostacyclins in infants, including the absence of easy and non-invasive administration methods, the short duration of their effectiveness, and the severe hemodynamic side effects if not closely monitored and adjusted.[6]

In adults, there is growing evidence from randomised controlled trials that triple therapy targeting each pathogenic pulmonary hypertension signalling pathway provides optimal disease control and improved long-term outcomes, especially in severe disease phenotypes.[25] A recent single-center retrospective observational study of 21 children with severe pulmonary hypertension who received upfront triple combination therapy with sildenafil, bosentan, and a prostacyclin found improved 3-year transplant-free survival rates of almost 90%.[32] Unfortunately, reports of triple therapy are limited in infants with pulmonary hypertension.[33] Our study revealed that triple or quadruple therapy was rare, as only 1% of infants in our cohort were treated with this approach. Further, drug utilisation characteristics did not follow any discernible pattern and varied substantially depending on the combination of medications used.

The strengths of our study include (1) a large sample size, (2) a multi-center study, (3) a long study period, (4) granular drug utilisation data, and (5) the ability to follow infants' medication regimen throughout their hospitalisation. With over 7500 infants included in our study, this is the largest observational cohort study investigating the use of combination therapy for pulmonary hypertension in critically ill infants. Furthermore, the more than 400 neonatal ICUs included in our study encompass a diverse group of academic and community facilities across North America, enhancing the universality of our results. Our study also included infants over an almost 25-year period, allowing us to track trends of combination and monotherapy use over time. Given the comprehensive information contained within the Pediatrix database, we were able to elucidate detailed drug utilisation characteristics with respect to age, frequency, timing, and duration of exposure for each combination of medications. This information helped us establish a pattern of drug usage and match it with a specific disease phenotype. Finally, given that we could obtain medication data from birth to discharge or death, this allowed us to track and visualise the complex nature of sequential or combination therapy during the natural history of pulmonary hypertension in infants.

This study has several limitations typical of observational cohort studies that rely on a large electronic health record database for administrative purposes. First, medication data is only presented at daily intervals, which precluded us from determining the exact time of day that an infant started, stopped, or transitioned to another medication. This could have overestimated the number of infants included in our study and the duration of exposure to each combination therapy. Second, there is no indication information in the medication data, so we could not ascertain whether prescribed drugs were intended for treating pulmonary hypertension. This hindered our ability to make definitive connections between select combination therapies and distinct pulmonary hypertension phenotypes. Third, our data source does not include information on the route of administration, and therefore we could not delineate differences in practice patterns between intravenous and enteral sildenafil. Fourth, our data source does not include or has limited data on several newer off-label pulmonary hypertension drugs, such as tadalafil, ambrisentan, selexipag, iloprost, and treprostinil. Fifth, we did not have access to data from echocardiograms, cardiac catheterizations, or dependable diagnostic information to precisely ascertain the presence of pulmonary hypertension. This limitation might have led to overestimating infants being treated for pulmonary hypertension, as some of these drugs could be prescribed for hypoxic respiratory failure or other pulmonary-related conditions. Sixth, our study is descriptive and does not adjust for the numerous confounders of illness severity between the combination and monotherapy groups. Therefore, any differences between the two groups should be considered descriptive and not necessarily indicative of the clinical efficacy of combination pulmonary vasodilator therapy. Lastly, we lacked detailed information on hemodynamic data and surgical procedures, including the type and timing of surgeries conducted

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in our CHD infants. It's common for pulmonary hypertension medications like iNO and sildenafil to be prescribed perioperatively for these infants. Considering that CHD infants comprised 15% of our study group, having data on whom and when these vasodilator therapies are administered would be valuable to provide further insights into the utilisation of these medications.

In conclusion, we found a significant increase and wide variation in the deployment of combination pulmonary vasodilator therapies among critically ill infants, with iNO and sildenafil constituting the most prevalent regimen. Additionally, our data found a tendency for iNO and epoprostenol use for younger, full-term infants over shorter durations compared to the use of sildenafil and bosentan. The study illuminates the urgent requirement for tailored research to define the natural progress of distinct clinical phenotypes linked to infantile pulmonary hypertension, develop strategies for identifying the ideal combination of medications for each phenotype, and elucidate the optimal timing, sequence, and dosing that would yield maximum benefits in combination therapy. The findings of our study can help inform the design and implementation of future high-quality prospective studies of combination therapy in infants.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124025976.

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References

1. Steinhorn RH. Neonatal pulmonary hypertension. Pediatr Crit Care Med 2010; 11: S79–84.
2. Roberts JD, Fineman JR, Morin FC et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med 1997; 336: 605–610.
3. Steurer MA, Baer RJ, Oltman S et al. Morbidity of persistent pulmonary hypertension of the newborn in the first year of life. J Pediatr 2019; 213: 58–65.e54.
4. Jain AMcNamara PJ. Persistent pulmonary hypertension of the newborn: advances in diagnosis and treatment. Semin Fetal Neonatal Med 2015; 20: 262–271.
5. Hansmann G. Pulmonary hypertension in infants, children, and young adults. J Am Coll Cardiol 2017; 69: 2551–2569.
6. Fike CD, Aschner JL. Pharmacotherapy for pulmonary hypertension in infants with bronchopulmonary dysplasia: past, present, and future. Pharmaceuticals (Basel) 2023; 16(4): 503.
7. Hilgendorff A, Apitz C, Bonnet D et al. 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: ii49–ii56.
8. Hansmann G, Sallmon H, Roehr CC et al. Pulmonary hypertension in bronchopulmonary dysplasia. Pediatr Res 2021; 89: 446–455.
9. Sharma M, Callan EKonduri GG. Pulmonary vasodilator therapy in persistent pulmonary hypertension of the newborn. Clin Perinatol 2022; 49: 103–125.
10. Filan PM, McDougall PN, Shekerdemian LS. Combination pharmacotherapy for severe neonatal pulmonary hypertension. J Paediatr Child Health 2006; 42: 219–220.
11. Spitzer AR, Ellsbury DL, Handler D et al . The pediatrix babySteps data warehouse and the pediatrix qualitySteps improvement project system–tools for "meaningful use" in continuous quality improvement. Clin Perinatol 2010; 37: 49–70.
12. Trembath A, Hornik CP, Clark R et al. Comparative effectiveness of surfactant preparations in premature infants. J Pediatr 2013; 163: 955–960.e951.
13. Rosvall M, Bergstrom CT, Rapallo F. Mapping change in large networks. PLoS One 2010; 5: e8694.
14. Nees SN, Rosenzweig EB, Cohen JL et al . Targeted therapy for pulmonary hypertension in premature infants. Children (Basel) 2020; 7: 97.
15. Clark RH, Kueser TJ, Walker MW et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. clinical inhaled nitric oxide research group. N Engl J Med 2000; 342: 469–474.
16. Hasan SU, Potenziano J, Konduri GG et al. Effect of inhaled nitric oxide on survival without bronchopulmonary dysplasia in preterm infants: a randomized clinical trial. JAMA Pediatr 2017; 171: 1081–1089.
17. Ellsworth MA, Harris MN, Carey WA et al. Off-label use of inhaled nitric oxide after release of NIH consensus statement. Pediatrics 2015; 135: 643–648.
18. Abman SH, Hansmann G, Archer SL et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015; 132: 2037–2099.
19. Thompson EJ, Perez K, Hornik CP et al. Sildenafil exposure in the neonatal intensive care unit. Am J Perinatol 2019; 36: 262–267.
20. Barst RJ, Ivy D, Dingemanse J et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. Clin Pharmacol Ther 2003; 73: 372–382.
21. Maneenil G, Talek S, Thatrimontrichai A et al. The use of bosentan and sildenafil as rescue therapy in persistent pulmonary hypertension of the newborn: a single center's experience. Prog Pediatr Cardiol 2022; 67: 101575.
22. Verma S, Lumba R, Kazmi SH et al . Effects of inhaled iloprost for the management of persistent pulmonary hypertension of the newborn. Am J Perinatol 2022; 39: 1441–1448.
23. Ferdman DJ, Rosenzweig EB, Zuckerman WA et al. Subcutaneous treprostinil for pulmonary hypertension in chronic lung disease of infancy. Pediatrics 2014; 134: e274–278.
24. Dweik RA, Rounds S, Erzurum SC et al. An official American Thoracic Society Statement: pulmonary hypertension phenotypes. Am J Respir Crit Care Med 2014; 189: 345–355.
25. Sitbon O, Gaine S. Beyond a single pathway: combination therapy in pulmonary arterial hypertension. Eur Respir Rev 2016; 25: 408–417.
26. Steffes LC, Austin ED. Upfront combination therapy: growing the case to get ahead of pediatric pulmonary arterial hypertension. Ann Am Thorac Soc 2022; 19: 163–165.
27. Hussain WA, Bondi DS, Shah P et al. Implementation of an inhaled nitric oxide weaning protocol and stewardship in a Level 4 NICU to decrease inappropriate use. J Pediatr Pharmacol Ther 2022; 27: 284–291.
28. Vijay Kumar JR, Natraj Setty HS, Jayaranganath M et al. Efficacy, safety and tolerability of bosentan as an adjuvant to sildenafil and sildenafil alone in persistant pulmonary hypertension of newborn (PPHN). Interv Med Appl Sci 2021; 11: 216–220.
29. Dardi F, Manes A, Palazzini M et al. Combining bosentan and sildenafil in pulmonary arterial hypertension patients failing monotherapy: real-world insights. Eur Respir J 2015; 46: 414–421.

30. Douwes JM, Zijlstra WMH, Rosenzweig EB et al. Parenteral prostanoids in pediatric pulmonary arterial hypertension: start early, dose high, combine. Ann Am Thorac Soc 2022; 19: 227–237.
31. Kinugasa H, Horigome H, Sugiura M et al. Intravenous prostacyclin combined with inhaled nitric oxide therapy for an infant with alveolar capillary dysplasia. Pediatr Int 2002; 44: 525–527.
32. Haarman MG, Lévy M, Roofthooft MTR et al. Upfront triple combination therapy in severe paediatric pulmonary arterial hypertension. Eur Respir J 2021; 57: 57.
33. Radicioni M, Bruni A, Camerini P. Combination therapy for life-threatening pulmonary hypertension in a premature infant: first report on bosentan use. Eur J Pediatr 2011; 170: 1075–1078.

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