Updates on Inhaled Nitric Oxide, Sildenafil and Milrinone.
Reese H. Clark, MD
Vice President of Clinical Research
MEDNAX

Etiology and pathophysiology of persistent pulmonary hypertension of the newborn (PPHN).
Satyan Lakshminrusimha, and Martin Keszler Neoreviews 2015;16:e680-e692
Etiology and pathophysiology of persistent pulmonary hypertension of the newborn (PPHN).

Report of Use of Pulmonary Vasodilators in the NICU. No Filters. Percent of All Infants Discharged from MEDNAX NICUs
INHALED NITRIC OXIDE

Distribution of Use of iNO by EGA Over Time

Year

Percent of Total Patient Treated
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Percent of Infants Treated with iNO by EGA
Based on Data from CDW (2017 and 2018)

Does iNO promote better survival in infants with RDS or RDS with pulmonary hypertension?
We queried the Pediatrix Medical Group Clinical Data Warehouse to identify all neonates born at 22 to 29 weeks' gestation from 2004 to 2014.

In our study sample, we included singletons who required mechanical ventilation for treatment of RDS and excluded those with anomalies. The primary outcome was death before discharge. Through a sequential risk set approach, each patient who received iNO during the first 7 days of life ("case patient") was matched by using propensity scores to a patient who had not received iNO at a chronological age before the case patient's iNO initiation age (defined as the index age for the matched pair).

Among 37,909 neonates in our study sample, we identified 993 (2.6%) who received iNO. The 2 matched cohorts each contained 971 patients.

We did not observe a significant association between iNO exposure and mortality (hazard ratio, 1.08; 95% confidence interval, 0.94-1.25; P = .29).

Overall survival by iNO status of patients in the matched cohort.
Overall survival by iNO status of (A) patients in the matched cohort with RDS and PPHN and (B) patients in the matched cohort with RDS.

Surprisingly, iNO exposure was associated with higher mortality among neonates whose RDS was not accompanied by PPHN.

DOES EARLY TREATMENT WITH INHALED NITRIC OXIDE IMPROVE SURVIVAL IN EXTREMELY PRETERM NEONATES DIAGNOSED WITH PULMONARY HYPOPLASIA?
This cohort study used data from the Pediatrix Medical Group's Clinical Data Warehouse. Since iNO was not randomly prescribed, we used *1-to-1 propensity score matching to reduce the imbalance of measured covariates between the 2 treatment groups.*

The initial, unmatched cohort included singleton neonates who were born *between 22 and 29 weeks' gestation, had a birth weight of 400 g or more, were diagnosed with pulmonary hypoplasia as a cause of their respiratory distress, remained free of major anomalies, and were discharged between January 1, 2000, and December 31, 2014.*

We defined exposure as the initiation of iNO on day t in days 0 to 7 of the life of a neonate. Each exposed neonate was matched 1-to-1 to a neonate who had not initiated iNO on a given day.

Among 92635 neonates in our study sample, *we identified 767 (0.8%) with pulmonary hypoplasia* who met all study inclusion criteria, of whom *185 (24%) were exposed to iNO.*

Among 151 matched pairs of exposed and unexposed neonates, we did not identify a significant association between iNO use and mortality (hazard ratio [HR], 0.79; 95% CI, 0.57-1.11).

Subgroup analyses of neonates with and without persistent pulmonary hypertension (PPHN) likewise revealed no significant association between iNO use and mortality (pulmonary hypoplasia with PPHN: HR, 0.67; 95% CI, 0.45-1.01; pulmonary hypoplasia without PPHN: HR, 1.11; 95% CI, 0.61-2.02), but these findings may have been influenced by ascertainment bias.
DOES TREATMENT WITH INHALED NITRIC OXIDE IMPROVE SURVIVAL WITHOUT CHRONIC LUNG DISEASE IN PREMATURE INFANTS.

- Randomized clinical trial performed at 33 US and Canadian neonatal intensive care units. Participants included 451 neonates younger than 30 weeks’ gestation with birth weight less than 1250 g receiving mechanical ventilation or positive pressure respiratory support on postnatal days 5 to 14.
- Enrollment spanned from December 23, 2009, to April 23, 2012, and neurodevelopmental outcome studies were completed by April 4, 2014.
- Interventions: Placebo (nitrogen) or iNO initiated at 20 ppm was decreased to 10 ppm between 72 and 96 hours after starting treatment and then to 5 ppm on day 10 or 11. Infants remained on the 5-ppm dose until completion of therapy (24 days).

222 infants received placebo, and 229 infants received iNO.

- Survival without BPD at 36 weeks’ PMA was similar between the placebo and iNO groups (31.5% vs 34.9%) (odds ratio, 1.17; 95% CI, 0.79-1.73).
- Rates for severe BPD (26.6% vs 20.5%) and postnatal corticosteroid use for BPD (41.0% vs 41.5%) and the mean (SD) days of positive pressure respiratory support (55 [40] vs 54 [42]), oxygen therapy (88 [41] vs 91 [59]), and hospitalization (105 [37] vs 108 [54]) were similar between the 2 groups.
- Respiratory outcomes on discharge, at 1 year, and at age 18 to 24 months’ PMA and neurodevelopmental assessments at 18 to 24 months’ PMA did not differ.
- iNO, initiated at 20 ppm on postnatal days 5 to 14 to high-risk preterm infants and continued for 24 days, appears to be safe but did not improve survival without BPD at 36 weeks’ PMA or respiratory and neurodevelopmental outcomes at 18 to 24 months’ PMA.

- An individual participant data meta-analysis was conducted, including 3 randomized, placebo-controlled trials that enrolled infants born at <34 weeks of gestation receiving respiratory support, had at least 15% (or a minimum of 10 infants in each trial arm) of African American race, and used a starting iNO of >5 parts per million with the intention to treat for 7 days minimum.
- The primary outcome was a composite of death or BPD.
- Secondary outcomes included death before discharge, postnatal steroid use, gross pulmonary air leak, pulmonary hemorrhage, measures of respiratory support, and duration of hospital stay.
- Compared with other races, African American infants had a significant reduction in the composite outcome of death or BPD with iNO treatment: 40% treated vs 63% controls (relative risk, 0.77; 95% CI, 0.65-0.91; P = .003; interaction P = .016). There were no differences between racial groups for death.
- There was also a significant difference between races (interaction P = .023) of iNO treatment for BPD in survivors, with the greatest effect in African American infants (P = .005). There was no difference between racial groups in the use of postnatal steroids, pulmonary air leak, pulmonary hemorrhage, or other measures of respiratory support.
- *iNO therapy should be considered for preterm African American infants at high risk for BPD. iNO to prevent BPD in African Americans may represent an example of a racially customized therapy for infants.*

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**Table: Outcome and Race/Ethnicity**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Race/Ethnicity</th>
<th>Inhaled iNO n/N</th>
<th>Placebo n/N</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or BPD at 36 weeks FMAA</td>
<td>White, not Hispanic</td>
<td>21 (33%)</td>
<td>15 (24%)</td>
<td>0.59 (0.39-0.91)</td>
<td>0.378</td>
<td>0.114</td>
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<tr>
<td>Hispanic</td>
<td>4 (6.5%)</td>
<td>6 (10%)</td>
<td>0.85 (0.44-1.63)</td>
<td>0.736</td>
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</tr>
<tr>
<td>African American</td>
<td>6 (9.0%)</td>
<td>14 (23%)</td>
<td>0.77 (0.45-1.19)</td>
<td>0.205</td>
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</tr>
<tr>
<td>Other</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>0.83 (0.99-1.02)</td>
<td>0.115</td>
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<tr>
<td>Interaction P-value = .036</td>
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<tr>
<td>Overall</td>
<td>31 (52%)</td>
<td>26 (42%)</td>
<td>0.96 (0.83-1.12)</td>
<td>0.645</td>
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<th>RR (95% CI)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Death at any time</td>
<td>White, not Hispanic</td>
<td>21 (33%)</td>
<td>15 (24%)</td>
<td>1.33 (0.63-2.83)</td>
<td>0.361</td>
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<tr>
<td>Hispanic</td>
<td>5 (7.8%)</td>
<td>12 (19%)</td>
<td>0.99 (0.38-2.84)</td>
<td>0.936</td>
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</tr>
<tr>
<td>African American</td>
<td>1 (1.5%)</td>
<td>5 (8.0%)</td>
<td>0.88 (0.28-2.98)</td>
<td>0.913</td>
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<tr>
<td>Other</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>1.00 (0.12-8.73)</td>
<td>0.997</td>
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<tr>
<td>Interaction P-value = .034</td>
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<tr>
<td>Overall</td>
<td>37 (62.0%)</td>
<td>29 (46.8%)</td>
<td>0.98 (0.83-1.13)</td>
<td>0.577</td>
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<th>Placebo n/N</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Death at 36 weeks FMAA</td>
<td>White, not Hispanic</td>
<td>25 (40%)</td>
<td>11 (17%)</td>
<td>1.46 (0.95-2.26)</td>
<td>0.094</td>
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<tr>
<td>Hispanic</td>
<td>5 (7.8%)</td>
<td>11 (17%)</td>
<td>1.00 (0.38-2.84)</td>
<td>0.936</td>
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</tr>
<tr>
<td>African American</td>
<td>1 (1.5%)</td>
<td>5 (8.0%)</td>
<td>0.88 (0.28-2.98)</td>
<td>0.913</td>
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<tr>
<td>Other</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>1.00 (0.12-8.73)</td>
<td>0.997</td>
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<td>Overall</td>
<td>49 (82.0%)</td>
<td>33 (53.8%)</td>
<td>0.92 (0.84-1.01)</td>
<td>0.034</td>
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</table>

**Table: Outcome and Race/Ethnicity**

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<tr>
<th>Outcome</th>
<th>Race/Ethnicity</th>
<th>Inhaled iNO n/N</th>
<th>Placebo n/N</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>BPD at any time</td>
<td>White, not Hispanic</td>
<td>19 (31%)</td>
<td>15 (24%)</td>
<td>0.99 (0.83-1.03)</td>
<td>0.735</td>
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<tr>
<td>Hispanic</td>
<td>4 (6.1%)</td>
<td>5 (8.0%)</td>
<td>0.99 (0.38-2.84)</td>
<td>0.936</td>
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<tr>
<td>African American</td>
<td>18 (28.1%)</td>
<td>11 (17%)</td>
<td>0.88 (0.28-2.98)</td>
<td>0.913</td>
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<tr>
<td>Other</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>1.00 (0.12-8.73)</td>
<td>0.997</td>
<td></td>
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<tr>
<td>Interaction P-value = .233</td>
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</tr>
<tr>
<td>Overall</td>
<td>33 (55%)</td>
<td>26 (42%)</td>
<td>0.99 (0.83-1.03)</td>
<td>0.156</td>
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Does iNO Reduce The Need For ECMO In Infants With CDH?


• Pediatric Health Information System data were queried for newborns with CDH admitted at <8 days of age at tertiary care US pediatric hospitals between 2003 and 2011. iNO treatment status and timing in relation to CDH repair were determined for each infant. Hospital-specific rates of iNO use, extracorporeal membrane oxygenation (ECMO) use, and mortality were determined.

• Data were analyzed for 1713 neonates with CDH admitted to 33 hospitals.

• More than half (57%) received iNO during their inpatient stay, and utilization varied dramatically between hospitals (34% to 92%).

• Neonates treated with iNO accumulated >$81 million in pharmacy charges.

• The proportion of infants receiving iNO as well as their duration of therapy increased significantly during the study period.

• The rate of ECMO utilization and mortality did not change significantly during the study period. Hospital-specific mortality rates did not correlate with iNO therapy, ECMO utilization, or case volume.


Relationship between mortality and rate of CDH repair (A), mortality and nitric oxide use (B), and ECMO use and nitric oxide use (C) among infants with CDH at 33 PHIS hospitals, 2003 to 2011.


- 17 randomised controlled trials of iNO therapy in preterm infants.
- We grouped these trials post hoc into three categories on the basis of entry criteria: treatment during the first three days of life for impaired oxygenation, routine use in preterm babies along with respiratory support and later treatment for infants at increased risk for bronchopulmonary dysplasia (BPD).
- Eight trials providing early rescue treatment for infants on the basis of oxygenation criteria demonstrated no significant effect of iNO on mortality or BPD (typical risk ratio (RR) 0.94, 95% confidence interval (CI) 0.87 to 1.01; 958 infants).
- Four studies examining routine use of iNO in infants with pulmonary disease reported no significant reduction in death or BPD (typical RR 0.94, 95% CI 0.87 to 1.02; 1924 infants), although this small effect approached significance.
- Later treatment with iNO based on risk of BPD (three trials) revealed no significant benefit for this outcome in analyses of summary data (typical RR 0.92, 95% CI 0.85 to 1.01; 1075 infants).
- Investigators found no clear effect of iNO on the frequency of all grades of IVH nor severe IVH. Early rescue treatment was associated with a non-significant 20% increase in severe IVH. We found no effect on the incidence of neurodevelopmental impairment.

Authors conclusions

- iNO does not appear to be effective as rescue therapy for the very ill preterm infant.
- Early routine use of iNO in preterm infants with respiratory disease does not prevent serious brain injury or improve survival without BPD.
- Later use of iNO to prevent BPD could be effective, but current 95% confidence intervals include no effect; the effect size is likely small (RR 0.92) and requires further study.


- iNO appears to have improved outcomes in hypoxaemic term and near-term infants by reducing the incidence of the combined endpoint of death or use of ECMO (high-quality evidence).
- This reduction was due to a reduction in use of ECMO (with number needed to treat for an additional beneficial outcome (NNTB) of 5.3); mortality was not affected.
- Whether infants had clear echocardiographic evidence of persistent pulmonary hypertension of the newborn (PPHN) did not appear to affect response to iNO.
- Outcomes of infants with diaphragmatic hernia were not improved; outcomes were slightly, but not significantly, worse with iNO (moderate-quality evidence).
- Fewer of the babies who received iNO early satisfied late treatment criteria, showing that earlier iNO reduced progression of the disease but did not further decrease mortality nor the need for ECMO (moderate-quality evidence).
- Incidence of disability, incidence of deafness and infant development scores were all similar between tested survivors who received iNO and those who did not.

• iNO therapy should not be used in premature infants for the prevention of BPD, as multicenter studies data have failed to consistently demonstrate efficacy for this purpose;
• iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios;
• iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention; and
• Placebo controlled trials are not feasible in the target population; therefore, alternate study designs such as the development of multicenter registries, informatics strategies, and other approaches should be used to address issues regarding the efficacy and safety of therapeutic options for preterm infants with life threatening PPHN physiology.

MILRINONE

- Milrinone is a bipyridine derivative that inhibits phosphodiesterase type III on cAMP degradation leading to increased intracellular calcium concentration. It is named as an inodilator because of intracellular calcemic actions in cardiac myocytes (improved contractility) and vascular smooth cells (vasodilation, both systemic and pulmonary).
- Milrinone is excreted by the kidneys with little or no metabolism (67), therefore, plasma concentration largely depends on renal function.


- We conducted a retrospective data analysis, identifying all infants who were exposed to milrinone and discharged from 322 neonatal intensive care units managed by the Pediatrix Medical Group from 1997-2010.
- We identified adverse events (AEs) during milrinone exposure. The unit of observation for clinical AEs was the first course of milrinone and for laboratory AEs it was an infant-day of exposure to milrinone. RESULTS: Overall, 1446 of 716,821 (0.2%) infants received milrinone for a total of 6894 infant-days.
- The proportion of infants exposed to milrinone increased from 0 in 1997 to 4/1000 infant cases in 2010.
- Persistent pulmonary hypertension (40%) was the most commonly reported diagnosis at the start of milrinone administration.
- Overall, 606/1446 (42%) of infants had at least 1 clinical AE recorded during milrinone therapy.
- Hypotension requiring pressors and thrombocytopenia (<100,000/mm^3)) were the most commonly reported clinical and laboratory AEs, respectively.
- Death was reported in 8% of infants during the first course of milrinone therapy.

- To describe the pharmacokinetics and pharmacodynamics of milrinone in infants with persistent pulmonary hypertension of the newborn (PPHN) and to explore the impact of age on milrinone disposition.
- Randomized, open label pilot study.
- *Six infants >34 weeks’ gestational age and <10 days of life with persistent hypoxemia receiving iNO.*

  Intervention Intravenous milrinone lactate in one of two dosing regimens: (1) low dose, 20 mcg/kg bolus followed by 0.2 mcg/kg/minute, and (2) standard dose, 50 mcg/kg bolus followed by 0.5 mcg/kg/minute.

- The final structural model was a two-compartment disposition model with interindividual variability estimated on clearance (CL). The estimated value of CL is 7.65 mL/minute/3.4 kg (3.05 mL/minute/kg). The addition of age improved the precision of the CL estimate, and CL increased with chronological age in days. The oxygenation index was highly variable within each participant and improved with time.
- *The CL of milrinone in newborns with PPHN is reduced and increases with age.*

- Data on pulmonary vasodilator management and outcome of CDH patients was collected from 18 university NICUs affiliated with the Neonatal Research Network (NRN) from 2011 to 2012.
- The proposed pilot will be a masked, placebo-controlled, multicenter, randomized trial of 66 infants with CDH with an oxygenation index (OI) ≥10 or oxygen saturation index (OSI) ≥5.
- Three hundred thirty-seven infants with CDH were admitted to NRN NICUs in 2011 and 2012 of which 275 were ≥36 weeks PMA and were exposed to the following pulmonary vasodilators: inhaled (INO) (39%), sildenafil (17%), milrinone (17%), inhaled epoprostenol (6%), intravenous epoprostenol (3%), and intravenous PGE1 (1%). ECMO was required in 36% of patients. Survival to discharge was 71%.


- Double-blind randomized placebo controlled trial of milrinone (loading dose 0.75 microg/kg/min for 3 hours then maintenance 0.2 microg/kg/min until 18 hours after birth) versus placebo.
- Infants born <30 weeks gestational age and <6 hours of age were eligible and were monitored with serial echocardiography, head ultrasound scanning, and continuous invasive blood pressure.
- Primary outcome was maintenance of superior vena cava (SVC) flow > or =45 mL/kg/min through the first 24 hours.
- The exit criterion was hypotension unresponsive to volume and inotropes.
- Ninety infants were enrolled, equal proportions maintained SVC flow > or =45 mL/kg/min after treatment commenced. No significant difference was observed in SVC flow, right ventricular output, and blood pressure during the first 24 hours; or grades 3 to 4 periventricular/intraventricular hemorrhage and death. Heart rate was higher and constriction of the ductus was slower in the infants randomized to milrinone.
- Milrinone did not prevent low systemic blood flow during the first 24 hours in very preterm infants, and no adverse effects were attributable to milrinone. Use of a preventative treatment with rescue model allowed comparison of an inotrope with placebo in this high-risk group of infants.
Figure


• Retrospective chart review was performed of all CDH infants admitted to two regional perinatal centers and infants classified into three groups: No-iNO group; iNO-responders and iNO-nonresponders.
• Oxygenation and hemodynamic effects of iNO and milrinone were assessed by blood gases and echocardiography.
• Fifty-four percent (39/72) of infants with CDH received iNO and 31% of these infants (12/39) had complete oxygenation response to iNO.
• **Oxygenation response to iNO was not associated with a decrease in right ventricular pressures (RVP) or ECMO use.**
• Four infants (33%) in the iNO-responder group and eight infants (30%) in the iNO-nonresponder group received milrinone.
• **Milrinone lowered RVP and improved ejection fraction (EF).**
• **Response to iNO was associated with improved oxygenation to milrinone and increased survival following ECMO (67 vs. 20% among nonresponders).**

- Searched for citations related to sildenafil use in term or near-term infants with pulmonary hypertension or premature infants at risk for BPD or with BPD-associated pulmonary hypertension.
- Five trials (4 full-text articles and 1 abstract) of the 802 screened citations met the criteria for inclusion. All 5 trials were randomized controlled trials; the largest had 51 participants.
- Four of the trials (with a total of 137 subjects) evaluated the use of sildenafil versus placebo for term or near-term infants with persistent pulmonary hypertension of the newborn in low-resource settings in which iNO was unavailable; there were no trials of sildenafil in areas in which iNO is routinely available. The trials showed improvements in oxygenation index and a reduction in mortality in the sildenafil groups (5.9% vs 44%).
- One trial evaluated early sildenafil use (after day 7 of life) in premature infants for the prevention of BPD (n = 20).
- More premature infants in the sildenafil group died, were exposed to postnatal steroids, and had higher right-sided ventricular pressures later during hospitalization; these differences were not statistically significant. No trials evaluated sildenafil versus placebo in premature infants with BPD-associated pulmonary hypertension.
- There is currently little evidence to support the use of sildenafil in term or near-term infants with persistent pulmonary hypertension of the newborn in areas in which iNO is available.

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


- Retrospective cohort study used data from the Pediatric Health Information System to determine variables associated with sildenafil exposure and between-hospital variations in sildenafil utilization patterns. The study included infants with BPD-PH who were discharged between January 1, 2006, and December 31, 2013.
- Within 36 US pediatric hospitals, 3720 infants were diagnosed with BPD, of whom 598 (16%) also had a diagnosis of PH (BPD-PH). Among infants with BPD-PH, 104 infants (17%) received sildenafil.
- The odds for sildenafil treatment among infants born between 25 and 26 weeks' gestational age (GA) and <24 weeks' GA, respectively, were 2.26 (95% confidence interval [CI]: 1.20-4.24) and 3.21 (95% CI: 1.66-6.21) times those of infants born at 27 to 28 weeks' GA. Severity of BPD correlated with sildenafil exposure, with adjusted odds ratios (ORs) for moderate BPD (OR: 3.03 [95% CI: 1.03-8.93]) and severe BPD (OR: 7.56 [95% CI: 2.50-22.88]), compared with mild BPD. Greater rates of sildenafil exposure were observed among small for GA neonates (OR: 2.32 [95% CI: 1.21-4.46]). The proportion of infants with BPD-PH exposed to sildenafil varied according to hospital (median: 15%; 25th-75th percentile: 0%-25%), as did the median duration of therapy (52 days; 25th-75th percentile: 28-109 days).
- The odds of sildenafil treatment were greatest among the most premature infants with severe forms of BPD.

Division of Pediatric Cardiology, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York Presbyterian Hospital, New York, NY.

- A retrospective cohort study of children with pulmonary hypertension (PH) treated with sildenafil at a single institution between 2004 and 2015.
- There were 269 children included in this study: 47 with idiopathic pulmonary arterial hypertension, 53 with congenital heart disease, 135 with bronchopulmonary dysplasia, 24 with congenital diaphragmatic hernia, and 7 with other causes.
- Sildenafil was initial monotherapy in 84.8% and add-on therapy in 15.2%. Median follow-up time was 3.1 years (2 weeks-12.4 years). On follow-up, 99 (37%) remained on sildenafil or transitioned to tadalafil, 93 (35%) stopped sildenafil for improvement in PH, 54 (20%) died, and 20 (7%) were lost to follow-up.
- PH was most likely to improve in those with bronchopulmonary dysplasia, allowing for the discontinuation of sildenafil in 45%.
- Eighteen deaths were related to PH and 36 from other systemic causes. Two patients stopped sildenafil owing to airway spasm with desaturation.
FDA Drug Safety Communication: FDA clarifies Warning about Pediatric Use of Revatio (sildenafil) for Pulmonary Arterial Hypertension.

https://www.fda.gov/Drugs/DrugSafety/ucm390876.htm

- [03-31-2014] The U.S. Food and Drug Administration (FDA) is clarifying its previous recommendation related to prescribing Revatio (sildenafil) for children with pulmonary arterial hypertension (PAH). Revatio is FDA-approved only to treat PAH in adults, not in children; however, health care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient.

- FDA revised the Revatio drug label in August 2012, adding a warning stating that “use of Revatio, particularly chronic use, is not recommended in children.” This recommendation was based on an observation of increasing mortality with increasing Revatio doses in a long-term clinical trial in pediatric patients with PAH.

ADDITIONAL DATA FROM STUDY POSTED ON FDA WEB SITE – HTTP://WWW.FDA.GOV/DRUGS/DRUGSAFETY/UCM317123.HTM#DATA

Figure: plot of mortality in the pediatric clinical trial as a function of Revatio dose.


- Despite the increased risk for pulmonary hypertension in children with Down syndrome, the response to treatment with targeted therapies for pulmonary hypertension in these patients is not well characterized.

- The Sildenafil in Treatment-naive children, Aged 1-17 years, with pulmonary arterial hypertension (STARTS-1) trial was a dose-ranging study of the short-term efficacy and safety of oral sildenafil in children with pulmonary arterial hypertension.

- This was a post-hoc analysis of children with Down syndrome and pulmonary arterial hypertension enrolled in the STARTS-1 trial.

- Of 234 patients randomized and treated in the STARTS-1 trial, 48 (20.5%) had Down syndrome. Although sildenafil produced dose-related reductions in PVRI and mPAP, compared with placebo, in non-Down syndrome patients and children developmentally able to exercise, this was not satisfactorily marked in patients with Down syndrome. The dose-related reductions in PVRI, compared with placebo, occurred in all subgroups, with the exception of the Down syndrome subgroup. Sildenafil appeared to be well tolerated in the Down syndrome subpopulation and the most frequently reported AEs were similar to those reported for the entire STARTS-1 population.

- **Sildenafil treatment for 16 weeks had no effect on PVRI or mPAP in children with Down syndrome and pulmonary arterial hypertension.**


- A retrospective review of hospitalized infants at Children’s Hospital Los Angeles who received sildenafil between 2008 and 2012 was conducted. Patient characteristics, comorbidities, and treatment characteristics were analyzed. Primary outcome was mortality at discharge. Sildenafil dosage ranges were based on the Sildenafil in Treatment-Naive Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension trial and were categorized as small (<1.5 mg/kg/day), medium (1.5-3.75 mg/kg/day), large (3.76-7.5 mg/kg/day), and very large (>7.5 mg/kg/day).

- A total of 147 infants were studied. A total of 82% of patients had severe pulmonary hypertension. Our data revealed 29% mortality at discharge. Mortality increased with increasing sildenafil dosage: 14% (small), 19% (medium), 49% (large), and 90% (very large).

- On multivariate analysis of sildenafil dosage, other pulmonary hypertension therapies, presence of persistent cardiac shunts, and duration of sildenafil, odds of dying were significantly higher with combined high and very high sildenafil dosage groups compared with combined low and medium dosage groups (OR, 13.2; CI, 4.4-39.5; p < 0.0001).

- Sildenafil was given to critically ill infants with multiple risk factors for mortality. Although higher doses cannot be causally related to mortality, there appears to be no added benefit by escalating the sildenafil dose.
Summary

• We still have lots to learn about how to best treat pulmonary hypertension in infants.
• Data on pharmacokinetics is lacking.
• Site variability is significant for all of the most commonly used pulmonary vasodilators.
• Only iNO has been studied in large randomized clinical trials.