Treprostinil Improves Persistent Pulmonary Hypertension Associated with Congenital Diaphragmatic Hernia

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Objective To evaluate the effect of continuous treprostinil in infants with severe pulmonary hypertension associated with congenital diaphragmatic hernia (CDH) on specific markers of pulmonary hypertension severity and to report the safety and tolerability of treprostinil.

Study design We conducted a retrospective cohort study of infants with CDH-associated pulmonary hypertension treated with treprostinil from January 2011 to September 2016. Severity of pulmonary hypertension was assessed by echocardiogram and serum B-type natriuretic peptide (BNP) by using time points before initiation and 24 hours, 1 week, and 1 month after treprostinil initiation. Fisher exact tests, Wilcoxon-rank sum tests, and mixed-effects models were used for analysis.

Results Seventeen patients were treated with treprostinil for a median of 54.5 days (IQR 44.3-110 days). Compared with the concurrent CDH population (n = 147), infants treated with treprostinil were more likely to require extracorporeal support (76.5% vs 25.2%, $P < .0001$), to have a longer hospital stay (144 vs 60 days, $P < .0001$), and to need longer mechanical ventilator support (76.5 vs 30.9 days, $P < .0001$). Following treprostinil initiation, there was a significant reduction in BNP at 1 week (1439 vs 393 pg/mL, $P < .01$) and 1 month (1439 vs 242 pg/mL, $P = .01$). Severity of pulmonary hypertension by echocardiogram improved at 1 month (OR 0.14, CI 95% 0.04-0.48, $P = .002$). Despite these improvements, overall mortality remained high (35%). There were no adverse events related to treprostinil, including no hypotension, hypoxia, or thrombocytopenia.

Conclusions In this cohort, treprostinil use was associated with improved severity of pulmonary hypertension assessed by echocardiogram and decreased BNP, with no significant side effects. *(J Pediatr 2018;■■:■■-■■).*

Congenital diaphragmatic hernia (CDH) is a major congenital anomaly affecting ~1:3000-1:4000 live births.[1-5] Despite advancements in surgical techniques and pharmacologic and respiratory-support strategies, mortality remains 20%-30% at tertiary care centers.[6,7] Pulmonary hypertension, an abnormal elevation of pulmonary artery pressure, is associated with significant morbidity and mortality in infants with CDH.[8] Although pulmonary hypertension is present in most infants in the immediate neonatal period, persistent severe pulmonary hypertension beyond the first few weeks of life is associated with increased morbidity, including ventilator days and extracorporeal membrane oxygenation (ECMO), and mortality.[8-10] In a cohort of infants with CDH from 1991 to 2002, Dillon et al found no survivors among infants with severe, persistent pulmonary hypertension at 6 weeks of age, despite medical therapies including inhaled nitric oxide and ECMO.[10]

Treprostinil is a synthetic prostacyclin analog and potent pulmonary vasodilator that is approved for the treatment of idiopathic pulmonary arterial hypertension in adults.[11,12] In addition to inhaled nitric oxide and sildenafil, treprostinil has been used to treat severe, refractory pulmonary hypertension associated with CDH in infants.[13-15] Evidence to support its use remains limited to a retrospective review of treprostinil among a heterogeneous population of infants with pulmonary hypertension that found treprostinil to be well tolerated, although the authors did not investigate its ability to modulate pulmonary hypertension severity,[13] and several case series of infants with CDH showing clinical improvement after treprostinil initiation.[14,15] In this study, we sought to evaluate treprostinil treatment of pulmonary hypertension associated with CDH using specific markers of pulmonary hypertension severity, echocardiogram and serum B-type natriuretic peptide (BNP), as well as to evaluate the safety and tolerability of treprostinil in this population.

BNP	B-type natriuretic peptide
CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation
LHR	Lung area to head circumference ratio
RVSP	Right ventricular systolic pressure

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Methods

We performed a retrospective chart review of patients diagnosed with CDH treated at the Children's Hospital of Philadelphia and enrolled in the Pulmonary Hypoplasia Program study, a single-center prospective registry. We included patients treated from January 2011 until September 2016, as this corresponded with available electronic medical records. All patients with CDH were eligible for enrollment in the Pulmonary Hypoplasia Research Program study (n = 167), and all patients who provided consent (n = 164) were included in this analysis. The study was approved by the Children's Hospital of Philadelphia institutional review board, Committee for the Protection of Human Subjects (institutional review board no. 06-003779).

Patients with a diagnosis of CDH who received treprostinil during their initial hospitalization were identified through the electronic pharmacy order entry system. Recorded data on patient demographics, prenatal course and imaging, and postnatal care, including surgical repair, vital signs, laboratory values, and medication use, were analyzed. When available, prenatal imaging including detailed ultrasonography scan and ultrafast fetal magnetic resonance imaging was used to calculate observed/expected lung area to head circumference ratio (LHR) and fetal lung volumes as previously described.[16,17] Echocardiograms were obtained as part of routine clinical practice, typically at hospital admission and as clinically indicated. BNP values typically were obtained weekly or more frequently during treatment changes at the discretion of the treating providers. Categorical variables were analyzed with χ^2 or Fisher exact tests and continuous variables by Wilcoxon rank-sum tests. A linear mixed-effects model was used to analyze BNP change over time. In addition, to determine whether age at initiation altered results observed over time, the model was adjusted for chronologic age at initiation.

Treprostinil was begun at the discretion of clinical providers for patients with a diagnosis of CDH and evidence of significant pulmonary hypertension by clinical assessment, including BNP elevation and echocardiogram, despite inhaled nitric oxide administration. Patients with uncontrolled coagulopathy, history of grade 3 or 4 intracranial hemorrhage, or refractory hypotension were typically excluded from consideration for treatment. In patients who were treated with treprostinil, the medication generally was initiated at a dose of ~4 ng/kg/min given intravenously through a central venous line and titrated up over a period of days to clinical effect, typically to a dose of 20-30 ng/kg/min. Doses were adjusted for weight gain at the discretion of the treating provider, typically with weight gain of >10% of body weight.

For patients treated with treprostinil, we reviewed images from clinically indicated echocardiograms performed via standard pediatric views on a Phillips IE33 machine (Phillips, Andover, Massachusetts). Images were digitally stored using Syngo Dynamics (Siemens, Ann Arbor, Michigan). Transthoracic echocardiograms performed before the initiation of treprostinil and at approximately 1 week, 1 month, and 6 weeks after initiation were reviewed offline in a standardized manner by a reader blinded to treatment and outcome. Echocardiographic assessment of pulmonary hypertension included right ventricular systolic pressure (RVSP) using peak tricuspid regurgitation Doppler jet velocity, direction of flow across a patent ductus arteriosus if present, and interventricular septal position, in a manner similar to previously described methods.[4,5,14] RVSP measurements were compared with the systolic blood pressure at the time of echocardiogram. Severity of pulmonary hypertension was graded as mild/none (RVSP less than one-half systemic), moderate (RVSP one-half to systemic), or severe (RVSP greater than systemic). RVSP was estimated by the use of tricuspid regurgitation jet velocity measured by continuous-wave Doppler using the modified Bernoulli equation ($4V^2$) without correction for right atrial pressure. When present, the direction of blood flow across the patent ductus arteriosus was assessed with left-to-right flow scored as mild, bidirectional shunting scored as moderate, and pure right-to-left shunting scored as severe pulmonary hypertension. Finally, qualitative assessment of interventricular septal flattening at end systole was graded as rounded (none/mild), flat (moderate), or bowing into the left ventricle (severe).

To analyze echocardiographic outcomes over time, binary generalized estimating equation models were used to model the odds of severe pulmonary hypertension after treatment. To determine whether age at initiation altered results observed over time, models were adjusted for chronologic age at initiation. In patients for whom long-term analysis was not possible due to early death, data points were coded as missing in the statistical models. Statistical significance was accepted at $P < .05$. All data analysis was conducted with SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

This retrospective cohort included a total of 164 infants with CDH, 17 of whom were treated with treprostinil for severe pulmonary hypertension. Patient demographics, prenatal imaging, and outcomes for the cohort are summarized in the **Table**. The cohort treated with treprostinil and general cohort with CDH were not significantly different for infant sex, mean gestational age at delivery, or mean birth weight. There were also no significant differences in frequency of right-sided CDH, intrathoracic liver position, or presence of other congenital anomalies. However, there was significantly greater lung hypoplasia by prenatal assessment in the treprostinil group with a lower mean ultrasound LHR and mean observed/expected LHR. Infants treated with treprostinil had greater maximum BNP during their hospitalization that peaked later, consistent with severe, late pulmonary hypertension. Infants treated with treprostinil were more likely to be treated with additional pulmonary hypertension therapies, including inhaled nitric oxide, sildenafil, prostaglandin E1, and ECMO. They were also more likely to have a longer length of hospital stay and longer duration of mechanical ventilation. Although overall mortality was not different between the groups, the cohort

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Table. Patient demographics, prenatal imaging, and outcomes of the cohort

Demographics	Treated with treprostinil n = 17	All others n = 147	*P* value*
Male	12 (71%)	83 (56%)	.26
Gestational age at delivery, wk	38.3 (37.4-38.9)	38.6 (37.3-39)	.58
Birth weight, g	3000 (2795-3390)	3120 (2820-3459)	.41
LHR	0.82 (0.61-1.08)	1.01 (0.82-1.31) *n = 140*	.02
Observed/expected LHR	0.29 (0.22-0.34)	0.37 (0.28-0.42) *n = 140*	.01
Right-sided CDH	4 (24%)	18 (12%)	.25
Intrathoracic liver	13 (76%)	88 (60%)	.18
Other congenital anomalies	8 (47%)	64 (44%)	.78
Overall mortality	6 (35%)	37 (25%)	.39
Age at death, d	77 (39-175)	1 (0-20)	<.01
Underwent CDH repair	16 (94%)	116 (79%)	.20
Patch repair	12 (75%) n = 16	74 (50%) n = 116	.06
Age at CDH repair, d	30 (22-59) n = 16	14 (6-21) n = 116	<.01
Duration of hospital stay, d	113 (70-208)	48 (20-76)	<.01
Duration of intubation, d	60 (43-119)	23 (9-37)	<.01
Maximum BNP, pg/mL	2289 (1234-2929)	1032 (485-1833) n = 129	<.01
Age at maximum BNP, d	19 (11-94)	11 (5-17) n = 129	<.01
Treatment with ECMO	13 (76%)	37 (25%)	<.01
Treatment with nitric oxide	17 (100%)	96 (65%)	<.01
Treatment with sildenafil	9 (53%)	15 (10%)	<.01
Treatment with prostaglandin E1	15 (88%)	32 (22%)	<.01

Categorical data expressed as n (%) and continuous data points expressed given as median (25%-75% IQR) unless otherwise noted. N specified for individual fields if different than total.
**P* values represent results of χ^2 or Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

treated with treprostinil had a later mean age of death (**Table**). The untreated cohort was heterogeneous, including patients with lower acuity as well as those with severe CDH and early mortality. When the nontreated patients with early death (<48 hours of life) were compared with the treprostinil cohort, there were no differences in LHR (0.95 ± 0.14 vs 0.90 ± .07, $P = .7$) or observed/expected LHR (0.29 ± 0.02 vs 0.34 ± 0.04, $P = .3$), suggesting similar fetal lung volumes between these groups.

The average age at treprostinil initiation was 37 days of life (range 6-180 days), and the median duration of treatment in hospital was 54.5 days (IQR 44.3-110 days). Timing, dosage, and duration of treprostinil treatment varied based on the clinical course. Before treatment initiation, all patients had moderate-to-severe pulmonary hypertension, as detected by echocardiogram and elevated BNP levels (1495 ± 122 pg/mL) despite treatment with inhaled nitric oxide. The timing of treprostinil initiation was heterogeneous related to ECMO and surgical repair: 5 patients (29.4%) before ECMO, 4 patients (23.5%) while on ECMO with anticipation of assisting decannulation, 4 patients (23.5%) for persistent pulmonary hypertension after discontinuation of ECMO, and 4 patients (23.5%) never required ECMO. In 9 patients (53%), treatment was initiated before CDH repair and 8 (47%) started treprostinil after CDH repair. Median treprostinil dose was 10 ng/kg/min (IQR 6-13) at 24 hours (n = 17), 16 ng/kg/min (IQR 14-22) at 1 week (n = 16), 20 ng/kg/min (IQR 14-30) at 1 month (n = 15), and 19 ng/kg/min (IQR 16-30) at 6 weeks (n = 13). Patients remained on the maximum dose for an average of 32 ± 11 days until death, dose decrease due to clinical improvement, or transition to subcutaneous administration in anticipation of hospital discharge.

There was a significant decrease in BNP associated with treprostinil treatment. Compared with baseline, BNP was not significantly changed at 24 hours after treprostinil initiation but was significantly reduced after 1 week and 1 month of treatment (**Figure 1**). After adjustment of the statistical model for age at treprostinil start, there remained a significant reduction in BNP after 1 week (adjusted values 1412 vs 393 pg/mL, $P < .01$) and 1 month (1412 vs 265 pg/mL, $P = .02$) of treatment. Furthermore, we found no relationship between BNP reduction and age at initiation ($P = .2$) when models were adjusted for age.

Over the same period of time that BNP decreased, there was also an improvement in pulmonary hypertension as assessed by echocardiogram (**Figure 2**). Although most patients continued to have evidence of pulmonary hypertension, the odds of severe pulmonary hypertension improved significantly after ~1 month (27 ± 8 days) of treprostinil treatment (OR 0.14, CI

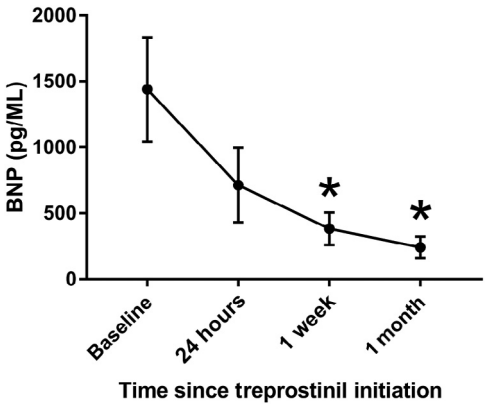

Figure 1. Serum BNP values over time. *$P < .02$ relative to baseline. *Error bars* represent SEM.

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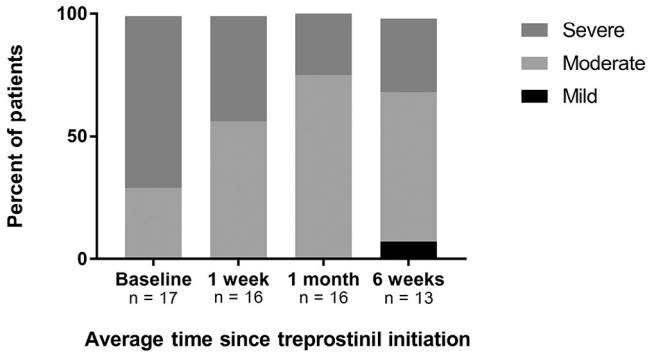

Figure 2. Echocardiographic assessment of pulmonary hypertension severity over time. Sequential echocardiograms were evaluated before treprostinil initiation and 1 week (8 ± 2 days), 1 month (27 ± 8 days), and 6 weeks (42 ± 4 days) after treatment initiation. Binary generalized estimating equation models were used to determine the odds of severe pulmonary hypertension over time. The severity of pulmonary hypertension improved significantly at 1 month ($P = .002$) and remained significant at 6 weeks ($P = .001$) after treprostinil initiation.

95% 0.04-0.48, $P = .002$) and remained significant at 6 weeks (42 ± 4 days) of treatment (OR 0.15, CI 95% 0.05-0.47, $P = .001$). Although the odds of severe pulmonary hypertension by echocardiogram were reduced at ~1 week (8 ± 2 days) after treprostinil initiation, this reduction was not significant (OR 0.33, 95% CI 0.10-1.10, $P = .07$). When adjusted for age of initiation, the odds of severe pulmonary hypertension remained significantly reduced at 1 month (OR 0.17, 95% CI 0.04-0.62, $P < .01$), but the odds of severe pulmonary hypertension were no longer significantly improved at 6 weeks of treatment (OR 0.27, 95% CI 0.06-1.19, $P = .09$). This model adjustment also showed that the odds of pulmonary hypertension severity were not related to age at initiation (OR 0.99, CI 0.97-1.01, $P = .5$).

Treprostinil was well tolerated in this cohort. No patients required discontinuation of therapy or dose reduction secondary to adverse events. Specifically, there was no change in mean arterial pressure (55 ± 3 vs 54 ± 3 mm Hg, $P = .8$) or increase in dopamine dose (4 ± 1 vs 3 ± 1 μg/kg/min, $P = .9$) within 24 hours of initiation. There was also no hypoxia requiring significant change in oxygen therapy (0.41 ± 0.05 vs 0.39 ± 0.04 fraction of inspired oxygen, $P = .9$) or ventilator mean airway pressure (17 ± 3 vs 17 ± 3 mm Hg, $P = .8$). There were no episodes of central line–associated sepsis or thrombocytopenia (defined as platelets <50 K/μL) within 1 month of treatment (178 ± 42 vs 357 ± 35 K/μL, $P = .08$).

Of the 17 patients treated during their initial hospitalization, treprostinil was discontinued in 6 patients (35%) due to clinical improvement. Four patients (24%) continued treprostinil at time of hospital discharge at a median dose of 28 ng/kg/min (range 16-51.2 ng/kg/min). All patients were transitioned from intravenous to subcutaneous therapy at the same dose before discharge, with 3 patients (75%) also discharged on sildenafil and 2 patients (50%) with supplemental oxygen. At the time of study completion, 1 patient (6%) remained hospitalized on treprostinil at 30 ng/kg/min. Six patients (35%) died despite treatment with treprostinil: 4 died of respiratory failure and care was withdrawn in 2 patients due to poor neurologic prognosis, including 1 patient who died 2 days after initiation preventing evaluation of long-term response to treprostinil.

Discussion

In this retrospective cohort study, we examined treprostinil use in 17 patients with CDH and associated moderate or severe, persistent pulmonary hypertension and demonstrate improvement in BNP and echocardiographic measures of pulmonary hypertension over the treatment period. In this series, the subset of infants treated with treprostinil generally had greater morbidity than the total CDH cohort. The treprostinil cohort had greater lung hypoplasia as assessed prenatally and greater acuity postnatally. Infants treated with trepostinil were more likely to have a greater maximum BNP, require a longer duration of mechanical ventilation and hospitalization, require pulmonary vasodilator therapies and ECMO, and undergo delayed operative repair compared with the larger CDH group. There are limitations to this comparison, as the concurrently treated CDH population was a heterogeneous group, including infants without significant morbidity as well as infants with early mortality due to severe disease. Interestingly, there was no difference in LHR between those infants with early mortality and the treprostinil cohort, suggesting lung hypoplasia may contribute to both early death and persistent pulmonary hypertension. Greater acuity has been described in patients with severe, persistent pulmonary hypertension.[9,10] Unlike other reports,[14,15] the majority of patients in our treprostinil cohort were treated with ECMO: some received early treprostinil treatment before ECMO, and others were treated for severe pulmonary hypertension that persisted during or after ECMO.

Treprostinil was well tolerated in our cohort. Several studies also have shown safety and tolerability of treprostinil use in infants with CDH, although there have been some reports of associated hypotension and hypoxia.[13,14] In our cohort, there was no significant hypotension or thrombocytopenia following treprostinil initiation; however, the majority of patients treated with treprostinil also were treated with low-dose dopamine at time of initiation for pre-existing hypotension or for empiric inotropic support in the setting of right ventricular dysfunction. Although there was no escalation of dopamine dose related to treprostinil start, the concurrent therapy potentially could have prevented or ameliorated hypotension. This experience supports safety of treprostinil even in this hemodynamically tenuous population of patients.

In our cohort, treprostinil was associated with significant improvement in pulmonary hypertension severity by echocardiogram and BNP over time with treatment. BNP, a protein secreted from both ventricles in response to volume or pressure load, is used widely as a biomarker of pulmonary hypertension severity and right ventricular dysfunction in adults and children.[18,19] We and others have shown that BNP

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levels correlate with pulmonary hypertension presence[20] and pulmonary hypertension severity[21] by echocardiography in infants with CDH. In addition, BNP levels correlate with ECMO treatment[20] and outcomes in infants with CDH.[22] We observed a trend toward improvement in echocardiography and BNP at early time points that was significant across the treatment period. BNP decreased after treprostinil before improvements seen by echocardiogram, suggesting it may be a more sensitive marker of small changes in right ventricular pressure and reduced afterload not detectable by echocardiographic measures such as ventricular septal position. The timing of response also may reflect the escalation of treprostinil dose; patients were started on a low dose with gradual increase in the dose over a period of days to minimize potential side effects. The dose was titrated to clinical effect in each patient and the range of doses used was similar to previous reports[14,15]; however, no studies to date have determined the optimal dosing of treprostinil in infants.

Despite improvement after 1 month of treatment, the mean BNP remained elevated in this cohort, and most patients still showed some evidence of pulmonary hypertension by echocardiogram, although the degree of severity was significantly improved. Persistence of pulmonary hypertension despite vasodilator therapy may reflect a fixed component of pulmonary vascular disease. In addition, BNP also can be influenced by factors other than pulmonary hypertension, including left ventricular dysfunction, renal failure, and sepsis, which were not evaluated in this study.[23]

The etiology of pulmonary hypertension in our cohort was likely multifactorial, with some degree of elevated pulmonary vascular resistance that may be reversible with pulmonary vasodilators and some due to fixed resistance secondary to underlying pulmonary vascular hypoplasia.[10] Studies in animal models and humans suggest there may be contribution from structural and functional abnormalities of the pulmonary vasculature associated with CDH, including pulmonary artery remodeling and imbalanced vasoconstrictor/vasodilator pathways.[24-27] In this small, nonrandomized study, we were unable to assess the degree of improvement directly attributable to treprostinil, as growth of the vascular bed over time may contribute as well. The later peak in BNP and later mortality in the treprostinil cohort may reflect persistent (late) pulmonary hypertension and profound lung hypoplasia, as these factors have been associated with poor short-term and longer-term outcomes and may not be improved by pulmonary vasodilator therapies.[9,28] Differentiating predictors of response requires further study. In addition, we cannot exclude potential contribution from other concomitant therapies, including long-term effects of inhaled nitric oxide, prostaglandin E1, and sildenafil, in patients who received those therapies.

Although we cannot exclude the possibility of spontaneous resolution of pulmonary hypertension in this cohort, we found no significant relationship between age and improvement in BNP or echocardiogram when statistical models were adjusted for age at treprostinil initiation. In addition, improvements in BNP and echocardiogram remained significant regardless of age at initiation, favoring an independent treatment effect. The median in-hospital treprostinil treatment duration of 54 days also supports a more persistent pulmonary hypertension phenotype. Olson et al reported 2 infants who were able to come off treprostinil after months of treatment,[14] and we also describe patients who were able to be weaned off treprostinil due to improvement in pulmonary hypertension. It remains unclear whether the improvement observed with treprostinil is due to reducing pulmonary vascular resistance directly or whether it contributes to decreasing strain on the right ventricle, perhaps contributing to clinical stability during a period of lung growth. Specific predictors of adequate duration of therapy remain unclear but may be related to timing of operative repair, severity of lung hypoplasia at birth, underlying vascular dysfunction, and interval growth of the pulmonary vascular bed.

Despite the overall improvements in BNP and echocardiographic indices of pulmonary hypertension severity, mortality remained high in our cohort (35%). Our cohort included infants with high acuity, the majority requiring support with ECMO. Although several of the deaths were due to poor neurologic prognosis and not thought to be related to pulmonary hypertension or right heart failure, pulmonary hypertension could have contributed to death related to respiratory failure. This study was not designed to evaluate mortality or outcomes, but we do suggest that it may be reasonable to use treprostinil in this population, given the high mortality rates in infants with CDH and severe, persistent pulmonary hypertension by Dillon et al and others.[8-10]

This study is limited by its small size, heterogeneous age distribution, and retrospective nature. Despite these limitations, we found that treprostinil improved pulmonary hypertension severity assessed by echocardiogram and BNP in a cohort of critically ill infants with CDH and persistent pulmonary hypertension. Larger, prospective studies are needed to elucidate ideal patient selection and timing of initiation of therapy, as well as effect on mortality related to pulmonary hypertension. ■

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