Trends in pediatric pulmonary hypertension–related hospitalizations in the United States from 2000–2009

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Abstract: There are few data on the epidemiology of pulmonary hypertension (PH)–related hospitalizations in children in the United States. Our aim was to determine hospital mortality, length of hospitalization, and hospital charges pertaining to PH-related hospitalizations and also the effects of codiagnoses and comorbidities. A retrospective review of the Kids' Inpatient Database during the years 2000, 2003, 2006, and 2009 was analyzed for patients ≤ 20 years of age with a diagnosis of PH by ICD-9 (*International Classification of Diseases, Ninth Revision*) codes, along with associated diagnoses and comorbidities. Descriptive statistics, including Rao-Scott χ^2 , ANOVA, and logistic regression models, were utilized on weighted values with survey analysis procedures. The number of PH-related hospital admissions is rising, from an estimated 7,331 (95% confidence interval [CI]: 5,556–9,106) in 2000 to 10,792 (95% CI: 8,568–13,016) in 2009. While infant age and congenital heart disease were most commonly associated with PH-related hospitalizations, they were not associated with mortality. Overall mortality for PH-related hospitalizations was greater than that for hospitalizations not associated with PH, 5.7% versus 0.4% (odds ratio: 16.22 [95% CI: 14.78%–17.8%], $P < 0.001$), but mortality is decreasing over time. Sepsis, respiratory failure, acute renal failure, hepatic insufficiency, arrhythmias, and the use of extracorporeal membrane oxygenation are associated with mortality. The number of PH-related hospitalizations is increasing in the United States. The demographics of PH in this study are evolving. Despite the increasing prevalence, mortality is improving.

Keywords: pulmonary hypertension, pediatrics, epidemiology, survival.

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Pulmonary hypertension (PH) is a result of developmental lung abnormalities or aberrant remodeling, leading to both reversible and irreversible lesions of the pulmonary vasculature that result in elevated pulmonary artery pressures.¹ Over time, the disease can propagate to right heart failure and death. PH is defined by the World Health Organization (WHO) as a persistently elevated mean pulmonary arterial pressure of ≥ 25 mmHg and includes an additional requirement of a pulmonary capillary wedge pressure of ≤ 15 mmHg for precapillary PH.^{1–7} Although excluded in the newer definition of PH, a pulmonary vascular resistance of ≥ 3 indexed Wood units is still considered in the diagnosis of children with PH.^{8,9} Currently, PH in adults and children is classified into 5 groups: pulmonary arterial hypertension (PAH); PH associated with left-sided heart disease; PH associated with lung disease and/or hypoxia; chronic thromboembolic disease; and PH of unclear etiology or related to multiple factors.^{7,10}

PH is an uncommon but serious disease in children, with few data on its prevalence, morbidity, and mortality. Recent PH registries have revealed some information on the epidemiology of PH.^{2,4–7}

Previous results estimated the incidence of PAH in adults and children at 1–2 new cases per million each year.^{8,11–15} However, several recent studies have shown varying incidence and prevalence. The annual incidence rates in the Netherlands for all PH diagnoses averaged 63.7 cases per million children per year, with transient PAH accounting for nearly 52 cases per million children per year.^{7,16} Progressive PAH incidence rates in this study are smaller and include about 3 new cases per million children per year, with congenital heart disease (CHD)–related cases constituting a majority of new cases. The prevalence varies in registries, ranging from 3.7 cases per million in France to 20 million cases per million in the Dutch registry.^{2,5–7,17} Importantly, data from population-based studies on hospital admissions among children with PH are scarce, and most existing data on PH-related hospitalizations pertain to transient forms of PH, such as persistent pulmonary hypertension of the newborn (PPHN).^{11–15,18}

Morbidity and mortality remain high despite improvements in the treatment of PH in the past 20 years. Before the advancements in treatment of PH, survival rates for 1, 3, and 5 years were estimated

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at 66%, 52%, and 35%, respectively.^{16,19,20} Modern-day treatment has improved survival for PH, with 1-, 3-, and 5-year survival rates of 73%–96%, 63%–88%, and 60%–81%, respectively.^{2,5-7,17,21}

Data on the epidemiology of pediatric PH in the United States are scarce, with very little analysis of inpatient mortality, length of stay, and comorbidities associated with PH-related hospitalizations. Given this lack of data, the National Heart, Lung, and Blood Institute has listed defining the natural history, epidemiology, and course of pediatric pulmonary vascular disease as a priority.^{18,22} Therefore, this study was designed to examine prevalence and outcomes in PH-related hospitalizations in children to test the hypothesis that there has been an increase in PH-related hospitalizations. We also hypothesized that with advancements in medical therapy, mortality and morbidity have decreased.

METHODS

Data

The study was designed to retrospectively analyze a public database of nationwide pediatric hospital admissions over the past decade. Details of the database and modalities used for analysis have been previously described.^{4-7,17,19,20,23} Briefly, the Kids' Inpatient Database (KID) is part of the Healthcare Cost and Utilization Projection run by the Agency for Healthcare Research and Quality in the Department of Health and Human Services.^{20,21,24-27} The data have been collected every 3 years since 1997 and arise from specialty hospital, public hospital, and academic medical center admissions from 27 states with 2,874 hospitals in 2000, 36 states with 3,438 hospitals in 2003, 38 states with 3,739 hospitals in 2006, and 44 states with 4,121 hospitals in 2009. Patient data included are primary and secondary diagnoses, admission and discharge status, patient demographics, hospital characteristics, total charges, length of stay, and severity and comorbidity measures.

Data can be weighted to provide national estimates. The KID was analyzed for pediatric patients ≤20 years old. We reviewed discharge data from the years 2000, 2003, 2006, and 2009. PH was designated the primary diagnosis and identified by the *ICD-9 (International Classification of Diseases, Ninth Revision)* codes 415.0 (acute cor pulmonale), 416.0 (primary pulmonary hypertension), 416.8 (other chronic pulmonary heart disease), and 416.9 (chronic pulmonary heart disease, unspecified). The *ICD-9* codes used for other secondary diagnoses are listed in Table S1, available online. Data collected included associated diagnoses, hospitalization duration, hospital mortality, and hospital charges, which are not corrected for inflation. Hospitals were identified as children's hospitals if they were identified as such by the National Association of Children's Hospitals and Related Institutions. The details and results of procedures, imaging, or laboratory studies are not included.

Statistical analysis

Baseline characteristics of PH-related admissions were analyzed with descriptive statistics. Calculations of prevalence rates for PH-related hospital admissions used age-related number estimates from US Census data for the years 2000, 2003, 2006, and 2009.^{22,28} Rao-Scott χ^2 and ANOVA were used to test for a lack of association between characteristics and years. For univariable analysis, a contingency table analysis was performed for categorical variables and ANOVA for continuous variables. For multivariable analysis, logistic regression models were utilized. The variables in the model included urban location, children's hospital, large hospital, teaching hospital, female, nonwhite, age at admission, CHD, chronic respiratory disease arising in the perinatal period or bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH), chromosomal abnormalities, systemic lupus erythematosus (SLE), sickle cell disease (SCD), sepsis, respiratory failure, acute renal failure, hepatic insuffi-

Table 1. Baseline characteristics of pulmonary hypertension-related hospitalizations

	2000	2003	2006	2009	P ^a
Hospitalizations, <i>n</i>	7,331 (5,556–9,106)	6,359 (4,898–7,821)	9,097 (7,013–11,170)	10,792 (8,568–13,016)	<0.001
Hospitalization rate ^b	8.7 (6.6–10.8)	7.4 (5.7–9.1)	10.5 (8.1–12.9)	12.3 (9.8–14.8)	<0.001
Urban location	95.5 (94.1–96.4)	96.7 (95.7–97.2)	98 (97.6–98.5)	97.8 (97.2–98.2)	0.003
Children's hospital	59.6 (52.6–63.8)	70.2 (65.2–73.3)	72.5 (67.3–75.9)	74.4 (70.3–77.2)	<0.001
Large hospital	54.6 (47.4–59.0)	53.5 (43.8–59.6)	59.4 (52.1–64.0)	64.0 (56.6–68.9)	0.093
Teaching hospital	83.6 (78.9–86.4)	87.0 (83.6–89.2)	85.6 (83.2–87.2)	86.5 (83.3–88.6)	0.424
Female	48.7 (47.5–49.4)	51.5 (50.8–51.9)	49.1 (49.1–49.1)	55.7 (55.4–56.0)	0.640
Nonwhite	40.3 (37.4–42.1)	39.8 (36.4–41.9)	44.6 (39.7–47.7)	54.8 (52.1–56.5)	0.010
Age at admission, years					
<1	55.2 (42.9–67.7)	43.9 (35.1–52.8)	46.4 (37.0–55.9)	44.7 (36.2–53.2)	<0.001
1–12	26.4 (17.8–35.0)	34.3 (24.9–43.7)	31.9 (22.6–41.2)	34.8 (26.5–43.1)	<0.001
13–20	18.3 (13.6–23.0)	21.8 (15.2–26.9)	21.7 (17.1–26.3)	20.4 (16.3–24.6)	0.045

Note: Unless otherwise specified, data are percentage of hospitalizations; 95% confidence intervals are presented in parentheses.

^a Comparing characteristic across years.

^b Hospital admissions per 100,000 children.

ciency, extracorporeal membrane oxygenation (ECMO), arrhythmias, and cardiomyopathy. The calendar year 2009 was compared against all other years, as it was the year with lowest mortality. Only age <1 year was used as a variable in the final model, because of multicollinearity. All analyses were performed on weighted values, with survey analysis procedures from SAS, version 9.3 (SAS, Cary, NC). Statistical significance was defined as $P < 0.05$.

RESULTS

Baseline characteristics

The number of hospital admissions related to a diagnosis of PH increased significantly over the past decade (Table 1). In 2000, there were an estimated 7,331 (95% confidence interval [95% CI]: 5,556–9,106) PH-related admissions, which corresponds to 8.7 admissions for every 100,000 children. The number of admissions briefly decreased in 2003, but it steadily increased over the next 6 years, with an estimated 10,792 admissions (95% CI: 8,568–13,016), or 12.3 admissions for every 100,000 children, in 2009 ($P < 0.001$). While infants accounted for more admissions than any other age group, the proportion of admissions from infants decreased from 55.2% in 2000 to 44.7% in 2009 ($P < 0.001$). Conversely, from the year 2000 to 2009, the percentages of children aged 1–12 and 13–20 years steadily increased, from 26.4% to 34.8% and from 18.3% to 20.4%, respectively ($P < 0.001$ for ages 1–12 years and $P = 0.045$ for ages 13–20 years). Nonwhite patients now account for a majority of PH-related hospital admissions, rising from 40.3% in 2000 to 54.8% in 2009 ($P = 0.010$). Although the increase was not statistically significant, the number of PH-related hospitalizations for the female sex

rose from 48.7% in 2000 to 55.7% in 2009 ($P = 0.640$). Almost all of the PH-related hospital admissions occurred in hospitals in urban locations, and a significant portion of admissions were at teaching hospitals and large hospitals. Likewise, a majority of PH-related hospital admissions were at children's hospitals, and the proportion rose from 59.6% in 2000 to 74.4% in 2009 ($P < 0.001$).

Codiagnoses and comorbidities associated with PH-related hospitalizations

Among examined comorbidities, CHD was the most common, being associated with nearly 50% of PH-related hospitalizations in all years ($P = 0.025$; Table 2). While not as common, PH-related admissions with BPD rose more than 2-fold, from 4.2% in 2000 to 13.7% in 2009 ($P < 0.001$). Other less commonly associated comorbidities that grew in incidence include sepsis, respiratory failure, acute renal failure, hepatic insufficiency, arrhythmias, cardiomyopathy, and the use of ECMO. Diagnoses of CDH, SLE/connective-tissue disorder (CTD), and SCD were uncommon in all years, at 1%–2% of patients, and this did not change significantly over time.

Factors associated with length of PH-related hospitalization

In comparison with non-PH hospitalizations, length of stay for a PH-related hospital admission averaged 14.3 days ($P < 0.001$), and it increased from 2000 to 2009 (from 14.2 ± 0.6 to 15.6 ± 0.5 days, $P = 0.001$; Fig. 1). The shortest length of stay was found in 2003, at

Table 2. Associated comorbidities in pulmonary hypertension-related hospitalizations

	2000	2003	2006	2009	P^a
CHD	49.8 (48.8–50.4)	52.6 (52.0–53.0)	47.9 (47.4–48.3)	52.8 (52.5–52.9)	0.025
BPD	4.2 (3.9–4.4)	8.6 (8.3–8.8)	10.5 (9.7–11.1)	13.7 (13.2–14.0)	<0.001
CDH	2.4 (1.8–3.0)	1.7 (1.3–2.1)	1.7 (9.7–11.1)	1.9 (1.5–2.3)	0.1868
Chromosomal abnormalities	15.5 (13.8–17.2)	19.0 (16.8–21.2)	17.6 (15.6–19.6)	17.6 (15.8–19.4)	0.0561
SLE/CTD	1.4 (0.8–1.7)	1.4 (1.2–1.5)	1.8 (1.1–2.3)	1.8 (1.5–2.1)	... ^b
SCD	1.6 (0.9–2.0)	2.8 (1.9–3.4)	3.5 (3.2–3.6)	5.1 (4.2–5.7)	... ^b
Sepsis	7.6 (7.4–7.7)	10.4 (10.0–10.6)	11.8 (11.7–11.9)	13.3 (13.2–13.4)	<0.001
Respiratory failure	8.6 (7.9–9.0)	11.7 (11.4–11.9)	13.0 (12.3–13.5)	19.2 (18.4–19.8)	<0.001
Acute renal failure	1.8 (1.5–2.0)	1.7 (1.5–1.8)	2.4 (2.3–2.5)	3.7 (3.5–3.9)	<0.001
ECMO	2.3 (1.6–2.8)	1.4 (1.2–1.6)	1.5 (1.3–1.7)	2.0 (1.8–2.2)	0.045
Hepatic insufficiency	1.5 (1.2–1.6)	2.0 (1.7–2.2)	2.2 (2.0–2.3)	2.9 (2.8–3.1)	0.003
Arrhythmias	8.5 (7.9–8.9)	9.4 (9.3–9.6)	10.0 (9.7–10.2)	12.7 (12.5–12.8)	0.001
Cardiomyopathy	5.1 (4.9–5.3)	5.4 (5.1–5.7)	4.2 (3.9–4.4)	4.4 (4.2–4.6)	0.016

Note: Data are percent of hospitalizations (95% confidence interval). BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; CHD: congenital heart disease; CTD: connective tissue disease; ECMO: extracorporeal membrane oxygenation; PH: pulmonary hypertension; SCD: sickle cell disease; SLE: systemic lupus erythematosus.

^a Comparing associated comorbidities across years.

^b P value could not be calculated because of rarity of the event.

Figure 1. A, Mean length of stay, in days, for pulmonary hypertension (PH)-related hospitalizations in children across the years studied; $P < 0.001$ from ANOVA across years. B, Associated diagnoses' effect on mean length of stay, in days, for pulmonary hypertension-related hospitalizations. An asterisk indicates $P < 0.05$ for diagnoses associated with a change in length of stay compared to non-pulmonary hypertension-related hospitalizations. BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; CHD: congenital heart disease; ECMO: extracorporeal membrane oxygenation; SLE/CTD: systemic lupus erythematosus/connective-tissue disorder.

12.9 ± 0.6 days, and the longest mean length of stay was in 2009, at 15.6 ± 0.5 days ($P = 0.001$, 2003 vs. 2009). The most significant comorbidities associated with increased duration of hospitalization included ECMO use (38.4 ± 2.1 days, $P < 0.001$), sepsis (32.9 ± 1.5 days, $P < 0.001$), BPD (30.9 ± 1.3 days, $P < 0.001$), respiratory failure (29.8 ± 1.2 days, $P < 0.001$), hepatic insufficiency (19.1 ± 1.4 days, $P = 0.001$), and age <1 year (20.1 ± 0.6 days, $P < 0.001$). Of note, sex and hospitalization in a large hospital were not significantly associated with increased length of stay.

Mortality and factors associated with PH-related hospitalizations

The overall mortality for PH-related hospitalizations was significantly greater than that for hospitalizations not associated with PH, 5.7% versus 0.4% (odds ratio: 16.22 [95% CI: 14.78–17.8]). However, mortality during the study years decreased over time, ranging from 7.7% in 2000 to 4.5% in 2009 ($P < 0.001$; Fig. 2). Mortality in association with other comorbidities varied from 0.3% with SCD to as high as 34.3% in association with the use of ECMO ($P < 0.001$ for both). Although most comorbidities were associated with in-

creased mortality in PH-related hospitalizations, compared to that in non-PH-related hospitalizations, mortality in association with a large hospital, female sex, nonwhite race, ages 1–12 and 13–20 years, CHD, chromosomal abnormalities, SLE/CTD, SCD, and cardiomyopathy were not associated with increased mortality. On univariable analysis, urban location, teaching hospitals, age <1 year, BPD, CDH, sepsis, respiratory failure, acute renal failure, ECMO, hepatic insufficiency, and arrhythmias were all associated with increased mortality (Table 3). Factors associated with reduced mortality include a later calendar year, older age (1–12 years: odds ratio: 0.593 [95% CI: 0.494–0.711]; 13–20 years: odds ratio: 0.707 [95% CI: 0.600–0.833]), and chromosomal abnormalities. On multivariable analysis, only urban location, teaching hospital, CDH, sepsis, respiratory failure, acute renal failure, ECMO, hepatic insufficiency, and arrhythmias retained statistical significance.

Hospital charges for PH-related hospitalizations

Hospital charges for PH-related hospitalizations rose from 2000 to 2009. In 2000 the average charge for a PH-related hospitalization was \$66,457 ± \$4,487, and in 2009 it was \$135,572 ± \$5,144 ($P < 0.001$;

Figure 2. A, Hospital mortality, in percent, for pulmonary hypertension–related hospitalization in children across the years studied; $P < 0.001$ from ANOVA across years. B, Association of codiagnoses and mortality. An asterisk indicates $P < 0.05$ for factors significantly associated with increased or decreased mortality. BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; CHD: congenital heart disease; ECMO: extracorporeal membrane oxygenation; SLE/CTD: systemic lupus erythematosus/connective tissue disorder.

Fig. 3). Compared to those for non-PH hospitalizations, comorbidities associated with increased charges included CHD, BPD, CDH, sepsis, respiratory failure, acute renal failure, ECMO, hepatic insufficiency, and arrhythmias ($P < 0.001$ for all). Conversely, a large hospital, female sex, chromosomal abnormalities, SLE/CTD, and SCD were associated with a reduction in charges.

DISCUSSION

This is one of the first studies to determine prevalence, cost, and outcomes for most forms of PH in hospitalizations of children in the United States. The data collected were obtained from hospital records of patient discharges from more than 4,000 hospitals in the United States. Unlike PH registries, this study does not derive prevalence of PH in a population on individual records but rather on the number of all hospitalizations due to PH of all types.^{4-7,17,23,27} In addition, these data are representative of the entire United States and include admissions from all types of hospitals. As a result, the study provides important information on outcomes of PH-related hospitalizations as well as on morbidities and diagnoses associated with them. Likewise, this study is the first to identify hospital-related morbidities contributing to poor outcomes in PH-related mortality.

Similar studies have been performed in children with heart failure, adults with right heart failure, and neonates.^{20,24-27,29,30}

These data demonstrate an increasing prevalence of PH-related hospitalizations over the past decade. While it is certainly possible that the number of children being diagnosed with PH has increased during this time period, this study is limited by a large national database based on hospital admissions and not on individuals. Consequently, increasing prevalence can be related to alternative reasons, including an improved ability to diagnose less severe disease, an increased awareness of PH associated with other diseases, and an improved ability to recognize the disease earlier, with resultant hospitalization for more rapid and earlier treatment of PH. Nonetheless, this study adds important information to the very few data on hospitalizations related to PH as well as to longitudinal epidemiological data on PH in children. Likewise, there are only a few similar studies in adult PH. Data from a surveillance report published in 2005 by the Centers for Disease Control and Prevention revealed that hospitalization rates for adult Medicare patients with PH in the United States increased from 1980 to 2002.^{7,28} Likewise, a study examining the National Inpatient Sampling database and the US National Center for Health Statistics database

Table 3. Factors associated with mortality in pulmonary hypertension–related hospitalizations

Factor	Univariable		Multivariable	
	Odds ratio	95% CI	Odds ratio	95% CI
Year 2009 vs. other years	0.716	0.621–0.825	0.507	0.421–0.611
Urban location	10.862	3.448–34.222	5.659	1.281–24.997
Children's hospital	1.356	1.126–1.634	0.915	0.730–1.146
Large hospital	0.946	0.806–1.111	1.013	0.819–1.254
Teaching hospital	1.894	1.500–2.390	1.491	1.131–1.966
Female	1.038	0.917–1.174	1.118	0.941–1.328
Nonwhite	1.106	0.946–1.294	1.103	0.919–1.323
<1 year of age	1.878	1.595–2.211	1.180	0.879–1.585
CHD	1.086	0.942–1.252	1.044	0.848–1.286
BPD	1.524	1.268–1.831	1.142	0.901–1.447
CDH	2.774	2.047–3.759	1.937	1.250–3.001
Chromosomal abnormalities	0.683	0.568–0.823	0.882	0.680–1.144
Sepsis	3.670	3.145–4.284	2.421	1.987–2.950
Respiratory failure	5.158	4.549–5.848	4.446	3.736–5.290
Acute renal failure	8.390	6.779–10.384	4.851	3.460–6.801
ECMO	9.599	7.823–11.779	5.113	3.730–7.009
Hepatic insufficiency	3.306	2.534–4.312	1.967	1.295–2.987
Arrhythmias	1.969	1.647–2.354	1.941	1.573–2.395
Cardiomyopathy	1.183	0.867–1.614	1.171	0.744–1.844

Note: BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; CHD: congenital heart disease; CI: confidence interval; CTD: connective tissue disease, ECMO: extracorporeal membrane oxygenation; SLE: systemic lupus erythematosus.

published similar findings on the number of individual diagnoses of adult PH.^{2,5,6,16,23,27,31,32} Furthermore, a recent study on data from the ASPIRE registry (Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre) and a study examining hospitalization and mortality data on adults with PH from several referral centers in the United Kingdom and Ireland both demonstrated an increase in the number of new cases of PH per year from 2001 to 2009.^{3,29,30,33} In contrast, the number of new patient diagnoses for all forms of PH in children in the Netherlands PH registry declined from 2000 to 2006.^{2,4,7} However, yearly prevalence data were not examined for pediatric patients with all forms of PH. Given the improvement in survival with today's therapies, prevalence is likely to have at least remained stable, if not increased.^{2,5,6,16,23,31,32,34–36}

The patient characteristics of PH-related hospitalizations are changing. As the treatment of PH has become more specialized and is done mostly at PH-specific centers, the increase in the percentage of PH-related hospitalizations at children's hospitals is not unexpected. The diagnosis and treatment of the disease require a team of specialists most often found at children's hospitals. In addition, guidelines today suggest that care be given at PH centers.^{3,4,33} Interestingly, the percentage of nonwhite patients associated with PH-related hospitalizations rose over the study period, and nonwhite races accounted for the majority of PH-related hospitalizations. Again, the

study by Hyduk et al.²⁸ observed similar increasing prevalence of nonwhite Medicare patients hospitalized because of PH. Whether the actual number of individual PH diagnoses in nonwhites has increased cannot be ascertained by this study. Nonetheless, these observations would be in contrast to those from several PH registries, in which 67%–70% of PH patients are of the white race.^{2,4,5,7}

Hospitalizations for all forms of PH were most often associated with CHD, a factor in nearly 50% of the admissions in this study. Interestingly, these numbers contrast with those from studies in adults, where CHD is less commonly associated with PH and CTD-related PH is more common.^{34–37} CHD is associated with nearly 50% of patients with all forms of PH in the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry as well,^{4,7} and it also represents anywhere from 24% to 72% of patients in PAH registries.^{2,5,7,38} Our study does not delineate between simple and complex cardiac lesions and may overestimate the number of patients with PH due to CHD. This study is also limited in the ability to decipher whether CHD caused the PH. In addition, many patients with CHD will have undergone a cardiac procedure for repair or palliation, both of which can be associated with the development of postprocedural or postsurgical PH, as the risk of acidemia, hypercarbia, alveolar hypoxia, and acute pulmonary endothelial injury can lead to acute postoperative PH cri-

Figure 3. A, Hospital charges, in US dollars, for pulmonary hypertension–related hospitalizations in children across the years studied; $P < 0.001$ from ANOVA across years. B, Associated diagnoses effect on hospital charges for pulmonary hypertension–related hospitalizations. An asterisk indicates $P < 0.05$ for diagnoses associated with a change in hospital charges compared to non-pulmonary hypertension–related hospitalizations. BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; CHD: congenital heart disease; ECMO: extracorporeal membrane oxygenation; SLE/CTD: systemic lupus erythematosus/connective tissue disorder.

ses.^{4,37,39–41} Nonetheless, despite being commonly associated with PH-related hospitalizations, CHD did not affect mortality in our study, and it had only a minor effect on hospital length of stay and charges.

While not as common as CHD-associated PH, BPD was codiagnosed in up to 13.7% of PH-related hospitalizations, a finding that increased with time. In the TOPP and Dutch PH registries, 1.8%–3.7% of patients with PH had coexisting BPD.^{4,7,41} BPD is a developmental lung disease that is associated with a reduction in the pulmonary vascular area of the lung due to arrest of growth and injury, leading to the development of PH.^{38–41} Therefore, it is little surprise that studies examining the prevalence of PH in patients with BPD reveal that the codiagnoses are not uncommon, occurring in 15%–25% of these patients.^{4,38–43} These results may be partially explained by the increasing incidence of diagnosis of BPD as premature and very-low-birth-weight neonates receive improved care and survival in the surfactant era.^{2,6,7,17,23,41} Similar reasoning may explain the higher prevalence of infants associated with PH-related hospitalizations. However, the benefit of survival came with an increase in the length of stay, thereby compounding to the cost of each hospitalization, a finding generally observed in BPD

admissions with and without codiagnosed PH.^{39–41,44–46} And despite the improved care and survival in BPD patients, BPD associated with PH increased mortality up to 4-fold, as seen in previous studies.^{20,38–40,42,43}

The overall mortality for all years of PH-related hospitalizations was markedly high. There was a more than 15-fold increase in hospital mortality in patients with PH, compared to those patients without PH. Fortunately, mortality is declining. A reduction in mortality has been observed in almost all pediatric studies in the modern treatment era, including several patient registries, such as the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), the UK Pulmonary Hypertension Service for Children, and the Netherlands PH registry, as well as studies done at individual institutions.^{2,6,7,17,23,25,47,48} Improvement in mortality is most likely a product of improved inpatient care, new therapies derived from large adult trials and smaller pediatric studies, and the development of standardized algorithms to treat PH.^{44–46,49,50} However, it also possible that some component of the improved mortality seen may be secondary to increases in the diagnosing of less severe disease, improvement in recognizing the disease, and earlier hospitalization for treatment.

Comorbidities with increasing frequency in PH-related hospitalizations included sepsis, respiratory failure, acute renal failure, and arrhythmias. Concomitant with increasing frequency, these comorbidities were associated with increased duration of hospitalization, cost of hospitalization, and mortality. These findings are in congruence with those of a previous study of heart failure in children,^{20,51,52} and similar comorbidities are found associated in PH-related hospitalizations in adults.^{25,47,48,53} On the other hand, the use of ECMO is declining. But despite its declining use, its influence on increased hospitalization duration, charges associated with hospitalization, and mortality was greatest among the comorbidities examined. Outcomes with the use of ECMO in the treatment of PH in children vary. Most success has been accomplished in children with PH associated with CHD or PPHN, where survival has been quite high in several studies involving smaller population sizes, with up to nearly 100% survival.^{49,50} However, in pre-lung transplant patients with severe PH, mortality is as high as 60%.^{51,52} Our study revealed a hospital mortality of 34% and is a reflection of results obtained from all forms of PH rather than a single subgroup.

The charges for hospitalizations associated with PH are increasing over time. Our results indicate that this is not a result of increasing duration of hospitalization, because that measure has not changed significantly over the past decade. Some component of these increased charges is likely from newer pharmacological therapies for PH.⁵³ It should be noted that, whereas in 2000 there was only one FDA-approved medication for PH, by 2009 there were 6 different medications approved by the FDA in 3 separate pharmacologic classes. The use of these medications likely has resulted in greater longevity and higher cost of care for pediatric patients. In one cost-analysis study, the use of prostacyclins can be more than \$100,000 each year.⁵⁴

This study has several limitations. It is a retrospective study, and the findings may certainly differ from those for a prospectively enrolled cohort. There are also notable limitations of this administrative database. Admissions are identified by an ICD-9 code and not by the WHO classification of PH, and the nature of coding can change over the years.⁵⁵ This is true for idiopathic PAH (IPAH), as there was a change in the default code in 2000 that corresponded to the reduction in IPAH hospital discharges for that year.²⁷ Therefore, we elected to include all codes for PH in this study. It is also not known whether an expert in PH made the diagnosis, and the standards used to diagnose patients are not identified in this database. Furthermore, there is no information for lab values, catheterization data, echocardiograms, and other imaging studies to help determine the severity of the disease. As mentioned above, the database does not identify individual patients, as do registries, and for that reason multiple admissions from the same patient cannot be ascertained. Only hospital data are available, and thus it is not possible to determine the burden of prior hospitalizations or hospital readmissions for a given patient. Alternatively, registries may suffer from a referral bias, as registries are often associated with specialized PH centers, which are mostly found in urban areas. Therefore, large databases like the KID allow a larger and more diverse sampling of a population. Finally, the 10-year time period

of the study is relatively brief and thus may not accurately reflect trends that may be evident over longer time periods.

Conclusions. This is the first longitudinal study to examine prevalence and outcomes in pediatric PH-related hospitalizations. Our analysis demonstrates that prevalence is increasing, with a changing demographic of patients. Despite comprising the majority of PH-related hospitalizations, CHD is not associated with increased mortality. While hospital mortality is improving, it is still significantly higher than that for hospitalizations due to non-PH etiologies. The charges associated with PH-related hospitalizations continue to rise, with non-PH-related comorbidities being associated with these increased charges.

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