Resource utilization at the time of prostacyclin initiation in children in pulmonary arterial hypertension: a multicenter analysis

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Abstract

There are limited data investigating the epidemiology and resource utilization associated with parenteral prostacyclin use in children. We sought to examine national trends in treatment practices and resource utilization during prostacyclin initiation for pulmonary arterial hypertension (PAH) at children's hospitals in the United States. Patients with PAH initiated on parenteral epoprostenol and treprostinil (2004–2014) were identified using a nationwide administrative database. Demographics, clinical characteristics, and resource utilization were compared between epoprostenol and treprostinil groups. Costs were indexed in 2014 US dollars. Among 1448 children admitted with a primary or secondary diagnosis of PAH, 280 (19%) were initiated on parenteral prostacyclins (epoprostenol n = 195 and treprostinil n = 85). Epoprostenol predominated early (97% of initiations in 2005); however, treprostinil predominated recently (52–67% of initiations/year). Children initiated on treprostinil had shorter ICU stays (1 [IQR = 0–4] vs. 4 [0–10] days, P < 0.001), shorter total lengths of stay (4 [2–9] vs. 8 [4–18] days, P = 0.001), and lower in-hospital mortality (1 vs. 12%, P = 0.001) with no difference in 30-day (13 vs. 19%, P = 0.19) or one-year readmission rates (56 vs. 61%, P = 0.41). Inpatient costs were lower for treprostinil initiation ($23,779 [11,830–39,535] vs. $32,976 [11,904–94,082], P = 0.03), with a greater difference in the recent era (2009–2013). Though significant variation exists regarding prostacyclin use for PAH across US centers, prostacyclins are common among children with PAH. Treprostinil initiation has been increasing and is associated with less resource utilization and lower cost compared to epoprostenol initiation. Post-discharge outcome data are needed to fully inform decision-making about the relative benefits of parental prostacyclin drug choice.

Keywords

pulmonary hypertension, pediatric, cost, prostacyclin

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Pulmonary hypertension (PH) is a complex and devastating disease. Pulmonary arterial hypertension (PAH) is an important class of PH comprising largely patients with idiopathic PAH and familial PAH (historically classified as “primary pulmonary hypertension”).¹⁻⁴ Estimates of five-year mortality for PAH are in the range of 20–30% in the pediatric population.¹

The most recent pediatric guidelines recommend continuous parenteral prostacyclin therapy with either epoprostenol or treprostinil for patients with PAH at high risk of disease progression and those that have failed oral combination therapy.⁵,⁶ Prostacyclins have been shown to improve
hemodynamics, functional class, exercise capacity, and survival, but there are few data comparing the two drugs or evaluating the economic impact of these therapies.7,8

Recently, there has been increasing emphasis on enhancing healthcare value by reducing costs and improving outcomes.9 While much PAH research has focused on outcomes, there are scant data relating to the cost associated with PAH care which is resource-intensive. A number of small cost comparison studies have estimated the relative costs of epoprostenol and treprostinil in mostly adult populations with mixed findings.10–13 None of these studies have evaluated prostacyclin use among patients with PAH or resource utilization and costs associated with prostacyclin therapy in the pediatric population.

We sought to examine national trends in the use of prostacyclin therapy and describe resource utilization associated with initiation of either epoprostenol or treprostinil in children with PAH. We hypothesized that prostacyclin therapy is frequently used in the pediatric population and that treprostinil is associated with less total resource utilization and cost than epoprostenol during initiation of therapy despite being a more expensive drug.

Methods

Data source

Data for this study were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation encounter-level data from over 45 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children’s Hospital Association (Overland Park, KS, USA). Data quality and reliability are assured through a joint effort between the Children’s Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI, USA). Data are de-identified at the time of data submission and data are subjected to a number of reliability and validity checks before being included in the database. This study was approved by the Institutional Review Board of the University of Pittsburgh.

Study population

All inpatient and observation encounters at PHIS member hospitals for patients aged 2–22 years at the time of admission between 1 January 2004 and 31 March 2014 were included. Patient encounters in PHIS are classified using the ubiquitous International Classification of Disease, Ninth Revision (ICD-9) coding scheme. We included patient encounters with an ICD-9 diagnosis code of “primary pulmonary hypertension” (416.0) but did not include “chronic pulmonary embolism” (416.2), “other chronic pulmonary heart diseases” (416.8), or “chronic pulmonary heart disease unspecified” (416.9), in an effort to include only those patients with idiopathic or familial PAH. The lower age limit of two years was chosen to exclude cases of acute PH related to prematurity which we also considered outside the focus of our study.

Demographics, clinical characteristics, in-hospital outcomes, readmission rates, charges, and costs were queried. Included in this were PHIS-defined elements of surgical and medical complications as well as clinical, pharmacy, imaging, supply, and “other” charge subgroups. We defined prostacyclin initiation as the first encounter with either an epoprostenol or treprostinil charge. This method excluded the potential to “double-count” patients who were initiated on epoprostenol and transitioned during a later admission to treprostinil (or vice versa). Also, to account for potential lack of knowledge about prostacyclin use before 2004 (i.e. left-censored prostacyclin use), we excluded patients whose first prostacyclin use occurred in 2004 from our initiation analysis. To examine the frequency at which prostacyclins were used relative to the volume of patients with PAH (i.e. rate of prostacyclin initiation), we divided the number of prostacyclin initiations by the number of unique patients with PAH by year or by institution.

Charges and cost

Each PHIS hospital reports charges after adjusting for local cost-of-living difference according to the Centers for Medicare & Medicaid Services. Most hospitals report institutional cost-to-charge ratios which were used to estimate hospital costs. For initiation encounters without a reported cost-to-charge ratio (n = 32, 11%), the cost-to-charge ratio was estimated by using the median cost-to-charge ratio of initiation encounters among reporting hospitals (0.34).

We then indexed all dollar amounts to 2014 US dollars using the annual consumer price index published by the US Bureau of Labor Statistics.14

Statistics

Categorical data are presented as n (%) and continuous data as mean ± standard deviation or median [interquartile range]. Comparisons between groups were made using Wilcoxon rank-sum test for continuous variables and the chi-square or Fisher’s exact test for categorical data. Epoprostenol was available during the entire study period while treprostinil was adopted later and was not widely available at the beginning of our study period. To control for the potential confounding effect of treatment era, we performed additional, era-stratified analyses (early 2005–2008 vs. late 2009–2014) or included treatment era as a covariate in select linear and logistic regression models. Statistical tests were two-sided and P ≤ 0.05 was considered significant. Statistical analyses were performed using JMP Pro 9 (SAS Institute, Inc., Cary, NC, USA).
Results

Study population

Between 2004 and 2014, 41 of the 45 PHIS member hospitals had at least one admission for a patient with PAH. There were 2647 hospital admissions with a diagnosis of PAH in 1448 unique children. Of these, 280 patients (19%) were initiated on either parenteral epoprostenol (n = 195, 70%) or treprostinil (n = 85, 30%). Thirty-six encounters were identified where both medications were administered. For these encounters, only the first drug administered was considered. Similarly, encounters for initiation of treprostinil preceded by an encounter where epoprostenol (or vice versa) were not included in the analysis, as these likely represented transitions in therapy, perhaps under different clinical circumstances, and could have biased the analysis. Demographics and clinical characteristics of those initiated on parenteral prostacyclins are shown in Table 1. No differences in sex, age, race, medical co-morbidities, or insurance status between patients initiated on epoprostenol vs. treprostinil were found. Children initiated on epoprostenol were more likely to be receiving calcium channel blockers (11% vs. 4%, \( P = 0.03 \)) and digoxin (44% vs. 27%, \( P = 0.01 \)) and less likely to be receiving endothelin receptor antagonists (29% vs. 44%, \( P = 0.02 \)).

Prevalence of prostacyclin initiation

Figure 1 shows the prevalence of prostacyclin initiation as a function of institutional PAH volume as measured by patients hospitalized for PAH. The median proportion of PAH patients initiated on prostacyclins per hospital was 16% with a range of 0–53%. Among centers with >50 patients admitted with a diagnosis of PAH (n = 8), the prevalence of parental prostacyclin initiation was in the

Table 1. Demographics and clinical characteristics during prostacyclin initiation.

|                      | Epoprostenol initiated (n = 195, 70%) | Treprostinil initiated (n = 85, 30%) | \( P \) value |
|----------------------|--------------------------------------|-------------------------------------|---------------|
| Females (%)          | 105 (54)                             | 55 (65)                             | 0.09          |
| Age (years)          | 10.4 ± 5.4                           | 10.9 ± 6.0                          | 0.53          |
| Race (%)             |                                       |                                     |               |
| White                | 134 (69)                             | 49 (58)                             | 0.24          |
| Black                | 18 (9)                               | 14 (17)                             |               |
| Asian                | 12 (6)                               | 5 (6)                               |               |
| Other/Missing        | 31 (16)                              | 17 (20)                             |               |
| Medical co-morbidities* (%) |                            |                                     |               |
| Any chronic condition| 106 (54)                             | 39 (46)                             | 0.19          |
| Cardiovascular       | 89 (45)                              | 31 (37)                             | 0.18          |
| Respiratory          | 9 (5)                                | 4 (5)                               | 0.97          |
| Neuromuscular        | 8 (4)                                | 4 (5)                               | 0.82          |
| Gastrointestinal     | 2 (1)                                | 1 (1)                               | 0.91          |
| Metabolic            | 5 (3)                                | 2 (2)                               | 0.92          |
| Hematologic/Immunologic | 5 (3)                              | 1 (1)                               | 0.44          |
| Malignancy           | 4 (2)                                | 2 (2)                               | 0.87          |
| Renal                | 2 (1)                                | 2 (2)                               | 0.41          |
| Primary payor (%)    |                                       |                                     |               |
| Private              | 91 (47)                              | 36 (42)                             | 0.72          |
| Public               | 82 (42)                              | 37 (44)                             |               |
| Other                | 22 (11)                              | 12 (14)                             |               |
| Concurrent therapy (%) |                                     |                                     |               |
| Phosphodiesterase-5 inhibitor | 54 (28)                          | 27 (32)                             | 0.49          |
| Endothelin receptor antagonist | 56 (29)                          | 37 (44)                             | 0.02          |
| Calcium channel blocker | 21 (11)                           | 3 (4)                               | 0.03          |
| Oxygen               | 92 (47)                              | 51 (60)                             | 0.05          |
| Diuretic             | 136 (70)                             | 49 (58)                             | 0.05          |
| Digoxin              | 85 (44)                              | 23 (27)                             | 0.01          |
| Anticoagulant        | 114 (59)                             | 40 (47)                             | 0.08          |

Data presented as n (%) or mean ± SD.

*As defined by PHIS.
range of 6–29%. Figure 2 displays the relative proportions of epoprostenol and treprostinil initiations at each hospital. Eight of the 41 (20%) centers with PAH admissions had no patients initiated on parental prostacyclins. Except for a single institution (#18) with all four prostacyclin initiations as treprostinil, epoprostenol initiation showed no association with institutional PAH volume. As shown in Fig. 3, epoprostenol predominated over treprostinil early, accounting for 97% of total initiations in 2005. However, since 2011, treprostinil initiation has been predominant (52–67% of initiations/year).

Resource utilization and inpatient outcomes
As shown in Table 2, epoprostenol initiation was associated with longer median lengths of stay (LOS) in the ICU (4 vs. 1 days, \( P < 0.001 \)) and for the overall hospitalization (8 vs. 4 days, \( P = 0.001 \)). Right heart catheterization was performed during the initiation hospitalization in only 35% of patients, with no significant difference between those initiated on epoprostenol vs. treprostinil. Mechanical ventilation and extracorporeal membrane oxygenation (ECMO) were both more commonly utilized during the initiation encounter among patients started on epoprostenol (35% vs. 14%, \( P < 0.01 \) and 6% vs. 1%, \( P = 0.04 \), respectively). We observed no differences in the prevalence of medical and surgical complications between the groups; however, those initiated on epoprostenol had higher in-hospital mortality during the initiation encounter (12% vs. 1%, \( P < 0.01 \)). No out-of-hospital mortality data were available. After controlling for era in multivariable regression analyses, total LOS, ICU LOS, use of mechanical ventilation, and in-hospital mortality all remained significantly greater among children initiated on epoprostenol.

Readmission following prostacyclin initiation
All cause readmissions at 30, 90, and 365 days following the prostacyclin initiation encounter were queried. We found no differences in the frequency of readmissions between those initiated on epoprostenol vs. treprostinil (Table 2).

| Table 2. Resource utilization, in-hospital outcomes, and hospital readmission rates at the time of prostacyclin initiation. |
|---|---|---|
| Epoprostenol initiated (n = 195, 70%) | Treprostinil initiated (n = 85, 30%) | \( P \) value |
| Length of stay (days) | 8 [4–18] | 4 [2–9] | 0.001* |
| Intensive care utilization | 145 (74%) | 53 (62%) | 0.05* |
| Intensive care length of stay (days) | 4 [0–10] | 1 [0–4] | <0.001* |
| Right heart catheterization | 62 (32%) | 35 (41%) | 0.13 |
| Mechanical ventilation utilization | 68 (35%) | 12 (14%) | <0.001* |
| ECMO utilization | 12 (6%) | 1 (1%) | 0.04 |
| Medical complication | 3 (2%) | 2 (2%) | 0.64 |
| Surgical complication | 59 (30%) | 20 (24%) | 0.25 |
| In-hospital mortality | 23 (12%) | 1 (1%) | 0.001* |
| 30-day readmissions | 25 (13%) | 16 (19%) | 0.19 |
| 90-day readmissions | 52 (27%) | 26 (31%) | 0.5 |
| 365-day readmissions | 109 (56%) | 52 (61%) | 0.41 |

Data presented as number (%) or median [IQR].

*Remained significant in multivariate analysis.

ECMO, extracorporeal membrane oxygenation.

Charges and cost
Hospital charges and cost for parenteral prostacyclin initiation are shown in Table 3. Median total hospital cost was $9197 greater for initiation of epoprostenol ($32,976 [$11,904–$94,082]) than treprostinil ($23,779 [$11,830–$39,535]; \( P = 0.03 \)). We also observed a trend toward higher median total hospital charges for epoprostenol initiation ($102,694 [$33,722–$277,713] vs. $65,794 [$34,850–$141,306]; \( P = 0.06 \)). When broken down into subgroups, we found no significant differences in clinical, pharmacy, and imaging charges between the groups. Epoprostenol initiation was associated with greater lab and other charges, which includes service-related charges such as hospital room and nursing care charges.

As shown in Table 4, epoprostenol remained associated with higher initiation hospitalization costs and charges in the most recent era (2009–2014). We also observed nearly a fourfold increase in the difference between median hospital costs for epoprostenol and treprostinil initiation in the most recent era ($36,362 relative to the entire study period ($9197). A similar 2.7-fold increase in the difference between median hospital charges for epoprostenol and treprostinil initiation was also observed.

Discussion
This study demonstrates that initiation of parenteral prostacyclin therapy is common among children who are admitted with PAH to US children’s hospitals, and there
has been an increase in prevalence of children initiated on parental prostacyclins over the past five years. We have also shown that epoprostenol, once the only option for parental prostacyclin treatment, has been overtaken by treprostinil as the most commonly initiated parental prostacyclin in the pediatric PAH group in the US. Median hospital costs associated with treprostinil initiation were 39% less than those associated with epoprostenol initiation, with shorter lengths of stay and lower resource utilization. While epoprostenol was widely used throughout the study period, intravenous and subcutaneous treprostinil became more widely utilized during the late years of the study period (albeit at a poorly defined time), potentially contributing to the significant era effect we observed. Nonetheless, the differences we observed in cost and resource utilization remained after accounting for drug era, suggesting that the associations of treprostinil with lower cost and charges are not fully due to differences in practice norms or experience managing pediatric PAH during the earlier years of the analysis when epoprostenol initiation was much more common.

One possible reason for the cost, charge, and resource utilization associations we found could be a quicker initial dose titration with fewer initial side effects. Though we could find no study which directly compared side-effect profiles of the two medications given parenterally, our clinical experience and a review of the reported frequency of some of the common prostacyclin side effects (flushing, jaw pain, diarrhea, headache) suggests this is a plausible assertion. Another possible reason could be that less sick patients were initiated on treprostinil. Because the PHIS database is an administrative dataset which does not collect clinical findings, hemodynamics, or echocardiographic parameters, we cannot exclude this possibility. Though endothelin receptor antagonists were more likely to be prescribed in those initiated on treprostinil therapy, while calcium channel blockers, diuretics, and digoxin were less likely to be prescribed, we believe this reflects an era difference and not a difference in disease severity between the groups.

To our knowledge, this is the largest cohort of pediatric PAH reported and the first to describe use of, and resource utilization surrounding, parental prostacyclin therapy on a national scale. Current guidelines recommend continuous parenteral prostacyclin therapy for advanced disease (World Health Organization functional class III–IV) or for patients who have failed to respond to oral therapies. Recent reports, however, have suggested that treatment with prostacyclins earlier in the disease course may be beneficial. The rate of intravenous prostacyclin use in the REVEAL registry was 26% in adults and 29% in children, both of which are greater than the 16% we observed in this pediatric cohort. This may suggest underutilization of parental prostacyclins in children with PAH who are cared for at US pediatric hospitals, some of which are not PAH specialty centers, or alternatively is a result of our conservative method for identifying prostacyclin initiations. Because of the lack of baseline hemodynamic and functional class data in our cohort, caution with respect to drawing firm conclusions on the use of prostacyclins between our

### Table 3. Hospital charges and costs at the time of prostacyclin initiation.

|                | Epoprostenol initiated (n = 195, 70%) | Treprostinil initiated (n = 85, 30%) | P value |
|----------------|--------------------------------------|-------------------------------------|---------|
| Total cost     | 32,976 [11,904–94,082]               | 23,779 [11,830–39,535]             | 0.03    |
| Total charges  | 102,694 [33,722–277,713]             | 65,794 [34,850–141,308]            | 0.06    |
| Clinical charges | 10,989 [1314–77,122]                 | 7514 [1125–22,759]                | 0.16    |
| Pharmacy charges | 10,399 [3991–50,023]                 | 14,189 [6201–31,223]              | 0.46    |
| Imaging charges | 3642 [178–11,474]                   | 2785 [662–7352]                   | 0.22    |
| Lab charges    | 7597 [2084–26,476]                   | 4501 [1245–14,276]                | 0.01    |
| Supply charges | 2126 [219–8882]                     | 2609 [363–5755]                   | 0.76    |
| Other charges  | 48,654 [15,071–107,488]              | 26,326 [11,375–51,814]            | 0.007   |

Data presented as median [IQR]. All data in 2014 USD.

### Table 4. Charges and costs at the time of prostacyclin initiation during late era (2009–2013).

|                | Epoprostenol initiated (n = 79) | Treprostinil initiated (n = 69) | P value |
|----------------|---------------------------------|---------------------------------|---------|
| Total cost     | 61,892 [28,372–97,214]          | 25,530 [12,337–45,339]          | <0.01   |
| Total charges  | 169,806 [85,691–292,421]        | 70,631 [36,072–150,113]         | <0.01   |

Data presented as median [IQR]. All data in 2014 USD.
cohort and the pediatric REVEAL cohort is important. Of note, the pediatric REVEAL cohort appeared to be enriched for patients with more significant PAH based on reported demographics of 49% with functional class III–IV and group mean pulmonary arterial pressure 72 ± 17 mmHg with pulmonary to systemic vascular resistance ratio of 0.8 ± 0.5.1

We found a wide degree of institutional variation in prostacyclin initiation, particularly among centers with lower volumes of PAH patient encounters. The centers following the largest number of patients with PAH (>50) had less variation in their parenteral prostacyclin use with rates in the range of 15–30%. Current recommendations suggest prostacyclin therapy be administered at experienced centers given the complexities of prostacyclin administration.19,20 High volume centers have been demonstrated to have superior outcomes for congenital heart surgery21,22 and in pediatric heart transplantation.23,24 Whether this also applies to pediatric PAH care is unclear and not answerable by our analysis. Because we were unable to assess longitudinal outcomes such as progression to lung transplantation or death, we are unable to comment on whether the variability we observed in parental prostacyclin initiation among centers is clinically meaningful.

There are a number of limitations to this study that must be considered. The PHIS database incorporates robust validation measures, but medical coding errors may exist. PAH does not have an associated ICD-9 code but we believe our surrogate ICD-9 code (“primary pulmonary hypertension”) has a high sensitivity and specificity to identify our intended study population. Nonetheless, we cannot exclude the possibility that prostacyclin use in the immediate postoperative period after congenital cardiac surgery may have been captured in some proportion of the cases analyzed. Also, in-hospital outcome measures may also be prone to case ascertainment error as has recently been described in the congenital heart disease population.25 Furthermore, the PHIS database is an administrative database which lacks granular clinic data preventing a robust comparison between baseline illness severity between the treatment groups. As a result, we were unable to compare the groups with respect to severity of PAH (i.e. functional class, pre-therapy hemodynamics) and we cannot exclude that the resource utilization, LOS, and total hospital costs may be related to the severity of patients’ clinical condition and not to the type of prostacyclin. A portion of patients in our cohort may have received inhaled prostacyclin therapy that may not have been captured and we were not reliably able to determine subcutaneous from intravenous delivery of treprostinil which may have had impacts on outcomes and resource utilization. The PHIS database lacks the ability to capture out-of-hospital clinical outcomes hindering fully informed decision-making on drug choice.

Prostacyclin use is common in children with PAH and treprostinil has become the most frequently initiated prostacyclin. There is significant variation across institutions regarding use of prostacyclin, suggesting the need for further recommendations. Our data suggest less resource utilization and lower cost for those patients initiated on treprostinil; however, more robust data from clinical registries are needed to support these findings.

Conflict of interest
The author(s) declare that there is no conflict of interest.

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