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# Advances in Prostanoid Infusion Therapy for Pulmonary Arterial Hypertension

**ABSTRACT**

Pulmonary arterial hypertension is a rare but progressive and life-threatening disease that presents considerable challenges for both the patient and the caregiver. Though complex, intravenous epoprostenol and treprostinil may improve long-term survival, exercise capacity, hemodynamics, and other clinical symptoms of pulmonary arterial hypertension. Recent advances in infusion pump technology offer ambulatory pump sizes as small as a pager and continuous infusion flow rates as low as 0.1 mL/h, which may provide quality-of-life advantages for patients treated with treprostinil. Transition methods from epoprostenol to treprostinil vary and require close patient monitoring for up to several months. Patients and clinicians must be aware of the differences among delivery systems and the potential for adverse events.

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Pulmonary arterial hypertension (PAH) is a rare but progressive and life-threatening disease that presents considerable challenges for both the patient and the clinician. Pharmacotherapeutic interventions at later stages of PAH include continuous parenteral prostanoids that are infused through a central venous catheter using an ambulatory infusion pump. Currently, 2 prostanoids are approved by the Food and Drug Administration (FDA) in the United States for parenteral administration: epoprostenol (Flolan®, GlaxoSmithKline, Research Triangle Park, North Carolina) and treprostinil (Remodulin®; United Therapeutics Corp, Research Triangle Park, North Carolina). Continuous parenteral prostanoid therapy improves long-term survival rates, exercise capacity, hemodynamics, and other clinical symptoms of PAH.[1] Recent advances in infusion pump technology offer the PAH patient options that can allow up to 48 hours between reservoir changes and ambulatory pump sizes as small as a pager. These advances in pump technology are less cumbersome and have the potential to improve patient quality of life as well as treatment satisfaction. This review provides an overview of PAH, intravenous (IV) prostanoid therapies, and ambulatory infusion devices. A series of case studies illustrate insights and issues regarding transition methods and pump selection for adults and pediatric patients, as well as the role of nurses in helping patients meet the challenges of these lifelong therapies.

## PULMONARY HYPERTENSION OVERVIEW

Pulmonary arterial hypertension is a rare but progressive disease affecting the pulmonary vasculature, leading to right ventricular dysfunction and death. Classification of PAH was established by the 2003 Third World Health Organization Symposium on Pulmonary Hypertension in which pulmonary hypertension was grouped according to similar pathobiology and treatment options.[1] Within this classification, group 1 consists of idiopathic, familial, or PAH associated with an underlying disease

state or pathology, such as collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, appetite suppressants, or illicit drugs (Table 1).[2] This classification is also appropriate to the pediatric population.[3] However, children typically present with PAH associated with congenital heart disease and have a lower incidence of PAH related to HIV infection, portal hypertension, chronic thromboembolic disease, or drugs/toxins than adults.[3,4] The majority of PAH patients are adults with either idiopathic PAH or PAH related to a secondary insult and tend to develop the disease later in life. To date, there is no known cure for this disease. Data from the Primary Pulmonary Hypertension Registry prior to the availability of treatment showed a median survival of 2.8 years for adults and 10 months for children.[4,5]

Pulmonary arterial hypertension is difficult to diagnose and is often a diagnosis of exclusion. Presenting symptoms are similar to other cardiopulmonary diseases and include dyspnea on exertion, fatigue, syncope, and chest pain. Diagnostic tests such as chest radiographs, electrocardiograms, echocardiograms, pulmonary function tests, ventilation perfusion scans, and multiple serology tests are part of the diagnosis of PAH and its underlying cause; however, the right heart catheterization (RHC) remains the gold standard for establishing the diagnosis and the severity of PAH.[5,6]

The RHC determines the severity of the disease by directly measuring the pulmonary artery pressures and cardiac output. A mean pulmonary arterial pressure of 25 mm Hg or higher at rest with a normal left atrial pressure is considered a confirmatory diagnosis of PAH. The RHC also provides information on intracardiac shunting, pulmonary venous pressure, and the presence or the absence of left-sided heart disease. Table 2 provides a list of hemodynamic assessments captured during the RHC and the relationship with the diagnosis of PAH.[5,6]

Unless contraindicated, a vasoreactivity test is conducted during the initial RHC. In this test, a short-acting vasodilator (epoprostenol, adenosine, or inhaled nitric oxide) is given and hemodynamic parameters are measured. A *positive vasoreactivity test* is defined as a reduction in mean pulmonary arterial pressure by at least 10 mm Hg to a value of 40 mm Hg or less following vasodilator administration and considered predictive that a patient may have a clinical response to calcium channel blocker therapy.[5]

## TREATMENT

The American College of Chest Physicians recommends treatment based on the World Health Organization (WHO) Functional Classification. This classification is modeled on the New York Heart Association (NYHA) Classification for Heart Failure.

**TABLE 1**

### WHO Classification of Pulmonary Arterial Hypertension

| |
|---|
| *1. Pulmonary arterial hypertension* |
| 1.1. Idiopathic |
| 1.2. Familial |
| 1.3. Associated with: |
| 1.3.1. Collagen vascular disease |
| 1.3.2. Congenital systemic to pulmonary shunts |
| 1.3.3. Portal hypertension |
| 1.3.4. HIV infection |
| 1.3.5. Drugs and toxins |
| 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, sickle cell disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy) |
| 1.4. Associated with significant venous or capillary involvement: |
| 1.4.1. Pulmonary veno-occlusive disease |
| 1.4.2. Pulmonary capillary hemangiomatosis |
| 1.5. Persistent pulmonary hypertension of the newborn |
| *2. Pulmonary hypertension associated with left-sided heart disease* |
| 2.1. Left-sided atrial or ventricular heart disease |
| 2.2. Left-sided valvular heart disease |
| *3. Pulmonary hypertension associated with lung disease and/or hypoxemia* |
| 3.1. Chronic obstructive pulmonary disease |
| 3.2. Interstitial lung disease |
| 3.3. Sleep-disordered breathing |
| 3.4. Alveolar hypoventilation disorders |
| 3.5. Chronic exposure to high altitude |
| 3.6. Developmental abnormalities |
| *4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (chronic thromboembolic pulmonary hypertension)* |
| 4.1. Thromboembolic obstruction of proximal pulmonary arteries |
| 4.2. Thromboembolic obstruction of distal pulmonary arteries |
| 4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material) |
| *5. Miscellaneous* |
| Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis) |

*From Simonneau et al.*[2]

**TABLE 2**

## Right Heart Catheterization Diagnostic Criteria

| Value | Abbreviation | Normal Parameter | Parameter Indicative of Pulmonary Arterial Hypertension |
|---|---|---|---|
| Mean pulmonary artery pressure | mPAP | 9–17 mm Hg | >25 mm Hg at rest |
| Systolic pulmonary artery pressure | sPAP | 15–30 mm Hg | Above normal parameters |
| Pulmonary vascular resistance | PVR | 80–120 dynes/cm$^2$ | Above normal parameters |
| Right atrial pressure | RAP | 0–8 mm Hg | Above normal parameters |
| Systolic right ventricle pressure | sRVP | 15–25 mm Hg | Above normal parameters |
| Diastolic right ventricle pressure | dRVP | 0–8 mm Hg | Above normal parameters |
| Cardiac index | CI | 2.4–4.2 L/min/m$^2$ | Normal or below normal parameters |
| Pulmonary capillary wedge pressure | PCWP | 4–12 mm Hg | ≤15 mm Hg |

Although both classifications primarily focus on the exercise tolerance of the patient, the WHO classification was adapted specifically for the PAH patient (Table 3).[6]

The goal of PAH treatment is to lengthen survival time, ameliorate symptoms of PAH, and improve quality of life. Response to therapy is periodically evaluated, and it is based on the reduction of PAH symptoms and improvement in hemodynamics, WHO Functional Classification, and exercise capacity as measured by the 6-minute walk test. Conventional treatments include diuretics to manage volume overload, supplemental oxygen if necessary, anticoagulants, and calcium channel blockers in the few patients who exhibit a positive vasoreactive response during the RHC.[5] Phosphodiesterase 5 inhibitors (ie, sildenafil) and endothelin receptor antagonists (ie, bosentan and ambrisentan) have recently been approved by the FDA for the treatment of PAH. Sildenafil and ambrisentan are indicated for patients with Functional Class (FC) II–IV symptoms, whereas bosentan is indicated for FC III–IV.[7-9] Of the prostanoids, treprostinil is indicated for FC II–IV, whereas epoprostenol and iloprost are indicated for FC III–IV patients.[10-12] However, because of the difficulties associated with parenteral therapy, epoprostenol and treprostinil are often reserved for patients with more advanced disease states or those who are unresponsive to oral therapy.[13,14] Because of the potential for serious adverse events with continuous IV prostanoid therapy, it is strongly recommended that patients be referred to centers of excellence for the treatment of PAH, allowing for state-of-the-art care and monitoring.

## PARENTERAL PROSTANOIDS

The term *prostanoid* encompasses members of the prostacyclin and prostaglandin families such as prostacyclin $I_2$ ($PGI_2$) and prostaglandin $E_1$ ($PGE_1$). Throughout this review, the term *prostanoid* refers to $PGI_2$ and $PGI_2$ analogs. Prostanoids have potent pulmonary vasodilatory and platelet antiaggregatory properties. Increasing pulmonary vasodilation reduces the workload of the right ventricle, increases blood flow through the lungs, and lowers the pulmonary artery pressure, resulting in the improvement of PAH symptoms and exercise capacity.[15]

Currently, there are 3 FDA-approved prostanoids for the treatment of PAH in the United States. Continuous intravenous administration of epoprostenol is carried out through a central venous catheter.[11] Administration of treprostinil is done either through a central venous catheter or by continuous subcutaneous infusion.[10] Iloprost was recently approved for inhalation treatment of PAH.[12] Adverse effects common to all prostanoids include headache, flushing, hypotension, jaw pain with initial mastication, diarrhea, nausea, a blotchy erythematous rash, and musculoskeletal aches and pain predominantly involving the legs and the feet. The severity of these adverse effects may vary among patients and with dose escalation.[10-12] For the purpose of this review, only the parenteral prostanoids, epoprostenol and treprostinil will be discussed.

Epoprostenol sodium (Flolan®), or prostaglandin $I_2$, is an endothelial-derived prostaglandin with potent pulmonary and systemic vasodilatory and antiplatelet

**TABLE 3**

## WHO Functional Classification of Pulmonary Arterial Hypertension

| Class | Description |
|---|---|
| I | Patients with PAH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope. |
| II | Patients with PAH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope. |
| III | Patients with PAH who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope. |
| IV | Patients with PAH who are unable to perform any physical activity at rest and may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity. |

*Abbreviation: PAH, pulmonary arterial hypertension.*
*From Barst et al.* [6]

aggregation properties. It was the first prostanoid approved by the FDA to treat PAH in 1995 and is indicated for the treatment of PAH in WHO FC III–IV patients. Epoprostenol demonstrated efficacy with improvement in exercise capacity in 2 prospective, open-label, randomized trials comparing epoprostenol and conventional therapy with conventional therapy alone.[16,17] Epoprostenol is initiated at 1 to 3 ng/kg/min and gradually increased over several months to a dose of 30 to 50 ng/kg/min or higher. It is crucial to individually titrate doses depending on the therapeutic response and emergence of prostanoid-related adverse effects. Regardless of the dose, all concentrations must be diluted to allow a minimal infusion rate of 1.2 mL/h or higher.[11]

Epoprostenol has a short half-life of 2 to 3 minutes and is unstable at room temperature. Any rapid rate decrease or interruption of the infusion owing to either an occluded catheter or a pump malfunction can cause severe rebound pulmonary hypertension and death.[18,19] Continuous IV therapy using epoprostenol is complex; the patient must reconstitute multiple vials of the drug (dose dependent), transfer the mixture into the reservoir attached to the pump, and either replace the reservoir every 8 hours or keep the solution cool in the reservoir with freezer cold packs for up to 24 hours.

In 2002, the FDA approved treprostinil sodium (Remodulin®), a stable tricyclic benzindene analog of epoprostenol, as a continuous subcutaneous infusion for the treatment of PAH. Treprostinil demonstrated safety and efficacy in 2 randomized, placebo-controlled trials for PAH in WHO FC II–IV patients, with improvement in exercise capacity.[20] Recently, a large open-label trial of 860 patients reported a long-term survival benefit of treprostinil in patients with idiopathic pulmonary hypertension comparable with the survival benefit of epoprostenol, relative to published registry survival curves.[21] However, subcutaneous infusion site pain was a treatment-limiting factor for some patients despite the clinical benefit. A bioequivalence study comparing IV and subcutaneous routes of administration was conducted, and based on the results, IV treprostinil received FDA approval in 2004 for patients who are unable to tolerate subcutaneous infusion.[22] In addition, as of February 2008, treprostinil was also indicated to diminish the clinical deterioration in patients requiring transition from epoprostenol sodium.[10]

Treprostinil is stable for 48 hours in an IV diluent at room temperature (the use of freezer cold packs is not required) and has a plasma elimination half-life of approximately 4.5 hours.[10] Treprostinil (available as 1.0, 2.5, 5.0, or 10 mg/mL solutions) can be diluted with sodium chloride to achieve an appropriate concentration for IV delivery. Intravenous treprostinil is initiated at 1 to 3 ng/kg/min and gradually increased by 1 to 2 ng/kg/min 2 to 3 times weekly to a chronic dose of 80 to 120 ng/kg/min or higher. Again, it is crucial to individually titrate the patient's dose depending on the emergence of prostanoid-related adverse effects and therapeutic response.[10,23]

## CONTINUOUS PROSTANOID INFUSION THERAPY AND QUALITY OF LIFE

The decision to begin continuous IV prostanoid therapy is difficult for PAH patients. This type of therapy is usually offered at a time when oral treatment is no longer effective and the patient is experiencing worsening symptoms of PAH. Furthermore, the patient may be making a lifelong commitment to continuous IV therapy and must have the resources and skills to meet the requirements of this type of therapy. For clinicians, patient selection and education are critical factors to the success of this therapy. For patients, multiple external factors such as disease severity, financial resources, comorbidities, social support, psychological support, and previous treatment failure can influence prostanoid treatment success. Health-related quality of life (HRQOL) reflects a patient's satisfaction with his or her life; thus, HRQOL will also affect treatment satisfaction.

A patient's perception of treatment satisfaction can impact compliance with treatment. An HRQOL report on PAH patients found that those on IV prostanoid therapy had less emotional distress and a greater feeling of control over their disease.[24] Taichman et al[25] studied HRQOL in a large population of PAH patients and found no difference in HRQOL between patients who were receiving oral PAH therapies and patients who were receiving IV therapies. The authors suggested that patients who choose IV therapy may be influenced by a sense of control over one's disease and its treatment.[25] Although therapies can influence HRQOL and treatment satisfaction in PAH patients, few studies have examined changes in HRQOL and satisfaction before or after therapy changes.

## AMBULATORY INFUSION PUMPS FOR IV PROSTANOID THERAPY

Long-term continuous IV prostanoid therapy requires thorough education to ensure patient safety and treatment compliance. Patient education on medications, infusion pump operation, and infusion equipment (ie, tubing, syringes, and cassettes) usually begins at home prior to the start of treatment. Intravenous prostanoid therapy requires a single-lumen, tunnelled central venous catheter because this is often a lifelong therapy, and any sudden interruption in the infusion can be life threatening. As central catheter infections and bacteremia are well-documented risks of long-term IV therapy, patient education regarding the risks and care of the central catheter is critical. After placement of the central venous catheter and initiation of treatment in the hospital, patients are discharged only when they can demonstrate proficiency in sterile mixing techniques, aseptic catheter care, and pump management.[26]

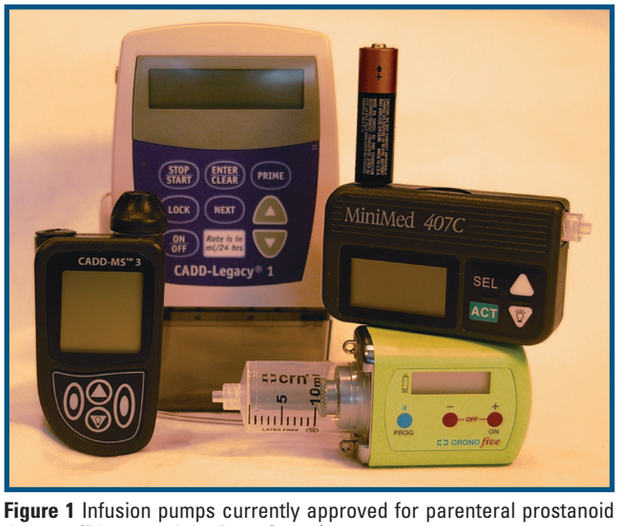


**Figure 1** Infusion pumps currently approved for parenteral prostanoid therapy. (Photograph by Brett Goetz.)

Over the past few years, several smaller ambulatory pumps were approved for continuous IV use, providing PAH patients with infusion delivery options (Figure 1). Table 4 provides a list of the features of ambulatory infusion pumps available for continuous IV prostanoid therapy. Selection of the most appropriate ambulatory pump is based on the IV prostanoid therapy administered (epoprostenol or treprostinil) and should match patients' needs and preferences. The ambulatory pumps currently used for prostanoid therapy—CADD-Legacy 1, CRONO Five, CADD-MS3, and MiniMed 407C—are designed to provide continuous flow.[27-30] The CADD-Legacy 1 is approximately the size of a videocassette tape and offers the largest reservoir volume with 50- and 100-mL cassettes. The CRONO Five, approximately the size of a large cellphone, uses reservoir syringes of 10 and 20 mL. The smallest pumps, approximately the size of a large pager, are CADD-MS3 and MiniMed 407C with a reservoir syringe volume of 3 mL. Acceptable infusion rates vary on the basis of the reservoir volume. All pumps have many safety features including alarms for occlusions or low reservoir volume.

Epoprostenol requires a minimal infusion rate of 1.2 mL/h or higher. Because of the comparatively high flow rates required, the CADD-Legacy 1 is the only ambulatory infusion pump currently used for epoprostenol. The smaller pumps—CRONO Five, CADD-MS3, and MiniMed 407C—use a lower flow rate than is recommended for epoprostenol.[28-30] To date, there have been no published reports using infusion pumps smaller than the CADD-Legacy 1 with epoprostenol.

Conversely, treprostinil's chemical stability at room temperature and its pharmacologic properties allow it to be infused at lower flow rates, thus enabling the clinician to safely use smaller infusion pumps. In a preliminary study of low-flow treprostinil administration via the MiniMed 407C at a rate of 0.1 mL/h, catheter patency was maintained with continued long-term anticoagulation therapy with warfarin (international normalized ratio [INR] = 2.0–2.5).[31] Because of the high number of pump malfunctions in this trial resulting in several adverse events, the MiniMed 407C is no longer recommended for parenteral treprostinil infusion and has been replaced by the CADD-MS3.

As the CADD-Legacy 1 must be used with epoprostenol, a transition from epopoprostenol to treprostinil for smaller pump options may be considered for some patients. Several recent clinical trials demonstrated the safe and effective transition from epoprostenol to treprostinil.[32-35] One clinical trial evaluated the transition from IV epoprostenol to IV treprostinil in adult patients with PAH; the trial results at week 12 showed no significant difference between exercise capacity at baseline (while receiving epoprostenol) than at week 12 (while receiving treprostinil).[35] Sitbon et al[36] also demonstrated the same results after 12 weeks while

**TABLE 4**

## Infusion Pump Characteristics

| Model | Manufacturer | Dimension (mm) | Battery Type | Weight (g) (with batteries) | Prostanoid | Reservoir Change Period (h) |
|---|---|---|---|---|---|---|
| CADD-Legacy 1 | Smiths Medical, St Paul, Minnesota | 112 × 95 × 41 | AA | 391 | Epoprostenol, treprostinil | Epoprostenol: 24<br>Treprostinil: 48 |
| CADD-MS3 | Smiths Medical, St Paul, Minnesota | 80 × 47 × 24 | AAA | 90 | Treprostinil | 24 |
| CRONO Five | Canè SRL Medical Technology, Torino, Italy | 77 × 47 × 29 | 3-V lithium | 115 | Treprostinil | 48 |
| MiniMed 407C | Medtronic MiniMed, Sylmar, California | 50 × 86 × 20 | 1.5-V lithium | 107 | Treprostinil | 24 |

observing a decrease in the severity of prostanoid-related adverse effects after implementing a rapid transition method from IV epoprostenol to IV treprostinil.[36] Furthermore, in an open-label trial, patients who transitioned from IV epoprostenol to subcutaneous treprostinil maintained exercise capacity and cardiopulmonary hemodynamics after 8 months.[34] Data from these transition studies suggest that the appropriate treprostinil dose may be 2 to 3 times the epoprostenol dose.[32-35]

Patients transitioning from epoprostenol may require frequent dose changes to reach the optimal treprostinil dose. Therefore, the CADD-Legacy 1 or the CRONO Five should be used because the reservoir volume in these pumps is larger and allows for more dose adjustments without changing the reservoir or the concentration. The CADD-MS3 has a small 3-mL reservoir and should be reserved for those patients who have reached a stable treprostinil dose level and desire an even smaller pump.

Treprostinil delivered by the CRONO Five and the CADD-MS3 is more concentrated than when infused with the CADD-Legacy 1. To prevent accidental overdose, patients using these pumps should be attentive while preparing treprostinil and connecting to the central catheter. Furthermore, smaller syringes are used for measuring and diluting treprostinil with these pumps. Fine motor dexterity and acute vision are critical for correct use of these smaller pumps. Patients with scleroderma and associated Raynaud's or digital ischemic ulcers that limit dexterity or patients with visual impairment may not be good candidates for small-pump technology.

Safety alarms to alert patients to catheter occlusions and low reservoir volumes are present with all the pump options; however, there is some variability among alarms. The CADD-Legacy 1 has the loudest alarm and is the most appropriate pump both for patients with hearing impairment and for young children who require an adult to respond, whereas the CADD-MS3 has the softest alarm. The time from occlusion/nondelivery of medication until alarm notification varies between pumps; thus, the half-life of the prostanoid infusion as well as a patient's sensitivity to any abrupt changes in dose, should be considered. The occlusion alarm for the CADD-Legacy 1 occurs at 45 seconds after occlusion at recommended rates.[26] As the half-life of epoprostenol is 2 to 3 minutes, the CADD-Legacy 1 is the only appropriate pump for epoprostenol delivery.

The CRONO Five occlusion alarm is triggered by pressure to the piston; hence, the slower the rate, the longer the time to activation of the alarm. An infusion rate of 0.1 mL/h will trigger the alarm in 5 hours;[27] this would exceed the half-life of treprostinil and is not recommended. However, an infusion rate of 0.3 mL/h will decrease the occlusion to alarm trigger time to approximately 3 hours and still allow the 20-mL syringe reservoir to last 48 hours. For patients sensitive to any changes in their treprostinil dose, a rate of 0.5 mL/h will decrease the occlusion to alarm time to 45 minutes in the event of flow interruption; however, this requires daily changing of the 20-mL syringe. The CADD-MS3, at a rate of 0.1 mL/h, will trigger the alarm in approximately 45 minutes with occlusion and requires daily mixing of the 3-mL reservoir syringe.[28]

## CASE STUDIES

Pump options for patients as well as transition procedures from epoprostenol to treprostinil have evolved over time. Early transitions were gradual, with

epoprostenol titrated down as treprostinil was titrated up. As PAH centers became more comfortable with the safety of transitioning from epoprostenol to treprostinil, the procedure evolved to a rapid switch method for many patients. The rapid switch method entails discontinuing epoprostenol, aspirating the remaining epoprostenol from the central catheter, and then flushing the central catheter with sodium chloride solution. Once the central catheter is cleared, treprostinil is initiated at the same dose as epoprostenol, or 20% to 30% higher, and then titrated up for clinical effect. The following case studies—obtained from 2 leading PAH centers in the United States: University of Washington Medical Center, Seattle, and The Children's Hospital, Aurora, Colorado—illustrate numerous transition options and the procedures implemented to ensure that the safety of the patient is maintained.

## UNIVERSITY OF WASHINGTON MEDICAL CENTER, SEATTLE

All patients in the case studies provided by Washington University Medical Center were admitted to the hospital for a 1-night stay with the exception of the case study 1 patient, who was admitted for 48 hours of direct patient observation. All patients received education regarding treprostinil therapy and the infusion pump prior to hospitalization, which continued during the inpatient phase through discharge until the patient was fully competent with self-administration procedures. The first 2 patients started on treprostinil at a rate 20% higher than the epoprostenol dose; however, both of these patients subsequently required a dose increase for oxygen desaturation. Patients are now transitioned by starting treprostinil at 30% or higher than the equivalent epoprostenol dose to reach a therapeutic dose in a shorter period. Typically, titrating to increase the dose of treprostinil is required for symptoms such as shortness of breath with exertion and lower oxygen saturations. Currently, University of Washington Medical Center has transitioned 15 patients from epoprostenol to treprostinil.

### Case Study 1

This 24-year-old woman had been on epoprostenol for 7 years at a stable dose of 17 ng/kg/min prior to transition and requested to be weaned off epoprostenol because of the time and complexity required for this medication. Following placement of a peripheral IV catheter, epoprostenol was discontinued and aspirated from the central venous catheter and infused via a peripheral IV catheter at 17 ng/kg/min. Treprostinil was initiated via the central catheter at a rate of 20 ng/kg/min (20% higher than her epoprostenol dose). After starting the treprostinil infusion, epoprostenol continued to infuse for 1 hour and was then discontinued. During her hospital stay, treprostinil was titrated over a period of 2 days to a dose of 30 ng/kg/min in response to an episode of oxygen desaturation. The patient was discharged but continued to experience shortness of breath with daily activities over the next month. She was titrated to a dose of 46 ng/kg/min, and her shortness-of-breath episodes were resolved. Her 6-minute walk distances remained stable between 335 and 331 m (1099–1086 ft).

### Case Study 2

This 49-year-old female patient had been on epoprostenol for 3.5 years at a stable dose of 25 ng/kg/min and was transitioned to treprostinil and the smaller CRONO Five pump. The rapid switch method was used: epoprostenol was discontinued and aspirated from the central venous catheter, the catheter was flushed with sodium chloride solution, and a volume equal to the exact internal volume of the central catheter lumen was filled with treprostinil. The infusion was started at a dose of 32 ng/kg/min (20% higher than the epoprostenol dose). The patient was stable at this dose and discharged home. Her dose of treprostinil was gradually titrated over the course of 2 weeks to her current dose of 37 ng/kg/min. The patient's 6-minute walk distances remained between 305 and 366 m (1001–1201 ft), and she did not experience any adverse reactions during the transition.

### Case Study 3

This 53-year-old female patient had been on epoprostenol for 2.5 years at a stable dose of 48 ng/kg/min and was transitioned to treprostinil using the CRONO Five infusion pump. Epoprostenol was discontinued and treprostinil started at 62 ng/kg/min (30% higher than her epoprostenol dose) using the rapid switch method. The patient was stable at this dose and discharged home. Her dose of treprostinil was gradually titrated over the course of 2 weeks to her current dose of 67 ng/kg/min. Her 6-minute walk distance average was 305 m (1001 ft), and she did not experience any adverse reactions during the transition.

## THE CHILDREN'S HOSPITAL, AURORA, COLORADO

Thirteen patients have transitioned from epoprostenol to treprostinil at The Children's Hospital over 1 year, using either slow or rapid transition methods described in the following case studies. All patients were stable at the time of transition, with a mean epoprostenol dose of 36 ng/kg/min. Patients were transitioned in the cardiac

step-down unit and closely monitored for symptoms of pulmonary hypertension, prostanoid adverse effects, and efficacy (ie, cardiac catheterization, echocardiogram, exercise testing). The mean dose after transition to treprostinil was 51 ng/kg/min at 24 hours, 79 ng/kg/min at 6 months, and 86 ng/kg/min (2.4 times the epoprostenol dose) at 12 months. The 6-minute walk distance prior to transition was 516 ± 115 m (1693 ± 377 ft) (n = 9) and did not change significantly after the transition. Mean severity scores for the adverse effects of rash, diarrhea, headache, jaw pain, and gastrointestinal adverse reactions improved following the transition; however, leg pain increased.[37] Patient transitions from epoprostenol to treprostinil were done with the CADD-Legacy 1 and, more recently, with the CRONO Five.

Later, 5 patients transitioned from the CADD-Legacy 1 to the MiniMed 407C in a pediatric miniaturization trial. Catheter patency was maintained with anticoagulation therapy using warfarin (INR = 1.5).[38] However, mechanical issues such as microboluses and "nondelivery" of medication with this pump prompted transition of these patients to the CADD-MS3 once it became available, providing a more consistent and safer delivery system. The CRONO Five is now used for patients younger than 5 years because the higher alarm volume is more audible for parental monitoring.

## Case Study 4

This 11-year-old girl with PAH associated with congenital heart disease was treated with epoprostenol for 3 years at a dose of 41 ng/kg/min. The rapid switch method was used: epoprostenol was discontinued and aspirated from the central venous catheter, the catheter was flushed with sodium chloride solution, and a volume equal to the exact internal volume of the central catheter lumen was filled with treprostinil. Treprostinil was initiated at a dose of 41 ng/kg/min, using the CADD-Legacy 1. Dose escalation of treprostinil continued every 20 to 60 minutes by 5 ng/kg/min, while constantly monitoring for symptoms of pulmonary hypertension and adverse effects, to a dose of 51 ng/kg/min. The patient initially experienced pallor that improved with dose escalation. She was discharged the following day without PAH symptoms and no change in the echocardiogram. Biweekly phone contact occurred during the first month; the treprostinil dose gradually increased to 71 ng/kg/min for symptoms of pallor and decreased exercise tolerance. Dose escalation continued for a total of 9 months to 114 ng/kg/min for intermittent pallor and decreased exercise tolerance, both of which subsequently improved. Overall, serial echocardiograms remained stable throughout the year, and the initial decrease in exercise capacity eventually returned to the patient's baseline.

Following stabilization of the treprostinil dose at 1 year on the CADD-Legacy 1, the patient transitioned to the MiniMed 407C at a rate of 0.1 mL/h. Warfarin was continued, and the patient did not experience catheter occlusions with the INR maintained at 1.5. Pump-related complications concerning "no delivery" alarms and infrequent small medication boluses occurred, resulting in increased treprostinil adverse effects. Once it became available, the patient was transitioned to the CADD-MS3. The patient has not experienced any medication bolus or pump malfunction, and central catheter patency has been maintained. Hemodynamics 2 years after the initial transition remain unchanged.

## Case Study 5

This 4-year-old girl with idiopathic PAH was treated with epoprostenol for 2 years at a dose of 55 ng/kg/min prior to transition. Because the patient was starting preschool, the patient's parents requested the transition to treprostinil because of its longer half-life and the decreased weight of the infusion pump backpack from the elimination of freezer cold packs. A slow transition method was performed using the CADD-Legacy 1. A peripheral IV catheter was placed, and the epoprostenol was moved to the peripheral catheter and infused with 0.9% sodium chloride solution at 5 mL/h. The epoprostenol was decreased by one-half of the dose to 27 ng/kg/min. The central catheter was aspirated and flushed with sodium chloride solution, and treprostinil was initiated through the central catheter at the original epoprostenol dose of 55 ng/kg/min. Epoprostenol was decreased every 1 to 2 hours by 10 ng/kg/min, and treprostinil was increased by 5 to 10 ng/kg/min depending on adverse effects and symptoms, until the epoprostenol was discontinued. The patient experienced pallor and an episode of stomach pain. The patient was discharged without PAH symptoms and an unchanged echocardiogram 24 hours after the transition with treprostinil infusion at 75 ng/kg/min. Continued titration was required for 8 months for occasional fatigue and pallor to a dose of 121 ng/kg/min (2.2 times the epoprostenol dose).

Once a stable dose of treprostinil was achieved, the patient and the family requested a transition to the MiniMed 407C. Patency of the 4.2-French Broviac catheter was maintained with the MiniMed 407C at a rate of 0.1 mL/h, with warfarin titrated to achieve an INR of 1.5. The patient experienced a pump malfunction approximately 3 weeks later but did not experience any adverse effects. For safety, the patient was transitioned back to the CADD-Legacy 1 because of the parents' concern that the alarm was not audible in the adjoining room.

## Case Study 6

This 13-year-old with systemic PAH associated with an unrepaired atrial septal defect was treated with epoprostenol for 11 years. The patient and the family

requested transition to treprostinil owing to the longer half-life and miniaturization options. Although the patient had stable hemodynamics and exercise tolerance for several years, the transition was performed in the intensive care unit for closer monitoring. The slow transition method was used and well tolerated without any decrease in systemic blood pressure. Treprostinil was initiated with the CRONO Five at the original epoprostenol dose of 38 ng/kg/min and epoprostenol was decreased by one-half to a dose of 19 ng/kg/min. Every 1.5 to 2 hours, epoprostenol was decreased by 5 ng/kg/min while increasing treprostinil by 5 to 10 ng/kg/min. The patient was discharged in 24 hours with treprostinil 71 ng/kg/min. For several months following transition, the patient reported increased fatigue, and an echocardiogram showed an increased estimated right ventricular systolic pressure. With aggressive treprostinil dose increments to the current dose of 135 ng/kg/min, the symptoms and a follow-up echocardiogram returned to the patient's baseline. The patient liked the well-concealed pump and reported feeling better overall on treprostinil because the epoprostenol adverse effects of rash, flushing, and anorexia were no longer present.

## CONCLUSION

Pulmonary arterial hypertension remains a complex disease without a cure. Prostanoid therapy is a long-term, complex, costly therapy that requires intensive teaching and constant reinforcement throughout the course of treatment; however, when these medications are delivered in a consistent, effective, and safe manner, the symptoms of the disease may be improved over time. Epoprostenol has a proven mortality benefit, is infused with the CADD-Legacy 1, must be kept cold to maintain stability, and has a half-life of 2 to 5 minutes. Intravenous treprostinil has shown efficacy in de novo patients and those who transition from epoprostenol to treprostinil. Treprostinil is stable at room temperature, has an elimination half-life of 4.5 hours, and can be used with new, smaller pumps. Patients transitioning from epoprostenol to treprostinil require close monitoring during transition and for several months afterward because varying degrees of dose escalation are required to maintain efficacy. Prostanoid adverse effects may be fewer with IV treprostinil than with epoprostenol.

Clinicians need to be aware of the issues that can impact the quality of life with PAH patients. It has long been assumed that the introduction of IV prostanoid therapy negatively affects quality of life owing to the complexity of the treatment; however, the ability to conceal a smaller, lightweight pump and the option to extend reservoir changes from 24 to 48 hours may have a positive impact. Patients and clinicians must be aware of the potential for adverse events with higher concentration of treprostinil used in the smaller pumps. Parenteral prostanoid therapy, though complex, can improve survival and quality of life for many patients. Physician and nursing expertise, as well as the patient's acceptance and compliance, affects treatment outcomes; therefore, it is important to discuss medication and infusion pump options with the patient.

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