The Art and Science of Infusion Nursing

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Pulmonary Arterial Hypertension: A Focus on Infused Prostacyclins

ABSTRACT

Pulmonary arterial hypertension (PAH) is characterized by vasoconstriction and cell proliferation in the pulmonary vasculature. Guideline-driven interventions with infused prostacyclin treatment are the mainstay for patients with advanced symptoms. Infused prostacyclin therapy is complex. It is critical to manage prostacyclin therapy with precision because boluses or interruptions can be fatal. Education of patients and inpatient staff nurses is necessary to prevent negative outcomes. Nurses are an essential part of the multidisciplinary team caring for patients with PAH. The diagnostic evaluation and treatment of PAH are reviewed here, and challenges associated with the care of patients on prostacyclin therapy are discussed.

Key words: epoprostenol, prostacyclin, pulmonary arterial hypertension, pulmonary hypertension, treprostinil

There have been many advances in the treatment of pulmonary arterial hypertension (PAH) over the past 20 years. Providers have many oral and inhaled therapies to choose from, but infused therapies are still the gold standard for those with the most advanced symptoms and those who have progressive disease despite oral and/or inhaled therapies. Health care providers who treat patients with PAH must have the knowledge to safely initiate and manage infused treatments and must be familiar with the risks associated with parenteral therapy and the precautions necessary to minimize those risks. This review provides an overview of pulmonary hypertension (PH) types and management, with special focus on recognizing appropriate patients for infused therapy and the education necessary to successfully initiate therapy and minimize complications in these patients.

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OVERVIEW OF PH

Definition

PH is defined by a mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg at rest when measured by a right heart catheterization.[1] PAH is characterized by 3 major factors that lead to increased pulmonary vascular resistance (PVR): vasoconstriction, smooth-muscle hypertrophy of the small arteries, and thrombosis in situ.[2] Chronic excessive vasoconstriction leads to endothelial dysfunction, inadequate production of nitric oxide (NO) and prostacyclin, and excessive endothelin-1.[3] In addition to an elevated mPAP, patients with PAH have a normal pulmonary artery wedge pressure (PAWP) $\leq$ 15 mm Hg and PVR $>$ 3 Wood units.[4,5] Potential underlying causes for PH must be considered and excluded before a diagnosis of idiopathic PAH can be definitive.

Classification

It is essential to differentiate the underlying cause of PH because treatment varies depending on the underlying condition. Experts in the field have classified PH into 5 groups of similar underlying causes, taking into consideration the underlying pathophysiology, symptoms on presentation, and strategies for treatment.[3] These World Health Organization (WHO) groups are:[6]

- Group I: Pulmonary arterial hypertension
- Group II: Pulmonary hypertension due to left heart disease
- Group III: Pulmonary hypertension due to lung disease and/or hypoxia

- Group IV: Chronic thromboembolic pulmonary hypertension (CTEPH)
- Group V: Pulmonary hypertension with unclear multifactorial mechanisms

PAH, WHO group I, is caused by a group of illnesses causing endothelial dysfunction and remodeling to the pulmonary vasculature with consequential elevation in pulmonary arterial pressure, PVR, and, ultimately, right ventricular failure. Early recognition and accurate diagnosis of PAH is essential because it is a progressive and fatal disease without treatment.

PH can develop from left-sided heart dysfunction, such as heart failure with reduced or preserved ejection fraction and aortic or mitral valve disease. WHO group II PH, caused by left-sided heart disease, is the most common type of PH in the Western world and is often referred to as pulmonary venous hypertension.[7] WHO group II PH is characterized by elevated left atrial pressure and passive back flow into the pulmonary venous system. Thus, when hemodynamics are measured, the PAWP or left ventricular end diastolic pressure (LVEDP) is elevated and the PVR is normal or near normal.[8]

WHO group III consists of PH that is the result of chronic lung diseases and/or hypoxia. This group includes obstructive and restrictive lung diseases and sleep disorders, such as emphysema, pulmonary fibrosis, and sleep apnea. Vasoconstriction correlates with chronic hypoxemia in lung disease, eventually leading to PH and right heart failure symptoms. Dyspnea out of proportion to pulmonary function testing with severe hypoxia on exertion is commonly seen in PH related to lung diseases and is associated with a poor prognosis.[9]

CTEPH, WHO group IV, is a potentially curable type of PH. If there is persistent evidence of obstruction of at least 1 major pulmonary artery and PH by right heart catheterization after 3 months of anticoagulation, a risk assessment for pulmonary thromboendarterectomy surgery should be completed.[10,11]

Finally, WHO group V PH consists of a variety of disorders that have unclear or multifactorial causes. This group consists of hematological, systemic, and metabolic disorders. Disorders such as hemolytic anemia, splenectomy, sarcoidosis, thyroid disorders, and renal failure are included in this group.[6]

PULMONARY ARTERIAL HYPERTENSION

Etiologies and Statistics

Idiopathic PAH is a diagnosis of exclusion that can be made after all other types of PH and PAH have been eliminated. Heritable PAH has been recognized to be associated with an abnormal bone morphogenetic protein receptor type 2 (BMPR2) gene, and more recently, additional gene mutations in the tumor growth factor-beta family have been identified, but are less common. Approximately 50% to 80% of familial PAH and 11% to 40% of idiopathic PAH have a mutation in the BMPR2 gene.[12]

PAH can develop from exposure to drugs and toxins. Diet drugs, such as aminorex, fenfluramine, dexfenfluramine, and benfluorex, have been directly associated with PAH. Multiple case studies have reported development of PAH after use of amphetamines and illicit use of methamphetamines, making these likely causes for PAH. There also have been case studies linking dasatinib, used for treatment of chronic myeloproliferative disorders, to PAH.[13]

Other conditions associated with PAH include connective tissue diseases, human immunodeficiency virus (HIV), portal hypertension, congenital heart defects, and schistosomiasis. Results from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) indicate that 46% of patients with PAH are idiopathic, 3% have heritable PAH, and 51% have PAH from associated conditions.[14] Of the associated types of PAH, 50% were related to connective tissue disease, 19% due to congenital heart disease, and 11% related to portal hypertension.[14]

The incidence of idiopathic PAH is 1 to 5 per million, while the prevalence of WHO group I PAH is 15 to 50 per million.[15] In the REVEAL registry, the mean age of diagnosis was 47 years, and the female-to-male ratio was 4 to 1.[16,17] The time from symptom onset to diagnosis was unacceptably long, equaling more than 1 year for 50% of patients and more than 2 years for 20% of patients.[17] Almost 75% of patients in the REVEAL registry had functional class (FC) III to IV symptoms (Table 1) at the time of right heart catheterization, demonstrating delay in both diagnosis and initiation of treatment.[17] Survival has improved since PAH treatments have become available. The National Institutes of Health registry in the 1980s predicted a median survival of 2.8 years in patients with idiopathic PAH, before treatments were available. In the current treatment era, survival at 1, 3, and 5 years has increased to 92%, 75%, and 66%, respectively.[18]

Diagnostic Evaluation

Since PAH is rare, early recognition and diagnosis may be difficult because symptoms related to PAH are often vague and are associated with more common diseases. Exertional dyspnea, fatigue, and decreased exercise tolerance are symptoms reported at early stages. As resistance increases through the pulmonary vasculature, exertional dyspnea, lightheadedness, chest pain, or pressure become more pronounced and can occur at rest. Syncope with abdominal fullness and lower extremity swelling are associated with advanced disease and right heart failure.

Diagnostic evaluation is aimed at determining the underlying etiology of PH to initiate appropriate treatments. A detailed patient history should include review of

TABLE 1

World Health Organization Functional Classification for Patients With Pulmonary Arterial Hypertension

Functional Class	Symptom Limitations Description
I	No limitation. Ordinary physical activity does not cause dyspnea or fatigue, chest pain or near syncope.
II	Slight limitation. Ordinary physical activity causes dyspnea or fatigue, chest pain or near syncope.
III	Marked limitation. Less-than-ordinary activity causes dyspnea or fatigue, chest pain or near syncope.
IV	Severe limitation. Dyspnea and/or fatigue present at rest.

illicit and diet medications, along with investigating family history for similar and possibly undiagnosed cases of PH. Identification of symptom onset and progression can help guide treatment decisions. Physical exam findings correlating with PH include those of right heart failure: jugular venous distention, edema, hepatomegaly, and ascites. Palpation of right ventricular heave, along with an auscultated pronounced pulmonic second heart sound and tricuspid regurgitation murmur, are common in PH. An electrocardiogram, although not specific or sensitive, can indicate right atrial enlargement and right axis deviation associated with right ventricular hypertrophy.[19] Enlarged central pulmonary arteries with an enlarged right ventricle along with pruning of pulmonary vasculature can be seen on imaging studies of the chest.

Echocardiogram is able to estimate the pulmonary artery pressure by measuring the velocity of regurgitation through the tricuspid valve. It also provides information on right atrial size and right ventricular size and function. A bubble study, performed by injecting agitated saline into a peripheral vein, can detect right-to-left septal shunting to identify atrial or ventricular septal defects. In addition to indicators of PAH, an echocardiogram is helpful to gain information to assess for WHO group II characteristics of left atrial enlargement from left-sided heart problems and chronically elevated preload as seen with systolic or diastolic dysfunction or valve disease. An echocardiogram is not able to distinguish between pre- and postcapillary elevations in pressure, which is essential to differentiate WHO group II PH from other types of PH.[3]

Additional testing required for an evaluation of dyspnea and PH includes pulmonary function testing to assess for obstructive or restrictive lung disease. Measuring diffusing capacity of the lung is important to screen patients with connective tissue disease for development of PAH.[19] A lung ventilation perfusion (VQ) scan is highly sensitive to detect pulmonary embolism and exclude CTEPH. VQ scans have a higher sensitivity of 96% compared with a sensitivity of 51% for computed tomography angiogram in determining that a negative result is indicative of a negative study (no pulmonary embolism).[20] Serologies to identify connective tissue disease, HIV, and liver disease are indicated. An overnight oximetry study to screen for nocturnal hypoxia may require a follow-up polysomnography to identify and initiate treatment of obstructive sleep apnea.

When noninvasive testing has been completed, a right heart catheterization is necessary to diagnose PH. Hemodynamics are precisely measured to determine exact pulmonary artery pressures. An end-expiration PAWP or LVEDP and cardiac output are also measured. These numbers are then used to calculate PVR. Measuring right atrial pressures and cardiac output and indices establishes the severity of the disease and helps better determine appropriate treatment options. Screening for a left-to-right shunt is completed by measuring oxygen saturations as the catheter is advanced. If there is an increase in oxygen saturation, a full shunt study is done. Unless they are hemodynamically unstable, patients with idiopathic PAH are assessed for vasoreactivity with an acute vasodilator challenge. Patients demonstrating specifically defined parameters of vasoreactivity may be candidates for treatment with high-dose calcium channel blockers.[5] In certain cases, a fluid or exercise challenge may be done if there is suspicion of left-sided heart disease with a preserved ejection fraction despite a normal PAWP.

ORAL AND INHALED PAH THERAPY

Conventional Therapy

According to the PH treatment guidelines, diuretics, oxygen, and digoxin should be considered for background therapy. In patients with idiopathic, heritable, or PAH due to anorexigens, oral anticoagulation with warfarin should be considered.[21] Patients may need oxygen during sleep, with activity, or continuously. As disease state improves or progresses, oxygen flow, measured in liters per minute, will need to be titrated to maintain saturations at 90% or higher.[21] Patients will need education on

pregnancy prevention and referral for appropriate birth control. Pulmonary rehabilitation referral for monitored and guided exercise has shown to improve 6-minute walk distance, fatigue, and quality of life in PAH.[22,23]

Oral PAH Therapy

Over the past 15 years, clinical research has led to the development of oral preparations that have been approved by the US Food and Drug Administration (FDA) for PAH treatment and treatment of CTEPH. These therapy options are outlined in Table 2. Deficiencies of NO as the result of endothelial dysfunction are treated with phosphodiesterase-5 inhibitors (PDE5-I) or a newer agent, a soluble guanylate cyclase (sGC) stimulator that is approved for PAH and CTEPH. NO is responsible for increasing guanylate cyclase, which, in turn, causes increased vasodilation by activating cyclic guanosine monophosphate (cGMP). PDE5-Is slow the degradation of cGMP, promoting vasodilation in the smooth muscle of the pulmonary arteries, while sGC stimulators directly increase cGMP independently of NO.

TABLE 2

Approved Oral Treatments for Pulmonary Arterial Hypertension[a]

Medication Name	Drug Class	Indication: Functional Class I-IV	Starting/Usual Dose	Frequency	Common Side Effects
Bosentan	ERA	PAH: II-IV	62.5 mg/125 mg	Twice daily	Liver function testing elevations
					Respiratory tract infections
					Edema
Sildenafil	PDE-5 inhibitor	PAH: II-III	20 mg	3 times per day	Epistaxis
					Headache
					Dyspepsia
Ambrisentan	ERA	PAH II-III	5 mg/5 or 10 mg	Daily	Peripheral edema
					Nasal congestion
					Sinusitis
Tadalafil	PDE-5 inhibitor	PAH: II-III	40 mg	Daily	Headache
					Flushing
					Myalgia
Riociguat	sGC stimulator	PAH: II-III	1.0 mg (0.5 mg)/2.5 mg	3 times per day	Dyspepsia
		CTEPH: inoperable or persistent			Headache
					Dizziness
Macitentan	ERA	PAH: II-III	10 mg	Daily	Anemia
					Respiratory tract infections
					Headache
Treprostinil	PCA	PAH: II-III	0.125 mg/max tolerated	Twice daily or 3 times per day	Headache
					Diarrhea
					Nausea
Selexipag	Selective IP receptor agonist	PAH: II-III	200 mcg/max tolerated up to 1600 mcg	Twice daily	Headache
					Diarrhea
					Jaw pain

[a]*Drugs listed in order of FDA approval.*

Abbreviations: CTEPH. chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; FDA, Food and Drug Administration; IP, prostacyclin; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogue; PDE-5, phosphodiesterase 5; sGC, soluble guanylate cyclase.

Vasoconstriction and cell proliferation from excessive levels of endothelin are treated with 1 of 3 FDA-approved endothelin receptor antagonists (ERAs). ERAs block the vasoconstrictive and proliferative effects of endothelin on the endothelial receptors. Bosentan and macitentan are nonselective, blocking both the A and B receptors, while ambrisentan is selective to the A receptor.

Because of endothelial dysfunction, patients with PAH have a deficit of endogenous prostacyclin. Administering prostacyclin therapies increases cyclic adenosine monophosphate, which leads to vasodilation in the pulmonary vasculature, while inhibiting platelet aggregation and smooth-muscle proliferation.[24] Oral prostacyclin derivatives have proven to be difficult to deliver because of bioavailability and side effects and have only recently been approved for use in the United States.

Inhaled PAH Therapy

Prostacyclin therapy is available in 2 inhaled options that are FDA approved for chronic outpatient use: iloprost and treprostinil (Table 3). Iloprost is delivered using the I-neb adaptive aerosol delivery (AAD) system (Philips Healthcare, Andover, MA). Medication is available in a glass ampule of 10 mcg/mL or 20 mcg/mL ampule for patients with prolonged treatment times. The glass ampule is opened and medication is pipetted into the I-neb AAD for each treatment.

Inhaled treprostinil is delivered using the Tyvaso inhalation device Optineb or TD-100 devices (United Therapeutics, Research Triangle Park, NC). The medication comes in a 2.9-mL ampule containing 1.74 mg of treprostinil. Once per day, the ampule is emptied into the Tyvaso inhalation device and aerosolized with a small volume of distilled water, which is inhaled at intervals indicated by the delivery device. If hypotension occurs, frequency of treatments for iloprost and number of inhalations per session for treprostinil are reduced. As with most inhaled preparations, cough is a common side effect.

INFUSED PAH THERAPY

Infused prostacyclin options include intravenous (IV) epoprostenol and IV and subcutaneous treprostinil. Treatment with parenteral therapy is complex and requires expertise on the part of the prescriber and PH coordinators. Careful patient selection is essential for safe outcomes. Patients require support persons, physical and emotional ability, intense training, and understanding to manage the therapy after discharge.[25] Comprehensive and annual training for staff nurses caring for patients on parenteral prostacyclin therapy is essential for patient safety in the inpatient setting.[26]

Initiation of IV Prostanoid Therapy

Inpatient initiation of prostacyclin therapy may be planned after diagnostic evaluation is completed or when progressive symptoms occur on other PAH treatments. Emergent initiation may be medically necessary in patients who present with advanced symptoms or if rapid deterioration occurs. Criteria for considering prostacyclin initiation have been outlined and include worsening symptoms of dyspnea, lightheadedness, syncope, and chest pain or pressure. In addition, decreased 6-minute-walk distance less than 300 meters, increasing N-terminal pro brain natriuretic peptide (NT-proBNP) levels, and signs of worsening right heart failure requiring diuretic dose adjustment are consistent with worsening prognosis.[27] Indicators of worsening by echocardiogram include new pericardial effusion or tricuspid annular plane systolic excursion < 15 mm. Hemodynamic criteria of concern for disease progression include elevated right atrial pressure > 15 mm Hg or worsening cardiac index < 2.0 L/min/m^2.[28]

TABLE 3

Approved Inhaled Treatments for Pulmonary Arterial Hypertension

Medication Name	Drug Class	Indication: Functional Class I-IV	Starting/Usual Dose	Frequency	Common Side Effects
Iloprost	PCA	PAH: III-IV	2.5-mcg test dose/5.0 mcg	6-9 times per day while awake; allow 2 hours between treatments	Flushing Cough Headache
Treprostinil	PCA	PAH: III	3 breaths (18 mcg)/ increase by 3 breaths every 1-2 weeks to 9 breaths	4 times per day while awake; allow 4 hours between treatments	Cough Headache Nausea

Abbreviations: PCA, prostacyclin analogue; PAH, pulmonary arterial hypertension.

Epoprostenol and Delivery

Epoprostenol was the first agent approved for treatment of PAH in 1995. Epoprostenol is a prostacyclin that works by vasodilating the pulmonary and systemic vasculature and inhibiting platelet aggregation. It has been shown to improve survival in several small unblinded studies in idiopathic PAH and in PAH associated with systemic sclerosis.[29-31] Experts recommend epoprostenol as initial therapy for PAH in patients with FC III-IV symptoms.[21] Because the half-life of epoprostenol is 2.7 to 6 minutes, it requires continuous delivery with an infusion pump through a central vascular access device (CVAD).[32] In the inpatient setting, peripheral IV access is acceptable to initiate therapy or when central venous access is compromised. It is recommended to have 2 patent short peripheral catheters (SPCs) at all times. In the outpatient setting, the CADD-Legacy 1 (Smiths Medical ASD, Minneapolis, MN) pump is used for delivery (Figure 1). This pump delivers infusion rates calculated in milliliters per 24 hours and infuses at intervals less than 3 minutes to prevent lapses in therapeutic dose. The pump has alarms for low volume and occlusion. Using infusion tubing with a 0.22-micron filter with a light-protected 50- or 100-mL cassette is also required.

Once initiated, epoprostenol requires close monitoring and a dedicated IV access. No medication or saline infusion should be allowed to infuse with or push the epoprostenol infusion, despite slow delivery rates. Epoprostenol is a potent vasodilator; accidental boluses of the drug can lead to profound hypotension, nausea, vomiting, and flushing. Delivery must be maintained to prevent interruptions, which can cause rebound of PAH symptoms. Transferring the infusion from 1 access site to another requires cautious handling by experienced inpatient staff nurses and PH coordinators to prevent bolus and interruption of therapy, both of which can be fatal.

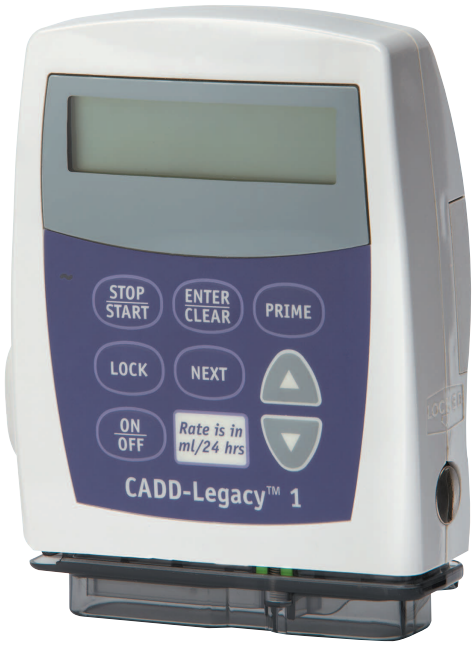

Figure 1 CADD-Legacy 1 infusion pump. Courtesy of Smiths Medical, Minneapolis, MN.

Epoprostenol Dosing and Titration

Epoprostenol is initiated in the hospital setting at 2 ng/kg/min and increased by 1- to 2-ng/kg/min increments at intervals of at least every 15 minutes or longer (every 12-24 hours), until the patient is stable for discharge or dose-limiting side effects occur.[32,33] Common side effects during initial dose escalation include nausea, vomiting, headache, and hypotension.[33] A stable dosing weight is typically used throughout the infusion, but the infusion dose may be recalculated with significant weight changes. Up-titration of dose continues after discharge 1 to 2 times per week and is specific to individual response and toxicity, but typically averages 25 to 60 ng/kg/min at 1 year.[19,25] Common side effects with chronic infusions include headache, jaw pain, flushing, diarrhea, and nausea.[32] Patients may develop a rash and musculoskeletal pain, especially in the lower extremities.

Epoprostenol is available as brand epoprostenol (Flolan, GlaxoSmithKline, Research Triangle Park, NC), a generic form, and a more temperature stable version epoprostenol (Veletri, Actelion Pharmaceuticals, South San Francisco, CA). All versions come in 0.5-mg and 1.5-mg vials. Multiple vials are reconstituted to make a cassette concentration of epoprostenol that is patient-specific to weight and allows enough medication to last until the cassette is due for change, yet prevents waste.

Flolan and generic epoprostenol require reconstitution from powder form into a 100-mL cassette with a special sterile diluent at a consistent time every 24 hours. The cassette is refrigerated and used the following day and serves as a backup cassette, if needed emergently. Once infusing, the medications are stable at room temperature for 8 hours and stable for 24 hours if chilled to 36°F to 46°F with ice packs during the infusion. A new pH 12 sterile diluent for Flolan is now available that allows cassettes to be premixed and stored in the refrigerator for 7 days and then infused for 24 hours of temperatures up to 95°F.

Veletri is reconstituted with sterile water for injection or sodium chloride 0.9% injection and has increased stability at room temperature. Veletri is stable at room temperature for up to 48 hours after mixing. Multiple 100-mL cassettes can be reconstituted and are stable for up to 24 hours after being stored in the refrigerator for up to 8 days.[33] Consulting Veletri's full prescribing information for drug stability at temperatures at and above room temperature at specific cassette concentrations is recommended. Patients have been shown to have higher convenience perceptions when transitioned from Flolan to Veletri.[34]

Treprostinil and Delivery

Treprostinil is a prostacyclin analogue that works by vasodilating the pulmonary and systemic vasculature and inhibiting platelet aggregation in the same manner as epoprostenol. Treprostinil has been shown to improve exercise capacity[35,36] and hemodynamics.[37] It has a longer half-life of 4 hours than epoprostenol and is stable at room temperature. Treprostinil is approved for FC II-IV symptoms related to WHO group I diagnosis of idiopathic and heritable PAH and PAH associated with left to right shunts and connective tissues disease.[38] Initially, treprostinil was approved for continuous infusion subcutaneously, then later approved for IV infusion if subcutaneous infusion is not tolerated and in patients requiring transition from epoprostenol. Subcutaneous infusion eliminates the risk of CVAD complications. Subcutaneous infusion is, however, associated with redness (Figure 2) and pain at the site of infusion in 85% of patients.[35,39] Occasionally, infections occur in the soft tissue surrounding the infusion site. Prostacyclin side effects are common with treprostinil infusions, including headache, diarrhea, nausea, jaw pain, and hypotension.

Treprostinil is available in 1.0-, 2.5-, 5.0-, and 10-mg/mL multiuse vials containing 20-mL volume. Subcutaneously infused treprostinil is undiluted and delivered with a CADD-MS 3 (Smiths Medical ASD, Minneapolis, MN) infusion pump (Figure 3). The 3-mL pump reservoir is filled with a volume to last up to 72 hours at room temperature based on an hourly pump rate of milliliters per hour and using a constant dosing weight. Pump alarms exist for low reservoir volume, low battery, occlusion, and pump malfunction. Infusion rates are exceedingly small and increase by as little as 0.002 mL per hour

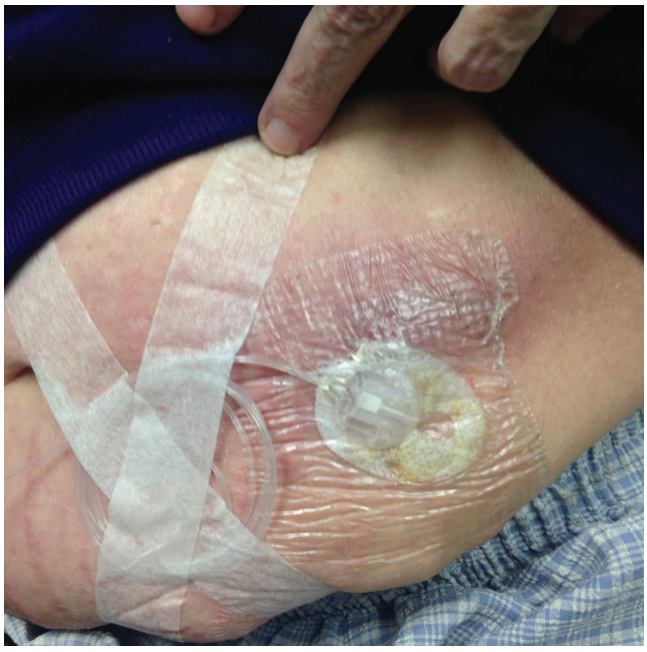

Figure 2 Subcutaneous infusion site.

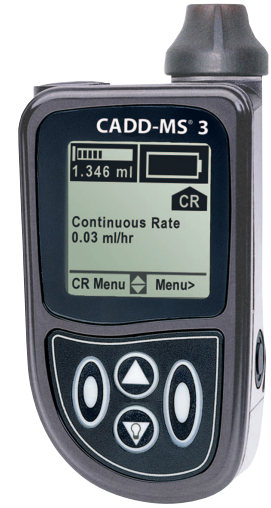

Figure 3 CADD-MS 3 infusion pump. Courtesy of Smiths Medical, Minneapolis, MN.

with dose increases. Patients are trained to insert the catheter into the subcutaneous tissue of the abdomen. Subcutaneous tissue of the flank, thigh, or upper arm can be used, but may require assistance from a support person. Site pain and duration varies per individual and specific location used. A newly inserted site is often painful for the first several days, but typically the pain subsides and the site can be used for 2 to 4 weeks or longer.[39] Management of site pain can be challenging and often warrants a "try-and-see" approach of topical and oral medications to manage site pain. Patients are started on pluronic lecithin organogel with compounded topical ingredients including ketoprofen, lidocaine, and gabapentin. Other topical options such as ice, heat, hydrocortisone, diphenhydramine ointment, and aloe vera gel may be used. Medications such as gabapentin, hydroxyzine, amitriptyline, and/or histamine 1 and 2 blockers can be trialed. Pain management with occasional narcotics for new sites has been beneficial.[39] If more than occasional narcotic use is necessary, candidacy for IV delivery should be considered.

Intravenously infused treprostinil is diluted with sterile water for injection, 0.9% sodium chloride for injection, or epoprostenol diluent to make 100-mL concentration. Cassettes can be stored for 4 hours at room temperature or 24 hours when refrigerated, then infused over 48 hours if diluted with sterile water or sodium chloride. If diluted with epoprostenol diluent, cassettes can be mixed and then stored at room temperature for 14 days while increasing pH and decreasing the potential for gram-negative infections.[38] Using infusion tubing with a 0.22-micron filter is required. Typically, delivery with the CADD-Legacy 1 pump is used. Once dosing is stable, it is possible to transition to smaller pumps such as the CADD-MS 3 or the Crono Five pump (IntraPump Infusion Systems, Grapevine, TX) to allow patients more discrete pump options. The Crono Five pump uses a

20-mL reservoir and delivers infusion rates in milliliters per hour. The Crono Five pump is no longer being manufactured; however, pumps in existence are being supported. Advances in technology will improve patient satisfaction with infusion pumps. New technologies, including prefilled reservoirs and disposable pumps, are expected to be available in the near future. Patients maintained on warfarin have a low incidence of catheter occlusions, despite low infusion rates with these highly concentrated infusions.[40]

Treprostinil Dosing and Titration

Treprostinil subcutaneous can be initiated in the home or inpatient setting. Dosing is typically started at 1.25 to 2 ng/kg/min and increased by 1 to 2.5 ng/kg/min once to twice weekly.[19,38,41] Optimal dosing is not standard, but tailored to patient response, and ranges from 60 to 150 ng/kg/min at 6 months to maximum dose, respectively.[25,41]

Transition from epoprostenol to treprostinil has been described in various protocols, ranging from up-titration of treprostinil and down-titration of epoprostenol to rapid switch. If a patient exhibits prostacyclin toxicity, the drug that is tapering off is further reduced. In 1 transition study, at 12 weeks treprostinil doses were approximately twice that of epoprostenol.[42]

CLINICAL CONSIDERATIONS

Appropriateness of Prostacyclin Infusion Therapy

Many variables are considered before initiating IV prostacyclin therapy. Medical and social variables must be assessed for each individual. Discussions with the patient and caregivers should include a rationale that addresses the benefits, responsibilities of the patient, and potential complications of infusion options. To determine whether a therapy is feasible and suited to an individual's lifestyle, a detailed discussion is necessary, with follow-up time to allow for questions and consideration. When a patient is critically ill and unable to make decisions, family caregivers and support persons may have to determine the appropriateness of initiation for the individual requiring advanced PH therapy.

Medical considerations

Patients with poor prognostic factors who are critically ill on presentation and patients who do not meet treatment goals on noninvasive therapies should be considered for infused prostacyclin therapy. An assessment of clinical signs and symptoms of right heart failure, WHO functional class for PAH, NT-proBNP levels, and hemodynamic parameters, including right atrial pressure and cardiac output, determine whether a patient is at high or low risk for disease progression. Presence of a pericardial effusion, shorter 6-minute walk distance, and rapid progression of symptoms are predictors of poor prognosis.[43]

It is important to recognize how other comorbid medical conditions will impact PAH infusion therapy before initiation. Patients on immunosuppressive therapies are at increased risk of CVAD infections. Learning difficulties, dementia, or confusion related to elevated ammonia levels in liver diseases may predict negative outcomes. Issues with past substance abuse may have an impact on decisions between IV and subcutaneous routes of administration. Finally, dexterity and strength to mix medication and manipulate the syringes and pump is another consideration and is especially important in patients with scleroderma.

Social considerations

Before starting infusion therapy, patients and/or family need to be provided adequate information to make informed decisions. If therapy needs to be initiated emergently, discussion between the family and PH providers is essential to understand the long-term implications of infusion therapy. When possible, demonstrations of the pump, opportunities to practice drug mixing, and meeting with patients who are already on infusion treatment can help patients ask appropriate questions and determine whether the therapy is conducive with the patient's lifestyle. Practice sessions can provide insight to the prescribing provider on safe handling of infusion therapy before initiation.

Patients must have adequate caregiver support to manage infused prostacyclin therapy. During the duration of treatment, patients may develop physical or cognitive deficits that require caregiver support to maintain treatment. Initially, symptoms of shortness of breath, fatigue, and decreased concentration due to hypoxia or decreased perfusion can make it difficult or impossible for patients with PAH to manage therapy independently. Therefore, social support is necessary for prolonged and potential lifelong therapy. Identifying 2 or more support persons trained in procedures of drug reconstitution and pump management is essential in anticipation of situations in which the patient requires assistance.

Determining the appropriateness of infusion therapy is essential. It may not be safe to initiate therapy if a patient is not capable of managing the therapy because of nonadherence, lack of social support, or cognitive inability. When there is a concern for safe management of therapy, other PAH treatment options should be considered, as the risk of harm due to medication error, bolus, or interruption of therapy may be higher than natural disease progression on oral or inhaled treatment options.

CHALLENGES ASSOCIATED WITH INFUSION THERAPY

Challenges exist for patients on IV prostacyclin therapies. The medications are expensive, and medication errors can have life-threatening consequences, making lifelong therapy a challenge for patients.

Cost of Therapy

Prostacyclin therapy is expensive, and identifying coverage before initiating therapy is needed, unless the patient is unstable and delay of therapy may pose serious risk. Reimbursement for therapy can be complicated and may delay initiation of therapy. Patient assistance programs may provide coverage for patients with no insurance until disability is approved or insurance is obtained. PH providers and coordinators may need to provide additional documentation and educate third-party payers about PAH, WHO group classification, and justification for therapy. Clinical documentation is required to be faxed to a specialty pharmacy with expertise in prostacyclin management at the time of a referral for parenteral therapy.

Obtaining reimbursement for PAH therapy requires tedious documentation of history, physical examination, and functional class, including symptoms present and symptom progression. Documentation of testing results—including echocardiogram, 6-minute walk distance, antinuclear antibody screen, lung VQ scan, and hemodynamic data with response to vasodilator challenge—must be submitted with referral for prostacyclin therapy. Rationale for inappropriateness of treatment with calcium channel blockers is required. Additional data may be required when PAH is out of proportion to other contributing causes of PH. Occasionally, a third-party payer may require additional letters of medical necessity or direct contact between the insurer's medical director and the prescribing PAH provider.

The cost of ongoing close follow-up required for monitoring infusion therapy may present financial burdens. Patients may live far from PAH providers, and travel for frequent appointments can pose a challenge for patients with limited incomes. Patients may benefit from working with a social worker to help identify transportation options in the community. Insurance coverage may change over the patient's course of treatment. Symptoms may improve to the extent that patients may be able to return to work and may not require disability benefits.

Additional Nursing Care

Unique barriers exist for patients who require daily skilled nursing care or hospice support while on prostacyclin therapy. Reimbursement is inadequate to cover these services when combined with the cost of these therapies. As patients approach end of life, prostacyclin therapy palliates symptoms; however, hospice administrators are unable to accept patients when Medicare considers infused prostacyclin therapy as life prolonging. Patients and families may benefit from nursing services but be unwilling to wean infusions for concerns of expediting end of life and worsening PAH symptoms. Home health nursing to assess fluid retention, set up medications, and draw blood is often helpful when the patient is no longer able to leave the home because of the progressive symptoms. A home health aide and homemaker services can provide assistance to caregivers.

Travel

Prostacyclin infusions can present challenges for patients who desire or need to travel. Initially, patients may be fearful of leaving home. These fears may exist because of not having necessary supplies or of having an interruption in therapy. Patients may be concerned about going through airport security with a CVAD, pump, and supplies. Encouraging preparedness can alleviate some anxiety with initial travels. Consulting with the PH provider about destinations and individual concerns specific to altitude, air travel, infection, and temperature extremes should be encouraged. Supplemental oxygen or a prescription for higher liter flow may be needed for air travel or travel to higher altitudes.

It is recommended that patients carry a letter from the prescribing provider detailing prostacyclin therapy and current oxygen prescription. The letter should emphasize the importance of therapy not being interrupted and possible rebound PH symptoms related to interruption of the infusion. In addition, the letter should describe the supplies needed for the duration of the travel and the necessity that all supplies for the duration of the travel be carried on the aircraft because of temperature extremes and the potential for vials being broken during handling. Planning to identify the location of emergency services or destinations suitable for the specialty pharmacy to ship additional supplies may decrease stress during travel. Shorter expeditions can encourage patients and caregivers that extended travel is feasible.

MULTIDISCIPLINARY APPROACH TO CARE

PH providers and coordinators work together to educate patients on diagnostic evaluation, disease state, prognosis, and treatment options. Together, they educate patients and caregivers on how to monitor their condition and make lifestyle changes necessary to manage right heart failure and complex medical regimens. Assessing for cognitive deficits, adherence, and

depression is ongoing throughout the spectrum of caring for patients in chronic illness. Managing symptoms and side effects of PAH therapies requires close monitoring by experienced providers and coordinators using frequent clinic follow-up and assessment over the telephone. Involving palliative care specialists can improve quality of life and lessen symptom and side effect burdens. Recognizing when patients need advanced treatments, transplant evaluation, or transition to end-of-life care because of subtle or rapid deteriorations requires close monitoring. Early conversation with the patient and caregivers regarding goals of care and the patient's wishes help providers guide therapy decisions with disease progression.

Multidisciplinary care also includes pharmacists, dietitians, social workers, and exercise or rehabilitation specialists. Multidisciplinary care is essential to provide complex care needed for patients with PAH by encouraging lifestyle changes, improving patient satisfaction, and quality of life. For patients on parenteral therapy, pharmacists oversee drug reconstitution, correct ordering of therapy, and dosing calculations during dose titration. After discharge, pharmacists can assist with side effect management, drug interactions, and anticoagulation. Dietitians help with strategies to increase caloric intake in patients with unintentional weight loss and anorexia. Dietitians provide education in interventions to promote adherence to low-sodium diet and fluid restrictions when right heart failure is an issue. Rehabilitation specialists assess and document supplemental oxygen requirements, teach energy conservation techniques, and create exercise programs to increase physical strength and endurance specific to the limitations of PAH. Social workers facilitate recruitment of additional support in the home and assist with applications for disability.

Specialty pharmacy nurses and pharmacists provide additional resources in teaching and managing these complex medical therapies and are critical in identifying potential and emerging problems. Patient adherence, skin reactions to catheter dressings, and identifying potential drug interactions require ongoing monitoring. Pharmacists often identify deficits in self-motivation, adherence, and knowledge during reorder calls to the patient.

PATIENT EDUCATION

Patient education is critical for the success of IV prostacyclin therapy. Educating the patient, caregiver, and family is the focus and responsibility of the specialty pharmacy nurses and PH coordinators. When initiating infusion therapy, one-on-one sessions of patient education with return demonstrations are scheduled until the patient and/or caregiver are deemed independent and safe to manage therapy after discharge. Patients and support persons are encouraged to practice drug mixing between teaching sessions, which may increase comfort with handling supplies and the pump without being under the pressure of being observed by the nurse. Training done in pairs of patient and support person is a helpful strategy allowing 1 person to perform the mixing steps while the other person reads the step-by-step instructions. This allows both to concentrate on 1 task and provides a double-check method to prevent contamination while mixing the drug and connecting the pump.

Before discharge, discussing potential scenarios that may arise after leaving the hospital can prepare patients and caregivers for consequences requiring quick intervention. Having the patient verbalize or role-play a plan for an emergency situation, such as CVAD dislodgment or high-pressure alarm, forces patients to troubleshoot and identify solutions. In addition to drug reconstitution and pump management, patients should be able to identify signs of infection and demonstrate how to change the dressing for the CVAD. Patients will need to know who to call for worsening PH symptoms, fluid retention, or signs and symptom of infections. It is important for the patient to know when to contact their primary care provider, PH provider, or specialty pharmacy, and when to go to the nearest emergency treatment center.

CVAD CARE AND COMPLICATIONS

Care of the CVAD site is an important part of continuous infusion therapy. Guidelines for prevention of catheter-related infections in patients with PAH who are receiving prostacyclin therapy have been established. Inserting a tunneled, single-lumen catheter that is dedicated to the prostacyclin infusion is recommended. Dressing changes to the site may require assistance of a support person. Dressing and cleansing agents may vary depending on skin reactions. Once a skin reaction occurs, every attempt should be made to identify a dressing or cleansing agent that is tolerated. Chlorhexidine 2% solution is the preferred antiseptic agent. The dressing should be changed if it becomes damp, nonocclusive, or if drainage is present under the dressing. Nontransparent dressings should be changed every other day, and transparent dressing should be changed weekly. Catheter sites and connections should not be submerged in water.[44]

Infection

Infection prevention is an important part of the patient education process. Aseptic drug reconstitution techniques must be demonstrated. Patients and support persons can work together to monitor each other and identify unintentional breaks in aseptic technique while mixing drug or connecting tubing. Patient technique should be observed after an infection, as it may identify deviation from original aseptic instructions. Infections

can occur at the exit site of the catheter and may be treated with oral or IV antibiotics with resolution. Infections with exudate extending up into the tunnel are often more difficult to resolve, and typically require catheter removal. A fever with suspected bacteremia or sepsis requires immediate evaluation. Blood cultures should be drawn from the catheter and periphery. Patients should be started on broad-spectrum antibiotics until sensitivities are available. Removal of the central catheter is recommended.[44] If it is determined that the CVAD will not be removed, IV antibiotics should be infused through the infected lumen(s) of the CVAD while prostanoid therapy is infused peripherally. Until a peripherally inserted central catheter can be safely placed, SPCs can be used. It is recommended to have 2 working SPCs at all times to prevent drug interruption. Once an antibiotic has been selected according to the bacterial sensitivities and the duration of the course has been determined, the patient may require ongoing IV antibiotics in the home, medical office, or local infusion suite, depending on reimbursement. After antibiotic treatment, repeat blood cultures must be negative before reinsertion of a new CVAD.

Loss of Venous Access

If a tunneled CVAD becomes occluded, dislodged, or develops a leak, it is necessary to activate emergency services to place SPCs until the CVAD can be repaired or replaced. Patients should be instructed to remain calm and assertive and to convey the critical nature of maintaining the infusion. The patient is encouraged to contact the PH provider to communicate with the community providers. If the catheter is repaired, the patient will require admission for peripheral infusion while the glue dries for 24 hours. Contacting the specialty pharmacy hotline phone number on the pump provides 24-hour access for information on the dose, pump rate, and patient dosing weight. Access to a CVAD repair kit and CVAD emergency clamp should be included in the patient's bag of supplies. Patients are encouraged to seek out emergency personnel before needing services to discuss potential issues and therapy considerations. Discussing prostacyclin therapy and potential symptoms associated with interrupted drug in advance of an emergency may facilitate timely reinitiation of drug.

CONCLUSION

PAH is a complex disease state requiring a detailed diagnostic evaluation. As more patients are diagnosed and treated in the community, early referral to PH centers experienced with parenteral therapy is encouraged to help confirm diagnosis, collaborate on initial treatment considerations, and expedite advanced treatment when necessary.[28] When patients are not meeting goals of oral or inhaled therapy, recognizing deterioration and advancing treatment is easier when a rapport has already been established and previous discussions with patients have provided a foundation for treatment decisions. Referral for infused prostacyclin treatment requires input from the multidisciplinary team to identify potential barriers before initiation. Intense education of patients and staff providing infusion therapy is essential to ensure safety and avoid negative outcomes.

REFERENCES

1. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1 suppl):S55-S66.
2. Gaine S. Pulmonary hypertension. *JAMA*. 2000;284(24):3160-3168.
3. Waxman AB, Zamanian RT. Pulmonary arterial hypertension: new insights into the optimal role of current and emerging prostacyclin therapies. *Am J Cardiol*. 2013;111(5 suppl):1A-16A.
4. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2009;30(20):2493-2537.
5. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D42-D50.
6. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D34-D41.
7. Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. *Clin Chest Med*. 2007;28(1):233-241, x.
8. Hansdottir S, Groskreutz DJ, Gehlbach BK. WHO's in second? A practical review of World Health Organization group 2 pulmonary hypertension. *Chest*. 2013;144(2):638-650.
9. Seeger W, Adir Y, Barberà JA, et al. Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol*. 2013;62(25 suppl):D109-D116.
10. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D92-D99.
11. Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. *Eur Respir Rev*. 2010;19(115):59-63.
12. Tuder RM, Archer SL, Dorfmuller P, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D4-D12.
13. Montani D, Bergot E, Günther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation*. 2012;125(17):2128-2137.
14. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest*. 2010;137(2):376-387.
15. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;36(3):549-555.

16. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. *Chest*. 2011;139(1):128-137.
17. McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. *Eur Respir Rev*. 2012;21(123): 8-18.
18. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J*. 2010;35(5):1079-1087.
19. McLaughlin VH, Humbert M. Pulmonary hypertension. In: *Braunwald's Heart Disease: A Textbook of Cardiovasular Medicine*. 10th ed. Philadelphia, PA: Saunders; 2015:1682-1702.
20. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med*. 2007;48(5):680-684.
21. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013; 62(25 suppl):D60-D72.
22. Chan L, Chin LM, Kennedy M, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. *Chest*. 2013;143(2): 333-343.
23. Weissmann N, Peters DM, Klopping C, et al. Structural and functional prevention of hypoxia-induced pulmonary hypertension by individualized exercise training in mice. *Am J Physiol Lung Cell Mol Physiol*. 2014;306(11):L986-L995.
24. Barst R. How has epoprostenol changed the outcome for patients with pulmonary arterial hypertension? *Int J Clin Pract Suppl*. 2010;168:23-32.
25. McLaughlin VV, Palevsky HI. Parenteral and inhaled prostanoid therapy in the treatment of pulmonary arterial hypertension. *Clin Chest Med*. 2013;34(4):825-840.
26. Kingman MS, Tankersley MA, Lombardi S, Spence S, Torres F, Chin KS. Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey. *J Heart Lung Transplant*. 2010;29(8):841-846.
27. McLaughlin VV, Gaine SP, Howard LS, et al. Treatment goals of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl): D73-D81.
28. Champion HC. When to initiate intravenous therapy and/or refer. *Am J Cardiol*. 2013;111(8 suppl):21C-24C.
29. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996; 334(5):296-301.
30. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol*. 2002;40(4): 780-788.
31. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med*. 2000;132(6):425-434.
32. Flolan [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2016.
33. Veletri [package insert]. South San Franciso, CA: Actelion Pharmaceuticals US, Inc; 2016.
34. Sitbon O, Delcroix M, Bergot E, et al. EPITOME-2: an open-label study assessing the transition to a new formulation of intravenous epoprostenol in patients with pulmonary arterial hypertension. *Am Heart J*. 2014;167(2):210-217.
35. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(6): 800-804.
36. McLaughlin VV, Gaine SP, Barst RJ, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol*. 2003;41(2):293-299.
37. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. *Eur Respir J*. 2006;28(6):1195-1203.
38. Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2014.
39. White RJ, Levin Y, Wessman K, Heininger A, Frutiger K. Subcutaneous treprostinil is well tolerated with infrequent site changes and analgesics. *Pulm Circ*. 2013;3(3):611-621.
40. Tapson VF, McLaughlin VV, Gomberg-Maitland M, et al. Delivery of intravenous treprostinil at low infusion rates using a miniaturized infusion pump in patients with pulmonary arterial hypertension. *J Vasc Access*. 2006;7(3):112-117.
41. Oudiz RJ, Farber HW. Dosing considerations in the use of intravenous prostanoids in pulmonary arterial hypertension: an experience-based review. *Am Heart J*. 2009;157(4):625-635.
42. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. *Am J Respir Crit Care Med*. 2005;172(12): 1586-1589.
43. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation*. 2006;114(13):1417-1431.
44. Doran AK, Ivy DD, Barst RJ, et al. Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension. *Int J Clin Pract Suppl*. 2008;160:5-9.