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Abbreviated Class Review: Intravenous/Subcutaneous Pulmonary Arterial Hypertension Agents

Month/Year of Review: September 2012 **End of literature search:** July 2012

Drugs Included: Epoprostenol (Flolan® and Veletri®)
Treprostinil (Remodulin®)

Issues:

- Is there evidence of efficacy differences between intravenous (IV)/ subcutaneous (SQ) agents for pulmonary arterial hypertension (PAH)?
- Is there evidence of safety advantages between the available IV/SQ PAH agents?
- Are there unique patients or situations where one agent may be more effective or safer than other available agents?
- Is there evidence to suggest IV/SQ agents are superior or safer than oral or inhaled agents for PAH?

Conclusions:

- The efficacy and safety evidence for IV epoprostenol and IV/SQ treprostinil is very limited. There are no head to head trials comparing them for PAH.
- IV epoprostenol increases survival, exercise capacity, functional class and hemodynamic status in idiopathic PAH (IPAH) patients. Studies in patients with PAH associated with scleroderma spectrum of diseases (SSD) demonstrated improvements in exercise capacity and hemodynamics but no survival benefit.
- IV epoprostenol produces a substantial benefit in New York Heart Association (NYHA) functional class III and IV patients and is strongly recommended based on good evidence in the American College of Chest Physicians (ACCP) Guidelines.[1] IV epoprostenol is the treatment of choice in class IV patients in the ACCP Guidelines and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Consensus Document. [1,2]
- IV epoprostenol use requires a central venous catheter for continuous infusion and has a maximum of 24 hours stability at room temperature. Disruption in the infusion may cause rebound pulmonary hypertension and death due to short half-life (6 minutes).[3,4]
- IV/SQ treprostinil has been show to improve exercise capacity and hemodynamics.
- IV/SQ treprostinil is approved for use in patients with NYHA functional class II symptoms but ACCP Guidelines do not recommend it due to complex administration, side effects and cost (low level of evidence with small benefit).[1] IV/SQ treprostinil is associated with an intermediate benefit in functional class III and IV patients based on low to fair evidence in the ACCP Guidelines.[1]
- SQ treprostinil can be given without dilution and is stable at room temperature for up to 72 hours. IV treprostinil requires sterile dilution and is stable for up to 48 hours at room temperature. Due to the longer half-life of treprostinil, it is thought to be less likely to cause rebound pulmonary hypertension if discontinued. However, dose changes and discontinuations should not be done abruptly.[5]
- Blood stream infections, sepsis and death were associated with chronic use of a central venous catheter required for IV epoprostenol and IV treprostinil.[3.4.5]
- Oral and inhalation therapies are an appropriate option for class II-IV patients but do not negate the need for IV/SQ prostycyclins.[2]

- Due to limited evidence and substantial risk associated with administration, one IV/SQ product cannot be recommended over another.

Recommendations:

- Require prior authorization for both IV epoprostenol and IV/SQ treprostinil to insure appropriate use. Requirements should include: diagnosis of PAH with NYHA functional class III or IV and prescribed in consultation with a specialist (pulmonologist or cardiologist).

Reason for Review:

- PAH is progressive and associated with high mortality rates. There are four classes of therapies to treat PAH, which include oral, inhalation, and IV and SQ therapies. The role of IV/SQ therapies in PAH in relation to other agents will be reviewed.
- Epoprostenol is available in a generic formulation and can only be given IV. Treprostinil can be given SQ or IV and is available as the branded product, Remodulin. Data analysis of OHP patients revealed that Remodulin claims were in the top 40 drugs by cost. This review will evaluate available evidence to formulate recommendations to optimize the use of IV/SQ PAH agents.

Methods:

A Medline literature search ending July 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing epoprostenol and treprostinil to placebo and/or conventional therapy for PAH was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Introduction/Background:

PAH is the result of constricted flow through the pulmonary vasculature resulting in increased pulmonary resistance. PAH is defined as a mean pulmonary artery pressure (mPAP) >25 mm Hg with a pulmonary capillary wedge pressure (PCWP), left atrial pressure or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units.[2] The cause of PAH is not fully understood but includes idiopathic, heritable (often from a mutation in the bone morphogenic protein receptor-2), drug and toxin induced or PAH caused by an underlying medical condition (e.g. connective tissue diseases and HIV infection).[6] Regardless of the etiology, PAH is usually progressive with the most common cause of death being right ventricular failure.[1]

Changes in vascular structure and function within the pulmonary arteries account for the common symptoms of PAH including dyspnea, syncope, fatigue, edema and others. Exercise tolerance, as measured by the 6 minute walk (6MW) distance, and hemodynamic improvements have been good prognostic indicators of survival. The 6MW is the most common outcome measured, which reflects the distance walked in meters. In patients with chronic obstructive pulmonary disease, a mean change of 54 m was associated with a noticeable clinical difference and another study in heart failure patients found a mean difference of 43 m

to be associated with a noticeable difference in their global rating of worsening symptoms.[6] Other outcomes measured in clinical trials are: functional class, dyspnea and/or quality of life and mortality.

The World Health Organization (WHO) classifies pulmonary hypertension (PH) into five groups based on etiology. WHO Group I includes PAH caused by idiopathic PAH (IPAH), heritable PAH, and PAH as a result of connective tissue diseases, HIV and portal hypertension. These same groups of PAH were formerly referred to as primary pulmonary hypertension (Table 1).[7] PH caused by secondary sources are included in Groups 2-5 and won't be the focus of this review. The WHO functional assessment classification system for PAH has been adapted from the New York Heart Association (NYHA) functional classification. Both systems are utilized in guidelines and studies to classify patients based on symptoms as well as for treatment guidance (Table 2).[8]

Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)[7]

WHO Group I: Pulmonary Arterial Hypertension	
1. Pulmonary arterial Hypertension	1.4 Associated with
1.1 Idiopathic PAH (IPAH)	1.4.1 Connective tissue diseases
1.2 Heritable	1.4.2 HIV infection
1.2.1 Bone morphogenetic protein receptor (BMPR) type 2	1.4.3 Portal hypertension
1.2.2 Activin receptor-like kinase 1 (ALK1) endoglin (with or without hereditary hemorrhagic telangiectasia)	1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
1.2.3 Unknown	1.4.6 Chronic hemolytic anemia
1.3 Drug induced	1.5 Persistent pulmonary hypertension of the newborn 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

Table 2. WHO Functional Assessment Classification[8]

Class	**Description**
I	Patients with PH with no limitation in physical ability
II	Patients with PH with slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
III	Patients with PH with marked limitation of physical activity; les than ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
IV	Patients with PH unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest

Significant advances in therapeutic options to treat PAH have evolved over the last 15 years including the use of combination therapy. Standard treatment options include calcium channel blockers (for those responsive to acute vasoreactivity testing), anticoagulants, diuretics, digoxin, oxygen, prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan and ambrisentan) and phosphodiesterase-5 inhibitors (sildenafil) .[1] Patients with symptomatic PAH are provided treatment based on functional class. According to ACCP guidelines, general treatment measures include oral anticoagulants, diuretics and oxygen.[1] Patients whom respond well to acute vasodilator testing during cardiac catherization are good candidates for calcium channel blocker therapy. This usually applies to small subset of patients with IPAH with a sustained response to CCB therapy (functional class I or II with normal or near-normal hemodynamics after several months of treatment). Long-acting nifedipine or diltiazem or amlodipine are recommended. For functional class II patients sildenafil is strongly recommended and treprostinil (IV/SQ) is a less highly recommended option. Bosentan, sildenafil, epoprostenol, iloprost inhalation are strongly recommended for functional class III patients. In functional class IV patients epoprostenol is the treatment of choice.[1,2] There is fair evidence to support the use of bosentan and iloprost inhalation in functional class IV patients.[2]

Oral PAH agents have been reviewed previously, therefore, this review will focus on IV/SQ PAH agents, epoprostenol and treprostinil (Table 3). Epoprostenol and treprostinil are prostacyclins that cause vasodilation and inhibition of platelet aggregation. Deficiencies in prostacyclins are thought to be involved in the underlying pathology of PAH.

Issues with administration make both epoprostenol and treprostinil complex to use. Epoprostenol is limited in its use due to a short half-life (6 minutes or less) which requires continuous IV infusion via a central venous catheter. Interruption in the infusion may result in rebound pulmonary hypertension and death. Patients are asked to reconstitute epoprostenol using sterile technique and use reconstituted product within 24 hours if at room temperature.[3,4] Treprostinil may be given SQ or IV with the SQ route being preferred but associated with a high incidence of injection site pain. The half-life of treprostinil is longer (around 4 hours) making disruptions in infusion less prone to cause rebound hypertension.[5] SQ treprostinil does not have to be diluted and is stable at room temperature for 72 hours. IV treprostinil has to be diluted, using sterile technique, and is stable at room temperature for 48 hours.[5]

Table 3. IV/SQ Pulmonary Arterial Hypertension Agents

Drug Products	FDA approval	FDA approved indications	Usual Dose/Duration	Potential Off-label Uses	Other Considerations
Epoprostenol (Flolan®, Veletri®)[3,4]	Flolan 1995 Veletri 2008	Treatment of PAH (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective	Administer continuous chronic infusion of epoprostenol through central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Initiate chronic infusion of epoprostenol at 2 ng/kg/min and increase in increments of 2 ng/kg/min every 15 minutes or longer until dose-	PAH WHO Groups 2-5	Average doses in clinical trials range from 9-11 ng/kg/min at 12 weeks. Infusion disruption may cause rebound pulmonary hypertension and death. Most studies are open-label due to safety concerns with central venous catherization and obvious side effects of drug.

		tissue disorders.	limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted.		Due to the complex nature of administration and safety concerns it is recommended that epoprostenol only be administered by clinicians experienced in diagnosis and management of PAH.
Treprostinil (Remodulin®)[5]	2002 (SQ) 2004 (IV)	Treatment of PAH (WHO Group I) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies or idiopathic or heritable PAH, PAH associated with congenital systemic-to-pulmonary shunts, or PAH associated with connective tissue diseases. Patients who require transition from epoprostenol to reduce the rate of clinical deterioration.	Initial dose to prostacyclin naive patients : 1.25 ng/kg/min (or 0.625 ng/kg/min if not tolerated); dose increase based on clinical response (increments of 1.25 ng/kg/min per week). Limited experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided. * Continuous SQ infusion (undiluted) is the preferred mode. Use intravenous infusion (dilution required) if SQ infusion is not tolerated.	PAH WHO Groups 2-5	The average dose in clinical trials was 9 ng/kg/min after 12 weeks. It is recommended that treprostinil only be administered by clinicians experienced in diagnosis and management of PAH. Half-life of treprostinil is 4 hours and is stable at room temperature.

Guidelines:

2007 UPDATED ACCP EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES[1]

Prostacyclins are recommended by ACCP Guidelines for functional class II and higher. SQ and IV treprostinil were found to have a low level of evidence for benefit in functional class II patients with only a small benefit noted. Complex administration, adverse effects and cost make treprostinil a seldom used option for functional class II patients. In functional class III patients, IV epoprostenol is strongly recommended with a good level of evidence for substantial benefit. For this same class SQ treprostinil is found to have intermediate benefit with a fair level of evidence to support its use. IV treprostinil is considered to have low evidence for intermediate benefit in which the recommendation was considered weak for functional class III patients. In functional class IV, epoprostenol is considered the treatment of choice with good evidence of substantial benefit and strongly recommended. SQ treprostinil is considered to have a fair amount of evidence of intermediate benefit with a moderate recommendation. IV treprostinil was determined to have low level of evidence of intermediate benefit with a weak recommendation. The guidelines recognize that IV treprostinil may be a suitable alternative to epoprostenol in critically ill functional class IV patients. Due to the complexity of PAH it is recommended that patients be referred to a center that specializes in the treatment of PAH.

The ACCP guideline recommendations are based on quality of the evidence and the strength of the recommendation combined to produce the net benefit of the therapy to the patient (Table 4). Recommendations receive a quality of evidence rating of Expert opinion to Good and the strength of the recommendation ranges from "negative based on expert opinion only" to a "strong" recommendation.[1]

Table 4. Relationship of Strength of the Recommendations Scale to Quality of Evidence and Net Benefits*[1]

	Net Benefit					
Quality of Evidence	Substantial	Intermediate	Small/Weak	None	Conflicting	Negative
Good	A	A	B	D	I	D
Fair	A	B	C	D	I	D
Low	B	C	C	D	I	D
Expert Opinion	E/A	E/B	E/C	I	I	E/D

** Strength of recommendation is based on a negative recommendation based on expert opinion only (E/D) to strong (A).*

ACCF/AHA 2009 EXPERT CONSENSUS DOCUMENT ON PULMONARY HYPERTENSION: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc. and the Pulmonary Hypertension Association.[2]

The ACCF/AHA Expert Consensus document regard prostacyclin agents as a mainstay of PAH treatment. The committee recommends treatment selection be considered based on severity of illness, route of administration, side effects, co-morbid illness, treatment goals, and clinician preference. The ACCF/AHA Consensus document recommends treatment with IV epoprostenol or IV treprostinil as first line in patients considered high-risk. SQ treprostinil is an alternative if the IV route cannot be utilized. Epoprostenol is the preferred treatment option for critically ill patients based on improvements in functional class, exercise tolerance, hemodynamics and survival in patients with IPAH. Oral therapy with an endothelin receptor antagonist or phosphodiesterase inhibitor is recommended first line for lower risk patients, not responsive to acute vasoreactivity testing.[2]

Data to support the ACCF/AHA recommendations for epoprostenol is based on two, open-label, randomized trials and observational studies showing changes in the 6MW of 47-94m. A survival benefit was demonstrated in the epoprostenol group of one study, however, a second study found no survival differences. Efficacy data to support the use of SQ treprostinil is based on one blinded, randomized controlled trial showing a median increase of16m in the 6MW. Data for IV treprostinil is from one open-label, uncontrolled trial demonstrating improvements of 82m in the 6MW.[2]

* This expert consensus document was peer reviewed and based on available limited evidence.[2]

Systematic Reviews:

PROSTACYCLIN FOR PULMONARY HYPERTENSION IN ADULTS COCHRANE REVIEW[9]

A 2009 Cochrane review included three studies of IV epoprostenol compared to usual care (diuretics, calcium channel blockers, oral anti-coagulants, cardiac glycosides, supplemental oxygen therapy and oral vasodilators) and two studies involving SQ treprostinil versus placebo. All studies were considered to be of adequate quality. The studies involving IV therapy were open-label due to the inherent risks of central line placement. Studies ranged from 8 -12 weeks. Studies with IV epoprostenol demonstrated improvements in exercise capacity (approximately 90 meters/98 yards), cardiopulmonary hemodynamics and NYHA functional class (Table 5). SQ treprostinil studies produced mixed results with one showing a significant improvement in exercise capacity, median improvement of 16 meters, as well as improved hemodynamics and symptom scores. However, a second study failed to show a difference between treprostinil and placebo (Table 5).[9]

Table 5. Cochrane Review Summary of Results[9]

Therapy	Outcome	Results	Comments
IV Epoprostenol vs. Usual Care * Pooled data on patients with IPAH and scleroderma unless otherwise indicated	Exercise Capacity (6MW)	SMD 0.69, 95% CI 0.40 to 0.97, p<0.00001	- Difference from pooled estimates translates into difference of 90 meters in 6MW.
	Improvement in at least one NYHA Functional Class	OR 37.99, 95% CI 8.43 to 171.22, p<0.00001	
	Mortality	OR 0.32, 95% CI 0.06 to 1.58 (all patients) OR 0.11, 95% CI 0.02 to 0.62 (exclusion of scleroderma patients)	- Survival benefit was demonstrated in IPAH patients - No survival benefit was demonstrated when data on scleroderma patients were included.
SQ Treprostinil * No studies on IV treprostinil available at time of review	Exercise Capacity (6MW)	Treprostinil: 10 meters Placebo: 0 meters p=0.006	- Second study found no significant difference between treprostinil and placebo. - Subgroup analysis showed greatest improvements in those with severe disease (NYHA class III)
	Improvement in at least one NYHA Functional Class	Not reported	
	Mortality	Treprostinil: 9 deaths Placebo: 10 deaths	No deaths reported in second study.

SMD- standard mean difference, WMD- weighted mean difference

Randomized Controlled Trials

There are no published head to head trials comparing epoprostenol to treprostinil. Previously discussed literature includes pivotal efficacy trials with the exception of one newly published study listed below.

TREPROSTINIL

A poor quality, randomized, multi-center (non-United States sites), placebo-controlled, double-blind study was done in 44 patients receiving IV treprostinil (n=30) or placebo (n=14).[10] Patients were treatment naïve to prostacyclin therapy and a majority (95%) were NYHA Class III with IPAH. Patients were also included if they were NYHA Class IV with PAH associated with HIV or collagen vascular disease. Inclusion criteria required a mean PA >35 mm, selecting out a severely ill population. The primary endpoint was change from baseline in the 6MW at 12 weeks. There is low strength of evidence that treprostinil is superior to placebo with a mean placebo-corrected difference of 93 meters in favor of treprostinil (p=0.022). Eleven patients in the treprostinil group experienced serious adverse events, 3 resulting in death, compared to 21 serious adverse events in the placebo group, 5 resulting in death. Adverse events that were more common in the treprostinil group include; headache, pain in extremity, diarrhea, and jaw pain. Details on randomization and blinding were not included, potentially increasing the risk of selection and performance bias. This factor as well as the high attrition rate (25% in the treprostinil group and 33% in the placebo group) and small number of patients contributed to the poor quality rating. Additionally, the use of sites outside of the United States and only in patients of Indian nationality limits the external validity of the results.[10]

Safety/tolerability:

EPOPROSTENOL

Clinical studies show epoprostenol use is associated with adverse effects, including: flushing, jaw pain, diarrhea, headaches, hypotension, anxiety, chest pain, dizziness and nausea and vomiting. More serious adverse effects include catheter-related sepsis, paradoxical embolism, sepsis, cellulitis, pneumothorax and hepatic failure.[3,4] In a study by Barst, attrition rates were around 4% due to adverse reactions with a similar rate noted in other studies.[11]

TREPROSTINIL

Pooled data from studies with treprostinil show that infusion site pain is more common with SQ treprostinil than with placebo (OR 17.32, 95% CI 10.96 to 27.39).[5] Studies have cited infusion site pain as reason for study withdrawal in the treprostinil group and pooled data shows withdrawal due to drug-related adverse events is more common with treprostinil (OR 13.47, 95% CI 2.57 to 70.48).[9] Treprostinil use is also associated with diarrhea, jaw pain, vasodilation, and nausea. More serious adverse effects associated with IV treprostinil are sepsis, arm swelling, paresthesias, hematoma, and pain.[5]

References:

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2) McLaughlin V, Archer S, Badesch D, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: Developed in Collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation 2009; 119:2250-2294.
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Appendix 1: Drug Information

Pharmacology:

Epoprostenol[3,4]	**Treprostinil**[5]
Epoprostenol causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.	Treprostinil causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

Pharmacokinetics:

Table 1. Pharmacokinetic comparison

Parameters	Epoprostenol[3,4]	Treprostinil[5]
Half-life (h)	~ 6 minutes	4 hours
Metabolism	Spontaneous degradation and enzymatic	CYP2C8
Elimination	82% renal, 4% feces	79% renal, 13% feces
Renal Dose Adjustment	None	Not studied
Hepatic Dose Adjustment	None	In mild to moderate hepatic insufficiency decrease dose to 0.625 ng/kg/min ideal body weight. Not studied in severe hepatic insufficiency
Food effect on pharmacokinetics	None	None

Contraindications/Warnings

Epoprostenol[3,4]

- **Contraindication:** Congestive heart failure due to severe left ventricular systolic dysfunction, pulmonary edema, and hypersensitivity to epoprostenol.
- **Warnings:**
  - **General:** Epoprostenol should only be administered by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. Do not abruptly lower the dose or withdraw dosing. All dosing initiation and changes should be closely monitored.

Treprostinil[5]

- **Contraindication:** None

- **Warnings:** Administration of treprostinil via an indwelling central venous catheter has been associated with blood stream infections and sepsis, which may be fatal. Treprostinil should only be used by clinicians experienced in the diagnosis and treatment of PAH. Dosage adjustments should be based on clinical response and doses should not be abruptly lowered or discontinued.

Appendix 2 : New Authorization Criteria

IV/SQ Pulmonary Arterial Hypertension Agents

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which agents for pulmonary arterial hypertension (PAH) has been shown to be effective and safe.

Length of Authorization: 12 months

Requires PA:

- Epoprostenol (Flolan®, Veletri ®)
- Treprostinil (Remodulin®)

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of pulmonary arterial hypertension (PAH) classified as World Health Organization (WHO) Group 1 (see table 1 below)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Does the client have WHO or New York Heart Association (NYHA) Functional Class III-IV symptoms (see table 2 below)?	**Yes:** Go to #4	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the drug being prescribed by a PAH specialist (pulmonologist or cardiologist)?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny (medical appropriateness)

Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

WHO Group I: Pulmonary Arterial Hypertension	
1. Pulmonary arterial Hypertension	1.5 Associated with
1.2 Idiopathic PAH (IPAH)	1.4.1 Connective tissue diseases
1.2 Heritable	1.4.2 HIV infection
1.2.1 Bone morphogenetic protein receptor (BMPR) type 2	1.4.3 Portal hypertension
1.2.2 Activin receptor-like kinase 1 (ALK1) endoglin (with or without hereditary hemorrhagic telangiectasia)	1.4.4 Congenital heart disease
	1.4.5 Schistosomiasis
1.2.3 Unknown	1.4.6 Chronic hemolytic anemia
1.3 Drug induced	1.5 Persistent pulmonary hypertension of the newborn
	1'. Pulmonary veno-occulsive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

** Simonneau, G, et al. Updated Clinical Classification of Pulmonary Hypertension. J AM Coll Cardiol 2009; 54:S43-S54.*

Table 2. World Health Organization (WHO) Functional Classification of Pulmonary Hypertension

Class	**Description**
I	Patients with pulmonary hypertension (PH) with no limitation in physical ability
II	Patients with PH with slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
III	Patients with PH with marked limitation of physical activity; les than ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
IV	Patients with PH unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest

** Rubin, Lewis. Diagnosis and Management of Pulmonary Arterial Hypertension: ACCP Evidende-Based Clinical Practice Guidelines. CHEST 2004; 126:7S-10S)*

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