Executive Summary of the American Heart Association and American Thoracic Society Joint Guidelines for Pediatric Pulmonary Hypertension

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for the AHA/ATS Joint Guidelines for Pediatric Pulmonary Hypertension Committee *

ONLINE DATA SUPPLEMENT

Supplemental Table

American Heart Association and American Thoracic Society Clinical Practice Guidelines: Pediatric Pulmonary Hypertension

Supplemental Table: Evidence supporting each recommendation

Evidence supporting each recommendation					
Diagnostics, Assessments, and Monitoring					
Type of evidence (rationale for the level of evidence)	**Potential upsides (i.e., benefits)**	**Potential downsides (i.e., harms, burdens, and benefits)**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#1) At the time of initial PH diagnosis, a comprehensive history and physical examination in combination with diagnostic testing for assessment of PH etiology/classification and formal assessment of cardiac function should be performed prior to the initiation of therapy at an experienced center. (I,B)					
Case series + clinical experience	History, physical examination and evaluation of cardiac function: Identifies anatomic cardiac abnormalities. Many may be repaired surgically, improving clinical outcomes. Identifies cardiomyopathy. Medical therapy improves clinical outcomes. Guides the clinician to the appropriate next test (e.g., right heart catheterization, chest CT scan), reducing the harms, burdens, and costs of inappropriate testing. Determines the severity of disease. Finding severe disease prompts earlier treatment and affects which agent is selected, both of which improve clinical outcomes. Finding mild or no disease prevents inappropriate therapy and its related harms, burdens, and costs.	False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	The recommendation places a high value on early diagnosis and treatment; it places a lower value on the consequences of misleading test results and the burdens and costs of diagnostic testing.	I	B
#2) Imaging to diagnose pulmonary thromboembolic disease, peripheral pulmonary artery stenosis, pulmonary vein stenosis, pulmonary veno-occlusive disease and parenchymal lung disease should be performed at the time of diagnosis. (I,B).					
Case series +	Imaging:	False-negative results lead to false	The recommendation places a high value	I	B

clinical experience	Identifies pulmonary thromboembolic disease, prompting anticoagulant therapy, which improves clinical outcomes. Identifies pulmonary artery and pulmonary vein stenosis. For patients whose symptoms are severe enough to warrant an intervention, clinical outcomes can be improved by balloon dilation, stenting, or surgery. For patients whose disease is too mild for an intervention, diagnosis allows additional diagnostic testing to cease, thereby eliminating the associated harms, burdens, and costs. Identifies pulmonary veno-occlusive disease, prompting anticoagulant therapy, which improves clinical outcomes. For patients whose symptoms are severe enough to warrant additional therapy, pulmonary vasodilators improve clinical outcomes. Identifies parenchymal lung disease, which allows further diagnostic investigations to cease and prevents related harms, burdens, and costs. Also, redirects care toward supportive care, which improves symptoms. Can exclude all of the above mentioned diagnoses and guide the clinician to the appropriate next test (e.g., right heart catheterization, chest CT scan), reducing the harms, burdens, and costs of inappropriate testing.	reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results may lead to inappropriate treatments, with their associated risks, burdens, and costs.	on early diagnosis and treatment; it places a lower value on the consequences of misleading test results and the burdens and costs of diagnostic testing.		
#3) After a comprehensive initial evaluation, serial echocardiograms should be performed. More frequent echocardiograms are recommended in the setting of changes in therapy or clinical condition. (I,B)					
Case series + clinical experience	<u>Serial echocardiograms</u>: Increases the likelihood of detecting disease; thus, also increases the likelihood of obtaining the beneficial outcomes described in #1 above. Allows the rate of disease progression to be determined, which will prompt early initiation of treatments that improve clinical outcomes	The potential harms for a single echocardiogram were described in #1 above and are also relevant to serial echocardiography. In addition, serial echocardiograms are more costly and burdensome than single echocardiograms.	The recommendation places a high value on early diagnosis and treatment; it places a lower value on costs and burdens.	I	B

	if disease progression is fast, or avoidance of unnecessary therapy if disease progression is slow, including its related risks, burdens, and costs.				
#4) Cardiac catheterization is recommended before initiation of PAH targeted therapy. (I,B) Exceptions may include critically ill patients requiring immediate initiation of empirical therapy. (I,B)					
Case series + clinical experience	<u>Cardiac catheterization is the gold standard for diagnosing pulmonary hypertension. It</u>: Confirms the diagnosis so that further diagnostic testing may be directed toward identifying the underlying cause rather than seeking alternative causes of the patient's symptoms. This limits further diagnostic testing, reducing related harms, burdens, and costs. Confirms the diagnosis so that PAH-targeted therapy is directed toward the correct population; this maximizes the benefits and mitigates harms due to inappropriate therapy. Determines the severity of disease. Finding severe disease affects which agent is selected, which improves clinical outcomes. Finding mild or no disease prevents inappropriate therapy and its related harms, burdens, and costs, and also redirects the clinician to resume searching for alternative causes of the patient's symptoms. Should be performed at an experienced pediatric PH center	Arrhythmias, bleeding, cardiac or blood vessel injury, and cardiac arrest.	This recommendation places a high value on definitive diagnosis and the initiation of beneficial therapy, and a lower value on the risks of the procedures.	I	B
#5) Cardiac catheterization should include acute vasoreactivity testing (AVT) unless there is a specific contraindication (I,A)					
Case series + clinical experience	<u>Vasoreactivity testing</u>: Determines whether a patient is likely to respond to calcium channel blockers or requires pulmonary vasodilators. For patients who are vasoreactive, as defined by a drop in mPAP of at least 10 mm Hg to values below 40 mm Hg without a reduction in cardiac output, calcium channel blockers improve clinical outcomes, are less	Vasoreactivity testing may cause acute pulmonary edema in the context of cardiomyopathy or pulmonary venoocclusive disease.	This recommendation places a high value on identifying patients for whom there exists a less harmful, less burdensome, and less costly option. It places a lower value on the risks associated with the test itself.	I	A

	burdensome, are less expensive, and have fewer adverse effects than pulmonary vasodilators. Thus, cardiac catheterization minimizes the risk of unnecessarily harmful, costly, and burdensome therapy.				
#6) The minimal hemodynamic change that defines a positive response to AVT for children should be considered as a > 20% fall in PAP and PVR/SVR without a decrease in CO (I,B)					
Case series + clinical experience	Compared with using a lower threshold (e.g., >15% fall or >10% fall), the threshold of a >20% fall provides the following benefits: The higher threshold excludes more patients who are unlikely to respond to calcium channel blockers. As a result, fewer patients undergo unsuccessful trials of calcium channel blockers and the duration to initiation of beneficial therapy with pulmonary vasodilators is reduced.	Compared with using a lower threshold (e.g., >15% fall or >10% fall), the threshold of a >20% fall provides the following harms: Some patients whose fall in PAP and PVR/SVR is <20%, but would have responded to calcium channel blockers, will not be offered calcium channel blockers and, therefore, will not benefit from their fewer side effects, lower burden, and lower cost.	This recommendation places a high value on reducing delays to beneficial therapy; it places a lower value on missing patients who may have responded to safer and less expensive calcium channel blocker therapy.	I	B
#7) Repeat cardiac catheterization is recommended within 3-12 months after initiation of therapy to evaluate the response or with clinical worsening. (I,B)					
Case series + clinical experience	Repeat cardiac catheterization provides a hemodynamic assessment of the patient's response to therapy. Some patients appear over-treated and have their therapy reduced, which decreases the harms, burdens, and cost of therapy. Other patients appear under-treated and have their therapy escalated with subsequent improvement in clinical outcomes.	Arrhythmia, bleeding, cardiac or vessel injury, and cardiac arrest.	This recommendation places a high value on maximizing benefits and minimizing the harms, burdens, and costs of therapy; it places a lower value on the potential complications of the catheterization procedure.	I	B
#8) Serial cardiac catheterizations with AVT are recommended:					
i) during follow-up to assess prognosis and potential changes in therapy. (I,B)					
Case series + clinical experience	Vasoreactivity can change over time. Patients who are receiving calcium channel blockers, but are no longer vasoreactive on repeat testing, may not be receiving benefits from their therapy; changing their regimen to pulmonary vasodilator therapy may improve clinical outcomes. In contrast, patients receiving pulmonary vasodilator therapy who are found on repeat testing to be vasoreactive, can be changed to a calcium channel blocker which has fewer side effects, less burden, and lower cost.	For each catheterization, risks include arrhythmia, bleeding, cardiac or vessel injury, and cardiac arrest.. For each vasoreactivity test, risks include acute pulmonary edema if performed in the context of cardiomyopathy or pulmonary venoocclusive disease.	This recommendation places a high value on maximizing benefits and minimizing the harms, burdens, and costs of therapy; it places a lower value on the potential complications of the catheterization procedure and vasoreactivity testing.	I	B
ii) Intervals for repeat catheterizations should be based on clinical judgment but include worsening clinical course or failure to improve during treatment. (I,B)					

Case series + clinical experience	A worsening clinical course or failure to improve suggests either under-treatment or a new problem. Repeat cardiac catheterization distinguishes between these possibilities. This is essential because inappropriate empiric escalation of therapy will unnecessarily increase the risk of side effects and costs of therapy.	For each catheterization, risks include arrhythmia, bleeding, cardiac or vessel injury, and cardiac arrest.	This recommendation places a high value on avoiding the downsides of inappropriate therapy. It places a lower value on the potential complications of cardiac catheterization.	I	B
#9) Magnetic resonance imaging (MRI) can be useful as part of the diagnostic evaluation and during follow-up to assess changes in ventricular function and chamber dimensions. (IIa,B)					
Case series + clinical experience	MRI assesses right and left ventricular shape, size, mass, and function. This may identify additional contributors to the patient's symptoms and signs that can be effectively treated. As an example, a patient with cardiomyopathy detected by MRI may benefit from the addition of an afterload reducing agent. By avoiding under-treatment, clinical outcomes improve.	Sedation is generally performed for MRI, which has a risk of adverse effects and there is the burden of additional monitoring. In addition, MRI is more costly than many diagnostic tests. MRI requires some specific expertise and may not be possible at all centers. Also, as with any non-gold standard diagnostic test, there are false-positive and false-negative results: False-negative results lead to false reassurance of the patient and clinician. The latter may delay treatment opportunities. False-positive results may lead to inappropriate treatments, with their associated risks, burdens, and costs.	This recommendation places a high value on improving outcomes by avoiding under-treatment and a lower value on the harms, costs, and burdens of additional diagnostic testing.	IIa	B
#10) Brain natriuretic peptide (BNP) or NT-pro BNP should be measured at diagnosis and during follow-up to supplement clinical decision. (I,B)					
Case series + clinical experience	BNP and NT-pro-BNP measurements help monitor therapy. Persistently elevated levels may prompt additional diagnostic tests to determine whether the elevation is due to under-treatment, an additional problem affecting the right ventricle, or an additional problem affecting the left ventricle. Escalation of therapy in the setting of under-treatment and additional therapy in the context of additional contributors will improve clinical outcomes.	False-positive results are common because BNP and NT-pro-BNP are not specific for the right ventricle. False-positive results may lead to unnecessary diagnostic testing, which may have harms, burdens, and costs. False-negative results may lead to false reassurance of patients and clinicians, with the latter resulting in missed diagnostic and treatment opportunities, leading to poorer outcomes.	This recommendation places a high value on quickly identifying and correcting under-treatment, which is expected to improve clinical outcomes. It places a lower value on the harms, burdens, and costs of false-positive results.	I	B
#11) Six minute walk distance test should be used to follow exercise tolerance in pediatric PH patients of appropriate age. (I,A)					

Case series + clinical experience	The 6MWT helps monitor therapy. Poor performance may prompt additional diagnostic tests to determine whether the poor performance is due to under-treatment or a new additional problem. Escalation of therapy in the setting of under-treatment and additional therapy in the context of a new problem will improve clinical outcomes.	False-positive results are common because the 6MWT is not specific for pulmonary hypertension. False-positive results may lead to unnecessary diagnostic testing, which may have harms, burdens, and costs. False-negative results may lead to false reassurance of patients and clinicians, with the latter resulting in missed diagnostic and treatment opportunities, leading to poorer outcomes.	This recommendation places a high value on quickly identifying and correcting under-treatment, which is expected to improve clinical outcomes. It places a lower value on the harms, burdens, and costs of false-positive results.	I	A
#12) A sleep study:					
i) should be part of the diagnostic evaluation of patients with PH at risk for sleep-disordered breathing. (1,B)					
Case series + clinical experience	A sleep study may identify sleep-disordered breathing, which can contribute to the development and severity of pulmonary hypertension. Treatment of the sleep disorder can improve clinical outcomes and may also permit the amount of pulmonary vasodilator therapy to be reduced, decreasing the risks, burdens, and cost of pulmonary vasodilator therapy.	Sleep studies are not harmful, but they can be burdensome and costly. False-negative results may lead to false reassurance of patients and clinicians, with the latter resulting in missed treatment opportunities and poorer outcomes. False-positive results may lead to unnecessary treatment, which has burdens and costs.	This recommendation places a high value on identifying contributors that can be treated, improving clinical outcomes. It places a lower value on the costs and inconvenience of a sleep study.	I	B
ii) is indicated in the evaluation of patients with poor responsiveness to PAH-targeted therapies. (I,B)					
Case series + clinical experience	A sleep study may identify sleep-disordered breathing, which can contribute to an insufficient response to therapy. Treatment of the sleep disorder can improve clinical outcomes and prevent the unnecessary escalation of pulmonary vasodilator therapy, thereby decreasing the risks, burdens, and cost of pulmonary vasodilator therapy.	Sleep studies are not harmful, but they can be burdensome and costly. False-negative results may result in missed opportunities to treat a contributing cause, leading to the unnecessary escalation of pulmonary vasodilator therapy and its associated harms, burdens, and costs. False-positive results may lead to unnecessary treatment, which has burdens and costs.	This recommendation places a high value on identifying contributors that can be treated, improving clinical outcomes and preventing the downsides of inappropriate escalation of pulmonary vasodilator therapy. It places a lower value on the costs and inconvenience of a sleep study.	I	B
Genetics					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**

#13) Genetic testing with counseling can be useful for children with IPAH or in families with heritable PAH (HPAH) to allow for definition of etiology, identification of family members at risk, and to inform family planning. (IIa,C)					
Case series + clinical experience	Genetic testing may identify family members who have or are at risk for PAH. Such identification prompts a search for an underlying etiology, the treatment of which may mitigate progression or development of PAH. It also leads to closer monitoring of the individual for indications to initiate various therapies that improve clinical outcomes. Finally, it also informs family planning, which has benefits that cannot be quantified. Counseling improves how families are informed of the genetic test results, which likely prevents misunderstandings of the results, reduces guilt and blame associated with the diagnoses, and mitigates other related problems.	Genetic test results may be misunderstood and can lead to guilt, blame, and/or related problems.	This recommendation places high value on the duty of physicians to inform patients that PAH may affect other family members and a lower value on the potential psychological impact of positive test results. It attempts to mitigate the latter via counseling.	IIa	C
#14) Genetic testing of first-degree relatives of patients with monogenic forms of HPAH:					
i) is indicated for risk stratification (I,B).					
Case series + clinical experience	Genetic testing of the first-degree relatives of patients with monogenic forms of HPAH may identify family members who have or are at risk for PAH. The former may be stratified for their risk of certain clinical outcomes, and the latter may be stratified for their risk of developing disease. Risk stratification leads to personalization of the individual's monitoring, so that therapies that improve clinical outcomes can be initiated as soon as indicated.	Genetic results may be misunderstood and can lead to guilt, blame, and/or related problems. In addition, incorrect stratification can lead to a) excess worry and over-monitoring if the risk estimate is too high or b) false-reassurance if the risk estimate is too low.	This recommendation places a high value on monitoring and early initiation of therapy and a lower value on the potential psychological impact of incorrect risk stratification.	I	B
ii) is reasonable to screen asymptomatic carriers with serial echocardiograms or other non- invasive studies. (IIa,B).					
Case series + clinical experience	Early identification of probable PAH by echocardiography or an alternative non-invasive test prompts closer monitoring so that interventions that improve outcomes can be initiated as soon as indicated.	Serial echocardiograms and other non-invasive studies are neither sensitive nor specific. False-positive results may lead to unnecessary confirmatory testing, including potential complications, burdens, and costs. False-negative results may provide false reassurance to patients and clinicians, with the latter potentially leading to delayed diagnosis and treatment.	This recommendation places a high value on monitoring and early initiation of therapy and a lower value on the undesirable consequences of false results and the burdens and costs of testing.	IIa	B
#15) Members of families afflicted with HPAH who develop new cardio-respiratory symptoms should be evaluated immediately for PAH. (I,B).					
Case series +	Family members of patients with HPAH who	Assuming that the family member is aware	This recommendation places a high value	I	B

clinical experience	develop new cardio-respiratory symptoms are at increased risk of those new symptoms being due to PAH. Earlier confirmation of PAH and initiation of therapy decreases morbidity and mortality from untreated PAH.	that their evaluation is being expedited due to concerns about potential PAH, the period of diagnostic evaluation may be characterized by extreme worry until PAH is either excluded or confirmed to be the cause of the new symptoms. In addition, all diagnostic tests have burdens and costs, and many have potential harms.	on the early initiation of therapy and a lower value on the potential psychological impact, harms, burdens, and costs of the diagnostic evaluation		
#16) Families of patients with genetic syndromes associated with PH should be educated regarding symptoms of pulmonary hypertension and be counseled to seek evaluation of the affected child should symptoms arise. (I,B)					
Case series + clinical experience	Education of the families of patients with genetic syndromes associated with PH leads to earlier recognition, earlier diagnostic evaluation, earlier diagnostic confirmation, and earlier initiation of therapies known to decrease morbidity and mortality from untreated PH.	Education about the signs and symptoms of PH may cause family members excess worry whenever an associated symptom or sign manifests because they fear that the new symptom or sign is heralding the onset of PH. In addition, all diagnostic tests that are prompted by the new symptom or sign have burdens and costs, and many have potential harms.	This recommendation places a high value on the early initiation of therapy and a lower value on the potential psychological impact, harms, burdens, and costs of the diagnostic evaluation	I	B
Persistent PH of the Newborn (PPHN)					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#17) Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with PPHN or hypoxemic respiratory failure who have an oxygenation index that exceeds 25. (I,A).					
Multiple randomized trials	Inhaled nitric oxide therapy improves oxygenation and reduces the need for ECMO therapy; the latter prevents the potential harms and extensive burdens and costs that are associated with ECMO.	Adverse effects of inhaled nitric oxide are exceedingly rare and largely theoretical; however, they include methemoglobinemia (due to excess nitric oxide concentrations), direct pulmonary injury (due to excess levels of nitric dioxide), and ambient air contamination.	This recommendation places a high value on preventing the need for a more invasive, harmful, burdensome, and costly therapy and a lower value on the rare adverse consequences of inhaled nitric oxide.	I	A
#18) Lung recruitment strategies can improve the efficacy of iNO therapy and should be performed in patients with PPHN associated with parenchymal lung disease. (1,B)					
Multiple randomized trials	In patients with PPHN associated with parenchymal lung disease who are receiving inhaled nitric oxide, lung recruitment maneuvers improve oxygenation and reduce the need for ECMO therapy; the latter prevents the potential harms and extensive burdens and costs that are associated with ECMO.	Lung recruitment maneuvers can be burdensome to the nursing staff and respiratory therapists, and rare adverse effects such as dislodgement of venous catheters and the endotracheal tube can occur.	This recommendation places a high value on preventing the need for a more invasive, harmful, burdensome, and costly therapy and a lower value on staff burden.	I	B
#19) ECMO support is indicated for term and near-term neonates with severe PH and/or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function. (I,A).					
Case series +	In patients with hypoxemic respiratory failure	Adverse effects of ECMO therapy include	This recommendation places a high value	I	A

clinical experience	due to PH that is refractory to inhaled nitric oxide and optimization of cardiorespiratory function, ECMO may be life-saving.	vascular injury, bleeding, emboli, and CNS injury. In addition, ECMO is burdensome and costly.	on preventing mortality and a lower value on complications, burdens, and costs.		
#20) Evaluation for disorders of lung development, such as alveolar capillary dysplasia and genetic surfactant protein diseases, is reasonable for infants with severe PPHN who fail to improve after vasodilator, lung recruitment and/or ECMO therapy. (IIa,B)					
Case series + clinical experience	In patients with severe PPHN who fail to improve after inhaled nitric oxide, lung recruitment maneuvers, and ECMO therapy, further evaluation may reveal a disorder of lung development. Confirmation of such diseases provides prognostic information that may inform judgments about lung transplantation and end-of-life care and decision-making.	Assuming that family members are aware of the severity of the disorders being sought, the period of diagnostic evaluation may be characterized by extreme worry until such disorders are either excluded or confirmed. In addition, all diagnostic tests have burdens and costs, and many have potential harms. For example, lung biopsy may be associated with prolonged air leak, atelectasis, and worsened respiratory failure.	This recommendation places a high value on obtaining definitive information to guide decision-making a lower value on the psychological impact of the diagnostic evaluation and the potential harms, burdens, and costs of the diagnostic tests.	IIa	B
#21) Sildenafil is a reasonable adjunctive therapy for infants with PPHN who are refractory to inhaled NO, especially with an oxygenation index that exceeds 25. (IIa,B)					
One randomized trial, multiple case series, + clinical experience	In patients with PPHN that is refractory to inhaled nitric oxide, sildenafil improves oxygenation, reduces the need for ECMO, and reduces mortality. Studies suggest that sildenafil can be administered by either the oral or intravenous routes, depending on the clinical setting..	Sildenafil may induce hypotension, especially during the initial loading infusion when administered by intravenous route.	This recommendation places a high value on reducing mortality and avoiding a potentially harmful, burdensome, and costly alternative intervention, and a lower value on the risk of hypotension during the initiation of therapy.	IIa	B
#22) Inhaled prostacyclin analogues may be considered as adjunctive therapy for infants with PPHN that are refractory to iNO and have an oxygenation index that exceeds 25.(IIb,B)					
Controlled observational studies, case series, + clinical experience	In patients with PPHN that is refractory to inhaled nitric oxide, inhaled prostacyclin analogues improve oxygenation and reduce the need for ECMO.	Inhaled prostacyclin analogues can cause airway irritation and systemic hypotension; dosing is imprecise.	This recommendation places a high value on avoiding a potentially harmful, burdensome, and costly alternative intervention, and a lower value on the adverse effects of therapy.	IIb	B
#23) Intravenous milrinone is reasonable in infants with PPHN and signs of left ventricular dysfunction. (IIa, B)					
Controlled observational studies, case series, + clinical experience	In patients with LV dysfunction, milrinone increases cardiac contractility and cardiac output, while also reducing afterload and increasing pulmonary vasodilation. The net effect is both improved oxygenation and hemodynamic stability, which delay and may reduce mortality.	Milrinone can cause systemic hypotension and impaired myocardial perfusion, and therefore, requires close hemodynamic monitoring. Pulmonary vasodilators can cause pulmonary edema and worsen systemic hemodyncamics in the setting of LV dysfunction.	This recommendation places a high value on delaying and potentially reducing mortality and a lower value on potential side effects and the burden of additional monitoring.	IIa	B
#24) iNO can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios. (IIa,B)					
Controlled observational	Inhaled nitric oxide therapy improves oxygenation and pulmonary hemodynamics in	In preterm infants who have severe hypoxemia due to PPHN physiology and either	This recommendation places a high value on preventing the need for a more invasive,	IIa	B

studies, case series, + clinical experience	preterm infants with severe hypoxemia due to PPHN physiology, reducing the need for ECMO therapy. This prevents the potential harms, burdens, and costs that are associated with ECMO.	a large patent ductus arteriosus or cardiac dysfunction, inhaled nitric oxide therapy may lead to pulmonary. In addition, rare and largely theoretical side effects of inhaled nitric oxide include methemoglobinemia (due to excess nitric oxide concentrations), direct pulmonary injury (due to excess levels of nitric dioxide), and ambient air contamination.	harmful, burdensome, and costly therapy and a lower value on the potential harmful effects of inhaled nitric oxide.		

Congenital Diaphragmatic Hernia (CDH)

Quality of the evidence (i.e., rationale for the level of evidence)	Potential benefits	Potential harms and burdens	Values and preferences	Classification of recommendation	Level of evidence
#25) Minimizing peak inspiratory pressure and avoiding large tidal volumes is recommended to reduce ventilator-associated acute lung injury in infants with CDH. (I,B)					
Controlled observational studies, case series, + clinical experience	In infants with CDH who are mechanically ventilated, minimizing peak inspiratory pressure and avoiding large tidal volumes reduces ventilator-induced lung injury and its consequences, which include hypoxemia, tachypnea, tachycardia, infiltrates, respiratory distress and worsening PH. This is particularly important because such adverse effects may be additive to those caused by the underlying disease that required mechanical ventilation.	Minimizing peak inspiratory pressure and avoiding large tidal volumes may cause hypercapnia and/or tachypnea; however, these abnormalities are seldom associated with clinically important adverse outcomes.	This recommendation places a high value on avoiding the iatrogenic complication of ventilator-associated lung injury and its additive effects on the underlying respiratory disease and PH progression and a lower value on the hypercapnia and tachypnea that may result.	I	B
#26) High frequency oscillatory ventilation is a reasonable alternative mode of ventilation for subjects with CDH when poor lung compliance, low volumes and poor gas exchange complicate the clinical course. (IIa,B)					
Controlled observational studies, case series, + clinical experience	In infants with CDH who are mechanically ventilated and have poor lung compliance, low tidal volumes, and poor gas exchange, high frequency oscillatory ventilation may reduce ventilator-induced lung injury and its consequences, which include hypoxemia, tachypnea, tachycardia, infiltrates, respiratory distress and worse PH. This is particularly important because such adverse effects may be additive to those caused by the underlying disease that required mechanical ventilation.	High frequency oscillatory ventilation involves a very high respiratory rate, which shortens the expiratory time and may lead to auto-PEEP and dynamic hyperinflation, which increase the risk of barotrauma and hemodynamic instability. In addition, the success of the high frequency oscillatory ventilation is dependent upon institutional experience.	This recommendation places a high value on avoiding the iatrogenic complication of ventilator-associated lung injury and its additive effects on the underlying respiratory disease progression and a lower value on the risk of barotrauma and hemodynamic instability.	IIa	B
#27) iNO therapy can be used to improve oxygenation in infants with CDH and severe PH but should be used cautiously in subjects with suspected LV dysfunction. (IIa,B)					
Controlled observational studies, case series, + clinical experience	Inhaled nitric oxide therapy improves oxygenation and pulmonary hemodynamics in infants with CDH and severe PH, reducing the need for ECMO therapy. This prevents the potential harms, burdens, and costs that are	In infants with CDH, severe PH, and suspected LV dysfunction, inhaled nitric oxide therapy may lead to pulmonary edema. In addition, rare and largely theoretical side effects of inhaled nitric oxide include	This recommendation places a high value on preventing the need for an invasive therapy that is potentially harmful, burdensome, and costly. It places a lower value on the potential side effects of	IIa	B

	associated with ECMO. If ECMO is required, inhaled nitric oxide therapy may allow for a more safe transition to ECMO in CDH.	methemoglobinemia (due to excess nitric oxide concentrations), direct pulmonary injury (due to excess levels of nitric dioxide), and ambient air contamination.	inhaled nitric oxide therapy.		
	A brief trial of inhaled nitric oxide therapy to assess for benefits in severe CDH is suggested. Lack of improvement may be related to LV dysfunction or poor lung recruitment.				
#28) ECMO is recommended for CDH patients with severe PH who do not respond to medical therapy. (I,B)					
Controlled observational studies, case series, + clinical experience	In patients with CDH and severe PH that is refractory to medical therapy, ECMO may be life-saving.	Potential complications of ECMO therapy include vascular injury, bleeding, emboli and CNS injury. In addition, ECMO is burdensome and costly.	This recommendation places a high value on preventing mortality and a lower value on complications, burdens, and costs.	I	B
#29) Prostaglandin E1 may be considered to maintain patency of the ductus arteriosus and improve cardiac output for infants with CDH and supra-systemic levels of PH or right ventricular failure to improve cardiac output. (IIb,C)					
Controlled observational studies, case series, + clinical experience	Prostaglandin E1 maintains patency of the DA, which improves cardiac output and tissue perfusion. This mitigates metabolic acidosis, hemodynamic insufficiency, and organ failure.	Sustained patency of the DA due to Prostaglandin E1 therapy may increase extra-pulmonary shunting and worsen hypoxemia.	This recommendation places a high value on the maintenance of tissue perfusion and a lower value on impaired oxygenation.	IIb	C
#30) Evaluation for chronic PAH-specific therapy for PH in infants with CDH should follow recommendations for all children with PH, which includes cardiac catheterization. (I,B)					
Controlled observational studies, case series, + clinical experience	Evaluation for chronic PAH-specific therapy includes a history, physical examination, echocardiogram, other non-invasive cardiac tests and, potentially, cardiac catheterization with vasoreactivity testing. The evaluation may identify one of several cardiopulmonary co-morbidities that are associated with CDH and may contribute to PH. Identification of such co-morbidities may lead to therapy that mitigates the PH. Even if contributing co-morbidities are not identified, confirmation of the PH, assessment of its severity, and determination of whether the patient is vasoreactive will affect the decision of whether to institute PAH-specific therapy and, if so, using which agent. PAH-specific therapy improves clinical outcomes.	In addition to the burdens and costs of evaluation, testing may yield false-positive and false-negative results. False-positive results may lead to unnecessary confirmatory testing, while false-negative results may lead to false reassurance of the patient and the clinician, with the latter leading to delayed diagnosis and treatment. Moreover, some evaluations may be harmful; for example, cardiac catheterization has risks of bleeding, blood vessel injury, pneumothorax, and cardiac arrest.	This recommendation places a high value on identifying contributing factors that can be treated, as well as confirming PH prior to the initiation of PAH-specific therapies that improve outcomes; it places a lower value on the burdens, costs, and adverse consequences of diagnostic testing.	I	B
#31) Longitudinal care in an interdisciplinary pediatric PH program is recommended for infants with CDH who have PH or are at risk of developing late PH. (I,B)					
Controlled observational	Children with CDH have multiple pulmonary, cardiac, gastrointestinal and neurologic	Interdisciplinary pediatric PH programs are not available in all geographic locales. Thus,	This recommendation places a high value on communication that minimizes the	I	B

studies, case series, + clinical experience	sequelae that persist throughout infancy and late childhood. Multiple chronic conditions are best managed in a setting where all providers may easily communicate. This reduces the likelihood that the treatment of one condition may adversely impact another condition.	follow-up in such programs may be burdensome for some patients and families.	impact of potentially conflicting goals when treating patients with multiple chronic conditions; it places a lower value on convenience.		
Bronchopulmonary Dysplasia (BPD)					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#32) Screening for PH by echocardiogram is recommended in infants with established BPD (I,B).					
Controlled observational studies, case series, + clinical experience	Screening patients with BPD for PH by echocardiography: May identify contributing factors, such as anatomic cardiac abnormalities or cardiomyopathy. The former may be repairable surgically and the latter may be treatable medically, improving clinical outcomes. Echocardiography may also guide the clinician to the appropriate next test (e.g., right heart catheterization, chest CT scan), reducing the harms, burdens, and costs of inappropriate testing. In cases in which the next appropriate test is right heart catheterization, PH may be confirmed and its severity determined. Finding severe disease prompts earlier treatment and affects which agent is selected, both of which improve clinical outcomes. Finding mild or no disease prevents inappropriate therapy and its related harms, burdens, and costs.	False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	The recommendation places a high value on early diagnosis and treatment; it places a lower value on the consequences of misleading test results and the burdens and costs of diagnostic testing.	I	B
#33) Evaluation and treatment of lung disease, including assessments for hypoxemia, aspiration, structural airways disease and the need for changes in respiratory support, is recommended in infants with BPD and PH before initiation of PAH-targeted therapy. (I,B)					
Controlled observational studies, case	Respiratory disease contributes significantly to PH in infants with BPD. Treatment that improves lung function and gas exchange can	Both the diagnostic evaluation and treatment of respiratory diseases may be burdensome and costly. Some diagnostic tests have	This recommendation places a high value on identifying and treating underlying lung disease in order to both improve clinical	I	B

series, + clinical experience	lower PH in BPD infants, which may either eliminate the need for PAH-specific therapy or reduce the amount of PAH-specific therapy required, both of which reduces the potential side effects and costs of PAH-specific therapy.	complications and most have undesirable consequences due to false-positive and false-negative results. Most therapies for lung disease have at least a small risk of side effects.	outcomes and reduce the need potentially harmful, costs, and burdensome PAH-specific therapy; it places a lower value on the harms, burdens, and costs of the diagnostic evaluation and the therapies of various lung diseases.		
#34) Evaluation for chronic therapy for PH in infants with BPD should follow recommendations for all children with PH and include cardiac catheterization to diagnose disease severity and potential contributing factors such as LV diastolic dysfunction, anatomic shunts, pulmonary vein stenosis and systemic collaterals. (I,B)					
Case series + clinical experience	Evaluation for chronic PAH-specific therapy includes a history, physical examination, echocardiogram, other non-invasive cardiac tests and, potentially, cardiac catheterization with vasoreactivity testing. The evaluation may identify one of several cardiopulmonary co-morbidities that are associated with CDH and may contribute to PH. Identification of such co-morbidities may lead to therapy that mitigates the PH. Even if contributing co-morbidities are not identified, confirmation of the PH, assessment of its severity, and determination of whether the patient is vasoreactive will affect the decision of whether to institute PAH-specific therapy and, if so, using which agent. PAH-specific therapy improves clinical outcomes.	In addition to the burdens and costs of evaluation, testing may yield false-positive and false-negative results. False-positive results may lead to unnecessary confirmatory testing, while false-negative results may lead to false reassurance of the patient and the clinician, with the latter leading to delayed diagnosis and treatment. Moreover, some evaluations may be harmful; for example, cardiac catheterization has risks of bleeding, blood vessel injury, pneumothorax, and cardiac arrest.	This recommendation places a high value on identifying contributing factors that can be treated, as well as confirming PH prior to the initiation of PAH-specific therapies that improve outcomes; it places a lower value on the burdens, costs, and adverse consequences of diagnostic testing.	I	B
#35) Supplemental oxygen therapy is reasonable to avoid episodic or sustained hypoxemia and with the goal of maintaining O2 saturations between 92% - 95% in patients with established BPD and PH. (IIa,C)					
Controlled observational studies, case series, + clinical experience	Prevention of intermittent or chronic hypoxemia via supplemental oxygen may prevent or mitigate progressive PH in infants with BPD.	Supplemental oxygen has no reported adverse effects in BPD and, in the hospital setting, is minimally burdensome and costly.	This recommendation places high value on preventing progressive disease and a lower value on inconvenience and cost.	IIa	C
#36) PAH-targeted therapy can be useful for infants with BPD and PH on optimal treatment of underlying respiratory and cardiac disease.(IIa,C)					
Controlled observational studies, case series, + clinical experience	In patients with BPD who have PH that is severe enough to warrant treatment despite optimal treatment of potential contributing factors, PAH-specific therapy improves clinical outcomes. Sildenafil is the most common first-line therapy in this setting.	Sildenafil may decrease oxygenation in some infants with BPD and has other adverse effects, including frequent erections. Vision and hearing changes are theoretical risks with prolonged therapy, although they have not been reported.	This recommendation places a high value on improving clinical outcomes, particularly when added to the beneficial effects of treating underlying respiratory and cardiac diseases, and a lower value on avoiding medication-related side effecs.	IIa	C
#37) Treatment with iNO can be effective for infants with established BPD and symptomatic PH. (IIa,C)					
Controlled observational	Inhaled nitric oxide therapy improves oxygenation and pulmonary hemodynamics in	In infants with BPD and symptomatic PH, inhaled nitric oxide therapy may lead to	This recommendation places a high value on improving gas exchange and pulmonary	IIa	C

studies, case series, + clinical experience	infants with BPD and symptomatic PH,. This may allow weaning of ventilator and respiratory support, reduce PH crises, improve cardiac outoput and may prevent the potential harms, burdens, and costs that are associated with ECMO therapy.	hypoxemia due to ventilation-perfusion mismatch and cessation of inhaled nitric oxide can lead to rebound PH. In addition, rare and largely theoretical side effects of inhaled nitric oxide include methemoglobinemia (due to excess nitric oxide concentrations), direct pulmonary injury (due to excess levels of nitric dioxide), and ambient air contamination.	hemodynamics while preventing the need for more invasive therapy that is potentially harmful, burdensome, and costly. It places a lower value on the potential side effects of inhaled nitric oxide therapy.		
#38) Serial echocardiograms are recommended to monitor the response to PAH-targeted therapy in infants with BPD and PH. (I,B).					
Controlled observational studies, case series, + clinical experience	Among infants with BPD and PH who are being treated with PAH-specific therapy, a worsening or non-diagnostic echo may indicate under-treatment. Repeat cardiac catheterization is generally performed in the context of such echocardiographic findings; if insufficient treatment is confirmed, additional diagnostic testing may be performed to look for new contributing factors and, if none are identified, PAH-specific therapy may be escalated. Treatment of new contributing factors or escalated PAH-specific therapy improves clinical outcomes.	Echocardiography itself is safe. However, it is neither sensitive nor specific and should be interpreted in the context of clinical findings and other information (e.g., BNP or NT-pro-BNP results). False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	This recommendation places a high value on detecting and correcting under-treatment in order to improve clinical outcomes; it places a lower value on of the undesirable consequences of misleading results from echocardiography.	I	B
Pharmacotherapy					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#39) Supportive care with digitalis and diuretic therapy is reasonable with signs of right heart failure but should be initiated cautiously (IIb,C)					
Case series + clinical experience	Digitalis can improve myocardial contractility in children with signs of right failure; as a result, patients have less peripheral edema, less pleural effusion, less ascites, and less hypotension. Diuretics increase the renal excretion of excess fluid; as a result, patients have less peripheral edema, less pleural effusion, and less ascites.	Digitalis can cause heart blocks and dysrhythmias, as well as anorexia, nausea, diarrhea, lethargy, vertigo, delirium, blurred vision, diplopia, and tinnitus. Diuretics can cause hypokalemia and hypochloremia. They can also cause hypovolemia, which may lead to hyponatremia, alkalosis, and hypotension.	This recommendation places a high value on improving symptoms and signs of right heart, and a lower value on avoiding medication side effects.	IIb	C
#40) Chronic anticoagulation with warfarin:					

i) may be considered in patients with IPAH/HPAH, patients in low cardiac output, chronic indwelling catheter and those with hypercoagulable states. (IIb,C)					
Case series + clinical experience	In patients with IPAH/HPAH, low cardiac output, a chronic indwelling catheter, or a hypercoagulable state, anticoagulation is associated with lower mortality due to thromboembolic events.	Patients who receive anticoagulant therapy are at increased risk for both minor and major bleeding complications, such as gastrointestinal hemorrhage and hemorrhagic stroke.	This recommendation places a high value on decreasing mortality and a lower value on hemorrhagic complications.	IIb	C
ii) Targeting the therapeutic range for INR between 1.5 and 2.0 is recommended for young children with PAH. (I,C)					
Case series + clinical experience	Compared with an INR <1.5, an INR 1.5-2.0 is associated with fewer thromboembolic events. Compared with an INR >2.0, an INR 1.5-2.0 is associated with fewer bleeding complications.	Compared with an INR <1.5, an INR 1.5-2.0 is associated with more bleeding complications. Compared with an INR >2.0, an INR 1.5-2.0 is associated with more thromboembolic events.	This recommendation seeks to find the range at which the reduction of thromboembolic events most exceeds the increased risk of hemorrhagic complications.	I	C
iii) Anticoagulation should not be used in young children with PAH due to concerns for harm from hemorrhagic complications.(III,C)					
Case series + clinical experience	Anticoagulant therapy is associated with fewer thromboembolic events.	Anticoagulant therapy is associated more bleeding complications.	This recommendation places a high value on avoiding hemorrhagic complications and a lower value on preventing thromboembolic events.	III	C
#41) Oxygen therapy is reasonable for hypoxemic PAH patients who have oxygen saturations < 92%, especially with associated respiratory disease. (IIa,B)					
Case series + clinical experience	Supplemental oxygen is associated with decreased dyspnea and increased exertional capacity. It may also prevent sequelae of chronic hypoxemia, such as poor growth, developmental delays, systemic or pulmonary hypertension, polycythemia, and others.	Supplemental oxygen is not harmful to most patients and its burden and cost are minimal in the hospital and ambulatory settings.	This recommendation places a high value on the potential benefits of supplemental oxygen and a lower value on burdens and costs.	IIa	B
#42) A trial of calcium channel blockers (CCB):					
i) should be given only to those patients who are reactive as assessed by AVT and over one year of age. (I,C)					
Case series + clinical experience	Calcium channel blockers are associated with sustained hemodynamic improvement, functional improvement, and survival among patients who are vasoreactive. They are also less expensive and less burdensome that pulmonary vasodilator therapy.	Calcium channel blockers may be associated with hypotension, hypoxemia due to loss of auto-regulation, and deterioration of right ventricular function. Young infants < 1 year of age may be more susceptible to effects on myocardial function.	The recommendation places high value on achieving benefits using a less expensive and less burdensome therapy, and a lower value on the potential side effects of the therapy.	I	C
ii) are contraindicated in children who have not undergone or are non-responsive to AVT, and in patients with right heart dysfunction due to the potential for negative inotropic effects of CCB therapy. (III,C)					
Case series + clinical experience	Not using calcium channel blockers in patients who are not vasoreactive or who have right ventricular dysfunction avoids potential side effects (i.e., hypotension, hypoxemia, decreased right ventricular function) in	Withholding calcium channel blockers from children who are not vasoreactive or who have right ventricular dysfunction may miss a few children who would have benefited from the therapy.	This recommendation places a high value on avoiding the harmful consequences of therapy in patients who are unlikely to benefit or particularly susceptible to harm, and a lower value on capturing all patients	III	C

	populations that are unlikely to have improved clinical outcomes from the therapy (those who are not vasoreactive) or that are particularly susceptible to the side effects (those with right ventricular dysfunction).		who might benefit from the therapy.		
#43) Oral PAH-targeted therapy in children with lower risk PAH is recommended and should include either a phosphodiesterase type 5 (PDE5) inhibitor or an endothelin receptor antagonist (I,B).					
Case series + clinical experience	In children with lower risk PAH, PDE5 inhibitors and ERAs improve exercise capacity.	PDE5 inhibitors are associated with flushing, headache, dyspepsia, epistaxis, and vision changes. ERAs are associated with hepatotoxicity, headache, inhibited spermatogenesis, and anemia. Therapy with PDE5 inhibitors and ERAs is costly.	This recommendation places a high value on improving clinical outcomes and a lower value on side effects and costs.	I	B
#44) A "goal-targeted therapy" approach in which PAH-specific drugs are added progressively to achieve specified therapeutic targets can be useful. (IIa,C)					
Case series + clinical experience	PAH-specific drugs improve clinical outcomes, such as dyspnea, exercise capacity, and possibly survival. Their effects appear additive.	All PAH-specific drugs have side effects. While there are agent-specific side effects, among the most common are flushing, headache, hepatotoxicity, and dyspepsia. In addition, PAH-specific drugs are expensive. Intravenous medications confer an additional burden and risk of central venous catheter complications such as infection and thrombosis.	This recommendation places a high value on improving clinical outcomes and a lower value on side effects and costs.	IIa	C
#45) Intravenous and subcutaneous prostacyclin or its analogues should be initiated without delay for patients with higher risk PAH.(I,B)					
Case series + clinical experience	In children with higher risk PAH, intravenous and subcutaneous prostacyclin analogues improve survival and quality of life. Iv prostacyclin therapy has been shown to improve survival in advanced (functional class 4) disease.	Prostacyclins are associated with nausea, diarrhea, jaw pain, bone pain, and headaches. In addition, they are expensive and, if administered intravenously, they are burdensome and associated with catheter-related complications such as infection and thrombosis.	This recommendation places a high value on improving clinical outcomes and a lower value on side effects and costs.	I	B
#46) Transition from parenteral to oral or inhaled therapy:					
i) may be considered in asymptomatic children with PAH who have demonstrated sustained, near-normal pulmonary hemodynamics (IIb,C)					
Case series + clinical experience	Oral and inhaled therapy is less burdensome than intravenous or subcutaneous therapy.	Some children will not tolerate the transition to oral or inhaled therapy and, therefore, will be disappointed when efforts to transition fail.	This recommendation places high value on trying to make therapy as burden free as possible and a lower value on the disappointment that may ensue if it cannot be accomplished.	IIb	C
ii) requires close monitoring in an experienced pediatric PH center. (I,B)					
Case series +	Close monitoring in an experienced center	Close monitoring in an experienced center has	This recommendation places high value on	I	B

clinical experience	facilitates the rapid resumption of parenteral therapy if the transition fails, thereby lowering the risk of harm due to the transition.	minimal risk, but can be burdensome if the center is located far from the patient's home.	patient safety and a lower value on burden.		
Idiopathic PAH					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#47) Lung biopsy may be considered for children with PAH suspected of having pulmonary veno- occlusive disease, pulmonary capillary hemangiomatosis or vasculitis. (IIb,C)					
Case series + clinical experience	Lung biopsy is the gold standard for confirming pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, or vasculitis. Definitive diagnosis allows early referral for lung transplantation, which is life-saving.	Lung biopsy is a surgical procedure. Risks include post-operatives complication such as a prolonged air leak, bleeding, hypoxemia, atelectasis, infection, respiratory failure, and pain.	This recommendation places a high value on life-saving treatment and a lower value on complications.	IIb	C
#48) Referral to lung transplantation centers for evaluation is recommended for patients who are WHO functional class III or IV on optimized medical therapy or who have rapidly progressive disease. (I,A)					
Case series + clinical experience	For patients who are WHO function class III or IV despite an optimized regimen or who are rapidly deteriorating, lung transplantation may be life-saving.	Referral is a harmless intervention. However, the evaluation is extensive and can be burdensome.	This recommendation places a high value on life-saving treatment and a lower value on burden.	I	A
#49) Referral to a lung transplantation center for evaluation is recommended for patients who have confirmed pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease. (I,B)					
Case series + clinical experience	For patients who have confirmed pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease, lung transplantation may be life-saving.	Referral is a harmless intervention. However, the evaluation is extensive and can be burdensome.	This recommendation places a high value on life-saving treatment and a lower value on burden.	I	B
Pediatric Heart Disease					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#50) In children with significant structural heart disease (ie, ASD, VSD, and PDA) that have not undergone early repair (as generally defined by *age at 1 - 2 years, depending on the lesion and overall clinical status*):					
i) cardiac catheterization should be considered to measure PVRI and determine operability. (II,B)					
Controlled	Cardiac catheterization provides direct	Complications of cardiac catheterization	This recommendation places a high value	II	B

observational studies, case series, + clinical experience	measurements of the PVRI and transpulmonary pressure gradient, which are used to identify patients for whom surgical correction of the structural heart disease will improve survival. Measures of cardiac output according to the Fick equation for more accurate calculation of PVRI is mandatory.	include respiratory depression due to the sedation, pneumothorax, arrhythmias, cardiac or vascular perforation, and bleeding.	on the identification of patients who will benefit from surgical correction and a lower value on the complications of cardiac catheterization.		
ii) repair should be considered if PVRI < 6 Wood Units (WU)*m2 or PVR/SVR < 0.3 at baseline. (I,B)					
Controlled observational studies, case series, + clinical experience	Surgical correction in those whose PVRI is < 6 Wood Units (WU)*m2 or PVR/SVR is < 0.3 improves survival.	Compared with a higher PVRI and PVR/SVR threshold to identify operable patients, the recommended thresholds are more likely to exclude patients who may have benefited from surgery. Compared with a lower PVRI and PVR/SVR threshold to identify operable patients, the recommended thresholds are more likely to allow surgery on patients for whom the risks exceed the benefits. Surgical repair is associated with post-operative complications such as bleeding, atelectasis, hypoxemia, infection, prolonged respiratory failure, and pain.	This recommendation places a high value on identifying a range in which the patients deemed operable are more likely to benefit from surgery than be harmed; it places a lower value on operating on every patient who stands to benefit from surgical correction.	I	B
#51) In children with evidence of right to left shunting and cardiac catheterization revealing a PVRI > 6 WU*m2 or PVR/SVR > 0.3, repair can be beneficial if AVT reveals reversibility of PAH (absolute PVRI < 6 WU*m2 and PVR/SVR < 0.3). (IIa,C)					
Controlled observational studies, case series, + clinical experience	A vasoreactivity test that demonstrates reversibility of PAH identifies patients for whom post-operative survival is increased and the risk of PH is decreased.	Vasoreactivity testing may cause acute pulmonary edema in the context of cardiomyopathy or pulmonary venoocclusive disease.	This recommendation places a high value on identifying additional patients who may benefit from surgical correction and a lower value on the risks of vasoreactivity testing.	IIa	C
#52) If cardiac catheterization reveals a PVRI > 6 WU*m2 or PVR/SVR > 0.3 and minimal responsiveness to AVT:					
i) repair is not indicated.(III,A)					
Controlled observational studies, case series, + clinical experience	Patients in whom the PVRI is > 6 WU*m2, the PVR/SVR is > 0.3, and the vasoreactivity test does not reverse the PAH are less likely to benefit from surgical correction. The decision to not operate on such patients decreases the likelihood unnecessary post-operative complications including bleeding, atelectasis, hypoxemia, infection, prolonged respiratory failure, and pain.	By not offering surgery to patients in whom the PVRI is > 6 WU*m2, the PVR/SVR is > 0.3, and the vasoreactivity test does not reverse the PAH, a few patients who would have benefitted from the operations will be missed.	This recommendations places a high value on avoiding unnecessary post-operative complications, and a lower value on ensuring that no patient who may benefit will be missed.	III	A
ii) it is reasonable to implement PAH-targeted therapy, followed by repeat catheterization with AVT after 4 - 6 months and to consider repair if the PVRI < 6WU. (IIb,C)					
Controlled observational	Vasoreactivity can change over time. Patients who become vasoreactive on repeat testing	PAH-specific therapy has side effects and is costly. If administered intravenously or	This recommendation places a high value on maximizing the likelihood that everyone	IIb	C

studies, case series, + clinical experience	and then undergo surgical correction have increased survival and a low risk of post-operative complications including PH. In the interim, while awaiting repeat cardiac catheterization with vasoreactivity testing, PAH-specific therapy improves clinical outcomes.	subcutaneously, it is also burdensome. For each catheterization, risks including bleeding, pneumothorax, cardiac or vascular perforation, and arrhythmia. For each vasoreactivity test, risks include acute pulmonary edema if performed in the context of cardiomyopathy or pulmonary venoocclusive disease. False-negative results cause patients who would have benefited from surgery to be excluded. False-positive results allow patients who are unlikely to benefit to undergo surgery with its associated risks. For those who undergo surgical correction, complications include bleeding, atelectasis, hypoxemia, infection, prolonged respiratory failure, and pain.	who may benefit from surgery has the opportunity; it places a lower value on the risks of cardiac catheterization and vasoreactivity testing.		
PH Crises/acute RV Failure					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#53) General postoperative strategies for avoiding PH crises include avoidance of hypoxia, acidosis and agitation should be used in children at high risk for PH crisis. (I,B)					
Controlled observational studies, case series, + clinical experience	Prevention of PH crisis includes vigorous monitoring, greater caution with the use of anesthetics especially during endotracheal (ETT) intubation, avoidance of hypoxia, avoidance of acidosis, and avoidance of agitation including pretreatment prior to ETT suctioning and airway management. Prevention of PH crisis avoids it harmful sequelae, including hypoxemia, RV failure, hemodynamic collapse, and death.	The harms, burdens, and costs of the strategies described to prevent PH crises are minimal.	This recommendation places a high value on preventing a potentially lethal post-operative complication and a lower value on the burden of implementing the preventative strategies.	I	B
#54) Induction of alkalosis can be useful for the treatment of PH crisis. (IIa,C)					
Controlled observational studies, case series, + clinical experience	Acidosis contributes to the development of PH crisis. Induction of alkalosis may mitigate this effect, leading to improvement or reversal of hypoxemia, RV failure, and hemodynamic collapse, as well as the prevention of death.	Potential adverse effects of alkalosis include hypokalemia, hypocalcemia, hypophosphatemia, and lung injury due to the use of hyperventilation to induce the alkalosis.	This recommendation places a high value on the treatment of a potentially lethal post-operative complication and a lower value on the side effects of the treatment.	IIa	C
#55) Administration of opiates, sedation and muscle relaxation is recommended in reducing postoperative stress response and the risk for or severity of PH crises (I,B)					
Controlled	Post-operative stress contributes to the	Potential adverse effects of opiates, sedation,	This recommendation places a high value	I	B

observational studies, case series, + clinical experience	development of PH crisis. Opiates, sedation, and muscle relaxation may mitigate this effect, leading to improvement or reversal of hypoxemia, RV failure, and hemodynamic collapse, as well as the prevention of death.	and muscle relaxation via pharmacological paralysis are minimal but include respiratory depression and prolonged weakness.	on the treatment of a potentially lethal post-operative complication and a lower value on the side effects of the treatment.		
#56) In addition to conventional post-operative care, iNO and/or inhaled prostacyclin should be used as the initial therapy for PH crises and right heart failure. (I,B)					
Randomized trials, controlled observational studies, case series, + clinical experience	Inhaled nitric oxide and/or inhaled prostacyclin may decrease the severity of a PH crisis with or without accompanying right heart failure. This may lead to improvement or reversal of hypoxemia, RV failure, and hemodynamic collapse, as well as the prevention of death.	Adverse effects of inhaled prostacyclin include mild worsening of hypoxemia in some patients with PH. Adverse effects of inhaled nitric oxide include worsening of and cessation of inhaled nitric oxide can lead to rebound PH. In addition, rare and largely theoretical side effects of inhaled nitric oxide include methemoglobinemia (due to excess nitric oxide concentrations), direct pulmonary injury (due to excess levels of nitric dioxide), and ambient air contamination.	This recommendation places a high value on the treatment of a potentially lethal post-operative complication and a lower value on the side effects of the treatment.	I	B
#57) Sildenafil should be prescribed to prevent rebound PH in patients who have evidence of a sustained increase in pulmonary artery pressure (PAP) upon withdrawal of iNO and require reinstitution of iNO despite gradual weaning of iNO dose. (I,B)					
Randomized trials, controlled observational studies, case series, + clinical experience	An adverse effect of inhaled nitric oxide therapy is rebound PH, which can be life-threatening. Sildenafil may prevent sudden rises of PH during inhaled nitric oxide (iNO) withdrawal, preventing a lethal complication of therapy. Sildenafil use should be limited to patients who show evidence of hemodynamically significant rebound after iNO withdrawal.	Adverse effects of sildenafil include systemic hypotension and worsened hypoxemia, particularly in the setting of lung disease.	This recommendation places a high value on the prevention of a potentially lethal complication and a lower value on the side effects of the treatment.	I	B
#58) In patients with PH crisis, inotropic/pressor therapy should be used to avoid RV ischemia due to systemic hypotension. (I,B) Mechanical cardiopulmonary support should be provided in refractory cases. (I,B)					
Controlled observational studies, case series, + clinical experience	Inotropic or vasopressor support improves both PH-related systemic hypotension and coronary artery perfusion during a PH crisis. This enhances right and left ventricular function and presumably prevents death. Mechanical cardiopulmonary support similarly improves right and left ventricular function among patients who are refractory to inotropic or vasopressor support.	Vasopressor support may elevate systemic and pulmonary vascular resistance, reducing blood flow to peripheral organs. This may result in metabolic acidosis and/or organ failure.	This recommendation places a high value on the prevention of a potentially lethal post-operative complication and a lower value on the side effects of the treatment.	I	B
#59) Atrial septostomy is recommended for patients with right ventricular failure, recurrent syncope or PH crises that persist despite optimized medical management, but must be performed in an experienced PH center. (I,B)					
Controlled observational	Atrial septostomy (AS) sustains cardiac output and oxygen delivery to the peripheral tissues	Atrial septostomy can worsen oxygenation due to extra-pulmonary shunting.	This recommendation places a high value on perfusion and the maintenance of vital	I	B

studies, case series, + clinical experience	and organs; this is associated with improved survival among patients with congenital heart disease or shunt lesions.		organ function, and a lower value on the maintenance of oxygenation.		
Lung Diseases					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#60) Children with chronic diffuse lung disease should be evaluated for concomitant cardiovascular disease or PH by echocardiogram, especially with advanced disease. (I,B)					
Controlled observational studies, case series, + clinical experience	Patients with chronic diffuse lung disease have diminished exercise capacity, respiratory symptoms and signs, and increased mortality. These characteristics are also found in cardiac disease and PH. Echocardiography may determine whether or not cardiac disease and/or PH may also be contributing to the patient's syndrome. Echocardiography identifies anatomic cardiac abnormalities; many abnormalities may be repaired surgically, improving clinical outcomes. It also identifies cardiomyopathy, for which medical therapy improves clinical outcomes. Echocardiography also guides the clinician to the appropriate next test (e.g., right heart catheterization), potentially reducing the harms, burdens, and costs of inappropriate testing. Finally, echocardiography can estimate the severity of disease for concomitant cardiac disease or PH is found. Severe disease prompts earlier treatment and affects the approach selected, both of which improve clinical outcomes. Mild or no disease may warrant follow-up only, preventing inappropriate therapy and its related harms, burdens, and costs.	False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	This recommendation places a high value on identifying all contributors to the patient's clinical findings and treating those that improve clinical outcomes; it places a lower value on the consequences of misleading results and the burdens and costs of echocardiography.	I	B
#61) Echocardiography is recommended to assess PH and RV function in patients with severe obstructive sleep apnea (OSA). (I,B)					
Controlled observational studies, case	Patients with OSA are at increased risk for PH, particularly when combined with chronic hypoxic lung disease. Echocardiography may	False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment	This recommendation places a high value on the early detection and treatment of PH prior to the accrual of morbidity and	I	B

series, + clinical experience	determine whether or not PH coexists with a patients OSA and lung disease. Echocardiography guides the clinician to the appropriate next test (i.e., an echo suggestive of PH may prompt right heart catheterization to confirm PH, while an echo that is not suggestive of PH may prompt clinical or echocardiographic follow-up to monitor for the development of PH), potentially reducing the harms, burdens, and costs of unnecessary testing. Finally, echocardiography can estimate the severity of disease if PH is found. Severe disease prompts earlier treatment and affects the approach selected, both of which improve clinical outcomes. Mild or no disease may warrant follow-up only, preventing inappropriate therapy and its related harms, burdens, and costs.	opportunities. False-positive results lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	mortality; it places a lower value on the consequences of incorrect results and the burdens and costs of echocardiography.		
#62) For exercise-limited patients with advanced lung disease and evidence of PAH,					
i) a trial of PAH-targeted therapy is reasonable. (IIa,C)					
Controlled observational studies, case series, + clinical experience	In patients with advanced lung disease and PAH, PAH-specific therapy improves exercise tolerance, respiratory symptoms and signs, and quality of life.	PAH-specific therapy can worsen oxygenation in some patients with chronic lung disease; this is generally a small change in oxygenation and is readily treated with small increases in supplemental oxygen therapy.	This recommendation places high value on improving clinical outcomes and a lower value on the potential side effects of therapy.	IIa	C
ii) right heart catheterization may be considered. (IIb,B)					
Controlled observational studies, case series, + clinical experience	In patients with advanced lung disease and PAH, right heart catheterization can: a) determine the severity of the underlying PH, b) look for evidence of additional contributors to the PH, such as left heart disease, structure vascular disorders and PVOD. This may lead to additional therapies that are less expensive, less harmful, and less burdensome than PAH-specific therapies).	For each catheterization, risks including bleeding, pneumothorax, cardiac or vascular perforation, arrhythmia, and cardiac arrest. For each vasoreactivity test, risks include acute pulmonary edema if performed in the context of cardiomyopathy or pulmonary venoocclusive disease.	This recommendation places high value on reducing the need for PAH-specific therapy and, therefore, on reducing the harms, burdens, and costs of such therapy; it places a lower value on the potential harms of cardiac catheterization and vasoreactivity testing.	IIb	B
Hypobaric Hypoxia					
Quality of the evidence (i.e., rationale for the level of	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**

evidence)					
#63) Patients with symptomatic high altitude – related PH may be encouraged to move to low altitude (IIb,C)					
Controlled observational studies, case series, + clinical experience	Moving to a low altitude resolves or improves high altitude-related PH.	Moving to a low altitude is not harmful. However, it may be burdensome and/or costly in some circumstances.	This recommendation places a high value on improving clinical outcomes and a lower value on convenience and cost.	IIb	C
#64) Calcium channel blocker therapy (with amlodipine or nifedipine) may be reasonable for high altitude pulmonary edema (HAPE) prophylaxis in children with a previous history of HAPE (IIb,C).					
Controlled observational studies, case series, + clinical experience	In patients with a history of HAPE, calcium channel blockers can prevent the development of PH and pulmonary edema.	Side effects of calcium channel blockers include decreased cardiac contractility and systemic hypotension.	This recommendation places a high value on preventing poor clinical outcomes due to PH and pulmonary edema; it places a lower value on potential side effects of prophylactic therapy.	IIb	C
#65) Therapy for symptomatic HAPE should include supplemental oxygen therapy and consideration of immediate descent (I,B).					
Controlled observational studies, case series, + clinical experience	Supplemental oxygen reduces pulmonary edema and PH, improves hypoxemia, and improves or alleviates respiratory symptoms and. Moving to a low altitude resolves or improves high altitude-related PH.	Supplemental oxygen is not harmful to most patients and its burden and cost are minimal in the hospital setting. Moving to a low altitude is not harmful. However, it may be burdensome and/or costly in some circumstances.	This recommendation places a high value on improving clinical outcomes and a lower value on convenience and cost.	I	B
#66) Children with HAPE should undergo evaluation to rule out abnormalities of pulmonary arteries or pulmonary veins, lung disease or abnormal control of breathing. (I,B)					
Controlled observational studies, case series, + clinical experience	In patients with HAPE, diagnostic evaluation may include chest CT scanning to look for both abnormalities of the pulmonary vessels and lung disease, and a sleep study to look for abnormal control of breathing. Children with such disorders are at higher risk for developing HAPE. Finding such abnormalities may lead to therapies that improve clinical outcomes and prevent future HAPE or to strategies that prevent future HAPE, such as avoidance of high altitude.	Diagnostic testing is not harmful, but may be burdensome and costly. False-negative results lead to false reassurance of the patient and clinician (which may delay diagnostic and treatment opportunities) and false-positive results may lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	This recommendation places a high value on preventing future HAPE and its clinical consequences, and a lower value on the undesirable consequences, burdens, and costs of diagnostic testing.	I	B
Systemic Disease					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#67) Early evaluation for PH including a Doppler echocardiogram is reasonable for children with hemolytic hemoglobinopathies, hepatic, renal or metabolic diseases who develop cardio- respiratory symptoms. (IIa,C)					
Controlled observational	Cardio- respiratory symptoms and signs are more likely to be due to PH in children who	Echocardiography itself is not harmful, or overly burdensome or costly.	This recommendation places a high value on identifying the cause of the	IIa	C

studies, case series, + clinical experience	have hemolytic hemoglobinopathies, hepatic disease, renal disease, or metabolic disease. Echocardiography indicates the likelihood that the symptoms and signs are attributable to co-existing PH. It may also identify alternative causes of the symptoms and signs. In doing so, it guides the clinician to the appropriate next test (e.g., right heart catheterization if the echocardiogram is suggestive of PH and alternative testing if the echocardiogram is not suggestive of PH), potentially reducing the harms, burdens, and costs of inappropriate or unnecessary testing. In addition, echocardiography can estimate the severity of disease if concomitant PH is suggested. Severe disease prompts earlier confirmation of PH and treatment, which improves clinical outcomes, including dyspnea, respiratory distress and exercise intolerance, and progressive PH. Probable mild or no disease may warrant follow-up only, preventing inappropriate therapy and its related harms, burdens, and costs.	False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	cardiorespiratory symptoms and initiating therapy that improves clinical outcomes, and a lower value on the undesirable consequences of misleading results, burdens, and costs of echocardiography.		
#68) In children with chronic hepatic disease, an echocardiogram should be performed to rule out portopulmonary hypertension and pulmonary arterio-venous shunt prior to listing for liver transplantation (I,B).					
Controlled observational studies, case series, + clinical experience	Children with liver disease are at higher risk for developing progressive and severe PH, which if untreated, can be fatal. Echocardiography may help with early identification of PH in this population. Echocardiography can suggest PH, which will prompt right heart catheterization for confirmation. Confirmed PH warrants either treatment that improves clinical outcomes such as dyspnea, respiratory signs, exercise capacity, and quality of life if moderate or severe, or close ongoing follow-up for indications for treatment if mild. Confirmed PH may also affect decision-making regarding the timing and appropriateness of liver transplantation.	Echocardiography itself is not harmful, or overly burdensome or costly. False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	This recommendation places a high value on identifying PH so that therapy can be promptly initiated before the accrual of morbidity and mortality if indicated, and a lower value on the undesirable consequences of misleading results, burdens, and costs of echocardiography.	I	B
#69) It is reasonable for children with sickle cell disease (SCD) to undergo an echocardiogram to screen for PH and associated cardiac problems by 8 years of age or earlier in patients with frequent cardio-respiratory symptoms (IIa,C).					

Controlled observational studies, case series, + clinical experience	Children with SCD are at high risk for developing progressive and severe PH, which can be fatal. Echocardiography can suggest PH, which will prompt right heart catheterization for confirmation. Confirmed PH warrants either treatment that improves clinical outcomes such as dyspnea, respiratory signs, exercise capacity, quality of life, and possibly mortality if moderate or severe, or close ongoing follow-up for indications for treatment if mild. Treatments include systemic therapies (e.g., hydroxyurea, chronic transfusion) as well as PAH-specific therapies.	Echocardiography itself is not harmful, or overly burdensome or costly. False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results are particularly common due to anemia and high cardiac output. They may lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	This recommendation places a high value on identifying PH so that therapy can be promptly initiated before the accrual of morbidity and mortality if indicated, and a lower value on the undesirable consequences of misleading results, burdens, and costs of echocardiography.	IIa	C
#70) Children with SCD who have evidence of PH by echocardiogram:					
i) should undergo further cardiopulmonary evaluation, including pulmonary function testing, polysomnography, assessments of oxygenation, and evaluation for thromboembolic disease.(I,C)					
Controlled observational studies, case series, + clinical experience	PH in SCD may be due to underlying lung disease, intermittent or sustained hypoxia, or thromboembolic disease. Identification of the underlying cause leads to targeted therapy that may improve the PH and related symptoms and signs, and may prevent or reduce the need for PAH-specific therapies, which can be harmful, burdensome, and costly.	Pulmonary function testing, polysomnography, and assessment of oxygenation are not harmful. Evaluation of thromboembolic disease is associated with radiation exposure and the potential for a contrast reaction if CT pulmonary angiography is the method chosen. None of these diagnostic tests is overly burdensome or costly. However, each test can give misleading results. False-negative results lead to false reassurance of the patient and clinician. The latter may delay diagnostic and treatment opportunities. False-positive results may lead to inappropriate confirmatory diagnostic testing, with its associated risks, burdens, and costs.	This recommendation places a high value on identifying the underlying cause of the PH and initiating therapy that improves clinical outcomes and decreases the need for PAH-specific therapy; it places a lower value on the undesirable consequences of misleading results, burdens, and costs of diagnostic testing.	I	C
ii) should undergo cardiac catheterization before the initiation of PAH-specific drug therapy (I,C)					
Controlled observational studies, case series, + clinical experience	In patients with SCD, right heart catheterization can: a) determine the severity of the underlying PH, b) elucidate whether to PH is due to anemia, high cardiac output, left ventricular dysfunction, or intrinsic pulmonary vascular disease. This may lead to additional therapies that are less expensive, less harmful, and less	For catheterization, risks including bleeding, pneumothorax, cardiac or vascular perforation, arrhythmia, and cardiac arrest. For vasoreactivity testing, risks include acute pulmonary edema if performed in the context of cardiomyopathy or pulmonary venoocclusive disease.	This recommendation places a high value on identifying the underlying cause of the PH and initiating therapy directed at the underlying (i.e., PAH-specific therapy only for those with high PVR and normal pulmonary capillary wedge pressure) cause in order to improve clinical outcomes and avoid the unnecessary use of PAH-specific therapy, which can be harmful, burdensome, and costly. It places a lower value on the harms of cardiac	I	C

	burdensome than PAH-specific therapies). c) if due to intrinsic pulmonary vascular disease, test for acute vasoreactivity to determine prognosis and to assess whether calcium channel blockers are a viable option (calcium channel blockers are less expensive, less harmful, and less burdensome than PAH-specific therapies)		catheterization and vasoreactivity testing.		
#71) BNP and NT-pro-BNP measurements can be useful in screening for PH in patients with SCD. (IIa,C).					
Controlled observational studies, case series, + clinical experience	BNP and NT-pro-BNP measurements can be used in conjunction with echocardiography to screen patients for possible PH. Elevated levels combined with echocardiographic findings suggestive of possible PH may prompt additional diagnostic tests (i.e., right heart catheterization) to confirm or exclude PH. Confirming PH leads to the initiation of therapies that improve clinical outcomes, while excluding PH avoids unnecessary therapies that have side effects, burdens, and costs.	False-positive results are common because BNP and NT-pro-BNP are not specific for the right ventricle. False-positive results may lead to unnecessary diagnostic testing, which may have harms, burdens, and costs. False-negative results may lead to false reassurance of patients and clinicians, with the latter resulting in missed diagnostic and treatment opportunities, leading to poorer outcomes.	This recommendation places a high value on selecting appropriate patients for confirmatory diagnostic testing (i.e., right heart catheterization) and a lower value on the undesirable consequences of misleading results and the burdens and costs of BNP and NT-pro-BNP testing.	IIa	C
#72) With the diagnosis of PH in children with SCD, optimization of SCD –related therapies (e.g., blood transfusions, hydroxyurea, iron chelation, and supplemental oxygen) is recommended. (I,C)					
Controlled observational studies, case series, + clinical experience	Patients with SCD-related PH may benefit from more aggressive treatment of their SCD. This may reduce mortality, the frequency of acute chest syndrome and sickle cell crises, and symptoms and signs of PH.	Each potential therapy may have adverse consequences. Hydroxyurea may cause neutropenia or leukemogenesis, while chronic transfusion therapy may cause iron overload, volume overload, and transfusion reactions.	This recommendation places a high value on improving clinical outcomes and a lower value on the adverse effects of therapy.	I	C
#73) PAH-targeted therapy should not be used empirically in SCD-associated PH due to potential adverse effects (III,C).					
Controlled observational studies, case series, + clinical experience	PAH-specific therapy may be harmful (e.g., sildenafil therapy may be at increased risk for vaso-occlusive disease and acute chest syndrome), burdensome, and costly. Using PAH-specific therapy only in the setting of RHC-confirmed PH reduces the frequency of side effects due to inappropriate therapy.	By avoiding empiric therapy, there is a subset of patients who may have benefited from empiric therapy who will not receive such therapy.	This recommendation places a high value on not causing harmful effects from PAH-specific therapy in patients who are unlikely to benefit from therapy, and a lower value on ensuring that everyone who may benefit from therapy receives a trial of therapy.	III	C
#74) PAH –targeted therapy may be considered in patients with SCD in whom there is confirmation of PH with marked elevation of PVR without an elevated pulmonary capillary wedge pressure by cardiac catheterization. (IIb,C)					
Controlled observational studies, case series, + clinical experience	Patients with SCD-related PAH characterized by an elevated PAH and normal wedge pressure who receive PAH-specific therapy have improved clinical outcomes including increased exercise capacity, better quality of life, and reduced respiratory symptoms and	PAH-specific therapy has side effects that vary according to the agent (e.g, headaches, flushing, and hepatotoxicity). In particular, when PH is due in part to elevated left sided cardiac pressures, PAH-specific therapy increases the likelihood pulmonary edema	This recommendation places a high value on improving clinical outcomes and a lower value on the adverse effects of therapy.	IIb	C

	signs.	and acute chest syndrome. These latter effects may be mitigated by recognizing left heart disease and high cardiac output and factoring these features into the decision of whether or not to institute PAH-specific therapy.			
#75) A trial of a prostacyclin agonist or ET receptor antagonist is preferred over PDE5 inhibitors in patients with markedly elevated PVR and SCD. (IIa,B)					
Controlled observational studies, case series, + clinical experience	The PDE5 inhibitor, sildenafil, has been associated with an increased risk for pain crisis and hospitalization in patients with SCD-related PAH. Therefore, avoiding this class of agent may prevent such adverse events.	Not using PDE5 inhibitors may reduce the benefits seen among patients who may have responded preferentially to a PDE5 inhibitor; this is more theoretical because differential responses to the various classes of agents have not been demonstrated.	This recommendation places a high value on avoiding adverse effects of therapy and a lower value on providing a wide array of choices for clinicians.	IIa	B
Outpatient Care of Children with PH					
Quality of the evidence (i.e., rationale for the level of evidence)	**Potential benefits**	**Potential harms and burdens**	**Values and preferences**	**Classification of recommendation**	**Level of evidence**
#76) Children with PH should be evaluated and treated in comprehensive, multidisciplinary clinics at specialized pediatric centers. (I,C)					
Controlled observational studies, case series, + clinical experience	Interdisciplinary teams, including cardiology, pulmonology, neonatology, critical care, and others, can provide the necessary expertise and experience in approaching the diverse causes of PH in children. It may also provide greater availability of the clinicians to the patient and family. Adverse events associated with such procedures as cardiac catheterization and instituting appropriate therapies (especially with chronic intravenous medications) are less in centers with more experience in managing severe PH.	Receiving care at an experienced center has minimal risk, but can be burdensome if the center is located far from the patient's home.	This recommendation places high value on patient safety clinician availability, and a lower value on burden.	I	C
#77) Outpatient follow-up visits at 3 - 6 month intervals are reasonable, with more frequent visits for patients with advanced disease or after initiation or changes in therapy. (IIa,B).					
Controlled observational studies, case series, + clinical experience	Frequent outpatient visits allow close monitoring of changes in disease course, which probably improve the accuracy of estimating prognosis and likely also leads to earlier detection and treatment of causes of deterioration, which would be expected to improve clinical outcomes. Frequent outpatient visits enhance communication of providers with patients and	Frequent outpatient visits are not harmful, but may be burdensome if the patient lives far from the clinical center.	This recommendation places a high value on communication and on early detection and treatment to improve clinical outcomes; it places a lower value on convenience.	IIa	B

	their families.				
#78) The following preventive care measures for health maintenance are recommended for pediatric patients with PH including: • RSV prophylaxis (if eligible) • Influenza and pneumococcal vaccinations • Rigorous monitoring of growth parameters • Prompt recognition and treatment of infectious respiratory illnesses • Antibiotic prophylaxis for the prevention of sub-acute bacterial endocarditis in cyanotic patients and those with indwelling central lines. (I,C)					
Controlled observational studies, case series, + clinical experience	Routine illnesses are common throughout childhood but may adversely affect outcomes and even be life-threatening in children with PH. Prevention of such illnesses improves clinical outcomes.	The recommended interventions have few adverse consequences except for rare side effects associated with vaccines or allergic reactions to antibiotics. In addition, none of the interventions is unduly burdensome or costly.	This recommendation places a high value on preventing illnesses that lead to poor clinical outcomes and a lower value on the rare side effects of the interventions.	I	C
#79) Careful pre-operative planning, consultation with cardiac anesthesia and plans for appropriate post-procedure monitoring are recommended for pediatric patients with PH undergoing surgery or other interventions. (I,C)					
Controlled observational studies, case series, + clinical experience	Children with PH are at risk for sudden death or respiratory and cardiac arrest due to PH crisis even with routine anesthesia. Careful pre-operative planning, consultation with cardiac anesthesia, and planning for appropriate post-procedure monitoring (even for routine surgical and dental procedures) may prevent such complications, leading to better clinical outcomes.	Careful pre-operative planning, consultation with cardiac anesthesia, and planning for appropriate post-procedure monitoring may be burdensome, but it is neither harmful nor costly.	This recommendation places a high value on preventing complications that lead to poor clinical outcomes and a lower value on convenience.	I	C
#80) Performance of elective surgery for patients with pediatric PH should be performed at hospitals with expertise in PH and in consultation with the pediatric PH service and anesthesiologists with experience in the peri-operative management of children with PH. (I,C)					
Controlled observational studies, case series, + clinical experience	Children with PH are at risk for sudden death or respiratory and cardiac arrest due to PH crisis, even with routine anesthesia during elective procedures. Providers with experience in pediatric PH can provide the necessary expertise and experience in preventing and managing the diverse complications of surgery in children with PH. This likely prevents complications and improves clinical outcomes.	Receiving care at an experienced center reduces risk, but can be burdensome if the center is located far from the patient's home.	This recommendation places high value on patient safety and a lower value on burden.	I	C
#81) Due to significant maternal and fetal mortality associated with pregnancy in patients with PH, it is recommended that female adolescents with PH be provided with age-appropriate counseling regarding pregnancy risks and options for contraception. (I,C)					
Controlled observational studies, case series, + clinical experience	Pregnancy in young women with PH can cause marked worsening of their underlying PH. Counseling and discussions with adolescent female patients and their families about the role of birth control and family planning may reduce pregnancy-related complications and poor clinical outcomes.	This topic may be especially difficult for some patients or their families and may cause distress if not handled in a respectful and sensitive fashion.	This recommendation places a high value on avoiding life-threatening complications of pregnancy in female PH patients and a lower value on the burdens and psychological effects of counseling and related services.	I	C
#82) Due to the risks of syncope or sudden death with exertion, it is recommended that a thorough evaluation, including cardio-pulmonary exercise testing and treatment is performed prior to					

engaging in athletic ("symptom-limited") activities. (I,C)					
Controlled observational studies, case series, + clinical experience	Children with PH have increased risk of syncope and sudden death with exertion. Physiologic studies including exercise testing may help determine the risk of such events and/or the maximum level of safe exercise, which helps advise patients and their families. Instructing patients and families on safe exercise reduces the risk of poor clinical outcomes.	Discussion of physical limitations may be difficult for some patients or their families and may cause distress if not handled in a respectful and sensitive fashion.	This recommendation places a high value on avoiding life-threatening complications of exercise and a lower value on the burdens and psychological effects of counseling.	I	C
#83) Pediatric patients with severe PH (WHO functional class III or IV) and/or recent history of syncope should not participate in competitive sports (III,C)					
Controlled observational studies, case series, + clinical experience	PH patients with severe, symptomatic PH are at risk for sudden death with extreme exertion. Not allowing the child to participate in competitive sports may prevent a fatal event.	Lack of involvement in competitive sports may be stressful and disappointing to some children and their families. Less demanding sports activities may be acceptable.	This recommendation places high value on safety and a lower value on psychological distress due to the patient's desire to compete in physically-demanding sports.	III	C
#84) During exercise, it is recommended that pediatric patients with PH should engage in light to moderate aerobic activity, avoid strenuous and isometric exertion, remain well hydrated, and be allowed to self-limit as required. (I,C)					
Controlled observational studies, case series, + clinical experience	PH patients with severe, symptomatic PH are at risk for sudden death with extreme exertion. Having the child to participate in light to moderate aerobic activity, and avoid strenuous and isometric exertion, may prevent a fatal event.	Lack of involvement in activities that require strenuous exertion may be stressful and disappointing to some children and their families.	This recommendation places high value on safety and a lower value on psychological distress due to the patient's desire to compete in physically-demanding activities.	I	C
#85) During airplane travel, supplemental oxygen use is reasonable in pediatric patients with PH. (IIa,B)					
Controlled observational studies, case series, + clinical experience	Airplane travel increases the risk for hypoxic pulmonary vasoconstriction, which my worsen PH. Treatment with supplemental oxygen may prevent the worsening of PH and its associated symptoms and signs.	Supplemental oxygen is not harmful, but there is an added burden when traveling with oxygen tanks and needing to make specific arrangements with airlines prior to travel. Not all patients with PH require oxygen therapy for air travel, and decisions to recommend oxygen for travel should be individually assessed.	This recommendation places high value on safety and a lower value on the burden of planning and using supplemental oxygen during airplane travel.	IIa	B
#86) Given the impact of childhood PAH on the entire family, children, siblings and caregivers should be assessed for psychosocial stress and be readily provided support and referral as needed. (I,C)					
Controlled observational studies, case series, + clinical experience	The roles of the family in supporting and improving outcomes of the child with PH are critically important. However, caring for a child with PH is very demanding for families and leads to diverse stresses, including social, psychological and economic issues. Psychosocial support of family caregivers may improve emotional outcomes.	Psychosocial support of caregivers is not harmful, burdensome, or costly.	This recommendation places a high value on recognizing the impact of PH on families and the potential benefits of providing support to families of children with PH.	I	C