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Interventional Strategies for Children with Progressive Pulmonary Hypertension Despite Optimal Therapy

An Official American Thoracic Society Clinical Practice Guideline

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Abstract

Background: Pulmonary hypertension in children is progressive with wide variability in prognosis. This document provides an evidence-based clinical practice guideline for the management of children with progressive pulmonary hypertension despite optimal therapy.

Methods: A multidisciplinary panel identified pertinent questions regarding the management of children with pulmonary hypertension that has progressed despite optimal therapy, conducted systematic reviews of the relevant literature, and applied the Grading of Recommendations, Assessment, Development and Evaluation approach to develop clinical recommendations.

Results: After reviewing the research evidence, the panel considered the balance of desirable (benefits) and undesirable (harms and burdens) effects of the interventions in each proposed question. Valuation of our main outcomes was also considered, together with resources required, equity, acceptability, and feasibility. Recommendations were developed for or against interventional strategies specific to children with pulmonary hypertension that has progressed despite optimal therapy.

Conclusions: Although there is a growing population of children with pulmonary hypertension, there is a striking lack of empirical evidence regarding management of those whose disease has progressed despite optimal pharmacotherapy. The panel formulated and provided the rationale for clinical recommendations for or against interventional strategies on the basis of this limited empirical evidence, coupled with expert opinion, to aid clinicians in the management of these complex pediatric patients. In addition, we identified important areas for future research.

Keywords: atrial septostomy; lung transplantation; pulmonary-to-systemic shunt; Potts shunt; extracorporeal membrane oxygenation

Overview

This 2024 American Thoracic Society (ATS) clinical practice guideline on interventional strategies for children with progressive pulmonary hypertension (PH) despite optimal therapy focuses on a high-priority clinical problem. The prior guideline related to this topic, a joint effort from the American Heart Association (AHA) and the ATS, was published in 2015 and focused on the diagnosis, evaluation, and treatment of PH in children. That guideline included limited discussion of the management of PH in children with disease that had progressed, especially to right ventricular (RV) failure, despite optimal therapy. This is the first document of its kind to use

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A data supplement for this article is available via the Supplements tab at the top of the online article.

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systematic reviews and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the roles of atrial septal defect (ASD) creation and/or enlargement (termed ASD intervention), pulmonary-to-systemic shunts, and lung transplantation in children with PH. The role of lung transplantation and pulmonary-to-systemic shunts for children who are on venoarterial (VA) or venovenous (VV) extracorporeal membrane oxygenation (ECMO) support without reversible cause is also addressed. Key recommendations include the following:

- We suggest ASD intervention (creation and/or enlargement) for children with progressive PH and RV failure despite optimal therapy (conditional recommendation, very low certainty of evidence).
- We suggest the creation of a pulmonary-to-systemic shunt in children with progressive PH and suprasystemic RV pressure despite optimal therapy (conditional recommendation, very low certainty of evidence).
- We suggest lung transplantation in children with progressive PH and RV failure despite optimal therapy (conditional recommendation, very low certainty of evidence).
- We suggest lung transplantation in children with progressive PH and RV failure despite optimal therapy who are on ECMO support without reversible cause (conditional recommendation, very low certainty of evidence).
- We suggest against pulmonary-to-systemic shunt creation for children with progressive PH and suprasystemic RV pressure despite optimal therapy who are on ECMO support without reversible cause (conditional recommendation, very low certainty of evidence).

Introduction

In 2018, the sixth World Symposium on Pulmonary Hypertension (WSPH) modified the definition for PH in adults to a mean pulmonary arterial pressure of $>$20 mm Hg and included pulmonary vascular resistance of $\geq$3 Wood units to identify precapillary PH (1). For consistency across all age groups, the Pediatric Task Force of the WSPH followed suit and adopted the same definition (2). Most existing epidemiologic data on pediatric PH were published before this updated definition, with an estimated incidence of sustained PH in children of all groups of 4–10 patients per million per year in European countries and 5–8 patients per million per year in the United States (3–5). Much of these data are derived from patient registries, and because of the inherent nature and reporting issues of such data related to disease definition, inclusion criteria, geographic distribution of disease, and referral patterns, the true incidence and prevalence of pediatric PH are unknown.

Despite the lack of precise epidemiologic data, more children are being diagnosed with PH, and a larger proportion have more severe disease, need more hospitalizations, and require significant healthcare resources (6, 7). To address the care of this growing population of complex patients, in 2015, a joint effort by the AHA and the ATS generated a clinical practice guideline for the diagnosis, evaluation, and treatment of PH in children (8). Although it included some discussion of management options for children with progressive disease despite optimal management, namely, ASD creation/enlargement (termed ASD intervention), that guideline was not focused on the use of interventional strategies for these patients. With no cure for pediatric PH, children whose disease is unrelenting will continue to progress to RV failure, ultimately resulting in death, with relatively few patients undergoing palliative catheter-based intervention, surgical intervention, or lung transplantation. Recognizing the need for clinical guidance regarding the treatment of pediatric PH that is progressing despite optimal "first-line" therapy guided by the AHA and ATS guideline, the ATS convened a task force of clinicians and clinician–scientists in adult and pediatric pulmonology, adult and pediatric cardiology, pediatric cardiac intensive care medicine, pediatric cardiac interventional medicine, and adult and pediatric cardiothoracic surgery. The purpose of the task force was to conduct systematic reviews and use available evidence to inform recommendations for interventional strategies in the management of children with PH that has progressed despite optimal therapy.

Use of the Guideline

These recommendations are intended to aid clinicians in the management of infants, children, and adolescents with PH who have progressive disease despite optimal therapy. This group of clinicians aided by this document include adult and pediatric pulmonologists, adult and pediatric cardiologists, neonatologists, pediatric cardiac intensivists, pediatric cardiac interventionalists, adult and pediatric cardiothoracic surgeons, primary care providers, other health care professionals, and policy makers. Clinicians, patients, third-party payers, stakeholders, and courts should not view the recommendations contained in this guideline as standards of care. Although evidence-based guidelines can summarize the best available evidence regarding the effects of an intervention in a given patient population, they cannot take into account all of the unique clinical circumstances that may arise when managing a patient. As such, their implementation is at the discretion of each treating physician who must work in concert with the patient and their family through a process of shared decision making.

Patient Population

The patient population for this guideline is children younger than 18 years with progressive PH despite optimal therapy. Because of the variable clinical presentations of children with PH, the characteristics of the patients this guideline targets include progressive deterioration in New York Heart Association or World Health Organization (WHO) functional class III or IV during escalating therapy, progressive hemodynamic deterioration on serial cardiac catheterizations independent of functional class, inability to tolerate maximal medical therapy with WHO functional class IIIa or IIIb, worsening RV function (moderate or greater dysfunction), life-threatening complications (e.g., recurrent hemoptysis or recurrent syncope) that progresses despite medical therapy or creation of a right-to-left shunt, secondary liver or kidney dysfunction due to progressive PH, and worsening quality of life as determined by the family, among other potential characteristics. In certain circumstances, some of these children will have suprasystemic pressures, which we define as RV or pulmonary artery systolic pressures greater than left ventricular (LV) or aortic systolic pressures.

Given the complexity of management decisions for many children with PH, we acknowledge that optimal therapy cannot be absolutely defined (2). Additional complexity is introduced by the fact that for some, optimal therapy may ultimately be surgical and not medical (e.g., pulmonary endarterectomy [PEA] in chronic thromboembolic PH [CTEPH]). This document is focused largely on children with Group 1 PH (i.e., pulmonary arterial hypertension) who experience disease progression, manifesting as worsening symptoms, hospitalization, or some other measure of severity, despite the use of PH-specific pharmacotherapies. However, under the correct circumstances, the interventions addressed in this guideline may be appropriate for children with other forms of progressive PH. Last, variability in the determination of what constitutes optimal therapy, as well as what constitutes disease progression, can influence referral practices related to the interventions described in our patient, intervention, comparator, outcome (PICO) format questions (2). In instances in which studies specified criteria for the receipt of an intervention, we have detailed those criteria to serve as parameters that may guide referral for suggested interventions.

Methods

This guideline was developed in accordance with policies and procedures of the ATS, using the GRADE approach to formulate clinical questions, identify and summarize relevant evidence, and develop recommendations for clinical practice (9). To report the systematic reviews, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (10). The guideline underwent anonymous peer review by five content experts and a methodologist. After multiple cycles of review and revision, the guideline was reviewed and approved by a multidisciplinary board of directors of the ATS. The guideline will be reviewed by the ATS three years after publication, and it will be determined if updating is necessary.

Panel Composition

The co-chairs (D.H. and D.L.S.M.) submitted a proposal that was reviewed and approved by the ATS Assembly of Pediatrics, Program Review Subcommittee, and Board of Directors. A multidisciplinary panel of international specialists with expertise in children with advanced PH and guideline development methodology was formed. Disciplines represented included pediatric cardiology, pediatric pulmonology, pediatric cardiac intensive care, interventional pediatric cardiology, pediatric cardiothoracic surgery, and adult cardiothoracic surgery. A parent of a child with PH who required lung transplantation was also included as a patient advocate (M.F.L.). Potential conflicts of interest were disclosed and managed in accordance with the policies and procedures of the ATS. A senior methodologist (A.L.J.) with expertise in evidence synthesis and guideline development was assigned to assist the panel, together with three ATS methodology scholars (E.A., S.M.H., H.L.) and a medical librarian (T.J.).

Meetings

All meetings were held via video conference. Our first meeting was in July 2022, at which time we reviewed the guideline development process and GRADE approach, and our final video conference was in December 2023.

Clinical Questions and Outcomes of Interest

The committee identified five specific questions addressing the clinical management of children with progression of PH despite optimal therapy. The PICO format was used to formulate each question. Potential outcomes for each PICO question were generated by the panel members using an online survey developed by the methodology team. Panel members were then asked to rate a curated list of outcomes, using a scale of 1–9, and ratings were used to categorize outcomes as critical, important, or not important (scores of 7–9 were considered critical, 4–6 important, and 1–3 not important). For GRADE assessments, only critical and important outcomes were considered.

Literature Search

With the assistance of a medical librarian, we searched multiple electronic databases, including Embase via Elsevier (1947 to the present), PubMed including both MEDLINE and PubMed Central articles (1946 to the present), CINAHL Complete via EBSCO (1937 to the present), and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews via John Wiley (from inception). We also identified additional studies by searching the

reference lists of the articles eligible for full-text review. Search results were deduplicated and screened using Covidence systematic review software (Veritas Health Innovation). Complete details of the literature search, by PICO, are available in the data supplement.

Given the expectation that literature on this topic would be sparse, we were liberal in our inclusion of study types, excluding only the following: narrative reviews, consensus statements, clinical practice guidelines, opinion pieces, editorials, workshop proceedings, protocols, unpublished trial data, and dissertations, and theses. Using prespecified inclusion and exclusion criteria, two members of the methodology team screened titles and abstracts independently, and then, for potentially relevant studies, full texts were obtained and independently reviewed. Once a final group of studies was selected for each PICO question, the methodology team then determined which studies would be included in GRADE evaluations, using the traditional hierarchy of scientific evidence to focus on the highest tier evidence available for each question. Because some studies contained a mixture of adults and children, we developed criteria to facilitate selection of the most direct evidence possible. For studies with both adults and children but no child-specific data, a population including $\geq$50% children and/or a mean or median population age $<$18 years was considered acceptable. All conflicts in study selection were resolved via discussion. When indicated, the lead methodologist contacted experts outside the panel for additional data related to selected studies. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagrams for numbers of records removed at each step are available in the data supplement.

Evidence Review and Development of Clinical Recommendations

For selected studies, descriptive summaries were generated and then study details extracted by the methodology team using a data extraction template. Extracted data were jointly reviewed by two methodologists and made available for the panel to review. The lead methodologist prepared evidence summaries using the GRADEpro Guideline Development Tool online application (www.gradepro.org). Given the characteristics of the evidence available, meta-analysis was not possible; thus, the evidence was presented in a narrative form. Evidence was evaluated using the GRADE approach (11), including an assessment of risk of bias, inconsistency, directness of the evidence, precision, risk of publication bias, magnitude of effect, plausible residual confounding, and presence of dose–response gradient. Certainty of evidence was categorized as high, moderate, low, or very low. Evidence summaries were provided to all panel members for review, and the panel developed recommendations using the evidence to decision framework (12–14). Final recommendations and their strengths were decided by consensus, requiring at least 80% agreement from at least 80% of voting members of the panel. We labeled recommendations as either "strong" or "conditional," using the words "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Our schema was based on a prior ATS statement on the grading of recommendations (15), and further details related to the implications of these labels for different stakeholders are described in the data supplement.

Manuscript Preparation

After recommendations were finalized, the chair (D.H.) drafted the guideline document, which was reviewed and edited by the lead methodologist (A.L.J.). The document was then reviewed by the entire panel, and feedback was circulated via e-mail correspondence until consensus on the final document was achieved. A final approved version was submitted to the ATS for peer review. Table 1 summarizes the potential interventions for children with severe PH that are discussed in this guideline, including considerations for patient selection, approach, and situations in which caution is advised. Table 2 provides a list of clinical characteristics that suggest the need for consultation or referral for lung transplantation in children with PH with progressive decline despite optimal therapy.

Comprehensive Approach to Care

Because of high mortality in these children with or without interventional treatment, the panel recommends the involvement of a multidisciplinary team of care providers that may help facilitate the best decision making for the patient and family. The multidisciplinary team should be inclusive, and its composition will be dictated by services available at the pediatric institutions. Palliative care service should be involved for treatment planning as patients and families have the potential to greatly benefit from comprehensive care that allows a parallel planning approach. Notably, ASD intervention is more widely available at children's hospitals compared with pulmonary-to-systemic (Potts) shunt or pediatric lung transplantation. Therefore, the panel universally agreed that early consultation or early referral should be considered to those hospitals with pulmonary-to-systemic shunt or pediatric lung transplantation capability.

The panel believes that early referral is in the best interest of the patient, as that may allow time for candidates to address modifiable barriers to transplantation, such as growth, nutritional, or weight concerns; medical comorbidities; and inadequate social support. Moreover, additional medical requirements could be completed that are necessitated for transplantation candidacy by some programs, such as the completion of required vaccinations, which could require multiple injections over time. For patient referrals that are too early for full evaluation or with contraindications for transplantation, specific parameters for the timing of rereferral and recommendations for ongoing optimization of candidacy should be provided.

Recommendations

Question 1: Should Children with Progressive PH despite Optimal Therapy Undergo ASD Intervention (creation and/or enlargement)?

Background. Survival of children with PH has improved over the past two decades because of the introduction of pharmacological agents; however, the disease remains progressive, with significant variability in severity and prognosis despite optimal medical therapy. Prior guidelines recommended ASD intervention for patients with symptoms of RV failure, recurrent syncope, or PH crises that persist despite optimized medical management (8). By generating a shunt at the atrial level, LV preload and cardiac output can be improved at the expense of decreased systemic oxyhemoglobin saturation. Importantly, the relief provided by ASD intervention for a failing right ventricle is only volume unloading rather than pressure unloading, with no direct reduction of RV afterload. The time elapsed since the previous

Table 1. Potential Interventions for Children with Severe Pulmonary Hypertension: Considerations for Patient Selection, Approach, and Caution Advised

	Patient Selection	Approach	Caution Advised
ASD intervention (creation and/or enlargement)	• Presence of right ventricular failure in a child with disease progression. • Children with impaired systemic blood flow due to reduced left heart filling that leads to syncope are more likely to respond favorably to creation or enlargement of an ASD. • For children with PH on ECMO without reversible cause for deterioration, ASD intervention can be an alternative strategy to avoid peripheral ECMO as a bridge to lung transplantation.	• Creation or enlargement of an ASD can be done using a balloon atrial septostomy, static balloon dilation, an atrial flow regulator device, a stent, or surgery. • For children with severe PH and a preexisting moderate to large ASD, an individualized approach to closure, partial closure, or no ASD intervention should be taken, considering underlying disease, age, severity of PH, and need for other procedures.	• For children with severe PH, a preexisting patent foreman ovale or small ASD should not undergo percutaneous or surgical closure. • Children with markedly elevated right atrial pressure or pulmonary vascular resistance are at risk for excessive right-to-left shunting from creating or enlarging an ASD. • For precautionary measures during ASD intervention, immediate ECMO cannulation should be considered as a backup.
Pulmonary-to-systemic shunt	• Presence of suprasystemic pulmonary arterial pressures, where the purpose of the pulmonary-to-systemic shunt is to be a pressure-unloading shunt for the right ventricle to improve its function. • In urgent situations, a pulmonary-to-systemic shunt is a better option than lung transplantation because of wait times for transplantation. • Compared with lung transplantation, complexity of care after a pulmonary-to-systemic shunt may be less burdensome on families.	• A transcatheter or surgical approach can be considered according to center expertise. • A transcatheter approach should be pursued if the PDA was recently closed or if there is a prominent aortic ampulla. • An anterior approach is considered the best surgical approach for a pulmonary-to-systemic shunt, to minimize complications and for future consideration of lung transplantation. • PDA recanalization and stenting can be feasible weeks to months after echocardiographic closure.	• There are insufficient data to support transcatheter creation of a pulmonary-to-systemic shunt when the PDA has been chronically closed or an alternative path from the left pulmonary artery to the aorta must be created. • For children on ECMO, pulmonary-to-systemic shunt should be considered only for palliative indications at a highly qualified center with expertise and experience. • For surgical pulmonary-to-systemic shunts, a lateral approach is considered a relative contraindication to lung transplantation.
Lung transplantation	• Considerations for referral for lung transplantation are outlined in Table 2. Early referral is recommended because of the limited availability of suitable organs for children. • ECMO is not a contraindication for lung transplant if the following criteria are met: ○ Single-organ (lung) failure ○ Neurologically intact with minimal sedation ○ Actively participating in physical rehabilitation, preferably ambulating if age appropriate ○ Receiving primarily enteral nutritional support • For consideration of ECMO before lung transplantation, it is preferable that the patient already be on the transplant wait list at time of initiation to reduce wait list mortality.	• Children with PH should be considered for lung transplantation at a pediatric-capable program with experience and expertise caring for this high-risk patient population. • Early consultation or early referral to a lung transplant program facilitates transplantation education for the patient and caregivers, addresses in potential barriers to transplantation, and optimizes the best chance for a successful outcome. • Bilateral lung transplantation is the best surgical approach for transplantation in children with PH, especially those with more severe disease that requires ECMO support.	• Combined heart and lung transplantation for PH is reserved for: ○ Uncorrectable congenital heart disease ○ Coexisting left ventricular dysfunction ○ Technical issues ■ Massive right heart enlargement in young children ■ Donor lung constraints ■ Lower likelihood of airway caliber compromise with tracheal versus bibronchial anastomoses in small children (as the child grows) • Children with PH, especially those on ECMO at the time of lung transplantation, are at high risk for PGD, so mitigation strategy for PGD includes supportive care and early initiation of ECMO with the need to balance benefits and risks.

Definition of abbreviations: ASD = atrial septal defect; ECMO = extracorporeal membrane oxygenation; PDA = patent ductus arteriosus; PGD = primary graft dysfunction; PH = pulmonary hypertension.

Table 2. Clinical Characteristics That Suggest the Need for Referral for Lung Transplantation in Children with Pulmonary Hypertension with Progressive Decline Despite Optimal Therapy

- Progressive deterioration in WHO or NYHA functional class III or IV during escalating therapy over two serial assessments at least 3 mo apart
- Progressive hemodynamic deterioration noted at serial cardiac catheterization at least 3 mo apart, independent of functional class change
- Inability to tolerate maximal medical therapy (WHO functional class IIIa or IIIb)
- Worsening right ventricular function (moderate or greater) regardless of other parameters
- Life-threatening complications (e.g., recurrent hemoptysis, recurrent syncope) that progress despite medical therapy or creation of a right-to-left shunt
- Development of secondary liver or kidney dysfunction (if reversible) or if requires multiorgan transplantation
- Development of worsening quality of life as determined by family
- Known or suspected pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease or similar diseases such as alveolar capillary dysplasia
- Progressive pulmonary vein stenosis not responding to medical or procedural interventions

Definition of abbreviations: NYHA = New York Heart Association; WHO = World Health Organization.

guideline, as well as the consideration of evolving approaches to this intervention prompted the panel to ask, should children with progressive PH despite optimal therapy undergo ASD intervention (creation and/or enlargement)?

Summary of the evidence. A systematic review of the literature identified 12 observational studies that met our inclusion criteria and provided the highest tier evidence available related to ASD intervention in children with PH (16–27). Most studies were purely descriptive, with few analyses performed. Five studies included children only (18, 20, 21, 25, 26). For the remaining studies, child-specific data were available for six (16, 17, 19, 23, 24, 27), and one study was without child-specific data but the median age of participants was 12 years (22). Across all studies, there was a total of 153 patients undergoing ASD intervention, including one patient who died intraprocedurally before ASD creation (17) and one patient in whom ASD creation failed and an occluder device was required (20). Ten studies provided some detail about the indication for ASD intervention (16, 19–27), while the remainder described population characteristics compatible with specified indications (17, 18). The most cited indications for ASD intervention were syncope and/or evidence of RV failure (16, 19–27). In earlier studies, the procedural technique was blade or balloon atrial septostomy, transitioning largely to balloon atrial septostomy and more recently to static ASD creation with balloons, atrial septal stent placement, and fenestrated ASD devices with the ability to regulate flow. One study included patients who did not undergo ASD intervention, but comparisons were not made among children only (17). Two studies coreported on several patients, and though we were not able to determine the degree of overlap with absolute certainty, careful review suggested that five or fewer children were presented in both texts (16, 22). Data were available for the following critical outcomes.

Mortality. Among 153 children who underwent ASD intervention, there were 18 "early" deaths (18/153 = 12%). We considered early mortality to include death during the procedure or within 30 days of the procedure. Comparing studies published before 2010 (16–22) with those published after 2010 (23–27), early mortality was lower in more recent years (14/93 = 15% vs. 4/60 = 7%). Nonearly or "late" deaths were consistent across time periods at 15% (14/93 = 15% vs. 9/60 = 15%), with a wide range of follow-up times (ranging from 0.04 to 7 yr, with a median follow-up duration of 2.3 yr when follow-up was reported as a median).

Syncope. In Law and colleagues (2007), of 33 patients surviving 30 days, 14 had symptoms of syncope before septostomy, and there were no reported episodes of syncope occurring in patients surviving >30 days (22). Of the remaining nine studies that reported child-specific data related to postprocedural syncope, descriptive results were also consistent, with fewer patients experiencing syncope after septostomy creation (16–21, 24, 25, 27).

Lung transplantation and lung transplantation–free survival. Lung transplantation was relatively infrequent, with 12 lung transplants reported among 132 patients who underwent ASD intervention (16, 17, 20–26). At last follow-up, 60% (79 of 132) of patients were alive and transplantation free over a wide range of follow-up times (including lung and heart and lung transplantation free). In Law and colleagues (2007), survival time for patients alive after 30 days was censored at the date of last follow-up or at the time of transplantation (22). The NIH registry survival probability equation was used to calculate the probability of survival before and after ASD intervention for the patients alive after 30 days. For patients surviving 30 days after ASD intervention, the probability of survival at 1, 2, and 3 years improved from 66% to 73%, 53% to 62%, and 42%–52%, respectively. The actuarial event-free survival of patients alive at 30 days at 1, 2, and 3 years was 84%, 77%, and 69%, respectively (22).

Procedure-related cardiac arrest. Among 153 patients undergoing ASD intervention (16–27), there were three reported intraprocedural deaths (17, 22) and two episodes of cardiac arrest with survival, including one patient with pre-procedural cardiac arrest (20).

Functional class and symptoms. Functional class was reported using either the WHO or the New York Heart Association functional class scale. In three studies, comparison of functional class before and after ASD intervention demonstrated improvement after ASD creation (20, 22, 24). Findings from two descriptive studies were consistent with comparative studies, with improvements in functional class after ASD intervention (17, 19), whereas in two other descriptive studies, evidence of improvement in functional class was less clear (21, 25). Five studies described symptomatic alleviation after ASD intervention (17, 18, 20, 21, 24), consistent with reports of improved functional class.

Neurologic events. One study explicitly noted the absence of stroke (23).

Important outcomes with available data included reintervention, PH medications, exercise tolerance, thromboembolic events, and 6-minute-walk distance (6MWD). These are described in the data supplement within the GRADE evidence table for PICO 1.

Certainty of the evidence. For all outcomes, both critical and important, the certainty of evidence was very low because of the observational nature of existing evidence together with *1*) variable follow-up times within and across studies, *2*) residual confounding in studies in which comparisons were made using unadjusted analyses, *3*) the absence of direct comparison of outcomes for patients who did and did not receive the intervention, *4*) small sample sizes and/or few events overall, and *5*) potential publication bias. Given the certainty of evidence, there is very low confidence in the reported effects.

Recommendation 1: We suggest ASD intervention (creation and/or enlargement) for children with progressive PH and RV failure despite optimal therapy (conditional recommendation, very low certainty of evidence).

Justification and implementation considerations. The panel discussed several key factors when developing this recommendation, with an emphasis on the role of ASD intervention in mitigating symptoms versus managing the underlying disease. Although evidence suggests that ASD intervention is associated with a reduction in syncopal events, there is an unclear link between resolution of syncope and prevention of death or delaying the need for transplantation among children with progression of PH despite optimal therapy. The panel also expressed concerns about inconsistent findings related to other patient-centered outcomes after ASD intervention, including the ability of ASD intervention to reliably improve functional class. However, the panel also considered the evolution of the approach to ASD intervention over time, with the procedure moving from balloon atrial septostomy to static ASD creation with balloons and placement of atrial stents or fenestrated atrial septal devices. Stents and fenestrated devices provide a more controlled process for an ASD intervention, and the evidence suggests that in recent years, the procedure may be safer. Notably, the development of novel devices, including an atrial flow regulator–type device (28, 29), has facilitated safer ASD intervention, while the use of radiofrequency-assisted perforation to create the initial ASD has made the procedure safer than the original transseptal needle puncture (30–35). In addition, ASD intervention, unlike some other procedures, such as pulmonary-to-systemic shunt creation, is performed by a large number of physicians who have significant experience creating a septostomy for a variety of conditions, not just the management of PH. Overall, the potential benefits of ASD intervention (e.g., resolution of syncope) were believed to outweigh the potential harms (e.g., procedural mortality) when patient selection is done thoughtfully in patients with RV failure and the procedure is performed at a center with personnel experienced in both ASD intervention and the management of advanced pediatric PH. Other important considerations pertain to possible planned subsequent interventions, such as either pulmonary-to-systemic shunt creation or lung transplantation. The presence of an atrial-level communication can complicate the conduct of those procedures as well as possibly affect subsequent outcomes; multidisciplinary discussion would be warranted in that regard. The term "RV failure" was added to the recommendation because the purpose of ASD intervention is to be a volume-unloading shunt for the right ventricle to improve its function in children with PH, particularly in the setting of acute RV failure with loss of forward flow through the pulmonary vasculature.

Question 2: Should Children with Progressive PH despite Optimal Therapy Undergo the Creation of a Pulmonary-to-Systemic Shunt?

Background. Similar to ASD intervention, the creation of a pulmonary-to-systemic shunt using a transcutaneous or surgical approach can offload the right ventricle and improve overall cardiac output at the expense of decreased systemic oxyhemoglobin saturation distal to the shunt insertion. In contrast to ASD intervention, normally saturated blood flow is maintained to the cerebral and coronary artery circulations. However, the left upper extremity, gastrointestinal tract, and lower extremities will receive more deoxygenated blood. Importantly, a pulmonary-to-systemic shunt reduces systolic pressures in the right ventricle, whereas an ASD provides relief only when RV diastolic pressures are elevated, typically a late, end-stage process. Thus, a pulmonary-to-systemic shunt has the potential to intervene earlier in a child's disease course compared with ASD intervention. Over time, the approach to shunt creation has evolved and now includes the use of a unidirectional-valved shunt in patients with suprasystemic pulmonary arterial pressure and poor RV function (36). Many centers offering pulmonary-to-systemic shunt as a treatment option are applying this novel approach, which eliminates the potential for a detrimental left-to-right shunt in the patient who does not have consistently suprasystemic right-sided pressures. To better understand the relationship between pulmonary-to-systemic shunt creation and patient-centered outcomes, the panel asked, should children with progressive PH despite optimal therapy undergo the creation of a pulmonary-to-systemic shunt?

Summary of the evidence. A systematic review of the literature identified 16 observational studies that met our inclusion criteria and provided the highest tier evidence related to the creation of pulmonary-to-systemic shunt in children with PH (36–51). Ten studies included children only (37–42, 44, 48, 50, 51). For the remaining studies, child-specific data were available for two (36, 43). Four studies included adults and did not provide child-specific data, but all had a mean or median age less than 18 years (45–47, 49). Across all studies, there was a total of 388 participants, with 263 patients receiving pulmonary-to-systemic shunts. Some patients are coreported in Grady and colleagues (2021), although it is unclear how many (those with shunts done before 2021 are most likely to be among potential coreports) (45). Nine studies provided some detail about the indication for a shunt (37, 39, 41, 43, 45–49), while the remainder described population characteristics compatible with specified indications (36, 38, 40, 42, 44, 50, 51). The most cited indication for a shunt was clinical worsening despite maximal medical management, where maximal medical management typically referred to receipt of a multidrug regimen. Descriptions of clinical worsening before shunt placement included deteriorating or sustained poor functional class, worsening signs or symptoms, recurrent syncope, and reduction in 6MWD. For studies in which shunt details were reported, the majority were surgical shunts, followed by transcatheter stenting of the patent ductus arteriosus (PDA) and then transcatheter shunt creation. Length of postprocedural

follow-up was variable. Four studies included patients who did not receive shunts (42, 43, 46, 47), and of those, three made direct comparisons between those with and without shunts (43, 46, 47). Data were available for the following critical outcomes.

Mortality. Using child-specific data where available, and all data where child-specific information was not provided, there were 43 early deaths among 257 patients receiving shunts (43/257 = 17%; of the 263 individuals with shunts, the denominator excludes five adults and one patient still hospitalized at study end). We considered early mortality to include death during the procedure or the immediate postoperative period, as well as inpatient death. In Grady and colleagues (2021), an adjusted analysis identified transcatheter shunt creation as a risk factor for early mortality (hazard ratio [HR], 3.2 [90% confidence interval (CI)], 1.1–9.5) (45). Late deaths were reported for 9% (22 of 257), but the median length of follow-up was variable, reducing confidence in the ascertainment of late deaths. In Bobhate and colleagues (2021), mean survival for patients undergoing pulmonary-to-systemic shunt ($n = 16$, including 4 adults) was 28 $\pm$ 4 months versus 13.6 $\pm$ 2.7 months for patients who did not receive shunts ($n = 36$, number of adults unknown) (43). In Lancaster and colleagues (2021), which included patients younger than 21 years, operative mortality was 20% (4 of 20) for a surgical pulmonary-to-systemic shunt and 6% (2 of 31) for lung transplantation, and postoperative survival of the patients undergoing pulmonary-to-systemic shunt was not different than that of lung transplant recipients (47). Importantly, of the four early deaths in patients undergoing surgical pulmonary-to-systemic shunt, three occurred in patients who were on ECMO before the shunt procedure (47). Since the publication of Lancaster and colleagues (2021), 21 additional surgical pulmonary-to-systemic shunts have been performed, with only one mortality (P. Eghtesady, M.D., Ph.D. and R. M. Grady, M.D., written communication, October 2024).

Functional class and symptoms. Fifteen studies reported data related to functional class (36–50), with six providing analyses of pre- and post-shunt functional class. Of these six, five noted significant improvement in functional class after shunt creation (37, 40, 45, 47, 49), whereas one did not (39). In general, findings from descriptive studies were consistent with comparative studies, with improvements in functional class after shunt creation (36, 38, 41–44, 46, 48). Two studies reported specific information on symptoms. Lancaster and colleagues (2021) noted that 83% (15 of 18) of surviving shunt patients reported subjective improvement in their overall functional status and absence of symptoms of RV failure (47). Rosenzweig and colleagues (2021) noted the resolution of exertional chest pain after shunt creation (36).

Lung transplantation and lung transplantation–free survival. Lung transplantation was relatively infrequent, with 10 transplants reported among 254 shunt patients (of the 263 individuals with shunts, the denominator excludes four patients from a study that did not mention lung transplantation and five adults) (36–47, 49–51). For those who underwent lung transplantation and for whom outcomes were reported ($n = 7$), two deaths occurred (45, 51). At last follow-up, 72% (183 of 254) of shunt patients were alive and transplantation free, including lung and heart and lung transplantation free, over a wide range of follow-up times (ranging from a median of 0.5–6.45 yr, with a median follow-up duration of 2.2 yr) (36–47, 49–51).

Procedural complications. Major complications as reported (for which some authors included death) ranged from 0% to 67% of cases (36–39, 43, 44, 46, 47, 51). Lancaster and colleagues (2021) reported major complications in 35% (7 of 20) of patients receiving pulmonary-to-systemic shunts, compared with 81% (25 of 31) of lung transplant recipients (47). Major complications were not described for those undergoing lung transplantation, but for those receiving shunts, complications included mechanical ventilation for >7 days, reintubation, reexploration for postoperative bleeding, cardiac arrest, and distal spinal cord ischemia.

6-Minute-Walk Distance. Five studies reported analyses of pre- and post-shunt 6MWD, and of these, two reported significant improvement (37, 45) whereas three did not (39, 47, 49). In Baruteau and colleagues (2015), among 19 long-term survivors without transplantation, mean pre-shunt 6MWD was 260.2 $\pm$ 85.1 m ($n = 9$ patients), and mean post-shunt 6MWD was 522.6 $\pm$ 93.2 m ($n = 12$ patients) at last follow-up (37). Grady and colleagues (2021) reported pre- and post-procedure 6MWD for 30 patients, and mean distance improved from 363 to 406 m (45). Descriptive findings from two studies were consistent with improvements in 6MWD (40, 44).

Syncope. Two studies reported analyses of pre- and post-shunt syncope (37, 49), with one noting a reduction in syncope after shunt creation (37). Findings from four descriptive studies were consistent, with fewer patients experiencing syncope or presyncope after shunt creation (36, 40, 43, 44).

Neurologic events. Spinal cord dysfunction was reported in two studies, affecting one patient in each, where one child experienced transient paraplegia on Postoperative Day 3 and another experienced distal spinal cord ischemia with lower extremity weakness with improvement at last follow-up (37, 47). Anoxic brain injury occurred in three patients who experienced cardiac arrest (39, 44).

Important outcomes with available data included PH medications, length of hospital stay, growth, reintervention, and shunt takedown at the time of lung transplantation. These are described in the data supplement within the GRADE evidence table for PICO 2.

Certainty of the evidence. For all outcomes, both critical and important, the certainty of evidence was very low because of the observational nature of existing evidence together with *1*) variable follow-up times within and across studies; *2*) residual confounding in studies in which comparisons were made using unadjusted analyses; *3*) the minority of studies included patients without a shunt, and when comparisons were made, the minority were direct comparisons across groups (i.e., shunt vs. no shunt); *4*) small sample sizes and/or few events overall; and *5*) potential publication bias. Given the certainty of evidence, there is very low confidence in the reported effects.

Recommendation 2: We suggest the creation of a pulmonary-to-systemic shunt in children with progressive PH and suprasystemic RV pressure despite optimal therapy (conditional recommendation, very low certainty of evidence).

Justification and implementation considerations. On the basis of the available evidence, the desirable anticipated effects of shunt creation were believed to be moderate, with this judgment influenced by improvements in functional class after shunt creation and the ability to delay the need for transplantation. The association between shunt creation and a reduction in PH medication needs (an important outcome) also influenced this determination (37, 45, 47). Related to undesirable anticipated effects of shunt creation, consideration was given to the following issues: *1*) changes to the procedure

over time, including improvements in technique and selection of candidates for the procedure (e.g., avoidance of those on ECMO); *2*) center experience, in terms of managing patients with severe PH; *3*) and approach taken, where some approaches to shunt creation may contraindicate future lung transplantation. These factors informed the judgment that the undesirable effects may vary. Overall, the potential benefits of shunt creation (e.g., improvements in functional class and delayed need for lung transplantation) were believed to outweigh the potential harms (e.g., early mortality). When patient selection is done thoughtfully and the procedure is performed at a center with significant experience in both the creation of pulmonary-to-systemic shunts, and the management of advanced pediatric PH, and the use of mechanical circulatory support in patients with pulmonary vascular disease (PVD), early mortality may be reduced or at least remain comparable with other cardiac procedures in patients with complex disease processes. Other key considerations yet to be ascertained are surgical versus transcatheter shunt creation in children without PDA or PDA remnant, the longevity or durability of the valved conduits currently being used for creation of the surgical shunts, the longevity of the circulation, and the potential for lung transplantation after pulmonary-to-systemic shunt procedures. The term "suprasystemic PH" was added to the recommendation because the purpose of the pulmonary-to-systemic shunt is to be a pressure-unloading shunt for the right ventricle to improve its function in children with suprasystemic pulmonary arterial pressures.

Question 3: Should Children with Progressive PH despite Optimal Therapy Undergo Lung Transplantation?

Background. Atrial or systemic shunts are often considered palliative treatment options for children with PH, whereas lung transplantation may be viewed as a definitive treatment approach because of an allograft having normal pulmonary vasculature. However, pediatric lung transplantation carries its own attendant risks, and outcomes remain less than ideal (50–60% 5-yr survival) (52). Moreover, there are limitations imposed by organ availability and center experience, meaning that pediatric lung transplantation is less available and occurs less frequently compared with adult transplantation. This led the panel to ask, should children with progressive PH despite optimal therapy undergo lung transplantation?

Summary of the evidence. A systematic review of the literature resulted in 12 observational studies that met our inclusion criteria and provided the highest tier evidence related to lung transplantation in children with PH (47, 53–63). Five of the 12 studies included adults, but all met prespecified age criteria for inclusion (47, 54, 56, 61, 62). Across all 12 studies, there was a total of 7,391 participants, with 1,007 undergoing lung transplantation for management of PH. A variety of comparisons were made, but most focused on disease groups (e.g., comparing patients with PH with those with cystic fibrosis). Data were available for the following critical outcomes.

Mortality. Overall, studies were suggestive of similar mortality after lung transplantation for children with PH as their transplantation indication (majority Group 1 PH) compared with children with other indications (e.g., cystic fibrosis), with some making direct comparisons across diagnostic categories (56, 58, 63). In Nelson and colleagues (2021), after transplantation, 1-year mortality risks were higher with a diagnosis of PH (HR, 1.478 [95% CI, 1.105–1.976]); however, in the 5-year survival analysis for recipients surviving the first post-transplantation year, a diagnosis of PH was associated with a lower risk of death (HR, 0.693 [95% CI, 0.511–0.973]) (59). In Ahmed and colleagues (2024), at 1, 5, and 10 years after transplantation, patients with PVD had survival rates of 81%, 58%, and 44%, and patients with other diagnoses had survival rates of 81%, 50%, and 35%, respectively, with no significant differences between the groups in both early and modern eras (63).

Complications (e.g., infection, development of cancer). Complications reported included primary graft dysfunction (PGD), infection, and post-transplantation lymphoproliferative disease (55, 56, 62). One study comparing the diagnostic groups of diffuse lung disease, cystic fibrosis, and PVD found no differences among the three groups with respect to time to post-transplantation lymphoproliferative disease at 1 and 5 years or in the number of respiratory, nonrespiratory, bacterial, viral, and fungal infections ($N = 104$, $n = 16$ with "PVD") (56).

Functional class. In Schaellibaum and colleagues (2011), among children with idiopathic pulmonary arterial hypertension listed for transplantation ($n = 23$), 61% were in WHO class IV, 26% in WHO class III, and 13% in WHO class II (55). At six months, most survivors ($n = 21$) had improvements in WHO functional class: 82% were in class I, 13% in class II, and 5% in class III (55).

Important outcomes with available data included acute or chronic rejection after lung transplantation and operative complication (e.g., bleeding). These are described in the data supplement within the GRADE evidence table for PICO 3.

Certainty of the evidence. For all outcomes, both critical and important, the certainty of evidence was very low because of the observational nature of existing evidence together with *1*) variable follow-up times within and across studies; *2*) residual confounding in studies in which comparisons were made using unadjusted analyses; *3*) comparisons were related mostly to diagnostic groups, and none directly compared patients with PH who did versus did not undergo lung transplantation; *4*) small sample sizes and/or few events overall; and *5*) potential publication bias. Given the certainty of evidence, there is very low confidence in the reported effects.

Recommendation 3: We suggest lung transplantation in children with progressive PH and RV failure despite optimal therapy (conditional recommendation, very low certainty of evidence).

Justification and implementation considerations. For children with progressive PH who have been listed for lung transplantation, the desirable effects of transplantation center largely on the survival benefit, whereas the undesirable effects relate more to the chronic complications incurred with solid organ transplantation. Overall, the evidence favors the intervention, given the lack of other alternatives for children with advanced disease. However, the panel acknowledges that not all patients will have the option for lung transplantation, that organs are a scarce resource, and that even when eligible, not all patients and their family members will be able to proceed with transplantation, because of geographic constraints and the limited availability of pediatric lung transplantation programs in the United States and globally. The term "RV failure" was added to the recommendation because the purpose of lung transplantation is to reduce elevated pulmonary arterial pressures and improve RV function in children with PH. Last, it is

important to note that combined heart and lung transplantation for PH is reserved for the rare situations of uncorrectable congenital heart disease, coexisting LV dysfunction, and technical issues such as massive right heart enlargement in young children, donor lung constraints, and lower likelihood of airway caliber compromise with tracheal versus bibronchial anastomoses in small children (as the child grows).

Question 4: Should Children with Progressive PH despite Optimal Therapy on ECMO Undergo Lung Transplantation?

Background. ECMO provides cardiopulmonary support to sustain life and allows children with PH to either recover from critical illness or undergo bridging to optimization of medical therapy, palliative shunt creation, or transplantation. VA or VV modes of ECMO provide cardiac, pulmonary, or cardiopulmonary support depending on configuration as deployed by the treating physician. The approach to mode and configuration of ECMO support is dictated by several factors, with the severity of RV dysfunction and the need to offload a failing right ventricle influencing these approaches for children with PH. Most important, when ECMO is planned to be used as a bridge to transplantation, pharmacotherapies treating the PH should be optimized and prolonged endotracheal intubation avoided if possible, coupled with active efforts to rehabilitate patients with physical therapy, avoid or minimize sedatives and neuromuscular blockade, and improve nutrition status (64–66). However, when full cardiopulmonary support requiring VA ECMO is needed for children with PH, cannula configuration and securement can be challenging when attempting to facilitate rehabilitation, especially ambulation, often requiring unique configurations to accomplish the aforementioned goals (67). The growing use of ECMO in children with PH, coupled with concerns about outcomes for those requiring this degree of support, led the panel to ask, should children with progressive PH despite optimal therapy who are on ECMO undergo lung transplantation?

Summary of the evidence. A systematic review of the literature identified eight observational studies that met our inclusion criteria and provided the highest tier evidence related to lung transplantation in children with PH who were on ECMO before transplantation (67–74). Studies providing details on ECMO configuration noted predominantly the use of VA ECMO for participants (67, 68, 72–74). Data were available for the following critical outcomes.

Mortality, including death on ECMO. Among children with PH on ECMO before lung transplantation ($n = 14$), there was one early death (7%, within 30 d or before hospital discharge), and there were four late deaths (29%, with variable follow-up times within and across studies). Of those with PH who were not on ECMO before lung transplantation ($n = 36$), three experienced early death (8%) and five experienced late death (14%, with variable follow-up times within and across studies). In Bridges and colleagues (1996), one child remained on ECMO and died on Postoperative Day 6 (71).

Time on ECMO. All eight studies reported the duration of ECMO before lung transplantation. For those with PH on ECMO before transplantation, the average time on ECMO before transplantation was 18.6 days (range, 1–68 d) (67–74). Five studies reported post–lung transplantation ECMO duration (68, 69, 71, 72, 74), where children with PH on ECMO before transplantation had a mean post-transplantation ECMO time of 4 days (range, 0–12 d), and for those with PH on post-transplant ECMO only, the mean time on ECMO was 11 days (range, 3–34 d) (68, 69, 71, 72, 74). Significant variability in support times was likely influenced by a multitude of factors, including wait time for donor organs, ECMO configuration, patient age, and transplantation center experience.

Complications due to ECMO or otherwise. Complications experienced by children with PH on pretransplantation ECMO included arterial cannulation site issues requiring surgical intervention, including surgical thrombectomy and embolectomy with vascular reconstruction (72); vascular perforation during cannulation with mediastinal hemorrhage requiring thoracotomy (74); and post-transplant bleeding requiring reoperation (67).

Neurologic events or neurocognitive outcomes. Neurologic deficits were explicitly mentioned in only one study, in which none were observed (74). In addition, in Stephens and colleagues (2023), there were no significant neurologic events in the cohort (R. Coleman M.D., written communication, June 2024) (67).

Acute or chronic rejection after lung transplantation. Relevant information was provided in one study, in which one child who required ECMO before lung transplantation had several episodes of rejection (all children in the study had at least one episode of rejection) (69).

Important outcomes with available data included length of hospital stay and hospitalizations. These are described in the data supplement within the GRADE evidence table for PICO 4.

Certainty of the evidence. For all outcomes, both critical and important, the certainty of evidence was very low because of the observational nature of existing evidence together with *1*) variable follow-up times within and across studies, *2*) residual confounding in studies in which comparisons were made using unadjusted analyses, *3*) lack of direct comparison groups, *4*) extremely small sample sizes and/or few events overall, and *5*) potential publication bias. Given the certainty of evidence, there is very low confidence in the reported effects.

Recommendation 4: We suggest lung transplantation in children with progressive PH and RV failure despite optimal therapy who are on ECMO support without reversible cause (conditional recommendation, very low certainty of evidence).

Justification and implementation considerations. Although we did identify some evidence related to our PICO, the number of included children was very small. On the basis of the clinical experience of panel members, there were concerns about underreporting of deaths for children with PH placed on ECMO, particularly VA ECMO, as a bridge to lung transplantation. In addition to concerns about underreporting of outcomes, the panel also acknowledged that substantial center practice variability occurs, including center-specific existing restrictions on transplantation of patients on VA ECMO, all of which limit the available data. Although the panel recounted experiences with success, particularly with VV ECMO (in the setting of a coexistent atrial communication), they agreed that patients with requirement for ECMO before lung transplantation would likely experience more difficulty postoperatively. However, the panel believed that with the evolution of novel cannulation approaches (67) and growing experience managing children on ECMO before transplantation (75–77), it is reasonable to proceed with lung transplantation for children with PH who are on ECMO support at centers with given expertise and success using this approach. Serious discussions about candidacy should

be a part of the decision-making process for these children, given the potential for unfavorable outcomes. For those requiring emergent ECMO, similar conversations should occur regarding morbidity and mortality. The panel engaged in significant discussion about patient selection and ultimately supported the recommendation in the context of children with single-organ (lung) failure, who are neurologically intact and fully awake with minimal to no sedation, actively participating in some form of physical rehabilitation, preferably ambulating, and receiving primarily enteral nutritional support. The term "RV failure" was added to the recommendation because the purpose of lung transplantation is to reduce elevated pulmonary arterial pressures and improve RV function in children with PH. In addition, clarity was provided to acknowledge that for our recommendation, we consider it important that ECMO be applied in the absence of a reversible cause. In the setting of accelerating RV failure on ECMO cannulated peripherally where central cannulation or placement of a paracorporeal lung assist device (PLAD) may be needed (78–80), the panel supported these same recommendations because of an even higher risk for unfavorable outcomes if transplantation is not pursued. If central ECMO cannulation or a PLAD is required for a child with progressive PH on peripheral ECMO without reversible cause, the panel universally agreed that this should occur at a center with expertise and experience with this high degree of care. One key consideration includes the potential morbidity from ECMO cannulation procedure if this entails a median sternotomy and the use of cardiopulmonary bypass, similar to the situation with a surgical pulmonary-to-systemic shunt. ASD intervention can be an alternative strategy to preclude emergent peripheral ECMO support for bridging to lung transplantation in children with PH who require ECMO without reversible cause (81). In most cases, regardless of the need for peripheral or central ECMO cannulation or a PLAD, lung transplantation is the procedure of choice, as RV function will recover after transplantation irrespective of the severity of RV adverse remodeling.

Regarding postoperative risks in children with PH undergoing lung transplantation, PGD is a specific concern. A single-center study identified that severe or grade 3 PGD after transplantation occurs more frequently in children with PH compared with those with other lung diseases (82), with anecdotal experience among panel members that ECMO support in children with PH further increases the risk for PGD. Thus, the panel believes that a mitigation strategy is reasonable to offset post-transplantation complications for children. Presently, no PGD-specific therapy exists, and supportive care remains paramount, with the early initiation of ECMO an increasingly used approach in adults with PGD (83). Despite the lack of evidence in pediatric lung transplantation, post-transplantation ECMO to mitigate the risks of PGD should be considered with the need to balance the benefits against the risks of ECMO, such as bleeding or stroke.

Question 5: Should Children with Progressive PH Unresponsive to Optimal Therapy on ECMO Undergo the Creation of a Pulmonary-to-Systemic Shunt?

Background. Similar to ECMO bridge to lung transplantation, there are limited data on children with PH receiving ECMO and undergoing pulmonary-to-systemic shunt. Because of concerns related to mortality when creating shunts for patients on ECMO and for those who survive shunt placement, the panel asked, should children with progressive and suprasystemic PH despite optimal therapy receiving ECMO undergo the creation of a pulmonary-to-systemic shunt?

Summary of the evidence. A systematic review of the literature identified four observational studies that met our inclusion criteria and provided the highest tier evidence available related to pulmonary-to-systemic shunt creation in children with PH on ECMO (45, 47, 48, 84). Across all studies, there was a total of 175 participants, with 144 patients receiving pulmonary-to-systemic shunts. Of the 144 receiving shunts, 17 were on ECMO at the time of shunt creation. Data were available for the following critical outcomes.

Mortality. Of the 17 children placed on ECMO before shunt, 11 experienced early death (11/17 = 65%) (45, 47, 48, 84). Early mortality included death in the immediate postoperative period, as well as inpatient death (before postoperative discharge). There were insufficient data to allow reporting of late deaths. In Grady and colleagues (2021), the use of ECMO was associated with early mortality for patients receiving shunts (HR, 5.1 [90% CI, 1.9–13.2]) (45). In that study, pre-procedural ECMO was associated with late death or transplantation (HR, 6.5 [95% CI, 1.8–23]) in a univariate analysis, but the association did not persist after adjustment (45).

Complications related to ECMO. One study reported thrombus formation in the ECMO bladder at hour 17 (84).

Important outcomes with available data included length of hospital stay. This outcome is described in the data supplement within the GRADE evidence table for PICO 5.

Certainty of the evidence. For all outcomes, both critical and important, the certainty of evidence was very low because of the observational nature of existing evidence together with *1*) a lack of direct comparison groups and *2*) extremely small sample sizes and/or few events overall. Given the certainty of evidence, there is very low confidence in the reported effects.

Recommendation 5: We suggest against pulmonary-to-systemic shunt creation for children with progressive PH and suprasystemic RV pressure despite optimal therapy who are on ECMO support without reversible cause (conditional recommendation, very low certainty of evidence).

Justification and implementation considerations. Very few data were available to inform this recommendation. Children with PH on ECMO are a very high-risk group of patients, and panel members raised concerns, on the basis of their clinical experience, about poor outcomes after shunt creation. Moreover, there were concerns that a recommendation for the intervention might lead clinicians to consider shunt creation equivalent to lung transplantation for children on ECMO, with transplantation currently being the preferred intervention in this situation. However, when transplantation is not an option, because of candidacy or otherwise, the appropriateness of shunt creation may be considered. In instances in which a decision is made to pursue a shunt in a child with PH requiring ECMO support, as with shunt creation in general, careful patient selection is paramount, with the procedure performed at a center with personnel experienced in the both the creation of pulmonary-to-systemic shunts and the management of pediatric PH. The term "suprasystemic PH" was added to the recommendation because the purpose of the pulmonary-to-systemic shunt is to be a pressure-unloading shunt for the right ventricle to improve its function in children with suprasystemic pulmonary arterial

pressures. As above for PICO 4, clarity was provided to acknowledge that for our recommendation, we consider it important that ECMO be applied to a child in the absence of a reversible cause of their cardiopulmonary failure.

Additional Considerations: Beyond Pulmonary Arterial Hypertension

Although the recommendations in this guideline focus on a population composed largely of children with Group 1 PH or pulmonary arterial hypertension whose optimal therapy is PH-specific pharmacotherapies, we provide additional considerations related to other important etiologies of PH in children that can progress disease despite optimal therapy.

WHO Group 3: PH Due to Lung Disease and/or Hypoxemia

PH is classified as Group 3, related to underlying lung disease and/or hypoxemia, in up to one-third of affected children (85). Bronchopulmonary dysplasia (BPD) is the most common underlying diagnosis; screening echocardiography is recommended for infants with severe BPD and for those not improving as expected (8, 85). Patients with severe BPD–PH have high mortality; however, PH typically resolves in those who survive (86, 87). Congenital diaphragmatic hernia and other causes of pulmonary hypoplasia also commonly result in PH, which typically resolves with time and lung growth (85, 88). Children with severe lung disease, as well as those with recurrent hypoxemia due to sleep-disordered breathing, are at risk for PH (85). As such, screening echocardiography is recommended for children with advanced diffuse lung disease or severe obstructive sleep apnea (8).

The foundation for managing Group 3 PH in children is to treat the underlying lung disease, minimize further insults to the lungs, avoid atelectasis, and normalize oxygenation and ventilation when possible (8). Despite concerns that indiscriminate dilation of the pulmonary vasculature could worsen $\dot{V}/\dot{Q}$ mismatch in patients with lung disease, sildenafil is often successfully used in infants with BPD and in congenital diaphragmatic hernia (85, 88–90). Although inhaled treprostinil is efficacious in PH associated with interstitial lung disease in adults, and appears to be safe in children, there are currently no published data regarding the use of inhaled treprostinil in children with PH associated with lung disease (91, 92). Lung transplantation is an accepted treatment option for children with Group 3 PH who have progressive disease despite optimal therapy, but their long-term outcomes after transplantation are less favorable compared with those with Group 1 PH (52). The creation of a pulmonary-to-systemic shunt or an ASD intervention in children with severe Group 3 PH may exacerbate any underlying hypoxemia and thus may be contraindicated. In addition, one study suggested higher early mortality in children with Group 3 PH who undergo pulmonary-to-systemic shunt compared with children with Group 1 or 2 PH (45).

WHO Group 4: PH Due to CTEPH

CTEPH results from the organization of thromboembolic material within the pulmonary vasculature (93). CTEPH is a rare cause of PH in children, accounting for fewer than 1% of pediatric PH cases (85, 94). Classic risk factors for pulmonary embolism, such as hypercoagulability and immobility, are common in patients with CTEPH (95–99). However, only a minority of pediatric patients with CTEPH have a known pulmonary embolism preceding the development of their PH (95). Chronic indwelling catheters in the right atrium (including central venous catheters and ventriculoatrial shunts) are a risk factor for CTEPH in children (100–111). There are also multiple reports of CTEPH in children with Behçet's disease (112, 113). Imaging (typically $\dot{V}/\dot{Q}$ scan) to evaluate for CTEPH should be performed as part of the initial diagnostic workup for CTEPH, especially in the absence of significant lung disease (2, 8).

PEA is the first-line treatment for eligible patients (114). PEA has been successfully completed in patients as young as six months (that patient weighed only 4 kg) (104). Children who undergo PEA have improvement in pulmonary hemodynamics and functional class, with low mortality (95). Balloon pulmonary angioplasty is an alternative for patients who are not candidates for PEA (114). Pulmonary vasodilators, particularly riociguat, may also be used (114).

PH due to PVS

Pulmonary vein stenosis (PVS) is a cause of PH in children that requires a multidisciplinary, coordinated, and often aggressive management approach. Infants with BPD and those with histories of complex congenital heart disease or anomalous pulmonary vein repair are at risk for PVS (115, 116). Computed tomography or magnetic resonance angiography and echocardiography are complementary noninvasive methods of evaluating for PVS, while cardiac catheterization is the gold standard (116–118). Chest imaging may reveal interlobular septal thickening, ground-glass opacities, and hilar enlargement (119).

Select patients with single-vein disease can be monitored without intervention (120). However, patients with more severe or multivessel disease require intervention, either surgical repair or catheter-based approaches, including stent placement and balloon angioplasty (121, 122). In patients with severe disease, antiproliferative agents such as sirolimus reduce in-stent stenosis and decrease mortality (123–125). PVS has historically been associated with high mortality, but with a multifaceted approach including the use of drug-eluting stents, frequent reintervention, and sirolimus or other antiproliferative medications, the outlook is improving (116, 122–126). Lung transplantation is an accepted treatment option for refractory cases of PVS (127). Early referral for consideration of transplantation is recommended to optimize chances for the best outcomes in children with refractory PVS.

PCH and PVOD

Pulmonary capillary hemangiomatosis (PCH) and pulmonary veno-occlusive disease (PVOD) are closely related disorders that are classified together by the WSPH as pulmonary arterial hypertension with overt features of venous or capillary involvement (2, 128). PCH is characterized by abnormal proliferation of alveolar capillaries; the pathologic hallmarks of PVOD are narrowing and fibrosis of inter- and intralobular pulmonary veins (129). PCH/PVOD accounts for fewer than 3% of cases of pediatric PH (3, 4, 85, 94). Patients with hereditary PCH or PVOD typically have mutations in *EIF2AK4*; this mutation may also be identified in young patients without family histories of PCH or PVOD (128, 130). Receipt of chemotherapeutic agents is also a risk factor for the development of PCH or PVOD (131).

PCH or PVOD should be suspected in patients with PH who have chest imaging notable for nodular ground-glass opacities, interlobular septal thickening, and/or lymphadenopathy (130, 132, 133). Pulmonary edema, at times severe, may develop with the use of pulmonary vasodilators. However, many patients with PCH or PVOD derive some benefit from carefully titrated pulmonary vasodilator therapy balanced with concomitant diuretic use (130, 134). Given increased risk and potentially limited benefit of pulmonary vasodilators in PCH or PVOD, caution should be used with the initiation and titration of pulmonary vasodilators. Early referral for lung transplantation evaluation is highly recommended for a child with PCH or PVOD (8).

Limitations and Future Research

Because of the limitations of the identified evidence, we chose not to make strong recommendations. Most studies were single-center experiences with small cohorts that did not expand on long-term outcomes, which limits their applicability and suggests that much is still to be learned from how we approach the management of children with progressive disease despite optimal therapy. To address the limitations of currently available data, multicenter studies are needed to investigate each of our recommendations more comprehensively. Specific areas of focus should include the best approach and timing for ASD intervention or pulmonary-to-systemic shunt, the timing of referral for lung transplantation, and optimal management strategies for ECMO as a bridge to lung transplantation. For children with progressive and suprasystemic PH receiving ECMO who are not candidates for lung transplantation, it will be imperative to acquire more data from the select centers capable of performing pulmonary-to-systemic shunt placement to determine if it is a viable treatment option for this very high-risk group. Finally, there is an increasing role of early whole-genome sequencing in evaluating children with PH of all age groups, so these data will play a key role in both clinical care and research in the future.

Conclusions

Pediatric PH manifests as a spectrum of disease severity. There is a subgroup of children with PH who have unrelenting disease despite optimal therapy that will progress to RV failure resulting in death. Given the lack of clinical studies in the area of severe pediatric PH, this guideline will aid providers in their consideration of interventional strategies for children with severe PH that is progressing despite optimal therapy. The most important factor in determining therapy for a child with severe PH progressing despite optimal medical management is the local and regional resources and center experience for surgical treatment options. If limited access does exist, early consultation or early referral to centers with comprehensive surgical capability should be considered. One important caveat for children undergoing ASD intervention or pulmonary-to-systemic shunt for progressive PH is that the right ventricle continues to have systemic or potentially subsystemic pressures, which places the child at continued risk for disease progression. Moving forward, it will be essential to elucidate biomarkers to predict benefit from ASD intervention or a pulmonary-to-systemic shunt and to identify those who should proceed to an evaluation for lung transplantation. Moreover, it will be important to develop the best strategies for managing children with PH who are on ECMO without reversible causes for their clinical deterioration. Because of the limited experience of pathologies and treatments at any single center, an approach to consider for the pediatric PH population is to create a learning network, similar to ACTION (https://www.actionlearningnetwork.org), to identify and share best practices, decrease learning curves, and improve patient-centered outcomes. Last, there is a dire need to understand more about the perspectives of patients and family members of patients experiencing this highly morbid condition.

The recommendations in this guideline were reviewed by the ATS Quality Improvement and Implementation Committee, and none is considered suitable for performance measure development. ■

This official clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Pediatrics.

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