JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 19, 2020

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Challenges and Special Aspects of Pulmonary Hypertension in Middle- to Low-Income Regions

JACC State-of-the-Art Review

Babar Hasan, MBBS,[a] Georg Hansmann, MD, PHD,[b] Werner Budts, MD, PHD,[c] Alexandra Heath, MD, PHD,[d] Zahra Hoodbhoy, MBBS,[a] Zhi-Cheng Jing, MD, PHD,[e] Martin Koestenberger, MD,[f] Katharina Meinel, MD,[f] Ana Olga Mocumbi, MD, PHD,[g] Ganna D. Radchenko, MD, PHD,[h] Hannes Sallmon, MD,[i] Karen Sliwa, MD, PHD,[j] R. Krishna Kumar, MD,[k] on behalf of the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, CSC, PASCAR, PCS, and PCSI

ABSTRACT

Challenges and special aspects related to the management and prognosis of pulmonary hypertension (PH) in middle- to low-income regions (MLIRs) range from late presentation to comorbidities, lack of resources and expertise, cost, and rare options of lung transplantation. Expert consensus recommendations addressing the specific challenges for prevention and therapy of PH in MLIRs with limited resources have been lacking. To date, 6 MLIR-PH registries containing mostly adult patients with PH exist. Importantly, the global prevalence of PH is much higher in MLIRs compared with high-income regions: group 2 PH (left heart disease), pulmonary arterial hypertension associated with unrepaired congenital heart disease, human immunodeficiency virus, or schistosomiasis are highly prevalent. This consensus statement provides selective, tailored modifications to the current PH guidelines to address the specific challenges faced in MLIRs, resulting in the first pragmatic and cost-effective consensus recommendations for PH care providers, patients, and their families. (J Am Coll Cardiol 2020;75:2463–77) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Pediatrics and Child Health, The Aga Khan University, Karachi, Pakistan; [b]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany; [c]Congenital and Structural Cardiology, University Hospitals Leuven, Leuven, Belgium; [d]Division of Pediatric Cardiology, Kardiozentrum, La Paz, Bolivia; [e]Department of Cardiology, Peking Union Medical College Hospital & Key Lab of Pulmonary Vascular Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [f]Division of Pediatric Cardiology, Department of Pediatrics, Medical University Graz, Graz, Austria; [g]Instituto Nacional de Saúde, Vila de Marracuene, Maputo, Mozambique; [h]Secondary Hypertension Department with Pulmonary Hypertension Center, State Institute National Scientific Center, MD Strazhesko Institute of Cardiology of Ukrainian National Academy of Medical Science, and Bogomolets National Medical University, Kyiv, Ukraine; [i]Department of Pediatric Cardiology, Charité University Medical Center, Berlin, Germany; [j]Hatter Institute for Cardiovascular Research in Africa, Departments of Medicine and Cardiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; and the [k]Department of Pediatric Cardiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India. This research received no specific grant from any funding agency or industry, except for travel grants from the not-for-profit European Pediatric Pulmonary Vascular Disease Network. Dr. Hansmann was supported by the German Research Foundation (KFO311 HA4348/6-2). Dr. Budts has served on the Speakers Bureau, received honoraria as a consultant, and has served on the Advisory Board for Abbott (moderate) and Occlutech (moderate). Dr. Heath own shares of PFM S.R.L. (none of the products are related to this work). Dr. Koestenberger has served on the Advisory Board for Johnson & Johnson and Actelion (moderate). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Endorsing scientific societies: AEPC = Association for European Paediatric and Congenital Cardiology; CSC = Chinese Society of Cardiology; PASCAR = Pan African Society of Cardiology; PCS = Pakistan Cardiac Society; PCSI = Pediatric Cardiac Society of India.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2020.03.047

ABBREVIATIONS AND ACRONYMS

AVT = acute pulmonary vasoreactivity testing

CHD = congenital heart disease

COR = class of recommendation

echo = echocardiography

EPPVDN = European Pediatric PVD Network

HFpEF = heart failure with preserved ejection fraction

HIR = high-income region

LHD = left heart disease

LOE = level of evidence

MLIR = middle- to low-income region

PVD = pulmonary vascular disease

SCD = sickle cell disease

WSPH = World Symposium on Pulmonary Hypertension

Pulmonary hypertension (PH) is a complex condition that associates with multiple diseases and may affect several organs beyond the cardiovascular and respiratory systems. Challenges intrinsic to clinical programs in middle- and low-income regions (MLIRs) affect diagnosis and treatment of PH. These challenges range from lack of resources to cost of care, limited expertise, unpredictable availability of medications, and the extremely rare option of lung transplant (1–4). The disease spectrum is further complicated by late presentation and coexisting comorbidities (i.e., infections, malnutrition, and hypercoagulability). Additionally, lack of data from MLIRs leads to extrapolation of etiology, diagnosis, and management algorithms from high-income regions (HIRs) that may not address some of the contextual issues intrinsic to MLIRs (2,3).

The purpose of this expert consensus statement is to highlight the specific challenges in the diagnosis and treatment of PH in MLIRs. Following a pragmatic approach with clear cost-risk-benefit consideration, we developed a consensus statement with a focus on PH in children and young adults. This consensus statement does not replace but must be seen as supplementary to previously published recommendations and guidelines by the European Society of Cardiology (ESC) and European Respiratory Society (5), the American Heart Association/American Thoracic Society (6), the publications produced by the World Symposium on Pulmonary Hypertension (WSPH) 2018 (7–9) and the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) (10). We will not discuss all aspects of PH covered in the aforementioned papers. Health care practitioners from MLIRs are encouraged to read the ESC/European Respiratory Society guidelines (5), along with the update on pediatric PH provided by the WSPH and the 2019 updated guidelines of the EPPVDN (10), and then use this document to help modify practices contextualized to their own setting.

The current PH registries in MLIRs have minimal information on patients <18 years of age; thus, the suggested recommendations on the care of children with PH in this document are an extrapolation from both adults with PH in MLIRs and children with PH in HIRs (10); they are primarily based on expert opinion. Several etiologies in children and young adults living in MLIRs are discussed. The importance of such a document still exists given the challenges associated with such a disease in a limited resource environment as MLIRs.

HIGHLIGHTS

- PH in MLIRs is under-recognized; PAH due to CHD/HIV/schistosomiasis and group 2 PH (left heart disease) are more prevalent in MLIRs than in HIRs.
- Unmet need for specific, feasible recommendations for the diagnosis and treatment of PH in MLIRs.
- Here, an expert consensus panel proposes such recommendations for the global management of PH in MLIRs.
- PH registries and intensified collaborations between MLIRs are required.

METHODS

GOALS AND COMPOSITION OF THE EPPVDN WRITING GROUP (PH IN MLIRs). The EPPVDN is a registered nonprofit organization that strives to define and develop effective, innovative diagnostic methods and treatment options in all forms of PH (Supplemental Methods). Most recently the EPPVDN has revised their 2016 executive summary (11) to develop 2019 updated guidelines on pediatric PH (10) acknowledging the changes put forward at WSPH 2018 (7–9).

Here, we highlight and discuss the challenges and special aspects in the diagnosis and treatment of PH in MLIRs, and for the first time, give specific expert recommendations. This expert consensus statement is not restricted to pediatric patients and includes disease etiologies and the management of PH in both children and (younger) adults in MLIRs. We defined MLIR as a region where the majority of people live in countries that have a gross national income (previously known as gross national product), below 10,000 U.S. dollars per capita, as published by The World Bank. The executive writing group members for this consensus statement on PH in MLIRs were recruited from Austria, Belgium, Bolivia, China, Germany, India, Mozambique, Pakistan, South Africa, and Ukraine.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received February 26, 2020; revised manuscript received March 19, 2020, accepted March 23, 2020.

LITERATURE SEARCH, GRADING SYSTEM OF RECOMMENDATIONS, AND REVIEW PROCESS. **Literature search.** We conducted computerized searches of the PubMed/MEDLINE bibliographic database from January 1990 to January 2020. Clinical trials, consensus statements, guidelines, meta-analyses, and comprehensive clinical reviews were searched using the terms "pulmonary hypertension" and up to 10 other key words. The writing group members discussed the topics during several face-to-face and web-based meetings (2018 to 2019).

Class of recommendation, Level of Evidence. Details on the ESC/American Heart Association grading system for Class of Recommendation (Table 1) and Level of Evidence (Table 2), as well as the voting, peer review, and endorsement process can be found in the Supplemental Appendix. Importantly, health care providers must adhere to the medication labeling and follow future drug recommendations/warnings, published by regulatory agencies, such as the European Medicines Agency and the U.S. Food and Drug Administration, when transferring these recommendations into clinical practice. Challenges specific to MLIRs will be discussed in each section of this paper and consensus recommendations will be presented at the end of the document.

DEFINITION OF PH AND PAH IN MLIRs. PH is currently defined as a mean pulmonary artery pressure (mPAP) >20 mm Hg at rest in patients >3 months, at sea level, determined by cardiac catheterization (8,12). Because invasive pressure measurements are infrequently used for diagnosis of PH in MLIRs, transthoracic echocardiography (echo) is the mainstay of diagnostic screening in such regions. The right ventricular (RV) to right atrial (RA) pressure gradient was estimated by continuous wave Doppler echo (via tricuspid regurgitation velocity [TRV]), and an estimated RV-RA systolic gradient >50 mm Hg (TRV >3.5 m/s) was used as a noninvasive cut-off to define PH (2,3). Of note, such a noninvasive definition may lead to an underestimation of patients with PH in these registries. The etiologies of PH are diverse and differ based on patients' age and geographic location. Such information may be important, especially when deciding on resource allocation and cost of care for diagnosing and managing patients with PH in MLIRs (3,5). Details on hemodynamic definitions of PH subtypes can be found in the Supplemental Appendix.

EPIDEMIOLOGY (DISEASE BURDEN) AND ETIOLOGY OF PH IN MLIRs

Data is sparse to determine the global prevalence and incidence of PH. The estimated global prevalence of PAH is between 15 and 60 per 1 million adults (13). There is a dearth of data on the incidence, prevalence, and causes of PH (pre-capillary, post-capillary, and combined forms) in MLIRs. Although there are registries in some of the MLIRs (**Central Illustration**), most of them only have data on patients with group 1 PH (e.g., PAH), include mostly patients >18 years of age, and have limited patient numbers (**Table 3**). Although the PAPUCO (Pan African Pulmonary Hypertension Cohort) (Africa) (3), PRO-KERALA (Pulmonary Hypertension Registry of Kerala, India) (India) (2), and Ukrainian (14) registries included most groups of PH patients (groups 1 to 5 PH), these data cannot be considered to be representative for all different causes of PH in other MLIRs. The overall burden of PH in MLIRs is several times higher than that of HIRs, as demonstrated in the Kerala registry where the estimated incidence was probably 48 per 1 million people in 2015 (2). The following conditions are likely to contribute substantially to the disease burden of PH in MLIRs:

- Rheumatic heart disease, which is still a scourge in most MLIRs.
- Untreated congenital heart disease (CHD): only a small fraction (<10%) of infants with shunt lesions from CHD receive timely intervention in MLIRs (surgery or percutaneous device closure).
- PH due to left heart disease (LHD) (group 2 PH) as a result of a high burden of coronary artery disease

TABLE 1 Classes of Recommendations

COR	Definition	Suggested Wording to Use
COR I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective.	Is recommended/is indicated
COR II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
COR IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
COR IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
COR III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful.	Is not recommended

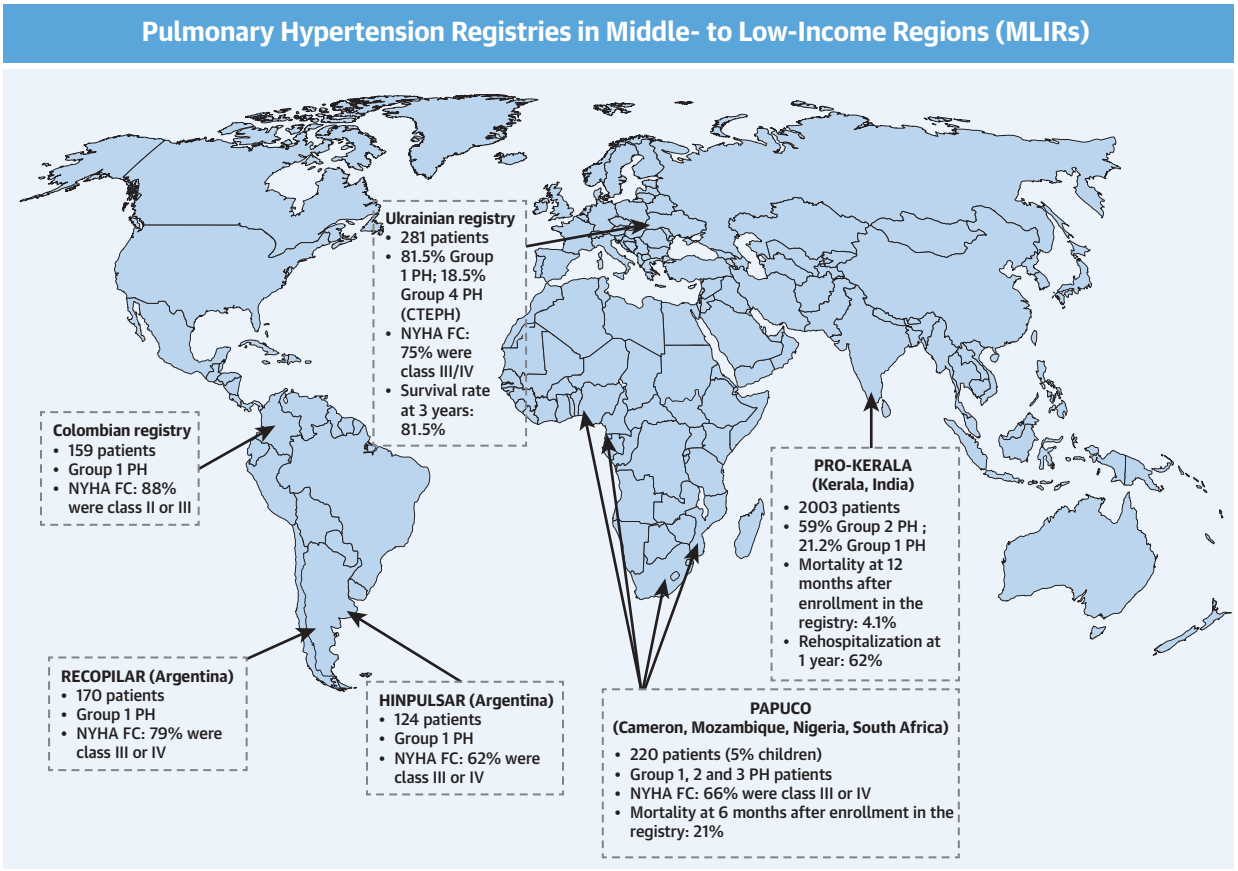
Classes of recommendations (COR), as currently proposed by the European Society of Cardiology and the American Heart Association. This color coding for COR can be found in Table 7.

TABLE 2 Levels of Evidence

LOE A	Data derived from multiple randomized clinical trials or meta-analyses.
LOE B	Data derived from a single randomized clinical trial or large non-randomized studies.
LOE C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Levels of evidence (LOE), as currently proposed by the European Society of Cardiology and the American Heart Association. This color coding for LOE can be found in Table 7.

CENTRAL ILLUSTRATION **6 Registries on Pulmonary Hypertension in Middle- to Low-Income Regions**



Hasan, B. et al. J Am Coll Cardiol. 2020;75(19):2463–77.

PAPUCO (Pan African Pulmonary Hypertension Cohort) involved 4 African countries; PRO-KERALA (Pulmonary Hypertension Registry of Kerala, India) included 50 centers across the state of Kerala in India; HINPULSAR (Hipertensión Pulmonary Asociaciones en la Argentina) included 31 centers in Argentina; RECOPILAR (Registro Colaborativo de Hipertensión Pulmonaren Argentina); a Colombian registry included 5 centers; and a prospective Ukrainian registry (adult PAH, CTEPH) from a single referral center in Kyiv, Ukraine. Overall, the majority of the patients in the 6 registries were >18 years of age. CTEPH = chronic thromboembolic pulmonary hypertension; NYHA = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

and unrecognized and untreated systemic arterial hypertension (15,16).

- PH due to lung disease: especially interstitial or parenchymal lung disease pertaining to high prevalence of tuberculosis (23% of patients in PAPUCO) in MLIRs (3). Parenchymal lung disease caused by smoking, exposure to air pollutants, and smoke generated during indoor cooking/heating without chimney (32% in PAPUCO) (3).
- Schistosomiasis is endemic in several parts of the world especially in South America, the Caribbean, Sub-Saharan Africa, and South Asia. It is estimated that 5 to 20 million people worldwide experience the clinical manifestation of PAH caused by Schistosoma parasite infection (17).
- Human immunodeficiency virus (HIV) infection in endemic regions (35% of patients in PAPUCO) (3).
- The burden of idiopathic pulmonary arterial hypertension (IPAH) and other conditions listed in the WSPH PH classification is also substantial, simply because of the large populations in MLIR regions.

Differences in etiologies between HIRs and MLIRs are evident from the finding that IPAH is the largest subgroup of PH in the European COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry (18) whereas PH-LHD (group 2 PH) was found to be the most common cause in PH registries from MLIRs. Among group 1 PH patients (here PAH), unrepaired CHD accounts for the majority of cases and

TABLE 3 Characteristics of Pulmonary Hypertension Registries in Middle- to Low-Income Regions (MLIRs)

Registry/Reference	Region	Demographic Data	Main Findings
PAPUCO Registry	Africa	209 adults (median age 48 yrs; IQR: 35.6) and 11 children (age 1–17 yrs) included, 9 specialist centers in 4 African countries (Nigeria, Cameron, South Africa, and Mozambique).	69% had left heart disease (Group 2 PH) and 16% had PAH (Group 1 PH), 11% PH due to lung disease (Group 3 PH); 66% had NYHA functional class III–IV status, 21% mortality over 6-month follow-up.
Pro-KERALA Registry	Kerala, Southern India	2,003 adults (mean age 56 ± 16.1 yrs) enrolled over 1 yr from 50 hospitals; estimated incidence is 48 per million adult population. Mortality (1 yr): 4.1%. Rehospitalization (1 yr): 62%.	Majority (59%) had left heart disease (Group 2 PH); ~20% were PAH (Group 1 PH); ~5% had IPAH (Group 1 PH); ~50% of PAH patients received oral PAH-targeted therapies.
HINPULSAR*	Argentina	124 adult patients (mean age 45 ± 17 yrs) from 31 centers recruited prospectively over 1 yr.	PAH patients only (Group 1 PH): 52% IPAH and 27% CHD-PAH, 78% females. 62% presented in NYHA functional class III/IV.
RECOPILAR†	Argentina	170 adult patients (mean age 51 yrs) recruited prospectively over 1 yr. Only PAH patients (Group 1 PH) enrolled.	PAH patients only (Group 1 PH). 52% IPAH, 27% CHD-PAH; 79% women. 70% presented in NYHA functional class III/IV.
Colombian Registry‡	Bogota, Colombia	159 patients (age >18 yrs) recruited retrospectively over 6 yrs from 5 centers. Only PAH (Group 1 PH) and CTPEH (Group 4 PH) patients enrolled.	PAH (Group 1 PH) and CTPEH (Group 4 PH) patients only. 33% had CTEPH, 58% men. 88% presented in NYHA functional class II and III.
Ukrainian Registry (14)	Kyiv, Ukraine	281 patients (mean age 41.7 ± 14.6 yrs) recruited prospectively between June 2014 and July 2018 from 1 center. 52 patients with CTEPH (Group 4 PH) and 229 with PAH (Group 1 PH).	Follow-up period was up to 51 months. The Kaplan-Meier survival rate for the total cohort was 93.3%, 86.8%, and 81.5% at 1, 2, and 3 yrs.

Data from: *Perna ER, Coronel ML, Echazarreta D et al. Epidemiological profile of pulmonary arterial hypertension in Argentina: insights from HINPULSAR registry. Eur J Heart Fail 2012:Suppl 1:S55. †Lescano A, Talavera L, Mazzei J, et al. on behalf of RECOPILAR. The advanced functional class and the variables of poor prognosis in pulmonary hypertension. Eur J Heart Fail 2016;18 (suppl. 1):122. ‡Villaquiran C, Conde R, Torres A, Duenas R. Description of the clinical, functional and hemodynamic characteristics of patients with CTEPH in five reference centers in Bogota-Colombia, at 2.640 meters above sea level. Am J Respir Crit Care Med 2015;191:A4846.

CHD = congenital heart disease; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; IQR = interquartile range; MLIR = middle- to low-income region; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

contributes substantially to the overall disease burden of PH in MLIRs. **Table 4** summarizes the features of different PH groups and some of the specific recommendations relevant to MLIRs.

CLINICAL PRESENTATION AND DIAGNOSIS OF PATIENTS WITH PH IN MLIRs

Untreated, undiagnosed PH patients in MLIRs present late at definitive diagnosis and with more advanced functional deterioration compared with HIRs (**Table 3**). Similar functional impairment at presentation was observed in the Latin American registries too (**Table 3**) (19). Such late presentation with advanced disease is a major contributor to the very high mortality in PH patients living in MLIRs (**Table 3**) (2,3). Indeed, patients with CHD and significant left-to-right shunts frequently present late in MLIRs and often have severely increased pulmonary vascular resistance (PVR). Some of these PAH-CHD patients may still be operable, despite their older age at presentation, thus warranting comprehensive and careful invasive assessment to determine operability (20,21). Our recommendations for the overall approach to determine operability of a cardiovascular shunt lesion in MLIRs is summarized in Supplemental Table 1.

DIAGNOSTIC WORK-UP. Identifying PH. Transthoracic echo is the main diagnostic modality for diagnosis of PH, as many patients in MLIRs do not undergo a diagnostic "gold standard" cardiac catheterization (2,3). Using TRV, based on the continuous wave Doppler envelope, as a measure of RV systolic pressure in PH may still result in underdiagnosing the disease. A detailed, multiparameter assessment of the right heart using a standardized protocol (10,22) will likely increase the accuracy of echo in detecting PH. Once PH is judged to be highly likely, a diagnostic approach should be adopted that helps identify causes with a high likelihood of occurrence and prevalence in a given region/country (**Table 4**).

Diagnostic work-up for suspected PH in MLIRs. A systematic approach to patients with PH in MLIRs may help identify causes in a cost-effective manner (**Figure 1**, Supplemental Table 2).

Detailed history and physical examination: Helps to identify a cause and evaluates the clinical status of the patient. A detailed family history is imperative to diagnose familial or hereditary PAH.

Chest x-ray: Identifies potential pulmonary etiology or indirect contributors, such as spinal deformity. Signs of left-sided heart disease may suggest group 2 PH (23).

Transcutaneous pulse oximetry and arterial blood gas analysis: Can provide information regarding parenchymal/interstitial lung disease (diffusion impairment) and also operability in CHD shunt lesions (24). Pulse oximetry screening in both the right upper and

TABLE 4 The 5 PH Groups and Specific Considerations in Middle- to Low-Income Regions (MLIRs)

PH Classification	Global Prevalence*	Features to be Considered in MLIRs	Recommendations to be Considered in MLIRs
Group 1: Pulmonary arterial hypertension (PAH) 1 PAH 1.1 Idiopathic PAH 1.2 Heritable PAH 1.3 Drug- and toxin-induced PAH	Prevalence 15-60 per million	True incidence and prevalence of HPAH may be higher in regions with high rates of consanguinity	Genetic testing may not be feasible due to cost or lack of availability; detailed family history is imperative
1.4 PAH associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis	Some report prevalence of 0.5 per 1,000 adults with HIV-related PAH in Africa (probably overestimated)	Higher incidence and prevalence of late presenting and unrepaired CHD, HIV, HBV/HCV-induced cirrhosis and portal hypertension	Screening for unrecognized or latent infections (HIV, HBV/HCV, schistosomiasis) may be included in the initial workup
1.5 PAH long-term responders to calcium-channel blockers			
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement		Underrated due to unrecognized HIV, history of excessive radiation exposure, consanguinity	
1.7 Persistent PH of the newborn syndrome		High incidence of prematurity, IUGR and intrauterine infections may lead to significant burden of PPHN or CLD	Education of neonatologists to recognize PPHN- and CLD-related pulmonary hypertension; proper follow-up of neonates with PPHN
Group 2: PH due to left heart disease 2.1 PH due to heart failure with preserved LVEF 2.2 PH due to heart failure with reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH	3-4 million people with rheumatic heart disease (RHD)-related PH worldwide	High incidence and prevalence of advanced RHD valvular disease	Reduction in RHD burden is an enormous challenge that needs a concerted global effort. The World Heart Federation roadmap serves as a foundation for the development of tailored plans of action to improve RHD control in specific contexts.
Group 3: PH due to lung diseases and/or hypoxia		High incidence and prevalence of TB-related lung disease	
Group 4: PH due to pulmonary artery obstructions 4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions			
Group 5: PH with unclear and/or multifactorial mechanisms 5.1 Hematological disorders 5.2 Systemic and metabolic disorders 5.3 Others 5.4 Complex congenital heart disease	1-2.5 million people affected by sickle cell-related PH worldwide	High incidence and prevalence of sickle cell disease, thalassemia, chronic renal failure	Centers are needed with expertise in treating benign hemoglobinopathies and its related complications

*Per million adults or individuals affected worldwide. PH classification according to the World Symposium on PH 2018, see Simonneau G, et al. (8).

CHD = congenital heart disease; CLD = chronic lung disease; HCV = hepatitis C virus; HBV = hepatitis B virus; MLIR = middle- and low-income regions; IUGR = intrauterine growth restriction; TB = tuberculosis.

any lower extremity is recommended for evaluating post semilunar valve shunt lesions (i.e., patent ductus arteriosus or aorto-pulmonary window).

Lung function tests: May help to identify airway pathologies such as unrecognized asthma or interstitial lung disease.

Specific laboratory tests: Work-up to evaluate for autoimmune disorders, when clinically appropriate (23), should be performed. Screening for and diagnosis of HIV in endemic areas is essential.

Abdominal ultrasound: Can help identify diseases leading to porto-PH or other rare diagnoses such as the Abernethy malformation (25).

Computed tomography chest and lung perfusion scans: Might help identify chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is potentially treatable and can be identified through either of these tests. Chest computed tomography, if available, is important to rule out parenchymal/interstitial lung disease in suspected PH.

Cardiac catheterization and acute pulmonary vasoreactivity testing (AVT): A number of institutions in MLIRs now have cardiac catheterization laboratory facilities. Although inhaled nitric oxide is largely unavailable, preliminary data suggests that inhaled iloprost (5 μg through a nebulizer over 15 min) and intravenous sildenafil can be used effectively for AVT at a fraction of the cost compared with inhaled nitric oxide (iNO) (26). Oxygen alone is insufficient and not useful to test for AVT (5). However, oxygen alone may be useful when lung disease and diffusion impairment is suspected to be the major cause of PH and to determine oxygen-dependence of PAP elevation.

ASSESSMENT OF FUNCTIONAL STATUS AND PH RISK STRATIFICATION. After PH diagnosis is made

TABLE 5 PAH-Specific Medications and Special Considerations in Middle- to Low-Income Regions (MLIRs)*

Medication Class	Mode of Delivery	Special Considerations in MLIRs
CCBs (e.g., amlodipine)	Oral	• Lack of ability to perform AVT makes it difficult to diagnose acute responders vs. nonresponders; thus, use of CCB may not be feasible. • CCBs are contraindicated in PAH-CHD with large shunt and in Eisenmenger Syndrome. • CCBs are contraindicated in patients who have not undergone AVT, in proven non-responders to AVT, and in those with poor cardiac function and/or right heart failure, regardless of AVT response. • Ability to follow-up to ensure "responder" status may not be possible.
Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)	Oral i.v. (for special conditions, i.e., immediate post-operative)	• Relatively easily available in cheap generic forms (cost ~ U.S. $2 per 25-mg oral dose). • Less side effects; no drug-related adverse event monitoring required. • Use of medium dose should be encouraged (EMA recommendation 10 mg 3× daily for weight <20 kg and 20 mg 3× daily for weight ≥20 kg).
Endothelin receptor antagonists (e.g., bosentan, ambrisentan, macitentan)	Oral	• Making its way to the MLIR markets; still expensive (especially newer agents). • Monitoring of liver function may be challenging (bosentan). • Teratogenicity as risk of unplanned pregnancy may be high in MLIRs.
Prostacyclin analogues and oral prostacyclin IP receptor agonists	Oral, inhaled, subcutaneous, and intravenous	• Limited availability in few MLIR countries such as China. • Frequency of use may significantly impair compliance for inhaled medication. • i.v. infusion option is almost nonexistent in MLIRs because of fundamental health system challenges. • Expensive.
Soluble guanylate cyclase stimulators (e.g., riociguat)	Oral	• Limited availability in selected MLIRs. • Expensive.
Supportive medication:	Oral, intravenous	
Diuretic agents		• Diuretic agents (furosemide, thiazide) should be used with caution given RV hemodynamics.
Spironolactone		• Recommended use of spironolactone, a supportive medication in PAH and proven to be effective in HFpEF.
Digoxin		• Digoxin may be useful particularly in PAH with high heart rates.
Beta-blockers		• Avoid chronic use of beta-blockers in adults with PAH (negative RCT have been published; no pediatric data available).
Iron and vitamins		• Treat especially iron deficiency.
Oral anticoagulation		• Oral anticoagulant treatment may be considered in adult patients with IPAH, HPAH, and PAH due to use of anorexigens (COR: IIb, LOE: C). • Do not pursue oral anticoagulation without a clear indication and proper follow-up. • No data exist to recommend oral anticoagulation in children with PH. • Of note, many patients with severe PAH do have acquired von Willebrand syndrome and thus an increased bleeding risk per se.

*For specific and detailed dosing recommendations, refer to Hansmann et al. (11).

AVT = acute vasoreactivity testing; CC = cardiac catheterization; CCB = calcium-channel blocker; COR = Class of Recommendation; EMA = European Medical Association; ESC/ERS = European Society of Cardiology/European Respiratory Society; HFpEF = heart failure with preserved ejection fraction; iNO = inhaled nitric oxide; i.v. = intravenous; LOE = Level of Evidence; RCT = randomized clinical trials; RV = right ventricle; other abbreviations as in **Table 3** and Supplemental Table 4.

(noninvasively or preferably invasively), functional status (exercise capacity) and PH risk stratification of the patient can be determined using history (World Health Organization functional class), easily performed tests like the 6-min walk test (in patients age >6 years), echo assessment of RV function and catheter-based hemodynamic data (10) (Supplemental Table 3). The EPPVDN developed a new risk score for children with PH (10) that needs to be validated in future prospective studies.

MANAGEMENT OF PH IN THE CONTEXT OF FINANCIAL AND INFRASTRUCTURAL CONSTRAINTS IN MLIRs

Due to several factors intrinsic to MLIRs, ranging from access to health care to unavailability of treatment and cost (2,3,27–29), both managing PH patients and improving their ultimate outcome in MLIRs are major challenges (27–29) (**Table 6**, Supplemental Table 4). It is imperative that practitioners in MLIRs modify the management recommendations that apply in HIRs to keep the overall essence but to make it practical according to the constraints in the MLIR setting. Without such a pragmatic approach, maintaining patient compliance will be difficult and management will be ineffective in the end.

PAH-TARGETED PHARMACOTHERAPY. Targeted pharmacotherapy is approved for PAH (group 1 PH); some PAH-targeted medications are also approved for use in CTEPH (group 4 PH) (Supplemental Table 4). Using PAH-targeted medications in other groups of PH (e.g., combined pre- and post-capillary PH) should be

TABLE 6 Perspectives for PH Patients in Middle- to Low-Income Regions (MLIRs)

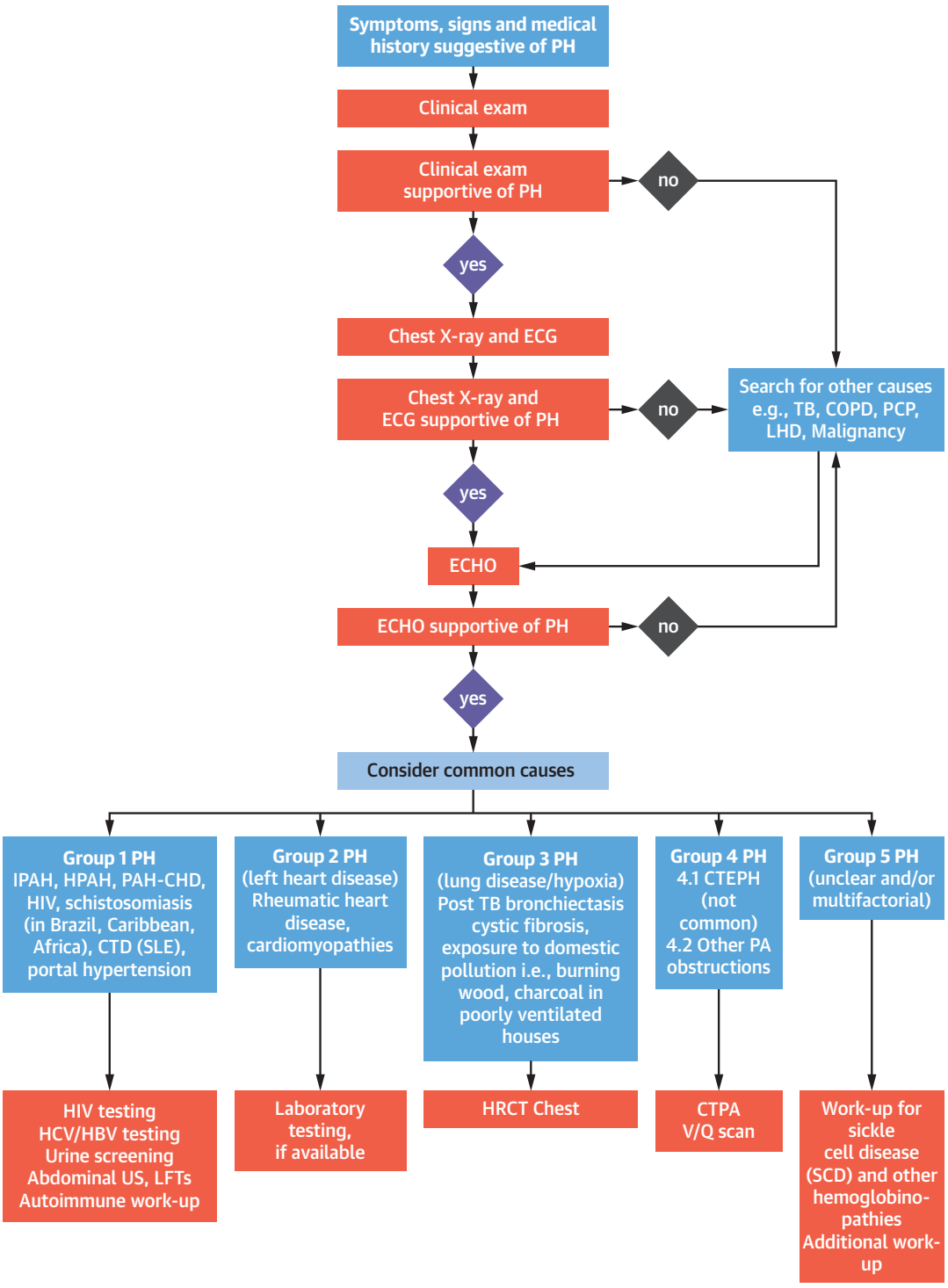
	Ukraine, Eastern Europe, Western Asia/Middle East	China and Southeast Asia	Indian Subcontinent	Africa	Middle and South America
Incidence of PH and disease entities	The only available registry is from Ukraine. The most common cause identified was PAH-CHD followed by IPAH. HIV, and TB-associated PH and group 3 PH probably common (no systematic data available).	In the Chinese pediatric PAH registry, the majority of pediatric PAH patients had PAH-CHD followed by IPAH/HPAH, similarly to the adult PAH population.	High prevalence of RHD and unrepaired CHD in the South Asia region. Indoor and outdoor pollution together with high prevalence of TB-related lung injury may contribute to group 3 PH.	The etiology of PH in Africa is broad and there is no systematically collected data on epidemiology. Estimates on the prevalence by underlying disease are: schistosomiasis (170 million), RHD (6.5 million), SCD (12 million), HIV (20 million), moderate to severe COPD (30 million).	IPAH has been reported as the most common type of PAH in Latin America, although this ranking may be due to reporting bias. More than 1 million with schistosomiasis-related PH in the Amazonas Region, high altitude-related PH (acute and chronic), and PAH due to untreated left-to-right cardiovascular shunting with CHD.
Diagnostic options	Echocardiography and cardiac catherization available only in selected centers.	Echocardiography and cardiac catherization available in urban centers.	Echocardiography and cardiac catherization available in selected centers.	Very limited access to cardiac catheterization and echocardiography usually restricted to major urban areas.	Echocardiography and cardiac catherization available in selected centers.
Treatment options	Diverse, for example, in Belarus, PAH drugs and lung transplantation available. In Kazakhstan, PAH drugs are usually available for free, but only to selected PAH patients. No HLTx in Kazakhstan.	PDE5i, ERA, inhaled and subcutaneous PCAs available. LuTx or HLTx available in selected centers.	Most pharmacological options (PDE5i, ERA, inhaled and subcutaneous prostanoids) available, but only affordable to some patients. Transplantation (LuTx, HLTx) available in selected centers.	Targeted PAH therapy and transplantation (LuTx, HLTx) out of reach for the majority of 1 billion Africans.	Oral sildenafil is the first-line PAH pharmacotherapy in Middle and South America. Availability of other drugs differs between countries. Transplantation (LuTx, HLTx) available in few selected centers.
Comments	The member countries of the European Union allow for free mobility within the European Union and, thus, specialized health care in Western Europe is often accessible to PAH patients.	Today, most PAH patients are treated with PDE5i monotherapy. National administration announced to cover bosentan, macitentan, riociguat, and selexipag by the health care insurance system from 2020.	High birth rates, overcrowding, poverty, and disorganized health system. Ongoing efforts to establish register studies (Pro-KERALA and Pakistan registry).	Preventive strategies aimed at reducing smoking, pollution, elimination of RHD, HIV, and schistosomiasis might eventually contribute to reducing the incidence of PH in Africa.	Despite principal availability, only a minority of PAH patients have access to the appropriate diagnostic technology and medication.

For details, see Appendix.

COPD = chronic obstructive pulmonary disease; ERA = endothelin receptor antagonist; HLTx = heart-and-lung transplantation; LuTx = lung transplantation; PCA = prostacyclin analog; PDE5i = phosphodiesterase 5 inhibitor; SCD = sickle cell disease; other abbreviations as in Tables 3 and 4.

decided upon by PH experts only. Vasodilatory agents may worsen clinical status and might cause pulmonary edema, especially in group 2 PH with heart failure with preserved ejection fraction and left atrial hypertension of other causes (11). The route of PAH drug administration, frequency of use, cost, and availability can be major limiting factors in the compliance with treatment, especially in MLIRs (2,3). Several of the PAH drugs are manufactured and available in some MLIRs, for example, India and China (Supplemental Table 4). Notwithstanding the substantially reduced prices, these medications are still very expensive for the average patient in MILRs. In India, the monthly cost of therapy with sildenafil is U.S. $30, whereas dual therapy (tadalafil plus ambrisentan) is ~$100/month (2). Because the majority of people in India are uninsured and live at or below $60/month, affording such therapies with effective treatment compliance is extremely challenging (2). Such a scenario holds true for other MLIRs, such as Pakistan, Indonesia, Bangladesh, Afghanistan, and others. **Table 5** describes the classes, different medications, and specific considerations for PH in MLIRs (see also **Table 6**, Supplemental Table 4). The objective of improving quality of life needs to be discussed up-front with families to make an informed decision on costly pharmacotherapy.

FIGURE 1 **Algorithm for the Diagnostic Work-Up of Suspected or Confirmed Pulmonary Hypertension in MLIRs Without Access to Cardiac Catheterization**



The algorithm applies to children and adults living in middle- to low-income regions (MLIRs) with limited health care resources. See Supplemental Table 2.
COPD = chronic obstructive lung disease; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = chest tomography pulmonary angiography; ECG = electrocardiogram; echo = echocardiogram; HIV = human immune deficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HRCT = high resolution computed tomography; LFT = liver function test; LHD = left heart disease; PCP = pneumocystis carinii (newer term: pneumocystis jirovecii); PH = pulmonary hypertension; SLE = systemic lupus erythematosus; TB = tuberculosis; US = ultrasound; V/Q scan = ventilation to perfusion scan.

TABLE 7 Recommendations for Diagnosis and Management of Pulmonary Hypertension in Middle- to Low-Income Regions (MLIRs)

Recommendations	COR	LOE
Children/young adults with suspected or confirmed PH must be referred to, comprehensively evaluated, and treated in specialized pediatric centers. In MLIRs, such pediatric centers often have limited resources, and thus children with PH may be referred to centers caring for adult patients with PH.	I	C
The initial evaluation of a child/young adult with PH must include a comprehensive medical history (specifically to identify causes like sickle cell disease, tuberculosis, or operability in shunt lesions), physical examination (in MLIRs specific causes like rheumatic heart disease) (2,3,23).	I	B
Patients in endemic areas of schistosomiasis who present with symptoms and physical signs of PH must undergo a detailed echocardiogram. Patients from such endemic areas with PH and signs of pre-hepatic portal hypertension may be suspected to have schistosomiasis-related PH (17,56).	I	C
Patients with schistosomiasis infection and PH benefit from PAH- directed therapy (mainly sildenafil) (31).	I	C
Patient with active schistosomiasis need treatment with an antihelmintic drug, such as praziquantel (32).	I	C
Patients with rheumatic heart disease (RHD) and PH documented by echocardiography must undergo treatment as per RHD valve treatment guidelines.	I	C
The need for PAH-targeted medications in patients with RHD should be carefully evaluated and eventually pursued only at centers specializing in PH.	I	C
In regions where HIV is highly prevalent, patients with symptoms or signs of PH should undergo a detailed transthoracic echocardiogram to detect PH (57).	I	C
Patients with HIV infection and PH, documented by echocardiography, benefit from PAH specific medication (especially bosentan). The role of HAART on the prevalence and outcome of PH secondary to HIV is still controversial (49,57,58).	I	C
Treatment with PAH-specific medication (especially sildenafil) in patients with SCD-related PH is highly controversial. Oral sildenafil appears to increase hospitalization rates for pain in SCD, probably related to vaso-occlusive crisis (36).	III harm	C
Patients living at high altitude and with symptoms and signs of PH may undergo a detailed transthoracic echocardiogram to detect PH.	I	C
The initial patient history needs to include all major socioeconomic determinants of compliance (profession, family structure, and proximity to treating center). Such information is critical to determine the compliance to treatment and subsequent follow-ups in PH patients (3).	I	C
Patients with high altitude-related PH probably benefit from PAH specific medications (50).	IIa	B
Children <2 yrs of age living in MLIRs with PH and so-called "simple shunts" (ASD, VSD, or PDA) who have normal saturations, signs of increased pulmonary blood flow, and exclusive left-to-right shunt on echocardiography may undergo shunt closure without invasive hemodynamic evaluation (59,60).	IIb	C
In children with cardiovascular shunt lesions, noninvasive oxygen saturations and—if possible—arterial PaO_2 during exercise should be measured. A drop in PaO2 of >10 mm Hg or SpO2 by 19% points during exercise indicates an inoperable shunt due to increased PVR (59–61).	I	C
A comprehensive echocardiogram at diagnosis is recommended as this is the main (and may be the only) modality of diagnosing PH. Features of operability in shunt lesions should also be assessed using echocardiogram. Serial echocardiograms and ECGs may not be feasible in MLIRs (due to lack of expertise and equipment) or not be cost-effective, and may be performed on a case-by-case basis (2,3,22).	I	B
Further imaging (mainly chest CT) is recommended to exclude underlying parenchymal/interstitial lung disease, in ex-premature infants, and in patients with BPD, Down syndrome, or other well-known risk factors (3,23,59).	I	B
Cardiac catheterization for diagnosis or routine follow-up should be performed in PH centers only. Lack of expert centers and standardization of cardiac catheterization in MLIRs may lead to erroneous data, wrong data interpretation, or little management value. In the absence of vasoreactivity testing, the value of cardiac catheterization (especially if done for shunt operability) is limited (2,3,62,63).	IIa	B
If no underlying cause of the PH is evident, specific tests for HIV, schistosomiasis, and chronic hepatitis (HBV and HCV) must be performed. An abdominal ultrasound is indicated to rule out liver cirrhosis and/or portal hypertension (2,3,64)	I	B
Serial 6MWTs must include pulse oximetry and are recommended to assess exercise tolerance and response to therapy, and to estimate prognosis in children with PH capable of performing such studies. A 6MWT is an inexpensive, reproducible measure of functional capacity. Equipment and expertise for CPET are rarely available in MLIRs (65).	I	C
PAH-specific therapy is recommended and can significantly improve quality of life. Safety of intravenous therapy in a low-resource setting is also of concern (higher risk of infection and catheter-based complications). Inhalation therapies are often ineffective due to lack of sufficient patient compliance and/or difficulties with applying the devices at home (2,3,66).	I	B
For children with PH/PHVD undergoing surgery or other interventions requiring sedation or general anesthesia, consultation with cardiac anesthesia and PH service and appropriate post-procedure monitoring are required (67,68).	I	C
Atrial septostomy and other surgical measures (e.g., reverse Potts shunt) and interventional procedures (ductal stenting, balloon atrial septostomy) may be considered in highly selected cases at very few specialized centers. These procedures are risky per se and especially in MLIRs, with inconclusive long-term benefits especially in the absence of a lung transplant program (54,55,69).	IIb	C
Serial measurements of serum NT-proBNP concentration may be indicated as changes in NT-proBNP reflect hemodynamic impairment. Cost-benefit assessment of this test is needed in MLIRs health care setting (5).*	IIb	C

Recommendations specific to MLIRs are predominantly based on expert opinion due to lack of publications from these regions. *Based on RCT study data not specific to MLIR, serial measurements of serum NT-proBNP concentration should be considered (COR IIa) as changes in NT-proBNP reflect hemodynamic impairment. These recommendations are taken with permission (slightly modified) from Table 12 in Hansmann et al. (10).

6MWT = 6-min walk test; ASD = atrial septal defect; CPET = cardiopulmonary exercise testing; HAART = high activity anti-retroviral therapy; NT-proBNP = N-terminal pro-brain natriuretic peptide; PaO2 = arterial partial pressure of oxygen; PDA = patent ductus arteriosus; PPHVD = pediatric pulmonary hypertensive vascular disease; PVR = pulmonary vascular resistance; PVD = pulmonary vascular disease; RV = right ventricle; SCD = sickle cell disease; SpO2 = oxygen saturation; VSD = ventricular septal defect; other abbreviations as in Tables 3 and 4.

PREGNANCY AND CONTRACEPTION. Pregnancy in female PH patients is associated with substantial risk of maternal and fetal mortality; thus, relevant counseling is very important, especially in MLIRs (30). Safer contraception options (i.e., progesterone impregnated intrauterine coils, subdermal or intramuscular progesterone implants/injections) may not be readily available in MLIRs. Standard oral estrogen-based contraceptive is associated with increased risk of thrombosis (30). In the event of pregnancy, if the mother wants to continue, close follow-up with high-risk obstetric care is recommended, especially at the time of delivery and within the 2 weeks postpartum, when the risk of death is the highest, often due to thromboembolic complications or heart failure (30).

SPECIAL THERAPEUTIC CONSIDERATIONS IN MLIRs

PH ASSOCIATED WITH SCHISTOSOMIASIS. Schistosomiasis is the most common parasitic disease associated with PH (17). The cause of PH in schistosomiasis is multifactorial, including parasitic pulmonary artery embolization, pulmonary vasculopathy, and portal hypertension related to hepatosplenic disease (17) that can be diagnosed by abdominal ultrasound. A high index of suspicion of schistosomiasis-induced PH should be present when patients present with cardiovascular symptoms and features of PH in schistosomiasis endemic areas (Supplemental Figure 1) (17). The cornerstone of current schistosomiasis control programs is delivery of praziquantel to at-risk populations. World Health Organization guidelines recommend annual treatment for schistosomiasis or soil-transmitted helminthiasis when prevalence in school-aged children is at or above a threshold of 50% and 20%, respectively. No specific test exists to diagnose schistosomiasis-induced PH. Patients with schistosomiasis infection and PH may benefit from PAH-directed therapy (mainly sildenafil) (31). Patients with active schistosomiasis need immediate treatment with an anthelmintic drug, such as praziquantel (32).

PH ASSOCIATED WITH SICKLE CELL DISEASE. In a systematic review of PH in Africa, the prevalence of PH in sickle cell disease (SCD) was 36.9% (29.7% to 44.3%) (27) with a mean age of 28.6 ± 5.8 years at presentation (33). The etiology of PH in SCD is multifactorial, so that all 5 groups of PH (mainly groups 1 to 3) occur (8,27). PH in SCD is often linked to left heart failure (27,34,35) due to chronically elevated cardiac output, LV diastolic dysfunction, or coronary ischemia. Furthermore, SCD patients may develop parenchymal lung disease from recurrent acute chest syndrome, while others develop CTEPH. Despite PAP being only moderately elevated in most SCD patients, PH has a negative influence on exercise capacity (33) and markedly increases the risk of death in SCD patients compared with those without PH. Treatment with PAH-targeted medication (especially sildenafil) in patients with SCD-related PH is controversial and may lead to an increase in SCD-related vaso-occlusive crisis (36). For most patients with SCD who have PH (confirmed by cardiac catheterization), we do not recommend administration of any PAH-targeted therapy (**Table 7**) (37). Furthermore, hydroxyurea is the first-line therapy in patients with SCD who are at increased risk for mortality, according to American Thoracic Society criteria from 2014 (TRV ≥2.5 m/s, serum N-terminal pro-brain natriuretic peptide ≥160 pg/ml, or presence of PH by cardiac catheterization, as defined at the time by mean pulmonary artery pressure ≥25 mm Hg) (37). Recently, promising results have been reported using chronic blood exchange transfusions in SCD with pre-capillary PH (38).

PH ASSOCIATED WITH THALASSEMIA. The prevalence of PH in patients with β-thalassemia intermedia (TI) is quite high, and exceeds those with β-thalassemia major (TM) (4.2% vs. 1.1%) (39). In contrast, PH is rarely found in patients with α-thalassemia (Bart or Hemoglobin H disease) (39). Of note, PH in thalassemia is multifactorial in nature, that is, chronic hemolysis leading to impaired NO bioavailability, restrictive cardiomyopathy due to myocardial siderosis, liver siderosis-related cirrhosis or viral hepatitis, pulmonary siderosis, transfusion-related HIV infection, change in circulating erythrocytes post splenectomy (40), and hypercoagulability leading to higher risk (1% to 4%) of thromboembolic episodes (41). Thus, suspected PH associated with any type of thalassemia requires a careful and systemic approach to confirm the diagnosis. A high index of suspicion is required, because symptoms of PH in thalassemia patients may mimic those related to anemia. Chronic transfusion protocol with appropriate iron chelation strategies may prevent and also improve PH in these patients (42). Hydroxyurea therapy in β-TI and L-carnitine in TM patients have been shown to improve PH (43). There is limited data on use of PAH-specific medication in thalassemia patients. Sildenafil therapy in β-TM patients (44), tadalafil in β-TI patients (45), and bosentan in β-TI patients have been used. Due to its liver toxicity, bosentan should be cautiously used with close monitoring (11). Limited

data exist on the use of prostacyclin analogs in these patients.

PH ASSOCIATED WITH HIV INFECTION. HIV-infected patients have a greater incidence of PH compared with the general population (46) and a 2,500-fold increased risk of developing PAH. A systematic review and meta-analysis of cardiac dysfunction in HIV reported a prevalence of PH of 11.5% in 125,382 HIV-infected adults (5.5% to 19.2%) (47). However, in a prospective cohort registry of 220 African PH patients, HIV/acute immune deficiency syndrome was found in <10% of PH cases (3). HIV-related PAH reduces the probability of survival by one-half compared with HIV-positive individuals without PAH (48). Patients with HIV infection and PH suspected by echo may benefit from PAH-targeted therapy (especially bosentan) (49). The role of high-activity antiretroviral therapy on the prevalence and outcome of PH associated with HIV is still controversial (49).

PH ASSOCIATED WITH HIGH ALTITUDE. PH in the presence of chronic hypobaric hypoxia is per definition endemic. In La Paz, Bolivia, at 3,350 m above sea level (a cohort of 4,469 patients), 206 of 1,217 (17%) infants <3 months had signs of PH. Based on the La Paz experience, it is recommended to treat these newborns and young infants with echo evidence of PH with PDE5 inhibitors (oral sildenafil 1 mg/kg bodyweight every 6 h). Older patients, who develop PH specifically related to high altitude, primarily need to be referred to lower regions, where pulmonary pressure usually drops to normal levels. No medication is needed in this clinical scenario in most instances. Prophylactic use of pulmonary vasodilators to prevent high altitude-induced PH is discouraged as in some studies it has been shown to cause harm (50).

CHD at high altitude occurs with a rather different anatomical distribution (e.g., patent ductus arteriosus [PDA], atrial septal defect, tricuspid atresia, and Ebstein anomaly are more common than at sea level). Children living at high altitude have a 10-fold chance of having a hemodynamically relevant PDA (51). The presentation and clinical evolution of CHD lesions also differs at high altitude compared with similar patients residing at sea level (52). For example, left to right shunt lesions (PDA, ventricular septal defect) have a delayed progression toward an inoperable state and should be assessed for operability even after childhood.

HYPOXEMIA AND EISENMENGER SYNDROME. Eisenmenger syndrome is present in unrepaired shunt lesions and is characterized by cyanosis, clubbing, and reverse (right-left) flow across the shunt. Goal of treatment is improving quality of life and dealing with complications (Supplemental Table 5) that arise in Eisenmenger syndrome (53). In patients with Eisenmenger syndrome and neurological symptoms (minor stroke), phlebotomy may be considered in severe hyperviscosity (hematocrit ≥70%); however, iron deficiency from frequent phlebotomies must be avoided. Routine phlebotomy is associated with increased risk of stroke and also leads to relative anemia and reduction in exercise tolerance.

ATRIAL SEPTOSTOMY OR REVERSE POTTS SHUNT AS PALLIATIVE OR BRIDGING THERAPIES. Atrial septostomy or reverse Potts shunt as palliative or bridging therapies are typically used to improve quality of life, as a bridge to lung transplantation (54,55), or as destination therapy (54). Both procedures carry significant risk and require a high level of expertise. Very few advanced centers in MLIRs attempt such interventional therapies (mainly reverse Potts shunt: surgery or catheter intervention) and consider them only in selected cases. Developing skills in performing these procedures may be beneficial, especially in countries where intravenous PAH therapy or lung transplantation are not available. Continuous combination PAH-pharmacotherapy is required after atrial septostomy or reverse Potts shunt for the underlying advanced pulmonary vascular disease/PAH.

EXPERT RECOMMENDATIONS ON THE DIAGNOSIS AND TREATMENT OF PH IN MLIRs

The majority of our recommendations (**Table 7**) are extrapolated from previously published European or North American guidelines and consensus statements (5,6,11). Modification pertaining to MLIRs has minimum data support and are predominantly expert opinions (Level of Evidence: C). The focus is on diagnosis and management of PH, keeping in mind a high prevalence and a broad etiology of the disease. Special attention is given to the diagnosis of LHD (i.e., rheumatic heart disease), acquired lung diseases (i.e., tuberculosis), infections such as HIV and schistosomiasis, and unrepaired CHD. The most significant challenge in PH management includes unavailability of PAH-targeted medication.

PERSPECTIVES FOR PH PATIENTS IN MLIRs

The perspectives for PH patients and their health care specific to certain region and countries in MLIRs are summarized in **Table 6**, and further discussed in more detail in the Supplemental Appendix.

SUMMARY AND GLOBAL PERSPECTIVES

PH is a progressive and often fatal condition that is more common in MLIRs than in HIRs; PH is underdiagnosed in MLIRs where it is handled by cardiologists who often serve both children and adults with limited access to advanced health care. Importantly, on a global scale, PH is not a rare disease but is a major health care burden worldwide, for example, when associated with rheumatic heart disease or CHD, SCD, thalassemia, HIV, or schistosomiasis. Data from MLIRs regarding epidemiology, etiology, management, and/or prognosis of PH is still limited but is emerging from 6 patient registries. Modifications to the international PH guidelines, which are mostly based on studies from HIRs, need to be made to address some of the specific challenges faced in MLIRs. We propose a pragmatic approach with clear cost-risk-benefit evaluation along with an honest discussion among health care providers, patients, and their families. Registry and other collaborative study data for national advocacy and government supported health care plans will be crucial for the managing of young PH patients in MLIRs with limited economic resources.

ADDRESS FOR CORRESPONDENCE: Dr. Babar S. Hasan, Department of Pediatric and Child Health, Stadium Road, P.O. Box 3500, The Aga Khan University Hospital, Karachi, Pakistan. E-mail: babar.hasan@aku.edu. OR Dr. Georg Hansmann, Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. E-mail: georg.hansmann@gmail.com. Twitter: @pvd_network.

REFERENCES

1. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med 2016;4:306–22.

2. Harikrishnan S, Sanjay G, Ashishkumar M, et al. Pulmonary hypertension registry of Kerala, India (PRO-KERALA)—clinical characteristics and practice patterns. Int J Cardiol 2018;265:212–7.

3. Thienemann F, Dzudie A, Mocumbi AO, et al. The causes, treatment, and outcome of pulmonary hypertension in Africa: Insights from the Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry. Int J Cardiol 2016;221:205–11.

4. Rich S, Haworth SG, Hassoun PM, Yacoub MH. Pulmonary hypertension: the unaddressed global health burden. Lancet Respir Med 2018;6:577–9.

5. Galiè N, Humbert M, Vachiery J, et al., for the ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Heart J 2016;37:67–119.

6. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037–99.

7. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Resp J 2019;53:1801916.

8. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Resp J 2019;53:1801913.

9. Galiè N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Resp J 2019;53:1802148.

10. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN). J Heart Lung Transplant 2019;38:879–901.

11. Hansmann G, Apitz C, Abdul-Khaliq H, et al. Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network. Heart 2016;102 Suppl 2:ii86–100.

12. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Resp J 2019;53:1801904.

13. Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. Eur Respir Rev 2015;24:621–9.

14. Radchenko GD, Zhyvylo IO, Sirenko YM. Analysis of pulmonary hypertension patient survival after treatment in referral center (data of first Ukrainian register). Pulm Circ 2019;9:2045894019845604.

15. Mocumbi AO, Thienemann F, Sliwa K. A global perspective on the epidemiology of pulmonary hypertension. Can J Cardiol 2015;31:375–81.

16. Sliwa K, Davison BA, Mayosi BM, et al. Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry. Eur Heart J 2013;34:3151–9.

17. Butrous G. Pulmonary vascular diseases secondary to schistosomiasis. Advances in Pulmonary Hypertension 2017;15:144–8.

18. Olsson KM, Delcroix M, Ghofrani HA, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation 2014;129:57–65.

19. Valverde AB, Soares JM, Viana KP, Gomes B, Soares C, Souza R. Pulmonary arterial hypertension in Latin America: epidemiological data from local studies. BMC Pulm Med 2018;18:106.

20. Talwar S, Keshri VK, Choudhary SK, et al. Surgical strategies for patients with congenital heart disease and severe pulmonary hypertension in low/middle-income countries. Heart Asia 2015;7:31–7.

21. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001–2006. Heart 2009;95:312–7.

22. Koestenberger M, Apitz C, Abdul-Khaliq H, Hansmann G. Transthoracic echocardiography for the evaluation of children and adolescents with suspected or confirmed pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network. Heart 2016;102 Suppl 2:ii14–22.

23. Lammers AE, Apitz C, Zartner P, Hager A, Dubowy K-O, Hansmann G. Diagnostics, monitoring and outpatient care in children with suspected pulmonary hypertension/paediatric pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network. Heart 2016;102 Suppl 2:ii1–13.

24. Laksmivenkateshiah S, Singhi AK, Vaidyanathan B, Francis E, Karimassery SR, Kumar RK. Decline in arterial partial pressure of oxygen after exercise: a surrogate marker of pulmonary vascular obstructive disease in patients with atrial septal defect and severe pulmonary hypertension. Cardiol Young 2011;21:292–8.

25. McKie PM, McCully RB, Kamath PS, et al. Amelioration of high cardiac output and pulmonary hypertension by occlusion of congenital

porto-systemic shunt. Circulation 2012;126:2533–4.

26. Milger K, Felix JF, Voswinckel R, et al. Sildenafil versus nitric oxide for acute vasodilator testing in pulmonary arterial hypertension. Pulm Circ 2015;5:305–12.

27. Bigna JJ, Noubiap JJ, Nansseu JR, Aminde LN. Prevalence and etiologies of pulmonary hypertension in Africa: a systematic review and meta-analysis. BMC Pulm Med 2017;17:183.

28. Mocumbi AO, Lameira E, Yaksh A, Paul L, Ferreira MB, Sidi D. Challenges on the management of congenital heart disease in developing countries. Int J Cardiol 2011;148:285–8.

29. Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet 2008;371:915–22.

30. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the Registry Of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. Eur J Heart Fail 2016;18:1119–28.

31. Fernandes CJ, Dias BA, Jardim CV, et al. The role of target therapies in schistosomiasis-associated pulmonary arterial hypertension. Chest 2012;141:923–8.

32. Crosby A, Jones FM, Kolosionek E, et al. Praziquantel reverses pulmonary hypertension and vascular remodeling in murine schistosomiasis. Am J Resp Crit 2011;184:467–73.

33. Amadi VN, Balogun MO, Akinola NO, Adebayo RA, Akintomide AO. Pulmonary hypertension in Nigerian adults with sickle cell anemia. Vasc Health and Risk Manag 2017;13:153.

34. Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. Blood 2016;127:820–8.

35. Hammoudi N, Lionnet F, Redheuil A, Montalescot G. Cardiovascular manifestations of sickle cell disease. Eur Heart J 2020 Apr 1 [E-pub ahead of print].

36. Machado RF, Barst RJ, Yovetich NA, et al. Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. Blood 2011;118:855–64.

37. Klings ES, Machado RF, Barst RJ, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med 2014;189:727–40.

38. Detterich JA, Kato RM, Rabai M, Meiselman HJ, Coates TD, Wood JC. Chronic transfusion therapy improves but does not normalize systemic and pulmonary vasculopathy in sickle cell disease. Blood 2015;126:703–10.

39. Derchi G, Galanello R, Bina P, et al. Prevalence and risk factors for pulmonary arterial hypertension in a large group of β-thalassemia patients using right heart catheterization: a Webthal study. Circulation 2014;129:338–45.

40. Phrommintikul A, Sukonthasarn A, Kanjanavanit R, Nawarawong W. Splenectomy: a strong risk factor for pulmonary hypertension in patients with thalassaemia. Heart 2006;92:1467–72.

41. Musallam KM, Taher AT. Thrombosis in thalassemia: why are we so concerned? Hemoglobin 2011;35:503–10.

42. Atichartakarn V, Chuncharunee S, Chandanamattha P, Likittanasombat K, Aryurachai K. Correction of hypercoagulability and amelioration of pulmonary arterial hypertension by chronic blood transfusion in an asplenic hemoglobin E/β-thalassemia patient. Blood 2004;103:2844–6.

43. Karimi M, Borzouee M, Mehrabani A, Cohan N. Echocardiographic finding in beta-thalassemia intermedia and major: absence of pulmonary hypertension following hydroxyurea treatment in beta-thalassemia intermedia. Eur J Haematol 2009;82:213–8.

44. Morris CR, Kim H-Y, Wood J, et al. Sildenafil therapy in thalassemia patients with Doppler-defined risk of pulmonary hypertension. Haematologica 2013;98:1359–67.

45. Jalalian R, Moghadamnia AA, Tamaddoni A, Khafri S, Iranian M. Comparing the efficacy of tadalafil versus placebo on pulmonary artery systolic pressure and right ventricular function in patients with beta-thalassaemia intermedia. Heart Lung Circ 2017;26:677–83.

46. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. Am J Respir Crit 2011;183:388–95.

47. Erqou S, Lodebo BT, Masri A, et al. Cardiac dysfunction among people living with HIV: a systematic review and meta-analysis. J Am Coll Cardiol HF 2019;7:98–108.

48. Bigna JJR, Sime PSD, Koulla-Shiro S. HIV related pulmonary arterial hypertension: epidemiology in Africa, physiopathology, and role of antiretroviral treatment. AIDS Res Ther 2015;12:36.

49. Degano B, Yaïci A, Le Pavec J, et al. Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. Eur Resp J 2009;33:92–8.

50. Jin B, Luo X-P, Ni H-C, Shi H-M. Phosphodiesterase type 5 inhibitors for high-altitude pulmonary hypertension. Clin Drug Investig 2010;30:259–65.

51. Heath A, Lang N, Levi DS, et al. Transcatheter closure of large patent ductus arteriosus at high altitude with a novel nitinol device. Catheter Cardiovasc Interv 2012;79:399–407.

52. Heath de Freudenthal A, Tichauer F-P-F, Taboada CRC, Mendes JCL. Pulmonary hypertension and congenital heart defects at high altitude. In: Yuan JX-J, Garcia JGN, West JB, Hales CA, Rich S, Archer SL, editors. Textbook of Pulmonary Vascular Disease. New York: Springer Science+Business Media, 2011:1223–30.

53. Kumar RK, Sandoval J. Advanced pulmonary vascular disease: the Eisenmenger syndrome. Cardiol Young 2009;19:39–44.

54. Boudjemline Y, Patel M, Malekzadeh-Milani S, Szezepanski I, Lévy M, Bonnet D. Patent ductus arteriosus stenting (transcatheter Potts shunt) for palliation of suprasystemic pulmonary arterial hypertension: a case series. Circ: Cardiovasc Interv 2013;6:e18–20.

55. Khan MS, Memon MM, Amin E, et al. Use of balloon atrial septostomy in patients with advanced pulmonary arterial hypertension: a systematic review and meta-analysis. Chest 2019;156:53–63.

56. McManus DP, Gray DJ, Ross AG, Williams GM, He HB, Li YS. Schistosomiasis research in the dongting lake region and its impact on local and national treatment and control in China. PLoS Negl Trop Dis 2011;5:e1053.

57. Butrous G. Human immunodeficiency virus-associated pulmonary arterial hypertension: considerations for pulmonary vascular diseases in the developing world. Circulation 2015;131:1361–70.

58. Sitbon O, Gressin V, Speich R, et al. Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2004;170:1212–7.

59. Lopes AA, Barst RJ, Haworth SG, et al. Repair of congenital heart disease with associated pulmonary hypertension in children: what are the minimal investigative procedures? Consensus statement from the Congenital Heart Disease and Pediatric Task Forces. Pulmonary Vascular Research Institute (PVRI) Pulm Circ 2014;4:330–41.

60. Viswanathan S, Kumar RK. Assessment of operability of congenital cardiac shunts with increased pulmonary resistance. Catheter Cardiovasc Interv 2008;71:665–70.

61. Douwes JM, Hegeman AK, van der Krieke MB, Roofthooft MT, Hillege HL, Berger RM. Six-minute walking distance and decrease in oxygen saturation during the six-minute walk test in pediatric pulmonary arterial hypertension. Int J Cardiol 2015;202:34–9.

62. Beghetti M, Berger RM, Schulze-Neick I, et al. TOPP Registry Investigators Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice. Eur Respir J 2013;42:689–700.

63. Beghetti M, Schulze-Neick I, Berger RM, TOPP Investigators, et al. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: Insights from the Global TOPP Registry (tracking outcomes and practice in paediatric pulmonary hypertension). Int J Cardiol 2015;203:325–30.

64. Condino AA, Ivy DD, O'Connor JA, et al. Portopulmonary hypertension in pediatric patients. J Pediatr 2005;147:20–6.

65. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, Haworth SG. Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with

pulmonary hypertension. Arch Dis Child 2011; 96:141–7.

66. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL registry. Chest 2012;142: 448–56.

67. Twite MD, Friesen RH. The anesthetic management of children with pulmonary hypertension in the cardiac catheterization laboratory. Anesthesiol Clin 2014;32:157–73.

68. Lovell AT. Anaesthetic implications of grown-up congenital heart disease. Br J Anaesth 2004; 93. 129–9.

69. Latus H, Delhaas T, Schranz D, Apitz C. Treatment of pulmonary arterial hypertension in children. Nature Reviews Cardiology 2015;12: 244–54.

KEY WORDS consensus statement, middle- and low-income countries, pulmonary hypertension

APPENDIX For supplemental Methods, figures, tables, and references, please see the online version of this paper.

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.