

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

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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/>).

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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 chal-

lenges 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

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.

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.

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](#).

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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

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.

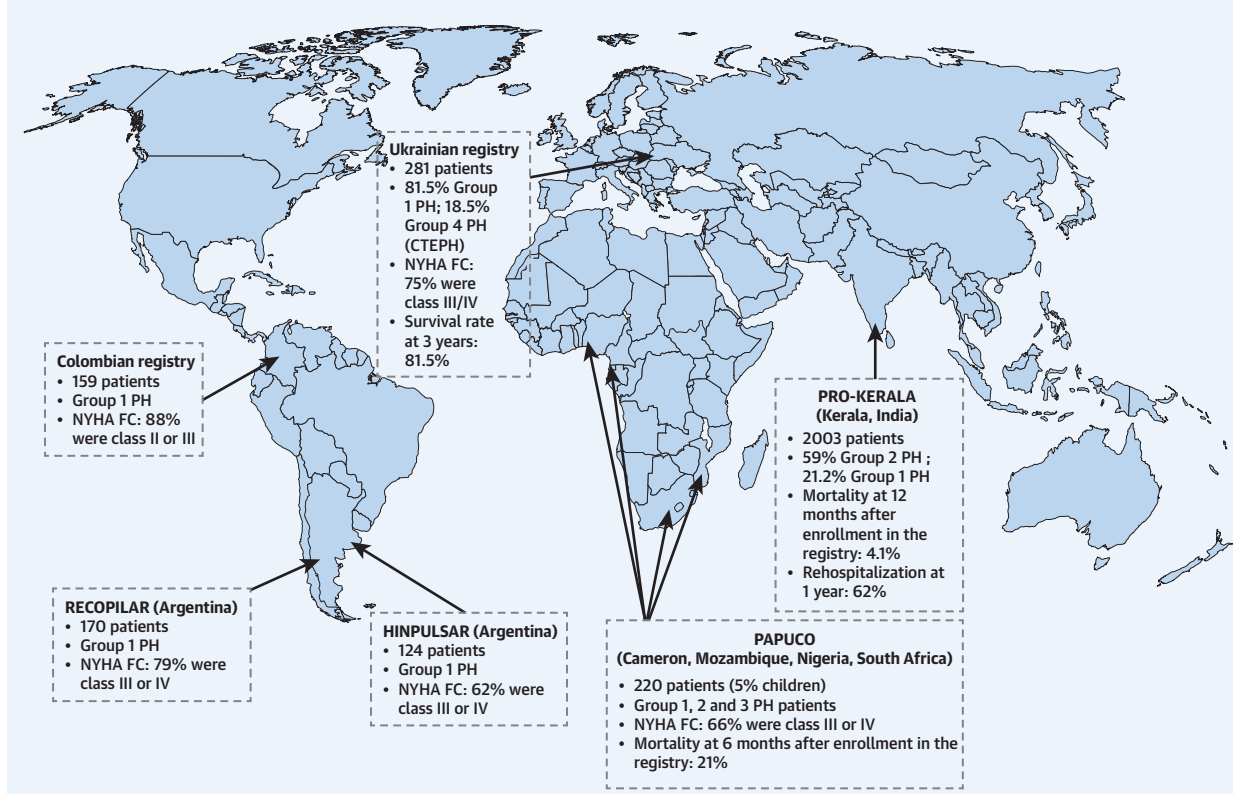
PAH is between 15 and 60 per 1 million adults (13). There is a dearth of data on the incidence, prevalence, and causes of PH (pre-capillary, post-capillary, and combined forms) in MLIRs. Although there are registries in some of the MLIRs (Central Illustration), most of them only have data on patients 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 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**Pulmonary Hypertension Registries in Middle- to Low-Income Regions (MLIRs)**

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, Cameroon, 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 CTEPH (Group 4 PH) patients enrolled.	PAH (Group 1 PH) and CTEPH (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	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Limited availability in selected MLIRs. Expensive.
Supportive medication:	Oral, intravenous	
Diuretic agents		<ul style="list-style-type: none"> Diuretic agents (furosemide, thiazide) should be used with caution given RV hemodynamics.
Spironolactone		<ul style="list-style-type: none"> Recommended use of spironolactone, a supportive medication in PAH and proven to be effective in HFpEF.
Digoxin		<ul style="list-style-type: none"> Digoxin may be useful particularly in PAH with high heart rates.
Beta-blockers		<ul style="list-style-type: none"> Avoid chronic use of beta-blockers in adults with PAH (negative RCT have been published; no pediatric data available).
Iron and vitamins		<ul style="list-style-type: none"> Treat especially iron deficiency.
Oral anticoagulation		<ul style="list-style-type: none"> 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 catheterization available only in selected centers.	Echocardiography and cardiac catheterization available in urban centers.	Echocardiography and cardiac catheterization available in selected centers.	Very limited access to cardiac catheterization and echocardiography usually restricted to major urban areas.	Echocardiography and cardiac catheterization 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.

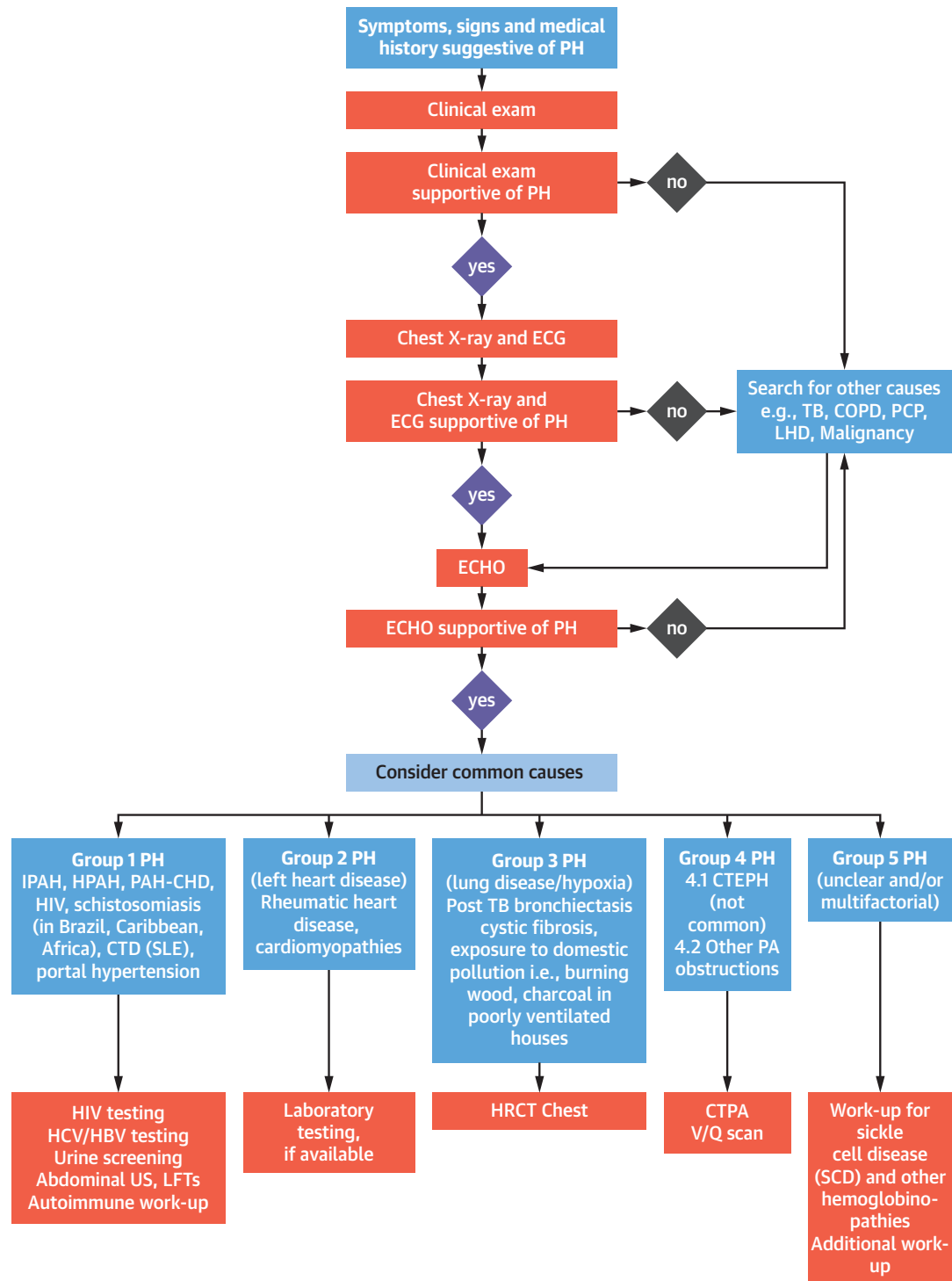
For details, see [Appendix](#).

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 MLIRs. 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 PaO ₂ of >10 mm Hg or SpO ₂ 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; PaO ₂ = 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; SpO ₂ = 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 $\geq 70\%$); 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.

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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.

SUPPLEMENTARY APPENDIX

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

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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
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Abbreviations and Acronyms

AIDS: Acute Immune Deficiency Syndrome

AS = atrial septostomy

AHA = American Heart Association

ASD = atrial septal defect

ATS = American Thoracic Society

AVT = acute pulmonary vasoreactivity testing

CCB = calcium channel blocker

CHD = congenital heart disease

CI = cardiac index

CO = cardiac output

COR = class of recommendation

cGMP = cyclic guanosine monophosphate

CPET = cardiopulmonary exercise testing

DPD = diastolic pressure difference

DPG = diastolic pressure gradient

ECHO = echocardiography

EMA = European Medicines Agency

EPPVDN = European Pediatric PVD Network

ES = Eisenmenger syndrome

ERS = European Respiratory Society

ESC = European Society of Cardiology

FDA = US Food and Drug Administration

HIR = high income regions

HIV = human immunodeficiency virus

IPAH/FPAH/HPAH = idiopathic/familial/heritable pulmonary arterial hypertension

LAP = left atrial pressure

LOE = level of evidence

LV = left ventricle

MLIRs = middle- and low-income regions

MR = mineralocorticoid receptor

NO = nitric oxide

NT-proBNP = NT-pro B-type natriuretic peptide

NYHA = New York Heart Association

PAH = pulmonary arterial hypertension

PAWP = pulmonary artery wedge pressure

PDA = patent ductus arteriosus

PDE5 = phosphodiesterase 5

PH = pulmonary hypertension

PVD = pulmonary vascular disease

PHVD = pulmonary hypertensive vascular disease

PPHN = persistent pulmonary hypertension of the newborn

RAP = right atrial pressure

RCT = randomized controlled trial

RV = right ventricle

TPG = transpulmonary pressure gradient

TI/TM= Thalassemia intermedia/Thalassemia major

VO₂ = oxygen consumption

VSD = ventricular septal defect

WHO = World Health Organization

WSPH = World Symposium on Pulmonary Hypertension

SUPPLEMENTARY TEXT

SUPPLEMENTARY INTRODUCTION

Currently, data pertaining exclusively to pediatric PH in MLIRs does not exist. PH is often a progressive and fatal condition that is common but underdiagnosed in MLIRs, and handled by cardiologists serving both children and adults with limited access to advanced health care resources. These recommendations are mostly based on expert opinion only, as a consequence of limited level of evidence, but this does not short cut the need for advice given the health care burden and limited resources in MLIRs.

SUPPLEMENTARY METHODS

The European Pediatric Pulmonary Vascular Disease Network

The European Pediatric PVD Network (EPPVDN) is a registered non-profit organization that is independent of any medical-scientific society and industry. The network strives to define and develop effective, innovative diagnostic methods and treatment options in all forms of pediatric pulmonary hypertensive vascular disease (PHVD), including specific forms such as PAH-congenital heart disease (CHD), pulmonary hypertension (PH) associated with chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD), persistent PH of the newborn (PPHN), and related cardiac dysfunction.

Goals and Composition of the EPPVDN Writing Group (PH in MLIRs)

The main focus of this manuscript is on group 1 PH, according to the World Symposium of Pulmonary Hypertension (WSPH, Nice, 2018), however, several other groups (2-5) are also discussed. Given the paucity of data on one hand and the unmet medical need on the other, we did include smaller retrospective studies and mono-center registries, where available. The executive writing group (EWG) consisted of 7 pediatricians (with expertise and board certifications in pediatric cardiology,

critical care, and/or neonatology), 5 internal medicine doctors with subspecialty certification for cardiology, including 2 physicians with subspecialty certification for adult congenital heart disease (ACHD; 1 adult cardiology, 1 pediatric cardiology), 1 pediatric intensivist and 1 neonatologist. Selection of EWG members was based on clinical expertise, patient volume, publication records and geographical distribution. Three co-authors are still in training.

Class of Recommendation (COR), Level of Evidence (LOE)

The recommendations in this article relate to the grading system for class of recommendation (COR) and level of evidence (LOE) currently proposed by the European Society of Cardiology (ESC) and the American Heart Association (AHA) (COR, **Table 1**; LOE, **Table 2**), and were primarily based on adult data sets. Specific pediatric recommendations were based on pediatric data only (pediatric studies, or those adult studies enrolling > 10% children). The EPPVDN executive writing group held one face-to-face-meeting, several teleconferences and multiple Email roundtables. 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 US Food and Drug Administration when transferring these recommendations into clinical practice. Challenges specific to MLIRs will be discussed in each section of this manuscript and consensus recommendations will be presented at the end of the document.

Definition of Pulmonary Hypertension and Pulmonary Arterial Hypertension

PH is currently defined as a mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest in patients > 3 months old at sea level, determined by cardiac catheterization (1,2). Pulmonary arterial hypertension (PAH), a form of pre-capillary PH belonging to WHO group 1 PH, is currently defined as mPAP > 20 mmHg, pulmonary artery wedge pressure (PAWP) or left ventricular end-diastolic pressure (LVEDP) \leq 15 mmHg, and pulmonary vascular resistance (PVR) \geq 3 Wood Units in adults, or PVR index \geq 3 Wood Units (WU) \cdot m² in children (under the age of 18 years) (1,3,4), with a

diastolic trans-pulmonary pressure gradient (dTPG) ≥ 7 mmHg as an adjunct criterion (5,6). It should be noted that no data support the cut-off mPAP value of 20 or 25 mmHg in children, but mPAP of > 20 mmHg was defined as PH in children for consistency with the definition for adults at the WSPH 2018 (1,3,6). Based on clinical presentation, pathological changes, hemodynamics and treatment strategies, PH is divided into 5 clinical class groups (1,3). Additionally, based on mPAP, PAWP, cardiac output (CO), diastolic pressure gradient (DPG) and PVR, PH can also be classified into different hemodynamic states (1,4). To account for the heterogeneous etiologies found in pediatric PH (some with pre-natal origin), type of circulation (single or biventricular) and presence or absence of pulmonary vascular disease (PVD), the PVRI Panama classification (2011) is also used to classify pediatric PH (7). For adults with PH, the WSPH 2018 recommends to use PVR (not indexed to body surface area, BSA) ≥ 3 WU, however it is open to debate whether adolescents with high BSA (“tall and heavy”) or adults with rather low BSA should have their PVR indexed to BSA or not, as patients may meet the criteria for PAH only when PVR is indexed to BSA.

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

Several factors intrinsic to MLIRs (8-13) add to the complexity of managing patients with PH. These factors include late presentation of diseases, existing multiple co-morbidities (e.g. infections, malnutrition), unreliable availability of medications, lack of expertise, cost of care, ‘out of pocket’ payment models, limited follow up and absence of multidisciplinary patient units where all services necessary to deal with chronic PH patients are available. Managing such patients and increasing the ultimate outcome of PH patients in MLIRs are a major challenge (10,11,14,15). The authors of this manuscript recommend the readers to refer to more detailed texts that cover different medications, mode of actions and its pharmacodynamics/kinetics.

PAH-Targeted Pharmacotherapy

Health care providers must be aware that PAH-targeted medications are approved for group 1 PH (particularly PAH) and some drugs also for chronic thromboembolic PH (CTEPH), and may be attempted in combined pre- and post-capillary forms of PH with pre-capillary predominance of PH. Phosphodiesterase inhibitors (PDE5i) such as sildenafil, and tadalafil, endothelin receptor antagonists (ERA) such as bosentan, ambrisentan, and macitentan, and the soluble guanylate cyclate stimulators (sGCS) riociguat are now manufactured in India and are locally available at a fraction of the costs compared to prices in HIRs. Parenteral prostacyclin analogues (PCA; inhaled and intravenous) and the oral PCA beraprost are manufactured in China and provided at a low cost there but are unavailable in most other MLIRs. It is important to have a clear discussion with families about the limited information on long-term survival benefit of these medications.

Non-Cardiac Surgeries

General anesthesia carries substantial risk; especially inhaled anesthetic agents (-fluranes) can decrease systemic vascular resistance substantially and may cause cardiorespiratory instability. The physician should have a clear risk-benefit discussion with the patients. An experienced cardiac anesthesiologist should be present and the need for continued intensive care monitoring after the surgery is critical in a child or adult with PH.

SPECIAL THERAPEUTIC CONSIDERATIONS IN MLIRS

PH associated with Schistosomiasis

Schistosomiasis is the most common parasitic disease associated with PH (16). The cause of PH in schistosomiasis is multifactorial including parasitic pulmonary artery embolization, pulmonary vasculopathy and portopulmonary PH related to hepatosplenic disease (16). A high index of suspicion

of schistosomiasis-induced PH should be present when patients present with cardiovascular symptoms and features of PH in a schistosomiasis endemic area, namely Africa, Eastern Mediterranean, South America, and Western Pacific regions (**Figure S1**) (16). In Africa, most of the 78 countries are considered endemic for schistosomiasis, and has 92% of all the people requiring preventive chemotherapy for schistosomiasis. The cornerstone of current schistosomiasis control programs is delivery of praziquantel to at-risk populations - called preventive chemotherapy.

PH associated with Sickle Cell Disease (SCD)

Most people with sickle cell disease (SCD) live in Africa, where the clinical course is more severe and probably influenced by the high co-prevalence of infectious diseases. The number of SCD patients with both pre- and post-capillary PH in France (25%) appears to increase with age, with a mean age of 36 ± 11 years and a prevalence peak at approximately 45 ± 10 years. However, in MLIRs, particularly in sub-Saharan Africa, limited access to health care and co-existing infections such as HIV act as additional risk factors for PH at even younger ages (< 25 years). In SCD, cell free plasma hemoglobin scavenges nitric oxide and generates reactive oxygen species, while binding of heme released from plasma hemoglobin to the toll-like receptor 4 activates the innate immune system (17). These events are the precursors of chronic vasculopathy that leads to PH in 10% of SCD patients, particularly those with the homozygous genotype, of which nearly 50% is pre-capillary while the remainder is post-capillary PH (18). The chronic intravascular hemolysis in SCD may be associated with endothelial dysfunction, including reduced NO bioavailability (see above), coagulopathy, and pro-oxidant and pro-inflammatory stress, which may contribute to the development of proliferative changes in the pulmonary vasculature, like those found in IPAH.

Many patients with SCD have elevated PAWP, as a surrogate of left heart filling pressures (54% in France), resulting from chronically elevated cardiac output, LV diastolic dysfunction, or coronary

ischemia. While cardiac catheterization is required for a formal diagnosis (1,3,4,19), in lower resourced areas ECHO is employed to estimate PAP, PVR, and right atrial (RA) pressure as well as to derive indirect information about right heart structure and function .

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 4469 patients), 206 of 1217 (17%) infants younger than 3 months of age have signs of PH. The latter was defined as an estimated RVSP of more than 40 mmHg (TRV \geq 3m/s) and/or pulmonary acceleration time (PAAT) < than 80 ms). Since the postnatal adaptation takes longer at such high altitude, transient tachypnea of the newborn with low saturation and oxygen dependency is associated with weeks of hospitalization until PVR drops.

CHD at high altitude occurs with a rather different anatomical distribution, e.g. PDA, ASD, tricuspid atresia and Ebstein anomaly are more common than at sea level. For example, children living at high altitude have a ten-fold chance of having a hemodynamically relevant PDA (20). Transposition of the great arteries and hypoplastic left heart syndrome being less frequent, but also evolves completely differently (21). Eisenmenger syndrome is not observed at pediatric age, and severe increase of PVR occurs mostly later in life, which means that patients with large left-to-right cardiovascular shunts (PDA, VSD) should be assessed for operability even after childhood.

PERSPECTIVES FOR PH PATIENTS IN MLIRs (EXTENDED TEXT)

Perspectives for Ukraine, Eastern Europe and Western Asia/Middle East

Data from the first published prospective Ukrainian registry (Table 3), which included 281 adult patients with PAH or CTEPH from a single referral center in Kyiv, showed 1-, 2- and 3 year survival rates of 93.3, 86.8, and 81.5%, respectively (22). These results are comparable to those reported from HIRs, despite many specific problems encountered in PAH treatment in the Ukraine i.e. only sildenafil and inhaled iloprost were approved during the study period (though bosentan and riociguat became available later), treatment was seldom provided due to organizational issues-. However, in 2016, a government drug supporting program for patients with PAH and CTEPH was initiated. The registry also revealed a high prevalence of patients with CHD (48.4%), which might help explain the overall high survival rate of PAH patients in the Ukraine. The majority of these PAH-CHD patients had unrepaired systemic-to-pulmonary shunts or Eisenmenger syndrome, despite a generally free pediatric healthcare system, including access to cardiac surgery. Late diagnosis and poor education of parts of the Ukrainian population might have contributed to the low rate of palliative/corrective cardiac surgery. While robust registry data is only available from the Ukraine, it is likely that these findings are generalizable to other (non-European Union) Eastern European countries/MLIR regions. For example, in Belarus and in Kazakhstan limited PAH drugs are approved for treatment: sildenafil and bosentan in Belarus and sildenafil, bosentan, ambrisentan, and iloprost in Kazakhstan. In Belarus, PAH drugs are supported by the government, and in 2016, a lung transplantation program was started. In Kazakhstan, PAH drugs are usually available for free, but not for all PAH patients. The option of heart or heart-lung transplantation does not exist in Kazakhstan. The member countries of the European Union allow for free mobility within the European Union and, thus, specialized healthcare in Western Europe is often accessible to PAH patients.

China's and Southeast Asia's PH Perspective

In China, the majority of pediatric PAH patients have PAH-CHD; IPAH/HPAH ranks second, which is similar to the adult PAH population (23). BMPR2 mutations occurred in 5.7% pediatric PAH-CHD patients (23). In IPAH/HPAH patients, the percentage of BMPR2 mutations was higher in children (25.6%) than in adults (14.5%) (24), which may be explained by a survival selection bias (25). Although not covered by health care insurance, PDE5i (tadalafil and sildenafil) are less costly than ERAs, and thus most PAH patients are treated with PDE5i monotherapy. Very few patients can afford inhaled or subcutaneous prostanoids, and the approval of intravenous prostanoids is still in process. But the National Healthcare Security Administration, a new agency recently established by the Chinese central government in May 2018, announced in November 2019 that the four main drugs for treating pulmonary hypertension, including Bosentan, Macitentan, Riociguat, and Selexipag, will be fully covered by the country's healthcare insurance system from 2020. The Chinese pediatric PAH registry study enrolled 348 patients under the age of 18 years diagnosed with PAH (in the years 2006-2016). Preliminary results indicate that more than 30% of children with PAH have been treated by the general pediatric physicians before the referral PH center confirmed the diagnosis "PAH" by cardiac catheterization. In the aforementioned Chinese registry, the 5- and 10-year transplantation-free survival for pediatric PH patients was 75% and 61%, respectively (unpublished data, Zhi-Cheng Jing).

Indian Subcontinent's PH Perspective

High birth rates, overcrowding, poverty and disorganized health system are responsible for a high burden of rheumatic heart disease (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. Thus, in these regions, index of suspicion for the above-mentioned conditions should be high on the list of differential diagnoses. There is an urgent need for establishing large registries across the

nations in the South Asia region to define disease burden and to study specific challenges that include defining thresholds for operability in borderline shunt lesions in CHD. The Pro-KERALA PH registry and upcoming registries from Pakistan are examples for such ongoing efforts.

Africa's PH Perspective

Diagnosing PH invasively in Africa is limited by the paucity or lack (e.g. Mali, Niger) of cardiac catheterization facilities, which are mainly provided in major urban areas. Therefore, any larger scale population studies must rely on non-invasive echocardiography. Even echocardiography is not freely available due to limited human resources and low health expenditure per capita. PH in Africa is therefore an under-recognized and undertreated health condition. The etiology of PH in Africa is broad; crude estimates of prevalences for the underlying high risk conditions are as follows: schistosomiasis (170 million), RHD (6.5 million), SCD (12 million), HIV (20 million), and moderate to severe COPD (30 million) (10). Preventive strategies aimed at reducing smoking, household air pollution, elimination of RHD by use of penicillin, treating schistosomiasis early, and avoidance of new HIV infections might eventually contribute to reducing the incidence of PH in Africa as targeted PAH therapy will be out of reach for majority of 1 billion Africans (9).

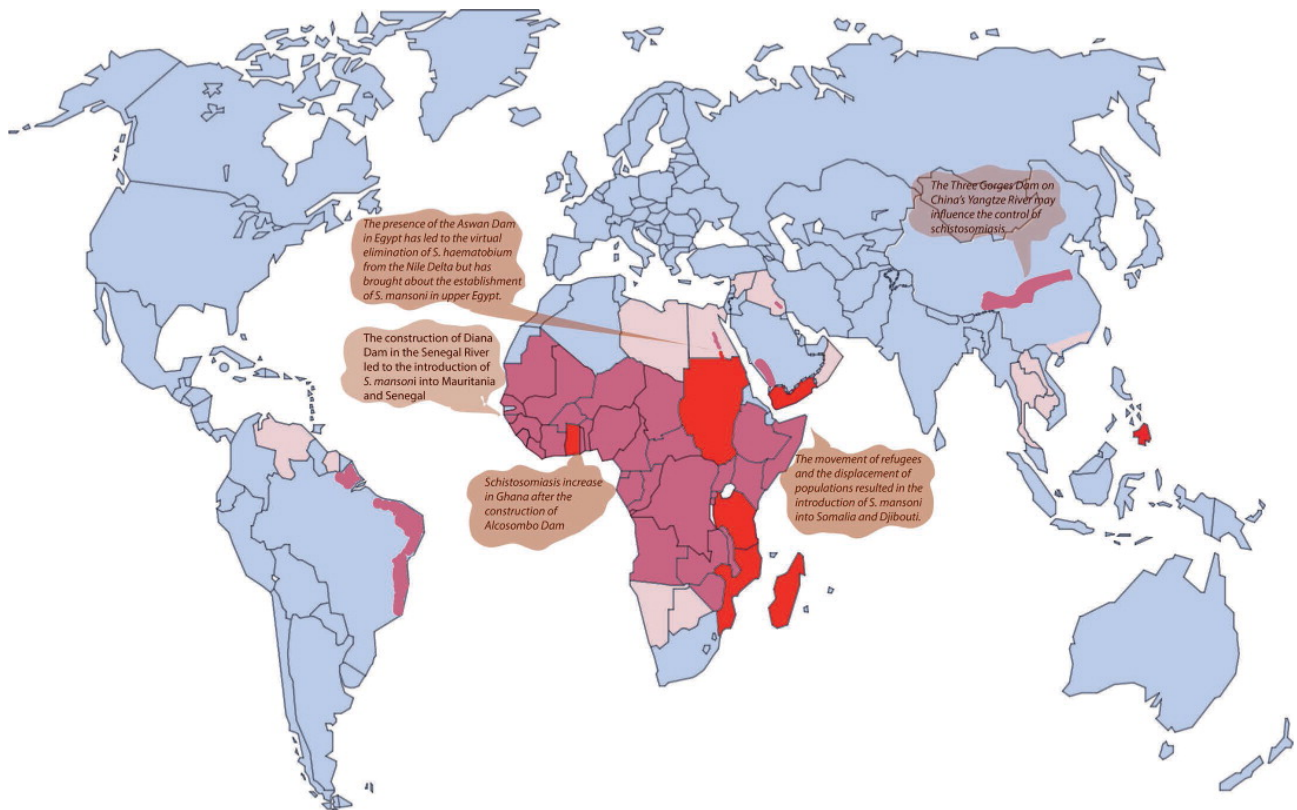
Middle and South America's PH Perspective

Although South American countries such as Chile, Brazil, Colombia and Argentina report to have European standards in the diagnosis and treatment of PAH, a minority of PAH patients have access to the appropriate diagnostic technology and medication, resulting in late diagnosis in majority. Three major etiologies related to geographical location and social inequalities, have been identified in Latin American patients with PH: more than one 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 (26). Nevertheless, in a recent review article covering a 30-year-period (1987-2016), idiopathic PAH has been reported as the most common type of PAH in Latin America – though this ranking may be due to reporting bias (27). In Chile, 80% of the cases were due to idiopathic PAH while connective tissue disease accounted for 13-26% of the cases. In Argentina, PAH-CHD is still prevalent despite a national program for CHD. Oral sildenafil is the first line PAH pharmacotherapy in Middle and South America (27).

SUPPLEMENTARY FIGURES

Online Figure S1: Map of Regions where Schistosomiasis is Endemic



Online Figure S1: Geographical location of schistosomiasis infections throughout the world. Bright red indicate the severe endemic areas. Bubbles indicate the factors that increase the infection rates and/or challenges in controlling the infection.

In Africa, most of the 78 countries are considered endemic for schistosomiasis, and has 92% of all the people requiring preventive chemotherapy for schistosomiasis**.

*With permission, the above map is taken from: Butrous G. Pulmonary Vascular Diseases Secondary to Schistosomiasis. *Advances in Pulmonary Hypertension* 2017; 15: 144-148.

** WHO. Schistosomiasis: World Health Organization; 2019 [cited 2019 March 19]. Available from: https://www.who.int/gho/neglected_diseases/schistosomiasis/en/

SUPPLEMENTARY TABLES

Table S1: Operability in post tricuspid valve left to right shunt lesion in young patients

Modality	Features of Operability	Features of Inoperability
History	Feeding difficulty due to tachypnea Failure to thrive/cachexia Repeated chest infections	“Improvement” in previous symptoms of tachypnea, feeding difficulty and weight loss
Physical Exam		
- Vitals	Normal oxygen saturation at rest with no desaturation on exercise, increased respiratory and heart rate for age*	Desaturation at rest or after exercise, normal respiratory rate Visible cyanosis and clubbing
- Chest and precordium	Sub/intercostal retractions, inspiratory crackles suggestive of pulmonary edema, hyperdynamic precordium and displacement of point of maximal impulse depicting LV volume load	Quiet precordium, no crackles on chest auscultation, parasternal heave depicting right ventricular dilation
- Cardiac auscultation	Splitting of S2, mid-diastolic murmur at the “mitral region” depicting increased flow through the valve	Narrow split S2, loud P2, absence of diastolic flow murmur in mitral region, diastolic murmur of pulmonary regurgitation
ECG	Features of LV volume load i.e. ‘q-waves’ in lateral precordial leads	Features of RV dilation and hypertrophy (prominent ‘R’ wave with ST segment depression in V1-V3), lack of ‘q’ waves in lateral precordial leads
Chest X-ray	Plethoric lung fields, cardiomegaly	Absence of pulmonary plethora
ECHO	Left atrial and ventricle dilation, exclusive or predominant left to right flow across the shunt	Normal LA and LV size, bi-directional flow across the shunt. Large RA and RV?
Exercise Testing	Absence of a decline in saturation or more specifically PaO2 on peak exercise	>10 mm Hg decline in PaO2, or SpO2 decline by 19%-points during exercise may indicate an inoperable shunt due to increased PVR (23, 24)

Table S1: * Thresholds for defining desaturation may vary somewhat depending on the exact conditions. A large ventricular septal defect with overriding of the aorta may still be operable in spite of saturations in the low 90s. ECG: electrocardiogram, ECHO: echocardiography, LA: left atrium; LV: left ventricle; PaO2: arterial partial pressure of oxygen; PVR: pulmonary vascular resistance; RA: right atrium, RV: right ventricle, SpO2: pulse oximeter oxygen saturations.

Table S2: Approach to Diagnosis and Work up for suspected PH in MLIRs

Investigation	Consideration in MLIRs
Detailed history and physical examination	<p>Helps to identify a cause and also evaluates the clinical status of the patient. Family history of sudden death or other members with PH can be a clue for hereditary PH. Similarly, past history of lung disease (group 3 PH) or unexplained anemia (sickle cell or thalassemia intermedia) may point towards other causes of PH. Birth history with postnatal development of PPHN may be a clue as it is a risk factor for onset of PH later in life. Consumption of herbal remedies may be causally related to the PAH (Bush tea and pulmonary veno-occlusive disease).</p> <p>Evaluation of small patella syndrome and toe abnormalities is important and an easy "clue" for the presence of a TBX4 mutation (28).</p>
Arterial blood gas	<p>Elevated arterial partial pressure of carbon dioxide (PaCO₂) levels may suggest a lung parenchymal etiology or hypoventilation. Decrease in arterial partial pressure of oxygen (PaO₂) after walking is predictive of increased PVR and thus can be used to determine operability of shunt lesions.</p>
Comprehensive echocardiogram	<p>Is used to diagnose left sided heart valve disease, obstruction to pulmonary vein drainage (cor triatriatum), undiagnosed pulmonary vein stenosis. Additionally, unrecognized shunt lesions such as patent ductus arteriosus, aorto-pulmonary window and apical muscular ventricular septal defect are easily missed unless carefully looked for.</p>
Abdominal ultrasound	<p>Porto-pulmonary hypertension caused by diseases like schistosomiasis, hepatitis etc. can be identified in most situations rather easily through careful evaluation of the portal vein, hepatic vein and inferior vena cava. Congenital communications between portal vein and the IVC (the Abernathy malformation) can manifest as PH and can potentially resolve if addressed.</p>

Table S2: Abbreviations: IVC: inferior vena cava, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, PPHN: primary pulmonary hypertension of the newborn , PVR: pulmonary vascular resistance

Table S3: Determinants of Risk in Pediatric Pulmonary Arterial Hypertension

Lower Risk	Determinant of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
Normal (height, BMI)	Growth	Failure to thrive
I, II	WHO functional class	III, IV
Minimally elevated for age or not elevated	Serum NT-proBNP	Significantly elevated for age >1200 pg/ml (> 1 yr old). Rising NT-proBNP level.
Mild RA/RV enlargement No RV systolic dysfunction RV/LV ratio < 1 (PSAX) TAPSE normal (> -2 SD) S/D < 1.0 (TR jet) PAAT > 100 msec (> 1 yr old)	Echocardiography, CMR	Severe RA/RV enlargement RV systolic dysfunction RV/LV ratio > 1.5 (PSAX) TAPSE decreased (< -3 SD) S/D >1.4 (TR jet) PAAT < 70 msec (> 1 yr old) Pericardial effusion
CI > 3.0 L/min/m ² mPAP/mSAP < 0.5 mRAP ≤ 10 mmHg AVT +	Invasive Hemodynamics	CI < 2.5 L/min/m ² mPAP/mSAP > 0.75 mRAP > 15 mmHg PVR > 15 WU x m ²

Table S3: Determinants of risk in pediatric PAH, as it refers to increased morbidity (clinical worsening) and mortality. Part of the data is extrapolated from adult studies. See also the 2019 EPPVDN pediatric PH risk score, i.e. Figure S1 in J Heart Lung Transplant 2019; 38(9):879-901.

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Abbreviations: AVT: acute vasoreactivity testing, BMI: body mass index, CI: cardiac index, LV: left ventricle, PAAT: pulmonary artery acceleration time, mPAP: mean pulmonary artery pressures, mSAP: mean systemic arterial pressure, mRAP: mean right atrial pressure, RA: right atrium, RV: right ventricle, TAPSE: tricuspid annular plane systolic excursion, S/D: systolic/diastolic time, PVR: pulmonary vascular resistance.

Table S4: PAH medications in highly populated middle and low income (MLI) countries that are approved for use in adults with PAH by national regulatory agencies in January 2020

MLI Country	Income and Population	Approved PAH Medication	Comment/ PAH Medication available via import/self-pay
China (1)	Upper middle income 1,439 Mio. people	Bosentan, macitentan, riociguat, selexipag (all imported). National administration accounced to cover bosentan, macitentan, riociguat, and selexipag, by the healthcare insurance system from 2020.	Sildenafil (g) (self-pay), tadalafil (g) (self-pay), ambrisentan (g) (self-pay), inhaled iloprost, SC treprostinil (g) self-pay), and IV prostacyclin analogs (PCAs), e.g., treprostinil (g) available but still under the approval process.
India (2)	Lower middle income 1,380 Mio. people	Sildenafil, tadalafil, bosentan, ambrisentan, macitentan, riociguat	IV and inhalational prostacyclin analogs.
Indonesia (4)	Lower middle income 274 Mio. people	Unknown.	Sildenafil (considered off label for PH), beraprost and iloprost
Pakistan (5)	Lower middle income 221 Mio. people	Bosentan	Bosentan, sildenafil, beraprost, and tadalafil are available for self-pay.
Nigeria (7)	Lower middle income 207 Mio. people	Sildenafil PO/IV, Tadalafil PO, both medications approved for use in private sector only (self-pay, imported).	Unknown. Health insurance coverage is only 5% of population.
Bangladesh (8)	Lower middle income 165 Mio. people	Unknown.	Ambrisentan, bosentan, sildenafil, tadalafil
Ethiopia (12)	Low income 115 Mio. people	Unknown.	Unknown.
Philippines (13)	Lower middle income 110 Mio. people	Unknown.	Bosentan, sildenafil, tadalafil
South Africa (25)	Upper middle income 59 Mio. people	Sildenafil, bosentan (private sector, self-pay), riociguat (private sector, self-pay)	Tadalafil (private sector, self-pay), inhaled iloprost (private sector, self-pay)
Colombia (29)	Upper middle income 51 Mio. people	Sildenafil (g), tadalafil (g), bosentan (g), ambrisentan, macitentan (g), riociguat, selexipag, iloprost, epoprostenol, treprostinil.	All approved PAH-medications are available and paid by the government health insurance EPS (in children only those drugs are covered which are approved). Sildenafil is produced in Colombia.
Ukraine (35)	Lower middle income 44 Mio. people	Sildenafil (g), bosentan, ambrisentan, riociguat, inhaled iloprost. While awaiting supply by government, patients may need to buy drugs such as sildenafil (self-pay).	Tadalafil is available for off-label use (self-pay). All approved drugs are supported by government (no health insurance system in Ukraine). All drugs, except sildenafil, are imported. Sildenafil (g), Bosentan (g), inhaled iloprost also available for self-pay.
Mozambique (46)	Low income 31 Mio. people	No PAH-medication is approved in public sector. Sildenafil PO/IV and tadalafil PO are imported (self-pay) and approved for private sector only.	Sildenafil PO/IV (g) (self-pay), tadalafil PO (g) (self-pay), CCBs (g: amlodipine, nifedipine). Supportive therapy: diuretics, digoxin, warfarin.
Kazakhstan (64)	Upper middle income 19 Mio. people	Sildenafil (g), bosentan, ambrisentan, inhaled iloprost (all imported except sildenafil, all self-pay).	Sildenafil (off-label, not imported, self-pay), tadalafil (off-label, not imported, self-pay).
Belarus (96)	Upper middle income 9 Mio.	Sildenafil (g), bosentan (g). All generic drugs supported by government. While awaiting supply by government, patients may need to buy drugs such as sildenafil (self-pay).	Tadalafil (g) (self-pay). Sildenafil and bosentan manufactured in country. Currently, PCAs (iloprost, epoprostenol, treprostinil) cannot be imported (was possible in the past).

Brazil* (6), no MLI country according to our definition	Upper middle income* 213 Mio. people	Sildenafil (g), tadalafil (g), bosentan, ambrisentan, macitentan, riociguat, iloprost (g)	Sildenafil, bosentan and ambrisentan are covered by public health insurance
Russia* (9), no MLI country according to our definition	Upper middle income* 146 Mio. people	Bosentan (g), ambrisentan, riociguat, inhaled iloprost, selexipag.	Sildenafil (g) and tadalafil (g) are available for off-label use. Generic bosentan, tadalafil and sildenafil are manufactured in Russia.
Mexico* (10), no MLI country according to our definition	Upper middle income* 132 Mio. people	Sildenafil (g), tadalafil (g), bosentan (g), macitentan, (g), beraprost, selexipag, riociguat, iloprost (g).	Sildenafil and bosentan are covered by public health insurance (Seguro de Gastos Médicos). All other drugs require self-pay.

Table S4. Highly populated middle and low income (MLI) countries are listed in the order of highest population. The population rank is shown in the first column in parentheses (1-100). Information on country classification by income is taken from the most recent World Bank report.

<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>

The estimated population per country is based on data of the United Nations Population Division

<https://www.worldometers.info/world-population/population-by-country/>

We defined a middle or low income country as a country with a gross domestic product (GDP) per capita of less than 10,000 USD per year. *In Brazil, Mexico and Russia (shaded in grey), the GDP per capita is > 10,000 USD per year, and thus, they do not qualify as MLIR, according to this definitio. The PAH-targeted medication approved by local regulatory agencies is shown in the third column, and comments on availability and approval process of PAH-targeted medications are given in in the fourth column.

Abbreviations: CCBs, calcium channel blocker (amlodipine, nifedipine); PO, per os; IV, intravenous; SC, subcutaneous, PCA, prostacyclin analog; (g), generic medication available at lower costs than originally approved medication.

Table S5: Management of Eisenmenger Syndrome: Special considerations in Low Resource Environments

	Principle	Specific considerations in low resource environments
1.	Thoughtful communication with patient and family	This requires careful balancing cautious optimism with hard facts. There is a need to mitigate feelings of despair and hopelessness resulting from widespread belief among many caregivers that the disease carries a dismal prognosis.
2.	Partner with patients to manage their lives	Many patients live under challenging socio-economic circumstances. Time spent in acquiring a good insight into the lives is necessary to tailor treatment and advice. Information on occupation, marriage, lifestyle, typical physical activity, desire to bear children and family support needs to be ascertained.
3.	Patient education is paramount	It is critical to counsel patient and their families on key triggers of serious events such as pregnancy, physical exertion, common infections. Comprehensive lifestyle advice can go a long way in preventing adverse events.
4.	Eisenmenger syndrome is a multisystem disease	While all services necessary for comprehensive management of Eisenmenger syndrome may be unavailable in most MLIR settings, it is still possible to effectively manage common complications (renal/hepatic/neurological). It is necessary to connect the patient and family with selected caregivers from other specialties.
5.	‘Routine’ phlebotomy should be avoided	Routine phlebotomy targeting a specific haematocrit is still widely practiced in most MLIRs with significant adverse consequences. Phlebotomy should be strictly reserved for patients with hyperviscosity symptoms associated with very high hematocrit levels (> 70-75%).
6.	Lives are potentially saved if we anticipate and prepare for common destabilizing events	Destabilizing events such as pregnancy and non-cardiac surgery require planning and preparation of care and engagement of other care providers.
7.	While PAH medications help to reduce symptoms, they are largely complementary	In most MLIRs, PAH medications are largely limited to certain PDE5 inhibitors (sildenafil/tadalafil) and endothelin receptor antagonists (bosentan, ambrisentan). Prostacyclin analogs are largely unavailable or difficult to administer. It is necessary to emphasize that medications for PAH do not obviate the need for other general measures listed in this table. The exact choice of medications are often dictated by what is available and affordable. In many circumstances, choices are limited to sildenafil or tadalafil. Bosentan or ambrisentan can be added if lifestyle limiting symptoms persist.
8	Surgical cure is largely <u>not</u> realistic	It is essential to emphasize that surgical cure for the cardiovascular defect is often unrealistic and likely harmful.

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