Joint Clinical Statement on the Medical Management of

Pulmonary Hypertension by PVRI Task Force – Sri Lanka

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Introduction

Pulmonary hypertension (PH) is a condition defined by a mean pulmonary artery pressure greater than 20 mmHg at rest and represents a group of disorders rather than a single disease. The World Health Organization classifies PH into five groups based on underlying cause, hemodynamic pattern, and treatment approach:

- **Group 1** is pulmonary arterial hypertension caused by structural changes in small pulmonary arteries;
- **Group 2** results from left heart disease and is the most common form;
- **Group 3** is linked to chronic lung disease or hypoxia;
- **Group 4** is due to pulmonary artery obstruction, most notably chronic thromboembolic pulmonary hypertension, which may be treatable or curable;
- **Group 5** includes multifactorial or unclear causes such as hematologic, systemic, metabolic, or renal disorders.

Overall, the classification highlights that PH has diverse mechanisms and requires cause-specific evaluation and management.

Pulmonary Hypertension (PH) – Comparison Table

WHO Group	Name	Main Mechanism	Common Causes / Examples	Hemodynamic Pattern
Group 1	Pulmonary Arterial Hypertension (PAH)	Structural remodeling of small pulmonary arteries causing increased pulmonary vascular resistance	Idiopathic, heritable (BMPR2), drugs/toxins, connective tissue disease, congenital heart disease, HIV	Precapillary
Group 2	PH due to Left Heart Disease	Backward transmission of elevated pressure from the left heart into pulmonary circulation	HFrEF, HFpEF, mitral/aortic valve disease	Post-capillary
Group 3	PH due to Lung Disease and/or Hypoxia	Chronic hypoxia and lung destruction causing vasoconstriction and loss of capillary beds	COPD, ILD, emphysema, sleep-disordered breathing	Precapillary
Group 4	PH due to Pulmonary Artery Obstruction	Mechanical obstruction of pulmonary arteries	CTEPH (chronic thromboembolic pulmonary hypertension)	Precapillary
Group 5	PH with Multifactorial/Unclear Mechanisms	Mixed or poorly understood pathways	Hematologic disorders, sarcoidosis, metabolic disease, chronic renal failure or dialysis	Variable / mixed

1. Pulmonary Arterial Hypertension (Group 1)

1.1 Scope and Principles

This section outlines the pharmacological management of Pulmonary Arterial Hypertension (PAH) only. These protocols are not applicable to PH associated with left heart disease (Group 2), chronic lung disease (Group 3), or chronic thromboembolic disease (Group 4).

Core Principles

- **International Standards:** Treatment should align with the 2022 ESC/ERS and 2024 WSPH guidelines whenever practicable.
- **Local Constraints:** Prescribing must account for local availability, commissioning agreements, and patient-born costs.
- **Continuity of Care:** PH therapies must never be stopped abruptly due to the high risk of rebound pulmonary hypertension. Long-term supply consistency should therefore be confirmed before treatment initiation.

1.2 Initial Assessment and Vasoreactivity

All patients with suspected Idiopathic (IPAH) or Hereditary (HPAH) PAH must undergo vasoreactivity testing during their baseline right heart catheterisation (RHC). ESC/ERS guidelines (Table 12) include protocols for IV epoprostenol, inhaled nitric oxide or inhaled iloprost, although all three agents can be difficult to source in Sri Lanka. IV adenosine is no longer recommended due to frequent side effects but may be the only practically available option.

Vasoreactive Responders

Patients demonstrating a positive acute response should be treated with high-dose Calcium Channel Blockers (CCB).

- **Preferred Agent:** Diltiazem is the most utilized agent. In patients with a long PR interval on ECG, alternative options include nifedipine and amlodipine.
- **Dosing:** Start modified-release preparations of diltiazem at 200 mg daily, increasing by 100 mg weekly toward the maximally tolerated dose (typically up to 700 mg daily).
- **Goal:** Reassess at 3–6 months aiming for “Low Risk” status and near-normalization of haemodynamics. Failure to reach these targets necessitates transition to the non-vasoreactive algorithm.

Algorithm for Intravenous Adenosine for vasoreactivity testing

Adenosine is an endogenous substance that activates adenosine-2 receptors, resulting in increased cAMP levels and resultant smooth muscle relaxation.

The European PH Guidelines considered it an acceptable alternative for vasoreactivity testing if access to inhaled nitric oxide is not available (Class II, Level a evidence). (1)

The U.S. Expert Consensus Document on PH also recognized its use if inhaled nitric oxide is not available. (2)

However recent guidelines no longer recommend Adenosine as a suitable agent for vasoreactivity test citing high incidence of side effects limiting optimal dosing of adenosine. (3)

Due to unavailability of the recommended agents like nitric oxide, epoprostenol or iloprost we feel it is reasonable to use IV adenosine, as an alternative agent fully understanding its limitations, until the preferred agents are made available in Sri Lanka.

Dosing

Acute vasodilator testing with adenosine is typically accomplished by initiating an infusion at 50 mcg/kg/min increments every 2-5 minutes, until a maximum dose of 250-350 mcg/kg is obtained. Pulmonary arterial pressures and cardiac output are then remeasured and compared to baseline measurements.

Side effects-

Frequent, but most are of short duration due to the short half-life of the medication. Commonly encountered side effects include palpitations, dyspnea, flushing, hypotension, headaches, bronchospasm, bradycardias, heart blocks and chest pain. Although these side effects tend to resolve quickly after the discontinuation of the infusion, they can be severe enough to limit the maximum infusion dosage, confounding the collection of accurate data.

1.3 Non-Vasoreactive PAH: First-Line Combination Therapy

For non-high-risk, non-vasoreactive patients, upfront dual oral combination therapy (ERA + PDE5i) is the recommended standard.

Phosphodiesterase-5 Inhibitors (PDE5i)

- **Sildenafil:** Available free of charge at the point of access in Sri Lanka.
- **Dosing:** Target 40 mg (or 50 mg if generic) TDS if tolerated. Start at 20 mg TDS (25 mg if generic) and uptitrate weekly to improve tolerance.
- **Tadalafil:** Available with a cost implication (~1600 LKR/day for 40 mg).
- **Dosing:** Start at 20 mg OD, uptitrating to 40 mg OD.
- **Clinical Note:** PDE5is are contraindicated with nitrates. PDE5i are usually well tolerated (headaches, flushing, nasal congestion, GI side typically settle with time) but stop if rare visual complication (non-arteritic anterior optic neuropathy, NAION) – rare painless loss of vision, usually occurs soon after starting.

Endothelin Receptor Antagonists (ERA)

- **Bosentan:** Available free of charge.
- **Constraint:** Requires mandatory monthly LFT monitoring due to hepatotoxicity risks.
- **Interaction:** Reduces Sildenafil levels by ~50% and Tadalafil by ~23%, possibly explaining inferior performance to newer ERAs such as macitentan and ambrisentan when used in combination therapy. All ERAs can cause mild anaemia.
- **Macitentan & Ambrisentan:** Available with a cost implication (~950–990 LKR/day).
- **Advantage:** Superior safety profile (low hepatotoxicity – 3 monthly LFT monitoring suffices), once-daily dosing, and better evidence in combination therapy (AMBITION/SERAPHIN trials).

Sri Lanka Recommendation: While Macitentan/Ambrisentan are internationally preferred, Sildenafil + Bosentan remains the most accessible combination due to the zero-cost factor. If the patient can afford it, Macitentan or Ambrisentan + Sildenafil is a more robust combination.

1.4 Advanced and Escalation Therapies

Riociguat (sGC Stimulator)

Riociguat is available in Sri Lanka with a cost implication.

- **Role:** Used as an alternative to PDE5 inhibitors, particularly in patients who have an inadequate response to Sildenafil/Tadalafil.
- **Dosing:** Titrated from 1.0 mg TDS up to a maximum of 2.5 mg TDS as tolerated.
- **Contraindication:** Never combine Riociguat with a PDE5 inhibitor due to the risk of severe hypotension and syncope.

Selexipag (Oral Prostacyclin Receptor Agonist)

Selexipag is available with a significant cost implication.

- **Role:** Typically utilized as the third agent in triple oral therapy for patients who remain at “Intermediate” risk despite dual ERA/PDE5i therapy.
- **Dosing:** Start at 200 mcg BD and titrate weekly in 200 mcg increments to the maximum tolerated dose (up to 1600 mcg BD).
- **Cost Management:** Costs range from 900 LKR to 7200 LKR per day depending on dose.

Inhaled Iloprost (Nebulised Prostacyclin)

- Available in Sri Lanka with a cost implication.
- **Role:** Used for patients requiring prostacyclin pathway intervention as an alternative to intravenous epoprostenol.
- **Administration:** Requires 6–9 inhalations per day via a dedicated nebulizer usually starting from 2.5 mcg.
- **Clinical Note:** The dose schedule and usage instructions will vary depending on the preparation and the appropriate Nebuliser device such as an adaptive aerosol delivery system. Due to the frequent dosing schedule, patient adherence is a significant factor in its efficacy.

1.5 Currently Unavailable Therapies

- As of August 2026, Epoprostenol (IV) and Sotatercept S/C are not currently available in Sri Lanka. Patients requiring these therapies should be managed with maximal available oral/inhaled triple therapy and prioritized for transplant evaluation where applicable.

1.6 IPAH ‘ with cardiopulmonary comorbidities’

- The 2022 ESC/ERS guidelines identify a distinct phenotype of PAH occurring in older patients (typically >60 years) with significant cardiovascular and/or respiratory comorbidities — for example, systemic hypertension, coronary artery disease, obesity, diabetes, or obstructive lung disease — who nonetheless demonstrate significant pre-capillary pulmonary hypertension on right heart catheterisation. This phenotype overlaps haemodynamically with Group 1 PAH but is associated with a less favourable response to PAH-targeted therapy, a higher burden of competing pathology, and greater susceptibility to the side effects of vasodilatory agents.

Clinical Approach

- In accordance with the 2022 ESC/ERS Recommendation Table 11, the guidelines advise **monotherapy** (ERA or PDE5i) rather than upfront dual combination therapy in this subgroup, reflecting the altered risk–benefit balance.
- **Sildenafil** is the preferred initial agent in the Sri Lanka context, for both safety and cost reasons (no monthly LFT monitoring required).
- **Dose escalation or addition of a second agent** may be considered, as per Section 3, on an individual basis if the patient achieves low-risk status and tolerates initial therapy without significant side effects; however, the threshold for escalation should be higher in this phenotype than in patients without comorbidities.

2. Pulmonary Hypertension associated with heart disease (Group 2)

- In patients with Group 2 pulmonary hypertension (PH due to left heart disease), **pulmonary vasodilators / PAH-targeted therapies are Not indicated for routine use**, as randomised trials have not shown clinical benefit and may cause harm, including worsening pulmonary oedema.
- Management should instead focus on **identifying and treating the underlying left heart disease**, including optimisation of heart failure therapy, blood pressure control, rhythm management, and correction of valvular disease where appropriate.

3. Pulmonary Hypertension associated with lung disease (Group 3)

3.1 Scope and Principles

- This section addresses patients with PH secondary to chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or combined pulmonary fibrosis and emphysema (CPFE).

- **Primary Focus:** Treatment must prioritize the optimization of the underlying lung disease (e.g., optimization of COPD, long-acting and short acting (Nebulized) bronchodilators, Home Oxygen Therapy , or pulmonary rehabilitation).

- **Guideline Adherence:** In accordance with 2022 ESC/ERS standards, the use of PAH-targeted therapies is generally Not recommended in Group 3 PH as they may worsen ventilation-perfusion mismatch and gas exchange.

3.2 Pharmacological Management

- **General Avoidance:** Routine use of PDE5 inhibitors, ERAs, or Riociguat is discouraged in most Group 3 patients.
- **Inhaled Treprostinil:** While international guidelines (based on the INCREASE trial) now support inhaled treprostinil for PH-ILD, this agent is not currently available in Sri Lanka.
- **Severe PH Phenotype:** For patients with "severe" PH (e.g., PVR >5 Wood Units) and relatively preserved lung function, some specialists trial Sildenafil — in this situation patients must be monitored closely for any deterioration in oxygenation due to shunting.

4. Chronic Thromboembolic Pulmonary Hypertension CTEPH (Group 4)

4.1 Scope and Principles

- CTEPH is a distinct clinical entity where PH is caused by organized thromboembolic material obstructing the pulmonary arteries.
- **Gold Standard: Pulmonary Endarterectomy (PEA**) surgery remains the treatment of choice for patients with ‘operable’ or 'proximal' disease as it is potentially curative.(currently Not available in Sri Lanka)
- **Multidisciplinary Review:** All patients should be evaluated for surgical operability. If PEA is not feasible, **Balloon Pulmonary Angioplasty (BPA) or medical therapy** should be considered.

4.2 Medical Management

- **Anticoagulation:** Lifelong anticoagulation is mandatory for all CTEPH patients. Either DOACs or warfarin can be used, depending on availability and cost.

- **Riociguat:** This is the only drug specifically licensed and strongly recommended for patients with inoperable CTEPH or persistent/recurrent PH after PEA.
- **Availability:** Available in Sri Lanka with a cost implication.
- **Dosing:** Titrate from 1.0 mg TDS to 2.5 mg TDS as tolerated, monitoring for hypotension.

- **Sildenafil:** In the Sri Lankan context, if Riociguat is cost-prohibitive, Sildenafil can be used "off- label" for inoperable CTEPH based on local specialist discretion, accepting that the evidence base is less robust than for Riociguat.
- **Macitentan:** There is some evidence (MERIT trial) of haemodynamic benefits of Macitentan in inoperable CTEPH. In the Sri Lankan context combination Macitentan and Sildenafil may be considered an alternative to Riociguat monotherapy, depending on costs and availability.
- **Contraindication:** As with Group 1 PAH, Riociguat and PDE5 inhibitors must never be used in combination.

5. Long-Term Oxygen Therapy (LTOT) in Pulmonary Hypertension

5.1 Introduction

Patients with pulmonary hypertension who need an Oxygen assessment should be referred to the local Home Oxygen Assessment pathway under the supervision of a Respiratory Physician. Patients with congenital heart disease (CHD)-associated pulmonary hypertension (PH) are increasingly referred for assessment of hypoxaemia and consideration of LTOT. The physiological interpretation and assessment differ from COPD, while current LTOT thresholds in PAH are largely extrapolated from COPD because PAH-specific outcome data are limited. In congenital heart disease the management differs significantly because oxygen saturation alone may be misleading in patients with shunt physiology or advanced pulmonary vascular disease. Studies have not demonstrated that nocturnal oxygen alters the natural history of advanced Eisenmenger syndrome. Therefore recommendation of home oxygen in Eisenmenger syndrome is only when it produces a documented, consistent and significant increase in arterial oxygen saturation together with symptomatic improvement**.**

5.2 Practical Approach to Oxygen Assessment in CHD-Associated Pulmonary Hypertension

- Objective confirmation of hypoxaemia (SpO_2, ABG, exercise desaturation, 6MWT, Overnight Oxymetry).
- Identify reversible contributors (anaemia, iron deficiency, infection, fluid overload, sleep- disordered breathing, chronic lung disease).
- If Clinically indicated , conduct a trial of Oxygen therapy with objective measurements and assess symptoms, exercise tolerance, walking distance and quality of life.

5.3 Consider LTOT in CHD associated PH when

- Demonstrable clinical benefit exists with objective LTOT assessment as per protocol with ABG.
- If Significant symptomatic improvement is demonstrated.
- Sleep-related hypoxaemia is present.
- Co-existing lung disease contributes to hypoxaemia.
- Oxygen-responsive hypoxaemia is documented.
- Advanced right heart failure is associated with hypoxaemia.

5.4 Do Not Routinely Prescribe LTOT For

- Stable Eisenmenger syndrome with chronic cyanosis.
- Fixed right-to-left shunt physiology.
- Mild asymptomatic desaturation without demonstrable benefit.

- **5.5 Pulmonary Hypertension-Specific Therapy**
- For many patients, pulmonary vasodilator therapy is more important than oxygen therapy. Options include endothelin receptor antagonists, PDE-5 inhibitors, combination therapy, and advanced therapies in selected patients, following the same drug-specific guidance and Sri Lankan availability/cost considerations set out in Section 1 for Group 1 PAH.

- **5.6 When to Refer Back to a Specialist PH Service**
- WHO FC III–IV symptoms, syncope, declining 6MWD, rising BNP/NT-proBNP, progressive RV dysfunction, worsening cyanosis, recurrent admissions, or consideration of advanced PAH therapy.

- **5.7 Key Take-Home Message**
- Any referral for LTOT / Oxygen Therapy should trigger a Re-assessment of PH severity and optimization of PH-specific therapies. Prescription of Home Oxygen if indicated should be done under the supervision of a Respiratory physician.

6. References

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