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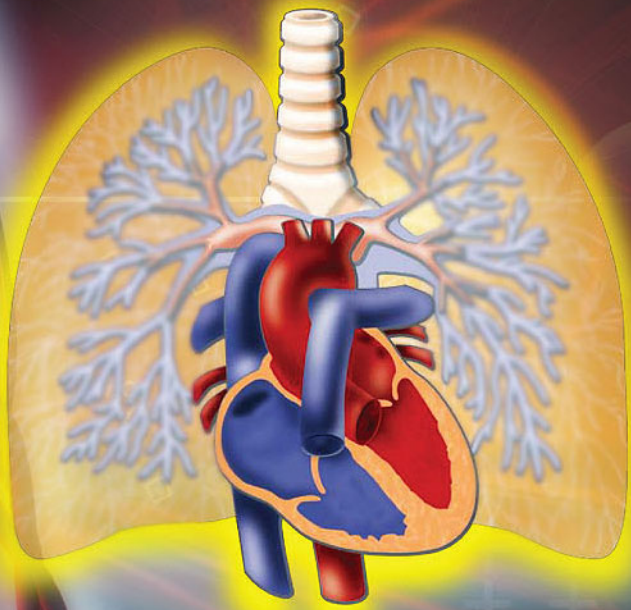
CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH)



MALAYSIAN THORACIC SOCIETY
Malaysian Paediatric Cardiac Society
NATIONAL HEART ASSOCIATION OF MALAYSIA
MINISTRY OF HEALTH MALAYSIA

STATEMENT OF INTENT

These guidelines were developed to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

REVIEW OF THE GUIDELINES

These guidelines have been issued in 2011 and will be reviewed in 2015 or sooner if new evidence becomes available.

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PREFACE

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterised by a progressive increase of pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death. Untreated, it is a potentially devastating disease. However, the past decade has seen remarkable improvements in our understanding of the pathology associated with the condition and the development of PAH-specific therapies with the ability to alter the natural history of the disease. Indeed, the diagnosis, assessment and treatment of PAH is a rapidly evolving area, with changes occurring in the definition of the disease, screening and diagnostic techniques, staging and follow-up assessment, and a growing armamentarium of PAH-specific therapies. These new advances provide a significant opportunity for practitioners to detect and treat patients with PAH in a timely and effective manner, thereby improving overall mortality, morbidity, and quality of life associated with this disease. Our intention is to provide clear and concise descriptions of the new pathological classification and of the recent pathogenetic insights. The diagnostic process will be discussed in order to propose a logical sequence of investigations for aetiology identification, disease assessment and follow-up. Special emphasis will be devoted to an evidence-based treatment algorithm that is unique to Malaysia, yet in-line with internationally accepted guidelines.

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GUIDELINES DEVELOPMENT AND OBJECTIVE

GUIDELINES DEVELOPMENT

The development group for these guidelines consisted of cardiologists (adult and paediatric), pulmonologists, and cardio thoracic surgeons from the Ministry of Health and Institut Jantung Negara, Malaysia. This is the first edition of the PAH CPG. These guidelines have been issued in 2011 and will be reviewed in 2015 or sooner if new evidence becomes available.

These guidelines provide:

a) A description of Pulmonary Arterial Hypertension (PAH) which reflects the devastating nature of PAH that have crucial bearing on the patient's management
b) A description of the basic pathophysiology of PAH
c) A brief discussion on the Dana Point Classification (2008) and WHO Functional Class Classification
d) Guidance on the recognition of clinical features and diagnostic approach of PAH.
e) An algorithm on treatment of PAH with available therapies locally
f) A guide on PAH disease monitoring in accordance with dynamic changes with therapy or with disease progression
g) A guide on management of PAH in congenital heart disease.

Literature search was carried out at the following electronic databases:
PUBMED, Journal full text via OVID search engine, International Health Technology Assessment Website, Cochrane Database of Systemic Reviews (CDSR). In addition, the reference lists of all relevant articles retrieved were searched to identify further studies.

The following MeSH terms or free text terms were used either singly or in combination:
"Pulmonary Arterial Hypertension", "Eisemengers", "PAH-Connective Tissue Disease",
Searches were conducted on databases and literature up to 31 Dec 2010. This date should be considered the starting point for searching of new evidence for future updates to these guidelines.

Reference was also made to 2 other PAH guidelines – American Heart Association/ American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC).

The clinical questions were divided into major subgroups and members of the development group were assigned individual topics within these subgroups. The group members met a total of 20 times throughout the development of the guidelines. All literature retrieved were appraised by at least two members and presented in the form of evidence tables and discussed during group meetings. All statements and recommendations formulated were agreed by the development group. Where the evidence was insufficient the recommendations were derived by consensus of the development group.

The evidence and recommendations were graded using the criteria below:

CLASSES OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

CLASSES OF RECOMMENDATIONS	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/ opinion is in favour of usefulness/ efficacy.
Class IIb	Usefulness/ efficacy is less established by evidence/ opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful.

LEVELS OF EVIDENCE	
Levels of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Levels of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.

Levels of Evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies and registries.

Adapted from the American Heart Association/ AmericanCollege of Cardiology (AHA/ACC) and European Society of Cardiology (ESC)

These guidelines were presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVES

GENERAL OBJECTIVES

To provide evidence-based guidance in the diagnosis and management of PAH in adults and pediatric patients.

SPECIFIC OBJECTIVES

- To guide early diagnosis of PAH in adults and pediatric patients so as to enable referral of PAH cases for prompt specialist care
- To guide in assessment of patients with suspected PAH
- To provide guidance on appropriate and timely PAH management
- To guide on monitoring response to treatment
- To guide on specific aspects of managing PAH in congenital heart disease

CLINICAL QUESTIONS

1. What is the definition of PAH?
2. What is the epidemiology and natural history of PAH?
3. How is PAH diagnosis made?
4. What are the investigations to evaluate PAH?
5. How to manage patients with PAH?

6. What are the conventional and PAH specific therapies available?
7. How to evaluate response to treatment?
8. What are the key issues in managing PAH in congenital heart disease?

TARGET POPULATION

Adult and paediatric patients with PAH as defined in the updated clinical classification of Pulmonary Hypertension (PHT) from Dana Point, 2008. The inclusion criteria are idiopathic PAH, heritable PAH, Connective Tissue Disease associated PAH and Congenital Heart Disease associated PAH. The other types of PAH are excluded.

TARGET GROUP/USER

These guidelines are applicable to physicians, cardiologists (paediatric and adult), pulmonologists, rheumatologists, critical care providers and primary care doctors involved in treating patients with PAH.

HEALTHCARE SETTINGS

Both outpatient and inpatient settings, in secondary and tertiary healthcare.

Proposed Clinical indicators for quality management

i. Exercise Capacity – 6 Minute Walk Distance

$$\text{Percentage of PAH patients who show improvement in serial 6MWD*} = \frac{\text{Number of PAH patients who show improvement in 6MWD}}{\text{Total number of PAH patients tested with 6MWD}} \times 100\%$$

*Serial 6MWD at baseline and after 3 to 6 months post treatment

ii. Survival Rate

$$\text{2 year survival rate on therapy *} = \frac{\text{Number of PAH patients on therapy alive}}{\text{Total number of PAH patients initiated on therapy}} \times 100\%$$

* Therapy for PAH initiated at least 2 years earlier

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EXTERNAL REVIEW
The draft guidelines were reviewed by a panel of independent expert reviewers from both public and private sectors, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence supporting the recommendations in the guidelines.

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SUMMARY OF GUIDELINES

SECTION A: PAH in adults

SECTION B: PAH in children

SECTION C: PAH in congenital heart disease

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SECTION C

REFERENCES

Abbreviations and acronyms

6MWT = six-minute walk test
ACCF = American College of Cardiology Foundation Task Force
ACCP = American College of Chest Physicians
AHA = American Heart Association
bd = twice-daily
BMPR2 =bone morphogenetic protein receptor type II
BNP = brain natriuretic peptide
CCB = calcium channel blocker
CHD = congenital heart disease
CTD = connective tissue disease
CTEPH = chronic thromboembolic pulmonary hypertension
CXR = chest X-ray
DLCO = diffusion capacity for carbon monoxide
EMEA = European Medicines Agency
EGF = epidermal growth factor
ERA = endothelin receptor antagonist
ESC = European Society of Cardiology
ET = endothelin
ETA = endothelin-A
ETB = endothelin-B
FDA = Food and Drug Administration
FGF = fibroblast growth factor
GPCR = G-protein-coupled receptor
HIF-1 alpha = hypoxia inducible factor-1 alpha
IGF-1 = insulin growth factor 1
INR = International normalised ratio
IPAH = idiopathic pulmonary arterial hypertension
LTOT = long term oxygen therapy
mPAP = mean pulmonary arterial hypertension
NFAT = nuclear factor activating T lymphocytes

NADPH = nicotinamide adenine dinucleotide phosphate
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PAP = pulmonary arterial pressure
PCWP = pulmonary capillary wedge pressure
PDGF = platelet-derived growth factor
PFTs = pulmonary function tests
PgI2 = prostacyclin
PHT = pulmonary hypertension
PTE = pulmonary thromboendarterectomy
PVR = pulmonary vascular resistance
QoL = quality of life
RAE = right atrial enlargement
RCT = randomised controlled trial
RHC = right heart catheterisation
RNP = ribonucleoprotein
RVE = right ventricular enlargement
tds = three-times daily
TxA2 = thromboxane A2
TRV = tricuspid regurgitant jet
WHO = World Health Organisation

SECTION A:
PAH IN ADULTS

SECTION A

1. Introduction

Pulmonary arterial hypertension (PAH) is a group of diseases that affect the small pulmonary arteries, and which form a subset of those with pulmonary hypertension (PHT). PAH can be idiopathic, heritable, or associated with a number of conditions, such as connective tissue disease (CTD); congenital heart disease (CHD); portal hypertension; HIV infection, and exposure to toxins and drugs, including appetite suppressants. All of these conditions are characterised by sustained elevations in pulmonary arterial pressure (PAP), increased pulmonary vascular resistance (PVR) with progression to right-sided heart failure and ultimately death.[1] Mortality rates in patients with PAH are high: historically, the median life expectancy of idiopathic PAH (IPAH) without specific therapy is 2.8 years from diagnosis, with 1-year, 3-year, and 5-year survival rates of 68%, 48% and 34%, respectively.[2] In addition, most patients with PAH have a compromised quality of life (QoL) with limited physical activity and social function.[3]

With our rapidly evolving knowledge of PAH, a number of drug classes have been approved based on positive results from randomised clinical trials (RCTs), namely prostanoids i.e. epoprostenol, iloprost, beraprost and treprostinil; phosphodiesterase-5-inhibitors(PDE-5) i.e. sildenafil and tadalafil; and endothelin (ET)-receptor antagonists (ERA) i.e. bosentan and ambrisentan. All of these drugs have the ability to significantly alter the natural course of the disease. However, not all these PAH-specific therapies are available in Malaysia, with patient's access to these drugs limited by cost.

These guidelines aim to highlight the challenges of diagnosing and managing PAH within the context of the Malaysian health care system. From a local perspective, this information may be more clinically useful, and provide a more accurate clinical hierarchy to guide treatment selection based on the weight of available evidence. It is hoped that these guidelines will provide a significant opportunity for practitioners to detect and treat patients with PAH in a timely and effective manner, thereby improving overall mortality, morbidity, and QoL.

2. Clinical classification

The classification of PHT has undergone a series of changes since the first criteria were proposed in 1973. Until recently, PHT was defined by a mean PAP (mPAP) >25 mmHg at rest or >30 mmHg with exercise. However, this classification was recently updated at the 4th World Symposium on PHT, which took place in Dana Point, California, in early 2008.[4] PHT is now defined simply as a resting mPAP>25 mmHg, thereby eliminating the diagnostic criteria associated with exercise. The new Dana Point definition also suggests that a resting mPAP of 8 to 20 mmHg should be considered as normal.[4]

PHT is classified into five categories based in part on aetiology: PAH, PHT owing to left heart disease, PHT associated with lung diseases and/or hypoxemia, PHT resulting from chronic thrombotic or embolic disease, and PHT with unclear multi-factorial mechanisms (Table 1).[4] The classification system aims to frame whether PHT is a manifestation of an underlying disease and provides an understanding of the context in which PHT occurs. PAH, a sub-category of PHT (the two terms are not synonymous), is defined as a mPAP >25 mmHg at rest with a normal pulmonary capillary wedge pressure (PCWP, ≤15 mmHg) and excluding pulmonary venous hypertension.[4-7]

Table 1: Updated clinical classification of PHT (Dana Point 2008)[125]

1. Pulmonary arterial hypertension (PAH)
- 1.1. Idiopathic PAH
- 1.2. Heritable
  - 1.2.1. BMPR2
  - 1.2.2. Activin receptor-like kinase 1(ALK-1), endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3. Unknown
- 1.3. Drug- and toxin-induced
- 1.4. Associated with:
  - 1.4.1. Connective tissue disease
  - 1.4.2. HIV infection
  - 1.4.3. Portal hypertension
  - 1.4.4. Congenital heart diseases
  - 1.4.5. Schistosomiasis
  - 1.4.6. Chronic haemolytic anaemia
- 1.5. Persistent pulmonary hypertension of the newborn
- 1.6. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension owing to left heart disease
- 2.1. Systolic dysfunction
- 2.2. Diastolic dysfunction
- 2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxemia
- 3.1. Chronic obstructive pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4. Sleep-disordered breathing
- 3.5. Alveolar hypoventilation disorders
- 3.6. Chronic exposure to high altitude
- 3.7. Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
- 5.1. Haematologic disorders: myeloproliferative disorders, splenectomy
- 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Patients with confirmed PAH can be classified according to their ability to function and symptom severity. A modified version of the New York Heart Association (NYHA) functional class was adopted by the World Health Organisation (WHO) in 1998 to facilitate the evaluation of patients with PAH (Table 2).[8] Functional class assessments are an important prognostic tool for clinicians.[2, 9, 10] However, the WHO classification system is based almost entirely on symptoms, and it is worth noting that wide variations in clinicians' assessment of PAH can occur.[11]

Table 2: WHO classification of functional status in patients with PHT modified from New York Heart Association classification

Class I	Patients with PHT but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
Class II	Patients with PHT resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class III	Patients with PHT resulting in marked limitation of physical activity. They are comfortable at rest. Less-than-ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV	Patients with PHT with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

3. Pathogenesis

Under normal conditions, the pulmonary circulation is a low-pressure (mPAP 12-16 mmHg), high-capacity circuit. Healthy individuals can accommodate up to a four-fold rise from the resting cardiac output with little increase in PAP, due to distensibility of the thin-walled pulmonary vasculature and to recruitment of vessels that are normally closed when at rest.[12] The excess capacity is such that approximately 70% of the vascular bed must be lost before there is an increase in resting PAP.[12]

Most forms of PAH share a common pathophysiology which includes pulmonary vasoconstriction, remodeling of the pulmonary vessel wall

characterised by intimal thickening, medial hypertrophy and, in advanced disease, thrombosis in situ.[13-15] A single primary cause remains elusive. One mechanism is believed to involve endothelial dysfunction, resulting in over expression of ET-1.[16] Endothelial dysfunction also reduces the synthesis of nitric oxide and prostacyclin (PgI_2), along with over-expression of vasconstrictors such as thromboxane A_2 (TxA_2).[17, 18] These factors work in concert, impairing vasodilatory responses and exacerbating the dysfunctional vasoresponses caused by elevated ET levels.[15, 17-19] Other important pathways in the process of pulmonary vascular remodeling include changes in potassium channel expression, activation of vascular elastases, and increased expression of inflammatory chemokines.[20] Various growth and transcription factors have also been postulated to be involved. These including serotonin[21], platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin growth factor-1 (IGF-1), epidermal growth factor (EGF), hypoxia inducible factor-1 alpha (HIF-1 alpha) and nuclear factor activating T lymphocytes (NFAT).[22, 23]

Genetic factors play an important role in the development of PAH. Mutation of the Bone Morphogenetic Protein Receptor Type II (BMPR2) gene has been identified in approximately 70% of patients with familial PAH and 25% or less of individuals with IPAH without family history.[24] However, the relationship of this gene mutation to the broad range of associated causes of PAH remains unknown, and not all individuals carrying the BMPR2 mutation develop PAH. A subject who possesses the mutation has a 10% to 20% lifetime risk of acquiring PAH, while an individual without the mutation has a lifetime risk of PAH no different to the general population.[25]

Despite the multitude of perturbations that have been demonstrated in clinical PAH as well as in animal models of PHT, it remains unclear which are 'causes' versus consequences of this disorder. Regardless, the end result includes increased vasoconstriction, smooth muscle cell proliferation, decreased vasodilation, and fibrotic changes in medium- to small-sized pulmonary arteries.[13-15] Both vasoconstrictive and hypertrophic changes lead to increased PVR, increasing the workload of the right ventricle. Initially, the right ventricle compensates to maintain adequate pulmonary flow, but as the increased workload causes the right ventricle to dilate, and eventually fails. Symptoms such as dyspnoea and fatigue appear, initially on exertion. Eventually and often suddenly, the right ventricle decompensates and right heart failure ensues.[26] Death occurs as a result of end-stage right heart failure or arrhythmia.[27]

4. Epidemiology and natural history

In 1981, the National Heart, Lung, and Blood Institute of the National Institute of Health (NIH) created a national registry of patients with PAH.[28] From this study it was concluded that the incidence of primary PAH (now referred to as IPAH) was 1-2 cases per million population. In the following 25 years, our understanding of PAH has significantly improved and more recent estimates of PAH in the general community vary from 5 to 52 cases per million population.[29, 30] Furthermore, it is now recognised that IPAH may manifest in both genders and all ages. During childhood, the condition affects both genders equally.[1] After puberty however, detection is more frequent in females (approximately 2:1 ratio).[31, 32]

For secondary causes, PAH is associated with scleroderma in 4.9% to 38.6% of patients[33-37], a condition which itself, has a point prevalence of between 30.8 and 286 cases per million population.[27]

The prevalence of PAH within Asian communities has not been specifically addressed. However, it is likely that more patients will come to the attention of clinicians as a result of awareness and greater access to medical care.

The natural history of IPAH has been well documented.[2] Survival for patients with PAH associated with the scleroderma spectrum of diseases appears to be worse than for IPAH, and the untreated 2-year survival rate may be as low as 40%.[38] With the advent of PAH-specific therapy, more recent registry data indicate that the one year mortality rates in patient with IPAH and connective tissue disease associated PAH (CTD-PAH) have dropped to approximately 12% - 15%.[29, 39, 40]

Predictors of poor prognosis include advanced functional class (IV)[2, 9, 10] and poor exercise capacity (<300m) as measured by the six-minute walk test (6MWT).[10, 41, 42] Several investigators have demonstrated the important prognostic value of cardiopulmonary haemodynamics on survival, namely mPAP, mRAP (>20 mmHg) and CI (<2.0 L/min/m^2).[2, 9, 10] Significant right ventricular (RV) dysfunction[43, 44] and elevated levels of brain natriuretic peptide (BNP)[45] also appear to be independent predictors of survival.

5. Screening

The availability of new therapies that have been shown to slow or prevent progression of PAH has caused a growing interest among physicians to diagnose PAH at an early stage. High risk conditions are shown in Table 3. The American College of Chest Physicians (ACCP) Consensus Statement recommends periodic Doppler echocardiography as part of a screening programme in patients with scleroderma because of the relatively high detection rates in this cohort.[25] Patients with more than one family member with PAH related to a mutation in the BMPR2 might be considered for genetic testing, since a negative test would imply that there is no higher than normal risk of developing PAH. However, any test should be preceded by extensive family and genetic counselling.[46] Other potential causes of PAH (e.g., previous use of appetite suppressants, HIV infection, other CTDs), do not warrant routine screening.

Table 3: Patients at risk of developing PAH[46]

Patient characteristics	Risk profile
Patients with known genetic mutations predisposing to PAH	20% chance of developing PAH
First degree relatives in a FPAH family	10% chance of developing PAH
Scleroderma spectrum of disease	27% prevalence of PAH (RSVP >40 mmHg)
Portal hypertension in patients considered for liver transplantation	5% prevalence of PAH (mPAP >25 mmHg and PVR >3.0 U)
Congenital heart disease with systemic to pulmonary shunts	Likely approximately 100% in high flow, non-restrictive L-R shunts
Use of flenfluramine appetite suppressants (>3 months)	Prevalence of 136/million users based on odds ratio of 23 times background
HIV infection	Prevalence 0.5/100
Sickle cell disease	Prevalence 9.0/100 (TRV >3.0)

PHT, pulmonary hypertension; PAH, pulmonary arterial hypertension; FPAH, familial pulmonary arterial hypertension; RVSP right ventricular systolic pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; L-R, left-to right; HIV, human immunodeficiency virus; TRV, tricuspid regurgitation velocity; RHC, right heart catheterisation.

6. Diagnosis

The diagnosis of PAH is, in part, through the exclusion of other diseases. It requires a series of investigations that are intended to make the diagnosis, clarify the clinical class of PAH, the type of PAH and to evaluate the degree of functional and haemodynamic impairment. Formal guidelines and consensus documents have been published by the European Society of Cardiology (ESC)[5], the National Pulmonary Hypertension Centres of the UK and Ireland[47], the ACCP[6, 25, 48] and the American College of Cardiology Foundation Task Force (ACCF)/American Heart Association (AHA).[49] In addition, systemic sclerosis groups have published proposed assessment pathways for the detection of PAH in this cohort.[26]For practical purposes it can be useful to adopt a sequential approach that includes four stages[5] as follows:

I. Clinical suspicion of PHT
    - Symptoms, physical examination and incidental findings.

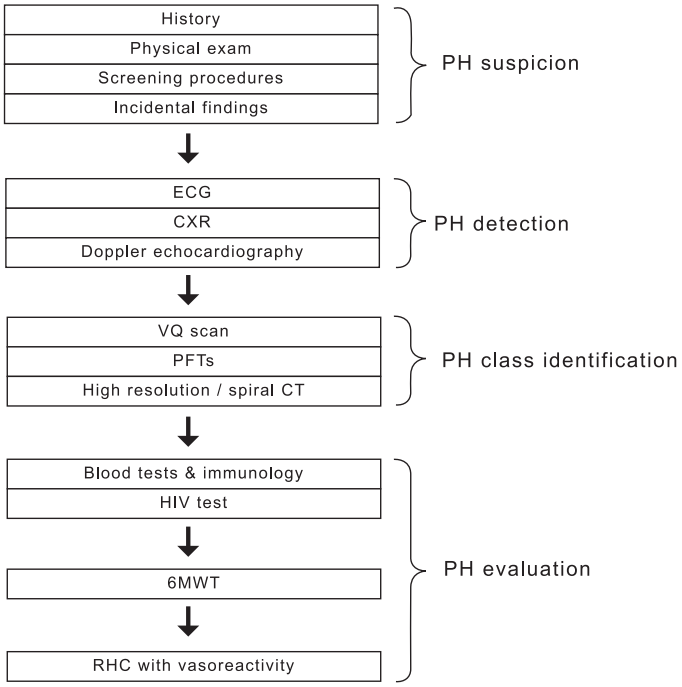
II. Detection of PHT
    - Electrocardiogram, chest X-ray and Doppler echocardiography.

III. PHT clinical class identification
    - Pulmonary function, ventilation/perfusion scans, computerised tomography (CT), and pulmonary angiography.

IV. PAH evaluation
    - Type, functional capacity, and cardiopulmonary haemodynamics.

The approach to diagnosis is summarised in Figure 1.[5, 49]

Figure 1: Diagnostic approach to PAH (adapted from McLaughlin et al.,[49] and Galie et al.[5])



6MWT , 6-minute walk test; CT, computerised tomography; CXR, chest X-ray; ECG, electrocardiogram; HIV, human immunodeficiency virus screening; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterisation; VQ Scan, ventilation-perfusion scintigram.

6.1. Clinical suspicion of PHT

In the initial stages, the most common symptoms of PAH include breathlessness, fatigue and near syncope.[28] Since these symptoms are non-specific, PAH is often overlooked or under-recognised until its later, more advanced stages (such as the onset of right heart failure).This pattern of presentation may also be responsible for underestimating the true prevalence of the disease.

The clinical suspicion of PHT should arise in any case of breathlessness without overt signs of specific heart or lung disease or in patients with underlying lung or heart disease whenever there is increasing dyspnoea unexplained by the underlying disease itself.[5, 47] Clinicians should also be alerted by the presence of symptoms in patients with conditions that can be associated with PAH such as CTD, portal hypertension, HIV infection and CHDs with systemic-to-pulmonary shunts.

6.1.1. Physical examination

The likelihood of PAH is increased when certain findings are present on physical examination. Notable findings include, a left parasternal heave produced by the impulse of the hypertrophied right ventricle, an accentuated pulmonary component of the second heart sound (S2), pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency, right ventricular S3, jugular vein distention, hepatomegaly, peripheral oedema, ascites and cool extremities.[25, 48] However, the absence of these findings does not exclude PAH.

PAH may also be associated with a variety of comorbid conditions. Therefore, past medical history and symptomatic evidence of a related illness should be considered. Potential exposure to toxic agents should be explored, including previous use of appetite suppressants and chemotherapy agents (e.g., mitomycin-C, carmustine, etoposide, cyclophosphamide and bleomycin). Known exposure to HIV infection, and a history of pulmonary embolism or deep vein thrombosis should also be considered.[26] Orthopnea and paroxysmal nocturnal dyspnea suggest elevated pulmonary venous pressure and pulmonary congestion due to left-sided cardiac disease. Raynaud phenomenon, arthralgias, or swollen hands and other symptoms of CTD in the setting of dyspnoea should raise the possibility of PAH related to CTD. A history of snoring or apnoea provided by the patient's partner warrants evaluation for sleep-disordered breathing as a potential causative or contributory factor.[25]

6.2. Detection of PHT

To confirm the diagnosis of PHT, several investigations are required, namely an electrocardiogram (ECG), chest X-ray (CXR) and transthoracic Doppler echocardiogram.

6.2.1. ECG

ECG changes associated with PAH include right ventricular hypertrophy and right axis deviation in 87% and 79% of patients, respectively.[25, 48] The ECG lacks sufficient sensitivity to serve as an effective screening tool for PAH, and it is important to note that a normal ECG does not exclude the presence of severe PHT.

6.2.2. CXR

In the majority of patients with mild PAH, a CXR is normal. In more advanced disease, signs suggestive of PAH include enlarged main and hilar pulmonary arterial shadows with concomitant attenuation of peripheral pulmonary vascular markings ('pruning'). Right ventricular enlargement is often detected by impingement of the anteriorly situated right ventricle silhouette into the retrosternal clear space on the lateral CXR.[25, 48]

6.2.3. Transthoracic Doppler Echocardiography

Doppler echocardiography is the most useful non-invasive tool and should be employed in patients with suspected PHT to assess pulmonary artery systolic pressure (PASP), right ventricular enlargement (RVE), right atrial enlargement (RAE) and RV dysfunction.25, 48 An adequate Doppler signal from the tricuspid regurgitation jet is required to estimate PASP and can be obtained in approximately 75% of patients.5 PASP is equivalent to right ventricular systolic pressure (RVSP) in the absence of pulmonary outflow obstruction. RVSP is estimated by measurement of the systolic regurgitant tricuspid flow velocity v(m/s) and an estimate of RAP applied in the formula: RVSP = 4v2 + RAP (mmHg). The new DanaPoint guidelines recognise that PASPs are dependant on age, gender and body mass index. In general, however, a tricuspid flow velocity >2.8 m/s and a tricuspid insufficiency peak gradient ≥31 mmHg at rest are considered suggestive of PHT.50 It should be noted that, using this definition, a number of false positive diagnoses can be anticipated especially in aged subjects and confirmation with RHC is required in symptomatic patients.

To exclude PHT due to left-heart disease, left ventricular systolic and diastolic function, and valve morphology and function should also be assessed. Finally, echocardiography with contrast should be used to identify or rule out PAH due to CHD (e.g., abnormal morphology; shunt).

6.3. PHT clinical class identification

Once PHT is detected, identification of associated aetiology by major classes (Table 1)[4] is required. This will be guided by clinical circumstances and may include pulmonary function tests (PFTs), ventilation and perfusion (V/Q) lung scanning, in addition to the Doppler echocardiography measures outlined above. Additional tests, such as high resolution CT, spiral CT and pulmonary angiography may also be required. (Table 4)

6.3.1. PFTs

Although lung function abnormalities have been described in association with PAH they are generally mild and unlikely to be the primary cause of symptoms. PFTs are therefore used to exclude significant lung disease. The exception is a marked impairment in DL_{CO} associated with systemic sclerosis. The DL_{CO} of 20% of patients with limited systemic sclerosis is below normal; however, a DL_{CO} of <55% of predicted increases the likelihood of the presence or future development of PAH.[25, 48]

6.3.2. V/Q lung scanning

V/Q lung scans should be performed to rule out chronic thromboembolic pulmonary hypertension (CTEPH) - a potentially curable cause of PHT.[25, 48] Patients with PHT who have normal V/Q scans are unlikely to have chronic pulmonary embolism and more likely to have IPAH. In three studies, V/Q scanning showed sensitivity of 90% to 100% with a specificity of 94% to 100% for distinguishing between IPAH and CTEPH. A positive V/Q scan in patients with CTEPH generally shows one or more segmental-sized or larger mismatched perfusion defects and warrants pulmonary angiography for definitive diagnosis.[25, 48]

6.3.3. Contrast enhanced spiral CT and pulmonary angiography

Contrast enhanced spiral CT is indicated in PHT patients when the V/Q lung scintigraphy shows segmental or sub-segmental defects of perfusion with normal ventilation. Although a V/Q scan is better at ruling out CTEPH, a common practice has been to subject patients to CT pulmonary angiography to assess for pulmonary embolism. Typical findings of pulmonary embolism include complete occlusion of pulmonary arteries, eccentric filling defects consistent with thrombi, recanalisation, stenoses or webs.[5]

Pulmonary angiography may be useful to confirm CTEPH and assess potential operability for pulmonary thromboendarterectomy.

Table 4: Specific tests to be considered when specific underlying cause is suspected

Causes	Test
Pulmonary hypertension owing to lung diseases and/or hypoxia	Lung function test, high resolution CT thorax, sleep study, lung biopsy
PAH associated with connective tissue diseases	Anti-ds DNA, rheumatoid factor, extractable nuclear antigen, anti-centromere antibody, anti SCL70, anti-RNP, complement levels
PAH associated with portal hypertension	Hepatitis viral serology, abdominal ultrasound (liver cirrhosis, portal hypertension)
Chronic thromboembolic pulmonary hypertension	Thrombophilia screen • Protein C, protein S, antithrombin III, lupus anticoagulant, anticardiolipin antibody, factor V Leiden Imaging for pulmonary thromboembolism • Doppler ultrasound of pelvic-femoral veins, ventilation-perfusion (V/Q) scan, CT pulmonary angiography, invasive pulmonary angiography

6.4. PAH evaluation

When the clinical class of PAH has been determined, additional investigations may be required for the exact identification of the type of PAH and to assess the severity of the disease. Blood tests, exercise capacity and cardiopulmonary haemodynamics are commonly assessed.

6.4.1. Blood tests and immunology

Routine biochemistry, haematology and thyroid function tests are recommended in all patients. Screening for CTD consists of antinuclear antibodies (ANA), and rheumatoid factor. Other tests may include dsDNA antibodies, extractable nuclear antigen, anti-centromere antibody, anti- SCL70 and ribonucleoprotein (RNP). A HIV serology test should also be performed.[5] A thrombophilia screen is useful and may include antiphospholipid antibodies (e.g., lupus anticoagulant, anticardiolipin antibodies) in patients with CTEPH.

6.4.2. Assessment of exercise capacity

Assessment of exercise capacity, using the 6MWT is a firmly established part of the evaluation for PAH.[51]The goals of exercise testing include, but are not limited to, determining maximal exercise tolerance; identifying functional capacity; obtaining prognostic data; establishing a baseline measure of exercise capacity and for monitoring response to therapy.[25, 48]

Distances of <300 m are predictive of poorer outcomes.[42] However, the sensitivity to change diminishes as the distance walked increases, particularly >450 m.[47] Consequently, the 6MWT may be less useful for patients in WHO functional class I and II.

6.4.3. Right-heart catheterisation

RHC is required to confirm the presence of PAH, establish the specific diagnosis including exclusion of pulmonary venous hypertension, determine the severity of haemodynamic impairment, test the vasoreactivity of the pulmonary circulation, and to guide subsequent therapy.[25, 48] Parameters that should be obtained during the RHC include RA pressure, RV pressure, PA pressure (systolic, diastolic, mean), PCWP and CO. Haemodynamic findings that confirm PAH include a mPAP ≥25 mmHg at rest and a PCWP ≤15 mmHg.[4] A PCWP >15 mmHg may indicate left heart disease and requires careful evaluation as PAH specific therapies may be contraindicated.[25, 48] An elevated mRAP, mPAP,

reduced cardiac output and central venous O_2 saturation in patients with IPAH is associated with a poor prognosis.[5]

A vasodilator study should be performed in patients with IPAH during RHC. A positive response is defined as a drop in mPAP of ≥10 mmHg to an absolute mPAP of ≤40 mmHg without a decrease in cardiac output[5], and indicates that a patient may be suitable for a trial of high dose calcium-channel blockers (CCBs).[48] It should be noted that less than 10% of patients with IPAH demonstrate a positive acute vasoactive response[52] and even less in other associated conditions, such as PAH related to CTD. In many centres the test is omitted because the response is so infrequent.[49] Furthermore, assessment of vasoreactivity is not without risk and may not be advisable in high-risk individuals (such as those with WHO functional class IV disease). Owing to the potential risk of severe life-threatening haemodynamic compromise occurring with the acute vasodilator challenge, testing should be performed using a safe, potent, and short-acting vasodilator with limited side effects (Table 5).[48]

Table 5: Route of administration, half-lives, dose ranges, increments and duration of administration of the most used substances on pulmonary vasoreactivity tests[5]

Drug	Route	Half-life	Dose range[a]	Increments[b]	Duration[c]
Epoprostenol	Intravenous	3 min	2-12 ng/kg/min	2 ng/kg/min	10 min
Adenosine	Intravenous	5-10 s	50-350 ug/kg/min	50ug/kg/min	2 min
Nitric oxide	Inhaled	15-30 s	10-20 ppm	-	5 min[d]

a Initial dose and maximal dose suggested.
b Increments of dose by each step.
c Duration of administration on each step.
d For NO a single step within the dose range is suggested.

Recommendation
Right heart catheterization is necessary to confirm diagnosis and assess severity of PAH

7. Treatment

The aim of therapy in patients with PAH is to improve survival, disease-related symptoms and QoL. Treatment can be classified as conventional therapy and targeted PAH-specific therapy.

7.1. Conventional treatment

Conventional treatment options include oxygen therapy in cases of hypoxaemia, anticoagulants such as warfarin, and digoxin with diuretics in cases of right-sided heart failure.

7.1.1. Oxygen (Level of evidence C)

Oxygen can be used in patients who have nocturnal hypoxaemia due to mild hypoventilation. Desaturation during sleep occurs in the early mornings and can be associated with syncope and seizures. Some patients with severe PAH develop hypoxaemia and may benefit from supplemental oxygen. Those with PO^2 < 60mmHg should be considered for long term oxygen therapy (LTOT)

Recommendation
Supplemental oxygen should be considered in PAH patients with hypoxaemia (Class of recommendation I)

7.1.2. Anticoagulation (Level of evidence C)

In the absence of contraindications, anticoagulation is recommended as a part of the general treatment regimen to decrease the likelihood of thromboembolic complications. Warfarin is the anticoagulant of choice and the International Normalised Ratio (INR) should be maintained between 2 to 3. However, for IPAH patients with a higher risk of bleeding, the target INR should be 1.5 to 2.5.[49]

The evidence for favourable effects of warfarin is based on two retrospective series: 3-year survival improved from 21% to 49% in the series reported by Fuster et al.,[13] and the 3- and 5-year survival rates increased from 31% to 47% and from 31% to 62%, respectively, in the series reported by Rich et al.[54] For patients with CTEPH, adequate anticoagulation is important to prevent further thromboembolism.

Recommendation
Anticoagulation should be considered in IPAH patients unless contraindicated (Class of recommendation II)

7.1.3. Digoxin (Level of evidence C)

Digoxin has been shown to improve cardiac output acutely in IPAH, although its efficacy is unknown when administered chronically.[47] It may be useful in patients with atrial fibrillation and in PAH patients with heart failure who remain symptomatic on medical therapy.

Recommendation
Digoxin can be considered in PAH patients with heart failure with or without atrial fibrillation (Class of recommendation IIb)

7.1.4 Diuretics (Level of evidence C)

In patients with right heart failure secondary to PAH, increased filling pressure can further distend an already dilated right ventricle, which in turn can worsen function and decrease cardiac output. Therefore, although no RCTs exist, decreasing right ventricular preload with the aid of diuretics is the mainstay of treatment for patients with right heart failure.

Recommendation
Diuretics should be given to PAH patients with right heart failure. (Class of recommendation I)

Recommendation
Only patients who demonstrate a positive vasoreactive response should be treated with high dose CCBs. (Class of recommendation I)

7.1.5. Calcium channel blockers (Level of evidence C)

If, during RHC, the pulmonary vasoreactive test is positive, the treatment of choice is high-dose CCBs (up to 240 mg/day of nifedipine or up to 900 mg/day of diltiazem), as improved survival with long-term use has been demonstrated in this cohort of patients.[54, 56] If CCBs demonstrate no clinical improvement after one month or are unable to achieve WHO functional class I or II with associated improvement in haemodynamics over three months, then patients should be treated as non-responders and PAH-specific therapies considered.

7.1.6. Vaccination (Level of evidence C)

Annual influenza and pneumococcal pneumonia vaccination are recommended in patients with PAH.[5, 47] Patients with PAH who develop pneumonia should be treated early and appropriately. Dehydration and vasodilatation during infection should be avoided and/or adequately treated.

Recommendation
Patients with PAH should receive influenza and pneumococcal vaccinations. (Class of recommendation I)

7.1.7. Avoid Pregnancy (Level of evidence C)

Pregnancy in patients with PAH is associated with a high risk of maternal death. PAH is a contraindication to pregnancy and an appropriate method of birth control is highly recommended in women with childbearing potential. Should the patient become pregnant, she should be informed of the high risk of pregnancy, and advised termination of pregnancy. For those who insist on

Recommendation
Patients with PAH must avoid pregnancy. (Class of recommendation I)

continuing pregnancy, management requires close collaboration between obstetricians and the PAH team and disease-targeted therapies.[57,58]

Recommendation
Appropriate physical activity is encouraged.
(Class of recommendation IIa)

7.1.8. Physical Activities (Level of evidence B)

Patients should be encouraged to be active as their symptoms allow.[47] However, excessive physical exertion leading to distressing symptoms should be avoided. A recent study demonstrated an improvement in exercise capacity in patients who took part in a training programme.[59]

7.1.9. QoL and non-pharmacological treatment

PAH is a chronic, life-shortening disease and many patients suffer from limitations in their physical mobility, energy, emotional reactions and social isolation. Understandably, many patients are affected by a degree of anxiety and/or depression that can have a profound impact on their QoL. Assisting patients to adapt to the uncertainty associated with their illness is important, as is referral to psychologists or psychiatrists when needed. Support groups for patients, families and carers are useful in improving the understanding and the acceptance of the disease.

7.2. PAH-specific therapy

In Malaysia, therapeutic options for patients classified with WHO functional class II, III or IV disease include bosentan, ambrisentan, iloprost and sildenafil. The following is a summary of the evidence from clinical trials performed with these agents. For a review of agents not available in Malaysia, readers are directed to Jacobs and Vonk-Noordegraaf 2009[60], Kingman 2009[61], and Barst 2007[62], respectively.

7.2.1. Bosentan (Level of evidence A)

Bosentan is an oral dual endothelin-A (ET_A) and endothelin-B (ET_B)-receptor antagonist. Activation of ET_A and ET_B-receptors on smooth muscle cells mediate the vasoconstrictive and mitogenic effects of ET-1, and the prominent role of ET-1 in the pathogenesis of PAH has been well documented.[63-68] The

efficacy of bosentan has been extensively studied in five RCTs[69-73] (including one in patients with CTEPH[74]), and several open-label studies.[3, 75-79] In these trials, bosentan was associated with improvements in exercise capacity,[69, 73, 76] WHO functional class,[69, 73, 76] cardiopulmonary haemodynamics,[69, 73, 76, 78] QoL,[3, 76] echocardiographic variables,[78] and time to clinical worsening[69, 73] compared with placebo and conventional therapy. On the basis of these results, bosentan has a level A recommendation in patients with WHO functional class II and III PAH. A summary of patient characteristics and results from RCTs with bosentan versus placebo is presented in Appendix 1 and Appendix 2.

Long-term administration of bosentan has also been shown to deliver favourable results. In 2005, McLaughlin et al., published survival data from an open-label extension study of patients involved in the pivotal bosentan clinical trials.[80] The Kaplan-Meier estimate of survival at 2-years was 89%. Similarly, Provencher et al., published a retrospective analysis of 103 PAH patients treated with bosentan and followed over 24 15 months.[81] One, 2- and 3-year estimates of survival were 92%, 89% and 79%, respectively. More recently, a prospective, multicentre, Australian registry enrolled 528 patients between 2004 and 2007.[39] All patients were initiated on first-line bosentan. The observed annual mortality in this 'real-life' registry was 11.8% in patients with IPAH and 16.6% in patients SSc-PAH. A summary of patient characteristics and results from long-term extension studies and registries with bosentan is presented in Appendix 3 and Appendix 4. Results are listed alongside historical data from the NIH registry.

The recommended dosage of bosentan in PAH is 62.5 mg bd to 125 mg bd. Common side effects include hepatic dysfunction, headache, flushing, lower limb oedema, palpitation, dyspepsia, fatigue, nasopharyngitis and pruritus. The most notable side effect is liver aminotransferase elevations - a class effect of all ERAs. Abnormal liver function tests occurred in 12.8% of patients in bosentan clinical trials but a post-marketing surveillance system (Tracleer PMS) reported elevated aminotransferases 7.6% patients and furthermore, only 3.2% patients discontinued bosentan as a result.[79]Liver function monitoring is recommended in all patients receiving ERAs. These results suggest that elevated liver aminotransferases can be effectively managed in the majority of patients receiving bosentan.

7.2.2. Ambrisentan (Level of evidence B)

Ambrisentan is a selective endothelin-A receptor antagonist and has been approved for the treatment of WHO-FC II and III patients with PAH. A pilot study and two large RCTs (ARIES 1 and 2) have demonstrated efficacy on symptoms, exercise capacity, haemodynamics, and time to clinical worsening of patients with IPAH and PAH associated with CTD and HIV infection.[82-84] The current approved dose is 5mg daily which can be increased to 10mg daily if tolerated. The incidence of abnormal liver function tests ranges from 0.8 to 3%. In a small group of patients who were intolerant to either bosentan due to liver function test abnormalities, ambrisentan at a dose of 5mg was well tolerated. However, patients treated with ambrisentan require regular liver function testing. Ambrisentan has been associated with increased incidence of peripheral oedema.

7.2.3. Iloprost (Level of evidence B)

Iloprost is a prostacyclin derivative and was approved by US Food and Drug Administration (FDA) in 2004 for WHO functional class III and IV PAH. Prostacyclin is a metabolite of arachidonic acid produced primarily in vascular endothelium. It is a potent vasodilator, affecting both the pulmonary and systemic circulation. There is evidence to suggest that a relative deficiency of prostacyclin may contribute to the pathogenesis of PAH.[18]Although other prostanoids have been developed (e.g. epoprostenol and beraprost), iloprost is currently the only commercially available agent in Malaysia.

Iloprost is administered via an ultrasonic nebuliser with a half-life of 20 to 25 minutes. Therefore, chronic use requires six to nine inhalations a day to obtain a sustained clinical benefit.[85]The recommended inhaled dose is 2.5-5 ug/inhalation. Common side effects include cough, headache, flushing and jaw pain.

At the time of writing, short-term data for inhaled iloprost as monotherapy was available from one RCT that enrolled patients with both PAH and CTEPH.[86] Overall, this study showed an increase in exercise capacity, an improvement in PVR, and a reduction in clinical events for patients receiving iloprost. However, other haemodynamic measures were not affected. In a study of 24 iloprost-treated IPAH patients, Hoeper et al.,[87] reported sustained benefits in exercise capacity and haemodynamics at 1 year. More recently, Opitz et al.,[88] reported event-free (death, transplantation, switch to i.v. therapy, or addition of other active oral therapy) survival rates of 53%, 29%, and 20% at 1-, 2-, and 3-years,

respectively, in IPAH patients treated with iloprost. Patient characteristics and results from these studies are presented in Appendix 5 and Appendix 6.

7.2.4. Sildenafil (Level of evidence A)

Sildenafil is an oral PDE-5 inhibitor. PDE-5 exerts its pharmacological effect by increasing the activity of endogenous nitric oxide, thereby inducing relaxation and anti-proliferative effects on vascular smooth muscle cells.[5]Early clinical studies with sildenafil in patients with PAH have demonstrated its ability to reduce mPAP and PVR, and to produce an increase in cardiac index.[89]

Three RCTs with sildenafil as monotherapy versus placebo have been performed in patients with PAH.[90-92]In these trials, the dose of sildenafil ranged from 60 to 240mg/day. In the largest RCT performed by Galie et al.,[91]278 patients were randomised to receive placebo or sildenafil (20, 40 mg or 80 mg) orally three-times daily for a period of 12 weeks. A significant increase in 6MWD was observed in all three sildenafil groups compared to placebo but there was no significant difference in effect between sildenafil doses. However, patients randomised to a higher dose of sildenafil demonstrated greater improvements in mPAP, CI, PVR and functional class. Results from RCTs performed with sildenafil are presented in Appendix 7 and Appendix 8.

At the time of writing, only one study has reported long-term efficacy with chronic administration of sildenafil.[91] In that study, all data was based on a dose of 80 mg three-times daily and a one-year survival rate of 96% was observed (Appendix 9). The most common side effects include headache, flushing, dyspepsia, epistaxis, nasal congestion and impaired vision.

The FDA-approved dose of sildenafil in patients with PAH is 20 mg tds administered orally. However, higher doses, up to 80 mg tds, may be more efficacious.

7.2.5 Tadalafil (Level of evidence B)

Tadalafil is a long actingPDE-5 inhibitor. An RCT (PHIRST) on 406 PAH patients (about half on background bosentan therapy) treated with tadalafil has shown favourable results on exercise capacity, symptoms, haemodynamics, and time to clinical worsening at the 40 mg daily dose.[93] The side effects are similar to that of sildenafil.

Recommendation

1. Patients with symptomatic iPAH should be started on PAH specific therapy (Class of recommendation I)
2. PAH secondary to CTD or CHD can be considered for PAH specific therapy (Class of recommendation IIa)
3. The choice of a PAH specific drug include an ERA, inhaled Iloprost or a PDE5 inhibitor (Class of recommendation I)

7.3. PAH-specific therapy and survival

Due to the short-term nature of RCTs with active treatments (12-16 weeks), survival is rarely an endpoint. To date, only the prostacyclin analogue epoprostenol has demonstrated a survival benefit compared to patients treated with conventional therapy.[41] Epoprostenol is approved by the FDA for the treatment of patients with IPAH in WHO class III and IV, and is recommended first-line for patients presenting with functional class IV symptoms. Despite its benefits, the complexity of drug administration significantly limits its use.

RCTs aside, several longer-term, open-label series with active treatments (namely epoprostenol and bosentan) have reported 1- and 2-year survival rates of 85% to 97% and 70% to 91%, respectively.[9, 10, 41, 80, 91, 94, 95] These results are in dramatic contrast to those observed in the 1981 NIH registry, where the median life expectancy for patients with IPAH, without specific therapy, was 2.8 years from diagnosis, with 1-year, 3-year, and 5-year survival rates of 68%, 48% and 34%, respectively.[2] Furthermore, a recent meta-analysis of RCTs in PAH, conducted by Galie et al.,[96] suggested that active treatments were associated with a reduction in mortality of 43% (relative risk: 0.57; 95% confidence interval: 0.35 to 0.92; p = 0.023). When viewed collectively, these data suggest an improvement in survival for patients treated with targeted therapies.

7.4. Evaluation of response to treatment

It is important to evaluate the response of PAH patients to treatment in order to modify therapy accordingly. The patients can be evaluated clinically based on symptoms (WHO functional class) and signs (right heart failure), and by using various parameters. Parameters that have been used include 6MWD, right ventricular function assessed by echo, natriuretic peptide, cardiopulmonary exercise testing, and hemodynamics assessed by RHC. (see Table 14, page 61 for suggested parameters and targets). Repeat testing is useful to assess response

to therapy. Patients with a satisfactory response to therapy can be continued on treatment and followed up regularly. Patients with an unsatisfactory response should be considered for combination therapy or other interventions including lung transplant.

> **Recommendation**
> The response to treatment should be monitored in patients who are on a PAH specific drug.

7.5. Combination therapy (Level of evidence B)

The management of patients who exhibit clinical deterioration despite targeted monotherapy is challenging.[47] A significant proportion of patients receiving PAH specific monotherapy deteriorate despite treatment. Combination therapy is an attractive option with the development of several therapeutic classes of agents with different mechanisms of action and potential synergy.

The goal of combination therapy is aimed at maximising therapeutic efficacy while limiting toxicity and potential drug-drug interactions. Although there is limited clinical data pertaining to combination treatment, it is a common practice in many PAH centres. Combination therapy may include, 1) initiation with 2 or more concomitant PAH-specific therapy, or more commonly, 2) sequential administration following clinical deterioration on a first-line agent.

Various combination therapies have been utilized. A single small trial of concomitant therapy with epoprostenol initiation and bosentan added on 48 hours later showed only trends in improvement, without significant benefits.[46]More trials achieving successful endpoints have been carried out with sequential add on therapy using a wide range of combinations: bosentan plusepoprostenol[97]; bosentan plus iloprost[98-101]; bosentan plus beraprost[98, 101]; bosentan plus sildenafil[102-107]; sildenafil plus epoprostenol[108-110]; sildenafil plus iloprost[111-113]; sildenafil plus beraprost[114] and sildenafil plus trepostinil.[115]

For patients with PAH in WHO functional class III, the most common combination is the addition of a second oral drug (i.e., sildenafil to an ERA or ERA to sildenafil). This combination provides additional clinical benefits such as improved exercise capacity, an increase in time to clinical deterioration and improved haemodynamics compared with either class of drug alone. A few

reports have addressed the significant pharmacologic interactions between sildenafil and bosentan.[116, 117] In a recent study, bosentan decreased maximum plasma concentration of sildenafil by 55%, while sildenafil increased bosentan concentration by 42%.[117] The clinical importance of this interaction remains unclear, and careful monitoring is advised.[118]

The second and third most common strategies involve the combination of a prostanoid with sildenafil, and the combination of a prostanoid with an ERA, respectively. For patients in WHO functional class IV, starting with two or more targeted therapies simultaneously can be considered in view of the poor prognosis and likelihood of failure of monotherapy.

At the time of writing, there are a number of well-designed studies ongoing which should help determine the potential benefits of a variety of combination therapies that should become available in the next one to three years (Appendix 10). In the meantime, combination therapy remains an attractive option and individuals with PAH who demonstrate an inadequate response to monotherapy should be considered for a combination of two or more disease-targeted therapies.

Recommendation
Patients with PAH who have an inadequate response to monotherapy using a PAH specific drug, should be considered for sequential combination therapy (Class of recommendation IIb)

7.6. Atrial septostomy (Level of evidence C)

Atrial septostomy creates a right to left inter-atrial shunt, decreasing right heart filling pressures and improving right heart function and left heart filling. In most cases it is performed as a palliative bridge to lung transplantation. Haemodynamics and clinical improvements have been reported, together with successful rates of bridging to transplantation in the order of 30% to 40%.[119, 120] However, its exact role in the treatment of PAH remains uncertain because its efficacy has been reported only in small series and case reports from single centers, usually with no matching controls.[119-121]

Current evidence suggests a benefit of atrial septostomy in patients who are in WHO functional class IV with right heart failure refractory to optimal medical therapy, or with severe syncopal symptoms.[5] Furthermore, the procedure should only be performed in experienced designated centers with an active thoracic transplant programme. The preferred choice is graded balloon atrial septostomy.[122]

> **Recommendation**
> Atrial septostomy is reserved for selected patients with refractory symptoms and should be performed in specialized centres (Class of recommendation I)

7.7. Transplantation (Level of evidence C)

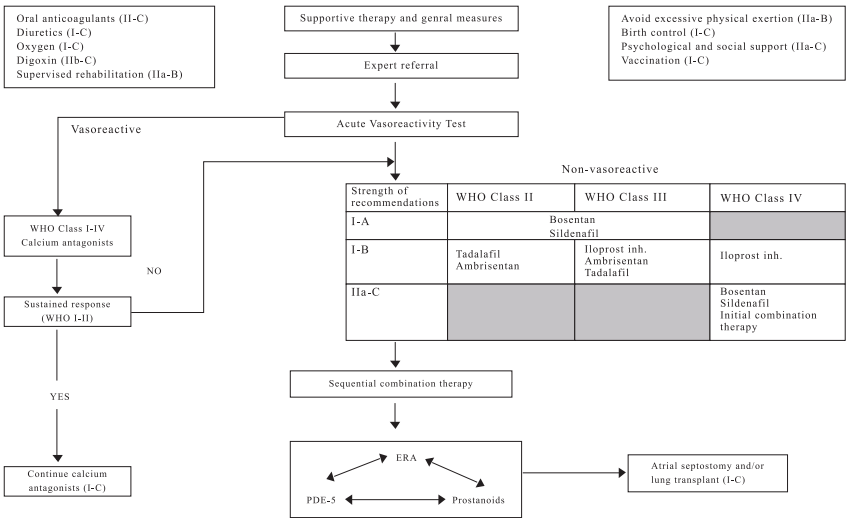
Lung and heart-Lung transplantation are indicated in PAH patients whose prognosis remains poor despite maximum medical therapy.[5, 47, 49] This treatment option should be considered and early discussion with experienced transplant physicians is recommended. However, the long waiting time and organ shortage significantly restricts its utility.

> **Recommendation**
> Lung and heart lung transplant is reserved for selected patients with refractory symptoms and should be performed in transplant centres (Class of recommendation I)

8. Evidence-based treatment algorithm for Malaysia

The optimal therapy for patients with PAH is a highly individualised decision, taking into account many factors including: drug availability, severity of illness, route of administration, side effects, treatment goals, and clinician preference. Figure 2 presents a proposed algorithm for the management of patients with PAH. This is based on evidence from RCTs performed to date and is focused on patients in WHO functional class II to IV, and on therapies that have been evaluated in IPAH and available locally, and in PAH associated with scleroderma or due to anorexigens. Extrapolation of trial results to other PAH subgroups should be done with caution.

Figure 2: PAH evidence treatment algorithm based on the availability of agents in Malaysia (adapted from Barst et al).[52]



International guidelines for management of PAH include drugs like epoprostenol which is currently unavailable locally. The algorithm presented in Appendix 12 includes these drugs based on WHO International conference at DanaPoint in 2008 and using different recommendations (Appendix 11).

9. Future therapies

Despite the fact that a cure for PAH remains elusive, we have witnessed great advances in early diagnosis, and a dramatic increase in the availability of therapeutic options over the past 20 years. Looking forward, several new areas of research hold promise, including pharmacogenomics and pharmacogenetics, anti-angiogenesis strategies, and growth factor inhibitors.

SECTION B:
PAH IN CHILDREN

SECTION B

Pulmonary Arterial Hypertension in Children

10. Introduction

The prevalence of PAH in adults was estimated to be 15 cases/million and 1-year survival was 88% as shown in a French National Registry 29. Pulmonary arterial hypertension in children has a poorer outcome compared to adults. The Data in the Primary Pulmonary Hypertension National Institutes of Health Registry2 showed the median survival without specific therapy for all of the 194 patients was 2.8 years, whereas it was only 10 months for children.

Children differ from adults due to several reasons:

a. The anticipated lifespan of children is longer

b. Children may have a more reactive pulmonary circulation hence greater vasodilator responsiveness [123]

c. Despite clinical and pathological studies suggesting increased vasoreactivity in children, before the advent of long-term vasodilator/ antiproliferative therapy, the natural history was significantly worse for children compared to adult patients [124]

11. Definition and Classification

The definition of PAH in children is the same as for adult patients i.e. mPAP > 25 mmHg at rest with PCWP ≤ 15mm Hg [5].

As with adults, PAH in children is caused by a variety of aetiologies as classified by the Revised WHO Classification of PAH 2008 [125]. However, the causes of pulmonary hypertension in children differ from adults with idiopathic PAH (IPAH) and PAH associated with congenital heart disease being the most common. Other causes of pulmonary hypertension in children are shown in the updated clinical classification of PHT (Dana Point 2008)[125] (Refer to Table 1 in Section A, pg23)

12. Diagnosis

12.1 Clinical Suspicion of PHT

The presenting symptoms in children with pulmonary hypertension may differ from adults. Pulmonary hypertension should be suspected in any child who presents with signs and symptoms as listed in Table 6 when there is no other explanation.

Table 6: Signs and symptoms of pulmonary hypertension in paediatric patients

Age group	Signs and symptoms
Infants	Signs of low cardiac output (poor appetite, failure to thrive, lethargy, diaphoresis, tachypnoea, tachycardia, irritability) Crying spells (chest pain)
Children	Poor effort tolerance Cyanosis with exertion(right to left shunt through a patent foramen ovale) Syncope (effort-related) Seizures (early morning hours) Nausea and vomiting
Older children	Exertional dyspnoea Chest pain or angina Clinical signs of right heart failure (hepatomegaly, peripheral oedema)

12.2 Detection of PHT

The initial tests to assist in detection of pulmonary hypertension are listed in Table 7.

Table 7: Initial test to detect pulmonary hypertension

Test	Findings
ECG	RVH, right ventricular strain, tall P wave
Chest Xray	Central pulmonary artery dilatation, ± pruning of peripheral blood vessels, right atrial and right ventricular enlargement
Transthoracic Doppler echocardiography	Most useful non-invasive tool. Right ventricular hypertrophy, dilated pulmonary arteries, right ventricular dysfunction and pericardial effusion in advanced cases Tricuspid regurgitation allows estimation of pulmonary arterial systolic pressure. Tricuspid regurgitation jet velocity of > 2.8 m/s or pressure gradient > 31 mmHg at rest would suggest PHT Also useful to detect PAH associated with congenital heart lesions and left heart diseases
Transoesophageal echocardiography	Rarely required, may be useful to detect presence of atrial septal defect

Once pulmonary hypertension is detected, all paediatric patients should be referred to the specialized centres for further investigations. Invasive right heart catheterization for confirmation of PAH, assessment of severity of PAH and vasoreactivity test should only be performed in the specialized centres.

12.3 PHT clinical class identification

Detailed history taking and further investigations should be made to determine the underlying cause for pulmonary hypertension. Diagnosis of idiopathic pulmonary arterial hypertension (IPAH) is made when no secondary cause is found.

Table 8: Important aspects of history taking in determining underlying cause for pulmonary hypertension

Perinatal factors Meconium aspiration syndrome, congenital diaphragmatic hernia, perinatal asphyxia, hypoplastic lung, group B streptococcal sepsis	Persistent pulmonary hypertension of newborn
Respiratory diseases Bronchopulmonary dysplasia, recurrent respiratory infections, bronchiectasis, interstitial lung diseases, obstructive sleep apnoea	Pulmonary hypertension owing to lung diseases and/or hypoxia
Family history of PAH	Heritable PAH
Congenital heart diseases Operated and un-operated	PAH associated with congenital heart diseases
Drug history Psychotropics and appetite suppressants (aminorex, fenfluramine, amphetamines, cocaine etc)	Drug and toxin-induced PAH
Underlying medical illnesses Connective tissue diseases, HIV infection, haemoglobinopathies, portal hypertension, thyroid diseases, glycogen storage disease, myeloproliferative disorders, splenectomy	PAH associated with various medical disorders or pulmonary hypertension with multifactorial mechanisms

Table 9a: General tests to be done in all PAH patients

General tests	Full blood count, renal profile, thyroid function test, liver function test, HIV screen, ESR, C-reactive protein, anti-nuclear factor, arterial blood gas

Table 9b: Specific tests to be considered when specific underlying cause is suspected

Causes	Test
Pulmonary hypertension owing to lung diseases and/or hypoxia	Lung function test, high resolution CT thorax, sleep study, lung biopsy
PAH associated with connective tissue diseases	Anti-ds DNA, rheumatoid factor, extractable nuclear antigen (anti-centromere antibody, anti SCL70, anti-RNP), complement levels
PAH associated with portal hypertension	Hepatitis viral serology, abdominal ultrasound (liver cirrhosis, portal hypertension)
Chronic thromboembolic pulmonary hypertension	**Thrombophilia screen** - Protein C, protein S, antithrombin III, lupus anticoagulant, anticardiolipin antibody, factor V Leiden **Imaging for pulmonary thromboembolism** - Doppler ultrasound of pelvic-femoral veins, ventilation-perfusion (V/Q) scan, CT pulmonary angiography, invasive pulmonary angiography

13. Assessment of Severity of PAH

Severity of PAH can be assessed by symptoms, non-invasive tests and invasive cardiac catheterization

13.1 Symptoms

Functional class can be categorized in older children using the modified New York Heart Association classification according to the World Health Organization 1998 [48]. However, in younger children, it may be more practical to use the Ability Index (table 10) [126].

WHO classification of functional status in patients with PHT modified from New York Heart Association classification (Refer to Section A, Table 2, pg24)

Table 10: Ability Index

Ability Index 1	Patients with normal life, activity or school
Ability Index 2	Patients able to work with intermittent symptoms, interference with daily life/school
Ability Index 3	Unable to work/school, limited in all activities
Ability Index 4	Extreme limitation, dependent, almost housebound

13.2 Non-invasive tests

These tests are useful in assessing baseline functional status as well as monitoring the disease progression and treatment response.

Table 11: Non-invasive tests to assess severity of PAH

Category	Tests
Blood tests	BNP or NT-proBNP, hs-CRP, uric acid
Exercise Capacity	6-min walk test (<300m) , cardiopulmonary exercise testing (in older children)
Echocardiography	Monitoring of right ventricular function (RV Tei index, tricuspid annular plane systolic excursion), TR velocity, RA size, pericardial effusion

13.3 Invasive Tests

Right heart catheterization is required to assess the haemodynamics and the response to vasodilators. It confirms the diagnosis of PAH, assesses the severity and guides the management.

Vasoreactivity test should be done in all cases of PAH with the exception of pulmonary venous obstruction (IV prostacyclin may induces pulmonary oedema)[127]. The purpose of vasoreactivity test is

a. To guide choice of initial therapy. Only positive vasoreactivity test responders should be started on trial of high doses calcium channel blockers.
b. To determine the operability of patients with congenital systemic-to-pulmonary shunt lesions with high pulmonary artery pressure (Refer to PAH and congenital heart disease section).

Table 12: Haemodynamic parameters to be measured during right heart catheterization

Mean right atrial pressure
Pulmonary arterial pressure (Systolic, diastolic and mean)
Simultaneous mean aortic : pulmonary arterial pressure ratio
Pulmonary capillary wedge pressure (mean left atrial pressure or left ventricular end-diastolic pressure if unable to obtain PCWP)
Cardiac output (Fick or thermodilution method)
Heart rate
Mixed venous blood oxygen saturation
Arterial blood gas or pulse oximetry
Calculation of pulmonary vascular resistance
Qp:Qs ratio if systemic-to-pulmonary shunt present

Positive vasoreactivity response is defined as a drop in mean PAP by 10 mmHg or more to an absolute mean pressure of 40 mmHg or less without a decrease in cardiac output. Types and regimens of vasodilators used are similar to recommendations for adults[5].(refer to Section A, table 5, pg35) However, the choice depends on the availability of the vasodilators and the practice of the individual centers.

14. Treatment of iPAH in Children

Treatment for IPAH in children has improved dramatically over the past several decades, resulting in improved clinical and hemodynamic status, as well as increased survival. Patients should be referred to designated centers for review and treatment of PAH.

Children are sometimes too ill to undergo cardiac catheterization and treatment may need to be commenced first.

Decision to treat with disease targeting therapies is determine by the WHO functional class and the vasoreactivity test response. The age of the patient is also important because not all drugs used in adults with IPAH are safe in children.

Goals of treatment are to improve symptoms, quality of life and survival.

General measures

a. Annual influenza vaccination and 5 yearly pneumococcal vaccination are recommended (Class of recommendation I, Level of evidence C)
b. Pneumonia should be treated early and aggressively to prevent life-threatening pulmonary hypertensive crisis
c. Dehydration should be avoided and/or adequately treated
d. Diet and/or medical therapy should be used to prevent constipation, since Valsalva manoeuvres may precipitate syncopal episodes
e. Competitive sports and isometric exercise are contraindicated (Class of recommendation IIa, Level of evidence B)

14.1 Pharmacological Therapy

14.1.1 Oxygen (Level of evidence C)

A small study demonstrated that supplemental oxygen improved long-term survival in children with Eisenmenger syndrome[53]. For children with IPAH, it may be recommended in patients who have nocturnal hypoxaemia, during intercurrent respiratory infections or in the presence of severe right ventricular failure.

> **Recommendation**
> Supplemental oxygen should be considered in PAH patients with hypoxemia (Class of recommendation I)

14.1.2 Anticoagulation (Level of evidence C)

The use as well as the benefit of chronic anticoagulation in children with IPAH is not well established. Thrombotic changes of the pulmonary microcirculation have been seen in IPAH. Therefore, in the absent of contraindications, long term warfarin therapy is recommended with the target INR between 2 to 3.[5]

> **Recommendation**
> Anticoagulation should be considered in IPAH patients unless contraindicated (Class of recommendation II)

14.1.3 Digoxin (Level of evidence C)

The value of digoxin is not proven in treatment of IPAH. However, it may be useful in patient with atrial fibrillation and in PAH patients with heart failure who remain symptomatic on medical therapy.

> **Recommendation**
> Digoxin can be considered in PAH patients with heart failure with or without atrial fibrillation (Class of recommendation IIb)

14.1.4 Diuretics (Level of evidence C)

Diuretics therapy may be useful in patients with symptomatic right heart failure (liver congestion, oedema). It must be used with caution as these patients are preload-dependent.

> **Recommendation**
> Diuretics should be given to PAH patients with right heart failure (Class of recommendation I)

14.1.5 Inotropes (Level of evidence C)

Short term intravenous inotropic support may be considered in patients with decompensated right heart failure. (Class of recommendation IIa)

14.1.6 Calcium channel blockers (Level of evidence C)

While only a minority (20%) of adult patients with IPAH will respond to chronic oral calcium channel blockade, a significantly greater percentage of children are acute responders (40%) and can be effectively treated with calcium channel blockers [128]. Dihydropyridine calcium channel blockers, such as nifedipine and amlodipine that act on vascular smooth muscle, are the preferred agents whereas negative inotropic calcium channel blockers, such as verapamil, should be avoided [129]. Children usually require higher dose (e.g. nifedipine 0.2 to 0.3 mg/kg/dose) but the optimal dose is still uncertain. They should be introduced cautiously and the dose titrated as tolerated.

Non responders should not be given calcium channel blockers as it may worsen clinical condition (systemic hypotension, pulmonary oedema, right ventricular failure and death).

If the patients do not improve by achieving functional class I or II after on several months of calcium channel blockers, they should be considered as non-responders and other disease-targeted therapy should be instituted.

> **Recommendation**
> Only patients who demonstrate a positive vasoreactive response should be treated with high dose CCBs (Class of recommendation I)

14.2 PAH Specific Therapy

14.2.1 Prostanoids

14.2.1.1 Inhaled iloprost (Level of evidence B)

Inhaled iloprost [132] have all been used to treat children with PAH with varying degrees of success. However, in practice, it can be difficult to deliver inhaled iloprost effectively in young children every 2 to 3 hours daily.

14.2.2 Endothelin Receptor Antagonists

14.2.2.1 Bosentan (Level of evidence A)

Bosentan has been shown to be safe and efficacious in treatment of IPAH in children [134-136]. In BREATHE-3 study, the pharmacokinetics of bosentan in pediatric patients with pulmonary arterial hypertension and healthy adults are similar, and treatment with bosentan resulted in hemodynamic improvement [134]. It has been used for PAH associated with congenital heart disease and connective tissue disease [135,136]. Clinical improvement has also been observed in patients as young as 9 months with severe disease [137,138].

Bosentan is indicated in stable WHO functional Class III and IV children with IPAH. Recent data suggests early treatment with Bosentan could even be beneficial for patients with functional Class II [70]. The dosing regimens for children are listed in Table 13. The most frequent adverse effect was flushing, headache, and elevated liver enzymes. Liver function test should be monitored.

14.2.2.2 Ambrisentan (Level of evidence B)

Other endothelin receptor antagonist include Ambrisentan. However, there is not enough evidence currently to support the routine usage in pediatric IPAH.

14.2.3 Phosphodiesterase 5 Inhibitors

14.2.3.1 Sildenafil (Level of evidence A)

Sildenafil is reported to improve exercise capacity, decrease PAP, and improve symptoms in adult and children with PAH. However, most studies in children are limited to small series [139-52].

The usual starting dose in 0.25 to 0.5 mg/kg/dose 4 to 8 hourly. Dose should be titrated up according to the response and the maximum dose is 2 mg/kg/dose 4 hourly. Doses beyond this have not shown any additional benefit. Headache, flushing and hypotension are the most commonly reported adverse effects.
Route of administration, half-lives, dose ranges, increments and duration of administration of the most used substances on pulmonary vasoreactivity tests[5] (refer to Section A, table 5, pg35)

1. Patients with symptomatic iPAH should be started on PAH specific therapy. (Class of recommendation I)
2. PAH secondary to CTD or CHD can be considered for PAH specific therapy (Class of recommendation IIa)
3. The choice of a PAH specific drug include an ERA, inhaled Iloprost or a PDE5 inhibitor (Class of recommendation I)

*14.3 Combination Therapy (*Level of evidence B)

Combination therapy using different PAH-targeted drugs in patients exhibiting clinical deterioration despite optimal targeted monotherapy has become widely adopted. The use of combinations of drugs acting on distinctly different pathways involved in the pathogenesis of PAH may maximize clinical benefit for patients with PAH. All the studies on combination therapy are currently limited to adult patients using various combinations of Bosentan with IV Epoprostenol (BREATHE-2 study) [97], nebulized Iloprost with Bosentan [100] and Sildenafil with Bosentan [103].

Meta-analysis included 21 trials revealed active treatments with any of the disease-targeted drugs were associated with a reduction in all cause mortality of 43% compared to placebo [96].

Table 13: Recommended Drug Dosages for Treatment of IPAH

Drug	Dosages
Nifedipine	Adults: Start with 10 – 20 mg tds up to maximum 240 mg/day Children: Start with 0.2 – 0.3 mg/kg tds
Diltiazem	Adults: Start with 30 mg tds up to maximum 900 mg/day Children: not established
Bosentan	Adults: Start with 62.5 mg bd up to 125 mg bd Children 10 – 20 kg : 31.25 mg bd 20 – 40 kg: 62.5 mg bd > 40 kg: adult dosage
Sildenafil	Adults: 20 – 80 mg tds Children: Start with 0.25 – 0.5 mg/kg tds up to maximum 2 mg/kg tds

Recommendation
Patients with PAH who have an inadequate response to monotherapy using a PAH specific drug, should be considered for sequential combination therapy (Class of recommendation IIa)

14.4 Follow up Assessment

All patients with IPAH who are started on treatment should be monitored for response to treatment and signs of clinical deterioration. Goal-directed therapy should be instituted to optimize treatment. This requires monitoring of the following parameters at appropriate intervals (Table 14)

Table 14: Follow Up Assessment

Parameters	Target
Functional class	To aim for improvement in functional class by 3 months, ideally to aim for Class I or II
6-min walk distance	> 380 m [143]
Cardiopulmonary exercise testing	Peak oxygen consumption > 10.4 ml/kg/min [143]
Biomarkers (BNP, NT-proBNP)	Reducing trend from baseline
Echocardiography (RV function, right ventricular myocardial performance index, TAPSE, pericardial effusion)	Improvement in parameters
Right heart catheterization	Right atrial pressure < 10 mmHg Cardiac index > 2.5 L/min/m^2 [144]

Clinical deterioration is defined as

- Hospital admission for PAH progression
- PAH progression not requiring hospital admission e.g. worsening of functional class, symptoms of right heart failure, need for additional therapy (diuretics, oxygen) as determined by physicians, worsening or lack of improvement of 6MWD

14.5 Atrial septostomy (Level of Evidence C)

Children with pulmonary hypertension and recurrent syncope are unable to maintain cardiac output by adequately shunting through the patent foramen ovale. Atrial septostomy allows right-to-left shunt, decompresses the right ventricle, increases systemic output and systemic oxygen delivery in spite of a decrease in systemic arterial oxygen saturation. It resulted in a significant

clinical improvement, beneficial and long-lasting haemodynamic effects at rest and a trend toward improved survival [145-147]

The indications for atrial septostomy are [148;149]:

a. Failure of maximal medical therapy with persisting RV failure and/or recurrent syncope

b. As a bridge to transplantation

c. When no other therapeutic option exist

Stepwise balloon dilatation is the procedure of choice. The interatrial orifice is created by puncture with a Brockenbrough needle, then dilated using progressively larger balloon catheters. A 10% drop in arterial oxygen saturation or an increase in LV end-diastolic pressure to 18 mmHg should preclude further dilatation. To minimize procedural related mortality, the recommendations listed in Table 15 should be strictly adhered to[150].

Table 15: Recommendations for Minimizing Procedure-related Mortality of Atrial Septostomy [150]

Only perform in a center experienced in pulmonary hypertension Contraindications to atrial septostomy a. Severe RV failure on cardiorespiratory support b. mRAP > 20 mmHg c. PVRI > 55 Units/m^2 d. Resting oxygen saturation < 90% on room air e. LV end-diastolic pressure > 18 mmHg
Pre-procedure: Optimize cardiac function with adequate right heart filling pressure and additional inotropic support if needed
During procedure: a. Supplemental oxygen b. Appropriate sedation to prevent anxiety c. Monitoring variables (LAP, SaO^2 and mRAP) d. Tailor the defect to < 10% drop in oxygen saturation
Post procedure: Optimize oxygen delivery with transfusion of packed cells

Recommendation
Lung and heart lung transplant is reserved for selected patients with refractory symptoms and should be performed in transplant centres (I)

14.6 Transplantation (Level of evidence C)

For paediatric lung and heart/lung recipients, the data from the registry of the International Society for Heart and Lung Transplantation demonstrates that current survival is 65% at 2 yrs and 40% at 5 yrs [151].
It should be reserved for patients whose disease progressed despite optimal medical therapy. Issues that should be taken into account are donor availability, regional expertise and outcome, and waiting time.

Recommendation
Lung and heart lung transplant is reserved for selected patients with refractory symptoms and should be performed in transplant centres (I)

15. Treatment Algorithm

The optimal therapy for patients with PAH is a highly individualised decision, taking into account many factors including: drug availability, severity of illness, route of administration, side effects, treatment goals, and clinician preference. Figure 2 presents a proposed algorithm for the management of patients with PAH.(refer to Section A, Figure 2, pg47)

SECTION C:

PAH IN CONGENITAL HEART DISEASE

SECTION C

Pulmonary Arterial Hypertension and Congenital Heart Diseases

16. Introduction

Many different congenital heart defects are associated with an increased risk for the development of pulmonary arterial hypertension. They can be classified into 3 categories according to the pathophysiologic mechanisms:

a. High volume high pressure shunts: Large VSD, large PDA, complete AVSD, aortopulmonary window, truncus arteriosus, transposition of great arteries with large VSD

b. High volume low pressure shunts: Large ASD, total or partial anomalous pulmonary venous drainage

c. High pulmonary venous pressure: Obstructed total anomalous pulmonary venous drainage, cortriatrium, pulmonary vein stenosis, supramitral ring

Initially these lesions cause reversible pulmonary hypertension. If left untreated, progressively obliterative vasculopathy of the pulmonary arterial tree eventually results in irreversible pulmonary arterial hypertension. In those with intracardiac shunts, reversal of flow (right to left shunt) across the cardiac defects will result in cyanosis; a phenomenon known as Eisenmenger syndrome.

Occasionally, progressive pulmonary arterial hypertension still develops following initial successful closure of cardiac defects and these patients will behave like idiopathic pulmonary arterial hypertension (IPAH).

17. Clinical Manifestations

In the Dana Point Classification of PAH [125], PAH associated with congenital heart disease is classified together with IPAH and PAH associated with systemic diseases. Despite significant similarities in the pulmonary vascular changes between Eisenmenger syndrome and PAH due to other causes, there are important differences which affect clinical presentation and outcome. The important differences are listed in Table 16 [152].

Table 16: Differences between IPAH and Eisenmenger syndrome

	IPAH	Eisenmenger
Right ventricular response		
Right ventricular dimension	Dilatation	Typically hypertrophied
Right ventricular function	Rapid deterioration	Usually preserved until late
Cardiac output	Reduced	Maintained by R to L shunt
Prognosis	Poor, survival limited to a few years after diagnosis	Fair, survival for decades is the rule
Cyanosis	None or mild when there is shunting across PFO	Severe even at rest
Secondary erythrocytosis	Rare	Common
Systemic complications (renal dysfunction, thromboembolism, stroke)	Rare	Common
Perception of exercise limitation	Normal perception	Known to underestimate

In patients with Eisenmenger syndrome, exercise limitation is present from childhood and results in chronic adaptation of 'normal' everyday activities to a lower intensity. Patients tend to underestimate the degree of exercise limitation compared to objective measures of exercise tolerance [153].

Another major difference between patients with Eisenmenger and IPAH is the presence and extent of cyanosis which is severe and occurs at rest in Eisenmenger syndrome. Cyanosis and chronic hypoxia causes secondary erythrocytosis. Iron deficiency is not uncommon and may cause hyperviscosity symptoms such as headache, visual disturbances, and paresthesias. Cyanosis and chronic hypoxia also contributes to other systemic complications associated with Eisenmenger syndrome such as nephropathy [154].

Table 17: Clinical manifestations and complications of Eisenmengers syndrome

Hyperviscosity syndrome

- Headache/dizziness
- Altered mentation/impaired alertness
- Fatigue/myalgia/muscle weakness
- Paraesthesia of fingers, toes, lips
- Tinnitus
- Visual disturbance

Bleeding complications

- Easy bruising/dental bleeding
- Haemoptysis
- Gastrointestinal bleeding, epitaxis, cerebral haemorrahge

Thromboembolism

- Stroke/transient ischaemic attacks
- Pulmonary artery thrombosis

Bacterial infections

- Infective endocarditis
- Cerebral abscess
- Pneumonia

Iron deficiency

Arrhythmias

- Supraventricular tachycardia: atrial flutter, atrial fibrillation
- Ventricular tachycardia

Progressive valvular disease

- Pulmonary regurgitation

Congestive heart failure – usually late

Hyperuricaemia and gout

Nephropathy

18. Assessment

The development of PAH in patients with CHD is very variable with some developing irreversible pulmonary vascular obstructive disease early in life while others with similar lesions remain operable even in the second decade and beyond. Approximately 50% of patients with large VSDs and large PDAs will develop Eisenmenger syndrome by early childhood whereas only 10% of patients with large ASDs will develop it towards second or third decade of life. This is in contrast to almost all the patients with unrepaired truncus arteriosus, complete atrioventricular septal defect and transposition of great arteries with large VSD will develop irreversible PAH by the end of 1st year.

The determination of whether a patient with CHD is still operable or has irreversible PAH is difficult. The decision on surgical operability requires an accurate determination of the degree of pulmonary vasoreactivity or reversibility. This requires careful clinical assessment including:

a. History and clinical findings (presence of cyanosis, heart failure, intensity of second heart sound and heart murmur)

b. Pulse oximetry

c. Chest X-ray (dilatation of central pulmonary artery, peripheral pruning of pulmonary vasculature)

d. ECG (RVH, P pulmonale, right axis deviation)

e. Echocardiographic evaluation (chamber sizes and function, the pressure gradient of shunt across the defect, tricuspid or pulmonary regurgitation velocity)

f. Exercise testing (6-minute walk test or cardiopulmonary exercise test)

g. Invasive hemodynamic assessment (pulmonary artery pressure, Qp : Qs ratio, pulmonary vascular resistance, cardiac output)

h. Vasodilator response to pharmacological agents. Acute vasodilator testing during right heart catheterization using pharmacological agents (e.g. inhaled nitric oxide or inhaled iloprost) have proven to be useful in the preoperative evaluations, as well as in the treatment of postoperative patients with elevated pulmonary vascular resistance *

i. Lung biopsy. Histologic grading of pulmonary vascular disease according to Heath and Edwards corresponds to the duration and

severity of injury caused by increased pressure and volume load and may predicts operability

- Stage I - Medial hypertrophy (reversible)
- Stage II - Cellular Intimal hyperplasia in an abnormally muscular artery (reversible)
- Stage III - Lumen occlusion from intimal hyperplasia of fibroelastic tissue (partially reversible)
- Stage IV - Arteriolar dilation and medial thinning (irreversible)
- Stage V - Plexiform lesion, which is an angiomatoid formation (terminal and irreversible)
- Stage VI - Fibrinoid/necrotizing arteritis (terminal and irreversible)

However, it is rarely performed nowadays as it is invasive and has limitations of sampling error and availability of histopathology expertise.

**** Intervention in patients with congenital heart disease associated with pulmonary hypertension involves high morbidity and mortality and should be performed in centers with experience managing these cases. To date, there are no studies that have established the pressures, flows, and resistances that define pulmonary reactivity and suitability for surgery in this group of patients***

19. Eisenmenger Syndrome

Patients with Eisenmenger syndrome may remain stable for many years [152;155] The main principle in the management of Eisenmenger patients is not to destabilize the balanced physiology and risk reduction strategies.

19.1 General principle

19.1.1 General Advice

a. Patients with Eisenmenger syndrome should *AVOID* the following:
    - Pregnancy
    - Dehydration
    - Moderate to severe strenuous exercise, particularly isometric exercise
    - Acute exposure to excessive heat (e.g. Hot tub, sauna)
    - Chronic high-altitude exposure
    - Smoking

b. Air travel in commercial airlines is not discouraged in stable Eisenmenger patients but care should be taken to avoid dehydration and inactivity during the flight [156].

c. All medications given to patients with Eisenmenger syndrome should be scrutinized carefully to prevent potential alteration in the balanced haemodynamic and adverse effects on renal and hepatic systems.

d. Long term oxygen therapy for at least 12 to 15h/day may improve symptoms but has not been shown to influence survival [157;158].

20. Supportive Therapy

20.1 Hyperviscosity and Phlebotomy

Routine phlebotomy (venesection) is NOT recommended [159].

Secondary erythrocytosis is physiological desirable response to chronic hypoxia

in Eisenmenger syndrome. Inappropriate and repeated phlebotomy to maintain a predetermined level of haematocrit can cause iron deficiency anaemia which worsens hyperviscosity symptoms and predisposes the patient to stroke [160;161].

Indications for phlebotomy:

- Patients with moderate to severe hyperviscosity syndrome in the absence of iron deficiency and dehydration [158;162]
- Preoperatively before non-cardiac surgery to improve haemostasis [163]

Method of phlebotomy [158;162]

- Withdrawal of 10 ml/kg whole blood (250 to 500 ml in adults) over 30 to 45 mins, preceded by or concurrent with volume replacement (15 to 20 ml/kg isotonic saline)
- Blood pressure should be monitored before, during and after procedure
- Not more than 2 to 3 phlebotomies should be performed in a year

Recommendation
Routine phlebotomy (venesection) is NOT recommended other than when indicated as above

20.2 Iron deficiency

Due to secondary erythrocytosis, sign of iron deficiency can be masked clinically. Iron-deficient red blood cells have less oxygen-carrying capacity and poor deformability that may lead to increased risk of strokes and vascular complications. Serum iron profile (Hb, MCV, MCH, serum iron, ferritin, transferin saturation) should be monitored at least annually or whenever indicated. If present, it should be corrected with iron supplementation to replete body iron store.

Recommendation
Monitor iron profile and correct iron deficiency if present

20.3 Bleeding complications

Eisenmenger syndrome is associated with a paradoxical state of the increased risk of thrombosis and bleeding diathesis [152]. Haemoptysis is common and is the main cause of death in 11 – 30% of patients [164]. Thrombocytopenia is often seen due to reduced platelet release from megakaryocytes, increased peripheral consumption, thrombasthenia and decreased platelet life. Primary fibrinolysis and coagulation factor deficiencies also contribute to high bleeding risk.

Anticoagulants and antiplatelets are generally avoided in Eisenmengers patients due to increased risk of bleeding.

Accurate assessment of the coagulation parameters requires the amount of sodium citrate in the coagulation test specimen tubes to be adjusted. In patients with high haematocrit, the plasma volume is too low for the amount of sodium citrate solution in the normal tubes and coagulation test results may be falsely prolonged because of the excess anticoagulant in the plasma. The formula to calculate the appropriate sodium citrate volume is: [165]

X = (100 – PCV) x Y /(595 – PCV)
X = volume of sodium citrate required for unit volume of blood
Y = volume of blood required in the blood specimen tube
PCV = packed cell volume in %

Haemoptysis is common and major cause of death in Eisenmenger patients although in most occasions, it is not severe and self-limiting.

The underlying causes of haemoptysis include pulmonary infarct from in-situ thrombus formation at central pulmonary artery, rupture of aortopulmonary collaterals, pulmonary infections, thrombocytopenia and coagulopathy. [164]

Every hemoptysis episode should be regarded as potentially life threatening and warrants meticulous evaluation, identification of underlying cause and appropriate management (Table 18).[158]

Table 18: Management of haemopytsis in Eisenmenger patients

General Management	
Bed rest, oxygen, cough suppression, tranexamic acid	
Specific Management	
Underlying cause Pulmonary infections Pulmonary thromboembolism Coagulopathy/thrombocytopenia Rupture of aortopulmonary collaterals Pulmonary artery rupture	**Management** Antibiotics IVC filter, Fresh frozen plasma, platelet concentrate, desmopressin Transcatheter embolization Surgery, transcatheter embolization

20.4 Thrombosis and Thromboembolic Complications

Prevalence of pulmonary artery thrombosis in Eisenmenger syndrome is estimated to be 20% [164]. Risk factors are increasing age, biventricular dysfunction, degree of the pulmonary artery dilatation, female sex and lower systemic arterial saturation.

Patients with cyanotic congenital heart diseases are also at increased risk of stroke (13.6%) [160]. Atrial fibrillation, systemic hypertension and iron deficiency are among the risk factors.

However, the role of long term anticoagulation in Eisenmenger patients is controversial because of the risk of bleeding and difficulty in controlling INR within targeted range in cyanotic patients. Therefore, the indication for anticoagulation should be individualized and limited to specific indications [166]

- Atrial flutter and fibrillation
- Recurrent thromboembolic events
- Mechanical heart valve

Using air filter in all intravenous line may prevent paradoxical air embolism and reduce risk of stroke.

Recommendation
Patients with Eisenmenger syndrome have a higher risk of bleeding
Avoid routine anticoagulation unless risk of thromboembolism outweigh risk of bleeding

20.5 Arrhythmias & Heart Failure

Supraventricular arrhythmias (atrial flutter, atrial fibrillation) and occasionally ventricular arrhythmias are significant cause of morbidity and mortality [167]. Unfortunately, pharmacological treatment of arrhythmias in Eisenmenger patients is limited by haemodynamic side effects and must be used with caution.

Sudden death is common mode of death in Eisenmenger patients [155]. It is precipitated by arrhythmias, massive haemoptysis and cerebrovascular events.

Right heart failure is a potential complication of Eisenmenger syndrome. Role of digoxin is controversial [168]. Diuretics may be indicated to relieve symptoms of congestion but care must be taken to avoid dehydration which may precipitate hyperviscosity and hypotension [158].

20.6 Perioperative Management of Non-cardiac Surgery

Any non-cardiac surgery can be potentially life threatening in Eisenmenger patients (perioperative mortality as high as 19%) [169]. They are very vulnerable to alteration in haemodynamics induced by anaesthesia and surgery [170]

- Drop in systemic vascular resistance increases right-to-left shunting and possibly cardiovascular collapse
- Bleeding diasthesis
- Thromboembolic complications
- Arrhythmias

Any non-essential surgery should be avoided if possible. When surgery is necessary, it should preferably be performed in centers with expertise in managing these patients.

Risk reduction strategies include

- Close monitoring during and post-procedure; ideally in intensive care unit
- Avoid hypovolaemia and dehydration; prolonged fasting should be avoided
- Systemic hypotension should be treated aggressively
- Avoid iron deficiency anaemia
- Meticulous attention to haemostasis; excessive bleeding should be treated promptly
- Preoperative phlebotomy if indicated to improve haemostasis
- Meticulous attention to intravenous lines to prevent paradoxical air embolism (use intravenous filters if available)
- Endocarditis prophylaxis
- Avoid prolonged post-operative immobilization; precaution should be taken against deep vein thrombosis

Recommendation
Measures to reduce peri-operative risk should be taken during non cardiac surgery for patients with ES

20.7 Nephropathy, Hyperuricaemia and Rheumatological Complications

Increased blood viscosity can lead to renal hypoperfusion with progressive glomerulosclerosis. Renal dysfunction involves proteinuria and hyperuricaemia [171]. Hyperuricaemia has been shown to be an independent poor prognostic marker for patients with Eisenmenger syndrome [172]. Renal profile and serum uric acid level should be measured regularly. Nephrotoxic drugs should be avoided.

Rheumatological complications include gout secondary to hyperuricaemia and hypertrophic osteoarthropathy. Gouty arthritis can be treated with colchicines or oral corticosteroid. Non-steroidal anti-inflammatory drugs should be avoided.

20.8 Infections

- Intercurrent infections must be treated aggressively
- Immunization against influenza and pneumococcal disease is recommended
- Antibiotic prophylaxis against infective endocarditis prior to dental/ surgical procedures is mandatory

20.9 Pregnancy and Contraception

PREGNANCY IS ABSOLUTELY CONTRAINDICATED

Pregnancy carries high maternal and fetal mortality [173;174]. Mothers may be particularly at risk in the first few days after delivery. All patients and their partners should be counseled regarding avoidance of pregnancy and appropriate contraception.

Women with Eisenmenger syndrome who become pregnant should [175]

- Undergo termination of pregnancy as early as possible. Termination in the first trimester is a safer option
- Termination of Pregnancy in the 2nd and 3rd trimesters poses a high risk to the mother. The risks of termination should be balanced against the risks of continuation of the pregnancy
- If a patient chooses to continue with the pregnancy, she should be managed by a multidisciplinary team (obstetricians, cardiologist, anaesthetist and intensivist) with expertise in managing patients with pulmonary hypertension)

20.9.1 Contraception

- Contraception counseling is strongly advised and the method of contraception should be discussed with the obstetrician
- Tubal ligation carries some operative risk and endoscopic technique is a preferred method
- Use of single-barrier contraception alone is not recommended because of high failure rate
- Oestrogen-containing contraceptives increase risk of thromboembolism and should be avoided Progesterone-only preparations may be considered
- Intrauterine device carries high risk of infection

> **Recommendation**
> Pregnancy is contraindicated and should be avoided with appropriate contraception

20.10 Specific Disease Targeted Treatment

There is evidence to suggest that the current available therapies for IPAH may have some beneficial effect in patients with Eisenmengers syndrome. However caution is required when using vasodilators as this may cause reduction in systemic vascular resistance and blood pressure which increases the right to left shunting and hypoxaemia.

The use of these specific disease targeted therapy in Eisenmenger patients should be limited to centers with experience managing these patients.

Bosentan Randomised Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) is the only large randomised double blind placebo trial conducted in patients with Eisenmenger syndrome [72]. Bosentan had a beneficial short term effect on exercise capacity and cardiopulmonary haemodynamics. The beneficial effects on exercise capacity were maintained up to 40 weeks in open label extension study (BREATHE-5 OLE) [176].

A small randomised trial on Sildenafil (10 Eisenmenger patients) showed improvement in functional status, exercise capacity and pulmonary arterial

pressure [177]. Other non-randomised observation studies have also reported beneficial effects of advanced therapy in this group of patients [178;179].

Similarly, data on prostanoid therapy in patients with Eisenmenger syndrome are limited to case reports and small series. Continuous intravenous epoprostenol was reported to improve functional class, oxygen saturation, exercise capacity and decrease pulmonary vascular resistance [180].

Recommendation
PAH specific drug therapies can be considered in patients with symptomatic Eisenmenger's Syndrome

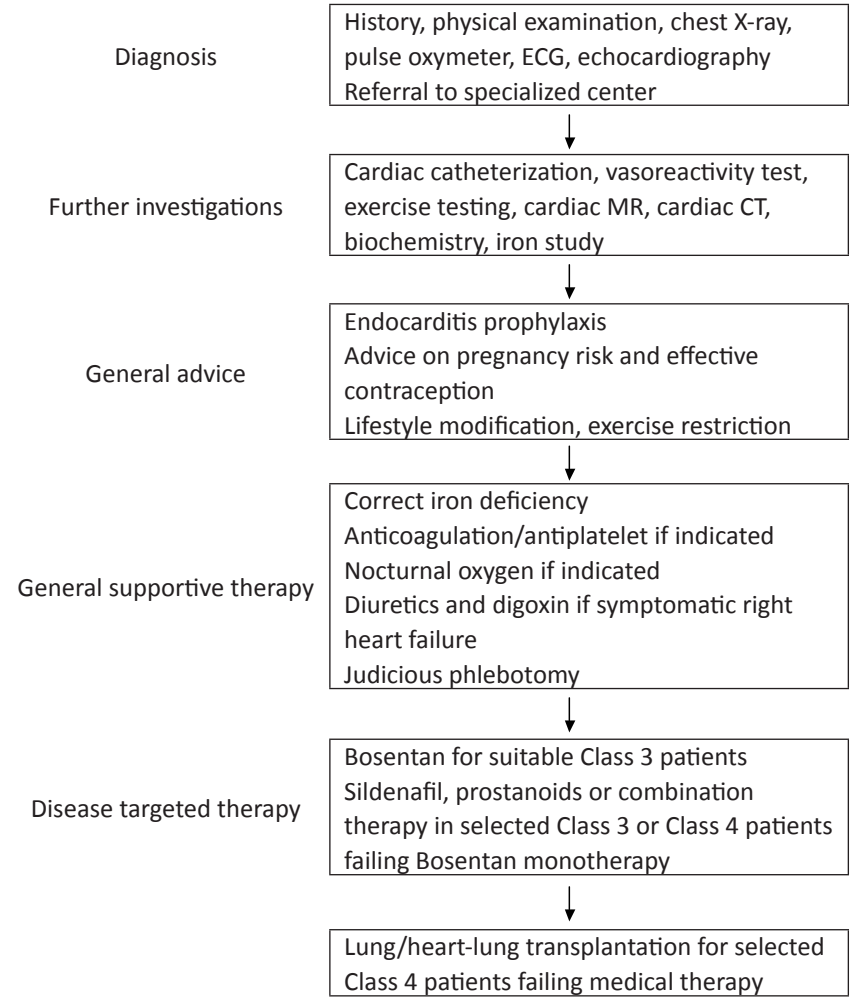
20.11 Transplantation

Lung transplantation with repair of the underlying cardiac lesion or heart and lung transplantation can be performed as the last option for patients with Eisenmenger syndrome. It improves symptoms and quality of life [181;182]. However, it is currently not practical due to shortage of organs. The current 5-year survival rate following transplantation is only 45% [183]. Most Eisenmenger patients tend to have better survival prospect without transplantation (10-year survival between 58% and 80%) [158;184].

Hopkins et al [185] described an actuarial survival in patients with Eisenmenger syndrome who did not receive transplantation of 97%, 89%, and 77% at 1, 2, and 3 years, respectively, compared with 77%, 69%, and 35% at 1, 2, and 3 years for patients with IPAH.

Recommendation
Lung or heart lung transplantation can be considered in suitable candidates

Management Algorithm for Eisenmenger Syndrome



Barriers and facilitators in implementing the guidelines

Access to PAH specific drugs can limit implementation of treatment strategies. Dissemination of information and educating medical personnel on PAH can aid in earlier detection and treatment of patients with PAH.

Training, financial support

Specialised centres for management of PAH should be established and expertise developed. Medical personnel can then receive appropriate training in these centres.

Since the cost of the PAH specific drugs are expensive, public funding of therapy would be necessary.

Conclusions

As new therapies have been developed for PAH, screening, prompt diagnosis, and accurate assessment of disease severity have become increasingly important. However, the diagnosis and treatment of PAH is often complex, and it is clear that patients benefit from referral to a centre that specialises in the treatment of this disorder.[141] In this review, we have proposed a treatment algorithm based on the evidence available. However, in clinical practice we recognise that the choice of drug is dependent on a variety of factors, including approval status, route of administration, side effect profile, patient preference, and the physician's experience and clinical judgment.

Moving forward, several unresolved questions remain. Firstly, none of the currently available therapies is curative, so the search for new treatment strategies continues. As we increase our understanding of specific disease pathways involved with PAH, there remains the possibility of developing targeted therapies that will further improve outcomes. Secondly, there remains a need to identify patients with PAH earlier, before the onset of extensive vascular remodeling. New tools and diagnostic techniques will be essential to deriving maximal benefit from our expanding therapeutic armamentarium. Finally, the transfer of this information from bench to bedside requires collaborative research. Accordingly, patients and physicians should be encouraged to foster such research by participating in RCTs conducted at specialised PHT centres.

APPENDIX

Appendix 1: Patient characteristics from RCTs with bosentan vs. placebo

	Study 351 (Channick et al.[69])	BREATHE-1 (Rubin et al.[73])	BREATHE-5 (Galie et al.[72])	EARLY (Galie et al.[70])	BREATHE-3 (Barst et al.)
Drugs and daily doses	Placebo/bosentan 125-250 mg	Placebo/bosentan 250 mg/bosentan 500 mg	Placebo/bosentan 250 mg	Placebo/bosentan 150-250 mg	Bosentan 31.25 mg, 62.5mg, 125mg
Setting	US and EUR	US and EUR	US/EUR/AUS	US/EUR/AUS	US
Dosing regimen	bd	bd	bd	bd	Bd
Study duration (wks)	12	16	12	26	12
Age inclusion	≥18	≥12	>12	≥12	3-15yrs
Baseline 6MWD for inclusion (m)	≥150 and ≤500	≥150 and ≤450	≥150 and ≤450	<80% predicted	-
PAH aetiology	IPAH (81%), SSc-PAH (19%) in bosentan group	IPAH (71%), SSc-PAH (23%)	CHD-PAH (100%)	IPAH (58%), SSc-PAH (19%) CHD-PAH (17%) Other (6%)	IPAH (53%), CHD-PAH (47%)
WHO functional class	III (100%)	III (90%) IV (10%)	III (100%)	II (100%)	II (79%) III (21%)
Patient disposition	36 screened, 32 randomised (2:1) No discontinuations	Screened nr, 213 randomised (1:1:1) 14 discontinued	76 screened, 54 randomised (2:1) 4 discontinuations	Screened nr, 185 randomised (1:1) 22 discontinued	19assigned based on body weight (7:6:6) No discontinuations
Male:Female (%)‡	19:81	29:71	28:62	24:76	9:10
Mean age (years)‡	52 (33-73)	49 (13-80)	37 (±12)	45 (±18)	5.7,10.0,14.2 (3-15)
Mean 6MWD at baseline (m)‡	360 (±86)	330 (±74)	332 (±83)	438 (±86)	492 (±86)
mPAP (mmHg)‡	54 (±13)	55 (±16)	78 (±15)	53 (±19)	60 (±18)

6MWD, 6-minute walk distance; AUS, Australia; bd, twice-daily; CHD, congenital heart disease; CTD, connective tissue disease; EUR, Europe; IPAH, idiopathic pulmonary arterial hypertension; mean pulmonary artery pressure; SSc, scleroderma; US, United States; WHO, World Health Organisation. ‡ Data are for patients

Appendix 2: Results from RCTs with bosentan vs. placebo

	Study 351 (Channick et al.[69])	BREATHE-1 (Rubin et al.[73])	BREATHE-5 (Galie et al.[72])	EARLY (Galie et al.[70])
Drugs and daily doses	Placebo/bosentan 125-250 mg	Placebo/bosentan 250 mg/bosentan 500 mg	Placebo/bosentan 250 mg	Placebo/bosentan 150-250 mg
6MWD (m)	-6/70*	-8/27*/47**	-9.7/43.4**	-7.9/11.2
mRAP (mmHg)	4.9/-1.3**	na	0.4/0.3	1.1/0.5
mPAP (mmHg)	5.1/-1.6*	na	-0.5/-5.0*	3.0/-2.7***
Cardiac output (L/min)	-0.5/0.5***	na	na	0.09/-0.15 (cardiac index)
PVR (dyn.s.cm^{-5})	191/-223***	na	155/-317*	107/-82***
Improvement in Borg dyspnoea index	1.4/-0.2	0.3/-0.1/-0.6	na	Ns
Improvements in WHO functional class (%)	9/43	30/43/41	13/35	Functional class worsening 13/3
Time to clinical worsening	Sig. improvement vs. placebo	Sig. improvement vs. placebo	na	Na
Incidence of clinical worsening (%)	27/0*	14/5/4	na	13/3
LFT elevations >3x ULN (%)	0/6.3	3/4/14	0/1†	3/8
Peripheral oedema (%)	5/8[b]	5/8[c]	6/19	8/6

6MWD, 6-minute walk distance; FC, functional class; LFT, liver function test; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; na, not available; ns, not significant; PVR, pulmonary vascular index; ULN, upper limit of normal; WHO, World Health Organisation.

Appendix 3: Patient characteristics from long-term extension studies and registries with bosentan

	BREATHE-1 and 351 pooled* (McLaughlin et al.[80])	(Provencher et al.[81])	Australian Patient Registry$ (Keogh et al.[39])	NIH Registry* (McLaughlin et al.[80])
Study details	Subgroup analysis of 2 open-label extension trials	Retrospective analysis from 1 institution	Registry data (15 centres)	Registry data
Drugs and daily doses	bosentan 250 mg	bosentan 250 mg	Bosentan 250 mg	BSC
Setting	US and EUR	EUR	AUS	US
Dosing regimen	bd	bd	bd	-
Study duration (wks)	16	Nov 1999 – May 2004	-	-
Age inclusion (yrs)	≥12	>15	ALL	1-81
6MWD (m) for inclusion	≥150 and ≤450	nr	na	-
PAH aetiology	IPAH (100%)	IPAH (100%)	IPAH (58%) CTD-PAH (42%)	IPAH (100%)
WHO functional class	I/II (9%) III (82%) IV (9%)	III (91%) IV (12%)	II (6%) III (70%) IV (19%)	II (29%) III/IV (71%)
Patient disposition	196 randomised	103 assessed	528 enrolled, 173 discontinued	187 patients
Male:Female (%)	21:79	27:73	23:77	37:63
Mean age (yrs)	46 (13-80)	54 (±16)	59 (2-89)	36 (1-81)
Mean 6MWD at baseline	345 (±87)	319 (±105)	nr	-

Appendix 4: Results from long-term extension studies and registries with bosentan

	BREATHE-1 and 351 pooled* (McLaughlin et al.[80])	(Provencher et al.[81])	Australian Patient Registry (Keogh et al.[39])	NIH Registry* (McLaughlin et al.[80])
Drugs and daily doses	bosentan 250 mg	bosentan 250 mg	bosentan 250 mg	BSC
1-year survival	96%	92%	86.4% (95% CI: 83.8-88.9)	69% predicted
2-year survival	89%	89%	Nr	57% predicted
3-year survival	nr	79%	Nr	Nr
LFT elevations >3x ULN (%)	14.9	nr	Nr	Nr
Peripheral oedema (%)	11.2	nr	Nr	Nr

BSC, best supportive care; CI, confidence interval; NIH. National Institute of Health; LFT, liver function tests; nr, not reported; ULN, upper limit of normal.

*IPAH only.

Appendix 5: Patient characteristics and results from RCTs with inhaled iloprost vs. placebo

AIR (Olschewski et al.[86])			
Characteristics		**Results†**	
Drugs and daily doses	Placebo/iloprost 2.5 – 5.0 ug	**6MWD**	nr/59**
Setting	EUR	**mRAP (mmHg)**	1.4/0.5
Dosing regimen	6 – 9 x daily	**mPAP (mmHg)**	-0.2/-0.1
Study duration (wks)	12	**Cardiac output (L/min)**	-0.19/0.05
Age inclusion	nr	**PVR (dyn.s.cm^{-5})**	96/-9**
6MWD (m) for inclusion	<50 and <500	**Improvement in Mahler dyspnoea index**	0.3/1.42*
PAH aetiology	IPAH (51%)	**Improvements in NYHA functional class**	13/25
	CTD-PAH (13%)	**(%)**	
	CTEPH (33%)		
	Other (4%)		
NYHA functional class	III (59%)	**Time to clinical worsening**	Nr
	IV (41%)		
Patient disposition	Screened nr,	**Incidence of clinical worsening (%)**	8.8/4.9
	203 randomised (1:1)		
	18 discontinuations (4/14)		
Male:Female (%)‡	32/68	**Cough (%)**	26/39
Mean age (years)‡	51 (±13)	**Peripheral oedema (%)**	16/13
Mean 6MWD at baseline (m)‡	332 (±93)	**Headache (%)**	20/30

Appendix 6: Patient characteristics and results from long-term extension studies with inhaled iloprost

	Hoeper et al.[87]	Opitz et al.[88]
Study details	One-year, open-label study	Open-label study
Drugs and daily doses	Iloprost 100 or 150 ug/day	Iloprost 100 ug/day
Setting	GERMANY	GERMANY
Dosing regimen	6-8 times daily	6 times daily
Study duration (wks)	52	76
Age inclusion (yrs)	nr	nr
PAH aetiology	IPAH (100%)	IPAH (100%)
WHO functional class	NYHA III (83%)	NYHA II (24%)
	IV (7%)	III (67%)
		IV (9%)
Patient disposition	31 Screened,	Screened nr,
	24 assessed,	76 enrolled,
	no discontinuations .	11 died, 6 transplanted, 12 discontinued.
Male:Female (%)	37/63	29/71
Mean age (yrs)	38 ± 12	43 ± 0.1
Mean 6MWD (m) or walk time (s) at baseline	278 ± 96 6MWD	339 ± 27 Walk time
mPAP (mmHg)	59 ± 10	61 ± 2
1-year survival	100%	79%†
2-year survival	nr	70%†
3-year survival	nr	59%†

6MWD, 6-minute walk distance; mPAP, IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; WHO, World Health Organisation.

†Event-free survival = death, transplantation, switch to i.v. therapy, or addition of other active oral therapy. All values are pre-inhalation.

Appendix 7: Patient characteristics from RCTs with sildenafil vs. placebo and sildenafil vs. bosentan

	Sastry et al.[90]	SUPER-1 (Galie et al.[91])			Singh et al.[92]	SERAPH (Wilkins et al.[71])
Drugs and daily doses	Placebo/sildenafil 75-300 mg	Placebo/sildenafil 60, 120, 240 mg			Placebo/sildenafil 75-300 mg	Sildenafil 150 mg/bosentan 250 mg
Setting	India	International			India	UK
Dosing regimen	tds	tds			Tds	tds/bd
Study duration (wks)	12	12			12	16
Age inclusion	12 - 65	nr			Nr	Nr
Baseline 6MWD for inclusion (m)	nr	>100 and <450			Nr	>150 and <450
		20 mg tds	**40 mg tds**	**80 mg tds**		
PAH aetiology	IPAH (100%)	IPAH (64%)	IPAH (64%)	IPAH (65%)	IPAH (50%)	IPAH (86%/92%)
		CTD (31%)	CTD (29%)	CTD (29%)	CHD (50%)	CTD (14%/8%)
		CHD (6%)	CHD (6%)	CHD (6%)		
WHO functional class	NHYA II (82%)	II (35%)	II (34%)	II (39%)	II (40%)	nr
	III (18%)	III (58%)	III (66%)	III (59%)	III (55%)	
		IV (7%)	IV (0%)	IV (1%)	IV (5%)	
Patient disposition	Screened nr,	360 screened nr, 278 enrolled, 8 discontinuations			Screened nr,	40 screened,
	22 enrolled				20 enrolled	26 enrolled
	1 discontinuation				0 discontinuations	0 discontinuations
Male:Female, (%)‡	45/55	29/71	30/70	21/79	25/75	79/21 & 83/17
Mean age (years)‡	Range 16 - 55	47 ± 14	51 ± 15	48 ± 5	Range 3 - 35	44/41
Mean 6MWD at baseline (m) or walk time (s)‡	440 ± 172 s	347 ± 90 m	345 ± 77 m	339 ± 79 m	262 ± 99 m	290/304 m
mPAP (mmHg)‡	nr	54 ± 13	49 ± 13	52 ± 16	99 ± 21 (PASP)	nr

6MWD, 6-minute walk distance; bd, twice-daily; CHD, congenital heart disease; CTD, connective tissue disease; EUR, Europe; IPAH, idiopathic pulmonary arterial

Appendix 8: Results from RCTs with sildenafil vs. placebo and sildenafil vs. bosentan

	Sastry et al.[90]	SUPER-1 (Galie et al.[91])			Singh et al.[92]	SERAPH (Wilkins et al.[71])
Drugs and daily doses	Placebo/sildenafil 75-300 mg	Placebo/sildenafil 60, 120, 240 mg			Placebo/sildenafil 75-300 mg	Sildenafil 150 mg/bosentan 250 mg
		20 mg tds	40 mg tds	80 mg tds		
6MWD (m) or walk time (s)	475/687 sec***	45m** Sild. placebo corrected	46m** Sild. placebo corrected	50m** Sild. placebo corrected	31/97***	114/59*
mRAP (mmHg)	nr	0.3/-0.8	0.3/-1.1	0.3/-1.0	Nr	nr
mPAP (mmHg)	nr	0.6/-2.1*	0.6/-2.6*	0.6/-4.7***	-4.2/-21 (PASP)	nr
Cardiac index (L/min/m^2)	2.8 ± 0.9/3.45 ± 1.16***	-0.2/0.21	-0.2/0.24*	-0.2/0.37**	Nr	0.3/0.3
PVR (dyn.s.cm^{-5})	nr	49/-122*	49/-143*	49/-261***	Nr	nr
Improvement in Borg dyspnoea index	nr	-1	0	-1	Nr	-1.5/0.2
Improvements in WHO functional class (%)	nr	7/28**	7/36**	7/42**		nr
Time to clinical worsening	nr	nr	nr	nr	Nr	nr
Incidence of clinical worsening	nr	10/4	10/3	10/7	Nr	nr
Headache (%)	5/14	39/46	39/42	39/49	Nr	nr
Flushing (%)	nr	3/10	3/9	3/15	Nr	nr

6MWD, 6-minute walk distance; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; nr, not reported; PASP, pulmonary artery systolic

Appendix 9: Patient characteristics and results from long-term extension studies with sildenafil

	SUPER-1* (Galie et al.[91])
Study details	Extension study of SUPER-1
Drugs and daily doses	Sildenafil 240mg
Setting	International
Dosing regimen	tds
Study duration (wks)	84
Age inclusion (yrs)	nr
Patient disposition	259 enrolled, 15 discontinuations
1-year survival	96%
2-year survival	nr
3-year survival	nr

tds, three-times daily; nr, not reported.

*All extension study data based on 80 mg three-times daily.

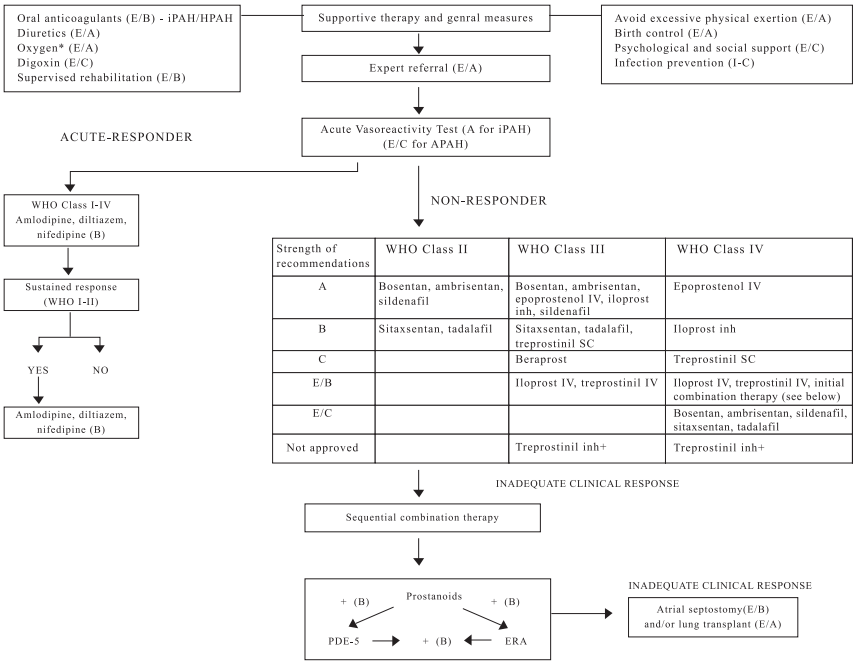
Appendix 10: Clinical trials in progress with combination therapy

Trial name	Intervention	Inclusion criteria	Duration	Recruitment target
VISION	Inhaled iloprost added to sildenafil	IPAH	16 wks + extension	180
COMPASS-2	Bosentan added to sildenafil	IPAH, APAH, HIV, CHD on sildenafil	16 wks + extension	600
A1481243	Sildenafil added to bosentan	PAH on bosentan	12 wks + extension	106

Appendix 11: Strength of recommendation as outlined by the Dana Point guidelines[52]

Variables	Description
A	Strong recommendation
B	Moderate recommendation
C	Weak recommendation
D	Negative recommendation
I	No recommendation possible (inconclusive)
E/A	Strong recommendation on the basis of expert opinion only
E/B	Moderate recommendation on the basis of expert opinion only
E/C	Weak recommendation on the basis of expert opinion only
E/D	Negative recommendation on the basis of expert opinion only

Appendix 12: PAH evidence-based treatment algorithm – Dana Point 2008[52]



Drugs within the same grade of evidence are listed in alphabetical order and not order of preference. Not all agents listed are approved or available for use in all countries. Strengths of recommendations are defined in Table 16. *To maintain oxygen at 92%. + Investigational, under regulatory review. APAH, associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; SC, subcutaneous; WHO, World Health Organization.

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