Research Review
EDUCATIONAL SERIES
Pulmonary Arterial Hypertension

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About this Review

This review is intended as an educational resource for health professionals. It discusses the incidence, prevalence, burden, diagnosis and treatment of pulmonary arterial hypertension (PAH) in New Zealand. This paper emphasises the importance of early diagnosis, and provides useful diagnostic and treatment algorithms. Peer-reviewed clinical trial evidence is presented with accompanying expert commentary that is intended to inform readers about advancing clinical practice in the treatment of this debilitating and life-threatening condition.

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Pulmonary Arterial Hypertension – Why we need to know more

Patients developing this devastating and fatal disease tend to present late with advanced disease, partly as a result of a lack of awareness of the condition among the general medical community and a resultant delay in the investigation of symptoms.

Pulmonary arterial hypertension (PAH) is a rare, chronic, progressive, multifactorial disease of the pulmonary arterial circulation. The condition is characterised by a progressive rise in pulmonary vascular resistance (PVR), leading to shortness of breath, dizziness, fainting, fatigue and other symptoms, all of which are exacerbated by exercise.[1-5] PAH can occur at any age and, if left untreated, can lead to decompensated right heart failure and death within 2-3 years.[1-4] The primary goal of treatment is to prolong and improve quality of life in affected individuals. Even with new approved therapies, PAH continues to be a progressive, fatal illness, with only lung transplantation offering a cure. Unfortunately, due to its difficult and often delayed diagnosis, this disease is frequently well progressed before appropriate therapy is initiated. Given the poor rates of survival with advanced disease, it is critical that PAH be diagnosed early and treated appropriately. Raising awareness of PAH is crucial for the timely management of this fatal but treatable disease.

Classifications

Pulmonary hypertension (PH) is classified into five different groups.[3]

1 PAH (further sub-divisions listed below)
  1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
2 PH due to left heart disease
3 PH due to lung diseases and/or hypoxia
4 Chronic thromboembolic PH
5 PH with unclear and/or multifactorial mechanisms

PAH is further subdivided into five aetiological subgroups, as outlined in **Table 1**.[3] Haemodynamically, PAH falls into the subgroup of pre-capillary PH, defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, a pulmonary wedge pressure (PWP) ≤15 mmHg, a PVR >3 Wood units and normal or reduced cardiac output at rest.[2]

Table 1: Updated clinical classification of pulmonary hypertension Group 1; Pulmonary arterial hypertension (PAH) (Adapted from Simonneau et al 2009[3])

1.	**Pulmonary arterial hypertension (PAH)**
	1.1. Idiopathic PAH*
	1.2. Heritable**
	1.2.1. BMPR2
	1.2.2. ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
	1.2.3. Unknown
	1.3. Drugs and toxins induced
	1.4. Associated with:
	1.4.1. Connective tissue diseases
	1.4.2. HIV infection
	1.4.3. Portal hypertension
	1.4.4. Congenital heart disease
	1.4.5. Schistosomiasis
	1.4.6. Chronic haemolytic anaemia
	1.5. Persistent pulmonary hypertension of the newborn

* Formerly known as primary PAH; **Formerly known as familial PAH

ALK1 = activin receptor-like kinase 1 gene; BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus

The severity of PH/PAH is determined by the degree of exertional intolerance and is quantitated using the World Health Organisation (WHO) classification of functional status as outlined in **Table 2**.[6] The New York Heart Association (NYHA) has a similar functional classification system for PH.[7] Functional classification is a critical element in the assessment of patients with PAH, because functional class has been shown to be strongly predictive of mortality[8] and is an important factor in the choice of appropriate therapy.[2]

Table 2: World Health Organisation classification of functional status of patients with pulmonary hypertension (PH). (Adapted from McGoon et al 2004[8])

Class	Description
I	Patients with PH who have no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or presyncope.
II	Patients with PH with mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or presyncope.
III	Patients with PH with a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or presyncope.
IV	Patients with PH unable to perform any physical activity without symptoms and who may have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest. Discomfort is increased by any physical activity.

Pathology/pathobiology

PAH results from a restriction in blood flow through the pulmonary arterial circulation (pulmonary veins are classically unaffected).[9] This restriction is primarily caused by a loss of vascular luminal cross section, brought about initially by vasoconstriction, then vascular remodelling due to excessive cell proliferation and reduced rates of apoptosis[2,9] involving all layers of the vessel wall with endothelial cells, smooth muscle cells, fibroblasts, platelets and inflammatory cells all playing a significant role.[10] Pulmonary arterial obstruction by vascular proliferation and remodelling are the hallmark of PAH pathogenesis.[10] Pathological changes in PAH include medial hypertrophy, intimal proliferative and fibrotic changes, adventitial thickening with moderate perivascular inflammatory infiltrates, plexiform arteriopathy and thrombosis *in situ* primarily affecting the distal small muscular pulmonary arteries measuring <500µM in diameter.[2,9,11]

Three major pathways have been identified that contribute to increased pulmonary vascular tone and vascular remodelling in PAH. These are an increase in activity of the endothelin-1 pathway and decreases in the activity of the nitric oxide (NO) and prostacyclin pathways.[9] Modification of these pathways has been shown to lead to improved disease outcomes and they are therefore the targets of modern therapy.[2]

Prognosis

- **The natural history of PAH is heterogeneous**, with some patients living for decades and others dying within months of diagnosis. Studies have revealed an estimated median survival for idiopathic PAH (IPAH) of approximately 2-3 years, and 1-, 2- and 3-year mean survival rates of 79%, 66% and 59%, respectively.[4,8] Survival rates for PAH associated with other underlying aetiologies vary, with 1-, 2- and 3-year mean survival rates for PAH associated with HIV being the lowest (58%, 39% and 21%, respectively) and those for PAH associated with congenital heart disease being the highest (92%, 88.5% and 77%, respectively).[8]
- **WHO functional class** has also been shown to be a powerful predictor of survival in untreated patients, with patients with IPAH or heritable PAH and WHO functional class IV, III, II and I showing median survival times of 6 months, 2.5 years, 6 years and 6 years respectively.[4]
- **Other factors** carrying a poor prognosis in IPAH include declining exercise capacity, syncope, haemoptysis, signs of right ventricular (RV) failure and extremes of age (<14 years or >65 years).[2]
- In fact, while **PAH in children** is similar to that in adults, children have a poorer prognosis if left untreated, with survival estimates of <1 year.[12] Children may also be less well than adults at their first presentation.

Individuals exhibiting a worse prognosis tend to be those with clinical evidence of RV failure, a rapid rate of disease progression, syncope, WHO-FC IV disease, a 6 minute walk test of <300m, a peak O_2 consumption <12 mL/min/kg, elevated and rising plasma levels of brain natriuretic peptide (BNP), pericardial effusion, tricuspid annular plane systolic excursion <1.5cm, right atrial (RA) pressure >15 mmHg or cardiac index ≤2 L/min/m^2.[9]

Factors that predict survival in PAH drive clinical management and a group of US-based researchers have recently devised a prognostic equation, based on data from the REVEAL trial, for the prediction of survival in patients with WHO-Functional Class (WHO-FC) I PAH.[13] They believe that this tool is potentially useful for individualising and optimising therapeutic strategies.

Recognised medical & genetic risk factors

Table 3: Risk factors for the development of PAH (Adapted from McLaughlin et al 2009[9])

BMPR2* mutation	Approx. 20% chance of developing PAH.
Systemic sclerosis (scleroderma)	Prevalence of PAH is approx. 8-27%.
HIV infection	0.5% prevalence of PAH (6-12 fold that of general population).
Portal hypertension	2-6% prevalence in patients with cirrhosis.
Prior appetite suppressant use (fenfluramine)	Incidence of PAH is approx. 0.005% if agent used >3 months.
Congenital heart disease	High probability of PAH developing in unrepaired shunt (Eisenmenger syndrome).
Sickle cell disease	Approx. 10% of sufferers develop PAH.

*BMPR2 = bone morphogenetic protein receptor, type 2

Incidence/prevalence

It is widely believed that PAH is a rare disease. The WHO says that while this is true for IPAH (recent epidemiological data indicate an IPAH prevalence of approximately 6 per million), the true burden of PAH is currently unknown and certainly underestimated.[14,15] Incidence estimates for PAH in Europe range from 2.4 to 7.6 cases per million population annually, with prevalence rates of 15 to 50 cases per million population.[14,16] The prevalence of PAH in New Zealand is estimated to be approx. 40 per million population. With changing demographics, chronic illnesses such as PAH are becoming more prevalent worldwide[17] with increasing identification of IPAH in many patients over 70 years of age.[18]

With regard to the different aetiological subgroups of PAH, French National Registry data has shown that of 674 patients with PAH, 39.2% had IPAH, 3.9% had heritable PAH, 9.5% had anorexigen-induced PAH, 15.3% had PAH associated with connective tissue diseases, 11.3% had PAH associated with congenital heart disease, 10.4% had PAH associated with portal hypertension and 6.2% had HIV-associated PAH.[14]

The burden of disease

The quality of life in patients with PAH has been shown to be significantly impaired.[19,20] Not only do individuals experience social limitations from their disease burden, but many live with the threat of right heart failure and premature death.[19,20] Not surprisingly, anxiety and depression are frequently reported in this patient population, with the prevalence of these disorders increasing with functional impairment.[20,21] Furthermore, many patients report cognitive difficulties and a high incidence of cognitive sequelae has been observed in patients with PAH.[20]

The economic burden of PAH in New Zealand has not been measured, however, a European study indicates a treatment cost of approximately €47,000 per patient per year.[19] Studies from the UK investigating the cost-effectiveness of agents such as bosentan, sildenafil and sitaxentan have shown treatment for PAH to be more cost-effective than no active intervention.[22,23]

Diagnosis

During the last 10 years, an expanding range of treatment options has dramatically improved outcomes for patients with PAH, improving quality of life and increasing survival. However, many patients still have a very poor prognosis, with their condition deteriorating rapidly. One of the key factors in the effective treatment of this disorder is the early initiation of therapy. Unfortunately, PAH is notoriously difficult to diagnose and patients often go undiagnosed or misdiagnosed for many years. Early identification represents a real challenge for the clinician, as patients are asymptomatic in the early stages of the disease. The first symptom is often progressive dyspnoea upon exertion. Patients may also present with fatigue, weakness, angina, syncope, presyncope, abdominal distension, weight gain or peripheral oedema.[5] Patients and physicians may misinterpret early symptoms, believing the patient to be simply `out of shape'. Furthermore, later symptoms may be attributed to more common cardiorespiratory diseases.

In advanced cases, symptoms may be present at rest and many individuals present with right heart failure. In fact, a large epidemiological study from France revealed that 75% of patients with PAH were in NYHA-FC III or IV at the time of their diagnosis.[14] Furthermore, most patients had a history of >2 years of dyspnoea.

In 2009, both American and European PH Task Forces released expert consensus and guideline documents on the diagnosis and treatment of PH with the aim of improving the management of this disease.[2,9] The evaluation of a patient with suspected PH requires a series of investigations to confirm the diagnosis (which is usually one of exclusion), separate PAH from the other types of PH, determine the specific PAH aetiology, and evaluate the haemodynamic and functional impairment (WHO-/NYHA-FC – see **Table 2**). Simple screening tools exist, such as ECG and chest radiography, but they are neither sensitive nor specific. While right heart catheterisation remains the gold standard in the diagnosis of PAH, the less invasive technique of Doppler echocardiography is a useful and non-invasive modality for estimating pulmonary pressure and for determining underlying anatomical and functional cardiac abnormalities. A high quality echocardiogram will usually provide information about pulmonary pressure as well as helping to steer the clinician toward PAH or PH associated with left heart disease (the most common cause of an elevated estimated PAP). In occasional cases, echocardiographic abnormalities may be very subtle and in patients where there is a high index of suspicion right heart catheterisation may be required.

Pivotal tests

Guidelines state that all of the following pivotal tests should be undertaken for a definitive diagnosis and baseline characterisation of PAH:[9]

Patient history, a physical examination, chest X-ray, ECG, echocardiogram, ventilation-perfusion scintigram (VQ scan), pulmonary function tests (PFT), overnight oximetery, HIV screening, antinuclear antibody (ANA) serology, liver function tests, functional tests (6-minute walk test and cardiopulmonary exercise test) and right heart catheterisation. It is essential that right heart catheterisation is carried out at a centre frequently undertaking this procedure in pulmonary vascular disease and experienced in pulmonary vasodilator challenges. Local expertise and resources determine whether investigations are undertaken locally or at a PAH clinic.

While lung sounds are usually normal, physical signs of PAH include left parasternal lift, an accentuated pulmonary component of the second heart sound, a diastolic murmur of pulmonary insufficiency, a pansystolic murmur of tricuspid regurgitation and an RV third sound.[2] Patients in an advanced state of PAH may exhibit jugular vein distension, hepatomegaly, ascites, peripheral oedema and cool extremities. The ECG in PAH may demonstrate RV hypertrophy and strain, and RA dilatation and supraventricular arrhythmias may be present in advanced stages.[2] The chest radiograph may show central pulmonary arterial dilatation and pruning of the peripheral blood vessels; 90% of patients exhibit an abnormal chest radiograph at the time of diagnosis.[24]

Contingent tests

Guidelines recommend contingent tests to elucidate or confirm the results of pivotal tests (these need only be performed in the appropriate clinical context):[9]

- Transoesophageal echocardiogram and exercise echocardiography to confirm the results of an echocardiogram.
- Pulmonary angiography, chest CT angiogram and coagulopathy profile for confirmation of VQ scan results.
- Arterial blood gases to confirm PFT findings.
- Polysomnography to confirm overnight oximetery findings.
- Connective tissue disease serologies (screening for scleroderma, systemic lupus erythematosis) including ANA, and if positive, extractable nuclear antigens (ENA).
- Vasodilator testing, exercise right heart catheterisation, volume loading and left heart catheterisation, following right heart catheterisation.[9] All patients with IPAH who might be considered potential candidates for long-term calcium-channel blocker therapy should undergo acute vasodilator testing.

Arterial blood gases and pulmonary function tests may show a decreased lung diffusion capacity for carbon monoxide and mild-to-moderate reduction in lung volumes in individuals with PAH.[2] Biopsy is discouraged as there is a low likelihood that the findings will alter the diagnosis and treatment.

There is a clear need for raised awareness of this condition and its timely and accurate diagnosis. To this end, a diagnostic algorithm has been developed by the European PH Task Force (see **Figure 1**).

The recent European guidelines introduced the concept of the `clinical probability of a PAH diagnosis' in order to assist decision-making in the individual patient.[1,2] The guidelines propose arbitrary criteria for predicting the likelihood of PH based on the tricuspid regurgitation peak velocity, the correspondent Doppler-calculated pulmonary artery systolic pressure at rest, and on additional echocardiographic parameters that might reinforce or raise the suspicion of PH, and consider these with symptoms, risk factors and associated conditions (see **Table 3**), in order to give a prediction of the probability of PAH.[2] The American Guidelines suggest that certain individuals with predisposing risk factors (see **Table 3**) warrant periodic screening for PAH.[9]

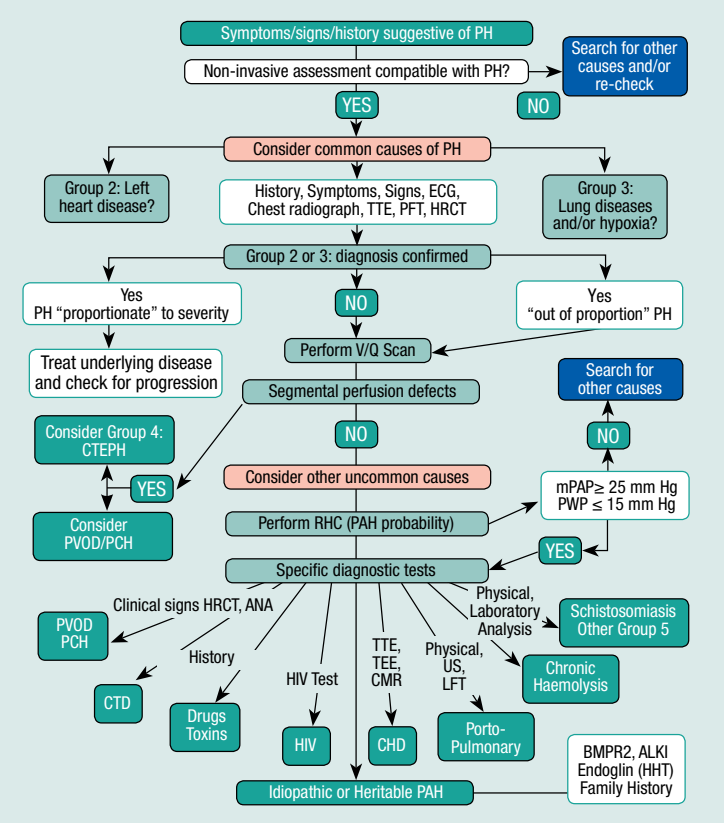
Evaluation of disease severity

The next step in the assessment of the patient is the evaluation of the severity of PAH. The severity of the disease influences the initial treatment choice, the evaluation of the response to therapy and the decision to escalate therapy. Such assessment should include clinical evaluation, exercise tests, evaluation of biochemical markers, echocardiographic and haemodynamic assessments (including right heart catheterisation). European guidelines recommend that all of these assessments be performed at baseline, 3-4 months after initiation or change in therapy, and upon the appearance of clinical worsening.[2] It is also recommended that clinical, exercise and biochemical marker evaluations be performed every 3-6 months in all patients with PAH.[2]

Take-home messages:

- Early diagnosis is essential to improve outcomes.
- Periodic screening for PAH in at risk individuals.[9]
- Doppler echocardiogram is the most appropriate screening tool when PAH is suspected, however, there is a false negative rate.[9]
- Accurate diagnosis and classification of the type of PAH requires right heart catheterisation.[9]
- The haemodynamic definition of PAH is: mPAP ≥25 mmHg, a PWP ≤15 mmHg, and a PVR >3 Woods units, at rest.[9]
- Perform follow-up assessments of severity every 3-6 months, including patients with stable PAH, in liaison with a dedicated PAH clinic in a `shared care' model (this is a basic standard of care).[2]

Figure 1: Diagnostic algorithm for pulmonary hypertension.[2]



ALK-1 = activin-receptor-like kinase; ANA = antinuclear antibodies; BMPR2 = bone morphogenetic protein receptor 2; CHD = congenital heart disease; CMR = cardiac magnetic resonance; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; Group = clinical group (1-5); HHT = hereditary haemorrhagic telangiectasia; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; LFT = liver function tests; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary haemangiomatosis; PFT = pulmonary function test; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PWP = pulmonary wedge pressure; RHC = right heart catheterisation; TEE = transoesophageal echocardiography; TTE = transthoracic echocardiography; US = ultrasonography; V/Q scan = ventilation/perfusion lung scan.

Treatment

Treatment of PAH aims to inhibit progressive vasoproliferation, to reduce PVR and to treat RV failure. Treatment endpoints include improved symptoms and quality of life, exercise tolerance and survival without hospitalisation. The clearest goal is improvement of patients to WHO-FC I or II, together with improvements in haemodynamic and functional parameters.[25]

General measures

Patients with PAH require sensible advice about general activities of daily living. Support groups can offer valuable advice on coping, and improve patient confidence and outlook.[2] Patients should be encouraged to be physically active (within symptom limits) and an exercise regimen may be beneficial. Pregnancy in patients with PAH has been associated with approximately a 30% mortality rate and therefore PAH is considered a contraindication to pregnancy.[26] The use of two methods of contraception is advised.[2] Individuals with WHO-FC III or IV disease should avoid going to altitudes above 1500-2000m without supplemental O_2.[2] Psychiatric referrals should be considered for those patients exhibiting severe anxiety and/or depression. Vaccination against influenza and pneumococcal pneumonia is also advised.[2]

Supportive therapy

Supportive treatment includes diuretics for the management of right heart failure, oxygen to maintain O_2 saturation >90%, and oral warfarin.[9] Warfarin is recommended in all patients with IPAH without contraindication.[9] Digoxin is sometimes used in patients with atrial arrhythmias and in patients with right heart failure and low cardiac output.[9]

Specific drug therapy

Vasoreactive IPAH patients may benefit from high doses of calcium-channel blockers, but such agents are not well tolerated in patients with severe RV dysfunction and failure.[27] Those patients without a positive response to acute vasodilator testing, and who are considered `lower risk', should be started on either an endothelin receptor antagonist (bosentan or ambrisentan) or a PDE-5 inhibitor (sildenafil).[9] Inhaled or IV iloprost is recommended for patients with WHO-FC III or IV disease.[2] A `treat-to-target' approach is recommended by the recent European guidelines and stresses the importance

of intervention before obvious clinical and functional worsening.[2,25] Waiting for symptoms of deterioration before intervention is not an acceptable approach in a rapidly progressing disease like PAH.[25]

One way of escalating therapy is to simultaneously use two or more classes of drugs. This approach is logical given that PAH is a disease involving three separate signalling pathways (endothelin, prostacyclin and NO) and recent large-scale trials show that this is an effective management option.[28,29] The most recent treatment algorithm from the European Society of Cardiology and the European Respiratory Society recommends a sequential add-on approach to combination therapy (see **Figure 2**).[2] The guidelines state that patients should be started on monotherapy and followed-up regularly, and recommend initial combination therapy only for patients with advanced disease (WHO-FC IV). Researchers from Germany have devised a useful goal-oriented treatment algorithm that promotes the use of add-on therapies if treatment goals are not met.[30]

In New Zealand, available therapies targeted at the pathways associated with PAH include the endothelin receptor antagonists ambrisentan [Volibris] and bosentan [Tracleer]), the synthetic prostacyclin analog iloprost [Ilomedin; Ventavis] and the phosphodiesterase type-5 inhibitors sildenafil [Revatio; Viagra] and Tadalafil [Cialis], which act on the NO pathway. Some agents in New Zealand are used for PAH off-label (Viagra, Cialis). See below for drugs registered for use in PAH in NZ.

Drugs with registered indications for PAH in NZ[31]

Bosentan is indicated for the treatment of IPAH, familial PAH, PAH associated with scleroderma or PAH associated with congenital systemic-to-pulmonary shunts including Eisenmenger's physiology in patients with WHO-FC Class III or IV symptoms. Bosentan may cause birth defects and is contraindicated in pregnancy. Rare cases of hepatic cirrhosis and hepatic failure have been reported in patients using this agent.

Ambrisentan is indicated for the treatment of IPAH and PAH associated with connective tissue disease in patients with WHO-FC II, III or IV symptoms. Ambrisentan may cause birth defects and is contraindicated in pregnancy.

Sildenafil is used to treat patients with symptom-limited PAH to improve exercise capacity.

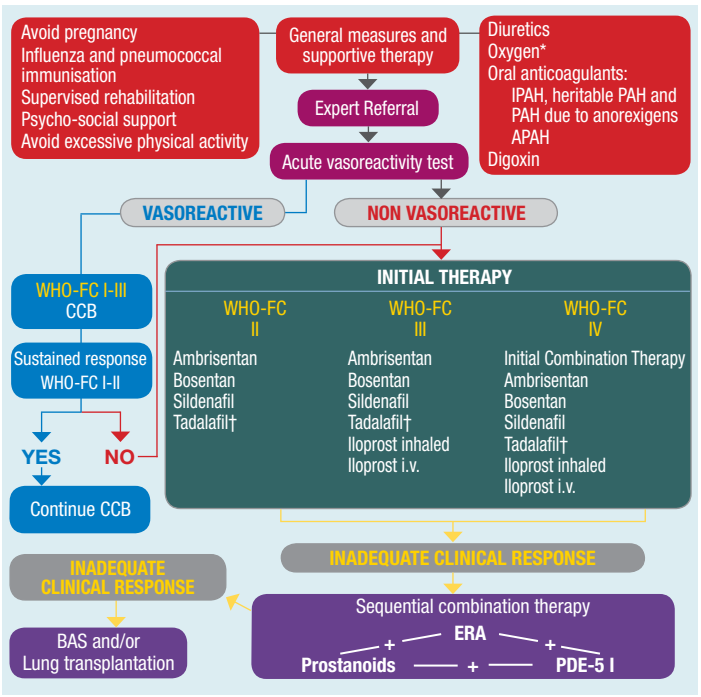
Iloprost for infusion [Ilomedin] is indicated for the treatment of moderate or severe (NYHA-FC III and IV) primary and secondary PH. Smoking, pregnancy and lactation are contraindicated.

Iloprost for inhalation [Ventavis] is indicated for the treatment of patients with primary PH or secondary PH (connective tissue disease- or drug-induced) in moderate or severe stages of the disease. In addition, for treatment of moderate or severe secondary PH due to chronic pulmonary thromboembolism, where surgery is not possible. Pregnancy and lactation are contraindicated.

Funding of PAH drugs in New Zealand

In New Zealand, Iloprost [Ventavis]), ambrisentan [Volibris], bosentan [Tracleer], and sildenafil [Viagra] may be fully subsidised by Pharmac for individuals with PAH and WHO-FC II-IV disease who meet specific criteria and gain Special Authority from the PAH Management Panel.[32] The schedule states that patients would generally be expected to start treatment with sildenafil and that patients who have failed to respond to two monotherapies within the first six months of treatment may be eligible for combination therapy. The schedule also states that combination bosentan/iloprost or ambrisentan/iloprost may be considered for patients who cannot tolerate a sildenafil regime, that combination sildenafil/bosentan/iloprost therapy will not be approved, nor will combination sildenafil/ambrisentan/iloprost therapy.

Figure 2: Evidence-based treatment algorithm for PAH. (Adapted from Galie et al 2009.[2])



*To maintain arterial blood O2 pressure ≥8 kPa (60 mmHg). †Under regulatory review in the European Union; APAH = associated pulmonary arterial hypertension; BAS = balloon atrial septostomy; CCB = calcium-channel blocker; ERA = endothelin receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension, PDE5 I = phosphodiesterase type-5 inhibitor; WHO-FC = World Health Organisation functional class.

Take-home messages:

- Implement goal-oriented treatment.
- Start with monotherapy in `low-risk' patients.
- Start with combination therapy in WHO-FC IV patients.
- Regularly review treatment response.
- Do not wait for symptoms of deterioration before altering therapy.
- Use a sequential add-on therapy approach when necessary.

Specialist commentary on current studies

Late diagnosis is common: data from two registry studies

Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry[33]

Authors: Brown LM et al

Summary: The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) enrolled 2967 adult patients with PAH in the US from 2006-7. Of those enrolled, 21.1% had exhibited symptoms for more than 2 years before PAH was diagnosed. Several factors were identified that increased the likelihood of delayed disease recognition; onset of symptoms before the age of 36 years (OR 3.07; 95% CI 2.03-4.66), a history of obstructive airways disease (OR 1.93; 95% CI 1.5-2.47), sleep apnoea (OR 1.72; 95% CI 1.33-2.22), 6-minute walk distance <250m (OR 1.91; 95% CI 1.16-3.13), right atrial pressure <10mmHg (OR 1.77; 95% CI 1.26-2.48), PVR <10 Wood units (OR 1.28; 95% CI 1.02-1.60).

Comment: Further `real life' data that confirms that even in recent years an unacceptable proportion of patients have prolonged symptoms prior to diagnosis and, in this progressive and irreversible disease, have advanced disease at the time of diagnosis. Particularly disadvantaged are younger breathless patients who will, like most PAH patients, have a normal physical examination and often assumed to be anxious or hyperventilating. Paradoxically, older breathless patients are investigated more aggressively and often have an echocardiogram that raises the possibility of pulmonary vascular disease. This paper highlights the importance of accurate diagnosis in breathless patients.

Pulmonary arterial hypertension in France: results from a national registry[14]

Authors: Humbert M et al

Summary: This French registry enrolled 674 patients with PAH between 2002 and 2003. A total of 553 patients had an existing PAH diagnosis at the time of enrollment (prevalent cohort), while 121 patients were diagnosed during the recruitment phase of the registry (incident cohort). Patients ranged in age from 18-85 years (mean age 50 years) and had the following aetiological types of PAH; idiopathic (39.2%), familial (3.9%), anorexigen induced (9.5%), connective tissue disease associated (15.3%), congenital heart disease associated (11.3%), portal hypertension associated (10.4%), HIV associated (6.2%). At the time of diagnosis, 75% of patients were in NYHA-FC III or IV. Patients had the following clinical and haemodynamic measurements at the time of diagnosis; mean 6-minute walk distance 329 ± 109m, mPAP 55 mmHg, mean cardiac index 2.5 L/min/m^2, mean PVR index 20.5 Wood units. The one-year survival rate in the incident cohort was 88%. Low estimates of incidence and prevalence of PAH in France were 2.4 cases per million and 15 cases per million.

Comment: The French have the most organised national network for PAH management yet, as this paper confirms, sadly the `norm' is patients having advanced disease (NYHA-FC III or IV) at the time of diagnosis. The incidence varies widely across France and is higher in the regions with expert centres, raising concerns that many cases are being misdiagnosed or missed. Raising awareness remains a crucial and central problem at all levels from general practitioners through to specialist physicians.

The limitations of echocardiography in PAH

Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis[34]

Authors: Janda S et al

Summary: This Canadian systematic review and quantitative meta-analysis was undertaken in order to ascertain the diagnostic accuracy of echocardiography (tricuspid regurgitant jet method) for diagnosing PH. A total of 29 studies, involving 1998 patients, correlating pulmonary pressure between echocardiography and right heart catheterisation were analysed. The correlation of systolic PAP by echocardiography and systolic PAP by right heart catheterisation was found to be modest and was generally the same in studies with mildly elevated mean systolic PAP (≤50 mmHg by right heart catheterisation) and those with moderately elevated mean systolic PAP (>50 mmHg); summary correlation coefficients of 0.65 (95% CI 0.61-0.69) and 0.71 (95% CI 0.65- 0.77), respectively.

Comment: Echocardiography is increasingly widely available and, in trained hands, an excellent screening tool for PH. It is important to remember that an elevated estimated pulmonary arterial systolic pressure is consistent with PH (but not necessarily PAH). However, it is not totally reliable for detecting elevated PAP as this paper demonstrates with a relatively poor correlation between systolic PAP from echocardiograph compared to the gold standard, right heart catheterisation. Critically, there may be other echocardiographic features that suggest PAH, even if an assessment of PAP is unable to be made, which may direct the physician toward an invasive assessment. However, if the pre-test probability of PAH is medium to high, a `normal' echocardiogram does not exclude the diagnosis and further investigation should be considered, usually right heart catheterisation.

The inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice[35]

Authors: Rich JD et al

Summary: A total of 160 consecutive patients with PH had their systolic PAP estimated by Doppler echocardiography and measured by right heart catheterisation in this US study designed to determine the accuracy of echocardiography (predefined as 95% limits of agreement within ±10 mmHg). Analysis revealed a moderate correlation between the two measurements ($r = 0.68$; $p < 0.001$), but Bland-Altman analysis showed a bias for Doppler echocardiographic estimates of systolic PAP of 2.2 mmHg, with 95% limits of agreement ranging from -34.2 to 38.6 mmHg. Systolic PAP estimates by Doppler echocardiography were found to be inaccurate in 50.6% of patients.

Comment: This paper examines the same question as the previous paper, but from a different angle and confirms that in general there is a reasonable agreement between echocardiographic and invasively assessed PAP, although there is wide inter-patient variation. In addition, there are a group of patients with insufficient tricuspid regurgitation to make an accurate assessment of PAP. As a result, both in the area of diagnosis and monitoring an individual's response to targeted therapies, it is essential to be aware of the possibility of such discrepancy. In some patients, echocardiography may correlate well and fewer repeat right heart catheterisations will be required, while in other patients the echocardiogram may have no place in the monitoring of their therapy if the correlation between echocardiographic pressures and pressures measured by right heart catheterisation is poor. It is important to recognise that relatively little prognostic information is obtained from the actual PAP. Other information such as RA pressure and the presence of a pericardial effusion (obtainable by echocardiography), cardiac index (requiring invasive assessment) and functional class, are more important prognosticators.

The impacts of therapy

A meta-analysis of randomized controlled trials in pulmonary arterial hypertension[36]

Authors: Galiè N et al

Summary: A meta-analysis of all randomised controlled trials of drugs used in the treatment of PAH published between 1990 and 2008 was undertaken. Drugs included epoprostenol, bosentan, terbogrel, treprostinil, beraprost, iloprost, sildenafil, epoprostenol + bosentan, sitaxsentan and ambrisentan. The primary analysis included 21 trials averaging 14.3 weeks in duration and involving 3140 patients. Overall, all-cause mortality was 2.48%; 1.54% in the treated group and 3.8% in the placebo group. Active treatments were associated with a 43% reduction in mortality (RR 0.57; 95% CI 0.35-0.92). The NNT to prevent one death was 61.6 and 16.2 deaths (95% CI 2.7-24) were prevented in every 1000 patients treated.

Comment: Excellent comprehensive review with clear evidence of short-term benefits from targeted therapies. The reduction in overall mortality in the first months of therapy is convincing and the NNT encouraging in such a devastating disease, especially in view of the costs of these therapies. Unfortunately, these studies were not designed to answer the question as to whether these impressive benefits are maintained in the medium to long term.

Compelling evidence of long-term outcomes in pulmonary arterial hypertension? A clinical perspective[37]

Authors: Gomberg-Maitland M et al

Summary: This review evaluated the strengths and weaknesses of current PAH therapies and looked at 20 long-term clinical trials published between 1990 and 2010. Drugs included ambrisentan, bosentan, bosentan/sitaxsentan, calcium-channel blockers, epoprostenol, sildenafil, tadalafil and treprostinil. The data indicate that the current medical therapy approved for the treatment of PAH can provide sustained benefits on exercise capacity and haemodynamic function.

Comment: The premise of this paper is that in the absence of RCT studies looking at medium-term outcomes and the ethical and practical difficulties of designing studies with placebo arms of more than one year in such a rapidly fatal disease, we have to examine the `less scientific' data generated from extension studies of the patients in the original RCT studies (in many, the placebo arm patients started active therapy on completion of the study; 12-16 weeks of placebo in the majority). Inevitably, the data is messy and it is likely there is both a `responder' and `survivor' bias in such data. Nonetheless, this potentially biased `observational' data does suggest a significant prolonged beneficial effect in exercise capacity and haemodynamics in the medium term. A major issue for the PAH community is endeavouring to produce more robust data of more prolonged benefits from these expensive therapies as 'cost benefit' and pharmacoeconomic analysis comes to the fore in funding decisions.

The bosentan patient registry: long-term survival in pulmonary arterial hypertension[38]

Authors: Keogh A et al

Summary: The Bosentan patients registry was a prospective, multicentre, Australian registry with the aim of collecting survival data in patients receiving bosentan for PAH. A total of 528 patients (mean age 59 years) were enrolled. The two main aetiological types of PAH were IPAH (58%) and scleroderma-associated PAH (42%); in both groups, the majority of patients were WHO-FC III at enrollment (66.4% and 75.8%, respectively). Exposure to bosentan ranged from 1.8 ± 1.1 years in scleroderma-associated PAH patients to 2.2 ± 1.5 years in IPAH patients. The observed annual mortality was 11.8% in the IPAH group and 16.6% in the scleroderma-associated PAH group, compared with 26.6% and 45% for respective groups in the untreated population (National institute of health [NIH] data).

Comment: It is excellent to see local data, in this case from an Australian registry. Bosentan is an endothelin receptor antagonist and the first targeted pulmonary vasodilator therapy funded by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia on the condition that all treated patients data (diagnostic and throughout therapy) was entered into a registry. This study compared outcomes of a large cohort of patients with PAH with historical controls; the original NIH US patient registry dated from the late 1980s and compared survival. There is a clear benefit with bosentan therapy in this comprehensive follow-up database. There is evidence from the REVEAL registry that, in the intervening 20 years, the natural history of PAH may have improved with better survival possibly due to other factors including the routine use of anticoagulants. Nonetheless, the improved survival is in the order of 50% and, even if an overestimate, strongly points to a positive survival benefit from this therapy.

Furthermore, over the last decade there has been an increased awareness amongst rheumatologists of the importance of screening for PAH in connective tissue diseases, particularly scleroderma. This may account for the relatively high percentage (42%) of patients with scleroderma –associated PAH in this Australian registry. The observed mortality in patients with scleroderma-associated PAH of 16.6% was much lower than expected for untreated patients (45%, historical data). Nonetheless, it is sobering to observe a 16% annual mortality in these patients of whom all were treated at specialised PAH clinics. This data is consistent with other similar registries where prognosis for scleroderma-associated PAH is consistently worse than IPAH. It is noteworthy that there was a higher percentage of WHO-FC III patients in the scleroderma-associated PAH cohort compared to the IPAH cohort (75.8% vs 66.4%). Class IV categories were similar (17.7% scleroderma-associated PAH vs 20.5% IPAH). This again reinforces the importance of early diagnosis in patients with scleroderma or mixed connective tissue disease. Most rheumatologists are now aware of importance of baseline and periodic screening for PAH in these at risk individuals.

Survival after the initiation of combination therapy in patients with pulmonary arterial hypertension: an Australian collaborative report[39]

Authors: Keogh A et al

Summary: In this prospective study, data was collected on 112 patients with WHO-FC II-IV PAH who had started combination therapy following deterioration on monotherapy. Drugs administered included bosentan, ambrisentan, sitaxsentan, iloprost and sildenafil. Survival estimates on combination therapy for additional 1, 2 and 3 years were 88%, 71% and 61%, respectively. Following the initiation of combination therapy in patients with scleroderma-related PAH, the survival estimates were 72% at 1 year and 48% at 2 years. For patients with IPAH/familial PAH, survival estimates were 93% at year 1 and 79% at 2 years. Mean WHO-FC improved from 3.1 on monotherapy to 2.2 at 12 months on dual therapy. Dual therapy also improved the 6-minute walk distance, and improved systolic PAP and RV function.

Comment: Again local data and addressing an area in the literature where there is a dearth of RCT evidence – does combination therapy when disease progresses on monotherapy provide clinical benefit? This is a situation all PAH doctors dread and changing to a different monotherapy is rarely helpful. Although this is observational data and the exact indications, clinical status of patients and the combination therapies used to escalate therapy varied, the survival figures achieved in advanced and progressing disease strongly suggest a useful response in a high proportion of this patient group.

The optimal management of PAH in patients deteriorating on monotherapy remains unclear. This observational Australian study supports emerging evidence for the addition of a second non-parenteral agent. It also offers additional evidence for patients with scleroderma-associated PAH exhibiting a poorer response to therapy than IPAH/familial PAH patients. Survival on dual therapy for scleroderma-associated PAH was 72% at 12 months and 48% at 24 months compared to the overall group (88% and 71%, respectively). However the survival data in the treated scleroderma-associated PAH cohort remains unequivocally superior to that for untreated historical controls. This study was also of interest in that the authors separated scleroderma and other connective tissue diseases (mainly SLE) and demonstrated a superior response to therapy in the SLE group. Although the numbers were small it is not surprising that these clinically heterogeneous conditions will respond differently to targeted PAH therapy. In most PAH studies connective tissue diseases are grouped together (dominated by scleroderma) which may skew results, hence for future studies, (particularly registry data) information on individual connective tissue conditions will be valuable.

Predicting survival

Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL)[13]

Authors: Benza RL et al

Summary: Data from 2716 patients enrolled in the REVEAL was analysed to assess predictors of 1-year survival. PAH associated with portal hypertension, a family history of PAH, modified NYHA/WHO-FC IV, PVR >32 Wood units and male gender with age >60 years were all independently associated with an increased risk of mortality (all exhibited a >2-fold increase in hazard ratio). Other factors significantly associated with an increased risk of death included PAH associated with connective tissue disease, NYHA/WHO-FC III, renal insufficiency, resting systolic BP <110 mmHg, resting HR >92 beats min, 6-minute walk distance <165m, BNP >180 pg/mL, predicted carbon monoxide diffusing capacity (DLCO) ≤32%, pericardial effusion on echocardiogram and mean right atrial pressure >20 mmHg within the year preceding enrollment. Variables associated with increased 1-year survival were modified NYHA/WHO-FC I, 6-minute walk distance ≥440m, BNP <50 pg/mL, and predicted DLCO ≥80%. Based on these multivariable analyses, the authors devised a contemporary prognostic equation for predicting survival in PAH.

Comment: This increasingly powerful US database is confirming and extending clinical impressions in terms of prognostic factors, including that patients with connective tissue related PAH, heritable PAH (previously familial PAH) and older patients do less well than patients with IPAH. This paper also rams home the message that patients with advanced disease at the time of diagnosis do less well. Prior to widespread clinical use, external validation of the prognostic equation is required.

Maximising patient outcomes

- Unexplained dyspnoea or syncope? Think PAH, especially in younger patients and remember a negative physical examination does not exclude PAH.
- Do not accept unexplained breathlessness or exercise limitation without an accurate diagnosis.
- If there is a lack of response to initial therapy the diagnosis needs to be reconsidered and further evaluation may be required.
- For patients with connective tissue diseases associated with PAH (scleroderma, CREST, SLE and much less frequently Rheumatoid disease), regular screening for PAH is mandatory unless contraindicated.
- Early diagnosis leads to earlier treatment and evidence strongly suggests better outcomes in terms of both quality of life and survival.
- A multidisciplinary team approach to treatment is essential in the management of complex PAH patients.
- For patients with connective tissue diseases associated with PAH (in particular scleroderma) baseline and subsequent regular screening for PAH is strongly recommended.

Local network/service availability

Dedicated PAH clinics exist in Auckland (Auckland City Hospital) and Christchurch, with interested clinicians (though not specific PAH clinics) in both Wellington/Hutt and Dunedin.

If you have a patient with unexplained symptoms that could be due to PAH then refer to General Medicine/Respiratory Medicine/Cardiology asking for appropriate investigation of their symptoms and to exclude PAH. Remember that echocardiography, though often very helpful, can occasionally be misleading.

There are several excellent patient-centred websites:
Scleroderma Australia: www.sclerodermaaustralia.com.au
Arthritis Foundation NZ: www.arthritis.org.nz
PHA Australia: www.phaaustralia.com.au

Commentary on future directions

- New agents with different modes of action on the pulmonary vasculature are under active development and show promise of further improvements in outcomes for this devastating group of diseases.
- Results of combination studies and of goal-orientated studies are awaited to justify earlier combination therapy and improved quality of life and survival for patients, and to more effectively delay further damage to the pulmonary vasculature.
- In NZ we need to raise awareness, implement screening programmes for high-risk groups (e.g. connective tissue disease) and strengthen networks to allow earlier diagnosis and treatment of our patients.
- There is a need to capture accurate international and local data on prevalence, response to therapy and prognosis for all aetiological types of PAH, including data on PAH associated with connective tissue disease (not only scleroderma, but also SLE, mixed connective tissue disease and Sjogrens syndrome).

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