Chapter 10
Pulmonary Hypertension: Transition Challenges in the Current Therapeutic Era

Jordan D. Awerbach and Wayne J. Franklin

Definition and Classification

Pulmonary hypertension (PH) is a general term describing elevated resting pulmonary arterial pressures (PAP) from any cause. Historically, PH has been defined by a mean PAP (mPAP) ≥ 25 mmHg on cardiac catheterization [1]. There has always been recognition that this cutoff, which has been used for nearly 50 years, was chosen somewhat arbitrarily. A systematic review by Kovacs et al. demonstrated that mPAP in normal subjects at rest was 14.0 ± 3.3 mmHg with an upper limit of normal of 20.6 mmHg [2]. Over time it has become increasingly clear that mPAPs of 21–24 mmHg are associated with an increased risk of progression to pulmonary arterial hypertension (PAH) and worsened survival [3–6]. This culminated in the redefinition of PH as a mPAP > 20 mmHg at the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018 [3].

PH may be further characterized based on whether the cause of elevated pulmonary pressures exists before or after the pulmonary capillary bed. Hemodynamically, pre- versus post-capillary PH is defined by a normal versus elevated pulmonary capillary wedge pressure (PCWP), respectively, which is used as a surrogate for the left atrial pressure. It is important to note that pre- and post-capillary PH may coexist in the same patient. Pulmonary arterial hypertension (PAH) refers to a subset of PH patients with purely pre-capillary disease. PAH is a rare disease marked by vasoconstriction and progressive endothelial dysfunction of the pulmonary vascular bed, leading to pathologic remodeling that results in the obliteration of the pulmonary vasculature and increased pulmonary vascular resistance [7]. This ultimately leads to right heart failure and death. The criteria for diagnosing

J. D. Awerbach (✉) · W. J. Franklin
Phoenix Children's Hospital, Department of Cardiology, Phoenix, AZ, USA
e-mail: jawerbach@phoenixchildrens.com

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PAH includes a mPAP > 20 mmHg (previously ≥ 25 mmHg), a PCWP ≤ 15 mmHg, and an elevated pulmonary vascular resistance (PVR) > 3 Wood units (Wu). In children, PVR is typically indexed to body surface area and is elevated >3 Wood units × m2 (iWu) [1, 8]. In 2011, the Pulmonary Vascular Research Institute (PVRI) introduced the term *pulmonary hypertensive vascular disease*, in an effort to better characterize patients with congenital heart disease (CHD) who have undergone single ventricle palliation [9]. The PVRI proposed that pulmonary vascular disease be defined in this group as a PVR > 3 iWu or a transpulmonary gradient >6 mmHg. Elevated mPAP was not included in the definition, as this population may have clinically significant pre-capillary PH in the face of lower pulmonary pressures.

In both children and adults, PH may occur as a primary illness (i.e., idiopathic PAH) or develop secondary to other disease states. The current World Health Organization (WHO) classification system for PH contains five clinical categories representing groupings of disease processes that share common clinical characteristics and PH pathophysiology (Table 10.1). When originally designed, the WHO classification was based on PH-causing diseases seen in the adult population. Numerous modifications to the WHO classification scheme have occurred since its initial creation at the second WSPH (Evian 1998) [10]. A Pediatric Task Force was formed at the fifth WSPH (Nice 2013), at which time modifications were proposed to better incorporate pediatric disorders associated with PH. With an increasing number of pediatric PH patients now surviving into adulthood, these changes recognized the importance of having a common classification system for all patients that would better facilitate a patient's transition into the adult care setting [11]. At the most recent WSPH (Nice 2018), additional pediatric-focused modifications were made to the WHO classification, such as the inclusion of developmental lung disorders (WHO Group 3.5) and separate designations for CHD associated with PAH (Group 1.4.4), CHD with post-capillary PH (Group 2.4), and complex CHD (Group 5.4) [12].

Epidemiology

PH is a heterogeneous disease associated with numerous underlying disorders. There is a significant variability in the distribution of these disorders throughout the world. For example, schistosomiasis affects at least 200 million people and is a leading cause of PH worldwide; however 85% of those affected live in sub-Saharan Africa [13, 14]. As such, characterizing the global incidence and prevalence of all-cause PH is challenging. In a large population-based study of Ontario, Canada, Wijeratne and colleagues reported an annual incidence of PH of 24.1 patients per 100,000 persons and that the prevalence of adult and pediatric PH was 127.3 and 57.9 per 100,000 persons, respectively [15]. There are also important differences in the distribution of PH-causing diseases between pediatric and adult patients (Fig. 10.1). PAH (Group 1) is the most common subgroup of PH seen in children,

Table 10.1 The World Health Organization classification system for pulmonary hypertension (Nice 2018)

1	*PAH*
1.1	Idiopathic PAH
1.2	Heritable PAH
1.3	Drug- and toxin-induced PAH
1.4	PAH associated with:
1.4.1	Connective tissue disease
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart disease
1.4.5	Schistosomiasis
1.5	PAH long-term responders to calcium channel blockers
1.6	PAH with overt features of venous/capillary (PVOD/PCH) involvement
1.7	Persistent PH of the newborn syndrome
2	*PH due to left heart disease*
2.1	PH due to heart failure with preserved LVEF
2.2	PH due to heart failure with reduced LVEF
2.3	Valvular heart disease
2.4	Congenital/acquired cardiovascular conditions leading to post-capillary PH
3	*PH due to lung diseases and/or hypoxia*
3.1	Obstructive lung disease
3.2	Restrictive lung disease
3.3	Other lung diseases with mixed restrictive/obstructive pattern
3.4	Hypoxia without lung disease
3.5	Developmental lung disorders
4	*PH due to pulmonary artery obstructions*
4.1	Chronic thromboembolic PH
4.2	Other pulmonary artery obstructions
5	*PH with unclear and/or multifactorial mechanisms*
5.1	Hematological disorders
5.2	Systemic and metabolic disorders
5.3	Others
5.4	Complex congenital heart disease

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PAH pulmonary arterial hypertension, *PVOD* pulmonary veno-occlusive disease, *PCH* pulmonary capillary hemangiomatosis, *LVEF* left ventricular ejection fraction

making up 60–90% of registry cohorts [9, 16]. It is also worth noting that PH due to developmental lung diseases (Group 3) is being seen with increased prevalence, and this group now represents 10–12% of the pediatric PH population [16–18]. PH in adults is far more common than PAH and is most often seen in association with

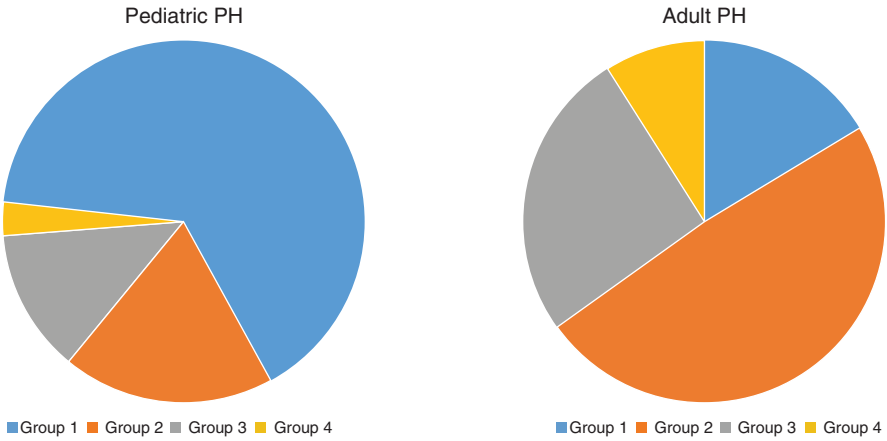

Fig. 10.1 Distribution of PH by the WHO group for pediatric and adult patients seen in a large population-based cohort. (Data taken from [15])

left-sided heart disease (Group 2) and pulmonary disease (Group 1) [7, 16, 19]. Chronic heart failure and chronic obstructive pulmonary disease currently affect 61 million and 250 million adults, respectively, worldwide [13]. All forms of PH have been associated with increased mortality in patients [15, 19].

PAH is a rare disease in both children and adults, with an estimated prevalence of 2–16 cases per million children and 15–60 cases per million adults [1, 7, 20]. A nationwide registry in the Netherlands found the majority of pediatric patients had transient forms of PAH, including persistent pulmonary hypertension of the newborn and flow-related PAH in children with systemic-to-pulmonary shunts (e.g., ventricular septal defect or patent ductus arteriosus) that were reversible after shunt closure [16]. Of the remaining patients with progressive PAH, 72% had CHD and 27% had idiopathic PAH (IPAH). The annual incidence rates for CHD-associated PAH and IPAH were 2.2 and 0.7 cases per million, and the point prevalence was 15.6 and 4.4 cases per million, respectively. The Spanish REHIPED registry reported similar findings; the incidence of IPAH versus CHD-APAH was 0.49 and 1.87 cases per million per year, and the prevalence was 2.9 and 10.1 cases per million, respectively [9]. IPAH makes up a larger proportion of adult PAH patients, representing about half of the cases seen in adult registries [21]. PAH demonstrates a female predominance in both children and adults. In the US REVEAL registry, 80% of adults and 64% of children were female [22, 23].

Prior to the introduction of targeted PAH pharmacotherapies in the 1990s, the natural history of PAH was extremely poor. Median survival in adults was 2.8 years with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34% [24]. Pediatric outcomes were even worse with a median survival of only 10 months [25]. In the modern therapeutic era, survival rates have improved although PAH continues to be associated with high morbidity and mortality. Adults with newly diagnosed PAH who were included in the REVEAL registry had 1-, 3-, and 5- year respective

survivals of 90.4%, 76.2%, and 65.4% [24]. Pediatric survival was found to have similarly improved to 96%, 84%, and 74%, at 1, 3, and 5 years [23].

Populations at Risk of Developing PH

PH is seen in association with numerous disease processes, and this increased risk of developing PH must always be kept in mind. Several barriers exist in effectively diagnosing PH in these patient groups. The presenting symptoms of PH are often nonspecific and depend on the age of the patients. Infants may present with feeding difficulties, tachypnea, poor growth, and a failure to meet developmental milestones. Common symptoms in older children include exertional dyspnea and fatigue, chest pain, lightheadedness, and syncope [25]. Patients may delay seeking treatment, and symptoms are commonly misdiagnosed at initial presentation. In the REVEAL study, the average time from the onset of symptoms to diagnosis was 33 months [26]. Additionally, many patients will be under the care of clinicians who do not routinely treat PH (e.g., patients with sickle cell disease who are primarily cared for by hematologists), and there are limited disease-specific screening guidelines for these patient groups.

Heritable PAH

Several genes have been associated with the development of PAH, the most significant of which is the bone morphogenic protein receptor II gene (BMPR2). Heterozygous mutations of BMPR2 are associated with 80% of cases of familial PAH and are found in 10–20% of sporadic (presumed idiopathic) cases [27]. Most BMPR2 mutations are inherited in an autosomal dominant manner, but disease penetrance is low. Patients with BMPR2 mutations carry a lifetime risk of PAH of 10–20%, and there can be significant differences in penetrance even within members of the same family [8, 28]. For patients who go on to develop PAH, the presence of the BMPR2 mutation has prognostic implications and is associated with an increased risk of death or need for lung transplantation. Current guidelines recommend screening patients with IPAH and first-degree family members of patients with known heritable PAH mutations. Given the potential psychosocial impact of a positive test, genetic counseling before and after testing is paramount [8]. Patients may also be concerned about insurance and employment implications. In the United States, the Genetic Information Nondiscrimination Act (GINA) was passed in 2008 and protects patients against insurance and employment discrimination based on genetic information [29]. There is general agreement that asymptomatic carriers of the disease should undergo periodic screening for PAH, although the optimal screening frequency in this population remains unclear [8, 28].

Congenital Heart Disease

All patients with CHD and systemic to pulmonary (left to right) shunts are at risk of developing PH. In the REVEAL study, 36% of children and 10% of adults had underlying CHD [22, 23]. The risk and timing of the development of PAH depend on both the size and location of the intracardiac shunt. Lesions that are distal to the tricuspid valve (e.g., ventricular septal defects, atrioventricular septal defects, truncus arteriosus) expose the pulmonary vascular bed to excess flow and pressure, and irreversible pulmonary vascular changes can be seen beginning in early infancy. Conversely, pre-tricuspid valve shunts (e.g., atrial septal defects) expose the pulmonary arteries only to excess flow, and the development of PAH may not be seen until the fifth or sixth decade of life [30]. In addition, patients who have undergone repair or palliation may still be at risk for development of PAH later in life, particularly patients who have undergone single ventricle palliation.

Unfortunately, the majority of young adults with CHD fail to transition appropriately, and lapses in care are common. A multicenter survey of adult CHD (ACHD) patients revealed that, beginning at an average age of 20 years, 42% experienced a lapse in care of greater than 3 years and 8% experienced a lapse greater than 10 years [31]. The reasons for this are multifactorial. Most often, patients become lost to follow-up either because they are feeling well or because they did not know continued follow-up was required [31]. There is also a significant shortage of ACHD-trained cardiologists to care for the rapidly growing ACHD population, which now outnumber pediatric CHD patients by more than 2:1 [32]. Ongoing efforts to improve transition and continuous care for patients with CHD include expanded patient education programs, formalized training for cardiologists who wish to specialize in ACHD, and an accreditation process to designate expert ACHD programs as Comprehensive Care Centers.

Sickle Cell Disease

PH occurs in about 10% of patients with sickle cell disease (SCD) [33, 34]. The pathophysiology of PH in SCD patients is multifactorial and remains incompletely understood. Numerous mechanisms have been proposed, with general agreement that chronic intravascular hemolysis, hypoxia-induced lung injury, and thromboembolic disease all play significant roles [35, 36]. Histopathologic lung samples from patients with SCD patients show features of PAH, chronic thromboembolic PH (CTEPH), and pulmonary veno-occlusive disease (PVOD) [35]. On heart catheterization, patients typically have an elevated cardiac output in the setting of their chronic anemia, with only mild elevations in pulmonary pressures and PVR. Given this profile, it has been proposed that a PVR of $\geq$ 2 Wu be considered abnormal in SCD patients [37, 38]. The presence of PH in SCD is associated with significantly increased mortality, upward of 5–10 times that of patients without PH [38].

Echocardiogram is the most frequently employed screening tool for PH. The peak velocity of the tricuspid regurgitation (TR) jet, a surrogate for systolic

pulmonary artery pressure, is elevated in about 30–40% of SCD patients [33, 39]. A TRJ ≥ 2.5 m/sec is considered abnormally elevated, although only a minority of patients with a TR jet of 2.5–2.9 m/sec will have PH on cardiac catheterization [35]. This number is increased in patients who have other markers of PH; the positive predictive value of an elevated TR jet increases from 25% to 62% in the setting of an elevated NT-proBNP (> 164.5 pg/mL) or reduced 6-minute walk distance (< 333 m) [35, 40]. More than 50% of SCD patients with a TRJ > 2.9 m/sec, regardless of symptoms, will have PH [35, 39].

Routine screening for PH in patients with SCD is essential. The basis of this screening should be a careful history and physical exam for signs and symptoms of PH. Routine echocardiogram screening every 1–3 years may be considered and is supported by the American Thoracic Society [38]. However, there is a lack of robust data supporting this, and the American Society of Hematology favors echocardiogram screening primarily in patients with signs or symptoms of PH and patients with associated comorbidities or disease complications known to be associated with PH (e.g., connective tissue disease) [39].

Human Immunodeficiency Virus

There are approximately 1 million people living in the United States (US) with human immunodeficiency virus (HIV). Pediatric patients make up a minority of this population (< 1%), with a significant increase in prevalence seen in the young adult population [41]. Global HIV statistics are starkly different. Nearly 40 million people, 1.7 million of which are children, are living with HIV. The majority of these patients live in developing countries [42]. While the prevalence of PAH in patients with HIV is overall low at about 0.5%, this represents a risk several hundreds of times above that of the general population [43–45]. The underlying mechanisms by which HIV leads to PAH are poorly understood, but histologically the features are the same as in patients with idiopathic PAH [43]. No guidelines exist for screening patients with HIV for PAH, but the development of symptoms should prompt early referral and further evaluation.

Bronchopulmonary Dysplasia

The incidence of PH in premature infants (born at ≤ 28 weeks) with bronchopulmonary dysplasia (BPD) is about 40%; it is the most common cause of pediatric PH due to lung disease [46, 47]. Pulmonary vein stenosis is seen with increased frequency in BPD patients and may further compound the risk of developing PH [48]. PH in infants with BPD is associated with high mortality. In the majority of patients who survive, PH typically resolves over time. However, evidence of persistent pulmonary vascular abnormalities have been seen in long-term follow-up, and PH may reoccur in early adulthood [48, 49]. Additionally, older children and teens with a history of prematurity and BPD have persistent reductions in lung function and

increased respiratory morbidities [50]. Data on adult BPD survivors are limited but have shown that these changes also persist into adulthood [51, 52]. Specifically, adults have been shown to have reduced lung function and impaired quality of life.

Considerations for Young Adults with PAH

The Need for Transition

In 1984, US Surgeon General C. Everett Koop, MD, hosted an invitational conference entitled, "Youth with Disability: The Transition Years" [53, 54]. This marked the first major acknowledgment that the healthcare system did not appropriately care for aging young adults with special healthcare needs. In a subsequent position paper, the Society for Adolescent Medicine defined transition as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems [54]." Central to this process is the evolution of the patient from a passive to active participant in his or her medical management, ultimately taking on the symbolic role of *CEO* of his or her own healthcare [55, 56]. There is substantial evidence that PAH patients who are well-informed, engaged, and involved in the medical decision-making process have better healthcare outcomes [57–59]. Thus, taking ownership of one's healthcare is critical to the successful management of PAH patients.

Transition Timing

The American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians endorse the beginning of the transition process between the ages of 12 and 14 years, with a goal of transfer of care to an adult provider in the 18–21 year age range [55]. The Pulmonary Hypertension Association (PHA), a major international patient advocacy group (www.phassociation.org), supports this transition timing for patients with PH. Institutions caring for PAH patients should have a standard transition protocol in place. It is important that there be inherent flexibility in these protocols, so that they may be adapted to a patient's developmental status [60–62]. Patients must demonstrate appropriate physical and emotional maturity for successful transfer into the adult care environment [31].

Patient Engagement and Quality of Life

In 2014, the US Food and Drug Administration (FDA) described PAH as a disease that, "can rapidly take a significant physical and emotional told on a patient's qualify of life, routine, and the ability of patients to engage in the activities of daily

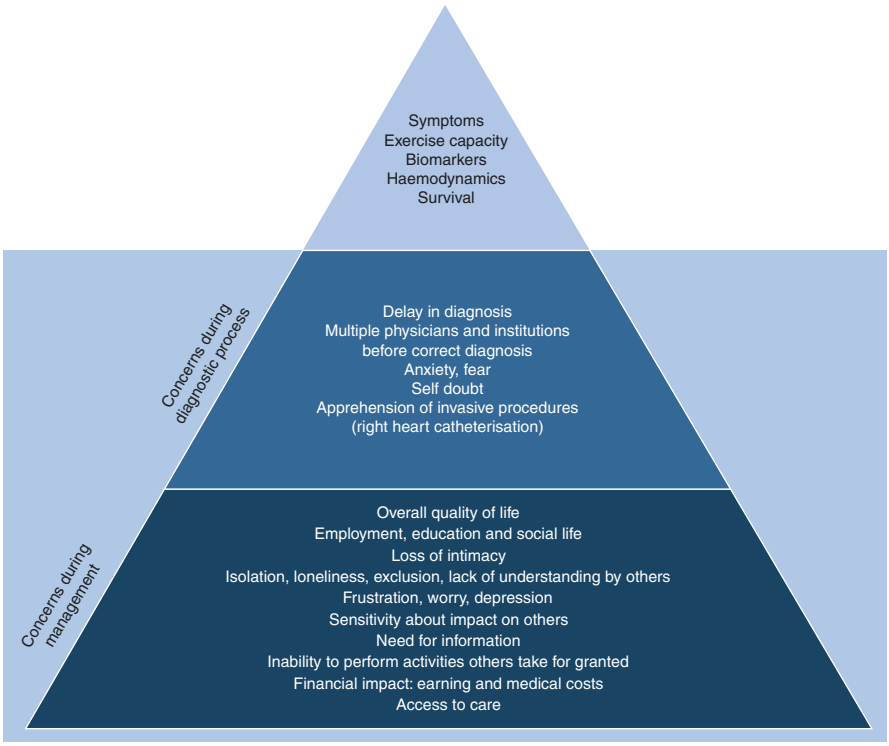

Fig. 10.2 "Tip of the iceberg" model of clinician versus patient that used indicators of health and quality of life. (Reproduced with permission of the © ERS 2020: McGoon et al. [59]. Published 24 January 2019)

living" [63]. This was the conclusion after conducting a public meeting with PAH patients to gain their insight on the disease process. Understanding patient insight is a necessity, and there is often a disconnection between what the provider and patient see as important components of quality of life. Clinicians typically judge disease severity based on objective measures such as symptomatology, biomarkers, and echocardiogram assessment. McGoon and colleagues have described these parameters as the "tip of the iceberg" when one considers the underlying physical, emotional, and psychosocial effects faced by patients and their caregivers (Fig. 10.2) [59]. It is important that both the patient and provider communicate their goals and concerns with one another and each understands the other's perspective.

As part of the transition process, patients are taken from a passive role to an active participant in their own healthcare. When surveyed, the majority of PAH patients express a desire for further information and a more engaged role in their medical care [64]. Patients who participate in a process of shared decision-making with their medical team demonstrate better healthcare outcomes and improved satisfaction [57]. They are more likely to seek out information, make positive lifestyle changes, voice concerns about their medical care, and demonstrate better coping skills [57, 58]. The burden is on the provider to determine how information is best

received and how to encourage patients to take on a more active role. Few providers have formal training in this involved and time-consuming process. Transition programs may wish to consider providing further education to their team members on improving patient engagement and shared decision-making [57, 59]. A multidisciplinary team that includes a dedicated transition nurse, social work support, and mental health services can also help support patients through this process.

It is also important that young adults and their caregivers be referred early to patient support organizations. Patients with PAH are frequently left feeling socially isolated. Support organizations are a key source of patient engagement where they can find shared experiences and be inspired by other PAH patients who have persevered through their disease and gone on to have successful careers, families, and a good quality of life. Many of these organizations also offer caregiver-focused support. Many involved patients also participate in activities to raise PAH awareness and contribute to registry studies and research trials; in doing so they may feel a sense of contributing back to the community and improving future patient care. For young adults who feel uncomfortable attending meetings and discussing their disease in person, these associations offer numerous online communities and forums where patients can engage others within a more comfortable environment [58, 59, 65].

Access to Expert Care

The introduction of intravenous epoprostenol in 1995 marked the beginning of a new era of treatment for patients with PAH. At that time, the use of advanced PAH therapies was delegated to a handful of experienced medical centers with expertise in PAH treatment. In the decade that followed, treatment options expanded, and the first oral agents became available (bosentan and sildenafil). As awareness of the disease grew and medication options became more widely available, the treatment paradigm shifted away from these expert centers, toward individual providers who often had little to no experience treating PAH [66–68]. Predictably, this has been a detriment to the care of PH patients, many of whom are subject to incomplete evaluations and inappropriate use of medications. Worse survival outcomes have been seen in patients with PAH cared for outside of expert centers; they are frequently maintained on oral agents despite their clinical status warranting the initiation of intravenous prostacyclin therapy [69]. The multicenter RePHerral study evaluated the accuracy of PH diagnoses and use of PAH pharmacotherapies in patients being referred to tertiary PH centers. Out of a total of 140 patients, 32/98 (32%) patients who had already received diagnoses of PH or PAH were found to be misdiagnosed. Additionally, 59% of patients referred had not previously undergone hemodynamic catheterization, which after being performed led to alternative diagnoses in 89% of these patients. Perhaps most staggering of all, 30% of referred patients had already been prescribed PAH pharmacotherapies, and more than half of patients were receiving therapies that conflicted with published guidelines [66, 70]. In the

Wijeratne study, oral PAH agents were frequently prescribed to patients with Group 2 and Group 3 disease [15]. The inappropriate use of PAH pharmacotherapies presents a serious risk of harm to patient and substantially increases unnecessary healthcare expenditures. The issue was brought into the national spotlight in 2014 when it was chosen as one of the top 5 pulmonary issues as part of the American Board of Internal Medicine's "Choosing Wisely" campaign [71].

These concerns were also recognized by the Scientific Leadership Council of the PHA. In 2011, they conceptualized an accreditation process for designating PH Care Centers (PHCCs) in the US. PHCC accreditation recognizes those expert centers that have the appropriate knowledge and infrastructure to deliver standardized care and guideline-based treatment to patients with PH. The PHA had multiple objectives in mind in creating this accreditation process, including raising disease awareness, increasing access to appropriate care, and fostering research and quality-improvement collaboratives, among centers [26, 66]. However, their primary goal was to improve the quality of care given to patients with PH and, ultimately, to improve patient outcomes [26]. The PHA recognizes two levels of PHCCs, Centers of Comprehensive Care (CCCs) and Regional Clinical Programs (RCPs), the latter of which has to meet less rigorous criteria and represents a program equipped to diagnose and initiate treatment in most patients who do not require parenteral therapies. A comprehensive list of program requirements can be found on the PHA website, referenced above. As of March 2020, there were 59 adult CCCs, 13 adult RCPs, and 8 pediatric CCCs [72].

As there are only a handful of pediatric PHCCs, the majority of pediatric PH patients receive care at non-accredited centers. Often, they are centers with one or a small group of providers with sufficient expertise in treating pediatric PH. Pediatric PH patients face additional challenges compared to adults with PH. The evidence base in children is very limited, and the majority of data regarding the evaluation and care of pediatric PH are extrapolated from adult management. Over the past several years, the United States and Europe have each released pediatric PH guidelines, representing a significant step forward in the standardization of care for children with PH [8, 73]. As part of the transition process, an appropriate adult PH provider should be identified early. This is especially important for young adults who will be relocating for school or work to a new environment. An adult provider at a PHCC is ideal but often not practical due to distance, in which case a local adult provider should have an established relationship with a PHCC to refer patients with advanced disease as needed. Insurance may also play a role in dictating which providers a patient can see. Some patients may receive routine care from both their local provider whom they see regularly and by a PHCC provider whom they see infrequently as needed. With the increasing use of telemedicine, it is also possible for patients to have all required testing done locally and undergo remote expert consultation and follow-up. Prior to the transfer of care, complete medical records should be sent to the adult provider, in addition to which the pediatric and adult providers should meet to discuss the patient. The pediatric provider should also follow up after the patient's first visit with their adult provider to ensure successful transfer [74].

The Burden of PAH Treatment

The treatment of PAH has evolved substantially over the past 30 years, prior to which no PAH-specific therapies were available to patients. There are now five classes of PAH pharmacotherapeutic agents and a total of 14 medications approved by the FDA for adult PAH treatment (Table 10.2). Of note, with the exception of bosentan, none are FDA-approved for pediatric use. Bosentan received FDA

Table 10.2 Targeted PAH medications, dosing, and common side effects

Medication class	Medication	Route	Dose/titration	Adverse effects
Phosphodiesterase-5 inhibitors	Sildenafil (Revatio)	Oral	20 mg TID	Headache, flushing, nasal congestion, dizziness, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, back pain, sensorineural hearing loss, ischemic optic neuropathy, priapism Co-administration with nitrates is contraindicated
	Tadalafil (Adcirca)	Oral	40 mg QD	Similar to sildenafil Co-administration with nitrates is contraindicated
Endothelin receptor antagonists	Bosentan (Tracleer)	Oral	Initial 62.5 mg BID Maintenance 125 mg BID	Abdominal pain, vomiting, fatigue, headache, edema, flushing, nasal congestion, anemia, decreased sperm count Risk of dose-related increases in liver enzymes Contraindicated in hepatic impairment (monitoring required) Caution with concomitant CYP3A4 inducers and inhibitors Teratogenic
	Ambrisentan (Letairis)	Oral	Initial 5 mg QD Maintenance 10 mg QD	Similar to bosentan Lower risk of liver enzyme elevation Teratogenic
	Macitentan (Opsumit)	Oral	10 mg QD	Similar to bosentan Lower risk of liver enzyme elevation Teratogenic

Table 10.2 (continued)

Medication class	Medication	Route	Dose/titration	Adverse effects
Prostacyclins	Epoprostenol [90] (Flolan, Veletri)	IV	Initial, 2 ng/kg/min Increase by 2 ng/kg/min in increments of at least 15 minutes Maintenance, determined by tolerability	Nausea, flushing, headache, diarrhea, rash, jaw discomfort, thrombocytopenia Hypotension and bleeding with concomitant use of anticoagulants, platelet inhibitors, or vasodilators
	Iloprost (Ventavis)	Inhaled	Initial, 2.5 μg 6 times per day Maintenance, 5 μg 9 times per day	Cough, wheeze, flushing, headache, jaw pain, diarrhea, rash, hypotension May exacerbate reactive airways disease
	Treprostinil [91] (Remodulin, Tyvaso, Orenitram)	IV/ subcutaneous	Initial, 1.25 ng/kg/min Maintenance, determined by tolerability	Flushing, headache, nausea, diarrhea, musculoskeletal pain, rash, hypotension, thrombocytopenia, hypokalemia, pain at injection site
		Oral	Initial, 0.25 mg BID or 0.125 mg TID Increase by 0.25 mg or 0.5 mg BID or 0.125 mg TID, not more than every 3–4 days Maintenance, determined by tolerability	Hypotension and bleeding with concomitant use of anticoagulants, platelet inhibitors, or vasodilators
		Inhaled	Initial, 18 μg QID	May exacerbate reactive airway disease at higher doses
Soluble guanylate cyclase stimulator	Riociguat (Adempas)	Oral	Initial, 0.5–1 mg T ID Maintenance, 2.5 mg TID	Headache, dizziness, dyspepsia, nausea, diarrhea, anemia, hypotension, vomiting, gastrointestinal reflux, constipation Co-administration with nitrates and/or PDE-5 inhibitors is contraindicated Teratogenic

(continued)

Table 10.2 (continued)

Medication class	Medication	Route	Dose/titration	Adverse effects
Prostacyclin receptor agonist	Selexipag [92] (Uptravi)	Oral	Initial, 200 mcg BID Maintenance, 1600 mcg BID or highest dose tolerated	Headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, arthralgia, anemia, rash, decreased appetite Contraindicated with concurrent use of CYP2C8 inhibitors

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approval in 2017 for children 3 years of age and older. The remaining therapies, in particular sildenafil, are frequently used off-label in the pediatric population, with safety and efficacy extrapolated from adult studies [75].

PAH pharmacotherapies are complex, and multiple patient-specific considerations need to be taken into account by prescribers. All PAH medications require prior authorization, and the availability of certain therapies may be limited by a patient's insurance company. Even when therapies are approved and covered, many patients are left with prohibitively high costs. Without insurance, the average wholesale cost of generic oral sildenafil, the least expensive prescription PAH therapy, is $563 per month. Parenteral prostanoids can cost as much as $14,000 per month [76]. On average, PAH patients pay $2000 a year in out-of-pocket pharmacy costs [77]. Patients and parents should be aware of these costs and coverage issues when making decisions about changes to insurance coverage. Under the Affordable Care Act, young adults may remain on their parents' insurance until age 26. Patients who will be losing their coverage, such as those aging out of government insurance programs, will need to plan in advance to avoid gaps in coverage. Many pharmaceutical companies offer patient assistance programs that provide additional cost coverage for patients over the age of 18. As part of the transition process, patients should be able to demonstrate knowledge of who their insurance provider is, where they get their medications and supplies from, and how to order their medications.

These medications can lead to substantial improvements in patients' PAH-related symptoms and functional class, but their use also comes with significant trade-offs. Side effects are common and can be significant, and medication use may be complex and time-consuming. Common side effects include flushing, headaches, nose bleeds, dizziness, nausea, diarrhea, and bone pain. Thus, between the disease and the medications, patients are seldom symptom-free [63]. Many PAH medications require frequent dosing and can be cumbersome for patients to take. Sildenafil and riociguat are dosed three times a day, and nebulized iloprost must be inhaled six to nine times per day. Patients on some endothelial receptor antagonists (ERAs) are required to get monthly liver function tests, and female patients who are of reproductive age must be on birth control and get monthly pregnancy tests [78]. Patients with advanced PAH (WHO functional class III/IV) typically require treatment with

intravenous (IV) prostanoids therapies, either epoprostenol or treprostinil. Parenteral administration requires central line placement, and patients must wear an infusion pump that continuously delivers drug. The use of these medications requires substantial time and responsibility on the part of the patient. Patients must be able to reconstitute the medication and fill their pump cassette appropriately. Some formulations can be prepared up to a week ahead of time, while others must be mixed every 24–48 hours. Patients must also be savvy enough to program dose adjustments into their pumps as instructed by their provider. Abrupt cessation of therapy, either due to running out of medication or central line complications, is an emergency and can precipitate a PH crisis. Traveling requires appropriate planning, and the patient must take sufficient spare equipment [79, 80]. Patients are also subject to central catheter complications, including infection and thrombus, and must be shown how to care for their IV line. Patients on established therapy will receive mail-order shipments of their supplies, which allows these patients to live in more remote areas of the country if needed. These patients should be given information and contact numbers that local emergency rooms, who may not be familiar with these PAH medications, can use for assistance [79].

Employment

Patients frequently express fears about what a diagnosis of PAH means for future employment. The majority of PAH patients and their caregivers report that the disease has an impact on their work ability. They are frequently forced to cut back hours, seek accommodations, take sick leave, change careers, and apply for medical disability. A significant loss of household income is frequently experienced [81, 82]. Globally, employment rates for persons with disabilities are significantly lower than in the general population [83]. In other disease states, it has been shown that structured career counseling and employment advice are associated with higher rates of employment [84]. Patients should also be made aware of workplace antidiscrimination laws, which exist in the United States and in many countries throughout the world, to protect persons with disabilities [83, 85]. Young adults with PAH must be educated on activities and career choices that are safe for them to pursue, with an understanding that their medical needs may change over time. For those with more advanced disease and significant exertional limitations, there are many work options available today that are either more sedentary in nature or permit working from home [65].

Intimacy, Pregnancy, and Contraception

Personal relationships and physical intimacy can be a challenge for both PAH patients and their partners. Anxiety, depression, and poor self-image are common in patients with chronic illnesses, including those with PAH [64]. Additionally, partners of patients often cite concerns over their physical ability to be sexually intimate

or that sexual intimacy may make them ill [64, 81]. Clinicians should actively address these topics, as patients may feel a sense of embarrassment in bringing these issues up themselves.

One of the most difficult things to address in patients with PAH is pregnancy. Pregnancy is poorly tolerated in women with PH, and they are among the highest-risk group for maternal and fetal complications, including death. Right heart failure is commonly seen, and women starting pregnancy with depressed right ventricular function have a worse prognosis [86]. Antepartum and postpartum mortality rates range from 16% to 30% [87]. Rates as high as 20–50% are seen in women with baseline cyanosis, such as in Eisenmenger patients [86, 87]. The prognosis for the fetus is equally poor with rates of fetal loss as high as 50% [86]. Due to these risks, pregnancy is contraindicated in women with PAH, and when pregnancy occurs, pregnancy termination should be strongly considered [86, 87].

Extensive education and counseling regarding pregnancy risks, avoidance of pregnancy, and appropriate methods of contraception should be provided to patients and their families. Ideally, this should be done at the time of PAH diagnosis, with recognition that reinforcement may be required later in life as patients form relationships and more strongly consider having a family. The PHA has resources to help patients consider and navigate adoption [65]. In prepubescent females, these discussions may be done with the parents alone. As the patient begins puberty, the topic should be introduced in a manner appropriate for the patient's age and maturity level. Certain PAH pharmacotherapies are teratogenic (all endothelin receptor antagonists and riociguat) and require that female patients who can become pregnant be enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program. The REMS program requires a monthly pregnancy test and appropriate contraception use [88]. Additionally, PAH is associated with a prothrombotic state, and methods of contraception that further increase the risk of thrombosis (such as estrogen-containing contraceptives) should be avoided [89].

As part of the family planning process, both men and women with IPAH or a heritable PAH should undergo genetic counseling and consider testing for genetic mutations associated with PAH. As previously discussed, the BMPR2 mutation is the most common associated with heritable PAH but is associated with low disease penetrance. Therefore, the prognostic value of testing must be weighed carefully against the implications of a positive test. Should a child develop clinical disease, there may be self-blame on the part of the parent who passed on the gene, and parents may be predisposed to treat their child as medically fragile in the face of a potential future illness [8].

Conclusions

PAH is a progressive and often unpredictable disease the affects all aspects of a patient's life. An increasing number of patients are being treated outside of expert centers; they often receive suboptimal care and treatment that is contradictory to

published guidelines. The complexity of the disease requires a dedicated transition team to provide high-quality education, understand patient concerns, and encourage patient engagement. This is best achieved through a multidisciplinary team and with early engagement by patients and their caregivers in PH support groups.

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