

## Pediatric Pulmonary Hypertension: Characteristics and Prospective Follow-Up of Children in Algeria

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**Received:** February 20, 2023; **Published:** February 28, 2023

**DOI:** 10.31080/ecpe.2023.12.01281

### Abstract

**Introduction:** Pulmonary hypertension (PH) in children is a serious disease. There is few data describing pediatric PH. PH, long considered to be outstanding, is poorly known in Algeria where the diagnostic means and the supply of care are significantly limited. Our work item on the situation in the West Algerian and is part of a strategy to improve the diagnosis and support.

**Objectives:** The objective was to describe the clinical features and management of PH in children, as well as its effects on the quality of life and its consequences, excluding patients with persistent pulmonary hypertension of the newborn.

**Methods:** This prospective non interventional study included children with PH who were prospectively followed for two years in in a pediatric center in Oran. The WHO functional classification, the 6-minute walk distance, were evaluated.

**Results:** Sixty children with a mean age of  $6,4 \pm 4,6$  years in 12 cities in the West Algerian were included from January 2020 to January 2022. The diagnosis is late (3 years on average). The prevalence of PH was estimated at 2,2 cases per 100.000 children in the wilaya of Oran. The patients had the following types of PH: associated with congenital heart disease (73%), idiopathic (6%), associated with an HIV (3%) or associated with diffuse interstitial lung disease (3%). Although there may be misleading clinical signs, it is therefore imperative that PH is recognised and that its severity is assessed. Echocardiography is the essential examination which is most often used to assess PAH and its effects. During follow-up there was an increase in the number of drugs prescribed specifically for pulmonary arterial hypertension (44% patients versus 22% at inclusion). The clinical status, 6-minute walk test and quality of life of the majority of patients remained stable. The survival at one and at two years was estimated at 95% and 93,3% respectively (95% confidence interval).

**Conclusion:** The majority of cases of PH in children are secondary to congenital heart disease or idiopathic. The prognosis depends largely on its etiology. The use of specific treatments for PAH may contribute to the stability of the disease and to better survival. Progress in understanding the pathophysiology will open the way to new therapeutic choices.

**Keywords:** Pediatric Pulmonary Hypertension; Congenital Heart Defect; Epidemiology; Pulmonary Vasodilators

## Abbreviations

PH: Pulmonary Hypertension; PAH: Pulmonary Arterial Hypertension; IPAH: Idiopathic PAH; PAH-CHD: PAH Associated with Congenital Heart Disease; PAP: Pulmonary Arterial Pressure; PAPS: Systolic Pulmonary Arterial Pressure; PAPm: Mean Pulmonary Arterial Pressure; WHO: World Health Organization; 6MWD: 6-Minute Walk Distance; RV: Right Ventricle, CI: Confidence Interval

## Introduction

Pediatric PH includes a highly heterogeneous group of children with diverse ages, disease severities, prognoses, and underlying causes. PAH is distinguished by a progressive increase in pulmonary vascular resistance, which eventually leads to right ventricular failure [1]. The impact on quality of life is significant, and the prognosis is bleak.

In the era before targeted therapy, the untreated median survival from diagnosis of idiopathic PAH (IPAH) was 10 months (adults from the same time period had a median survival of 2.8 years) [2]. Without treatment, increase of pulmonary arterial pressure (PAP) and resistance in patients with PH leads to right heart failure, clinical worsening, and death. Unlike with adult patients, however, PAH in children is linked to lung growth [3]. Because of this advantage, the child with PAH has greater potential to reverse the underlying pathologic condition with appropriate therapy. In the modern era, studies and guidelines offer tools for treating physicians to better risk stratify patients with PH and improve selection of children with PAH for surgical repair of associated congenital heart disease.

Adults and children with PH have the same histopathological lesions [4] and vascular and endothelial homeostasis abnormalities, including prostacyclin and thromboxane A2 imbalance and abnormal pulmonary clearance of endothelin-1 [5].

However, the spectrum of associated conditions, clinical presentation, and survival factors may differ between adults and children. Although there is limited data on the clinical responses of pediatric PH patients, children with severe PAH are currently treated with clinical strategies similar to those used in adults [6].

To meet a different set of practical, social, and therapeutic challenges, treatment goals for pediatric patients with PH may necessitate specific adaptations of adult treatments [7]. However, there is currently insufficient data to inform treatment objectives and decisions.

As a result, this prospective, monocentric, non-interventional study was launched to investigate the specific epidemiology of pediatric PH. This study also looked at the medical management of pediatric PH in the current treatment era, as well as the impact on quality of life and outcome over a two-year period.

## Methods

### Study design

This multicenter, prospective, non-interventional study was initiated in January 2020. Enrolled patients either had a known diagnosis of PAH before the beginning of the study or were diagnosed during the recruitment period. All enrolled patients were followed prospectively for two years (from January 2020 to January 2022). The study was conducted in the Pediatric Cardiology Unit, of the Pediatrics Department (Marfan) of the CHU Oran, where the cardiovascular explorations are carried out, in particular echocardiography and the management of children with PH from western Algeria. The protocol did not impose any procedures or therapies. Written, informed consent was obtained from the parents before data collection.

### Study patients

Patients aged between 28 days and 15 years were included.

### Inclusion criteria

Children aged < 15 years, residing in western Algeria, with significant PH, newly diagnosed or already known. The diagnosis of PH was established either by right heart catheterization or by echocardiography-Doppler according to the recommendations of the European

Society of Cardiology [8] (and systolic pulmonary arterial pressure (PAPs) > half the systolic arterial pressure). For patients with PAH associated with congenital heart disease (PAH-CHD), only patients with fixed irreversible PAH will be considered (Eisenmenger Syndrome).

### Non-inclusion criteria

Patients with persistent neonatal PH will be excluded insofar as this pathology is acute and different from other etiologies of PH; patients with PAH-CHD of group 1 (reversible PAH) and group 2 (Patient Border Line: Gray Zone) according to the hemodynamic classification.

### Patient characteristics

It included the history of PH with the date of the first clinical signs, date of diagnosis and WHO functional class at diagnosis. Age, height, weight and functional signs were documented at study inclusion and a complete physical and cardiac examination was performed.

In addition to functional class, physical abilities were assessed by a 6-min walk test (6MWD) in patients aged over 7 years, at inclusion, at 6 months, 1 year and at 2 years. From a biological point of view, the serum level of NTproBNP was assessed on inclusion and then every 6 months.

An echocardiography was performed on inclusion and then every 6 months until the end of the study. Echocardiographic examination was performed using a Vivid E9 machine (General Electric Healthcare, Milwaukee, WI). Doppler echocardiography was performed according to the recommendations of the American Society of Echocardiography (ASE). Hemodynamic parameters by cardiac catheterization were collected on inclusion.

### Statistical analysis

Data collection was done in an Excel table. Quantitative variables were described by the mean ( $\pm$  standard deviation and extremes). The bivariate comparisons were carried out using a Student's t test or a non-parametric Wilcoxon test depending on the distribution of the variables and the numbers to be compared. Qualitative variables were described as frequency and percentage.

The comparison of the groups on the qualitative parameters was carried out by the Chi-2 test or the exact test of Fisher. For all statistical tests, the significance threshold was set at 5% ( $p < 0.05$ ). Statistical analyzes were performed using SPSS software (version 20, SPSS Statistics, IBM Corporation) and Epi Info.

The height and weight of the patients were compared with the average values of a population of children of the same age according to the WHO curves. Growth retardation was defined as height or weight less than or equal to twice the standard deviation of the reference population.

Survival was estimated from the inclusion of patients in the study until the end of their follow-up or death, according to the Kaplan-Meier method (95% confidence interval).

## Results

In total, the number of patients with PH included in the study during this period is Sixty children. These patients come from 12 cities in western Algeria. A third of the patients are from the wilaya of Oran. Patients were followed for a median duration of 14,5 months (range 1 - 23). No patient was lost sight of.

### Prevalence of PH

We recorded 11 new cases in Oran in 2015, and 7 new cases in 2016. The incidence of PH (excluding persistent newborn PH) in children in the wilaya of Oran was estimated at least 2.2 cases/100,000 children in 2015 and at 1.4 cases/100,000 children in 2016. The prevalence of PH (excluding persistent newborn PH) in children in 2016 was estimated at least 35.2 cases/million children.

### Patient demographics and disease characteristics at inclusion

The characteristics at inclusion of the 60 patients are summarized in table 1.

Characteristic	
Boys/girls, n (%)	35 /25 (58% /42%)
Age (years)*	6,4 ± 4,6 (0,4 - 15)
Weight (kg)	16,7 ± 9,8 (5 - 52)
height (cm)	100 ± 25 (60 - 170)
<b>Background</b>	
- Prematurity	06 (10%)
- consanguinity	32 (53%)
- Trisomy 21	23 (38%)
- Death in siblings	11 (18%)
Oxygen saturation, %	86,3 ± 7,2 (65 - 97)
<b>Functional class NYHA (WHO)</b>	
- NYHA 1	13 (22%)
- NYHA 2	25 (42%)
- NYHA 3	20 (33%)
- NYHA 4	02 (3%)
6MWD, m (n= 31)	340.7 ± 122 (108 - 560)
NTproBNP, pg/ml (n= 43)	3156 ± 4424 (33 - 15106)
<b>Aetiology of PH</b>	
<b>Group 1: PAH</b>	
- Idiopathic	04 (6%)
- PAH-CHD	44 (73%)
- PAH associated with HIV	02 (3%)
- Portal hypertension	01 (1.5%)
<b>Group 3:</b>	
- Interstitial lung disease	02 (3%)
- Cystic fibrosis	01 (1.5%)
<b>Group 5:</b>	
- Chronic hemolytic anemia	01 (1.5%)
- Sickle cell disease	01 (1.5%)
- Mucopolysaccharidosis (MPS) type I, VI	02 (3%)
- Achondrodysplasia	01 (1.5%)
- Chronic renal failure/hemodialysis	01 (1.5%)
<b>Hemodynamic data:</b>	
- PAP mean, mmHg (n = 44)	62.3 ± 8.5 (38 - 78)
- PAP systolic, mmHg (n = 44)	88 ± 7,5 (70 - 103)
- PVR unités Wood (n = 11)	6.3 ± 0,98 (5 - 8)
Specific treatment:	
- Aucun	13 (23%)
- Sildénafil	25 (45%)
- Bosentan	15 (27%)
- Sildénafil + Bosentan	17 (30%)
Median duration of follow-up, month	14,5 (1-23)
Values are number (percentage) of patients or mean ± standard deviation (range).	

**Table 1:** Patient characteristics at study inclusion (n = 60).

A male predominance was recorded. The male to female ratio was of 1.4 (35 boys and 25 girls). The patients had an average age of  $3.2 \pm 3.5$  years at the onset of the first symptoms and  $6.4 \pm 4.6$  years at diagnosis. Twenty-six patients (43.3%) belonged to the age group of less than 5 years of which 15 patients were aged less than 2 years.

All patients are from Algeria; the parents of 32 of them (53.3%) are consanguineous. Consanguinity is found most often in PAH-CHD (27 cases out of 32, or 84% of cases).

Deaths in siblings are noted in 18.3% of cases. In addition, there is no family history of PH. The concept of prematurity was found in 6 cases (10%). Noting that, 23 out of 60 patients (38%) have facial dysmorphism evoking trisomy 21 type chromosomal aberration confirmed in all cases by a genetic study.

### Aetiology of PH

Patients were most frequently classified in group 1 (PAH) (85%) according to the ESC 2018 classification (Table 1). In children, PAH-CHD represent the majority of cases (44 of patients or 73% of cases) of which 17 patients had an interventricular communication VSD. IPAH was found in 4 patients. There are also two cases of HIV infection and a single case of portal hypertension.

The least represented group is group 3 with 3 patients with chronic respiratory pathologies. Six patients belong to group 5, with various etiologies: Two cases of haematological origin (chronic haemolytic anemia and sickle cell anemia), two cases of metabolic origin (Mucopolysaccharidosis MPS type I (Hurler syndrome), VI (Maroteaux-Lamy disease), one case of achondrodysplasia and one case with chronic renal failure on hemodialysis. There were no cases belonging to groups 2 and 4.

### Diagnosis of PH

The diagnosis of PH was confirmed by right heart catheterization in 44 of 60 patients (73%), where the mean PAP was measured at  $88 \pm 7.5$  mmHg. The 44 catheterizations performed were performed in patients with PAH associated with congenital heart disease. PVRs were only assessed in 11 patients with a mean value measured at  $6.3 \pm 0.98$  (5 - 8) Wood units. No patient benefited from an inhaled NO test (not available in Algeria).

For the remaining 16 patients, the diagnosis of PH was confirmed by echocardiography-Doppler, with the evaluation of the PAP from the maximum velocity of the tricuspid regurgitation. The mean PAPs value at inclusion was  $84.3 \pm 14.3$  mmHg.

The diagnosis of PH is made late with an average age of  $6.4 \pm 4.6$  years (6 months - 15 years) while the warning signs were present before the age of 12 months.

### Clinical symptoms

The mean weight of the patients at inclusion was  $16.74 \pm 9.8$  kg, while the mean height was  $98.8 \pm 25.8$  cm. Thus, a delay in weight and stature growth was observed in 17 (28%) and 10 (16%) patients, respectively.

The clinical expression of the disease was different according to age: In infants, the starting point was difficult in the majority of cases due to food associated with retarded growth in stature and weight. In older children, PH is revealed by functional signs, especially in serious and already advanced forms. Respiratory symptoms are at the forefront, especially on exertion: dyspnoea in 75% of cases, whereas cyanosis is only observed on inclusion in 15% of cases. Signs of right heart failure (hepatomegaly) were rare (6% of cases) (Table 2). Hemoptysis was recorded in only one severe case. On the other hand, syncope on effort was noted on inclusion in 7 patients with advanced forms. During the last evaluation, no significant change in these symptoms was observed, with the exception of cyanosis on exertion (28% of cases).

Clinical parameters	Inclusion (n = 60)	Last evaluation (n = 56)
Weight (kg)	17,1 ± 10 (5 - 52)	18,9 ± 9,9 (7 - 53)*
Height (cm)	101 ± 27 (60 - 170)	104,5 ± 25,9 (65-170)*
Dyspnoea	45 (75%)	47 (78%)
Fatigue	42 (70%)	30 (50%)
Cyanosis with exercise	09 (15%)	17 (28%) **
Syncope	07 (11%)	04 (6%)
Chest pain	04 (6%)	06 (10%)
Hepatomegaly	04 (6%)	07 (11%)
Values are number (percentage) of patients or mean ± standard deviation.		
* p = 0.0001, ** p = 0.03		

**Table 2:** Evolution of clinical signs between inclusion and the last evaluation.

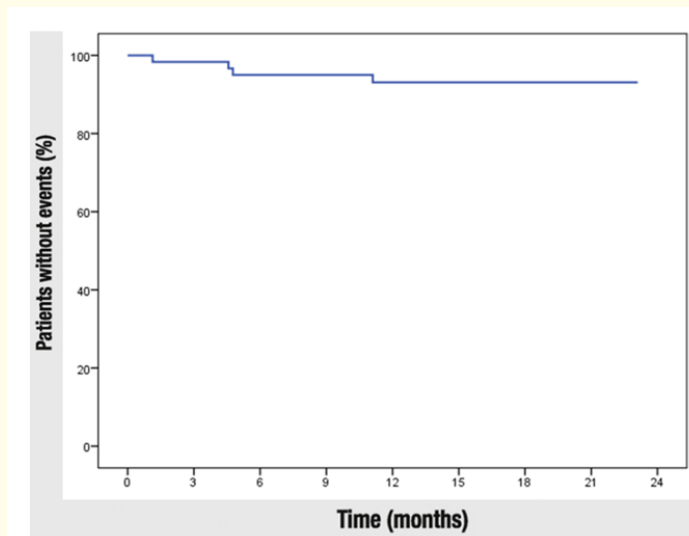
**WHO functional class and 6MWD**

All patients had their WHO functional class assessed at inclusion and 56 patients at the last assessment. On inclusion, the majority of patients in this study (45 patients, i.e. 75% of cases) were in WHO functional class II or III (Table 1). At last assessment, 24 patients (40%) had improved from baseline in at least one functional class, of which 2 patients improved by two classes (3%) and 7 patients (11%) had worsened by one class. The others kept the same class: I (11 cases), II (11 cases), III (3 cases).

The 6MWD was performed in 31 patients only. The mean distance traveled at inclusion was 340.7 ± 122m (108 - 560). Oxygen desaturation > 10% was noted at the end of the test in 70% of patients. The distance in the 6MWD performed for children over 7 years old improved significantly from 340.7 ± 122 m at inclusion (n = 31) to 448.2 ± 140 m at the last evaluation (n = 31, p = 0.0001).

**Survival**

Survival was estimated from the inclusion of patients in the study until the end of their follow-up or death, according to the Kaplan-Meier method (95% CI). Kaplan-Meier survival estimates at 1 and 2 years were 95% and 93.3%, respectively (Figure 1).



**Figure 1:** Survival estimates (Kaplan-Meier method).

We recorded 4 deaths. One patient was 3 years old on inclusion, male, WHO functional class III, had IPAH. Death occurred 5 months after inclusion in a sudden state of syncopal status. A patient with chronic idiopathic hemolytic anemia died at the age of 2 years, one month after her inclusion in the pediatric intensive care unit in a nosocomial infection. The 3<sup>rd</sup> patient was 2 years old with diffuse interstitial pneumonitis who also died in an acute respiratory failure picture. The last patient with HIV infection with tuberculosis died after one year of inclusion at the age of 13 from severe sepsis.

**Treatment**

While our study is non-interventional, we observed that a high proportion of our patients received specific treatments. Dual therapy with a specific treatment for PH was less frequent at the last assessment than at inclusion. Conversely, the number of monotherapy had remained the same. Only one patient was on triple therapy during the last evaluation. Sildenafil was the most frequently added treatment between inclusion and last assessment, and bosentan was the most frequently prescribed PH- specific treatment at inclusion and last assessment (Table 3).

<b>Changes in treatments</b>	<b>Inclusion</b>	<b>Last assessment</b>
No PAH-specific treatment	13 (23%)	15 (27%)
Monotherapy (Sildénafil or Bosentan)	26 (46%)	26 (46%)
Bitherapy (Sildénafil + Bosentan)	17 (30%)	14 (23%)
Bosentan	15 (27%)	20 (35%)
Sidénafil	25 (45%)	24 (43%)
Iloprost	0 (0%)	1 (2%)
Diuretics	35 (62%)	29 (52%)
Values are number (percentage) of patients.		

**Table 3**

**Discussion**

This prospective study investigated the characteristics and outcome of PH in the Algerian pediatric population. To our knowledge, this is the first study on pediatric PH in Algeria because until now there is no national study and few international studies have described the evolution of this very serious pathology in children and they were limited to small cohorts, performed before the advent of specific treatments for PH.

**Prevalence, incidence**

in our study, the prevalence of pediatric PH (excluding persistent PH in newborns) was estimated in 2016 at 35.2 cases per million children. The incidence of PH (excluding persistent newborn PH) in children was estimated at 2.2 cases/100,000 children in 2015 and 1.4 cases/100,000 children in 2016.

The frequency of this disease in our study is fairly comparable with other pediatric registers: in the French register, the overall prevalence of PH in children is estimated at 3.7 cases/million [9]. In the Dutch registry, for example, the annual incidence rates of pediatric PH were 63.7 cases per million children [10]. This prevalence is probably underestimated due to the low specificity of clinical signs dominated by exertional dyspnea.

### Clinical presentation

Our study included a heterogeneous pediatric population, with several age groups. Twenty-six patients (43.3%) belonged to the age group of less than 5 years, the majority of whom ( $n = 15$ ) were less than 2 years old. This age group is mainly represented by children with CHD with a left-to-right shunt not operated on in time ( $> 12$  months of life) and whose PAH has become supra-systemic and above all irreversible (Eisenmenger's syndrome) [11]. If the disease is more common in women in adulthood, in the pediatric population it affects both boys and girls. In our study, the male sex represents 58% of cases. This is comparable with data from different pediatric registries [9,10].

It can be seen that pediatric patients have forms of PH relatively similar to those of adults, but the percentages of the various forms encountered seem different. In effect, in our study, patients most frequently had group 1 PH (85%) according to the 2018 ESC classification. CHD represents the most frequent etiology of pediatric PH (73%). This is comparatively similar with other pediatric registries [12,13]. Unlike adults where PAH-CHD only represent 18 to 30% of cases only [13]. CHD with a left-to-right shunt is the main contributor to PAH in children [11]. However, the frequency remains relatively high in our study [12,13]. This is due to the delay still recorded in our country in the timely surgical management and the rapid evolution of these CHD towards Eisenmenger's syndrome.

It is particularly essential in this disease with an unfavorable prognosis to establish a diagnosis quickly. Unfortunately, it turns out that very often the diagnosis is delayed and that pediatric patients with PH are referred extremely late to specialists. In our study, patients had an average age of  $3.2 \pm 3.5$  years at the onset of the first symptoms and  $6.4 \pm 4.6$  years at diagnosis. In the French register, the summer was a little shorter, since the children had an average age of  $4.4 \pm 4.5$  years when the first symptoms appeared and  $5.1 \pm 4.8$  years when diagnosed [9]. In the Swiss register, the children had an average age of 3 years when the first symptoms appeared and  $5.1 \pm 4.8$  years when diagnosed [14].

Although WHO functional class is not designed specifically for infants and children, it correlates excellently with 6MWD and hemodynamic parameters [15]. On inclusion, the majority of patients in our study were in WHO functional class II or III (75%). Although the WHO functional class is difficult to assess in young children, this suggests an earlier diagnosis than for adults [16]. These patients had an elevated PAP. They had no signs of right heart failure which is a frequently observed difference between adults and children in PH. Children seem to tolerate increased RV afterload better than adults for the same degree of disease severity [17,18].

The distance in the 6MWD performed for children over 7 years old improved significantly from  $340.7 \pm 122$  m at inclusion ( $n = 31$ ) to  $448.2 \pm 140$  m at the last evaluation ( $n = 31$ ,  $p = 0.0001$ ). In recent pediatric studies, the 6MWD was not a predictor of survival, neither when expressed as an absolute value in meters, nor adjusted to reference values expressed as a z-score or as a percentage of the predicted value [19,20].

### Treatment, follow-up and survival

There are no approved guidelines for pediatrics and treatment approaches are derived from the adult algorithm [21]. There are no clear recommendations concerning pediatric dosages and in current practice, an adaptation of the treatment for adults is therefore very often used in the absence of studies evaluating pediatric dosages [22].

Endothelin receptor antagonists and more particularly bosentan (antagonist of A and B receptors), is an interesting drug in children thanks to oral administration. The results in children demonstrated the effectiveness of the drug. Several retrospective and prospective series have confirmed these results [23,24]. In our series, bosentan was the most frequently added treatment between inclusion and the last evaluation, often as a second-line treatment. Dual therapy is initiated after failure of monotherapy or immediately in severe forms.

Sildenafil is a specific inhibitor of phosphodiesterase type 5. There are currently a number of series that have been published demonstrating its effectiveness in the treatment of pediatric PAH [25,26]. In our study, Sildenafil was the most prescribed drug at baseline and at the last evaluation. At the end of the study, 43% of patients (24 cases) used sildenafil either in mono- or dual therapy, only one patient in triple therapy.



In our study, iloprost was introduced in a single 5-year-old female patient of WHO functional class 4, high risk class, not responding to combined treatment (sildenafil and bosentan). Triple therapy improved the patient clinically by changing WHO functional class 3 with regression of NTproBNP to 3400 pg/ml, after 4 months of treatment.

With the development of intravenous epoprostenol in the late 1980s and the more recent marketing of bosentan, sildenafil and iloprost, the treatment of pediatric PH has evolved considerably in recent years [23,27-29].

We observed that a high proportion of patients received specific treatments despite the absence of controlled trials validating their use in children. In addition, during the two years of follow-up, the patients received an increasing number of therapeutic combinations, which may have contributed to the relative stability of the clinical symptomatology (the WHO functional class of 73% of the patients was stabilized or even improved), 6MWD and quality of life. Given the dramatic prognosis of this disease, it is encouraging that the children are stable or improving, even at the cost of increased medication.

New survival data concerning pediatric PH under specific targeted treatments have been reported in different cohorts of patients. These include European cohorts (France, United Kingdom and the Netherlands) and cohorts from the United States of America [15,19,30,31]. In all of these studies, survival appeared to be improved compared to historical cohorts.

During the two years of the study, four children died. The survival in our study, 95% at 1 year and 93.3% at 2 years, compares favorably with the median survival of 24 months reported by the French registry in 2010 of 86% at 1 year and 82% at 2 years [9] and with the median survival of 10 months reported by the National Institutes Health Registry in 1991 [2] or with the survival estimate of 37% at 1 year, and 12% at 2.5 years observed in a Canadian study before the emergence of specific treatments for PH [32].

According to our results, the concept of starting a specific treatment for PH and then optimizing it with a drug combination in the event of worsening and/or insufficient response to monotherapy is beneficial, as demonstrated in therapeutic trials in adults and in recent pediatric studies [15]. A more precise evaluation of the treatment of pediatric PH is therefore necessary, in order to give the possibility to specialized pediatricians to prescribe specific treatments based on pediatric studies.

### Conclusion

Childhood PH is a severe condition. In children, PAH-CHD and IPAH represent the majority of cases. Its prognosis depends on the etiology, excellent most often in the context of CHD if the intervention is early, pejorative in the forms of IPAH. It is essential to evoke the diagnosis at the first signs.

The treatment of PH in children cannot be dissociated from the etiological diagnosis, the evaluation of the physiopathological characteristics and the evaluation of the functional tolerance of the disease. The treatment has undergone many changes in recent years. The better understanding of the pathophysiological mechanisms has allowed the introduction of new therapies that have changed the extremely poor prognosis of this disease. However, no curative treatment is available to date. Therapeutic combinations with different mechanisms of action are encouraging and could improve survival. Specific pediatric studies have been carried out or are in progress. They should further improve the prognosis. This study provides an overview of the current management of pediatric PH in Algeria. He argues for the use of specific PH drugs in children, as is already the case in adults. Finally, it identifies a subgroup of patients with PAH-CHD, whose pathophysiology and evolutionary profile require early and well-codified management.

### Conflicts of Interest

The authors have declared no competing interest.

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**Volume 12 Issue 3 March 2023**

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