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Updates in Management of Pulmonary Hypertension in Pediatrics: A Systematic Review

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Abstract

Objectives: To provide an updated synthesis of the evidence on the management of pulmonary hypertension (PH) in pediatric patients. ***Methods:*** We performed a thorough search of electronic databases such as PubMed, Science Direct, Cochrane Library, and Scopus. Two independent reviewers evaluated and retrieved information from qualifying papers. ***Results:*** Our data consists of eight studies with 2003 children, 930 (46.3%) of whom were female. Prostacyclin agonists were found to significantly improve hemodynamic parameters and reduced BNP levels, which implies that they have promising clinical efficacy and a good tolerance profile. No major side effects were noted except for headaches and gastrointestinal symptoms. Systemic glucocorticoids, inhaled NO, endothelin receptor antagonists, and PDE showed tolerability and clinical improvements in pediatric PH. Side effects such as acute kidney damage, renal failure, and methemoglobinemia were noted with the inhaled NO. ***Conclusion:*** Pediatric PH is still a difficult condition with high morbidity and mortality. All of the reported pharmacological interventions demonstrated good clinical outcomes and almost no adverse effects. Healthcare practitioners can improve the care of children with PH and eventually improve their quality of life and long-term survival by incorporating new research into clinical practice.

Keywords: Pulmonary hypertension; Children; Pediatrics; Management; Pharmacological approaches; Systematic review.

INTRODUCTION

Severe morbidity and death are linked to pediatric PH [1, 2]. The Pediatric Working Group of the 6th World Symposium on PH in France (2018) revised the definition of pediatric PH to include the following criteria: mean pulmonary artery pressure > 20 mmHg, normal pressure in the pulmonary capillary wedge ≤ 15 mmHg, and pulmonary vascular resistance > 3 WU [3]. This definition is similar to that of adult PH. As per Berger *et al.*, (2011), the Netherlands PH Service, which operates countrywide, reports that the annual incidence rate of all PH diagnostics is 63.7 cases per million children. The two conditions with the highest incidence rates were cardiogenic PH and persistent PH of the infant, at 30.1 and 21.9 instances per million children, respectively [3]. 3.0 incidences of progressive PH were reported annually per million youngsters. The frequency was considerably lower for idiopathic pulmonary arterial hypertension (PAH) and PH associated with congenital heart disease (PH-CHD), with 0.7 and 2.2 occurrences per million, respectively. Furthermore, one of the most prevalent types of PAH in children is the subset of patients with postoperative PH after CHD repair, which happens in 21.9 occurrences per million [2, 4].

Though the pathobiology and pathophysiology of PH remain incompletely understood, three main pathways have been identified as being involved in the development and progression of PH: decreased activity of the vasodilator nitric oxide, reduced expression of antiproliferative vasoactive mediators, including prostacyclin, and increased expression of endothelin, an effective endothelium-derived vasoconstrictor peptide that has potent mitogenic properties [5]. As a result, during the past 20 years, four classes of medications, including eleven PH-specific medications, have been

developed: (1) endothelin receptor antagonists, such as bosentan, ambrisentan, and macitentan; (2) prostacyclin analogs, such as selexipag, treprostinil, treprostinil, and iloprost; (3) phosphodiesterase type 5 inhibitors, such as sildenafil and tadalafil; and (4) guanylate cyclase stimulator, such as riociguat [6, 7]. The mean survival from the beginning of symptoms enhanced significantly with PH-specific therapy [6]. However, five years following diagnosis, mortality is still significant (25–29%) with either mono- or dual-pharmacotherapy, and it is even worse for patients with PH-related gene abnormalities [8].

Recent years have seen a substantial change in the therapy of PH in pediatric patients, mostly due to an increasing amount of research highlighting the distinctive features of the condition in children as opposed to adults. Unique difficulties with pediatric PH include variations in the course of the disease, how well patients respond to treatment, and the long-term consequences. Even with these developments, thorough advice specific to pediatric patients is still needed. The complexities of pediatric care may not be adequately addressed by current guidelines, which are primarily derived from adult research. This could result in diversity in treatment approaches and outcomes. Therefore, in order to give doctors the most up-to-date, scientifically supported patient care options, a systematic evaluation of recent advancements in the management of juvenile PH is important. This systematic review aims to provide an updated synthesis of the evidence on the management of PH in pediatric patients.

METHODS

Following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9], this systematic review was conducted. We performed an extensive electronic search using PubMed, Web of Science, SCOPUS, Cochrane Library, and Science Direct, among other bibliographic databases. English-language research on the updates of PH management in children was the focus of our search approach. To guarantee a comprehensive search, we employed pertinent terms associated with both PH and children. In order to preserve neutrality, two impartial reviewers went through the search results, chose studies that fit the inclusion requirements, took out data, and used reputable assessment instruments to rate the included research's methodological quality.

Eligibility Criteria

Inclusion Criteria:

- Studies that investigate the recent management of PH in children.
- Studies that discussed pharmacological interventions only.
- Studies included children only (<18 years).
- Studies conducted in 2023-2024.
- Only studies written in English.
- Randomized controlled trials (RTCs), observational studies, cohort studies (retrospective and prospective), case-control studies, or cross-sectional studies.

Exclusion Criteria:

- Studies that do not focus on the updated pharmacological interventions of PH in children.
- Studies written in languages other than English.
- Case studies, opinions, comments, letters, reviews that don't include original research, and abstracts from conferences.

Data Extraction

Titles and abstracts found from the search were screened for screening accuracy and consistency by using pre-established inclusion and exclusion criteria to determine their relevance to the research issue. To promote effective screening and lessen bias, reference management software such as Rayyan (QCRI) [10] was used. Research that at least one reviewer thought to be pertinent was advanced to full-text inspection by both reviewers. All disputes pertaining to inclusion were settled by consensus and dialogue. Using a standardized data extraction form, important data from the included studies was retrieved, including titles, authors, publication year, research setting, participant demographics (age and gender distribution), follow-up duration, intervention, adverse effects, and primary outcomes. In addition, the risk of bias in the included studies was assessed using a recognized instrument for methodological quality evaluation.

Data Synthesis Strategy

To give a qualitative review of the research findings and components, summary tables were created utilizing data from pertinent studies. Once the data collection for the systematic review is completed, the appropriate way to use the data from the included studies will be decided.

Risk of Bias Assessment

The study's quality was assessed using the Joanna Briggs Institute (JBI) [11] critical assessment criteria for studies reporting prevalence data. This tool consists of nine questions, with positive responses getting a score of one and negative, ambiguous, or irrelevant responses receiving a score of zero. Scores of less than 4, 5 to 7, and 8 or higher will be rated as poor, moderate, and high quality, accordingly. Researchers separately assessed the study quality, and any discrepancies were resolved through discussion.

RESULTS

Search results

Following the removal of 455 duplicates, a thorough search yielded 890 study publications. After 435 studies' titles and abstracts were reviewed, 342 papers were rejected. Two of the 93 reports that needed

to be retrieved could not be found. 91 publications were screened for full-text review; 57 were rejected because the study findings were incorrect, 24 because the population type was incorrect, 3 were abstracts, and 2 were editor's letters. Eight of the research publications in this systematic review met the qualifying criteria. **Figure 1** depicts an overview of the approach used to choose the research.

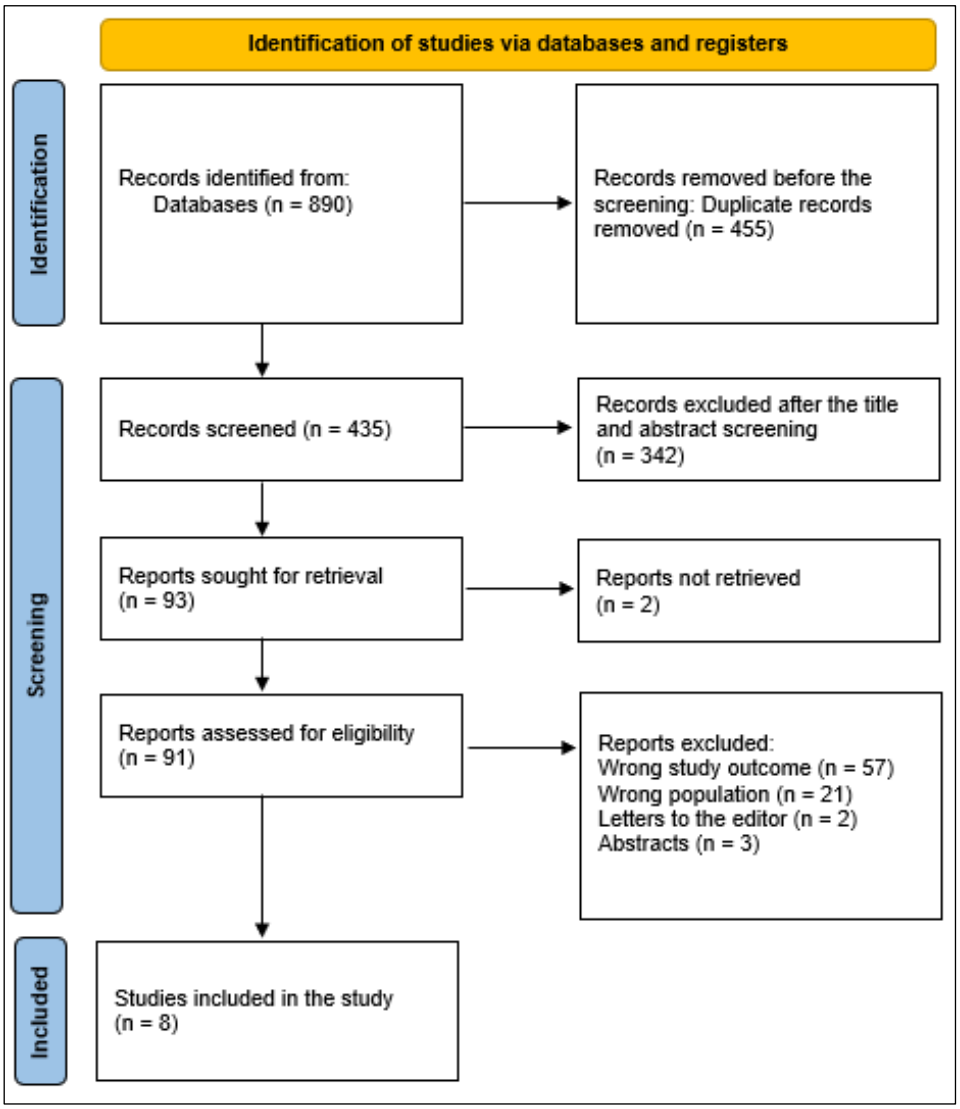

Figure 1: The study decision-making is summarized in a PRISMA diagram.

Sociodemographic parameters of the researched subjects

Table 1 illustrates the demographic data from the research articles. Our data consists of eight studies with 2003 children, 930 (46.3%) of whom were female. Five studies were retrospective cohorts [12-14, 17, 18], one was a retrospective case series [15], one was an RCT [16], and one was a prospective observational study [19]. Five studies were conducted in the USA [12, 13, 16, 17, 19], one in Japan [14], one in Turkey [15], and one in China [18].

Clinical Outcomes

The clinical parameters are displayed in **Table (2)**. Four studies discussed the use of prostacyclin agonists in managing PH in children. Prostacyclin agonists were found to significantly improve hemodynamic parameters and reduced BNP levels, which implies that they have promising clinical efficacy and a good tolerance profile [12, 15, 17, 18]. No major side effects were noted except for headaches and gastrointestinal symptoms [12]. Systemic glucocorticoids [13], inhaled NO [14], endothelin receptor antagonists [16], and PDE [19] showed tolerability and clinical improvements in pediatric PH. Side effects such as acute kidney damage, renal failure, and methemoglobinemia were noted with the inhaled NO [14].

Table 1: Sociodemographic variables of the interested populations

Study ID	Study design	Country	Participants	Mean age	Females (%)
Frank *et al.*, 2024 [12]	Retrospective cohort	USA	87	7 - 15.4	45
Hernandez *et al.*, 2024 [13]	Retrospective cohort	USA	17	NM	9
Matsugi *et al.*, 2024 [14]	Prospective cohort	Japan	1375	NM	604
Arslanoğlu *et al.*, 2024 [15]	Retrospective case-series	Turkey	9	6.92 ± 3.52 (months)	4
Ivy *et al.*, 2024 [16]	RCT	USA	38	125	25
De Bie *et al.*, 2023 [17]	Prospective cohort	USA	351	NM	157
Li *et al.*, 2023 [18]	Prospective cohort	China	83	11.3 ± 4.6	60
Issapour *et al.*, 2022 [19]	Prospective observational study	USA	43	4-17.5	26

Table 2

Study ID	Follow-up (months)	Pharmacological intervention	Adverse outcomes	Main outcomes	JBI
Frank *et al.*, 2024 [12]	12	Prostacyclin agonist	The majority of the higher rates of adverse effects were related to headaches, and both groups experienced similar rates of gastrointestinal distress.	The oral prostacyclin-agonist selexipag has promising clinical efficacy and a good tolerance profile.	Mod erate
Hernandez *et al.*, 2024 [13]	0.75	Systemic glucocorticoid	Over the course of the trial, there were no fatalities.	In newborns with PH, systemic glucocorticoid medication was well tolerated and showed promise for improving cardiopulmonary function.	Mod erate
Matsugi *et al.*, 2024 [14]	NM	Inhaled NO	In 14 pediatric patients, 20 ADRs (1.0%) were reported. Acute kidney damage, renal failure, and methemoglobinemia were the DRs in pediatrics.	Effectiveness-wise, pediatric patients who received inhaled-NOflo therapy saw increases in oxygenation and hemodynamics when compared to baseline.	Mod erate
Arslanoğlu *et al.*, 2024 [15]	NM	Prostacyclin agonist	NM	The possibility of inhaliloprost as a safe and efficient medication for treating PH in children who have had congenital heart surgery.	Mod erate
Ivy *et al.*, 2024 [16]	6	Endothelin receptor antagonists	The investigator most often attributed treatment related AEs to headaches, gastroenteritis, and anemia.	In children with PAH aged 8–<18 years, long-term weight-based ambrisentan dose, either alone or in conjunction with other PAH medications, demonstrated tolerability and clinical improvements that were in line with the findings of earlier randomized studies.	Mod erate
De Bie *et al.*, 2023 [17]	18-40.8	Prostacyclin agonist	There were no significant side effects noted.	Clinically, treprostinil treatment was linked to reduced BNP levels over time, as well as better RV size and systolic performance.	Mod erate
Li *et al.*, 2023 [18]	45.6-105.6	Prostacyclin agonist	NM	Hemodynamic parameters can be significantly reduced by an acute inhalation of iloprost.	High
Issapour *et al.*, 2022 [19]	5-112	PDE	NM	In a small subset of children, combination therapy using ambrisentan and tadalafil was well tolerated and had a satisfactory safety profile. Before starting ambrisentan with tadalafil, children who were either treatment naïve or on monotherapy with a PH medication showed improvements in their ability to exercise and hemodynamics.	High

***NM=Not-mentioned**

DISCUSSION

This systematic review's selection of reports indicates that there are not many high-quality, prospective clinical studies that address the use of pharmaceutical interventions in the acute management of children with PH. This deficiency in evidence sounds to

be a general problem in pediatric intensive care. Prostacyclin agonists were found to significantly improve hemodynamic parameters and reduced BNP levels, which implies that they have promising clinical efficacy and a good tolerance profile [12, 15, 17, 18]. No major side effects were noted except for headaches and gastrointestinal symptoms [12]. In a systematic review by Li *et al.*, found that the varying severities and etiologies of diseases may have contributed to the diverse effects of oral selexipag on clinical, invasive, and noninvasive measures. Nevertheless, despite its off-label use for this age group up to this point, selexipag is generally safe and effective when used in conjunction with regular monitoring as a transitional medication for children with PH or as an addition to prostacyclin analogs. It presents physicians with a treatment option that shows promise for managing pediatric patients with uncontrolled PH [20].

Wu *et al.*, reported that currently, there are four main prostacyclin compounds being used as treatments to treat Parkinson's disease. For cases of severe PAH, epoprostenol is still the suggested chemical. Severe PPHN can be treated with iloprost, and pulmonary vasoreactivity tests can benefit from its inhaled delivery. The longest-acting prostacyclin analog with the strongest antiproliferative effect is treprostinil. Finally, a single successful case report suggests that beraprost may be helpful for premature infants; this needs to be confirmed in bigger research, of course. Owing to the lesser prevalence of PAH in children, the effects of prostacyclin or its analogs have not been extensively studied in multicenter investigations [21].

We also found that systemic glucocorticoid [13], inhaled NO [14], endothelin receptor antagonists [16], and PDE [19] showed tolerability and clinical improvements in pediatric PH. Side effects such as acute kidney damage, renal failure, and methemoglobinemia were noted with the inhaled NO [14]. Mulligan & Beghetti, reported that when it comes to the acute treatment of newborn and pediatric PH, inhaled iloprost may play a variety of roles. It can be used as a "rescue" measure, in addition to or instead of inhaled NO in nations where the latter medication is not readily available. When inhaled NO is unavailable, it can specifically be a possibility for pulmonary vasoreactivity testing [22]. Awad *et al.*, also reported that since sildenafil has demonstrated its effectiveness in lowering PAP mean and systolic as well as in reducing ventilation time, intensive care unit stays, and hospital stays without affecting mortality rates, it is a well-tolerated treatment for PH caused by congenital heart diseases [23].

The results of this systematic study should be interpreted with some caveats in mind. Firstly, there could be biases and inconsistencies in the data because the included studies differ in terms of design, population size, and follow-up duration. There is an additional level of complexity when applying adult PH management techniques to pediatric populations since children may react differently to certain therapies. Furthermore, the robustness of the evidence base is limited by the dearth of large-scale, RCTs that explicitly target pediatric PH. Lastly, because therapy choices are evolving so quickly, it's possible that some newly developed medicines aren't fully covered in the literature yet, necessitating ongoing revisions to the review.

With additional choices to customize therapy to each patient's needs, the availability of novel pharmacological drugs may improve patient outcomes. Starting therapy on time depends on an early and correct diagnosis, which is made possible by improved awareness and cutting-edge diagnostic techniques. Additionally, the overall quality of treatment is improved by the inclusion of supportive care measures, such as psychosocial support for patients and their families. To add to the expanding body of knowledge in pediatric PH, clinicians should make a point of staying up to date on the most recent information and thinking about enrolling candidates in clinical trials.

CONCLUSION

Pediatric PH is still a difficult condition with high morbidity and mortality. All of the reported pharmacological interventions demonstrated good clinical outcomes and almost no adverse effects. Healthcare practitioners can improve the care of children with PH and eventually improve their quality of life and long-term survival by incorporating new research into clinical practice.

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