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Risk Stratification and Contemporary Therapeutic Strategies in Pediatric Pulmonary Hypertension: A Narrative Review

Agnieszka Zielińska, <https://orcid.org/0009-0001-4322-064X>, agzielinska44@gmail.com, National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland

Zuzanna Zofia Kamińska, <https://orcid.org/0009-0009-9803-0972>, kaminska2000@gmail.com, Nicolaus Copernicus Hospital in Gdańsk, Nowe Ogrody 1-6, 80-803 Gdańsk, Poland

Gabriela Senda, <https://orcid.org/0009-0004-9011-1480>, gabrysiasenda@gmail.com, Medical University of Białystok, Jana Kilińskiego 1, 15-089 Białystok, Poland

Michał Gorlo, <https://orcid.org/0009-0003-3977-6228>, michal.gorlo@gmail.com, Medical University of Białystok, Jana Kilińskiego 1, 15-089 Białystok, Poland

Corresponding author: Agnieszka Zielińska, agzielinska44@gmail.com

Abstract

Background: Pediatric pulmonary hypertension (PH) is a rare, heterogeneous disease marked by progressive pulmonary vascular resistance and right ventricular pressure overload, with significant morbidity and mortality. Targeted pharmacotherapy has advanced, yet management is complicated by diverse causes, developmental differences from adult disease, and limited pediatric evidence. Risk stratification is now the foundation for individualized treatment.

Aim: This review summarizes evidence on risk stratification and therapy in pediatric PH, focusing on prognostic tools and targeted treatments supporting personalized management.

Material and methods: We conducted a narrative review of PubMed/MEDLINE literature from January 2020 to mid-2026, using pediatric- and PH-specific search terms, supplemented by manual screening of reference lists. Priority was given to guidelines, registry-based and multicenter cohort studies, and recent work on multidimensional risk assessment, cardiac imaging, invasive hemodynamics, biomarkers, pharmacotherapy, and advanced interventions.

Results: Management has shifted from a disease-oriented toward an individualized, risk-guided approach. Reliable prognosis depends on integrating clinical evaluation, echocardiography, cardiac MRI, invasive hemodynamics, and biomarkers, rather than any single parameter. Dynamic risk stratification enables earlier detection of progression and timely escalation. Pharmacological management increasingly relies on combination therapy targeting nitric oxide, endothelin, and prostacyclin pathways, while emerging agents and interventions expand options for high-risk patients.

Conclusions: Risk stratification is the cornerstone of pediatric PH management. Individualized strategies based on continuous assessment enable earlier intervention, optimized treatment, and appropriate selection of advanced therapies. Further multicenter studies are needed to validate risk models and strengthen treatment guidance.

Keywords: pediatric pulmonary hypertension; risk stratification; targeted therapy; right ventricular dysfunction; biomarkers

1. Introduction

Pulmonary hypertension (PH) is a rare and life-threatening disorder in which pulmonary vascular pressure and resistance rise progressively, eventually causing right ventricular dysfunction and, if untreated, premature death. Pediatric PH is a distinct clinical entity: it differs substantially from the adult disease in its causes, pathophysiology, natural course and treatment. Adult pulmonary arterial hypertension (PAH) is often idiopathic or linked to connective tissue disease, whereas PH in children is more commonly tied to developmental lung disorders, congenital heart disease (CHD), genetic abnormalities, and neonatal conditions. This clinical heterogeneity is considerable and limits how far evidence from adults can reasonably be extrapolated to children [1].

Pediatric PAH remains uncommon, but its incidence and prevalence have risen gradually alongside improvements in neonatal care, better survival among children with complex CHD, and more sensitive diagnostics [2]. Recent registries point to a growing share of multifactorial disease relative to isolated idiopathic PAH, with survival heavily dependent on etiology [3]. This is one of the main reasons diagnostic and therapeutic approaches must be developed specifically for children instead of simply adapted from adult practice.

Even with the progress made in targeted pharmacotherapy, pediatric PH still carries significant morbidity and mortality. Deterioration can occur even when symptoms have appeared stable, and disease progression is often hard to predict from clinical assessment alone. Identifying at-risk children accurately has therefore become a central goal of modern PH management. Increasingly, therapeutic strategies are guided by a comprehensive risk assessment that draws on clinical status, imaging, hemodynamics, biomarkers, and how a patient has responded to treatment over time. This allows earlier escalation of therapy, better-tailored follow-up, and timelier referral for advanced interventions such as prostacyclin therapy, atrial septostomy, Potts shunt, or lung transplantation [1].

Large observational registries, multicenter cohorts, and international scientific statements have considerably sharpened prognostic thinking in recent years while also expanding the range of available therapies. Advances in echocardiography and cardiac MRI have improved right ventricular assessment, emerging biomarkers are providing new opportunities for risk stratification and increasing clinical experience with prostacyclin agonists, endothelin receptor antagonists and soluble guanylate cyclase stimulators has broadened treatment options for progressive disease. Together, these developments have transformed management from a largely descriptive approach into evidence-based, risk-oriented care. Much of the available literature, however, remains scattered across separate imaging, biomarker, or pharmacological studies instead of being drawn together into a coherent

clinical framework - a gap this review aims to help close by synthesizing findings in a way that supports everyday practice.

Accordingly, this narrative review summarizes current evidence on risk stratification and modern therapeutic strategies in pediatric pulmonary hypertension. It focuses on the prognostic assessment and treatment evidence most likely to influence clinical decisions, rather than attempting an exhaustive account of every aspect of the disease.

2. Materials and Methods

This narrative review draws on a literature search of the PubMed/MEDLINE database, supplemented by manual screening of the reference lists of retrieved articles. Search terms combined “pediatric” or “children” with “pulmonary hypertension,” “pulmonary arterial hypertension,” “risk stratification,” “echocardiography,” “cardiac magnetic resonance,” “biomarkers,” and the names of individual targeted therapy classes (phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, prostacyclin analogues, selexipag, riociguat). The search focused on English-language publications from January 2020 through mid-2026, supplemented where directly relevant by earlier foundational or guideline documents. We prioritized international guidelines and scientific statements, large registry-based and multicenter cohort studies, and recent original research addressing pediatric risk stratification or targeted pharmacotherapy directly; case reports, conference abstracts, and adult-only studies were excluded unless no pediatric-specific data existed on a given topic.

Because this is a narrative rather than a systematic review, no formal protocol was registered, and study selection and quality appraisal did not follow a standardized tool such as PRISMA or AMSTAR. Sources were instead selected on the basis of clinical relevance and recency, in keeping with the goal of synthesizing current evidence into a clinically usable overview rather than cataloguing every available publication. Section 8 discusses this limitation further and considers what it means for interpreting the strength of individual findings.

3. Current Concepts of Pediatric Pulmonary Hypertension

Pulmonary hypertension covers a heterogeneous group of disorders marked by abnormal pulmonary vascular remodeling, a progressive rise in pulmonary vascular resistance, and increasing right ventricular afterload. The pediatric disease differs fundamentally from the adult form because it develops alongside active lung growth, vascular maturation, and cardiac adaptation; as a result, its underlying biology more often reflects disturbances in cardiopulmonary development or congenital cardiovascular abnormalities than pulmonary vascular dysfunction in isolation.

The 2022 ESC/ERS guidelines define PH as a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg at rest on right heart catheterization. Pre-capillary PH, which includes PAH, additionally requires a pulmonary arterial wedge pressure of 15 mmHg or lower and a pulmonary vascular resistance above 2 Wood units [4]. In children, an indexed pulmonary vascular resistance (PVRi) above 3 Wood units·m² is used instead, reflecting how resistance depends on body size. Interpretation must also take pulmonary blood flow, age-related physiology, and congenital heart defects into account, since in systemic-to-pulmonary shunts elevated flow can precede irreversible vascular remodeling even when pressure elevation is only modest.

The WHO classification sorts PH into five clinical groups according to underlying mechanism, but several authors have pointed out that it captures pediatric complexity only incompletely. In children, PH often arises from several interacting conditions at once - congenital heart disease, bronchopulmonary dysplasia, congenital diaphragmatic hernia, developmental lung disorders, and genetic syndromes - which has prompted calls for classification systems better suited to developmental abnormalities and coexisting mechanisms, such as the pediatric-specific Panama classification [1,5].

Recent consensus documents reinforce this pediatric-specific view. The American Heart Association Scientific Statement by Jone et al. [6] emphasized that CHD-associated PH represents one of the largest and most heterogeneous pediatric PH populations, calling for individualized diagnostic algorithms incorporating clinical presentation, anatomical complexity, and ventricular performance rather than hemodynamics alone. Ivy et al. [7]

framed neonatal and pediatric PH in similar terms, as developmental disorders in which abnormal pulmonary vascular growth coexists with altered lung development and genetic susceptibility. Both documents converge on the same conclusion: risk assessment throughout childhood needs to be patient-centered.

A further distinction from adult disease is that children often keep relatively preserved functional capacity even with substantial pulmonary vascular disease, and deterioration can occur abruptly after something as minor as an infection or surgery. Symptom-based assessment can therefore underestimate severity, arguing for repeated, multi-domain evaluation. Because the disease is rare, most of what we know has come from international registries and multicenter cohorts more than from randomized trials - yet this evidence has still allowed more structured therapeutic algorithms and earlier initiation of targeted therapy than were possible a decade ago. Together, these developments have made risk stratification, rather than disease classification on its own, the organizing principle of modern pediatric PH management, forming the basis for the individualized treatment strategies discussed in the sections that follow.

4. Risk Stratification in Pediatric Pulmonary Hypertension

4.1 From Disease Classification to Individualized Risk Assessment

Risk stratification has become a core part of how pediatric pulmonary hypertension is managed today. Treatment decisions used to rest mainly on disease classification, hemodynamics, and symptoms, but patients with similar hemodynamic profiles can follow markedly different clinical paths, exposing the limits of relying on isolated measurements for therapeutic decisions.

Recent international recommendations instead advocate a multidimensional approach that integrates clinical evaluation, functional status, imaging, invasive hemodynamics, circulating biomarkers, and how treatment response evolves over time - treating pulmonary hypertension as a dynamic process, not a fixed diagnosis. The 2023 American Heart Association Scientific Statement [6] highlighted that continuous reassessment matters because disease can progress even when symptoms look stable, particularly in younger children and those with congenital heart disease. The clearest expression of this thinking is the report from the pediatric task force of the 7th World Symposium on Pulmonary Hypertension, published by Ivy et al. [7], which proposes a three-tier (low/intermediate/high) pediatric risk stratification tool. It combines WHO Functional Class (WHO-FC), growth and 6-minute walk distance, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and echocardiographic right ventricular parameters - including tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change, and right ventricular longitudinal strain - to guide both the intensity of initial treatment and the timing of escalation.

Pediatric risk stratification is still less developed than its adult counterpart, largely because the disease is rare, its causes are heterogeneous, developmental differences exist across age groups, and randomized trial data remain limited. These challenges were already noted by the 6th World Symposium pediatric task force [8] and were further addressed in the 2019 European Pediatric Pulmonary Vascular Disease Network consensus statement [9]; both called for structured, multidisciplinary follow-up in place of reliance on any single diagnostic snapshot. Current practice therefore combines several complementary prognostic indicators instead of depending on one standardized score. Constantine et al. [10] reported two decades of experience from a national pediatric pulmonary hypertension service and found that long-term survival had improved substantially with specialized multidisciplinary care and targeted pharmacotherapy, although outcomes still varied considerably by underlying etiology. This reinforces a simple point: prognosis cannot be read off from diagnosis alone, and management should instead be guided by ongoing evaluation of disease severity and treatment response.

These observations have shifted what treatment is trying to achieve. Management no longer aims solely to lower pulmonary arterial pressure. It aims to maintain a low-risk clinical profile through regular reassessment and timely adjustment of treatment, with multimodal assessment central to detecting deterioration early. Important limitations remain - many prognostic variables have only been validated in small observational cohorts, and follow-up protocols still differ between centers. Individual markers tend to complement rather than replace one another. As a result, risk stratification works best not as a single diagnostic step, but as a continuous process that runs alongside

every stage of disease management. It is this process that underlies the therapeutic decisions discussed in Section 5.

4.2 Clinical Assessment

Clinical evaluation is still the first, and one of the most important, steps in risk stratification. Pediatric patients often compensate well early in the disease, so deterioration may only become obvious after substantial pulmonary vascular remodeling has already occurred. For this reason, long-term follow-up is anchored not in a single baseline evaluation, but in serial assessment of symptoms, exercise tolerance, growth, and right ventricular function [6,7].

Assessing symptoms in children is considerably harder than in adults, because it depends so much on age and developmental stage. Infants often present with nonspecific signs such as poor feeding, growth failure, tachypnea, or irritability, while older children more typically describe exercise intolerance, dizziness, chest pain, or syncope - symptoms that usually only appear relatively late in the disease [11,12]. Current recommendations therefore stress combining several indicators - WHO-FC, growth velocity, exercise capacity, oxygen requirement, hospitalization frequency, and signs of right heart failure - into a full assessment at every visit [6,7], since no single symptom reliably predicts how a patient will do.

Constantine et al. [10] underscored just how much comprehensive, longitudinal clinical assessment matters: their 20-year national cohort data showed that prognosis tracks with etiology and clinical evolution more closely than with baseline diagnosis. Current consensus documents echo this. The American Heart Association Scientific Statement [6] recommends managing these patients within specialized multidisciplinary centers that integrate clinical, imaging, hemodynamic, and laboratory data, while Ivy et al. [7] stress that regular reassessment allows treatment failure to be identified earlier.

Functional classification remains useful, but it has recognized limits in children. WHO-FC was developed for adults, and may consequently underestimate severity in infants and preschool-aged children who cannot perform standardized exercise testing, or whose symptoms are harder to communicate [11,12]. Current practice increasingly treats functional class as one piece of a broader risk assessment rather than a stand-alone determinant of prognosis. Ultimately, serial clinical assessment remains the foundation of risk stratification. Its real value, however, lies less in any single evaluation than in tracking change over time. Combined with imaging, hemodynamics, and biomarkers, it provides earlier warning of disease progression than any one variable could offer alone [6,7,10].

4.3 Echocardiographic Assessment

Echocardiography remains the mainstay of non-invasive risk stratification and the most widely available imaging modality, both for initial evaluation and for long-term follow-up. Beyond confirming the diagnosis, serial echocardiography offers information on right ventricular adaptation, interventricular interactions, and disease progression. Because it is safe, non-invasive, and easy to repeat, it is indispensable for monitoring how a patient responds to treatment and for catching early deterioration [6,7].

Modern echocardiographic assessment increasingly focuses on the full picture of right ventricular performance instead of pulmonary artery pressure estimation in isolation, reflecting evidence that survival depends on whether the right ventricle can maintain cardiac output as afterload rises [11,12]. Lammers et al. [13] showed that echocardiographic parameters of right ventricular systolic performance and remodeling were linked to adverse outcomes during longitudinal follow-up - a finding consistent with the national-registry data from Constantine et al. [10] discussed above, where prognosis was shown to evolve over time. Those authors likewise emphasized that prognostic evaluation should rely on interpreting multiple parameters together, not on any single measurement.

No single echocardiographic parameter is, by itself, a reliable predictor of prognosis. Combining several variables - right ventricular size and systolic function, septal configuration, right atrial enlargement, tricuspid regurgitation, and pulmonary artery pressure estimates - gives greater accuracy, and serial imaging can pick up deterioration before it becomes clinically obvious, or track improvement after treatment is escalated [6,7]. Known limitations,

including image quality that varies with age, body habitus, or postoperative anatomy, and dependence on operator skill, have driven growing use of cardiac magnetic resonance imaging (CMR) as a complementary, more reproducible modality, particularly when echocardiographic findings are inconclusive [14]. It remains the first-line imaging modality for risk stratification precisely because its greatest strength lies in this kind of comprehensive, serial evaluation rather than in pressure estimation alone, and it is best read within a broader multimodal framework, supplemented with CMR where appropriate [6,10,13].

4.4 Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) provides a highly reproducible assessment of right ventricular morphology, function, and ventricular-vascular interactions that depends far less on operator skill than echocardiography, which makes it a valuable complement, particularly in children with progressive disease or inconclusive echocardiographic findings [6,7]. Since right ventricular failure is the leading cause of death in PAH, this reproducibility gives CMR real value for both prognosis and therapeutic decision-making.

In a two-center retrospective study of 89 children undergoing CMR, Ta et al. [14] found that an impaired global function index (GFI - the ratio of stroke volume to mean ventricular cavity and myocardial volume) was linked to a composite adverse outcome (death, lung transplant, Potts shunt, or initiation of parenteral prostacyclin). This suggests that CMR-derived functional indices can add prognostic information beyond what conventional ventricular size or ejection-fraction measurements capture. Since that composite outcome already includes advanced interventions such as Potts shunt and parenteral prostacyclin initiation, a low GFI is probably better understood as flagging patients approaching that treatment threshold than as a direct predictor of mortality in its own right. These findings complement rather than challenge the echocardiographic evidence: echocardiography remains preferred for accessible serial follow-up, whereas CMR offers a more precise picture of ventricular remodeling in selected patients and may help identify progressive remodeling before it becomes clinically apparent [6,7].

Practical constraints - longer scan times, the frequent need for sedation in younger children, and availability limited to specialized centers - mean that standardized CMR-based pediatric risk models do not yet exist. Current evidence therefore supports using CMR as a complement rather than a replacement.

Overall, CMR adds meaningful information for risk stratification by allowing accurate, reproducible assessment of right ventricular adaptation. Combining CMR with echocardiography may sharpen prognostic assessment and support more tailored treatment strategies, particularly in children with complex disease [6,7,14].

4.5 Hemodynamic Assessment

Right heart catheterization remains the gold standard for confirming diagnosis, and it gives the most complete picture of pulmonary vascular hemodynamics available, allowing direct measurement of pulmonary artery pressure, pulmonary vascular resistance, cardiac output, and acute vasoreactivity - information that clinical evaluation or echocardiography alone cannot provide [6,7]. Pulmonary artery pressure on its own, though, is not a sufficient predictor of severity or outcome; hemodynamic findings must be interpreted alongside functional status, right ventricular adaptation, imaging, and biomarkers [11,12]. In line with this, Constantine et al. [10] found that changes observed over follow-up, combined with clinical evolution and treatment response, carried substantially more prognostic weight than isolated catheterization results obtained at diagnosis - supporting the view that invasive assessment is best understood as one part of an ongoing process, not a single milestone.

Catheterization also remains essential for identifying candidates for advanced interventions. Acute vasoreactivity testing picks out the small subgroup of children with idiopathic or heritable PAH who may respond to calcium channel blockers, and detailed hemodynamic assessment is required before a Potts shunt is created or a lung transplant performed [6].

A newer hemodynamic parameter, the pulmonary artery pulsatility index (PAPi) - which reflects the relationship between pulmonary artery pulse pressure and right atrial pressure - illustrates both the promise and the present

uncertainty surrounding new markers. In a single-center study of 24 children with idiopathic PAH, Torun et al. [15] found that PAPI was associated with disease severity and the need for invasive intervention. A considerably larger analysis of 111 children with PAH of mixed etiology from the Dutch National Registry, however, found no additional prognostic value for PAPI beyond its individual components [16]. This discrepancy indicates that, unlike in some adult PAH cohorts, PAPI's prognostic value in pediatric PAH remains unsettled and will require validation in larger, etiologically homogeneous populations before routine use.

Because catheterization is invasive and carries a small but real complication risk, serial follow-up relies mainly on non-invasive methods, with invasive assessment reserved for diagnosis, major therapeutic decisions, unexplained deterioration, or reassessment before an intervention [7]. Right heart catheterization therefore remains indispensable for diagnosis and for guiding major therapeutic decisions, but it should no longer be treated as an isolated predictor of prognosis: its greatest value comes from being integrated with longitudinal clinical assessment, multimodal imaging, and biomarkers [6,10,15,16].

4.6 Circulating Biomarkers

Growing interest in tailored risk stratification has spurred research into circulating biomarkers, which are minimally invasive, easy to repeat, and may reflect pathophysiological changes before structural abnormalities become visible. No single biomarker has yet shown enough accuracy to work as an independent predictor. Current evidence instead supports biomarker panels that complement established assessment strategies rather than replace them [6,7].

In two pediatric PAH cohorts, Griffiths et al. [17] found that circulating ST2, which reflects myocardial stress and right ventricular remodeling, was associated with a shorter six-minute walk distance and a higher pulmonary vascular resistance index. Adding ST2 to the REVEAL Risk Score Calculator 2.0 also improved its ability to predict clinical worsening, with the hazard ratio rising from 1.88 to 2.05 - suggesting a role for ST2 as an adjunct to established clinical tools, not as a standalone marker. Elesawy et al. [18] similarly found that elevated plasma mid-regional proadrenomedullin (MR-proADM) was associated with disease severity in children with PH linked to congenital heart disease. Pamukçu et al. [19] reported significant changes in circulating kallistatin, a protein involved in anti-inflammatory, vasodilatory, and angiogenic pathways, in pediatric PAH, adding a further piece to the biological picture.

A shared limitation across these studies is small, single-center sample sizes and inconsistent methodology, which has so far prevented any single biomarker from being incorporated into universally accepted pediatric risk algorithms. Future work will likely combine several biomarkers spanning different pathophysiological pathways - myocardial injury, inflammation, endothelial dysfunction - together with imaging and clinical data.

Taken together, ST2, MR-proADM, and kallistatin have all shown promising links to disease severity and prognosis, but they need further multicenter validation before they can be built into standardized pediatric risk algorithms [17,18,19].

4.7 Summary of Risk Stratification

None of the tools reviewed above - clinical assessment, echocardiography, CMR, hemodynamics, or circulating biomarkers - is sufficient on its own. Each captures a different facet of disease severity, and their prognostic value is greatest when used together. This dynamic, multimodal approach to risk stratification is now the foundation of pediatric pulmonary hypertension management, and it directly shapes the selection and intensity of the targeted therapies discussed next.

Table 1. Domains of risk assessment in pediatric pulmonary hypertension.

Domain	Parameters with prognostic value	Cutoff / direction of risk	Advantages	Limitations	Suggested assessment frequency
Clinical assessment	WHO-FC, growth velocity, 6-minute walk distance, NT-proBNP	WSPH 2024 three-tier low/intermediate/high classification (Ivy et al., 2024)	No equipment needed; captures functional trajectory	WHO-FC insensitive in infants/preschoolers; symptom reporting unreliable in young children	Every visit (typically every 3-6 months)
Echocardiography	TAPSE, RV fractional area change, RV longitudinal strain, septal configuration, TR severity	Reduced TAPSE/RVFA C and worse RV strain associated with adverse outcome (Lammers et al., 2023)	Non-invasive, repeatable, widely available	Operator-dependent; limited by acoustic window in complex CHD	Every 3-6 months, or with clinical change
Cardiac MRI	Global function index (GFI), RV volumes	Lower GFI associated with a composite adverse outcome (Ta et al., 2023)	Highly reproducible; not limited by acoustic window	Long acquisition time; sedation often needed in young children; limited availability	As needed for complex or inconclusive echocardiographic cases
Invasive hemodynamics	mPAP, PVRi, cardiac output, vasoreactivity, PAPi	PAH defined as mPAP >20 mmHg + PAWP ≤15 mmHg + PVRi >3 WU·m ² in children (Humbert et al., 2022)	Gold standard; only method giving direct pressure/resistance data	Invasive, requires sedation/anesthesia; not repeatable for routine monitoring; PAPi's added value unconfirmed (Torun et al., 2026; Smits et al., 2024)	At diagnosis and before major treatment decisions
Circulating biomarkers	ST2, proADM, kallistatin	Elevated levels associated with greater severity/worsen	Minimally invasive, repeatable	Not yet validated in multicenter pediatric	Alongside routine follow-up visits

ing (Griffiths et al., 2021; Elesawy et al., 2023; Pamukçu et al., 2020) cohorts; no accepted cutoffs

5. Modern Therapeutic Strategies

5.1 Principles of Modern Pharmacological Management

The therapeutic landscape has changed considerably over the past two decades. A better understanding of the molecular mechanisms behind pulmonary vascular remodeling has driven the development of targeted therapies acting on the nitric oxide, endothelin, and prostacyclin pathways, and these have meaningfully improved survival and quality of life. Even so, most of the evidence is still extrapolated from adult studies and observational pediatric cohorts instead of coming from randomized trials [11,12].

Present-day strategies are guided more and more by individualized risk assessment rather than by disease classification alone. Current recommendations favor early initiation of targeted therapy in children with intermediate- or high-risk features, followed by regular reassessment and escalation whenever treatment goals are not being met [6,7] - a substantial departure from earlier approaches that held off on intensifying treatment until disease had already advanced. Clinical, imaging, hemodynamic, and biomarker findings therefore actively drive treatment decisions throughout the disease course rather than serving only as prognostic tools, and combination therapy targeting multiple pathways at once is increasingly preferred over monotherapy, especially in progressive disease.

5.2 Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 (PDE5) inhibitors, the best established of which is sildenafil, remain first-line treatment in many settings. They enhance nitric oxide signaling and lower pulmonary vascular resistance by inhibiting cGMP degradation, and their oral administration has supported widespread use in both idiopathic PAH and PAH associated with congenital heart disease [11]. Pediatric dosing, however, still calls for caution. In the long-term extension of the STARTS programme, higher sildenafil doses were associated with increased mortality relative to lower doses (hazard ratio 3.95 for high- versus low-dose), which led to a 2012 FDA warning against chronic high-dose use that was only partially clarified in 2014. The EMA, by contrast, approved sildenafil with a caution against high doses - a regulatory split that still shapes prescribing today. Current thinking emphasizes judging treatment success through repeated clinical reassessment of overall risk profile rather than isolated hemodynamic or echocardiographic improvement [7,12], with the goal of maintaining a low-risk clinical status instead of simply lowering pulmonary artery pressure [6].

Most of the available pediatric evidence is still observational or extrapolated from adult trials, and optimal dosing may vary with age, weight, and disease severity. Monotherapy can also become insufficient as disease progresses, so recognizing an inadequate response early and escalating treatment in time is essential. PDE5 inhibitors therefore remain a core first-line component of pharmacological management, but how well they work in practice depends on careful patient selection and timely escalation within a dynamic, risk-guided strategy, and not on the drug's pharmacology alone [6,11,12].

5.3 Endothelin Receptor Antagonists

Endothelin receptor antagonists (ERAs) block endothelin-1, a vasoconstrictor that also drives vascular smooth muscle proliferation and remodeling [11]. Agents such as bosentan and macitentan have shown favorable effects on hemodynamics, exercise capacity, and clinical stability in observational pediatric studies, and the supporting evidence is no longer purely observational [6,7].

Dedicated pediatric data on macitentan have expanded recently. In a multicenter observational study from the Spanish Registry of Pediatric Pulmonary Hypertension (REHIPED), Rodriguez Ogando et al. [20] evaluated 74 children with group 1 PAH (31 idiopathic/heritable, 43 associated with congenital heart disease). After six months of treatment, the proportion of patients in WHO functional class III/IV fell from 48% to 22% ($p=0.001$). Mean six-minute walk distance increased by approximately 45 m ($p=0.032$), and NT-proBNP fell by a mean of 438.9 ± 175 pg/mL ($p=0.015$). The proportion of children meeting all three low-risk criteria also rose, by 17% ($p=0.002$). Side effects occurred in four patients (5.4%), and macitentan was discontinued in one; even so, disease progression was still observed in six children - a reminder that a favorable group-level response does not rule out individual treatment failure, and that reassessment must continue regardless.

The evidence base for ERAs in children now includes a randomized trial. In the open-label, multicenter, phase 3 TOMORROW trial, 148 children aged 2 to under 18 years with WHO-FC I–III PAH were randomized 1:1 to bodyweight-based macitentan ($n=73$) or standard of care ($n=75$) [21]. Macitentan and aprocitentan exposure matched adult pharmacokinetic data, supporting the bodyweight-based dosing scheme, and quality-of-life scores at week 24 favored macitentan. Time-to-event analyses, however, including time to disease progression (HR 0.828; 95% CI 0.460–1.492) and PAH-related hospitalization (HR 0.912; 95% CI 0.393–2.118), did not reach statistical significance, and neither did the between-group difference in NT-proBNP. The trial therefore confirms adequate pediatric dosing and an acceptable safety profile rather than demonstrating clinical superiority over standard of care - a distinction worth keeping in mind when deciding how to use it.

ERAs are increasingly being introduced earlier in intermediate- or high-risk children, instead of being held in reserve for advanced disease, and are often combined with PDE5 inhibitors to maximize vasodilation while limiting remodeling. Ongoing monitoring for hepatic toxicity and drug interactions is required, ideally within specialized centers [7].

In short, ERAs, including macitentan, for which multicenter pediatric outcome data are now available, are most often incorporated into combination therapy as part of a personalized, continuously reassessed treatment strategy [6,7,20].

5.4 Prostacyclin Pathway Therapies

Prostacyclin is an endogenous vasodilator with antiproliferative, antithrombotic, and anti-inflammatory effects, and reduced synthesis contributes to vascular remodeling - which is the rationale for prostacyclin analogues (epoprostenol, treprostinil, iloprost) in advanced PAH [11]. Pediatric-specific dosing evidence has grown considerably. In a multicenter cohort of 275 children with PAH, 98 received intravenous or subcutaneous prostanoid therapy (20% as monotherapy, 46% dual, and 34% triple combination therapy), at a median time-averaged dose of 37 ng/kg/min (range 2–136). Douwes et al. [22] found that earlier initiation, higher time-averaged doses, and combination with additional PAH-targeted therapy were each independently linked to more favorable outcomes. The authors also identified hemodynamic thresholds - mPAP below 35 mmHg and/or indexed PVR below 4.4 Wood units $\cdot$ m² - that could safely guide the transition to oral or inhaled therapy, summarized as “start early, dose high, combine.” Since this is a historical cohort, the absolute dosing figures should be read alongside current practice, which has continued to evolve since.

In a single-center retrospective study, He et al. [23] added treprostinil-specific data in 49 higher-risk children with idiopathic or heritable PAH, compared against a reference cohort receiving oral therapy alone. Treprostinil was associated with significantly better survival and event-free survival (freedom from death, Potts shunt, or atrial septostomy), regardless of the underlying genetic background. Aggressive treatment aimed at preserving right ventricular function before irreversible decompensation sets in may therefore improve long-term outcomes. Prostacyclin therapies remain demanding to deliver, though: continuous intravenous epoprostenol requires permanent central access, with the attendant infection and thrombosis risk, while subcutaneous and inhaled formulations bring their own tolerability problems. Choosing among them means weighing disease severity, age, family support, and institutional expertise. Even so, prostacyclin- pathway therapies remain indispensable for

advanced or rapidly progressive PAH, and recent pediatric-specific cohort data now offer practical guidance on dosing, timing, and combination, instead of leaving clinicians to rely solely on adult extrapolation [6,7,22,23].

5.5 Combination Therapy and Emerging Targeted Treatments

Management has shifted from stepwise escalation after deterioration toward earlier combination therapy guided by individualized risk assessment, reflecting the recognition that PAH is driven by several dysregulated pathways at once [6,7]. Combination therapy most often brings together nitric oxide, endothelin, and prostacyclin pathway agents. Randomized pediatric trials remain scarce, but observational evidence and expert consensus support escalating treatment whenever follow-up reassessment shows inadequate improvement [6].

Selexipag, an oral selective prostacyclin receptor agonist, illustrates this shift well. In one of the largest retrospective multicenter cohorts to date, Frank et al. [24] analyzed 87 children with PAH treated with selexipag (32 as add-on therapy, 55 transitioned from another parenteral or inhaled prostanoid). Selexipag was generally well tolerated; the add-on group showed an improved indexed pulmonary-to-systemic vascular resistance ratio (PVRi/SVRi, where SVRi is the indexed systemic vascular resistance), and right ventricular function stayed stable after transition in most patients, though a subset showed late functional worsening - a reminder that ongoing monitoring is needed regardless of clinical scenario.

Riociguat, a soluble guanylate cyclase stimulator with a mechanism distinct from PDE5 inhibition, now has an established pediatric pharmacokinetic model from Willmann et al. [25] for children aged 6 years and older, supporting body-weight-based dosing to reach adult-comparable exposures. Clinical efficacy and outcome data in children, though, remain more limited than in adults, and further prospective study is still needed.

Beyond the vasodilator pathways, inhibiting activin signaling represents the first potentially disease-modifying approach in PAH. Sotatercept, an activin receptor type IIA-Fc fusion protein that rebalances growth-promoting activin/GDF signaling against growth-inhibiting BMP signaling, reduced pulmonary vascular resistance and improved exercise capacity and clinical worsening in the adult phase 3 STELLAR trial and is now approved for adult PAH [26]. Pediatric data are not yet available: the first dedicated pediatric study, MOONBEAM (NCT05587712), is an open-label phase 2 trial evaluating safety, tolerability, and pharmacokinetics in children aged 1 to under 18 years receiving background therapy. Because BMPR2-pathway dysfunction sits at the center of heritable pediatric PAH, this drug class is among the most anticipated developments in the field, although extrapolation is still constrained by etiological differences and by uncertainty about how activin inhibition behaves in a growing organism.

In sum, combination therapy is now central to management, particularly when initial treatment fails to achieve or hold a low-risk profile. Multicenter cohort data now support selexipag as both add-on and transition therapy, pediatric pharmacokinetic modeling supports rational riociguat dosing, and sotatercept's pediatric evaluation (MOONBEAM) is underway following its adult approval - together reflecting a broader shift toward personalized, risk-guided pharmacological management [6,7,24,25,26].

Table 2. Targeted pharmacological therapies in pediatric pulmonary hypertension.

Pathway	Agent(s)	Route	Pediatric evidence type	Pediatric registration status	Main adverse effects / monitoring
Nitric oxide (PDE5 inhibition)	Sildenafil	Oral	Long-term extension data (STARTS) (Frank and Ivy, 2020)	Approved in EU (EMA); off-label chronic use in some other regions	Higher doses linked to increased mortality in STARTS-2; use

						lowest effective dose
Endothelin receptor antagonism	Bosentan, macitentan	Oral	Retrospective multicenter cohort (Rodriguez Ogando et al., 2026); randomized controlled trial (TOMORROW) (Berger et al., 2026)	Used off-label/on registry basis in most pediatric settings	Hepatotoxicity - periodic liver enzyme monitoring; teratogenicity	
Prostacyclin parenteral tr	- Epoprostenol, eprostnil su	IV / bcutaneous do	Multicenter sing cohort sp (Douwes et al., 2022); single-center comparative cohort (He et al., 2024)	Used in specialized centers; not FDA/EMA-approved specifically for pediatric PAH	Catheter-related infection/thrombosis (IV); site pain (subcutaneous)	
Prostacyclin oral	- Selexipag	Oral mu	Retrospective multicenter pediatric cohort (Frank et al., 2024)	Off-label pediatric use	Headache, jaw pain, gastrointestinal effects; monitor tolerability during uptitration	
Soluble guanylate cyclase stimulation	Riociguat	Oral	Population pharmacokinetic model only (Willmann et al., 2023)	Not approved for pediatric use; dosing model only	Hypotension; contraindicated with PDE5 inhibitors	
Activin signaling inhibition	Sotatercept	Subcutaneous	Adult phase 3 trial only (Hoepfer et al., 2023); pediatric trial (MOONBEAM , NCT05587712) ongoing	Approved for adults only; no pediatric data yet	Thrombocytopenia, bleeding risk, telangiectasia (adult data)	

6. Advanced Therapeutic Interventions

A subset of children continue to have progressive disease and worsening right ventricular dysfunction despite optimized medical management. For these patients, timely referral to specialized centers for surgical or transplant-based therapies is essential before deterioration becomes irreversible [6].

The Potts shunt, which creates a communication between the left pulmonary artery and descending aorta to decompress the right ventricle while preserving coronary and cerebral oxygenation, is a palliative option for carefully selected children with suprasystemic PAH and preserved left ventricular function. Observational studies report improved functional status and quality of life, though long-term outcome data remain limited and patient selection is critical [12]. Balloon atrial septostomy, which creates a right-to-left shunt to decompress the failing right ventricle at the cost of systemic desaturation, remains a bridging option in selected children with severe right heart failure and syncope that has not responded to medical therapy; it was used as one component of the composite outcome in at least one of the cohort studies discussed above [23]. For refractory, progressive disease, lung transplantation, or combined heart-lung transplantation in selected cases with left-sided cardiac abnormalities, remains the only definitive option for end-stage disease. It carries substantial perioperative risk, requires lifelong immunosuppression, and is limited by donor availability, so referral should happen before irreversible multiorgan dysfunction sets in [6,7]. These interventions are best understood as components of an individualized strategy in which timing is driven by how overall risk is trending, not by isolated hemodynamic deterioration. For children with severe, progressive disease despite optimized pharmacotherapy, they remain indispensable, and early referral allows appropriate selection and timely intervention, guided by continuous risk assessment rather than delayed until right ventricular failure has already reached an end-stage [6].

7. Future Perspectives

Despite real progress in pharmacotherapy, imaging, and pathophysiological understanding over the past two decades, pediatric pulmonary hypertension still carries considerable morbidity and mortality. Disease rarity and heterogeneity remain major obstacles to building robust, evidence-based algorithms, which is exactly why continued international collaboration matters so much.

Refining patient-specific risk stratification is a key direction for future work. Management has already moved toward multimodal assessment, and future studies are expected to validate comprehensive pediatric risk models across different etiological subgroups. As the conflicting PAPI findings illustrate [15,16], that validation needs to happen in adequately powered, etiologically defined cohorts before any novel parameter is recommended for routine use [6,7]. Advances in imaging are likely as well: echocardiography will stay the main modality for serial assessment, while broader use of CMR may improve evaluation of ventricular remodeling in complex cases [14]. Novel biomarkers reflecting myocardial stress, endothelial dysfunction, and inflammation (ST2, MR-proADM, kallistatin) show encouraging early results but need larger multicenter validation, most likely as part of integrated panels rather than used individually [17,18,19].

Pharmacological treatment is likely to become increasingly personalized. Recent pediatric-specific cohorts on prostanoïd dosing [22], treprostinil [23], selexipag [24], and macitentan [20] mark a broader shift toward pediatric-derived evidence instead of continued reliance on adult extrapolation, and treatment timing is likely to become just as important as which agent is chosen. Generating further high-quality pediatric evidence, through expanded registries, multicenter collaboration, and prospective studies, remains an equally important priority, alongside continued integration of multidisciplinary expertise (cardiology, pulmonology, intensive care, surgery, transplant medicine, and allied health) to address the physical, developmental, and psychosocial needs of affected children and their families.

The future of pediatric pulmonary hypertension management, then, depends less on any single transformative therapy and more on the continued refinement of comprehensive, personalized care that brings together validated risk models, targeted pharmacotherapy, and multidisciplinary expertise.

8. Discussion

Two consistent, mutually reinforcing trends run through the literature summarized in this review. First, risk in pediatric pulmonary hypertension is best captured by combining several independent data streams instead of relying on any single test. Second, treatment intensity is increasingly set by that combined risk picture rather than by diagnosis alone. This pattern holds across otherwise very different kinds of evidence: a national outcomes registry [10], single-modality prognostic studies in echocardiography [13] and cardiac magnetic resonance imaging [14], exploratory biomarker cohorts [17,18,19], and pharmacological cohort studies spanning several drug classes [20,22,23,24]. That convergence gives confidence that the shift toward multimodal, risk-guided care reflects a genuine change in the field, not an artifact of any one dataset.

At the same time, this body of evidence is not uniformly strong, and the conflicting data on the pulmonary artery pulsatility index illustrate why individual findings should not be taken at face value. The index was reported as prognostically useful in a single-center cohort of 24 children with idiopathic pulmonary arterial hypertension [15], yet a considerably larger analysis of 111 children with PAH of mixed etiology from the Dutch National Registry found no additional prognostic value for the same index [16]. This discrepancy is not an isolated anomaly but representative of a broader pattern in pediatric PH research. Most prognostic markers, and several of the treatment-outcome associations discussed in this review, rest on single-center or modestly sized multicenter cohorts, and etiological heterogeneity between cohorts can plausibly explain conflicting results even when the underlying methodology is sound. Readers should weigh each finding by its sample size and etiological composition, not simply by the direction of the reported effect. Table 3 lays this variability out explicitly.

Table 3. Key pediatric studies cited in this review, by design and evidence strength.

Study	Design (centers)	n	Population	Main result	Evidence strength
Constantine et al. (2022)	Retrospective national registry (1)	970	Mixed pediatric PH etiologies	Transplant-free survival 86.7% at 1 year, 68.6% at 10 years; prognosis varies by etiology	Moderate - large but single-center registry
Lammers et al. (2023)	Retrospective cohort	Not stated in review	Pediatric PAH	Echocardiographic RV parameters associated with adverse outcome	Moderate - single-center
Ta et al. (2023)	Retrospective (2 centers)	89	Pediatric PH undergoing CMR	Lower GFI associated with composite adverse outcome	Moderate - small, two-center
Torun et al. (2026)	Retrospective (1 center)	24	Pediatric idiopathic PAH	PAPi associated with severity	Low - very small, single-center

						and need for intervention	
Smits et al. (2024)	Retrospective national registry (1)	111		Mixed pediatric PAH	PAPi added no prognostic value beyond components	Moderate - larger, but still single-center	
Griffiths et al. (2021)	Two cohorts (cross-sectional + longitudinal)	Not stated in review		Pediatric PAH	ST2 improved REVEAL 2.0 prediction of worsening (HR 1.88→2.05)	Moderate	
Rodriguez Ogando et al. (2026)	Retrospective multicenter registry	74		Group 1 pediatric PAH	WHO-FC III/IV fell 48%→22%; NT-proBNP and 6MWD improved	Moderate - multicenter but retrospective, no comparator arm	
TOMORROW (Berger et al., 2026)	Randomized, open-label, multicenter, phase 3	148		Pediatric PAH, WHO-FC I-III	Adequate pediatric dosing confirmed; time-to-event endpoints not statistically significant	High - only randomized controlled trial in this review	
Douwes et al. (2022)	Retrospective multicenter cohort	275 (98 on parenteral therapy)		Pediatric PAH	Early, high-dose, combination parenteral therapy associated with better outcomes	Moderate - multicenter, historical cohort	
He et al. (2024)	Retrospective (1 center), reference cohort	49 (treprostinil)		Higher-risk pediatric IPA/HPAH	Improved survival and event-free survival vs oral-therapy-only reference group	Low-moderate - single-center, non-randomized comparator	
Frank et al. (2024)	Retrospective multicenter cohort	87		Pediatric PAH on selexipag	Favorable tolerability; improved PVRi/SVRi ratio in add-on group	Moderate - one of the largest multicenter cohorts, but retrospective	

Willmann et al. (2023)	Population pharmacokinetic modeling	Not a clinical outcome cohort	Pediatric PAH, age ≥ 6 years	Supports body-weight-based riociguat dosing	Low for clinical efficacy - PK modeling only, no outcome data
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A second point worth making concerns the therapeutic evidence base. Several of the more recent pharmacological cohort studies reviewed here - on parenteral prostanoid dosing thresholds, treprostinil across genetic subtypes, selexipag as both add-on and transition therapy, and macitentan across mixed etiologies - represent genuine pediatric-specific evidence rather than extrapolation from adult trials, marking measurable progress compared with the evidence base available even five years ago. Still, apart from the randomized TOMORROW trial of macitentan, none of these studies are randomized controlled trials; most rely on retrospective cohorts with historical or contemporaneous comparison groups rather than randomization. That does not diminish their clinical usefulness - for a rare disease such as pediatric PAH, well-designed observational cohorts are often the most rigorous evidence realistically available. It does mean, though, that reported associations, such as improved survival with early, high-dose, combination prostanoid therapy, are best read as strong observational signals, not confirmed causal effects.

This review has its own limitations, which should be acknowledged. As a narrative rather than a systematic review, sources were selected for relevance and recency instead of through a predefined, reproducible search protocol, and no formal risk-of-bias or quality appraisal was performed on the included studies. The search relied mainly on PubMed-indexed, English-language publications, which may have left out relevant regional cohorts or non-English pediatric PH registries. Pediatric pulmonary hypertension spans several etiological subgroups (idiopathic and heritable PAH, PAH associated with congenital heart disease, and PH associated with chronic lung or developmental disease), and because most cited studies pool or focus on only one of these subgroups, findings grouped under a single heading in this review may not generalize evenly across all pediatric PH populations. These limitations come with the territory of narrative reviews of a rare and heterogeneous disease and do not undermine the overall conclusions, but they matter for how confidently individual recommendations here should be applied to a given patient.

9. Conclusion

Pediatric pulmonary hypertension remains one of the most complex disorders in pediatric cardiology, given its heterogeneous causes, variable presentation, and progressive course during a period of active cardiopulmonary growth. Because the pediatric disease differs fundamentally from adult PH in both pathophysiology and trajectory, management strategies borrowed directly from adult evidence are often insufficient, and pediatric-specific approaches remain essential.

The evidence reviewed here points to one overarching shift: management has moved from diagnosis-based to risk-based care. No single test - clinical assessment, echocardiography, CMR, hemodynamics, or a circulating biomarker - is enough on its own. The greatest prognostic accuracy comes from integrating these domains and reassessing them longitudinally rather than only at diagnosis, which allows earlier detection of deterioration and more timely escalation of therapy. This same risk-based logic now drives pharmacological decisions as well: early, combination-based treatment targeting the nitric oxide, endothelin, and prostacyclin pathways has replaced sequential escalation held in reserve for advanced disease. Recent pediatric-specific cohorts on prostanoid dosing, treprostinil, selexipag, and macitentan, together with pediatric population pharmacokinetic modeling for riociguat and an emerging randomized trial for macitentan, are gradually closing the evidence gap that once forced near-total reliance on adult data.

As discussed in Section 8, this evidence base is still predominantly observational, unevenly validated across etiological subgroups, and occasionally contradictory, with the divergent findings on the pulmonary artery pulsatility index a case in point. These limitations do not undermine the overall direction of the field, but they do mean that individual prognostic tools and treatment associations should be applied with some awareness of how strong and generalizable their supporting evidence actually is.

On balance, current evidence supports multidimensional risk stratification as the foundation of pediatric pulmonary hypertension management, and as the most promising route toward earlier intervention and better long-term outcomes. Prospective, multicenter, pediatric-specific research is still needed to validate risk models and refine treatment recommendations.

Disclosure

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