Review Article

A Review on Safety and Efficacy of Antihypertensive Drug Used in Paediatrics

Gunwant B. Patil[1]*, Satyam Z. Chemate[2], Komal S. Baride[3], Gauri S. Borkar[4]

[2]Professor and Head of Department (Pharmaceutics), Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar 414111, Maharashtra, India.

[1,3,4]Department of Pharmaceutics, Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar 414111, Maharashtra, India.

***Corresponding author's E-mail:** gunwantpatil30@gmail.com

Received: 12-03-2023; **Revised:** 20-05-2023; **Accepted:** 26-05-2023; **Published on:** 15-06-2023.

ABSTRACT

An established graded connection between childhood hypertension and adult hypertension places adult hypertension among the main preventable causes of premature death. A parallel trend that could lead to an exponential rise in cardiovascular, cerebrovascular, and renal disasters is unfolding in developing nations, with the concurrent growth in obesity and pediatric hypertension (HTN) over the previous 10 years in wealthy nations. It is rather alarming that China and India have cumulative pediatric HTN incidence rates of 50–70% and 23%, respectively. A review of pediatric hypertension and its management is necessary to address this under-attended burning issue, which is reflected in new guidelines for detecting, evaluating, and managing hypertension in children and adolescents published in 2017. These guidelines noted a rise in pediatric HTN prevalence. Early diagnosis and treatment of HTN are crucial since it typically persists into adulthood and is a risk factor for both renal and cardiovascular disease progression. We will learn about treating pediatric HTN in this review.

Keywords: Pediatric hypertension; Hypertension management; Blood pressure, Pediatric heart failure; Treatment.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2023.v80i02.014

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v80i02.014

INTRODUCTION

Pediatric hypertension definition

The systolic or diastolic blood pressure (BP) measurements above the normal range for the subject's age, height, and sex are defined to have pediatric hypertension (HTN). Recommendations for the investigation and diagnosis of pediatric HTN were updated in the 2017 Clinical Practice Guideline for Screening and Treatment of High Blood Pressure in Children and Adolescents. Because many obese people were included in the previous reference tables, the percentile values for blood pressure staging in this study have been updated. The classification of a patient's blood pressure is advised to be done throughout several sessions because BP values can differ between visits.[1]

Typically, measurements are acquired by auscultation in the right arm of a child comfortably seated while using the appropriate size blood pressure cuff. 80% of the arm's circumference and 40% of its length should be covered by the inflatable cuff. [2] Although commonly utilized in the clinical setting, oscillometric measures are known to overestimate the patient's blood pressure.[3] As a result, increased blood pressure readings from oscillometric devices should be verified by an auscultatory blood pressure reading. Studies have shown that HTN is frequently overlooked in children, is a significant risk factor for cardiovascular and renal morbidity in children and adults, [4] and can be linked to cardiovascular morbidity throughout childhood. An accurate diagnosis of HTN is crucial.

General pediatric population

By etiology, HTN can be further categorized:

1. Essential or primary HTN, in which no underlying cause can be found. [5]

2. Secondary HTN, which has an established organic cause.

Other HTN definitions include:

- White coat HTN is elevated blood pressure during medical visits but returns to normal after resting or in non-medical settings. [6]

The reason for 32–46% of HTN referrals in primary care settings can be attributed to this phenomenon. [7, 8]

- Masked HTN is frequently observed in patients with obesity and kidney disease but is characterized by normal blood pressure during office visits but increased in the ambulatory situation. [9, 10]

For Children Aged 1<13 y	For Children Aged ≥13 y
Elevated blood pressure in children under the age of 13 ranges from the 90th to the 95th percentile or from 120/80 mmHg to the 95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/ <80 mmHg
Stage 1 HTN: _95th percentile to <95th percentile þ 12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mmHg
Stage 2 HTN: _95th percentile þ 12 mmHg, or _140/90 mmHg (whichever is lower)	Stage 2 HTN: _140/90 mmHg

Special populations

The Kidney Disease Improving Global Outcomes (KDIGO) group defines HTN in pediatric patients with chronic kidney disease (CKD) as a BP value over the 90th percentile for age, height, and sex. [12]

CAUSES

Primary hypertension

Primary hypertension is the most prevalent kind of hypertension in children and adolescents in the United States. It is most commonly seen in older children (>6 years old), has a positive family history (mother/father or grandmother/grandfather), and is linked to overweight/obesity.

Blood pressure readings cannot distinguish between primary and secondary hypertension; however, it is believed that a higher diastolic blood pressure (DBP) denotes secondary hypertension in particular, while a higher systolic blood pressure (SBP) indicates primary hypertension.

The AAP guidelines state that if a kid is overweight or obese and older than 6 years old, has a positive family history, and neither a physical exam nor a history suggests secondary hypertension, a thorough study is not required.[13]

Secondary hypertension

Compared to adults, secondary hypertension is seen more frequently in children. Therefore, secondary causes should be considered when evaluating any child with a hypertension diagnosis. The most frequent causes of hypertension are renovascular disorders and renal illnesses.

Renal illnesses comprise 34–79% of renovascular diseases and 12–13% of secondary causes. Secondary hypertension should be considered in cases of severe hypertension accompanied by end-organ damage and in children younger than 6 years old. A rate of 0.05–6% of the causes of hypertension is endocrine-related. Although they are less common than other causes, the diagnosis is crucial since the etiology of hypertension may improve with treatment. [13]

Table 1: Common conditions associated with hypertension in a pediatric population.

Renal disease	Glomerulonephritis End-stage renal disease Acute renal failure Reflux uropathy Obstructive uropathy Polycystic kidney disease Severe hydronephrosis
Cardiac	Coarctation of the aorta Mid-aortic syndrome
Vascular	Renal artery stenosis (usually secondary to fibromuscular dysplasia) Takayasu arteritis Hemolytic uremic syndrome
Malignancy	Wilm's tumor Pheochromocytoma Neuroblastoma
Medications	Pseudoephedrine Cocaine Ectasy Amphetamines NSAID Contraception pills Corticosteroids Anabolic steroids
Endocrine	Congenital adrenal hyperplasia Hyperthyroidism Hyperaldosteronism Cushing's disease
Genetic	Liddle syndrome Congenital adrenal hyperplasia Glucocorticoid remediable aldosteronism Apparent mineral corticoid excess syndrome
Other	Obesity Bronchopulmonary dysplasia Obstructive sleep apnea Pseudohyperaldosteronism Neurofibromatosis Tuberous sclerosis Prematurity or low birth weight

ETIOLOGY

Currently, essential HTN is the most prevalent kind of HTN in children, especially in boys, adolescents, and patients who had abnormal birth events, including low birth weight or premature birth.

It's interesting to note that in the 1990s, essential HTN was less prevalent in children. With the rise in obesity, this situation altered, and today, over 50% of children with HTN have essential HTN. [13] Younger individuals and those with severe HTN are more likely to experience secondary HTN.

There are numerous potential causes of secondary HTN (Table 3). An illness of the kidneys or renal artery stenosis causes 50 to 60 percent of instances of HTN. The second most frequent cause, cardiac disease, is primarily caused by coarctation of the aorta or mid-aortic syndrome. Heart problems are frequently identified in the first few months of life, and the incidence gradually declines. As a result, it is uncommon in teenagers and young adults. Endocrine reasons that are less frequently occurring (approximately 5–10%) include hyperaldosteronism, hyperthyroidism, and Cushing's syndrome.

Particularly in teens, medications can have a significant role in HTN development.

Oral contraceptives, anabolic or androgenic steroids, ADHD stimulant prescriptions, and long-term usage of non-steroidal anti-inflammatory drugs are some of these medications (NSAIDs).

Although primary HTN affects most obese patients, these patients should be checked for obstructive sleep apnea because its therapy may reduce their HTN.

Particularly in young patients with severe, difficult-to-control HTN or with a significant family history of HTN with an early start, it is vital to consider genetic or monogenic types of HTN. All variants share a common pathophysiology of sodium retention that results in a considerable reduction of serum renin, despite various potential mutations and causes.

TREATMENT OPTION

Non-pharmacological treatment option

- ***Lifestyle modification***

All patients should be allowed to make lifestyle changes, particularly patients with essential hypertension and obese children. Using the DASH diet and engaging in moderate to vigorous exercise three to five times per week are examples of modifications. [1] High intakes of fruit, vegetables, low-fat dairy products, whole grains, chicken, fish, hazelnuts, and lean meat are advised by the "Dietary Approach to Stop Hypertension" (DASH) diet. [14] Limiting salt intake and increasing olive oil consumption is essential for blood pressure management.[15]

Pharmacological treatment option

Depending on the underlying cause, antihypertensive medicines should be chosen. For instance, an ACE inhibitor (ACEi) or an angiotensin-receptor blocker (ARB) is suggested in patients with LVH, diabetes mellitus, or CKD as long as the estimated glomerular filtration rate is higher than 30 mL/min/1.73 m2. [12] Treating steroid-induced hypertension with calcium channel blockers (CCB) is common.[16]

- **When should you use pharmacological treatment?**

Pharmacologic treatment may be started if the patient has stage 2 hypertension, symptomatic hypertension, or is hypertensive despite making lifestyle changes. The lowest possible dose of a single drug should be used to begin treatment. Blood pressure readings must be taken every two to four weeks after treatment begins. If the blood pressure doesn't decrease to the desired level, the dose must be raised. Also, when increasing amounts, adverse effects should be taken into account. Evaluations every 4-6 weeks are sufficient if hypertension is controlled. A second drug is administered if the single drug is not adequate to treat hypertension. As diuretics prevent salt and water retention, they should be used as the second agent. A follow-up evaluation is carried out three to four months after the targeted blood pressure has been met.[15]

- **What drugs are used in pharmacologic treatment?**

Information on the negative consequences and long-term cardiovascular results of antihypertensives used in children is limited.[15] The American Academy of Pediatrics recommends ACE inhibitors, ARBs, long-acting calcium channel blockers, or thiazide diuretics as initial treatments for hypertension.[1] To ensure their safety, children shouldn't be given beta-blocker medications as first-line therapy. [15]

Treatment-resistant hypertension

Treatment-resistant hypertension is the continuation of hypertension while taking three or more antihypertensive medications at the highest doses. [1,17] Make sure that the prescribed doses of the medicine are followed. Therapy for secondary hypertension involves limiting salt intake, avoiding substances that may raise blood pressure, and, if necessary, determining and dealing with any underlying causes that were not previously identified. [15] Extended-release medications should be chosen for pharmacologic therapy, and the most significant dose possible should be administered without producing adverse effects. It is essential to take all medications as directed, one of which should be a diuretic. [1,14]

Table 2: Pharmacological treatment for pediatric hypertension

Mechanism	Drug	Dose	Comment
Angiotensin-Converting Enzyme Inhibitor (ACEI)	Enalapril or Lisinopril	Initial: 0.08mg/kg/day Max: 0.6mg/kg/day up to 40 mg/day	It can be used once daily or for BID. It is improbable that ARB will make kids cough. For youngsters older than 6 years, losartan has FDA approval.
	Captopril	Initial: 0.1 mg/kg dose TID Max: 2 mg/kg/dose	Contraindicated in pregnancy Side effects – Hyperkalemia, cough, decreased GFR, loss of taste.
Angiotensin-Receptor Blocker (ARB)	Losartan	Initial: 0.7mg/kg/day Max: 1.4mg/kg/day up to 100mg/day	Long-term use causes damage to the kidney and lungs.
	Valsartan	Initial: 1.3–2.7 mg/kg Max: 40 mg/kg	Side effects- Dizziness and headache, Intermediate palatability
	Irbesartan	Initial: 2 mg/kg/d Max: 75–150 mg/d	
Calcium Channel Blocker	Amlodipine	Initial: 0.1mg/kg/day Adolescents:2.5mg/day Max: 10mg/day	Once daily or BID. It may cause gingival hyperplasia, tachycardia, and edema.
	Extended-release Nifedipine	Initial: 0.25-0.5mg/kg/day Max: 3mg/kg/day up to 120mg/day	Can cause a precipitous drop in blood pressure
	Nicardipine	Initial: 0.25–0.5 mg/kg/d Max: 120 mg/d	It may cause reflex tachycardia
	Felodipine	Initial: 5mg Max: 10 mg	Adverse effects: peripheral edema, headache, flushing, tachycardia.
	Isradipine	Initial: 0.05mg/kg/dose Max: 5mg/dose	Concurrent use of azoles antifungals leads to hypotension Side effect- headache, dizziness, tachycardia
Alpha-Beta Blocker	Labetalol	Initial: 1-3mg/kg day divided BID Max: 10-12mg/kg/day up to 1200mg/day divided BID	Avoid heart failure or asthma. Heart rate is a dose-limiting factor. Avoid Insulin-dependent diabetes
Beta Blocker	Atenolol	Initial: 0.5-1mg/kg/day Max: 2mg/kg/day up to 100mg/day	Side effects- Dizziness, wheezing or trouble breathing, sleep problems.
	Esmolol	Drip: 100-300 microg/kg per min	It may cause prolonged hypotension and acute renal insufficiency.
	Metoprolol	Initial: 0.1 mg/kg dose BID Max: 1 mg/kg dose	Contraindications: in sinus bradycardia, cardiogenic shock, avoided in asthma.
	Carvedilol	Initial:0.025mg/kg/dose BID Max: 0.5 mg/kg/dose BID	
	Propranolol	Initial: 1 mg/kg/d Max: 640 mg/d	Contraindicated in asthma patients
	Acebutolol	Initial: 1.5–3 mg/kg/d Max: 5–15 mg/kg/d	Side effects- extreme fatigue, irregular breathing, swelling of face, lower legs
Central Alpha Blocker	Clonidine	Initial: 0.2mg/day divided BID Max: 2.4mg/day divided BID	Causes dry mouth or sedation. Sudden cessation of therapy can lead to severe rebound hypertension.
	Prazosin	Initial: 0.05–0.1 mg/kg/d Max: 20 mg/d	Adverse effects: Vertigo, blurred vision, depression, liver function abnormalities.
Diuretic	Hydrochlorothiazide	Initial: 1mg/kg/day Max: 3mg/kg/day up to 50mg/day	Monitor electrolytes periodically. It can be used once daily or for BID, and it can cause urinary frequency and affect the school.
	Furosemide	Initial: 0.5-2mg/kg/day Max: 6mg/kg	Contraindicated in sports person and diabetes patients
	Chlorothiazide	Initial: 10 mg/kg dose BID Max: 2 gm/day	Causes constipation, upset stomach, and decrease appetite
	Metolazone	Initial: 0.1 mg/kg BID Max: 20 mg/day	Contraindications: hypersensitivity, hepatic coma, anuria

Vasodilator	Diazoxide	2-5 mg/kg/day	Slow injection ineffective: Duration unpredictable: use with caution - it may cause rapid hypotension
	Sodium nitroprusside	0.5-10 microg/kg per min	Thiocyanate toxicity can occur with prolonged (>72 h) use or in renal failure
	Minoxidil	Initial: 0.1-0.2mg/kg/dose Max: 10 mg/dose	Long-acting, titrated slowly, a most potent vasodilator
	Hydralazine	Bolus: 0.15-0.6 mg/kg per dose Drip: 0.75-5.0microg/kg per min	Tachycardia frequent side-effect: must administer Q 4 h when given IV bolus
Aldosterone antagonist	Spironolactone	Initial: 1 mg/kg dose BID Max: 200 mg/day	Contraindicated in sports person and diabetes patients

MANAGEMENT

General Guidelines

If there are no contraindications to their usage, simultaneous quick-acting antihypertensives are used to treat a pediatric hypertensive crisis after evaluation.

The main management objectives are to lower BP and guard against end-organ dysfunction gradually. The therapeutic purpose for children and adolescents with hypertensive crises should be reducing SBP and DBP to below the 90th percentile and, in teenagers 13 years of age and older, below 130/80mm Hg.[18,19] Since sudden, severe drops in blood pressure can themselves contribute to organ damage related to ischemia, the rate of BP reduction should be 25% over 6-8 hours, which is gradually reduced to an average over 24–72 hours [20,18]

Due to the possibility of abrupt decreases in blood pressure, which are best assessed with intra-arterial blood pressure monitoring, it is significant to underline the significance of monitoring during treatment.

When utilizing medications that have the potential to produce severe hypotension, as well as when treating critically ill children, this approach is favored.

Through catheterization of the radial artery, intra-arterial blood pressure monitoring is carried out, enabling the observation of minute variations in blood pressure. [1] Although it allows for highly accurate blood pressure monitoring, it has also been linked to an increased risk of distal ischemia, vasospasm, and systemic infection—risks that can all be reduced using the right equipment. [21]

Parenteral Therapy

While hypertension urgency can be treated with either IV or rapid-acting oral antihypertensives, hypertensive emergencies require parenteral medication. Labetalol, a combination alpha and beta blocker that acts by lowering peripheral vascular resistance and by its unfavorable chronotropic effect, is one of the most frequently used first-line IV medications.

Due to the bronchoconstriction's beta-blocking effect should be avoided in people with asthma and heart failure; however, because it is hepatically metabolized, it can be used in people with renal impairment. Although it has been linked to higher rates of hypotension in this patient population, Thomas et al. have shown that concurrent traumatic brain injury can be a contraindication for labetalol. [22] Esmolol, a beta-1 blocker with a quick onset of action, is also recommended for critically ill patients with multiorgan failure. Esmolol is preferred when treating hypertensive crises that come along with congenital cardiac disease. Another first-line IV drug is nicotripine, a powerful and quick-acting calcium channel blocker (CCB) that lowers blood pressure by reducing peripheral vascular resistance. Due to the risk of thrombophlebitis with peripheral use, nicotripine is preferentially supplied by central access as either a continuous infusion or a bolus therapy. [23] Last but not least, clevidipine is an ultra-short-acting intravenous CCB with a rapid onset that causes arteriolar vasodilation and has the added benefit of a simplified dose titration due to the fast inactivation by tissue and blood esterase, but it is categorically contraindicated in patients with egg and soy allergies as well as those who have lipid disorders.[24] It little affects the heart's inotropic or chronotropic properties.

The management of hypertensive crises also uses quick-acting, efficient vasodilators. Since it is simple to titrate to prevent BP fluctuations and has a short half-life, its effects start and end quickly. Sodium nitroprusside is a first-line drug from this group having direct arterial and venous smooth muscle relaxant activities. However, it can generate methemoglobinemia, cyanide, and thiocyanate toxicities.[25]

Hydralazine, an arterial dilator employed due to its quick onset while continuous infusion with IV medications is being prepared, is another frequently used vasodilator. Hydralazine reduces systemic venous resistance in hypertensive situations by inhibiting calcium-dependent adenosine triphosphatase and phosphorylating arteriolar smooth muscle. Since hydralazine activates the RAAS pathway without having a negative inotropic effect, its antihypertensive effects may be counteracted.[26] The most popular vasodilators are hydralazine and nitroprusside, but fenoldopam is also a viable option. Along with natriuresis, fenoldopam enhances renal blood flow and urine flow through activation at the dopamine 1 receptor and a-adrenoreceptors.

In patients with concomitant renal impairment, fenoldopam can be administered safely for hypertensive crises. [27]

Enalaprilat, phenoxybenzamine, doxazosin, and furosemide are some drugs with particular uses.

Enalaprilat is the only angiotensin-converting enzyme inhibitor available in an IV formulation for high-renin hypertension. In individuals with underlying chronic kidney disease, bilateral renal artery stenosis, or single kidney, the negative consequences, which are caused by the anti-renin characteristics, range from hyperkalemia to functional acute kidney damage (AKI). [28] Similarly, catecholamine-induced hypertension caused by paragangliomas and pheochromocytomas is treated with adrenergic blockers such as doxazosin and phenoxybenzamine. [29] In contrast, loop diuretic furosemide is useful in treating children with volume-dependent hypertension, including those with oliguric AKI, glomerulonephritis, or CHF. It causes both natriuresis and diuresis. However, repeated use might cause volume depletion or hypokalemia, so serum potassium levels and hydration conditions should be periodically checked. [30]

Oral Therapy

When there is enough time to begin oral medication, hypertensive urgency is the only condition in which oral medicines can manage the hypertensive crisis. Isradipine, the widely common oral treatment, is a second-generation dihydropyridine CCB that\santagonizes L-type calcium channels, causing vasodilatation. [31]

According to research by Flynn and Warnick, isradipine helped 51.4% of individuals lower their blood pressure enough. [32] It's important to note that Miyashita et al. showed that azole antifungals are a contraindication to using isradipine. All patients investigated experienced severe hypotension due to isradipine's metabolism inhibited by CYP3A/4. [33]

Another oral antihypertensive medication that activates alpha 2-adrenergic receptors and lowers the central sympathetic tone, and results in vasodilation, is clonidine.

The significant negative side effect of clonidine is that it frequently results in rebound hypertension.[34] On the other hand, Nifedipine and minoxidil are two orally acting medications that tend to cause severe hypotension. The historically shortest-acting CCB, Nifedipine, frequently results in an unexpected drop in blood pressure, which can cause problems such as cerebral ischemia or ventricular arrhythmia.[35] Similar to minoxidil, which acts as a potassium channel opener without altering the venous circulation, it primarily induces arteriolar dilatation. Even hypertension resistant to conventional antihypertensives, such as volume hypertension in hyperhydrated dialyzed youngsters, has a highly effective BP-lowering impact.[36] Due to the effects of salt and water retention, prolonged use of minoxidil has been linked to hirsutism, severe hypotension, and a potential pericardial effusion, necessitating the administration of the diuretic furosemide.

FUTURE DRUGS

Sildenafil

One effective alternative vasodilator is sildenafil citrate, which selectively and powerfully inhibits phosphodiesterase type-5, an enzyme known to degrade cyclic guanosine monophosphate (cGMP). Sildenafil's inhibitory effects increase cGMP levels, enhancing nitric oxide-mediated vasodilation. 9 For treating PPHN, sildenafil is offered in parenteral and oral forms. [37,38]

In the current study, oral sildenafil was given in 2 mg/kg doses three times daily.

Although sildenafil is a good alternative, combining it with bosentan was helpful for neonates who did not respond to sildenafil alone.[37,39]

Sacubitril/Valsartan

The first drug in a new class of medications called angiotensin receptor neprilysin inhibitors, sacubitril/valsartan, has been approved (ARNI). The drug has FDA approval to treat people with NYHA classes II, III, or IV who have chronic heart failure with decreased ejection fraction (HFrEF). Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be replaced with sacubitril/valsartan and other conventional heart failure medications (beta-blocker, aldosterone antagonist).

Sacubitril/valsartan is available as an oral tablet in three dose strengths: sacubitril (24 mg, 49 mg, or 97 mg) and valsartan (26 mg, 51 mg, or 103 mg).

Taking sacubitril/valsartan twice daily, possibly without regard to meals, is recommended.

Adverse effects include hypotension, hyperkalemia, renal failure, cough, and angioedema.

Contraindication

- Hypersensitivity to any component of the product
- A prior history of angioedema due to an ACEI or ARB

Milrinone

In (acute heart failure) AHFS, vasoactive agents are taken as a rescue therapy to increase systemic perfusion and prevent end-organ dysfunction. These drugs enhance myocardial contractility and may increase cardiac output if administered with suitable blood pressure regulation.[40]

The most often utilized vasoactive drug in children to enhance contractility and afterload reduction by vasodilation is milrinone, a phosphodiesterase-3 inhibitor (PDEI). PDEI also promotes diastolic cardiac relaxation, reducing filling pressure, as calcium absorption is likewise cAMP-dependent. Milrinone can result in hypotension; therefore, it is possible to balance blood pressure and cardiac contractility by combining milrinone with low doses of epinephrine or dopamine. [40,41]

Levosimendan

For AHFS, levosimendan may substitute in place of milrinone. Although it is not available in the US, it is prevalent in Europe. It has a significant inotropic effect and is a calcium-sensitizing drug that binds to troponin-C, increasing its sensitivity to intracellular calcium. Moreover, it releases the ATP-dependent potassium channels, resulting in smooth muscle relaxation, vasodilation, and reduced systemic vascular resistance. Levosimendan has an enhanced cardiac output and reduced filling pressure as its hemodynamic effects. It exerts a lusitropic impact on the heart and increases contractility without increasing myocardial oxygen demand.

Levosimendan was given to pediatric patients in two groups: those who received it as a preventative measure for low cardiac output in the postoperative period [42,43] and who did not significantly benefit from it, and those with end-stage HF and inotrope dependency who received it and showed improved status in terms of their need for inotropes and length of hospital stay.[44,45] Levosimendan therapy only lasts 24 hours. Levosimendan's function in children is yet unknown, but it works well for AHFS but has little effect on HF prophylaxis. [40]

Nesiritide

Recombinant human B-type natriuretic peptide (BNP) nesiritide is the same as naturally occurring BNP. It causes vasodilation and reduces afterload by increasing intracellular cyclic GMP (cGMP). It causes diuresis and natriuresis, suppresses neurohormonal activity, and boosts cardiac output.[40,46]

Nesiritide's value in AHFS has been demonstrated in limited studies in children. [47-49] Nesiritide should be studied as an adjunctive therapy in critically sick children with biventricular dysfunction who have edema and oliguria despite receiving standard HF care, according to the pediatric ISHLT HF consensus standards [40,50]

Ivabradine

In the SHIFT and BEAUTIFUL trials, ivabradine, an If current inhibitor in the sinoatrial node helped lower adult HF hospitalization and HF-related death rates. [51] In a pediatric phase II/III dose-finding clinical trial of children with stable HF, the safety of ivabradine was confirmed. [52] Ivabradine decreased heart rate, increased systolic function, and tended to improve quality of life in this study. There was no significant difference in NT-pro BNP levels in this trial between ivabradine and placebo. Based on research in adults, a-blockers or without them, additional heart rate management in children with HF may lead to better results.[40]

Omecamtiv mecarbil

A new class of myotropic called omecamtiv mecarbil interacts specifically with the cardiac myosin protein base, allowing ADP-P release from the myosin-actin-ATP complex. This boosts the number of myosin heads that can bind to the actin filament and improves the contractility of cardiac sarcomeres. Compared to vasoactive drugs, this results in longer systole but no increase in myocyte calcium or myocardial oxygen consumption. [40,53]

There is presently no information available regarding the effectiveness of this medication in children. However, omecamtiv mecarbil may, like other medications, be a helpful substitute for improving outcomes in pediatric systolic HF. [40]

Vericiguat

The cGMP pathway has been related to cardiac and vascular smooth muscle dysfunction in HF states. It is an essential regulator of endothelial function in both primary and secondary pulmonary hypertension.[54] Vericiguat is a cGMP pathway activator that increases cGMP production without affecting endogenous nitric oxide generation by acting directly on intracellular soluble guanylyl cyclase (typically depressed in HF). Children's data are not yet available, although they appear promising, especially for bi-ventricular HF and HF-related congenital heart disease.[40]

CONCLUSIONS

Pediatric Hypertension is affecting the life of neonates/infants worldwide. There is an urgent need to develop targeted therapies for Pediatric Hypertension. A careful diagnostic evaluation should lead to the determination of the underlying cause of hypertension in most infants. Treatment decisions should be tailored to the severity of hypertension and may include intravenous or oral therapy. Most infants will resolve their hypertension over time, although some may have persistent blood pressure elevation throughout childhood.

LIST OF ABBREVIATION

ACE	Angiotensin-Converting-Enzyme
ARB	Angiotensin Receptor Blockers
HTN	Pediatric Hypertension
BP	Blood Pressure
mmHg	Millimeters of Mercury
KDIGO	Kidney Disease Improving Global Outcomes
CKD	Chronic Kidney Disease
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
AAP	American Academy of Pediatrics
ADHD	Attention Deficit Hyperactivity Disorder
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
DASH	Dietary Approach to Stop Hypertension
LVH	Left Ventricular Hypertrophy
CCB	Calcium Channel Blockers
ACEi	Angiotensin-Converting-Enzyme Inhibitors
BID	Bis In Die
FDA	Food And Drug Administration
TID	Tolerable Daily Intake
GFR	Glomerular Filtration Rate
mg	Milligram

kg	Kilogram
min	Minute
h	Hour
IV	Intravenous
RAAS	Renin-Angiotensin-Aldosterone System
AKI	Acute Kidney Injury
CHF	Congestive Heart Failure
CYP3A\4	Cytochrome P450 3A4
cGMP	Current Good Manufacturing Practice
NYHA	New York Heart Association
PPHN	Pulmonary Hypertension
PDEI	Phosphodiesterase-3 Inhibitor
cAMP	Cyclic Adenosine Monophosphate
AHSF	Acute Heart Failure
ATP	Adenosine Triphosphate
US	United States
HF	Heart Failure
BNP	B-Type Natriuretic Peptide
ISHLT	International Society for Heart and Lung Transplantation
ADP-P	(Adenosine Di-Phosphate) + Phosphate

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.