REVIEW

Pediatric Chronic Heart Failure: Age-Specific Considerations of Medical Therapy

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Summary

Chronic heart failure (CHF) is a rare entity in children but carries a burden of high mortality and morbidity. Medical treatment of pediatric CHF is largely based on guidelines for the adult population. In contrast to adults, evidence for the efficacy of medications in treating CHF in children is sparse. This may be due to the difficulty of conducting high-powered studies in children or to true differences in the mechanisms of CHF pathophysiology. Recent observations suggest that CHF in children differs from adults at the molecular and cellular levels. Different pathways are involved, leading to less fibrosis and hypertrophy than in adults, with potential implications for therapy. The main pathophysiological goals of medical treatment of pediatric CHF due to systemic left ventricular dysfunction are discussed in this review. These include preload and afterload optimization, diminishing cardiomyocyte apoptosis and necrosis as well as interstitial fibrosis, and optimizing myocardial oxygen consumption. The pediatric myocardium should be provided with optimal conditions to achieve its regenerative potential. The cornerstones of medical CHF therapy are angiotensin converting enzyme inhibitors (ACEI), beta blockers and mineralocorticoid receptor antagonists. There are potential benefits of tissue ACEI and β1-selective beta blockers in children. Angiotensin receptor blockers are an alternative to ACEI and their slightly different mechanism of action may confer certain advantages and disadvantages. Diuretics are employed to achieve a euvolemic state. Digoxin is used more frequently in children than in adults. Promising new drugs already routinely used in adults include angiotensin receptor-neprilysin inhibitors and sodium-glucose contransporter 2 inhibitors.

Key words

Pediatric heart failure • Heart failure with reduced ejection fraction (HFrEF) • ACE inhibitor • Beta blocker • Digoxin

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Introduction

Chronic heart failure (CHF) is a rare entity in children but carries a burden of high mortality and morbidity [1]. Guidelines for the medical management of CHF in children have been developed [2,3] but due to the lack of large prospective multicenter randomized controlled trials in the pediatric population, the therapy is largely based on extrapolation of results from such trials conducted in adults. It is uncertain whether the inability to prove the efficacy of HF medications in children is due to actual differences between the adult and pediatric populations or due to the challenges in designing a robust pediatric CHF study [4].

The high-level evidence coming from adult trials cannot be simply transferred to children. The pediatric CHF population is a significantly different and more heterogenous one, regarding both the spectrum of diagnoses and age-dependent pharmacokinetics and pharmacodynamics [4].

The aim of this review is to highlight the specific features of the pediatric population concerning the medications used to treat CHF. Many comprehensive reviews focused on pediatric HF including aspects such as etiology, presentation, diagnostics and treatment have been published recently [5–8]. This review's focus is pediatric CHF resulting from systemic left ventricular systolic dysfunction. Specific types of congenital heart

disease such as the failing univentricular circulation are beyond the scope of this article.

Cellular and molecular mechanisms involved in pediatric failing myocardium

During development, numerous changes take place in the physiology of myocardial contraction, both on the cellular and molecular levels. Thus, the contraction and metabolism of the immature myocardium is markedly different from that of the adult. Underdeveloped mitochondria and abundant intracellular glycogen granules in the immature cardiomyocyte result in glucose being the predominant energy source, in contrast to fatty acids in adult cardiomyocytes. Similarly, the sarcoplasmic reticulum isn't fully developed, making the immature myocardium much more dependent on extracellular calcium due to insufficient intracellular stores [9]. Changes in the expression of sarcomeric proteins also occur during development, resulting in marked alterations of functional properties, both pre- and postnatally [10,11]. In the case of myocardial pathology in pediatric CHF, age-related differences are compounded by a number of additional disorders, which together may influence the response of pediatric patients to specific medications [12,13].

Cardiac growth, differentiation, proliferation and consecutively regenerative and repair mechanisms are inversely related to the patient's age. Replication of cardiomyocytes occurs mainly during embryonic and fetal development and deceases rapidly after birth. Human infants still show some evidence of minor cardiomyocyte proliferation, which decreases during childhood to nondetectable levels in adults [14]. Typically, further cardiac enlargement occurs only by cell hypertrophy. Factors involved in the cessation of proliferation after birth include cardiomyocyte polyploidization, transition from hypoxia to hyperoxia, acquisition of endothermy, changes in intercellular interactions, hormonal regulation, and subsequent downregulation of various cell-cycle factors and upregulation of cell-cycle inhibitors [15,16]. The increase in cardiac afterload resulting from changes of circulation after birth also very likely plays a role [17].

The adaptive growth response of the cardiac muscle to increased workload changes significantly with the transition from proliferation to hypertrophy. Results from animal studies suggest that the adaptation of the neonatal heart to increased pressure load is based on transient hyperplasia followed by hypertrophy of ventricular cardiomyocytes [16]. Preserved myocardial capillarization and the absence of fibrosis are unique features of cardiomegaly induced early after birth – in contrast to the adult myocardium where fibrosis is typical [16]. Although the switch in the myocardial response to load occurs early after birth, possible residual mechanisms of hyperplasia, presumably corresponding to the rate of cardiomyocyte proliferation, should be considered in infant heart failure. Cell-based therapies aiming to utilize the regenerative mechanisms are emerging [18].

The differences in the mechanisms involved in CHF in children versus adults that are still not fully understood. Notable distinctions have been shown on the levels of hypertrophy, myocardial fibrosis and gene expression profiles. The finding that adverse remodeling does not drive disease progression in pediatric patients with dilated cardiomyopathy could be an explanation why standard adult CHF medications don't work so well in children [19,20]. These drugs primarily target mechanisms of pathological remodeling (hypertrophy and fibrosis) that appear to be much less involved in the pathophysiology of heart failure in children than in adults.

The pathways dysregulated in the pediatric heart are distinct from those regulated in the adult failing heart (Table 1). Pediatric failing heart is maintained in an undifferentiated state unlike the adult heart that shows activation of the innate immune system, fatty acid and oxidative metabolism [19]. Dysregulation of both matrix metalloproteinases responsible for breakdown of extra-cellular matrix and their tissue inhibitors of leads to fibrosis in adults, whereas increased expression of MMP-2 in pediatric hearts could be a compensatory reaction to increased profibrotic stimuli and could account for the reduced fibrotic phenotype in children [20]. Differences between certain microRNAs expression have been suggested to play a role in better tolerability and outcomes with posphodiesterase-3 inhibition (treatment by milrinone) in children than in adults [21]. It would seem that pediatric age-specific mechanisms need to be focused on. However, which of the differences presented might be appropriate therapeutic targets remains to be clarified.

Striking differences in adrenoreceptor regulation have also been pointed out. Probably most significant is the fact that both β1- and β2-ARs are down-regulated in children with CHF, whereas β2-AR expression is preserved in adults [22]. This has potential therapeutic implications already, as discussed in the section on beta blockers.

Table 1. Distinct features of adult and pediatric heart failure. Data derived mainly from dilated cardiomyopathy [19–22].

Adults	Children
No cardiomyocyte proliferation	Some cardiomyocyte proliferation and highest regeneration potential in children < 1 year
Adverse remodeling	
Cardiomyocyte hypertrophy	Minimal cardiomyocyte hypertrophy
Myocardial fibrosis (interstitial and perivascular)	Minimal fibrosis (both interstitial and perivascular)
↔ coronary microvascular density	↑ coronary microvascular density
Molecular changes and gene expression	
↑ oxidative reduction, inflammation, fatty acid metabolism	↑ cell adhesion, ion and transmembrane transport, visual perception
Fibrosis-related: ↓ MMP-9, TIMP-3	Fibrosis-related: ↑ MMP-2, TIMP-2
↓ regulation of β1-AR	↓ regulation of both β1-AR and β2-AR
↓ regulation of connexin43	↑ regulation of connexin43
↑ phosphatase expression	↔ phosphatase expression
↓ phosphorylation of phospholamban	↔ phosphorylation of phospholamban
MicroRNAs involved: let-7, miR-1, miR-133a/b, miR-100, miR-195, miR-199, miR-214, miR-222, miR-23a/b, miR-29a/b, miR-30 family, miR-320	MicroRNAs involved: miR-130b, miR-204, miR-331-3p, miR-188-5p, miR-1281, miR-572, miR-765, miR-223, miR-125a-3p and miR-1268

β1-AR, β1-adrenoreceptor; β2-AR, β2-adrenoreceptor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases.

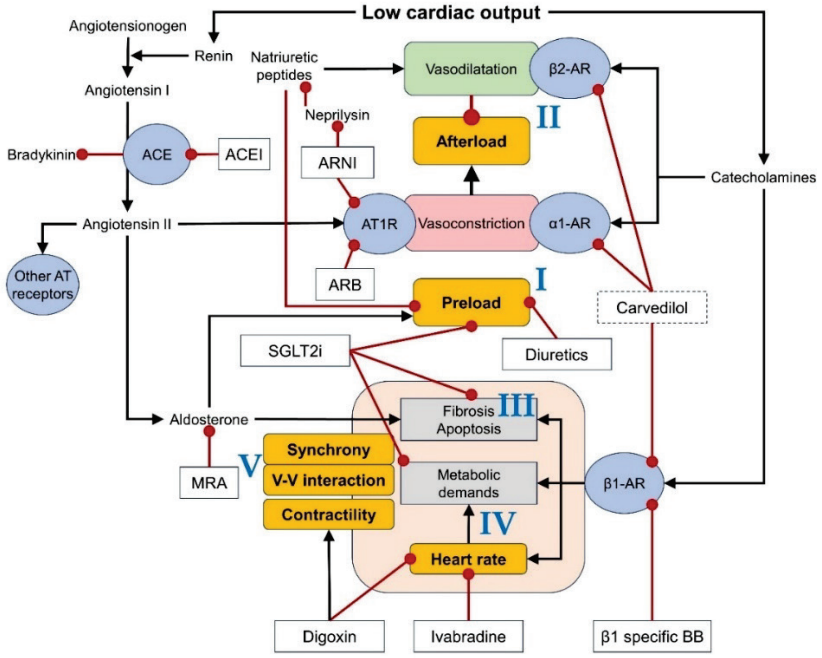

Fig. 1. Pathophysiology of pediatric chronic heart failure due to systemic left ventricular dysfunction and main targets for therapy:
I – Preload optimization, achieving normovolemia; **II** – Afterload reduction, ideally while preserving β2-adrenoreceptor function; **III** – Diminishing cardiomyocyte apoptosis and necrosis, and myocardial interstitial fibrosis; **IV** – Heart rate reduction to improve myocardial metabolic demands; **V** – Maintaining or re-establishing synchrony and taking into account the ventriculo-ventricular interaction (non-pharmacologic therapies). Determinants of cardiac output are shown in orange.
ACE, angiotensin converting enzyme; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor – neprilysin inhibitor; AT1R, angiotensin II receptor type 1; α1-AR, α1-adrenoreceptor; BB, beta blocker; β1-AR, β1-adrenoreceptor; β2-AR, β2-adrenoreceptor; MRA, mineralocorticoid receptor antagonist; SGL2i, sodium-glucose contransporter 2 inhibitor; V-V interaction, ventriculo-ventricular interaction.

Pathophysiology and therapeutic strategy in pediatric chronic heart failure

Cardiac output is determined by preload, afterload, myocardial contractility and synchrony, heart rate, and ventriculo-ventricular interaction [23]. Heart failure can be caused by pathologies of one or more of these factors. Correction of the underlying condition should always be the primary objective in children. However, if the cause of CHF cannot be eliminated, medical treatment is indicated to mitigate or reverse the pathophysiological consequences of CHF, increase the quality of life and prolong survival.

Low cardiac output leads to decreased renal perfusion and activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. This is beneficial in an acute setting, but chronic stimulation ultimately leads to progressive impairment of cardiac function. Catecholamine release causes vasoconstriction, decreases kidney perfusion and induces the production of renin, and conversion of angiotensin I to angiotensin II. Angiotensin II further exacerbates vasoconstriction and additionally stimulates aldosterone secretion by constriction renal afferent arterioles, increasing sodium and water reabsorption. High afterload due to vasoconstriction results in loss of functional cardiomyocytes and pathological myocardial remodeling, which further exacerbates cardiac dysfunction and ultimately leads to decompensation. Catecholamines contribute to myocardial apoptosis mainly through the activation of β1-adrenoreceptors (β1-AR), also negatively affecting myocardial metabolism and increasing oxygen and energy consumption [24]. Natriuretic peptides partially mitigate these negative consequences, attenuating cardiac remodeling, apoptosis, hypertrophy, and fibrosis, as well as decreasing renin and aldosterone production [25]. The main pathophysiological mechanisms of CHF and the points of pharmacological interventions are summarized in Figure 1.

The general goals of pediatric CHF therapy should be: I) preload optimization by achieving normovolemia (reducing congestion but avoiding intravascular volume depletion); II) afterload reduction without jeopardizing the coronary perfusion; III) diminishing cardiomyocyte apoptosis and necrosis as well as interstitial fibrosis; IV) optimizing myocardial oxygen consumption (particularly by heart rate reduction); V) re-establishing myocardial synchrony as well as ventriculo-ventricular interaction (non-pharmacological therapies), and VI) allowing time to establish repair mechanisms [23,26].

Heart rate reduction to the lowest effective level should be one of the main goals of CHF therapy [23]. Heart rate is inversely related to average life span in most organisms and negative effects of elevated heart rate include increased ventricular work, myocardial oxygen consumption, endothelial stress, arterial stiffness, and decreased myocardial oxygen supply [27]. Association of elevated resting heart rate with increased mortality has been shown both in adults [28] and children [29] with cardiovascular disease. Similarly, heart rate reduction was associated with improved outcomes in both populations [30,31]. Reducing the heart rate per se is probably more important than the specific drug used to achieve it (beta blockers, ivabradine, digoxin).

Reversible pulmonary artery banding in young children with dilated cardiomyopathy and preserved right ventricular function is also a novel strategy to improve ventriculo-ventricular interaction and left ventricular function [32,33]. This procedure utilizes the fact that the ability of each ventricle to eject blood is largely dependent on the function of the other ventricle and the position of the interventricular septum. The main effects or pulmonary artery banding in this setting include: 1) increase in right ventricular wall stress enhancing contractility due to the Anrep effect, 2) leftward shift of the interventricular septum that contributes to restoration of an ellipsoidal shape of the left ventricle, and 3) reduction in left ventricular preload and end-diastolic pressure, with subsequent optimization of the Frank–Starling curve and left ventricular diastolic and systolic function. Additionally, myocardial sensing apparatus might translate the mechanical stress stimulus into the activation of regulatory pathways of cardiomyocyte proliferation and regeneration [34]. The method shows encouraging results and may be an effective alternative to mechanical support or transplantation in selected infants. However, the selection of optimal candidates, timing and delicate setting of banding tightness remains a challenge. The banding may later be dilated using a catheter procedure depending on other findings.

Chronic heart failure medications

According to the guidelines for adults, every patient with heart failure and reduced ejection fraction should be treated with a combination of 4 drugs: 1) a drug

Table 2. Drugs commonly used to treat pediatric chronic heart failure.

Drug	Usual starting dose	Usual target dose	Dosing interval
Angiotensin converting enzyme inhibitors (ACEI)			
Captopril*	0.3 mg/kg/day	0.5 mg/kg/day in newborns 1-2 mg/kg/day in older children	Three times daily
Enalapril	0.1 mg/kg/day	0.2 – 0.4 mg/kg/day	Twice daily
Lisinopril	0.05 mg/kg/day	0.2 – 0.4 mg/kg/day	Once daily
Ramipril*	0.05 mg/kg/day	0.1 – 0.2 mg/kg/day	Once or twice daily
Angiotensin receptor blockers (ARB)			
Losartan	0.5 mg/kg/day	1 – 2 mg/kg/day	Once daily
Angiotensin receptor-neprilysin inhibitor (ARNI)			
Sacubitril-valsartan	1.6 – 3.2 mg/kg/day†	4.6 – 6.2 mg/kg/day†	Twice daily
Mineralocorticoid receptor antagonists (MRA)			
Spironolactone	1 – 2 mg/kg/day	1 – 3 mg/kg/day	One to three times daily
Beta blockers (BB)			
β-1 selective			
Metoprolol	0.2 – 0.4 mg/kg/day	1 – 2 mg/kg/day	Once or twice daily
Bisoprolol*	0.05 mg/kg/day	0.2 – 0.3 mg/kg/day	Once daily
Nonselective with α-blocking effect			
Carvedilol*	0.1 mg/kg/day	0.8 – 1 mg/kg/day ‡	Twice daily
Diuretics			
Furosemide	1 – 4 mg/kg/day	taper after other medications are set if tolerated	One to three times daily
Hydrochlorothiazide	1 – 3 mg/kg/day	taper after other medications are set if tolerated	Once or twice daily
Cardiac glycosides			
Digoxin	0.005 – 0.01 mg/kg/day §	Target trough level 0.5 – 0.9 ng/ml	Once or twice daily
Pacemaker current (I_f) inhibitor			
Ivabradine	0.1 mg/kg/day	0.1 – 0.3 mg/kg/day	Twice daily
Sodium-Glucose Co-transporter 2 (SGLT2) inhibitors			
Dapagliflozin	0.1 – 0.2 mg/kg/day (max 10mg)	0.1 – 0.2 mg/kg/day (max 10mg)	Once daily

* preferred agents (explained in the text in greater detail), † the total dose of sacubitril and valsartan summed, ‡ target dose may be up to 3 mg/kg/day in infants [69], § newborns may require lower doses and infants higher doses

interfering with the renin-angiotensin system (an angiotensin converting enzyme inhibitor – ACEI, an angiotensin receptor blocker – ARB, or an angiotensin-neprilysin inhibitor – ARNI), 2) a beta blocker (BB), 3) a mineralocorticoid receptor antagonist (MRA) and 4) a sodium-glucose cotransporter 2 inhibitor (SGLT2i) [35-37]. Diuretics are indicated to achieve euvolemic state as needed and relieve symptoms. Other medications with weaker evidence used in specific indications include ivabradine, digoxin, and an oral soluble guanylate cyclase stimulator vericiguat [35,36]. Mechanisms of action are summarized in Figure 1. Commonly used specific drugs, including their dosing, are summarized in Table 2.

The perspective on these drug classes in children is discussed in the following sections. The suggestions are based on the medications' impact on the pathophysiology of heart failure rather than evidence-based outcomes which are scarce. For each class, we discuss which specific drugs might be especially advantageous for the pediatric population.

Medications influencing the renin-angiotensin-aldosterone system

Angiotensin converting enzyme inhibitors (ACEI)

Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II has potent vasoconstrictor effects and also stimulates growth factors that regulate endothelial, cardiomyocyte, and fibroblast growth, development, and function, leading to myocardial hypertrophy and fibrosis [38]. ACE also inactivates bradykinin, a peptide with vasodilatory and natriuretic effects. ACE inhibition diminishes the deleterious effects of angiotensin II and also promotes the vasodilatory and vasoprotective effects of bradykinin.

Recommendations for the use of ACEI for children with left ventricular dysfunction are unequivocal [3]. The safety profile of ACEI in children is favorable, and probably similar to that seen in adults. Although they are usually well tolerated, side effects include hypotension, renal dysfunction, hyperkalemia, cough and angioedema [38] and seem to be largely independent of a specific ACEI. Because of the risk of renal dysfunction is higher in patients with lower cardiac output, ACEI should be started at a low dose and up-titrated. The pathophysiology of ACEI-induced cough is not completely clear, but it is usually attributed to an increased concentration of bradykinin [39].

In most pediatric trials, captopril and enalapril have been studied [38]. Captopril and enalapril are still currently the most widely used ACEI, although there is significant variability between centers [40]. Short-acting serum ACEI may be preferred in neonates, whose glomerular filtration rate is lower and the risk of renal dysfunction higher. However, a question arises whether another ACEI would be preferable in older children [23].

ACEI can be classified into tissue-affinity or serum-affinity groups, defined mainly by their lipophilicity. It has been hypothesized that that tissue ACEI might have a higher cardioprotective effect because of better tissue penetration [26,41]. However, there are studies that do not support such hypothesis [42,43]. Still, this factor may be taken into account when deciding for a specific ACEI. Fosinopril and quinapril are the ACEIs with highest tissue affinity, followed by Ramipril. Enalapril, captopril and lisinopril are at the opposite end of the spectrum [42,44].

The duration of action of different ACEI and the resulting dosing interval is another deciding factor. The recommended dosing interval for patients with CHF is usually three times daily for captopril, twice daily for enalapril, and once daily for lisinopril. Ramipril can be given once or twice daily [35,37]. It is worth noting that trough–peak ratios are quite similar for enalapril, lisinopril and ramipril [44]. Although there are some suggestions that twice-daily administration of long-acting ACEI might have advantages [45], no robust evidence supports this [46]. Especially in infants, once-daily dosing might decrease the risk of renal side effects. Experience with long-acting ACEI in children is based mainly on the hypertensive population, published results showing good tolerance of lisinopril from infant age [47] and ramipril from the age of 2 years [48].

To summarize, the optimal ACEI for children should be long-acting to allow once-daily dosing and should have high tissue activity [26]. In patients beyond newborn age, ramipril might be the drug to meet these requirements.

Angiotensin receptor blockers (ARB)

Inhibition of AT1 receptors to angiotensin II is a mechanism employed by angiotensin receptor blockers (ABR). Placing the blockade further downstream in the renin-angiotensin-aldosterone system has similar effects (as outlined in Figure 1), however, there are two major differences [49].

By keeping the ACE active, bradykinin

accumulation does not occur and the side effects of angioedema or cough are usually avoided. However, the positive effects specific to ACE inhibition are also lost. Besides the beneficial vascular effects of increased bradykinin concentration, these include increased nitric oxide bioavailability and decrease in von Willenbrand factor [49]. Greater anti-inflammatory effects of ACEI versus ARB have been pointed out [50].

The second difference relates to the concentration of angiotensin II. Chronic blockade of AT1 receptors by ARB induces an increase in plasma angiotensin II and results in overstimulation of its other available receptors (AT2 and AT4 receptors). AT1 receptors mediate the primary undesirable effects of angiotensin II. The role of AT2 receptors has been understood as a mechanism to counterbalance the pathological processes (preventing inflammation, apoptosis, fibrosis; and promoting NO-dependent vasodilation), their stimulation in the setting of ARB treatment potentially reaching or even exceeding the additional favorable effects of ACEI [51]. However, animal experiments focusing on them have produced conflicting results [49]. Therefore, the fact whether the effects of AT2 and AT4 receptors are rather beneficial or deleterious in heart failure is a matter of debate. Little is known about developmental changes in the types of angiotensin II receptors, except that AT2 receptors are abundant during the fetal period and decline rapidly after birth [51].

In adults with CHF and reduced ejection fraction, ARB have been reported to be similarly effective as ACEI [52]. However, as opposed to ACEI, no study has been able to show a reduction in all-cause mortality associated with ARB [37]. Direct comparisons between the two groups are missing and there are concerns about whether ARB achieve as high cardiovascular protection as ACEI [49].

The combination of ACEI and ARB therapy has also been investigated in adults with CHF. The addition of ARB to ACEI therapy has been shown to provide some benefits, but there are concerns about adverse effects especially regarding the combination with other high-evidence CHF medications [53,54]. Thus, the combination of ACEI and ARB is not typically used.

Little is known about differences between adults and children in this regard. The effects of both ACEI and ARB have their own distinct specifics, and whether one group has a clear benefit over the other remains to be clarified both in adults and children.

At present, ARB are usually reserved for children who do not tolerate ACEI, as in adults. They are generally considered effective and safe alternatives alternative to ACEI and were mostly tested in children above 1 year of age [55]. Losartan is the most commonly used ARB in children and is administered once daily.

Angiotensin receptor-neprilysin inhibitor (ARNI)

Sacubitril/valsartan is a new drug with a unique mechanism of action, inhibiting neprilysin in addition to being an AT1 receptor blocker. Neprilysin is an enzyme whose main role is the breakdown of natriuretic peptides. Its inhibition therefore results in an increase in the concentration of natriuretic peptides, enhancing their cardiovascular beneficial effects, particularly vasodilation and natriuresis [56].

The superiority of sacubitril/valsartan to ACEI was demonstrated in adults with CHF and reduced ejection fraction [57]. A similar study was designed in children but the results have not been published yet [58]. Sacubitril/valsartan was approved for children with CHF from 1 year of age based on partial data from this study and the results from the adult population.

Mineralocorticoid receptor antagonists (MRA)

Mineralocorticoid receptor antagonists block the renin-angiotensin-aldosterone system on the level of aldosterone receptors in renal distal tubules. In addition to preventing the long-term deleterious effects of aldo-sterone on the heart, they act as potassium-sparing diuretics, increasing sodium excretion and potassium reabsorption. However, they have only modest diuretic effect, are generally well tolerated, and have little or no chronic effect on blood pressure [8].

It has been shown that aldosterone levels are only transiently depressed by the use of ACEI in patients with CHF [59]. The additive beneficial effect of MRA on survival was clearly shown in adults with CHF and reduced ejection fraction who were already treated by ACEI [60]. Hence the recommendations to add a MRA to ACEI treatment for both adults and children [3]. There is pediatric experience with both spironolactone [61] and eplerenone [62].

Beta blockers (BB)

Beta blockers antagonize the deleterious effects of chronic sympathetic myocardial activation and can reverse pathologic left ventricular remodeling. Recom-

mendations for the treatment of heart failure with reduced ejection fraction by BB in adults [35,37] are based on the results of many large trials that have shown reductions in mortality and morbidity as well as symptom relief. Metoprolol, bisoprolol and carvedilol have been tested [63–65]. In children, only studies with carvedilol have been performed, retrospective studies suggesting that carvedilol improves ejection fraction and symptoms [66]. However, the only prospective randomized trial with carvedilol in children failed to demonstrate these benefits [67].

β1-adrenoreceptors (β1-AR) have been traditionally understood as the "cardiotoxic" subtype whereas the β2-adrenoreceptors (β2-AR) as "cardio-protective" [68]. This perspective is based on the fact that most of the undesirable effects of catecholamines on the heart (increase in heart rate, energy consumption, arrhythmogenesis, pro-apoptotic effects) are mediated by β1-AR, while β2-AR mediate beneficial cardiovascular effects (vasodilation and subsequent reduction of blood pressure, anti-apoptotic signaling). Although this relationship is not as black and white and a more complex cross-talk takes place between receptors' effects, most evidence suggests that β1-AR are more closely coupled to cardiotoxic pathways [68]. Differences regarding the response of beta receptors to CHF have been shown between adults and children. These differences include the down-regulation of both β1-AR and β2-AR in children, whereas β2-AR expression is maintained in adults. Stimulation of α1-AR is clearly undesirable as they cause vasoconstriction and subsequently increase afterload.

Carvedilol is a non-selective BB (antagonizing both β1-AR and β2-AR) with an additional α-blocking effect. Alpha-blockade confers the additional advantageous effect of reducing afterload. An unequivocal benefit in CHF treatment has been demonstrated in adults, as with β1-selective BB (metoprolol and bisoprolol). There may be numerous reasons why the same effect has not been demonstrated in children. One possible explanation relates to the design of the study – factors such as low power, heterogeneous population, high placebo effect, and a high proportion of very young children in whom much higher doses are required to achieve the same exposure to carvedilol as in adults [69]. However, another explanation is that in children the positive effects (α-blockade) may not outweigh the potential negative effects (β2-blockade). Thus, some authors have suggested a selective β1-blocker should be more beneficial in children than carvedilol [23,26]. Studies performed in a mouse model of cardiomyopathy would suggest the same. Selective β1-blockade was effective both in young and adult mice, whereas nonselective beta blockade was only effective in adult mice [70].

There is experience with both carvedilol and bisoprolol in pediatrics. The need for an inverse age-dependent increase in carvedilol doses, especially because of faster elimination in infants, has been pointed out previously [69,71]. Bisoprolol is not as widely used, but good tolerability has been described even in infants [26,72].

The importance of selective targeting of individual adrenergic receptors in children with CHF remains to be seen. At present, it is not clear whether any one BB is preferable to another. The choice of a particular drug may depend on individual patient factors. A failing heart should certainly not be burdened by high blood pressure, and a patient prone to hypertension will certainly benefit from the additional afterload reduction provided by carvedilol. In contrast, a patient with poor tolerance to CHF therapy and a tendency to hypotension may benefit more from selective β1-blockade. Taking into account the differences in β-AR expression in children and adults, preference should rather be given to β1-selective beta blockers, especially in patients with dilated cardiomyopathy on whom the research has been mainly focused.

Diuretics

Loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransporter in the loop of Henle, increasing the renal excretion of sodium chloride, potassium, and water. They should be used in acute HF to achieve a euvolemic state. However, long-term treatment with diuretics can be detrimental because of further stimulation of the neurohumoral axis by intravascular volume depletion [26]. Indications for treatment of pediatric CHF with diuretics should therefore be strict and efforts should be made to discontinue diuretic therapy in those patients in whom it is possible. Especially in the context of other modern drugs that promote diuresis and natriuresis (such as ARNI and SGLT2i), the need for chronic diuretic treatment is diminishing.

Digoxin

Digoxin is the most relevant drug from the group of cardiac glycosides. Its mechanism of action is the inhibition of Na^+/K^+ ATPase, which is involved in the exchange of intracellular sodium for extracellular potassium during the repolarization phase of the cardiac cycle. This results in an increase in intracellular calcium stores by a sodium-calcium exchange mechanism and subsequent increase in cardiac contractility. Another effect is the slowing of sinus rhythm and prolonging of atrioventricular nodal conduction [73]. The combination of inotropic and bradycardic action is unique for digoxin compared to all other sympathomimetic inotropes that cause tachycardia [73].

Digoxin has a very narrow therapeutic range with a risk of intoxication. The target level is 0.5 – 0.9 ng/ml [3,35], with the risk of adverse effects increasing at levels above 1.2 ng/ml [74]. Digoxin has numerous drug interactions, with its levels increasing, for example, with concomitant use of carvedilol or amiodarone. The toxicity presents with inappetence, nausea, and arrhythmias – in children usually sinus bradycardia or atrioventricular blockade, tachyarrhythmias are rare in contrast to adults [73].

In children, moreover, the pharmacokinetics of digoxin depend on age. Therefore, age-dependent dosing is necessary in addition to monitoring of plasma concentrations. Digoxin is excreted by the kidneys. Neonates require lower doses due to renal functional immaturity [73,75]. Infants, on the other hand, require increased doses due to their larger distribution area and higher clearance of digoxin [75].

Digoxin played an essential role in CHF treatment for centuries. Recently, however, it has been sidelined by more modern drugs, which have been clearly shown to reduce mortality in large studies in adults. This has not been demonstrated with digoxin, with some studies even suggesting increased mortality and risk of arrhythmias associated with it [76,77]. There are many factors to consider, such as the greater morbidity of patients treated with digoxin at baseline or the substantial concentration dependence of the beneficial and adverse effects of digoxin. Although the benefits of digoxin in adults are unclear, a meta-analysis suggests that digoxin reduces the risk of hospitalization and improves symptoms [78]. In children with CHF, there are only few small studies in patients with left to right shunts showing conflicting results [73]. However, there are reports emerging that digoxin decreases interstage mortality in patients with congenital heart disease with single ventricle physiology [79,80]. Hence, it is possible that certain specific groups of patients will benefit from digoxin treatment more than others.

To summarize, digoxin should be used cautiously at low levels (serum concentrations of 0.5 – 0.9 ng/mL), with careful use in patients with renal dysfunction, or in combination with medications that can alter digoxin levels [3,6]. Current guidelines recommend digoxin as a second-line drug reserved for children with CHF who remain symptomatic despite being treated by the higher-evidence medications [3].

Available data suggest that digoxin is still very widely used in children in current clinical practice [73,81]. We believe as well that digoxin still has a role in the treatment of pediatric CHF. Re-emphasizing the importance of heart rate reduction, digoxin's unique effect combines it with an enhancement of cardiac contraction. For certain patients at least, this effect can be highly beneficial.

Ivabradine

Ivabradine reduces heart rate via inhibiting the funny channels in the sinoatrial node, reducing the inward funny current (I_f) and slowing phase-4 repolarization of the pacemaker cells [82]. The importance of heart rate reduction has already been discussed above. The advantage of ivabradine is its heart rate-reducing effect is reasonably specific, having almost no other cardiovascular effects.

Ivabradine is a second-line drug in pediatric CHF therapy used to further reduce heart rate when it remains elevated despite BB treatment. The safety has been validated in children with CHF [83]. Ivabradine effectively reduced heart rate and increased ejection fraction of the left ventricle in this study.

Sodium-Glucose Co-transporter 2 inhibitors (SGLT2i)

Gliflozins act as inhibitors of the sodium-glucose co-transporter 2 (SGLT2) in the proximal tubule of the kidney. Their primary role has been as antidiabetic agents as they increase glucose excretion and thus improve glycemic control. A reduction of heart failure-related events has been observed in patients treated by SGLT2i and a clear survival benefit has

been later confirmed in patients with CHF, regardless of their ejection fraction and regardless of the presence of diabetes [84,85].

Although the exact mechanism of improving CHF by SGLT2 inhibition is uncertain, there are numerous proposed beneficial effects of SGLT2i. Diuresis and natriuresis are associated with glucose excretion. However, no concomitant activation of the renin-angiotensin-aldosterone system occurs, a unique feature that is clearly desirable in CHF [86]. Other beneficial effects on the heart are both direct and indirect. Direct mechanisms include anti-apoptotic effects, reduced oxidative stress and inflammation, improved ion handling and improved cardiac energy metabolism. Indirect effects include the decrease in ventricular filling pressures, decrease in afterload, improved vascular function, erythropoiesis, and improved renal function [87].

First clinical experience in children with CHF is emerging. SGLT2i appear to be well-tolerated, in a small study no patients experienced symptomatic hypoglycemia or hypovolemia and there were no clinically significant changes in blood chemistries or vital signs after initiation of dapagliflozin [88]. An improvement in ejection fraction was observed. However, urinary tract infection is a possible complication, especially in small children.

Given the numerous beneficial systemic effects of SGLT2i as well as direct effects on myocardial metabolism, it can be expected that at least some of these effects will be pronounced in children. We believe it is reasonable to consider treatment with a SGLT2i in children with severe CHF, with the threshold for the use of this medication decreasing with the patient's age.

Other new drugs

Omecamtiv mecarbil is a selective activator of cardiac myosin. It augments the speed of ATP hydrolysis, increasing the number of myosin heads binding to actin and thus increasing the contractile force. The duration of systole is increased but calcium cycling and energy consumption remains unchanged [89]. In adults with HF with reduced ejection fraction, benefits have been reported, particularly in patients with severely impaired ejection fraction [90]. However, The US Food and Drug Administration (FDA) has declined to approve omecamtiv mecarbil for treatment of adults with chronic heart failure with reduced ejection fraction recently, citing a lack of evidence on efficacy. No data is available in children.

Vericiguat is a soluble guanylate cyclase stimulator. Its mechanism of action involves the enhancement of the cGMP pathway stimulation and direct increase of endogenous nitric oxide. Benefits have been demonstrated in symptomatic adults with HF with reduced ejection fraction [91]. No data are currently available in children but there is a dedicated clinical trial in children with CHF in progress.

Initiation and escalation of pediatric CHF treatment

A stepwise approach to treat pediatric patients with CHF has been suggested both in the guidelines [2,3] and more recent reviews [7]. A suggested approach is summarized in Figure 2.

The therapy is usually initiated with an ACEI, and a MRA is added either upfront or depending on the next development. Target doses of these drugs can be reached relatively quickly. Alternatives to ACEI are either ARB or ARNI. ARNI instead of ACEI can be used in patients with insufficient response to ACEI treatment or upfront based on clinical decision (heart failure severity). Beta blockers are usually reserved for patients with more severe findings or symptoms, should be started at low dose, up-titrated more slowly and carefully and not always well-tolerated [7]. The selectivity of various BB to adrenergic receptors and advantages of selective β1-blockade should be taken into account.

The importance of heart rate reduction should be stressed and digoxin or ivabradine can be added if insufficient heart rate reduction is achieved with BB.

SGLT2 inhibitors proved to be very useful drugs with numerous beneficial effects in all types of CHF in adults and can be initiated at the target dose without the need of up-titration. They may be considered in older children.

When the target doses are reached, diuretic therapy should be reduced or discontinued, if possible, to avoid undesirable hypovolemia.

Conclusion

Medical treatment of pediatric chronic heart failure is largely based on guidelines for the adult population. In contrast to adults, evidence for the efficacy of medications in treating CHF in

children is very sparse. This may be due to the difficulty of conducting high-powered studies in children or to true differences in the mechanisms of CHF pathophysiology in children. Recent observations suggest that CHF in children differs from adults at the molecular and cellular levels. In order to improve the outcomes of pediatric CHF, it may be necessary to focus on certain pathways and pathophysiological mechanisms specific to children.

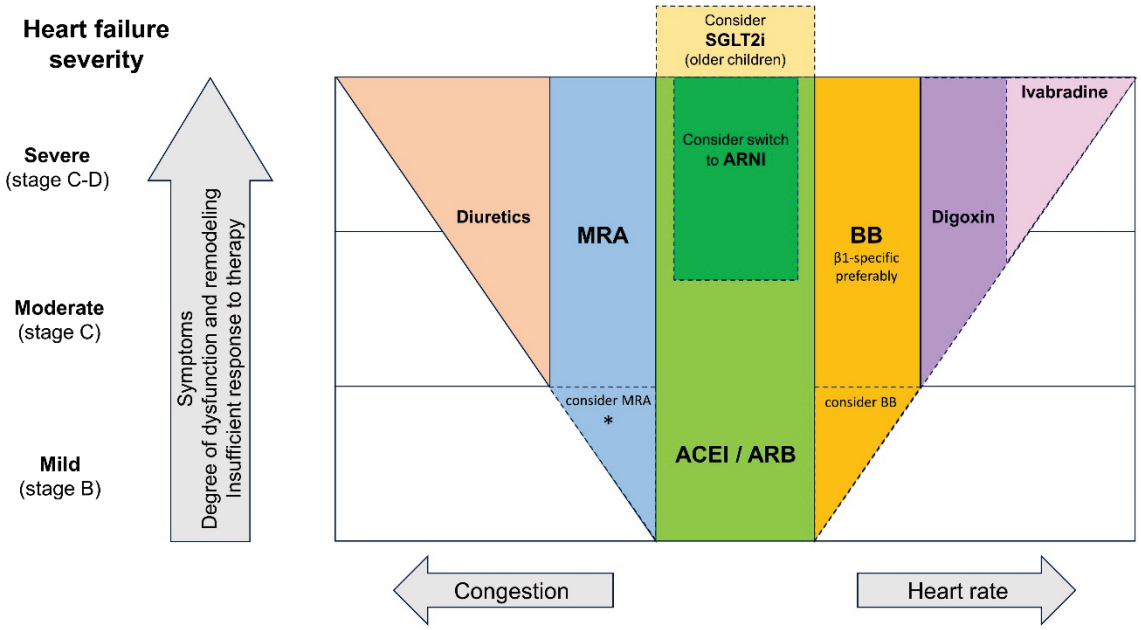

Fig. 2. Stepwise approach to treatment of pediatric chronic heart failure due to systemic left ventricular dysfunction. Created mainly based on [2,7,23,26]. Heart failure staging according to [35].
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor – neprilysin inhibitor; BB, beta blocker; MRA, mineralocorticoid receptor antagonist; SGL2i, sodium-glucose contransporter 2 inhibitor, * especially in cases of fibrosis

A stepwise approach to introducing medication is usually used. The cornerstones of pediatric CHF treatment are ACE inhibitors, beta blockers and mineralocorticoid receptor antagonists. There are potential benefits of tissue ACEI and β1-selective BB. Angiotensin receptor blockers are an alternative to ACEI and their slightly different mechanism of action may confer certain advantages or disadvantages, the significance of which is not entirely clear. Diuretics are employed to achieve a euvolemic state. Digoxin is used more frequently in children than in adults. Elevated heart rate should be reduced effectively according to the patient's tolerance. The exact role of newer drugs such as ARNI (sacubitril-valsartan), ivabradine and SGLT2 inhibitors has yet to be established.

Abbreviations

ACE, angiotensin converting enzyme; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor – neprilysin inhibitor; AT1R, angiotensin II receptor type 1; α1-AR, α1-adrenoreceptor; BB, beta blocker; β1-AR, β1-adrenoreceptor; β2-AR, β2-adrenoreceptor; BB, beta blocker; MRA, mineralocorticoid receptor antagonist; SGL2i, sodium-glucose contransporter 2 inhibitor; V-V interaction, ventriculo-ventricular interaction.

Conflict of Interest

The author received fees from Novartis for participation in clinical trials and lecture activities.

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