

Clinical practice

Heart failure in children. Part II: current maintenance therapy and new therapeutic approaches

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Abstract The current maintenance treatment for children with heart failure remains controversial: To a large extent, it is based on extrapolation of data derived from trials in adult populations. There are only a few randomized trials focused on the treatment of children with cardiac disease, especially in the subgroup with cardiomyopathy and heart failure. The goals of therapy are to maintain circulatory and end-organ function and to allow for recovery and reverse remodeling to occur. When maintenance therapy fails and medical treatment does not result in clinical improvement, the alternative of device therapy must be considered: In that case, the usual aim is to stabilize circulatory status, as a bridge to either recovery or to cardiac transplantation. Recently, carefully selected patients with electromechanical dyssynchrony of ventricular systolic function have demonstrated a benefit from biventricular pacing devices (cardiac resynchronization therapy), with improved functional capacity and quality of life and, in some patients, avoidance of the need for transplantation.

Keywords Congestive heart failure · Cardiomyopathy · Heart transplant · Therapeutics

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Introduction

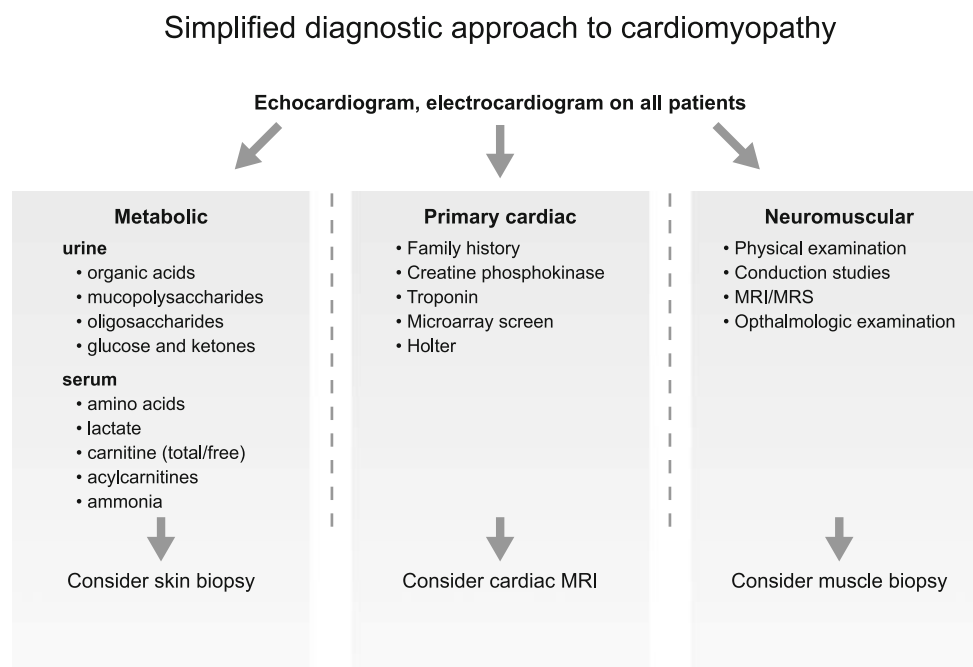
In the previous part of this clinical practice paper on the heart failure in children, we focused on the diagnosis, assessment, and acute medical treatment of children presenting with decompensated heart failure. In this part, we will focus on the maintenance medical treatment options available and discuss when device therapy or cardiac transplantation is indicated.

Prior to the introduction of therapy, the underlying diagnosis must be considered. It has been noted that the probability of attaining a specific diagnosis in any given case of cardiomyopathy is rather low, typically of the order of around 30%. A brief approach to the diagnostic workup is indicated in Fig. 1, with the more complete recommendations detailed in Table 3 (electronic supplement to part I). The tests are used to exclude known etiologies of cardiomyopathy once a patient has been stabilized and also those that are useful in determining the prognosis in any given patient.

Maintenance medical therapy

After initial stabilization and acute treatment, the selection and introduction of appropriate maintenance therapy for infants and children with heart failure is controversial, due to a lack of randomized trials in children for most medications. Nevertheless, a series of large multicenter randomized clinical trials conducted in adults with heart failure have shown unequivocally that medical therapy is able to reduce cardiovascular mortality (Fig. 2). Confronted with this powerful evidence of benefit, most practitioners in the field of pediatric heart failure have extrapolated this benefit to children. The evidence that this actually translates

Fig. 1 The aim of the initial testing is to determine the presenting anatomic and physiologic phenotype of the cardiomyopathy (dilated, hypertrophic, restrictive, LV noncompaction, or another form). Particular attention should be paid to the presenting cardiac rhythm. Additional screening tests are set out in three broad etiologic categories, for ease of understanding, although there is overlap between these categories. The reader is referred to Table 3 in the electronic supplement for a more complete overview of screening and diagnostic tests currently used by most institutions



into survival benefit is, however, limited to single center retrospective studies with no placebo control. We will review the theoretical and practical considerations associated with these major medical therapies.

Digoxin

The prototypical cardiac glycoside, well known for its mild inotropic and other effects and used since the eighteenth century, had remained the mainstay of treatment choices for heart failure for almost 200 years. In the 1990s, the data

from the Digoxin Investigators Group (DIG) trial [1] on 3,782 patients over 3 years indicated only a modest reduction on mortality and then only in those with serum digoxin levels below 1 nmol/L. The use of digoxin in long-term therapy was subsequently demonstrated to be of marginal benefit in males and again only at lower dosing ranges [2]. The results of this and other trials in the 1990s have discouraged the use of digoxin, especially since higher serum levels appeared to have a worse associated outcome in the DIG trial. Our own institutional preference has therefore been to avoid the use of digoxin except in situations where ventricular rate control is required, aiming for serum levels in the 0.5–0.9-nmol/L range (see Table 4, electronic supplement to part I).

Angiotensin-converting enzyme inhibitors

This class of agents, the angiotensin-converting enzyme inhibitors (ACEi; represented most frequently by captopril, enalapril, or lisinopril and more recently by the tissue specific ACEi agents ramipril and perindopril), has been available for 25 years. A large body of evidence and experience supports their use in almost all heart failure situations. There are likely several pathways for the class effect of these drugs, but the predominant benefit is thought to be due to a reduction in circulating angiotensin II levels, with a drop in systemic vascular resistance. The experience with these agents in pediatric heart failure has been summarized comprehensively elsewhere [26]. Our institutional practice is to initiate ACEi therapy with an age appropriate preparation (based on dosing flexibility and the need for uptitration) beginning with either captopril

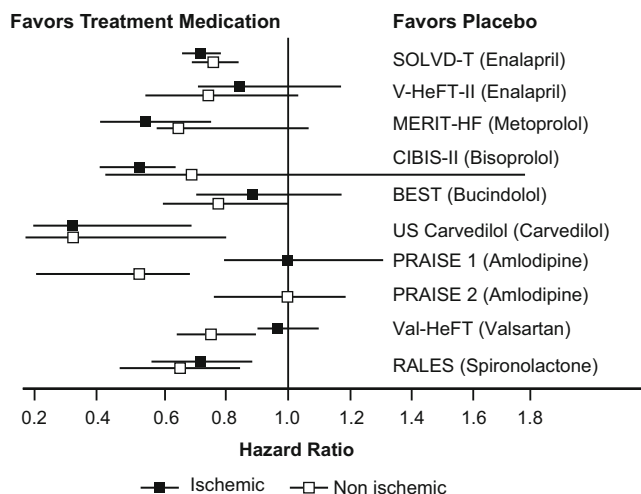


Fig. 2 A graphic depiction of the hazard ratios associated with some of the major heart failure drug treatment trials of the last 20 years. The outcome is all-cause cardiovascular mortality, and the bars indicate the 95% confidence interval of the effect of the agent vs. placebo in both ischemic and nonischemic etiologies of cardiomyopathy

(0.2 mg/kg/dose q8h, titrating up to 1 mg/kg/dose) or enalapril (0.1 mg/kg/dose, titrating to 0.3 mg/kg/dose q12h). Patients with heart failure require an initial observed smaller test dose (see Table 4, electronic supplement) in most cases, and uptitration typically proceeds over the period of 3–9 days as an inpatient or 2–4 weeks as an outpatient. During this phase, close attention is paid to diuretic requirements, renal function indices, and blood pressure. In our experience, only a small minority of patients, typically very young or premature neonates, are truly intolerant of ACEi following transition from a parenteral inotropic vasodilator; however, the transition does need to be carefully managed. We therefore advise caution with the use of ACEi in neonates, especially in the first 4 weeks of life, as renal insufficiency may easily be precipitated. There is continued interest in “tissue ACEi specific” agents. These drugs (ramipril and perindopril being the most popular) may have a more advantageous effect in regards to the myocardial benefits of ACE inhibition [12]. Perindopril in particular is reported to have less of a first-dose hypotensive effect, with a slow onset of action. We use the latter agent drugs as second-line drugs in general, although there has been evidence motivating for their primary usage in special circumstances [10].

Beta-Adrenergic receptor antagonists

If the use of ACEi has garnered widespread support, the use of beta-adrenergic receptor antagonists (BB) has remained controversial though widely practiced [27]. This is because the published experience of BB use in children with heart failure is much less robust and has not yet proven conclusive. There is good evidence that those who can tolerate the reduction in heart rate and blood pressure will show an improvement in echocardiographic indices. However, this has not been clearly associated with overall functional status improvement [28]. Our institutional experience suggests that there is a marginal survival benefit for patients receiving beta-blocker therapy at 24 months after initiation of treatment but that this does not continue out to 5 years post diagnosis [19].

Our approach has been to adopt the use of BB in patients who have at least moderate systolic dysfunction and to use carvedilol as our default choice. We commence dosing at 0.05 mg/kg/dose q12h doubling every 2 weeks to 0.5 mg/kg/dose q12h. For children under the age of 4, q8h dosing has been recommended. Alternatives include metoprolol (0.25–2.0 mg/kg/day) or another cardioselective agent in circumstances where systolic blood pressure is low or heart rate control is a primary goal of therapy. We have found that both agents are generally well tolerated, except in the setting of end-stage left ventricular (LV) dysfunction. Careful uptitration is required, usually on a one to two

weekly basis. Our approach to the transition from parenteral to oral therapy is illustrated in Fig. 3.

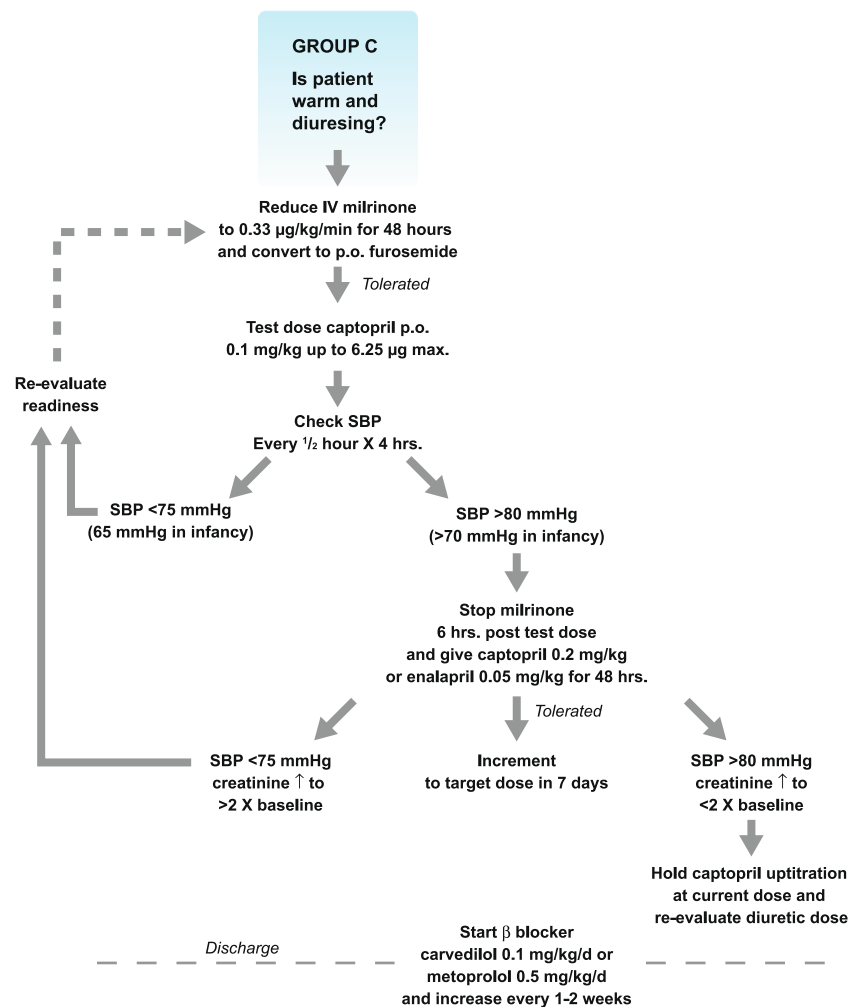
Diuretics

Diuretic therapy, considered a *sine qua non* in heart failure management, deserves further mention as a maintenance therapy. Once achieved, euvolemic status may be maintained by oral diuretic therapy if necessary; however, overdiuresis makes the introduction of ACEi and BB considerably more challenging and may lead to intolerance of the latter. We use loop diuretics (furosemide 0.5–2 mg/kg intravenously q6–12 h) initially and attempt to wean to oral therapy and completely off where feasible, relying on appropriate fluid restriction in preference. An exception would be in the hospitalized infant with high caloric requirements for growth. Any patient who remains on diuretic therapy should also remain on ACEi to counteract the effects of renin elevation that inevitably follows the initiation of diuretics. Multiple diuretic agents have an occasional role in maintaining urine output in a refractory heart failure patient, and in this setting, we have found metolazone (0.1 mg/kg q12h) to be the most useful adjunct to a loop diuretic (see Table 4, electronic supplement), although extremely potent. Cautious monitoring of hydration, renal function, and electrolytes with appropriate dosage adjustment is necessary when using this combination. Hypokalemia is common with loop diuretic usage and may be reduced somewhat by the logical addition of spironolactone. Additional complications of long-term diuretic therapy may become evident after several months, including hyponatremia, nephrocalcinosis (typically due to furosemide), hypomagnesemia, and occasionally hearing impairment due to ototoxicity associated with high-dose parenteral furosemide.

Aldosterone antagonists

Spironolactone, an aldosterone antagonist (or eplerenone, an available parenteral analog), has become popular in recent years to reduce the profibrotic effects of aldosterone on the heart [20, 36]. We have reserved this as an ancillary agent for advanced heart failure, for patients already on maximal dosing of conventional agents, but still requiring furosemide on an ongoing basis. We believe that this will target those patients who are likely to have the highest aldosterone levels. A logical case can, however, be made for the routine use of aldosterone antagonists in all patients on ACEi, due to the likelihood that renin and aldosterone levels will be broadly elevated and that secondary myocardial fibrosis can be reduced [25]. Dosing is 0.5–2.0 mg/kg q12h. Caution is required to avoid the problems of secondary hyperkalemia (especially in combination with

Fig. 3 The transition of parenteral to oral medical therapy in inpatients with acute management of decompensated heart failure (continued from part I; Fig. 3). This figure continues with the pathway of management for patients who are to be weaned from IV vasodilators and have oral maintenance therapy initiated. Note that some patients will not successfully tolerate introduction of captopril or enalapril. In some of these, milrinone may need to be restarted (*dashed arrow*). SBP systolic blood pressure



ACEi) and gynecomastia in males (an infrequent but nonreversible complication).

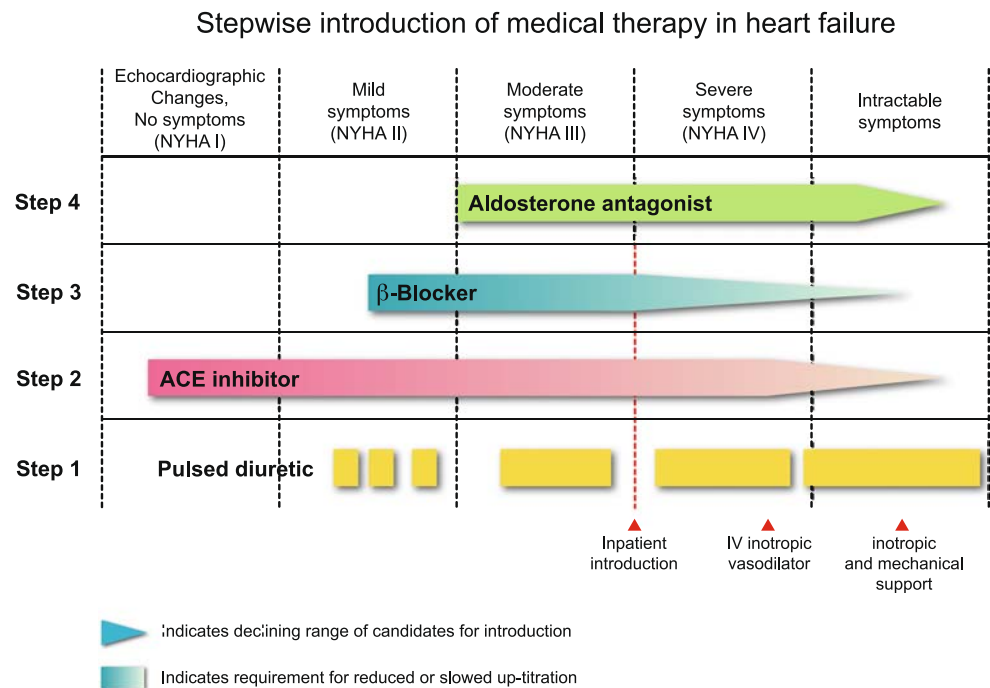
A full discussion of the numerous ancillary cofactors and other biological agents that have been suggested for various forms of dilated cardiomyopathy is beyond the scope of this practice review. These would include L-carnitine, dichloroacetate, coenzyme Q10, and other antioxidant compounds including vitamins (targeting mitochondrial electron transport and fatty acid oxidation disorders [8, 31]), coenzyme Q10 or its analog idebenone (for Friedreich's ataxia (FA)-related cardiomyopathy [33]), and of course specific enzyme replacement therapies which are available for Fabry disease [17] and Pompe disease [21]. There is no compelling evidence that any of these agents have a primary beneficial role in maintenance therapy for idiopathic dilated cardiomyopathy. We currently support the concurrent use of idebenone in FA for neurologic benefit although confirmation of any substantial benefit to the outcome of hypertrophic cardiomyopathy is still awaited. We have not endorsed its use in other conditions like the

dystrophin mutation cardiomyopathies, as this requires further investigation.

Which drug for which patient?

A consensus approach to the initiation of medical therapy is outlined in Fig. 4. The implication is that initiation of therapy takes time and that not all drugs are introduced simultaneously. In our experience, the initial introduction of therapy is best achieved as an inpatient in any child with active symptoms, and the supervision of a pediatric cardiologist is strongly advised. We suggest the use of diuretics primarily for symptom control and attempt to wean them when at all possible. We use ACEi in all patients with evidence of ventricular remodeling or reduced ejection fraction (EF). Beta-adrenoceptor blockers appear to have a benefit in some children, and they are added in patients who have symptoms or an ejection fraction of less than 40% in our institution. We reserve the use of spironolactone for those patients who have advanced

Fig. 4 The introduction of oral maintenance therapy in chronic heart failure. This indicates an approach based on patient symptoms. *Lighter shading* indicates the possibility of a lower target dose, or slower increment than usual, due to advanced heart failure with severely compromised systolic function. *Narrowing of the bars* indicates the possibility that fewer patients will tolerate the introduction of that agent at that given symptomatic stage. Note the preferred use of pulsed diuretic therapy, which becomes less likely as symptoms advance. *Red arrows* indicate the point at which additional support therapies may be required. *Red hatched line* indicates the threshold for admission to inpatient treatment in most circumstances



symptoms or severely decreased function (defined as an EF of less than 30% in our institution). As will be noted, we do not have any standard indications for digoxin. The use of systemic anticoagulation remains controversial: Current recommendations are again consensus based, and in our practice, we will initiate systemic anticoagulation with either coumadin or a heparin derivative in all children with an ejection fraction of less than 20% and in those with restrictive cardiomyopathy (regardless of ejection fraction). LV noncompaction cardiomyopathy appears to have a higher than expected incidence of thromboembolism in adults, but this has not been borne out in children as yet.

Device therapy options

Several different devices are currently used in the treatment of heart failure in children. These serve different purposes such as alleviating symptoms, treating underlying mechanisms like electromechanical dyssynchrony, reducing the risk of fatal arrhythmia, or bridging children to transplantation with circulatory support.

Positive pressure ventilatory assistance

Noninvasive positive pressure ventilation, especially the use of continuous positive airway pressure ventilation (CPAP), has been used to alleviate signs and symptoms of respiratory distress due to cardiogenic pulmonary edema [34]. CPAP prevents alveolar collapse and helps redistribute lung fluid,

reducing systemic venous return and decreasing left ventricular afterload [32], primarily through improved pulmonary compliance and reduced work of breathing. Its use may avert the need for endotracheal intubation, thus preventing respiratory complications. The exact indications in pediatric heart failure are not yet clearly defined. The authors' practice is to use this modality in patients in heart failure with non-hypercapnic respiratory distress: Theoretically, the patient most likely to benefit should not have restrictive or preload dependent LV physiology. When introduced and titrated carefully in an inpatient setting, this can be effective and achieve medium-term palliation of symptoms. Obstructive sleep apnea/hypopnea syndrome is clearly more common in adults with heart failure than in the general population, and effective long-term treatment with CPAP appears to lower mortality. The role for CPAP in the long-term management of pediatric cardiomyopathy and heart failure is currently being studied. We currently maintain a high index of suspicion for the presence of sleep-disordered breathing syndromes in all patients, including infants, and will treat this aggressively when it is confirmed by polysomnography.

Biventricular pacing

Electromechanical dyssynchrony can be present in pediatric heart disease in a number of conditions [13, 22]. Incoordinate electrical activation results in incoordinate mechanical activation and inefficient contraction. Resynchronization of electrical activity (cardiac resynchronization therapy, CRT) can improve cardiac function in well-selected patients [18]. In adult heart failure, resynchroniza-

tion therapy has been proven to be useful in cardiomyopathy patients not responding to optimal medical therapy, with wide QRS complex (>120 ms) due to left bundle branch block and low EF ($<35\%$). In pediatric and congenital heart disease, this is a rather unusual finding, and application of these adult criteria for resynchronization therapy may not be adequate [7]. There is still limited experience with CRT in children, but retrospective multicenter studies [9] do show an improvement in ejection fraction in selected patients. A significant proportion of pediatric patients studied to date have already had a single site pacing system in place, however. The second group with a favorable response are patients with systemic right ventricles with right bundle branch block and systemic ventricular failure [7].

In dilated or other cardiomyopathies, there is evidence that mechanical systolic dyssynchrony can readily be identified [13] and not necessarily have a wide QRS complex on the surface ECG. This may reflect regional differences in myocardial deformation (strain), and whether this is reversible by the use of CRT is debatable. In our own experience, the simple presence of systolic mechanical dyssynchrony determined by echocardiography did not independently constitute a risk factor for death or transplantation in patients with dilated cardiomyopathy [13].

Overall, the evidence to support the use of CRT in pediatric practice remains sparse: In our institution, the use of CRT is typically restricted to patients with clear electrical dyssynchrony (in the form of left bundle branch block), with the recognized adult criteria of effort associated dyspnea at rest or with minor activity (New York Heart Association Class III–IV functional status) and left ventricular ejection fraction $<35\%$ applied as well. This remains a very promising therapeutic modality, with indications in a few selected patients at present.

Mechanical circulatory support

If ordinary resuscitative measures show no sign of reestablishing adequate perfusion within 5 min, surgical services are alerted, and attention is turned to establishing mechanical circulatory support, typically through one or other extracorporeal method initially. In some settings, transvascular supplemental arterial flow of up to 3 L/min can be achieved temporarily through one of two percutaneous axial flow catheter devices now available in North America and Europe [5, 29] (Tandem Heart, Impella). These miniaturized percutaneous catheter-mounted axial flow devices have a low profile, making them appealing for short-term use in those with a minimum weight of around 25 kg. In general, however, urgent salvage of a patient has been achieved by either extracorporeal membrane oxygenation (ECMO) or one of several extracorporeal trans-

vascular centrifugal pump systems which are applied percutaneously (Bio-pump, Bio-medicus, or Levitronix Centrimag), which do not have an oxygenator.

ECMO has been more widely used and is also the traditional first option in the setting of cardiopulmonary arrest as stand-by primed ECMO systems have become available. ECMO is best suited to emergency perioperative salvage or to situations where short-time support is expected to be sufficient because recovery of function is likely. For those patients requiring a long-term mechanical support to bridge to cardiac transplantation, ventricular assist devices are being used with increasing frequency. These devices can offer univentricular or biventricular circuit support. Many different systems, incorporating an initially implantable centrifugal flow design (Thoratec) and later an axial flow design (Heartmate II, DeBakey Micromed, Jarvik 2000), have been introduced. The paracorporeal pulsatile pneumatic thin membrane systems (the MEDOS-HIA [23] and the EXCOR or Berlin Heart [14]) are available for use in children, with other miniaturized third generation devices in the preclinical design phase [11]. The interested reader is referred to a more detailed recent review of the history of ventricular assist device (VAD) devices and support [3].

Initial data from the North American Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [15, 16] suggest a benefit for continuous axial flow devices over pulsatile/centrifugal flow devices when applied for long-term salvage or bridging to definitive therapy: The availability of such continuous flow devices for children is, however, currently limited to those above 40 kg in weight. Long-term VAD support has become a reality for some patients in a society where the resource of donor hearts is scarce. A recent landmark trial, the Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure trial, has indicated that this is a potentially viable strategy for some adult patients [24, 30]. The application of VADs as a long term or “destination therapy” has yet to gain acceptance, however, in the pediatric heart failure arena. More attractive is the concept that a VAD may actually be a bridge to recovery. This is not a novel concept, as ECMO has been effectively used for just this purpose for decades. However, a recent report from the Harefield group [4] in the UK suggested that the application of an implantable VAD, together with the administration of a medical protocol, including the novel β_2 agonist clenbuterol, resulted in a reversal of remodeling and recovery of function in a majority of patients with dilated cardiomyopathy in their prospective single center experience. A multicenter trial in the USA and UK is currently under way to determine whether this can be recapitulated.

Complications of a VAD or ECMO can be devastating: They include bleeding, thromboembolic events, and infec-

tion. Theoretical benefits include survival rates to transplant that will range up to 80%. Once stabilized, a VAD should allow the child to be weaned from mechanical ventilation and to be mobilized out of the intensive care unit on relatively lower levels of anticoagulation. This is an unequivocal advantage for transplant preparation. Further, there are a percentage of patients in whom myocardial function will recover with ventricular rest and appropriate supportive therapy [4]

Surgical options and cardiac transplantation

The overall goal in the treatment of heart failure is the prevention of myocardial damage. For certain congenital lesions like aortic stenosis/insufficiency, this requires correct timing of surgery before irreversible ventricular remodeling and myocardial damage has occurred. Traditionally, the presence of ventricular dilatation with symptoms has dictated the need for surgical intervention, for most congenital lesions. With improving results, a trend toward early surgical intervention in the first year of life has become the default option in most centers. In specific cases where heart failure is adjudged to have resulted from severe valvular regurgitation, with relatively preserved ventricular function, valvular repair or even replacement may be indicated. There is limited experience with mitral valvuloplasty in the setting of dilated cardiomyopathy with mitral regurgitation; however, good outcomes, with a reduction in symptoms, have been reported [35]. The latest techniques (for percutaneous pulmonary valvular replacement and VSD device occlusion) illustrate how a significant number of corrective interventions will be performed in the catheter laboratory in the future.

When medical therapy fails, intractable heart failure symptoms are present, and corrective surgery is not feasible; then, cardiac transplantation is the only remaining option. With pulmonary vascular disease and extreme sensitization to human leukocyte antigens being virtually the only absolute contraindications to transplantation [6], optimal timing and candidate selection become crucial. The underlying basis for choosing transplantation is generally whether patient quality of life and longevity would be substantially improved and lengthened. Advances in technique, monitoring, and immunosuppression have lengthened the transplant half-life (the time at which 50% of the recipients remain alive) over the last 10 years. This currently is 11.3 years for those transplanted as teenagers while it is 15.8 years for those transplanted as infants, as reported in 2008 by the International Society for Heart and Lung Transplantation (ISHLT). For infants who survive the first year following transplantation, actuarial survival is still only 68% at 18 years posttransplant.

The data of the ISHLT registry also show an improved early (1 year) survival for all age groups in the more recent era of transplantation, averaging 80% in children and 90% in infants. Problems after transplant remain and will remain, however, with gradual long-term survival attrition still evident (infants being the possible exception to this). Systemic viral infections (CMV, EBV, adenovirus), acute cellular rejection, allograft vasculopathy with graft failure, renal dysfunction, hypertension, and malignancy (chiefly posttransplant lymphoproliferative disorders) are the major complications in children, and nonadherence to medication is the number one hazard in adolescent patients.

Conclusion

Management of heart failure in the adult setting has evolved into a subspecialty area within cardiology, and a similar trend is emerging in larger pediatric centers. The impetus for this is the recognition of the interdisciplinary needs of these patients, and the intensity of outpatient and inpatient care required. We support this approach and have developed comprehensive protocols for assessment and care of these patients.

We would stress, however, that the attainment of successful outcomes is not usually achieved by an inflexible or formulaic approach to children with heart failure. With considerable effort, incremental improvements to the current challenges of unraveling molecular triggers to dilated cardiomyopathy and improving short-term survival are possible.

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