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Original Article

Epidemiology and cost of heart failure in children*

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Abstract Heart failure in children is a complex disease process, which can occur secondary to a variety of aetiologies, including CHD, cardiomyopathy, or acquired conditions as well. Although the overall incidence of disease is low, the associated morbidity and mortality are high. Mortality may have decreased slightly over the last decade, and this is likely due to our ability to shepherd patients through longer periods of significant morbidity, with lasting effects. Costs of heart failure are significant – on the order of $1 billion annually as hospital charges for inpatient admissions alone. The value, or benefit to patient life and quality of life at this cost, is not well delineated. Further research is needed to optimise not only outcomes for these patients but also the high costs associated with them.

Keywords: Heart failure; cardiomyopathy; epidemiology; outcomes; costs; value

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Case presentation: LM, a 6-month-old daughter to new parents, had been struggling at home for the last few weeks with cough, congestion, and poor weight gain. She was initially diagnosed with an upper respiratory tract viral infection, but given the duration of symptoms and progressive difficulties with breathing, her parents brought her to the emergency department. On physical examination, she was afebrile and normotensive, but demonstrated tachypnoea and increased work of breathing. Cardiac examination revealed a new gallop, and the liver edge was palpated 3 cm below the costal margin. Her chest x-ray demonstrated cardiomegaly and pulmonary oedema. The cardiology department was consulted, and a bedside ultrasound demonstrated severe left ventricular dilation and dysfunction. Laboratory analyses were consistent with compensated metabolic acidosis, with significantly elevated B-type natriuretic peptide levels. She was transferred to the Cardiac Intensive Care Unit, where she became rapidly hypotensive with progressive acidosis. Inotropic support was initiated, but she eventually required intubation and paralysis to lower her oxygen demands. Although further investigation about the aetiology of her newly identified heart failure was pursued, possible next steps for management, including mechanical circulatory support, transplantation evaluation, or aggressive medical treatment, were discussed with the family. An inquisitive medical student helping to care for the patient asked the attending cardiologist, "I know the patient's life is paramount, but how much will all of this cost? And how much will it help?".

With increasing recognition of heart failure in the paediatric setting over the last 2 decades, cases like this are seemingly more common. Heart failure, regardless of the underlying aetiology, is commonly defined as a clinical and pathophysiological syndrome defined by impairment of ventricular filling or ejection of blood, leading to inadequate end-organ perfusion.[1] In children, heart failure can present as respiratory distress, easy fatigability, poor tolerance to exercise, or arrested growth and development, and is ultimately associated with substantial morbidity and mortality.[2–6] Among adults in the United States of America, the prevalence of heart failure is expected to rise from over 5 to 8 million adults, with annual costs of care growing to almost $70 billion by 2030 (Fig 1).[7,8] The prevalence and associated cost

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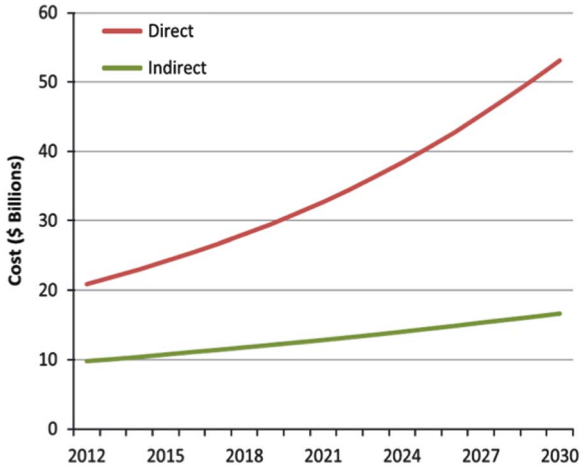


Figure 1.
The projected increase in direct and indirect costs attributable to heart failure from 2012 to 2030 is displayed. Direct costs – cost of medical care – are expected to increase at a faster rate than indirect costs because of lost productivity and early mortality. Reproduced from Heidenreich et al.[8]

burden of paediatric heart failure are largely unknown, although strides have been made to better characterise the underlying disease processes and their management. This article will review the epidemiology of paediatric heart failure and describe common diagnoses, treatment approaches, and costs associated with paediatric heart failure.

Epidemiology

In the United States of America and other western countries, the majority of heart failure in adults can be traced to ischaemic heart disease and hypertension, driven by the rise in obesity, insulin resistance, and associated heightened inflammatory states.[9] On the other hand, unlike what is seen in adults, heart failure in paediatric settings can arise from a myriad of different underlying aetiologies, with variable prognoses and outcomes. These include CHD, cardiomyopathies, rhythm disorders, as well as acquired heart disease, due to myocarditis, Kawasaki disease, or secondary to chemotherapies for oncological processes.[10,11]

CHD

CHD is likely the predominant underlying aetiology of heart failure in children worldwide. Of the ~14,000 hospitalisations related to heart failure annually in American children, 65% are associated with CHD.[5] Similarly, ~50% of admissions for heart failure in a tertiary-care paediatric hospital in Belgium was attributed to CHD.[12] There are numerous types of CHD that can lead to heart failure, ranging from "simple" lesions such as ventricular septal defects to more "complex" conditions such as hypoplastic left heart syndrome. Although cases of CHD are often combined together to present data on overall outcomes, the occurrence, natural history, and prognosis can all vary depending on the underlying congenital lesion leading to heart failure – for example, surgical correction of a septal defect can be curative, with resolution of heart failure in these patients, whereas patients with complex congenital lesions often receive only palliative treatments or surgeries, and thus develop chronic, and progressive, heart failure. Indeed, ~10–14% of single ventricle admissions are complicated by heart failure, and many of these patients may go on to require mechanical circulatory support and/or heart transplantation.[13] Of note, most types of CHD are diagnosed during infancy, thus accounting for the higher percentage of heart failure admissions among children <1 year of age, ~55–60%.[5]

Cardiomyopathies

Cardiomyopathies, representing another diverse group of possible aetiologies for heart failure, can be categorised as primary or acquired. The overall incidence of primary cardiomyopathies in children is an estimated 1.13–1.24 cases per 100,000, although not all of these patients will have heart failure. The greatest incidence of cardiomyopathy was observed in infants <1 year of age, with 8.34 and 7.84 cases per 100,000 infants.[14,15] Data on the incidence of heart failure in paediatric cardiomyopathy are limited. A study from the United Kingdom demonstrated an incidence of new-onset heart failure of 0.87 per 100,000 in patients younger than 16 years of age diagnosed with cardiomyopathy, inclusive of dilated cardiomyopathy, hypertrophic cardiomyopathy, and secondary causes such as myocarditis, anthracycline exposure, and arrhythmia.[16] Importantly, not all children with cardiomyopathy will develop heart failure by the time of diagnosis. Depending on the underlying condition, the prevalence of heart failure can range significantly – for example, 71% of children with dilated cardiomyopathy present with heart failure, compared with only 13% of those with hypertrophic cardiomyopathy.[17]

Dilated cardiomyopathy

Dilated cardiomyopathy is the most common cardiomyopathy diagnosed in childhood and leading indication for paediatric heart transplantation.[18] The incidence of dilated cardiomyopathy has been reported as 0.57–0.76 per 100,000;[14–16] these incidences likely underestimate the true burden of disease, given that many patients with dilated cardiomyopathy may go unrecognised until later in the disease course.

The aetiology of dilated cardiomyopathy is somewhat diverse. In one study from the Pediatric Cardiomyopathy Registry, when a cause of dilated cardiomyopathy was found, myocarditis (46%) was the most common aetiology, followed by neuromuscular disease (26%); however, the majority of cases were without an identifiable diagnosis and deemed idiopathic (66%).[17] Inherited disorders such as familial cardiomyopathy and inborn errors of metabolism comprised a small percentage of dilated cardiomyopathy cases, 4 and 3% of all cases, respectively.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is one of the most common of all inherited heart defects, with ~1 in 500 individuals living with the disease in the United States of America; however, many patients remain unaware of their disease.[19] In one study, 26% of the patients with hypertrophic cardiomyopathy had a known cause, roughly equally distributed among malformation syndromes, inborn errors of metabolism, and neuromuscular disorders. Unlike dilated cardiomyopathy, in which most patients present with heart failure, only 13% of hypertrophic cardiomyopathy cases develop heart failure by the time of diagnosis.[20]

Other cardiomyopathies

Restrictive cardiomyopathy, either pure (two-thirds) or mixed (one-thirds) with hypertrophic features, accounted for <5% of cardiomyopathies in the Pediatric Cardiomyopathy Registry.[21] The Australian registry found an overall incidence of restrictive cardiomyopathy of 0.03 cases per 100,000 children.[15] Heart failure can also occur secondary to acquired cardiomyopathy from a variety of conditions including exposure to chemotherapy. Anthracycline use can lead to acute and chronic heart failure. Acute dysfunction occurs in <1% of patients, and is often reversible. Early-onset heart failure occurs in 1.6–2.1% of patients within the first year of therapy. Late-onset failure, occurring more than a year after chemotherapy, develops in 1.6–5% of patients.[22] There are limited data regarding the incidence or prevalence of other forms of acquired cardiomyopathy or heart failure, such as secondary to thyroid disease, Kawasaki disease, and acquired or anatomic coronary disease.

Outcomes

The paediatric heart failure population as a whole faces substantial mortality, as well as morbidity, as measured by hospitalisations, re-admissions, and functional disability. These patients often have long, complicated, hospital stays, during which they can develop life-threatening co-morbidities including respiratory failure, renal failure, and sepsis, which substantially increase their risk of in-hospital mortality compared with patients without heart failure (Fig 2). The in-hospital mortality for patients with heart failure in 2009 was 6.7% compared with a 0.4% in-hospital mortality rate for children without heart failure.[5] Furthermore, infants <1 year of age with heart failure face a disproportionately high in-hospital mortality rate of 11%.[23] Owing to recent improvements in available therapies, patients with heart failure can be supported through more severe illness.[6] Thus, there has been a decrease in overall inpatient mortality over time, at least among patients with cardiomyopathy;[23] however, there has been a concomitant rise in the prevalence of important co-morbidities such as respiratory and renal failure, contributing to increased morbidity in these patients.

CHD

The outcomes for patients with CHD who develop heart failure are variable and are influenced by the underlying lesion. Thus, ascribing a single outcome to all patients with CHD is not very meaningful; however, when focussing on those patients with single ventricles, 10–13% of all single ventricle admissions were complicated by heart failure. These patients had higher mortality at 12% compared with their non-single ventricle counterparts at 7.9%, as well as higher rates of co-morbidity.[13] Furthermore, although most paediatric heart transplants overall occur in cases of dilated cardiomyopathy, the majority of transplants performed among children in the first year of life occur in those with underlying CHD. In 2012, this represented 67 patients, all of whom presumably had progressed to clinical heart failure, thereby requiring heart transplantation.[24]

Dilated cardiomyopathy

Dilated cardiomyopathy patients experience substantial morbidity and mortality, particularly in the first year after diagnosis of heart failure. In one study of patients with heart failure due to cardiomyopathy from the United Kingdom, 34% of them experienced the combined outcome of cardiac transplantation or death, at one year after diagnosis.[16] In the Australian and American cohorts, respectively, 29 and 31% experienced transplantation or death at 1-year follow-up (Fig 3);[25] however, after this initial period of high risk, patients appear to do well, with the yearly event rate for transplantation or death dropping to 1%.[26] Most of the events are transplantations; thus, the

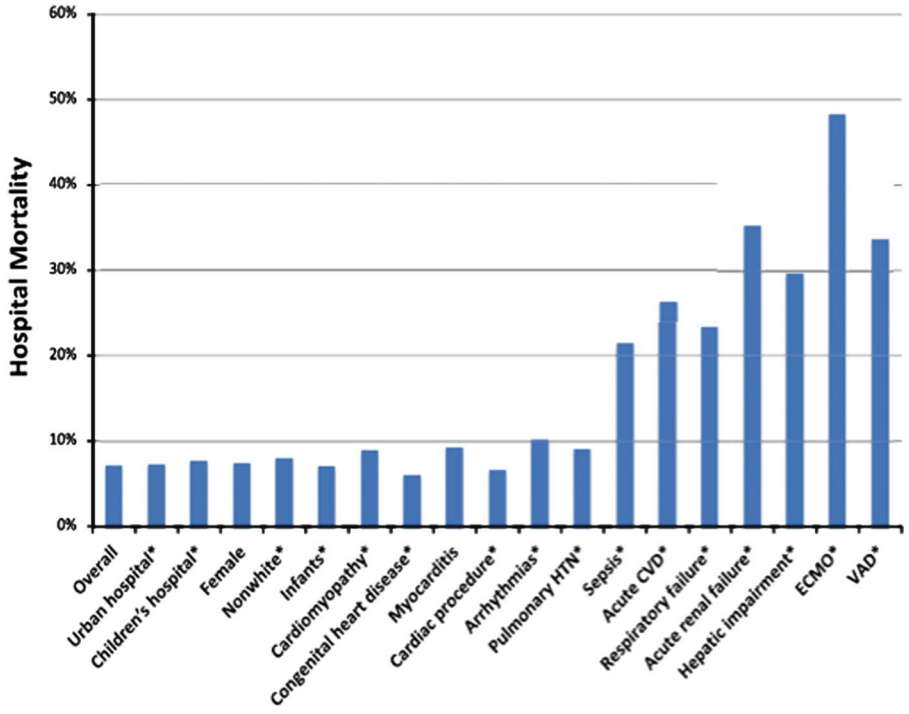
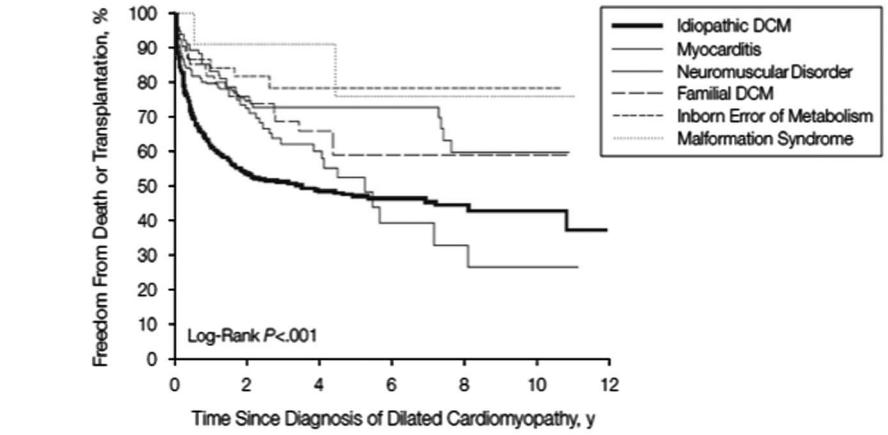


Figure 2.
*Hospital mortality in children with heart failure-related hospitalisations. *Factor associated with increased hospital mortality ($p < 0.05$). Reproduced from Rossano et al.*[5]



No. at Risk

Cohort							
Idiopathic DCM	941	252	132	68	30	13	0
Myocarditis	222	95	55	32	12	1	0
Neuromuscular Disorder	125	56	25	8	5	1	0
Familial DCM	66	33	21	11	4	1	0
Inborn Error of Metabolism	54	27	20	8	5	1	0
Malformation Syndrome	15	6	6	2	2	1	0

Figure 3.
Freedom from death or transplantation in patients with pure dilated cardiomyopathy (DCM). Reproduced from Towbin et al.[25]

natural history without transplantation is difficult to assess. Part of the ongoing event risk is due to sudden death. The 5-year incidence of sudden death in children with dilated cardiomyopathy is ~3% in the Pediatric Cardiomyopathy Registry[27] and 5% at the 15-year follow-up in the Australian registry.[28]

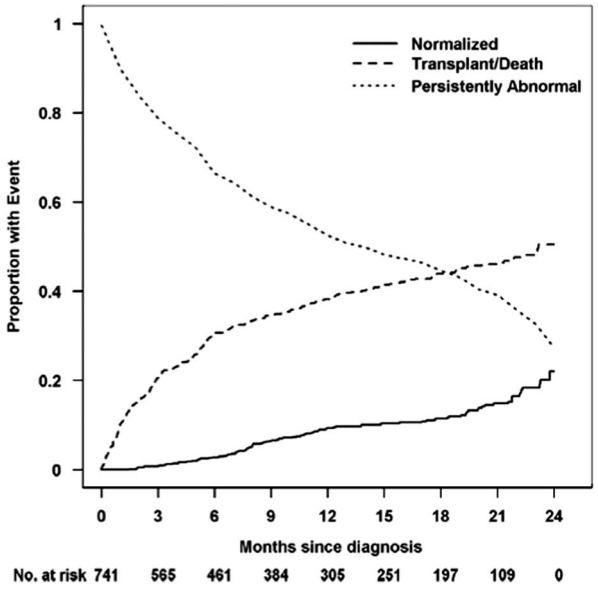


Figure 4.
Cumulative incidence of echocardiographic normalisation in Children with idiopathic DCM (N = 741) in the presence of competing risk of death or transplantation. At any given time point, the estimated cumulative incidence rates associated with the 3 states total to 1.0. At 2 years, 22% of children had normal echocardiographic values, 51% had died or had undergone transplantation, and 27% remained abnormal with respect to LV size and function. Reproduced from Everitt et al.[29]

Importantly, the number of children with dilated cardiomyopathy who present with significant ventricular dysfunction and who will have substantial improvement over time with normalisation of ventricular function is a substantial minority.[29,30] The time course of recovery can be variable, with some patients showing resolution of heart failure within 6 months, while others demonstrate late recovery, up to 2 years after initial presentation with heart failure (Fig 4).[26,31,32]

Hypertrophic cardiomyopathy

Importantly, outcomes for patients with hypertrophic cardiomyopathy vary depending on the underlying cause and age of presentation. Patients who develop idiopathic hypertrophy before 1 year of age have a 1-year survival rate of 85% compared with a 99% 1-year survival rate for those who develop idiopathic hypertrophy after 1 year of age.[33] Subsequently, for all patients with idiopathic hypertrophic cardiomyopathy surviving up to one year after presentation, the annual mortality rate is 1%. Patients who develop hypertrophic cardiomyopathy secondary to a neuromuscular disorders appear to have similar outcomes initially, with a reported 98% 5-year survival rate; however, by their second decade of life, these patients face substantial mortality rates.[20] Patients with hypertrophic cardiomyopathy due to a malformation syndrome or inborn error of metabolism appear to have worse outcomes even initially, with 5-year survival rates as low as 74 and 41%, respectively. Continued mortality risk is partially attributable to sudden death. For all patients with hypertrophic cardiomyopathy, the risk of sudden death was 6% over a mean follow-up period of 8 years in an American cohort[34] and 6% at the 15-year follow-up in an Australian cohort.[28]

Other cardiomyopathies

Survival is similar between the two subtypes of restrictive cardiomyopathy, with reported 1-year and 5-year survival rates, respectively, of 20 and 32%. Patients with a mixed restrictive/hypertrophic phenotype are less likely to go on to require heart transplantation compared with those with pure restrictive cardiomyopathy.[21] Many centres consider listing for transplantation at the time of diagnosis due to poor outcomes and the inability to accurately risk stratify patients. There is limited understanding about the efficacy of conventional medical therapy or the utility of ventricular assist devices, although some centres have reported some success with continuous flow ventricular assist devices in restrictive patients.[35]

Costs of paediatric heart failure

As noted previously, it is expected that the annual cost associated with heart failure in adults is expected to rise to $70 billion by 2030. Although it is difficult to directly apply these data to the paediatric setting, given the prevalence, poor outcomes, and medically complex therapeutics pursued in our patients with heart failure, the associated cost burden is anticipated to similarly comprise a large portion of total paediatric healthcare costs.

Costs of inpatient admissions

The mean hospital charge for a hospitalisation due to paediatric heart failure in the United States of America in 2009 was over $70,000. With 14,000 such admissions per year, the inpatient charges alone come to almost $1 billion yearly. As would be expected, as the complexity of medical care provided increases, the associated charges also rise. The presence of renal failure, respiratory failure, and stroke, all prevalent co-morbidities among patients with heart failure, independently are associated with twofold to threefold increases in mean charges per

hospitalisation. At the highest level of care, the use of mechanical support such as a ventricular assist device or extracorporeal membrane oxygenation is associated with inpatient charges of more than $450,000.[6] Similarly, the mean hospital charge for heart transplantation has been estimated to be $450,000 in 2009.

A major driver of cost is length of stay, which has increased over the past decade for patients with heart failure. In 2009, the average length of stay was 17 days, compared with an average of 15 days in 2000. Infants <1 year of age, comprising the greatest proportion of paediatric patients with heart failure, also have the longest average lengths of stay, at 26 days. Previous studies have demonstrated that a length of stay >18 days in patients with heart failure heart failure is associated with 24-fold increased mean hospital charges compared with a length of stay of <4 days.[6,23] A relatively long average length of stay also means that there are 240,000 inpatient hospital days for these children, with a substantial number of missed workdays for parents and guardians, which in turn has a significant cost burden to society.

Other costs

It must be stressed that inpatient costs only reflect a portion of total treatment costs associated with a chronic medical condition such as heart failure. Most, if not all, of these patients will undergo routine clinical examinations, frequent outpatient laboratory testings, echocardiograms and other non-invasive imaging, and possibly require cardiac catheterisations. Genetic testing has grown in use and utility, with added costs not only to the patient but also to potentially affected family members as well.[36] Development of important co-morbidities can also magnify costs, requiring visits to other specialty clinics or therapeutic centres – that is, haemodialysis. At present, the scope of these additional costs has not been explored.

Cost-effectiveness and value in heart failure

In recent years, a growing recognition of the uncontrolled spending in healthcare as well as clear limits in available resources and healthcare capacity gave rise to a focus on developing and providing cost-effective care. With this movement came the need to define cost-effectiveness. This can most simply be understood as the cost per unit of effectiveness derived from an intervention. Effectiveness is often measured using quality-adjusted life years in an effort to be able to compare relative effectiveness across different therapies. Cost per unit effectiveness calculations are frequently used to justify the cost of an intervention against pre-specified standards. Recent studies have calculated the cost-effectiveness of paediatric heart transplantation and ventricular assist devices to be between $50,000 and $100,000 per quality-adjusted life year, which is on par with commonly used life-sustaining technologies such as renal replacement therapy and adult heart transplantation.[5,37,38] In comparison, the cost-effectiveness of implantable cardioverter-defibrillators in children with dilated cardiomyopathy has been estimated to be greater than $280,000 per quality-adjusted life year, suggesting that defibrillators may not be cost-effective in this population due to the low event rate and high expense associated with the therapy.[39]

As the dialogue about cost in medicine has evolved over time, the emphasis has shifted to focus not simply on providing cost-effective care but ensuring that we provide optimal value to our patients. Value has been defined broadly as the outcome achieved on behalf of the patient divided by costs paid by them.[40] Indeed, indicators of value have been proposed as a driver for reimbursement under the Affordable Care Act.[41] To optimise value, there must be improvements in patient outcomes, reductions in total costs, or both.

For children with heart failure, it has been difficult to accurately assess what, if any, change there has been in the value of care provided over time. Depending on how outcomes and costs are defined or measured, there can be different interpretations of value. By focussing specifically on outcomes of mortality, the decline in inpatient mortality over the last decade may indicate that there has been improved value in care for heart failure patients; however, factoring in the increases in hospital length of stay and higher rates of co-morbid conditions with associated declines in functional status would indicate that outcomes for our patients may not have improved over this time period. Indeed, when comparing paediatric with adult heart failure admissions, children consistently have a greater degree of morbidity and mortality than adults, but still at much greater cost per hospitalisation (Fig 5).

Limitations to our current understanding of the costs of paediatric heart failure

Most of the data regarding the costs of paediatric heart failure are derived from analyses of administrative databases of inpatient admissions, and thus do not include the costs associated with the emergency department or outpatient visits, as well as home care. Second, administrative data provide hospital charges, which are subject to variable reimbursement rates depending on the payer, and thus can only serve as a proxy for actual costs, with charges being greater

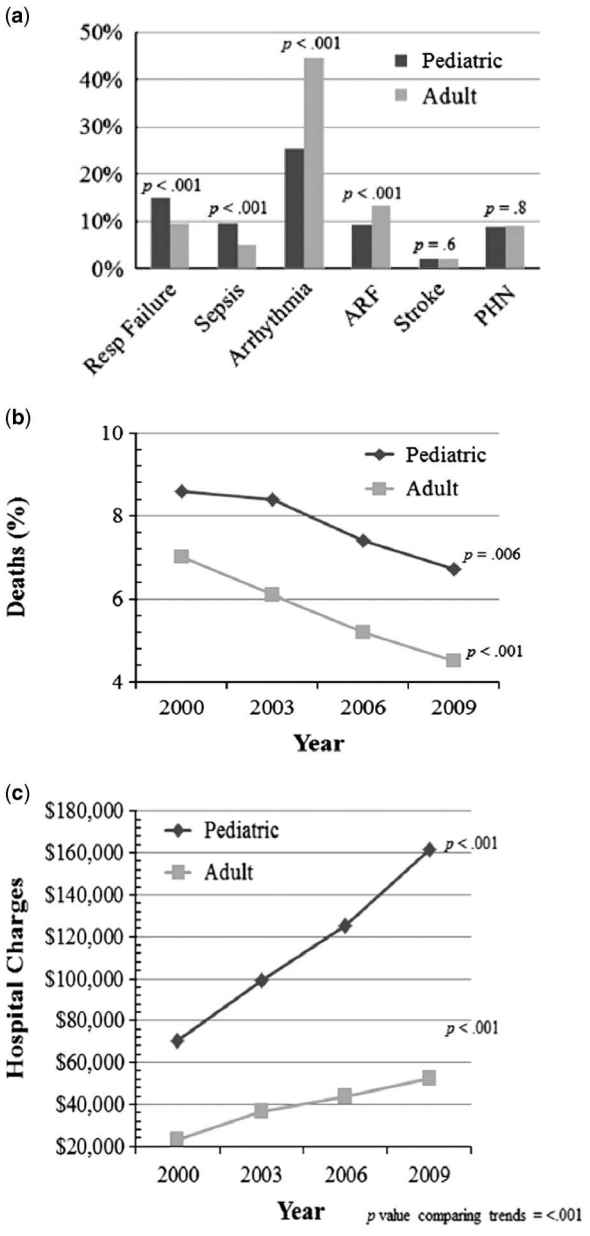


Figure 5.
*(**a**) Frequency of co-morbidities occurring during paediatric and adult cardiomyopathy and heart failure hospitalisations; (**b**) Mortality, as a percentage of the cohort, over time for paediatric and adult cardiomyopathy and heart failure-related hospitalisations according to year; (**c**) Hospital charges over time for paediatric and adult cardiomyopathy and heart failure-related hospitalisations according to year. ARF = acute renal failure; PHN = pulmonary hypertension. Reproduced from Wittlieb-Weber et al.*[23]

than the true costs. Finally, the indirect costs of missed parental work days and opportunity costs of scarce resources are difficult to estimate and are not readily measurable. No studies have sought to define or capture these indirect costs; however, the existing data on inpatient costs allow us to draw important conclusions and suggest future directions for exploration.

Targets of research

Our knowledge of the costs and value obtained for children with heart failure is still in its infancy. Moving forward, we must create tools to effectively and prospectively study this population, despite the limitations imposed by the relatively small population. Necessary targets of research include the following:

- Assessment of quality of life of children with heart failure and underlying syndromes.
- Evaluation of patient satisfaction with medical care received in the hospital and outpatient settings.
- More complete characterisation of the epidemiology and outcomes of paediatric heart failure and its underlying causes through the establishment of comprehensive, multicentre registries tracking these patients over time
- Prospective assessment of clinic, emergency department, pharmacy, laboratory, and inpatient costs
- Efforts to define and track indirect costs to the patient, provider, and healthcare system
- Determination of factors associated with variability of medical care provided to patients within and between medical centres
- Assessing the prevalence and utility of low-value interventions – for instance, intravenous immunoglobulin for the treatment of myocarditis[42,43]

Conclusion

Although heart failure in the paediatric population is relatively rare, hospital admissions for heart failure are only modestly less numerous than other severe paediatric conditions, such as sepsis.[44] Mortality is relatively low at 6–7%, but the associated morbidity is high. Inpatient admissions are expensive, and growing more so, with median charges greater than $70,000 per admission in 2009 and charges of more than $450,000 for admissions associated with mechanical support or transplantation. American hospital charges for inpatient care alone are near $1 billion. Our understanding of the full importance of paediatric heart failure and associated costs is in its infancy, and further steps are needed to fully elucidate this important aspect of paediatric heart failure care.

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Conflicts of Interest

None.

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