The Global Burden of Myocarditis


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ABSTRACT

Myocarditis contributes to the global burden of cardiovascular disease primarily through sudden death and dilated cardiomyopathy. A systematic approach to identify the cardiovascular mortality and major morbidity attributable to myocarditis has not been performed. A writing group convened by the GBD 2010 (Global Burden of Diseases, Injuries and Risk Factors) Study systematically reviewed the world’s literature by a manual review of all titles since 1966 on myocarditis identified using Ovid Medline, development of a disease model, and provision of estimates when possible of the incidence, prevalence, risk of death, and major morbidity for the world regions. Accurate population-based estimates of myocarditis incidence and prevalence are not directly available in any world region. However, a model that quantitates the risk of acute death and chronic heart failure following myocarditis was derived from the published data. Using hospital dismissal data, the burden of myocarditis as a percentage of prevalent heart failure varied by age and region from approximately 0.5% to 4.0%. The novel combination of multiple data sources may provide an estimate of the years of life lost and years of life disabled from myocarditis. Pending the integration of these data sources, the burden of dilated cardiomyopathy and myocarditis were reported together in the 2010 GBD report. The 2013 GBD project may refine these estimates with the inclusion of more comprehensive payor databases and more precise case definitions.

The GBD 2010 (Global Burden of Diseases, Injuries and Risk Factors) writing group on myocarditis was charged with the task of identifying when possible the global incidence, prevalence, morbidity, and mortality of myocarditis. The project goals included stratifying the available data into 21 world regions by age, sex, and income level. The original scope included pericarditis and endocarditis as well as myocarditis. Early in the writing process a section of the original writing group separated to investigate the global burden of endocarditis. A review of the world’s literature on idiopathic pericarditis and myocarditis revealed a low rate of sudden death and chronic heart failure [1,2]. Thus, idiopathic pericarditis and myocarditis were excluded from the disease model development and subsequent morbidity and mortality calculations. Other writing groups that focused on the burden of tuberculosis and HIV addressed pericarditis as a consequence of these specific disorders.

Although the causes of myocarditis are diverse and vary regionally, the GBD myocarditis writing group primarily described the impact of idiopathic, viral, and post-viral autoimmune myocarditis. Other writing groups that focused on Chagas disease, rheumatic heart disease, and HIV included heart failure from cardiomyopathy in their estimates of disease burden (Fig. 1). Thus, this report from the GBD writing group on myocarditis should be read in combination with the other GBD reports to gather a comprehensive picture of the global burden of inflammatory cardiovascular disease.

METHODS

An Ovid Medline search to January 2009 using the terms “myocarditis mp. or exp myocarditis” and “pericarditis mp. or exp Pericarditis” was performed. Case reports and reports without human subjects were excluded based on a manual review of all abstracts and titles. Only case series and clinical trials that included clinical outcomes of heart failure and death were held for further review. Additional studies were identified from the authors’ personal manuscript files. The results of this effort are illustrated in Figure 2. Myocarditis cases in hospital dismissal databases were identified using International Classification of Disease 10 (ICD-10) codes I40 (acute myocarditis) and I42 (myocarditis in diseases classified elsewhere).

The writing group met by teleconferences and several face-to-face meetings and communicated extensively to develop a myocarditis disease model that captured major disease features. By necessity, the model is a simplification of the actual disease process, intended to allow the combination of data from other writing groups by the GBD core analysts for an integrated calculation of years of life lost and years of life disabled. Several aspects of myocarditis influenced the development of the model. First, the clinical...
The symptoms of acute myocarditis are nonspecific and include the syndrome of heart failure, anginal-type chest pain, and occasionally sudden death from ventricular arrhythmias. The outcome of myocarditis is well known to vary with etiology and age, but the major long-term sequelae for all causes is chronic heart failure, generally associated with dilated cardiomyopathy [3]. Therefore, the writing committee evaluated all studies of myocarditis regardless of presenting clinical syndrome. Occasionally chronic chest pain following myocarditis can also be disabling; however, chronic symptomatic heart failure from myocarditis is the only long-term cause of morbidity in the disease model (Fig. 3).

The definition of myocarditis used in published studies varies widely. Many authorities recommend histological or immunohistological criteria that require endomyocardial biopsy (EMB), surgical heart specimens, or autopsy [4]. When possible, the committee used data from histologically confirmed registries and clinical trials to estimate the risks of death and chronic heart failure. However, much of the published literature and nearly all cases of myocarditis based on hospital dismissal diagnosis codes were not linked to a specific pathological diagnosis. The writing committee decided to review all of the available data, regardless of diagnostic criteria used, recognizing that myocarditis, as used in the final report, refers to a heterogeneous group of diseases with variable clinical and pathological features. As a consequence, there is an imperfect distinction between myocarditis and acute dilated cardiomyopathy, and the disease burden from the myocarditis and cardiomyopathy cohorts are usually reported together in the 2010 GBD tables and figures [5,6].

RESULTS

The major findings of the literature review are summarized below. Because of space limitations, this report cites mainly representative examples of the most important primary sources with the intent to convey the relevant epidemiological data on myocarditis by world region.

Asia

A review of the case series from Asia between 1966 to the mid 2000s revealed specific regional causes such as diphtheria (Afghanistan and India) [7], typhoid fever [8], rubella, scorpion bite (India), and a variety of virus infections including coxsackievirus B (CVB) [9] and chikungunya [10]. Hepatitis C virus seemed to be an important cause of myocarditis in Japan [11]. The data from these case series suggested temporal and regional variation in etiology but did not permit more than a qualitative analysis of myocarditis causes.

In Japan, the rate of myocarditis was estimated from an unselected national registry of 377,841 autopsies; 434 of these patients (0.11% or about 1:1000) had idiopathic, interstitial, viral, or nonspecific myocarditis [12]. In contrast, the rate of myocarditis was 3% (6 of 200) in autopsies of patients experiencing sudden death in Japan [13]. Of 97 (77 male, 20 female) school children who experienced sudden death in Kanagawa prefecture, 3 of the 18 (16.6%) had chronic heart failure of unknown etiology, suggesting a need for a sensitive and specific...
noninvasive diagnostic test to identify myocarditis as a cause of acute cardiomyopathy.

One clinical series of 20 patients from Japan with acute myocarditis and heart failure was followed for 49 months. Two patients (10%) died, 5 (25%) developed chronic dilated cardiomyopathy (DCM), and 10 (50%) recovered without arrhythmias [15]. Acute myocarditis with severe heart failure was associated with the 2009 influenza pandemic A (H1N1) in Japan. In a national survey on myocarditis associated with the 2009 pandemic, 15 patients were reported, 10 of whom had fulminant myocarditis (6 proven by biopsy). All 10 patients required mechanical circulatory support (intra-aortic balloon pumping and/or percutaneous cardiopulmonary support), and remarkably 8 survived. These findings support observations in other world regions that patients with fulminant myocarditis can frequently recover when managed with appropriate mechanical circulatory support [16].

These data suggest that acute myocarditis is an important cause of sudden death and chronic DCM in Japan and likely the rest of the Asian region. Fulminant myocarditis after a severe viral illness is uncommon but can resolve with management that includes timely hemodynamic support. There are substantial gaps in the outcome data for almost all countries and age groups. A strategy to fill these gaps may include the use of national clinical and death registries to identify cases coupled with precise diagnostic tools to validate the case identification.

Australasia

The literature from Australia and New Zealand described regional variations in etiologies and important contributions to the natural history of histologically confirmed myocarditis in children. Reports from this region included associations of myocarditis with CVB and enterovirus 71 viral epidemics [17,18], toxic myocarditis from clozapine and anabolic steroid use [19], and rarely myocarditis associated with smallpox vaccination. The reports regarding clozapine noted an incidence of 0.7% to 1.2%, with most patients presenting within 3 weeks from drug initiation [20]. The estimated rate of death was 10%, with recovery in about half of the patients and 19% with persistent left ventricular (LV) dysfunction [21]. Follow-up data were not available for about 25% of patients.

Several important contributions from the autopsy literature characterize the role of myocarditis in sudden death. In one series from Sydney of 193 patients younger than 35 years experiencing sudden death, 12% (39) were due to myocarditis [22]. A second autopsy series from eastern Sydney of patients aged 5 to 35 years reported myocarditis as a cause of sudden death in 11.6% of 241 nontraumatic cardiac cases [23]. In a slightly older series of 841 patients (aged 16 to 39 years) with out-of-hospital cardiac arrests from Melbourne, 3.5% were due to myocarditis [24]. An autopsy series from Adelaide Children’s Hospital described the spectrum of presentation in 32 confirmed myocarditis cases (in 16 of 32, myocarditis was the only cause of death; the remaining 16 were also associated with other severe diseases). Sudden death was the presentation of the disease in 5 of 15 children with myocarditis as the sole cause of death. In 3 of these 5, sudden death was not preceded by symptoms [25].

The National Australian Childhood Cardiomyopathy Study included all children with primary cardiomyopathy who presented between January 1, 1987, and December 31, 1996, and who were younger than 10 years of age at presentation. A series of reports from this national registry helped characterize the natural history of confirmed and suspected myocarditis in children. Lymphocytic myocarditis was present in 25 of 70 children with DCM who underwent cardiac histologic examination (35.7 percent), and in 25 of 62 children who underwent histological examination within 2 months after presentation (40.3%) [26].

Despite a high initial mortality, patients with lymphocytic myocarditis diagnosed during life had a better survival than those with nonspecific histological findings [27]. Survival and outcome for children with lymphocytic myocarditis in a previous Australian study was also better than for those with nonspecific histology [28]. Although the clinical status of long-term survivors of lymphocytic myocarditis is
substantial. Of all children with lymphocytic infiltrates, 50% died during the first days of hospitalization or presented with sudden death.

In summary, the data from the National Australian Childhood Cardiomyopathy Study and other autopsy data are similar to those reported from Japan and support the conclusion that myocarditis is an important cause of acute cardiovascular death in this region. The clinical outcomes data from the National Australian Childhood Cardiomyopathy Study provided one of 2 sets of national outcomes for myocarditis in children (the other being the North American Pediatric Cardiomyopathy registry). Similar long-term outcome data were lacking for adults with myocarditis in this region. The substantial contribution of the National Australian Childhood Cardiomyopathy Study to our understanding of the global burden of myocarditis suggests that similar strategies in the adult population may help to inform public policy and health resource management.

Mexico and Central and South America
The publications from this region either dealt with the incidence of myocarditis in the general population or addressed practical clinico-pathological issues including the diagnostic value of EMB in distinguishing myocarditis from DCM, the evolution of myocarditis into DCM, and the association of myocarditis with serological viral diagnosis. The regional literature described features of special etiologies like measles, meningococcal meningitis, AIDS, dengue fever, diphtheria and Kawasaki disease–related myocarditis. As noted previously, Chagas disease was excluded from this regional literature survey.

At a tertiary institution in Mexico during a 10-year period (1992 to 2003), acute myocarditis was diagnosed in 49 adult patients, 17 women and 32 men, with a median age of 24 and 28 years, respectively [29]. Patients with myocarditis represented 1 of 1,000 patients per year (0.1%), all of whom had positive serology for CVB or echovirus. Twenty-nine patients (61%) developed chronic DCM, and 3 patients (6%) died in the acute phase of the disease. Similarly, CVB serotypes B2 and B4 and echovirus serotype 1 were identified in the Brazilian Amazon region in a pediatric series of 15 patients (age 0 to 10 years) with myocarditis or DCM [30]. The diagnosis was made by evaluation of stool specimens, throat swabs, and when possible serum anti-CVB antibody titers.

The prevalence of histologically diagnosed myocarditis in DCM ranged from 13% in a study of 15 patients from Mexico [31] to 65% in a study of 23 patients from Chile [32]. Most patients with inflammatory infiltrates had a clinical history of less than 6 months’ duration, and 57% of the 23 patients from Chile [32] were diagnosed less than 3 months before the EMB. Although these cohorts are small, the regional prevalence of myocarditis in acute DCM was similar to the rates reported from Australia, Europe, and North America.

Special etiologies. During a 14-year period, 176 patients with measles were hospitalized at Hospital Infantil de Mexico and 23 (13%) died. Myocarditis was a rare complication of measles. Medical complications (including myocarditis) and mortality were more likely to occur in very young nonimmunized, malnourished children.

In a report from Brazil [33], the prevalence of myocarditis among children with fatal meningococcal meningitis was 42% (13 of 31 children, age 47.6 ± 39.8 months) but was minimal in 11 of the 13 (85%). Therefore,
a clear contribution of myocarditis and myocardial dysfunction to fatal outcome in meningococcal infection was not proven. The prevalence of myocarditis was 13% in a report from Colombia of 105 children with either dengue fever (12%) or dengue hemorrhagic fever (88%) [34].

In an autopsy series of 51 patients with AIDS from Mexico, myocarditis, pericarditis, and endocarditis were each found in 10% to 12% of cases [35]. Cardiovascular pathology, including coronary disease, pericardial effusion, and DCM, was diagnosed during life in 12% and remarkably in 43% at autopsy. Therefore, the authors recommend screening for cardiovascular disease with electrocardiography and echocardiography in patients with AIDS.

The clinical features and outcome of acute diphtheric myocarditis were described in 2 reports from Colombia [36] and Chile [37]. In the later report, 24 of 46 patients (52%) admitted with diphtheritic myocarditis had bradycardia-rhythmmas and 11 (17%) died. All 7 patients with third-degree atroventricular block, a patient with bifascicular block, and 3 of the 6 patients with bundle branch block died. Seven died of cardiogenic shock and 4 of ventricular fibrillation. Conduction system disturbances in patients with diphtherial myocarditis were markers of severe myocardial damage and a poor prognosis. In addition, ventricular pacing did not improve survival.

The incidence of myocarditis ranged from 5% to 46% in 3 series of pediatric patients with Kawasaki disease [38–40]. Kawasaki disease mainly affected children age 1 to 4 years, evolved with fever and vasculitis in diverse organs, and in the heart mainly affected the coronary arteries. The male to female ratio ranged from 3.3:1 to 9:1. Gamma globulin treatment combined with aspirin effectively controlled the disease process [40]. Death was related to coronary complications, not to myocarditis.

Taken together with observations from Western Europe and North America, the Mexican data suggested that between 10% and 50% of cases of acute DCM are likely due to myocarditis. Reasons for the heterogeneity in observed rates should be explored systematically. In addition, the causes of myocarditis in Mexico and Central and South America differed from those in developed nations in Asia, Western Europe, and North America, which suggests a need for region-specific screening and diagnostic strategies.

**Africa and the Middle East**

The published data on myocarditis in Africa revealed a regional and possibly temporal variation in causes that include viruses (particularly HIV) [41], peripartum cardiomyopathy, and occasionally infections such as trypanosomiasis [42] and shigelloses. As was the case in Asian myocarditis literature, the data did not permit an estimate of the relative contributions of specific etiologies to the burden of myocarditis.

The rate of myocarditis as a percent of heart failure varied by region and possibly by etiology. A study of 76 South African patients with DCM, all of whom had EMB, revealed that none had myocarditis and suggested that conditions other than myocarditis should be considered as causes of DCM [43]. A second study of LV EMB specimens from 18 African patients (14 men) with idiopathic DCM in Nairobi revealed that 9 patients (50%) had evidence of healing myocarditis [44]. In a study of 11 African women from Nairobi who presented with the clinical features of peripartum cardiomyopathy and who had EMB, 5 patients had evidence of a “healing myocarditis.” Of the 9 patients who were followed up, 3 of 4 with myocarditis had persistent heart failure and 4 of 5 without myocarditis improved.

Although there are several large African cardiovascular disease registries, most cases are characterized only by clinical and echocardiographic criteria. Few studies utilize heart biopsy or cardiac magnetic resonance imaging (MRI). For example, a report of 1,507 patients referred for echocardiographic evaluation in Harare, Zimbabwe, revealed 1,153 (76.5%) abnormal studies. The major diagnoses were rheumatic heart disease, pericardial disease, DCM, hypertensive heart disease, and peripartum cardiomyopathy. Only 34 of 1,153 cases were attributed to acute myocarditis [45]. In a registry of 572 consecutive patients with heart failure referred to the National Cardiothoracic Centre in Accra, Ghana, the main causes of heart failure were hypertension (21.3%), rheumatic heart disease (20.1%), and cardiomyopathy (16.8%). Myocarditis was not identified as a separate cause.

In a similar example, 167 patients (99 men and 68 women) presenting with clinical and echocardiographic signs of heart failure were reported from Yaounde General Hospital, Cameroon. The main etiologies were hypertension (54%), cardiomyopathies (26%), and valvular heart diseases (23%) [46].

The largest such heart disease registry is the Heart of Soweto Study, which characterized the heart disease burden in an urban African community. From January 1 to Dec 31, 2006, 4,162 patients with confirmed cardiovascular disease were evaluated at the cardiology unit at the Chris Hani Baragwanath Hospital in Soweto, South Africa. Although heart failure was the most common primary diagnosis, myocarditis was not evaluated as a separate diagnostic category [47].

A recent summary of the current state of knowledge on the epidemiology and etiology of cardiomyopathy in people living in Africa identified DCM as a major cause of heart failure throughout Africa [48]. Myocarditis as a separate entity was rarely identified due to a lack of readily available diagnostic tools. The authors noted marked regional variation in the pathogenesis of DCM, suggesting a heterogeneity of causative factors. In summary, the data regarding myocarditis in Africa were limited by a lack of available accurate diagnostic tools. Efforts to determine the disability-adjusted years of life for myocarditis in this region should focus on improving diagnostic strategies.
Western Europe

Much of the world’s data on the demographics, presenting symptoms, and natural history of histologically confirmed myocarditis comes from Western Europe. Multiple studies from this region have demonstrated that viral genomes in the heart are common in acute and chronic DCM and may be associated with poor prognosis [49,50]. Of the 3,044 patients in the ESETCID (European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases) trial with biopsy-confirmed inflammatory cardiomyopathy, 72% had dyspnea, 33% had chest pain, and 18% had arrhythmic events [51]. A series of 174 patients with biopsy-proven myocarditis (active and borderline) from Padua, Italy, had a similar distribution of presenting symptoms (54% cardiomyopathy, 27% chest pain, and 19% syncope or arrhythmia) [52]. In most series, men were affected slightly more often and may have more severe disease with a lower rate of LV functional recovery than women. For example, in a cardiac MRI study of 65 patients with acute myocarditis, myocardial fibrosis was more frequent in men and in patients younger than 40 years [53].

The rate of myocarditis as a percent of DCM or suspected myocarditis was described by several sources. Eighty-four of 202 patients (41.6%) screened for a trial of immunosuppressive therapy had myocarditis defined by increased HLA expression on EMB [54]. In a registry from Germany, patients with suspected viral myocarditis had myocarditis on EMB: 38% (69 of 181) using Dallas criteria (hematoxylin and eosin stain) and 50% (91 of 181) when immunoperoxidase criteria were used [55]. A total of 190 of 901 patients (21.1%) who underwent biopsy for possible myocarditis in the TIMIC (Tailored Immunosuppression in Inflammatory Cardiomyopathy) trial had myocarditis on EMB defined by immunoperoxidase criteria [56].

The likelihood of death or transplantation in acute and chronic inflammatory cardiomyopathy varied somewhat among reports. In the registry noted previously from Padua, Italy, the risk of death or transplantation was 27%, with an average follow-up duration of 23 months [52]. A series of 203 patients from Germany with viral genome—positive cardiomyopathy (median follow-up of 4.7 years) revealed a 19.2% all-cause, 15% cardiac, and 9.9% sudden cardiac death rate [57]. Only 22% of the patients (40 of 181) in another German registry followed up for a mean of 59 months died or underwent heart transplantation [55]. Among 84 patients from Poland with more than 6 months of symptoms enrolled in a clinical trial, the rate of death, heart transplantation, and hospital readmission was 22.8% for the immunosuppression group and 20.5% for the placebo (p = nonsignificant) after 3 years (approximately 7% per year) [54]. In the TIMIC trial from Rome, Italy, there were no deaths or transplantations among 85 patients with biopsy-proven myocarditis at the 6-month study endpoint [56].

The risk of chronic heart failure was also described in Western European registries and trials of confirmed myocarditis. In the TIMIC trial, the natural history of inflammatory cardiomyopathy was poor, with a decline in average LV ejection fraction (LVEF) from 27.6% to 19.5% over 6 months in the placebo arm [56]. In contrast, the average LVEF improved from 23.8% to 30.2% over 6 months in the trial from Poland [54]. In patients with both human herpesvirus 6 and parvovirus B19 infection, the likelihood of ventricular functional recovery was low (LVEF change 25% to 30% at follow-up) [49]. These studies support the conclusion that adult patients with biopsy-proven myocarditis (after 6 or more months of guideline-based treatment) or multiple cardiac viral infections rarely normalize cardiac function.

Western Europe has the infrastructure, including experienced investigators, trialist networks, cardiac MRI and EMB, and patient volumes, to conduct treatment trials in myocarditis. Insights into the pathogenesis of viral and autoimmune myocarditis in humans can arise from translational studies in these cohorts and large registries. Adequate enrollment rates are likely given the 20% to 50% regional rate of myocarditis in DCM.

North America

The trials and registries from North America provided invaluable data on the rate of LV recovery, death, and transplantation in myocarditis. The demographics of acute myocarditis were similar to those from European data sources. For example, 62% of the 111 patients enrolled in the US Myocarditis Treatment trial were male [58]. In a large series from Johns Hopkins Hospital, the rate of myocarditis as a percentage of patients with heart failure and suspected myocarditis varied by year with a peak of 17% in 1986 [59]. At this medical center, 12% of 673 patients referred for congestive heart failure due to DCM had myocarditis [60].

Distinct from many reports from Western Europe, viral genome analysis and EMB in general were not as commonly performed in North American studies of adult patients with cardiomyopathy or chest pain syndromes. Myocarditis case series from North America often relied on a composite of clinical and imaging features to infer the diagnosis of myocarditis [61].

Myocarditis is a common cause of DCM in children in North America. Etiology was determined in the 1,426 children with DCM from the United States and Canada enrolled in the Pediatric Cardiomyopathy Registry. Of the 485 patients (34%) with a known cause, the most common cause was myocarditis (46% [222 of 485]). In this study, half of myocarditis cases (52% [116 of 222]) met Dallas histopathologic criteria. The risk of death or heart transplantation was greater in DCM than in myocarditis [62].

The likelihood of LV recovery, death, and heart transplantation in children with new-onset DCM due to myocarditis was also described from the Pediatric
Cardiomyopathy Registry. Children with suspected myocarditis were diagnosed with biopsy confirmation (n = 119) or with probable myocarditis diagnosed clinically (n = 253) and were compared with children with idiopathic DCM (n = 1,123). The median follow-up time for survivors not undergoing heart transplantation was 3.1 years in the biopsy-confirmed myocarditis group and 2.7 years in the probable myocarditis group. The distributions of time to death, transplantation, and echocardiographic normalization in the biopsy-confirmed myocarditis and probable myocarditis groups did not differ (Fig. 4). Children with biopsy-confirmed or probable myocarditis had similar proportions of death, transplantation, and echocardiographic normalization 3 years after presentation and better outcomes than those of children with idiopathic DCM [3]. The degree of LV functional recovery more than 6 months after diagnosis seemed greater than the LV recovery reported in adult case series.

In contrast to recent Western European studies in which viral genome analysis was common, viral serology or polymerase chain reaction was documented in only 94 patients. Of these, 31 (33%) had a positive finding (10 cytomegalovirus, 6 CVB, 5 enterovirus, 3 adenovirus, 2 Epstein-Barr virus, 2 herpes simplex virus, and 1 each of hepatitis B virus, respiratory syncytial virus, and parvovirus).

The natural history of myocarditis in adults was determined prospectively in 111 patients with biopsy-proven myocarditis enrolled in the US Myocarditis Treatment trial. In the group as a whole, LVEF improved from 25% at baseline to only 34% after 28 weeks. The mortality rate for the entire group was 20% at 1 year and 56% at 4.3 years [58]. These data agree with those from the European findings that myocarditis presenting as acute DCM in adults has a high mortality and a low likelihood of complete LV recovery.

Reported survival was similar in a large single-center registry of biopsy-proven myocarditis from Massachusetts General Hospital. Of 112 consecutive patients with histopathologic confirmation of myocarditis (55% lymphocytic), 88 (79%) and 63 (56%) were alive without cardiac transplantation at 1 and 5 years [63]. In a series of patients with biopsy-proven myocarditis from Johns Hopkins Hospital, transplant-free survival of patients with fulminant myocarditis (93% after 11 years) was significantly better than that for patients with acute myocarditis (45%; p = 0.05 by the log-rank test) [64]. For comparison, the outcomes of 373 patients with recent-onset DCM enrolled in a multicenter North American registry revealed an increase in LVEF from 24% at entry to 40% at 6 months. Transplant-free survival at 1, 2, and 4 years was 94%, 92%, and 88%, respectively; survival free of heart failure hospitalization was 88%, 82%, and 78% [65]. In this registry, biopsy was performed infrequently, but histologically confirmed myocarditis predicted bridge to recovery from LV device support [66]. The North American experience in myocarditis suggested a composite rate of cardiomyopathy, transplantation, and death of more than 50% after 5 years. However, the impact of recent improvements in heart failure care may not be reflected in these data. In addition, the influence of inflammation on the outcome of more chronic DCM has not been studied in this region. The infrastructure for clinical investigation makes a randomized trial to evaluate the effect of EMB on the outcome of suspected myocarditis feasible.

**SUMMARY**

This review of the world’s literature on myocarditis identified gaps that hindered epidemiological analysis but also permitted the identification of strategies to address these gaps in the 2013 GBD project. Specific causes of myocarditis vary by world region and may require region-specific screening and diagnostic strategies. Globally, the diagnostic
tests for myocarditis, including EMB and MRI, are not widely available, limiting the ability to identify myocarditis in cross-sectional studies. Thus, the 2010 GBD report probably underestimated the true rate of myocarditis as a cause of heart failure (Fig 5). Clinical trials to test diagnostic strategies and treatments in acute and chronic myocarditis are currently feasible in Western Europe and North America. In the next GBD project, the use of large payor claims databases and standardized noninvasive diagnostic criteria may allow for population-based estimates for myocarditis separate from cardiomyopathy.

REFERENCES