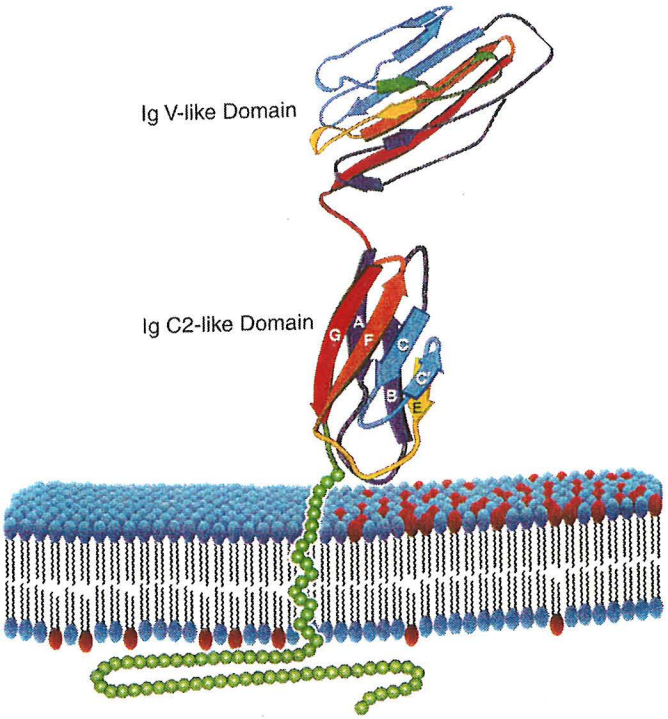
Internal Medicine Grand Rounds

Viral Myocarditis



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Dr. Benjamin is a member of the Division of Cardiology at UT Southwestern Medical Center. His clinical activities and interests are general consultative cardiology and ischemic heart disease, respectively. His investigative interests are focused on the mechanisms of ischemic cardioprotection, and studies on the regulatory circuitry and function of stress (HSP) proteins using genetically-engineered small animal models of human disease.

From the Cover (Figure 2). A schematic illustration of the structure for the human Coxsackievirus and adenovirus receptor protein as proposed by Kim and coworkers. The 365-amino acid polypeptide contains an extracellular domain consisting of two immunoglobulin (Ig) V-like and Ig C2-like domains. The transmembrane domain and the intracellular cytoplasmic tail follow the C2-like domain. [1].

I. INTRODUCTION

1. Definitions

Myocarditis is a self-limiting but, occasionally, life-threatening inflammatory condition of the heart that affects humans of all ages. "Viral myocarditis" refers to inflammation during active replication of virus in the myocardium or the subsequent autoimmune phase of the disease. "Postviral myocarditis" has also been used to describe specifically the autoimmune phase. When neither a direct causal relationship nor a specific etiology can be established, the term "lymphocytic myocarditis" has gained more widespread acceptance to reflect this predominant histological feature in affected patients [2].

In the United States, it is estimated that 25% of the 750,000 cases of heart failure have dilated cardiomyopathy (DCM), accounting for 50% of the cases requiring cardiac transplantation [3]. While DCM has multiple etiologies, viral infection, the focus of today's Grand Rounds, is widely believed to play a key role in its pathogenesis.

2. Historical Perspective & Overview: Myocarditis

The first report in the literature was attributed to Sobernheim who used the term "myocarditis" in 1837 [4]. Virchow popularized its use [5], and Feidler in 1899 subsequently referred to the disease as "isolated interstitial myocarditis" [6]. In 1912, Herrick's classical treatise [7] on the distinct morphologic features of ischemic myocardial necrosis led to a decline in the prevalence of myocarditis. For almost one century, cardiologists speculated about the clinical diagnosis at the bedside, and pathologists debated the diagnosis and classification of myocarditis at postmortem examination. By 1941, Saphir had remarked that "the incidence of the diagnosis of myocarditis has undergone more changes than perhaps the incidence of any other diagnosis" [8]. By now, some of the leading diagnosticians and scholars had begun to recognize the incongruence in clinicopathological correlation [8], and the differences in outcome between acute and chronic types of myocarditis [9].

The use of transvenous endomyocardial biopsy, introduced in 1962 by Sakakibara and Konno, radically changed clinical practice and ushered in a new era that, for the first time, facilitated the diagnosis and treatment of myocarditis in antemortem samples [10]. In 1984, a group of 8 cardiac pathologists met in Dallas to propose guidelines, to be based on reproducible morphologic criteria, for the diagnosis and reporting of myocarditis [11]. This commissioning is now known as the "Dallas criteria", which remains the standard used by pathologists and clinicians alike.

Recent years have witnessed substantial progress about the underlying mechanisms and pathogenesis of viral-induced cardiomyopathy. The recognition that myocarditis is both a viral and inflammatory disease, which progresses through multiple phases, has specific implications for therapy [12]. In today's Grand Rounds, I shall review the recent advances pertaining to the immunological aspects of the disease, and despite few proven therapies for viral-mediated myocarditis, discuss the chances that this complex and partially understood clinical entity could be effectively treated and, ultimately, prevented.

II. ETIOLOGIC FACTORS

1. Non-HIV viral myocarditis

Viral infection accounts for the majority of cases of myocarditis in industrialized societies [13] (Table 1). Enteroviruses such as Coxsackie B viruses are non-enveloped RNA viruses belonging the picornavirus family. The Coxsackievirus B group, in particular subtypes B3 and B4, and adenovirus, a close second, lead the list of human pathogens [14]. Coxsackieviruses are distinguished from other

types of picornaviruses on the basis of their pathogenesis in susceptible hosts (e.g., suckling mice) and antigenic classifications. These main classes are Coxsackievirus group A (A1 to A, A24) and the Coxsackievirus group B (B1 to B6). Group A Coxsackieviruses upon inoculation, either by subcutaneous or intracerebral routes, in suckling mice produces myositis and generalized paralysis [15]. In suckling mice, Group B Coxsackieviruses produce distinctive focal muscle lesions, necrosis of intrascupular fat pads, cerebral lesions, and spastic paralysis [15]. Besides Coxsackievirus and adenovirus [16], improvements in molecular detection have implicated other viruses, such as hepatitis C viruses [17], and human cytomegalovirus (CMV)[18], alone or in combination with other cardiotropic agents such as the human immunodeficiency virus [19,20].

Table 1

Viral Causes of Myocarditis	
Adenovirus	Junin virus
Arbovirus	Lymphocytic choriomeningitis
Arenavirus (Lassa fever)	Measles
Coxsackievirus	Mumps
Cytomegalovirus	Parvovirus
Dengue virus	Poliovirus
Echovirus	Rabies virus
Encephalomyocarditis virus	Respiratory syncytial virus
Epstein-Barr virus	Rubella
Hepatitis virus (A and C)	Rubeola
Herpes simplex virus	Vaccinia virus
Herpes zoster	Varicella virus
Human immunodeficiency virus	Variola virus
Influenza virus (A and B)	Yellow fever virus

2. HIV myocarditis

Human immunodeficiency virus (HIV) has emerged as a major etiologic agent in viral-induced dilated cardiomyopathy [21,22]. In HIV-positive patients, cardiac decompensation with lymphocytic interstitial myocarditis is a frequent complication, with an estimated prevalence between 8 to >50%, [20,23,24]. In a large prospective long-term clinical study of 952 asymptomatic HIV-positive patients, dilated cardiomyopathy was diagnosed by echocardiography in 76 patients (8 percent), primarily with New York Heart Association (NYHA) functional class III (84 percent) or class IV (16 percent) [20]. In this study, a lower CD4 count <400 cells per cubic millimeter was associated with a higher incidence of DCM. A histological diagnosis was established in the majority (83 percent) of patients with DCM.

The precise mechanism of HIV-induced cardiac disease has been debated but the available evidence suggests that the human immunodeficiency virus (HIV) *per se* exhibits cardiotropism. Among patients with active AIDS myocarditis, other viral (e.g., Coxsackievirus, Ebstein-Barr virus, influenza, and cytomegalovirsus), protozoa, and bacteria infections are commonly seen, suggesting that these comorbid conditions and autoimmunity might be contributing factors to HIV-induced myocarditis [23-25]. Although echocardiographic abnormalities are reversible in patients infected with HIV [19], the disease often progresses rapidly to dilated cardiomyopathy and has a poor prognosis, suggesting that prompt recognition and early institution of therapy could affect outcome [20].

III. EPIDEMIOLOGY

In an autopsy series, the overall prevalence of suspected myocarditis ranged between 2.3 to 5% [26] [25]. However, mostly, viral myocarditis is a self-limiting condition that resolves spontaneously [27]. The incidence of viral disease is also influenced by age, sex, season, sporadic outbreaks, and pregnancy. For example, in a 3-year survey of children from birth to age 17 years with sudden, non-accidental death, idiopathic myocarditis was documented in 17% [28]. In adults, different studies have reported the incidence between 7 to 10% in patients with dilated cardiomyopathy after Coxsackieviral myocarditis [29]. Nevertheless, the existing limitations in establishing the diagnosis and specific etiologic agent preclude the true incidence of the illness, in the general population, to be established with certainty.

IV. CLINICAL MANIFESTATIONS

The signs and symptoms of viral myocarditis range from an asymptomatic condition to congestive heart failure, ventricular arrhythmias, and sudden death [30] (Table 2). Most frequently, infection with Coxsackievirus is usually mild and subclinical. The symptoms mimicking influenza-like syndrome or upper respiratory illness are common with nonspecific febrile illness, myalgia, and rhinorrhea. However, patients with viral pericarditis or myocarditis can develop chest pain, dyspnea, fever, tachycardia, and, not infrequently, a pericardial friction rub. Other systemic manifestations of Coxsackieviruses include exanthematous disease, which is often confused with rubella, and aseptic meningitis. Group B Coxsackieviruses cause pleurodynia, also termed 'epidemic myalgia', which occurs with abrupt onset of fever, headaches, and stabbing pain in the chest, upper abdomen and muscles [15].

Table 2

Clinical Manifestations of Viral Myocarditis

Symptoms	Signs
- Fatigue	- Sinus tachycardia
- Dyspnea	- Pericardial or pleuropericardial rub
- Palpitations	- Cardiac arrhythmias (PACs,supraventicular tachycardia, Atrial fibrillation or flutter)
- Precordial pain	
- Dizziness or syncope	- Conduction disturbances (first- or second-degree; AV block; LBBB or RBBB; rarely, complete heart block)
- History of evidence of viral illness	
	- Heart failure (usually left-ventricular; may be biventicular)

Although humans are the only natural hosts of Coxsackievirus, the insignificant number of fatal human cases with the virus have precluded more in-depth knowledge about the pathology. However, neonates with generalized coxsackieviral infection show focal myocarditis and inflammation. Besides focal necrosis, patients with fatal myocarditis can also manifest meningo-encephalitis, hepatitis, and pancreatitis. Other neurotropic effects of Coxsackievirus seen in both white and gray matter can coincide with encephomyelitis involving the motor neurons with invasion of the brain stem and spinal cord [31].

V. PATHOGENESIS

The recognition that myocarditis is both a viral and inflammatory disease has led to the clinical evolution and recognition of 3 distinct phases of the disease (Figure 1).

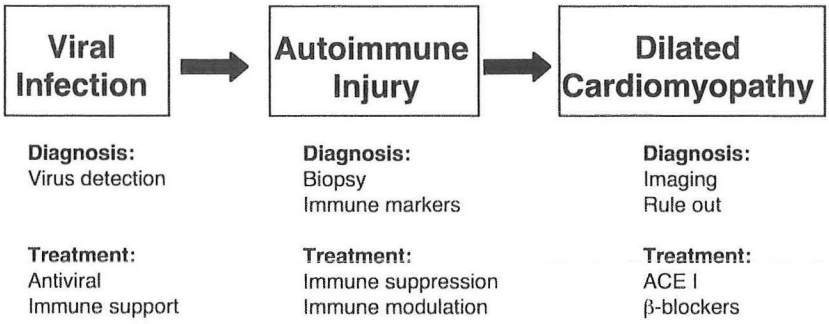

Figure 1. 3 Phases of viral myocarditis. From Liu and Mason [12].

In **Phase 1** (Viral Infection), I will review current concepts about how viruses gain entry to susceptible target tissues and how they instigate immune responses. The autoimmune phase, **Phase 2**, results from the intricate interactions among autoreactive T cells, cytokines, and cross-reacting antibodies. To date, there are no published trials of immunosuppressive therapy of proven benefit for viral/lymphocytic myocarditis. **Phase 3** of the disease exhibits overt dilated cardiomyopathy, a sequalae of ventricular remodeling, which, in part, could be specific to the viral infection. Therefore, a more thorough understanding about the patient's clinical stage, at either presentation or subsequent follow-up, enables the medical provider to make optimal use of resources, available diagnostic tools, and, perhaps, to plan appropriate, albeit yet unproven, therapy.

1. Viral Infection: Phase I

a. Early phase of infection. Once the viruses invade the host, from entry sites such as the gut in the case of enterovirus and respiratory tract for adenovirus, they travel in immune cells to the lymphoid organs. There, they escape immunological detection and invade other trophic sites such as the heart and pancreas.

After the viremic phase subsides, viral spread within the myocardium proceeds directly from one cell to another, followed by the appearance of active inflammatory foci predominantly of macrophages and T lymphocytes in experimental models and humans alike [32-34]. Infected myocardial cells trigger an early innate response, which serves to contain the state of infectivity before the adoptive immunological responses become fully developed. Lymphocyte-mediated immunity can successfully stave off most viral-induced challenges with complete recovery in most cases. Thus, successful residency with a low level of virulence in the host assures survival of these human pathogens (Figure 3).

b. Role of viral cell surface receptors in myocarditis. The presence of a limited number of receptors (1-10 x 10^4) for enteroviruses has longed been recognized in susceptible host cells [30]. However, the hypothesized role for a specific enteroviral-mediated host surface receptor was realized with the elegant studies by Bergelson and coworkers who first isolated the Coxsackie-adenoviral receptor, CAR [35], providing new avenues for exploring the mechanisms of viral targeting (Figure 2, Please turn to the cover). CAR is a 365-amino acid transmembrane protein consisting of an extracellular domain, a membrane-spanning helical domain, and a 107-amino acid cytoplasmic tail. This 46-kDa protein belongs to the immunologlobulin superfamily whose two Ig-like domains maintain disulfide

bonds between appropriate cysteines [35]. CAR serves bifunctional roles: first, its 222-amino acid extracellular domain is required for internalization of the Coxsackievirus [36]; and, second, it doubles as an attachment receptor for adenovirus. Based on competition studies not only does CAR mediate cell attachment and infection of all 6 Coxsackievirus serotypes, but also the receptor serves as an efficient attachment site for adenoviruses 2 and 5 serotypes [35]. Although CAR's cellular function remains unclear, studies of its deduced amino acid sequence indicate 91% overall homology between the human and mouse, and suggesting that genetic studies in the mouse would certainly illuminate its endogenous role.

Since CAR expression is greater in younger hearts than older animals, and tissue blots indicate higher mRNA expression in selective tissues (heart, brain and pancreas), this may explain the increased propensity and tissue-specific tropism of Coxsackievirus B in younger children and adults. This seminal finding has significantly advanced our understanding for the preponderance of Coxsackievirus and adenovirus in the pathogenesis of clinical myocarditis.

c. Co-receptors for Viral Internalization. Specific interactions between viral receptors and co-receptors, recruited from the host's cell, are essential for viral targeting. For example, the Coxsackie's B (CVB) recruits the function of the complement deflecting protein decay accelerating protein (DAF, CD55) as its coreceptor. In CHO cells, DAF overexpression increases viral progeny ~1000 fold compared with mocked transfected cells, and this response was similar for all six Coxsackievirus B serotypes [37]. Monoclonal antibodies against DAF or CD55 receptor effectively block viral uptake and viral infection of mammalian cells [37] (e.g., Hela, cardiomyocytes). Therefore, DAF cooperates with CAR such that the efficiency of Coxsackievirus docking with DAF-CAR receptor complex significantly enhances internalization by CAR. Thus, viral binding through the receptor-coreceptor complex is a stereochemical interaction between CAR, the end-effector for viral internalization.

A second example of coreceptor is the adenovirus that takes advantage of the integrins, $\alpha_{v\beta3}$ and $\alpha_{v\beta5}$ to be used as coreceptors to facilitate cardiomyocyte infection [38]. Given their central roles in instigating immune recognition in the cardiovascular system, recent investigations have logically focused on the repertoire of receptors and coreceptors whose roles in facilitating viral entry into cardiomyocytes could prove important for understanding pathogenesis and, conceivably, novel therapeutic interventions and prevention [39].

d. Viral infection and cardiomyocyte death. Fulminant myocarditis, more often in children and adolescents, is an uncommon sequalae[40]. High rates of transcription and translation of viral RNA leads to increased synthesis of both structural and nonstructural viral proteins, overwhelming the machinery and culminating in a myopathic state [41,42].

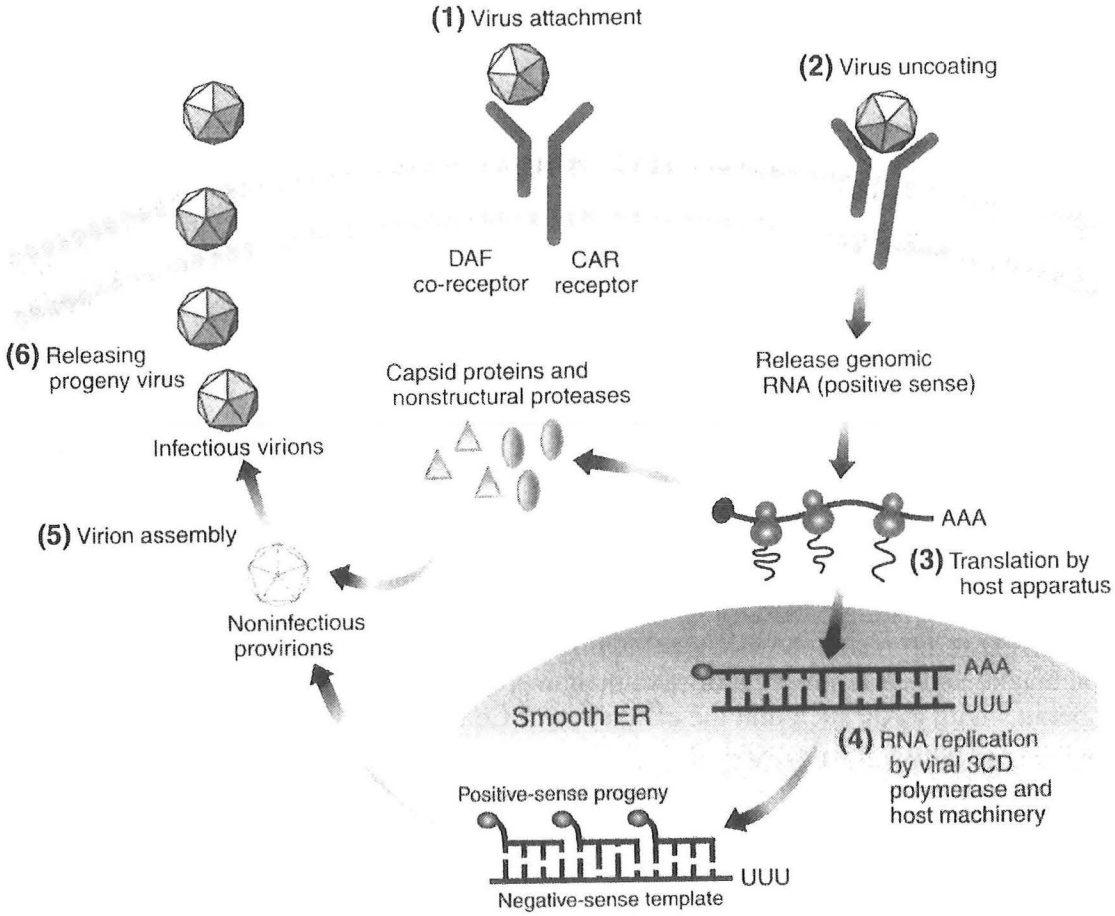

Figure 3. The Coxsackievirus and adenovirus cell surface receptor, CAR, and decay-accelerating factor (DAF) mediate viral attachment (1) and uncoating (2). In the host cell, protein translation (3) of proteases, capsid and other nonstructural proteins proceeds directly from its template, the viral RNA genome, which replicates in the smooth ER (4) from which noninfectious provirions are released for assembly (5). Virulence occurs with closure of the viral capsid and release after cytolysis (6) as infectious particles [43].

2. Inflammatory Response and Immune Activation: Phase 2.

The pathway that links viral infection to activation of the immune response remains a mystery in molecular terms but several possibilities are envisioned. Activation of the immune response can trigger two responses with dramatically different and opposing endpoints. On the one hand, immune-mediated processes effectively attenuate viral proliferation; on the other hand, despite elimination of virus, when the expected attenuation of the immune system does not occur, Phase 2 of the disease can ensue with attendant activation of T cells, release of proinflammatory cytokines, induction of cross-reacting antibodies, and the targeting of the host's tissues for destruction (Figure 4).

Since Phase 2 of immune activation is a pathologic diagnosis, endomyocardial biopsy is recommended when viral infection has resolved, and lymphocytic infiltration is abundant.

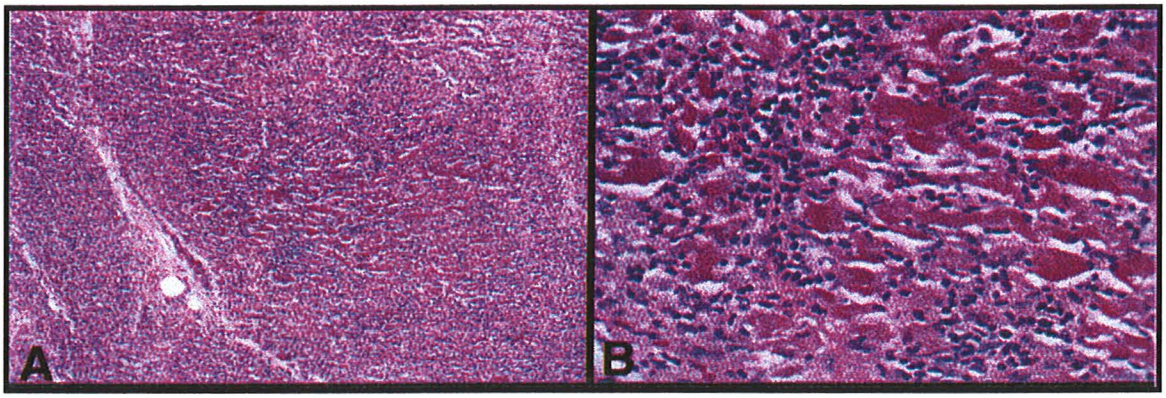

Figure 4. Idiopathic lymphocytic myocarditis in a 28-year-old man with upper respiratory tract infection and severe heart failure. Panel A shows florid lymphocytic infiltrates in biopsy specimen obtained at the time of left ventricular assist device placement (100X) and higher magnification revealing extensive myocyte necrosis and intense interstitial inflammation (B). From Berry and Atkins [44].

a. Autoreactive T cells. The classic cell-mediate immunity triggers T cell activation during viral infection in the myocardium. Peptide fragments are degraded in the ubiquitin-dependent proteolytic pathway, then internalized into the endoplasmic reticulum, and finally processed in the Golgi apparatus for presentation to the cell surface in a MHC-restricted manner. Infected cells with viral antigens on their cell surface are targeted for killing by autoimmune T cells using either increased cytokine-production or perforin-mediated cell cytolysis [12]. If stimulation of T cell killing does not abate, the premature and/or accelerated loss of terminally differentiated cardiomyocytes is, ultimately, detrimental to the host. Molecular mimicry, a mechanism by which immunological responses to viral peptides cross-react host's antigens from the myocardium, contributes to persistent T cell activation and myocardial damage. Likewise, viral-mediated hyperactivity of CD8 killer cells, termed T_H2 response, plays a well-established pathogenic role in Phase 2 of viral myocarditis [45]. In particular, the loss of contractile units has been proposed to reduce cardiac function and trigger the remodeling process, culminating in the final Phase 3 of the disease, during dilated cardiomyopathy [12].

Further demonstration on the pathogenesis of Coxsackievirus myocarditis by different T-cell subpopulations comes from studies in susceptible mice. Opavsky and coworkers have reported that myocarditis was exacerbated in the $CD8^{-/-}$ knockout but attenuated in $CD4^{-/-}$ mice, which is consistent with the deleterious effects by CD4 on viral pathogenesis [46]. Double knockout $CD4^{-/-}$ $CD8^{-/-}$ mice T lymphocytes were better protected from Coxsackievirus, as did deficiency of TCRβ [46]. Of interest, in the studies the elevation in interferon γ and reduction in TNFα levels were found in $CD4^{-/-}CD8^{-/-}$ mice with minimal myocardial damage, indicating specific interactions among different cytokines might participate in reciprocal effects on viral-mediated disease progression.

b. Role of Cytokine activation. Cytokines have long been implicated in cardiac diseases including viral myocarditis. In addition to T-mediated immunity, cytokines play important roles both in the activation and maintenance of the immune response [47]. For example, Matsumori and coworkers have reported that tumor necrosis factor α (TNFα) was elevated in 46%, an increased interleukin (IL)-1α in 23%, and as macrophage colony stimulating factor (M-CSF) in selected patients (n=13) with myocarditis [48]. The release of specific cytokines (e.g., TNFα) has been implicated in reversible cardiac dysfunction after viral infection that resolves with therapy[19].

c. Role of Cross-reacting Antibodies. Autoantibodies to different components of the myocardium such as the adenine nucleotide translocase 1, ANT1, and other mitochondrial proteins have been reported in patients with proven myocarditis [49]. ANT1, an inner mitochondrial membrane protein, along with the voltage dependent anion exchanger channel and cyclosporin D form the mitochondrial permeability transition pore and regulate ATP/ADP exchange (reviewed in [50]). Experimental animals exposed autoantibodies against ANT1 develop alterations in the cytosolic-mitochondrial phosphorylation of intracellular ATP, a finding that supports the notion that autoantibody contributes to viral pathophysiology by alteration in myocardial energetics. When SCID mice are transfused with peripheral blood lymphocytes from patients with myocarditis, the animals develop autoantibodies against ANT1, increased IL-2, and myocardial lymphocytic infiltration, indicating autoimmune disease plays a key role in myocarditis [51].

An autoimmune response against anti-α-myosin has been also reported during viral myocarditis. In addition, administration of antigen myosin evokes immunological activation that mimics immunological activation, establishing a non-infections route to produce immune activation or Phase 2 of the disease.

3. Dilated Cardiomyopathy: Phase 3

a. Nomenclature. According to the World Health Organization criteria, cardiomyopathies are diseases of the myocardium leading to cardiac dysfunction [52]. Based on revised criteria, dilated cardiomyopathy (DCM) is characterized by cardiac dilatation and ventricular dysfunction in the absence of systemic hypertension, ischemic and valvular heart disease. The origins of DCM may be idiopathic, genetic/familial, viral and/or immune, and alcohol/toxic, and this category has been revised to include conditions when cardiac dysfunction is disproportionate to either mechanical or ischemic causes.

Studies in molecular biology and human genetics have advances our understanding about the cellular mechanisms of cardiomyopathy, beyond their morphologic descriptors. For example, genetic studies on familial hypertrophic cardiomyopathy (HCM), which is characterized by left ventricular (LV) eccentric (i.e., septal) hypertrophy with normal LV volume, have paved the way to our understanding of the molecular mechanisms by which mutations of sarcomeric proteins in the pathogenesis of HCM [53]. In a similar manner, a small number of genes have been involved in heterogeneous DCM related disease such as dystrophin (e.g., X-linked DCM, Duchenne)[54,55], thin filament proteins (e.g., actin)[56], and other cytoskeletal–related proteins [57,58, 59] .

Heart failure is a complex syndrome whose onset, progression, and end-stages encompass a spectrum of interdependent processes that, ultimately, influence survival. However, recent biochemical, genetic and molecular studies using animal models are uncovering important mechanisms about how viral-specific events may lead to cardiac remodeling and the pathogenesis, both phenotypic analysis and functional, of DCM.

b. Viral protease and Cellular Dystrophin in Viral-Mediated Cardiac Dilatation. The sequalae of viral myocarditis, in children and adults alike, typically follow a subclinical course but in susceptible individuals develop into dilated cardiomyopathy. Badorff and Knowlton have reported recently that the expression of the replication-defective virus CVB3 genome causes ventricular dilatation in mice [60]. CVB3-encoded protease can cleave dystrophin [60,61] which is a large cytoskeletal protein (~427 kDa) that forms the sarcoglycan complex and is localized at the inner surface of the sarcolemma in close association with vinculin and β-spectrin [54]. Stabilization of the plasma membrane in muscle cells depends on the C-terminal domain of dystrophin in association with the large transmembrane glycoprotein complex and dystrophin-associated complex glycoprotein complex [62] & Figure 5. Evidence that CVB3-encoded protease can cleave dystrophin [60,61] and disrupts this multiprotein

complex supports the hypothesis that defects in the cytoarchitecture are causal mechanisms in the pathogenesis of viral-mediated DCM.

Furthermore, chamber dilatation is a common pathway for many acquired conditions (e.g., hypertension, ischemia), suggesting that animal models mimicking CVB3-protease mediated cleavage of dsytrophin might have broader application for understanding cardiac remodeling, too [61].

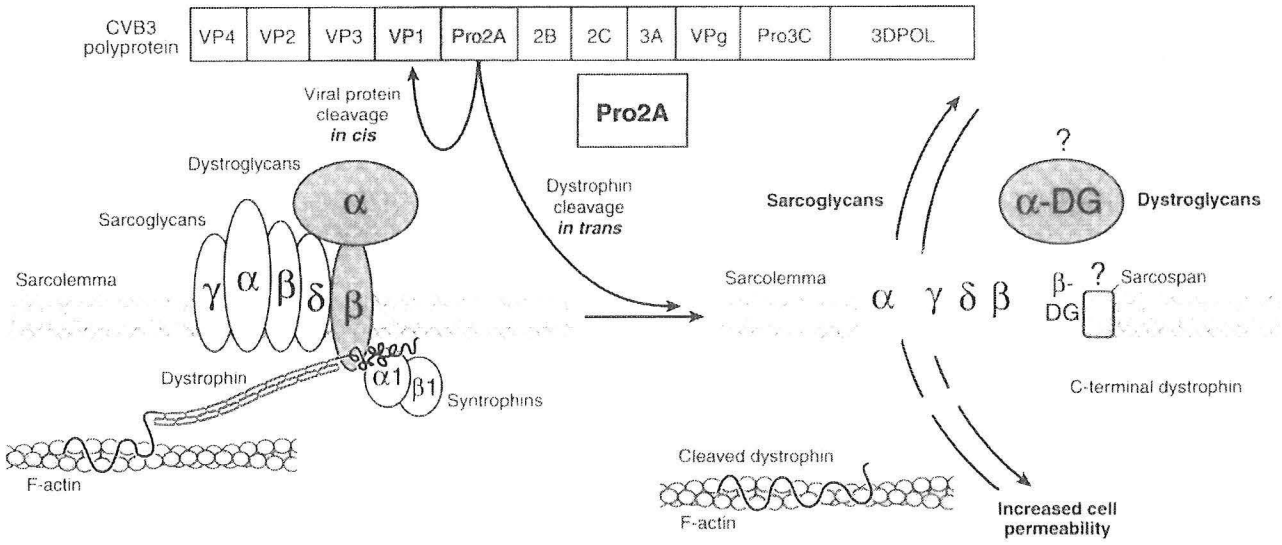

Figure 5. Schematic of the dystrophin-glycoprotein complex. Role of CVB3 Pro2A in Dystrophin cleavage. From Xiong, Badorff, and Knowlton [63].

c. NO signaling in viral myocarditis. (Figure 6) Recent studies have implicated the multifunctional signaling molecule, nitric oxide, in viral-induced myocarditis [64,65]. In Coxsackievirus B-treated mice, nitric oxide synthase 2 (NOS) activity is induced in myopathic hearts in parallel with increased expression seen in the infiltrating macrophages but not cardiac myocytes [66]. Genetic evidence that NO plays a direct role in innate immunity comes from NOS2 knockout mice, which exhibit increased viral titers, more extensive of inflammatory injury, myocyte necrosis, and dystrophic calcification compared with infected wild-type mice [67].

At least two molecular mechanisms have been identified for NO actions in viral myocarditis. First, proteolytic cleavage of large viral polyproteins by viral proteases such as 3Cpro, a cysteine protease is required for packaging during the viral life cycle [68]. NO can directly nitrosylate the catalytic site of 3Cpro, thus inactivating the enzyme and disrupting viral replication [69]. The second line of evidence is taken from studies by Bardoff and workers who demonstrated NO inhibits proteolytic attack on dystrophin by the 2Apro [70], indicating a direct cytoprotective mechanism in cardiomyocytes. Taken together, these studies reinforce that concept that advances in our understanding about the basic mechanisms could lead to potential strategies to mitigate the long-term effects of viral myocarditis.

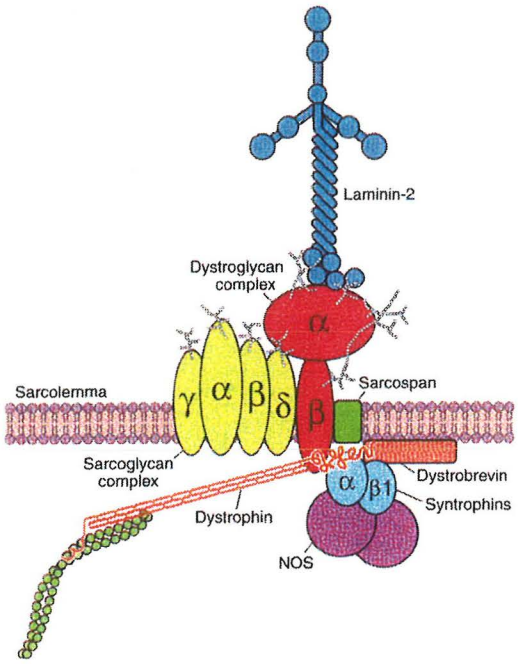

Figure 6. Schematic of the dystrophin-glycoprotein complex. Role of NOS signaling in viral myocarditis. Adapted from [52].

d. Alterations in Extracellular Matrix and viral myocarditis. Tissue repair after viral infection involves remodeling of the extracellular matrix, a process that is mediated by the activation of matrix metalloproteinases and their endogenous inhibitors, TIMPs [71,72]. For example, Li and coworkers have shown that increased levels of MMP-3 and MMP-9 in CVB3-induced myocarditis without commensurate changes in TIMP1 and TIMP-4, suggesting that imbalances in matrix turnover could tilt the balance towards exaggerated collagen degradation and adverse myocardial remodeling[72]. In experimental murine (DBA/2) myocarditis, Lee and coworkers have reported that pretreatment with the serine elastase inhibitor, ZD0892, markedly attenuated elastase activity, inflammation, and microvascular obstruction and chamber dilatation present in myopathic hearts [73].

Cytokines have been also implicated in ventricular remodeling leading to DCM. Ono and coworkers have reported that increased levels of pro-inflammatory cytokines such as IL-1β and TNF-α are associated with increased collagen deposition and cellular infiltration, suggesting that the involvement of cytokines in the remodeling process [74].

VI. DIAGNOSIS

1. New Recommendations for Diagnosis and Treatment

New insights about the molecular mechanisms related to the 3 phases from viral infection to cardiac remodeling, suggest the need to reevaluate existing practices for the diagnosis and treatment of viral myocarditis. We will discuss how specific knowledge pertinent to the specific Phase of the disease can help therapeutic considerations and avoid potential deleterious effects and/or consequences.

2. Clinical symptoms at presentation

Phase 1 of the disease can escape clinical recognition since viral replication may be entirely asymptomatic and go unnoticed without myocardial sequalae. In most instances, the signs and symptoms of viral infection are nonspecific and include fever, upper respiratory or gastrointestinal infection, lymphocytosis will occur in patients with acute myocarditis. Chest pain, palpitation, short of breath, and leg edema might occur with symptomatic heart failure. On physical examination, the presence of summation gallop, third heart sound, friction rub from pericardial involvement, and crackles consistent with pulmonary congestion can be obtained.

3. Laboratory findings at presentation

The classical findings on the electrocardiogram might include diffuse ST-segment elevation with or without widened QRS complex, left bundle branch block, nonspecific ST-T wave changes, and heart block [75]. Atrial and ventricular arrhythmias have been reported including ventricular fibrillation and sudden death on initial presentation. Echocardiography is needed to confirm the severity of systolic ventricular dysfunction, and, in some instances, affords qualitative changes in image texture heterogeneity, brightness indicative of myocarditis [76]. However, recent advances in tissue sampling techniques have made magnetic resonance imaging the diagnostic tool of choice for noninvasive assessment of suspected viral myocarditis with high sensitivity and specificity [77,78]. The coronary arteriography is usually negative for occlusive coronary artery disease and would support the diagnosis of idiopathic dilated cardiomyopathy.

4. Diagnosis by Endomyocardial Biopsy

a. Indications for endomyocardial biopsy. Based on the available literature, the indications for endomyocardial biopsy are 1) to establish the diagnosis of suspected myocarditis in a patient with new onset heart failure, 2) to consider alternative diagnoses (e.g., giant cell myocarditis) in patients unresponsive to conventional therapy for heart failure, 3) to monitor response after immunosuppression therapy if clinically indicated (e.g., disease recurrence or progression), and 4) to decide about placement of permanent pacemaker in cases caused by inflammatory process. Both the sensitivity and specificity of the endomyocardial biopsy are reduced when viral infection is remote or misdiagnosed.

b. Histomorphologic criteria. Suspected cases of inflammatory heart disease typically rely on right ventricular endomyocardial biopsy for histologic confirmation [79]. Before the current widely guidelines, termed the "Dallas criteria", were proposed in 1986 [11], the histomorphologic diagnosis of myocarditis varied substantially [79-81]. At a satellite meeting of the American College of Cardiology, the goals and objectives of a working group of cardiac pathologists were to devise a diagnostic scheme for the clinical recognition and reporting of viral myocarditis [11]. Many more analytical tools can be combined with endomyocardial biopsy during initial assessment of the viral myocarditis. In a series of 4000 patients, the prevalence of positive biopsy is approximately 10% and this frequency increases when the population is restricted to cases with acute or early myocarditis.

Active myocarditis requires the dual presence of both myocyte necrosis and inflammatory cell infiltrates. The composition of cellular infiltrates should be specified as predominantly lymphocytic, eosinophilic, giant cell, neutrophic, and granulomatous. Likewise, the temporal and spatial pattern of infiltration should be assessed for focal, confluent, diffuse with grades of mild, moderate and severe. Since evidence for myocyte necrosis might be uncommon, other corroborative findings such as mononuclear infiltrates, disruption of the sarcolemmal membrane, and either reactive or reparative fibrosis. Borderline myocarditis refers to limited amount of inflammatory infiltrates without myocyte damage, the latter requiring repeat biopsy in some cases [83]. No evidence of myocarditis is entertained

in the setting of dilated cardiomyopathy when neither morphological features are present. The presence of myocyte hypertrophy and interstitial fibrosis should be assessed for and commented upon in the setting of unexplained DCM.

Ongoing or persistent myocarditis is used to describe myocarditis that is either unchanged or worse than originally seen. Resolving or Healing Myocarditis and Resolved or Healed Myocarditis, as the terms imply, are used to describe decreases and absence amount of either inflammatory or myocyte damage, or both, respectively. With recurrence of either unequivocal or borderline myocarditis, current standards are to interpret these findings just like the first biopsy using the Dallas criteria [11].

Table 3

The Dallas Classification of Myocarditis	
First Biopsy	Subsequent biopsies
I) Unequivocal myocarditis	I) Ongoing (persistent) myocarditis
II) Borderline myocarditis	II) Resolving (healing) myocarditis
III) No evidence of myocarditis	III) Resolved (healed) myocarditis

Modified from Billingham[82].

c. Special Considerations for Diagnosis of myocarditis. The normal myocardium contains < 5.0 lymphocytes per high-powered field [80]. In young transplant donor, presumably free of cardiac disease, the prevalence of inflammatory foci was 9.3% containing least 5.0 lymphocytes per high power field [84]. The pathologist must be wary of the biopsy-sampling artifact such as contraction bands within myocytes that mimic acute myocardial infarction and catecholamine toxicity. The morphological appearance of phyknotic nuclei, the hallmark of ischemic injury and necrosis, can be distinguished from the sampling-induced contraction bands in cardiomyocyes that contain normal nuclei. Other pathological misdiagnoses, to be considered by the surgical pathologist, are intraluminal occlusion with thrombus, collapse of small arteries, ventricular perforation, and arrhythmogenic right ventricular dysplasia [44].

Sampling error is the major limitation of endomyocardial biopsy and, in one study performed at the Mayo Clinic of patients who died with myocarditis, the false negative rate was 37% in endomyocardial biopsies from the RV obtained at postmortem [85]. The low sensitivity, the high false negative rate and inconsistency in findings have led several authors to actively advocate against the use of endomyocardial biopsy in clinically suspected cases of myocarditis [86,87]. To improve the sensitivity, of biopsy sampling, proponents biopsies have suggested 1) careful patient selection, 2) the liberal use in the number of biopsies (minimum of 4 to 5 pieces), 3) tissue sectioning at 4- to 5 μM thickness, and 4) hematoxylin and eosin and connective tissue staining (Masson trichome) in suspected cases.

5. Virological diagnosis.

Some authors have placed more emphasis on virological studies, with secondary role for myocardial biopsy, for the diagnosis of viral myocarditis [12]. In most instances, the proof of viral infection is time consuming, the reliance solely on viral titers is impractical, detection procedures are not rapid, and there could be a paucity of materials for genetic studies. In recent years, virological

diagnosis has been substantially aided by the widespread availability of the polymerase chain reaction assay and in situ hybridization.

These formidable challenges aside, the clinician must be vigilant and maintain a high index of suspicion to the possibility of viral-induced myocardial disease.

a. Serologic markers. Serodiagnosis is usually confirmatory for viral myocarditis such as Coxsackievirus B since the cardiac manifestations occur much later after viral shedding has ceased [15]. In children, a four-fold rise in neutralizing antibody titer to a single serotype between paired sera over 2 weeks is diagnostic [25]. The greater exposure of adults to many viral agents reduces the specificity of an elevated titer. In some instances, an elevation in antibody titer is corroborative evidence for a recent or persistent viral infection, the latter with sustained elevation lasting for years.

Although viral serologic markers might be positive in this phase of the disease, these markers are common in the general population so that the sensitivity and specificity are not demonstrated. Highly sensitive or specific markers are not available to meet the most stringent criteria for immunological activation. However, evidence of immunological activation might include increased intracellular adhesion molecule-1 (ICAM-1), soluble FAS ligand, and T-cell activation, all of which are typically elevated in patients with viral myocarditis compared with controls [88,89].

b. Detection of viral genome and protein. Given the sensitivity for detection, the molecular detection studies such as polymerase chain reaction and *in situ* hybridization have handsomely complemented the serological detection of the frequent and even obscure viral causes of myocarditis. In addition, the timing and use of endomyocardial biopsy in Phase 1 remains challenging and controversial [11,90].

For example, using nested-PCR primers, the *Enterovirus* genome has been detected in ~20% patients with clinically suspected myocarditis or dilated cardiomyopathy [91], and this detection is expectedly highest during Phase 1. In addition, the application of *in situ* hybridization, which takes advantage of the temporal and spatial detection of viral genome, that has revealed important insights about disease entry, attachment and replication in the myocardium [33,92]. Because detection of viral genome in the normal heart is rarely seen, *in situ* studies for suspected viral myocarditis can be highly specific with prior knowledge of the suspected genome. However, the procedure requires specialized laboratory setting and considerable sophistication in both the personnel and high-quality tissue processing, making widespread application impractical.

By immunohistochemistry, enteroviral proteins such as VP4, VP3, and VP2 can be readily visualized in the postmortem heart and endomyocardial biopsy specimen [93].

6. Differential Diagnosis

In the pediatric population, a viral etiology is the diagnosis for new onset of heart failure and/or cardiogenic shock. In adults, viral myocarditis will present more insidiously and, without a high index of clinical suspicion, can be misdiagnosed as heart failure secondary to ischemic heart disease, diabetes, hypertension, or valvular heart disease.

For new onset heart failure of less than 3 months duration, idiopathic giant cell myocarditis (IGCM) should be considered the patients fail conventional therapy for heart failure [94]. The diagnosis requires endomyocardial biopsy with histologic evidence for diffuse inflammatory lymphocytic infiltrate and occasion myocyte necrosis interspersed with eosinophils, and multinucleated giant cells [94]. Immunosuppression therapy has been used for IGCM [95,96], but no published studies have established benefit [97].

Other infections agents that mimic viral and postinfectious myocarditis include Chagas' disease, the most common cause of congestive heart failure caused by *Trypanosoma cruzi* in endemic regions of South America. This parasitic infection is largely immune mediated for which treatment

with antiprotozoal therapy with nifurtimox or benzimidazole is beneficial. Likewise, diphteritic myocarditis has been reported in 22% of patients with a case-fatality rate of 3% during an outbreak [98]. Combination therapy with diphtheria antitoxin and antibiotics are usually effective.

VII. TREATMENT

The treatment of viral myocarditis has evolved considerably over the past decades. From basic and clinical research the recognition of multiple causes and triphasic processes of myocarditis has led to many potential therapies (Table 4). However, few treatments have been tested clinically and, to date, none has been shown to be effective in patients with myocarditis. Yet, several strategies remain remarkably innovative and promising. These approaches can be succinctly summarized as follows: 1) direct or immunological approaches are needed to identify the virus, if viral-specific therapy is to be initiated; 2) In Phase 2, endomyocardial biopsy is recommended before immunosuppression and immune modulation therapy, and 3) in Phase 3 of the disease, the clinical recognition and management of dilated cardiomyopathy should follow conventional standards of care to address specific common conditions such as heart failure, thromboembolic disease, and sudden death. Many patients with dilated cardiomyopathy will eventually become candidates for cardiac transplantation

Table 4

Therapy	Status
Intravenous immunoglobulins	Uncontrolled trials in humans suggest efficacy
IgG adsorption	Effective in case-control studies in humans with idiopathic dilated cardiomyopathy
Anti-tumor-necrosis factor-α antibody	Effective as early therapy in mice
Nitric oxide inhibition	Pimobendan efficacy in mice may be mediated by inhibition of inducible nitric oxide synthase
T-cell antigen receptor-based DNA vaccines	Effective in murine autoimmune carditis
Tacrolimus	Effective in various murine models
FTY720	Reduces inflammatory infiltration in rats when administered early
Vesnarinone	Improves survival and reduces myocardial damage in mice by inhibiting natural killer cell activity
β-adrenergic respetor blockers	Metropolol is ineffective but carteolol is effective in improving CHF in murine models, a β1-agonist is beneficial, no human studies
Calcium channel blockers	Amlodipine appears to be the most effective calcium antagonist in experimental models
α-adrenergic receptor blockers	Helpful as early and protracted therapy
Angiotensin –converting enzyme inhibitors	Enzyme inhibitors and receptors blockers reduce myocardial injury in experimental myocarditis
Mu-Fang-Ji-Tang	Chinese herbal medecine improves CHF in murine myocarditis

Mason J. Treatment of Lymphocytic Myocarditis. In: Cooper LT, ed. *Myocarditis From Bench to Bedside*. Totowa, New Jersey: Humana Press; 2002:391-403.

1. Treatment during Phase 1

During Phase 1 of infection, therapy is primarily supportive but several concerns pertaining to management of patients are noteworthy. Antivirals that inhibit enteroviruses (e.g. Coxsackieviruses,

adenoviruses), the predominant forms of human viral myocarditis, have not been clinically proven. In theory, the administration of specific viral inhibitors should be efficacious for influenza viruses (amantidine, rimantadine), non-HIV viruses (ribavirin, lamivudine), and herpesviruses (ganciclovir, acyclovir). However, these therapeutic agents have not yet been tested clinically in randomized trials of human viral myocarditis.

2. Immunosuppressive and immunomodulation therapies-Phase 2

a. clinical trial and immunosuppressive therapy. Despite the well-established role that autoimmunity plays in viral-mediated myocarditis, the results of completed clinical trials have been disappointing. Earlier studies were designed to module autoimmune mechanisms so that patients meeting the very stringent criteria of viral-induced myocarditis were randomized to receive either prednisone (60 mg/day) or placebo [99]. Eligibility for enrollment was based on the 'Dallas criteria' for viral myocarditis [11]. Despite an initial improvement, at 3 months, in patients randomized to receive steroid treatment, the clinical benefit such as improved left ventricular function was not sustained after 6 months [99].

The US Myocarditis Treatment Trial was sponsored by the National Institutes of Health to determine whether patients with Dallas Criteria for myocarditis could benefit from immunosuppressive therapy. In this multicenter trial, 111 patients were enrolled to received either conventional therapy or immunosuppression combined with either cyclosporin or azothioprine. At completion after 4.3 years follow-up, left ventricular function was indistinguishable between treatment groups, and, correspondingly, there was no benefit in mortality that reached 20% in 1 year and 56% after follow-up [100].

What lessons have we learned from immunosuppression trials? In retrospect, the patients randomized to receive either to immunosuppressive therapy or placebo in the US Myocardial Treatment Trial showed the 3 phases of disease progression. For example, evidence for an aggressive 'early' immune response and a higher proportion of cardiac-specific IgG in correlated with decreased mortality [100] & Figure 6.

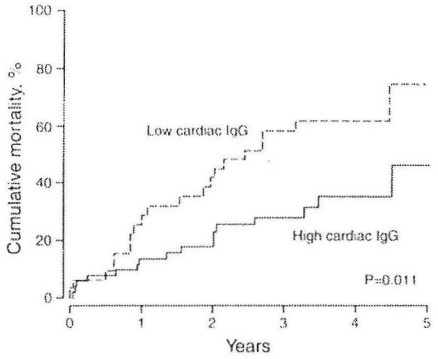

Figure 6. A high concentration of circulating cardiac-specific IgG and was a univariate predictor of decreased mortality. From Mason et al: Immunopathogenesis and treatment of myocarditis the United States Myocarditis Treatment Trial. J Card Fail Supp4:S173-1777, 1996 [101].

In contrast, the possibility that the autoimmune response was triggered by an increased late immune activation (e.g., CD2+ T cells) was more likely present in patients with a poor outcome with dilated cardiomyopathy, a sequalae in the late phase of the disease [2]. In the US Myocarditis

Treatment Trial, some observers have attributed the lack of a treatment benefit with immunosuppression to the scant evidence of inflammatory foci, and, indeed, progression into Phase 3 of the disease at enrollment [100]. It is conceivable that patients with Phase 3 and lymphocytic infiltrate would be unresponsive to immunosuppression therapy in this trial.

b. Immunoglobulin therapy. Ig has been proposed to ameliorate autoimmunity in the pathogenesis of dilated cardiomyopathy. In uncontrolled trials of patients with New York Heart Association (NYHA) class III to IV and depressed left ventricular ejection fraction (LVEF < 40%), treatment with high dose immunoglobulin infusions (2 g/Kg) improved clinical stage to class I to II on discharge and ventricular function when assessed after 12 months [102]. It is concurrently believed that immunoglobulin may act against antibody-mediated autoimmunity rather than viral suppression.

Ongoing trials such as the European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease, ESETCID, a multicenter randomized trial in progress, will address whether or not either immune globulin and/or interferon is effective in the treatment of viral myocarditis [103,104]. The results of this trial are soon anticipated but enrollment has been slow (Dr. Jay W. Mason, personal communication).

3. Management of Dilated Cardiomyopathy and heart failure-Phase 3

a. Conventional therapy. The management of idiopathic dilated cardiomyopathy and congestive heart failure entails well-established clinical therapy. The treatment of heart failure after myocarditis is primarily supportive and encompasses diuretics, inotropic agents, β-adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, and anti-arrhythmic therapy. ACE inhibitors can retard or ameliorate ventricular remodeling, and spironolactone is appropriate for the treatment of heart failure. There is no evidence that patients with IDCM and chronic heart failure should empirically receive immunosuppressive therapy. However, some authors have recommended monitoring for recurrent viral infection or relapsing autoimmunity [12].

Patients presenting with symptomatic supraventricular arrhythmias should be considered either for amiodarone or ablation therapy. After appropriate evaluation, the management of atrial fibrillation, may warrant long-term anticoagulation to prevent thromboembolic complications.

b. Sudden death and Implantable cardioverter defibrillators (ICD). Patients with viral-induced DCM are at increased risk of sudden death that accounts for one-half of all deaths in the United States [105]. An implantable cardioverter defibrillator (ICD) is a device that senses ventricular tachycardia or fibrillation and delivers an electrical shock, thus terminating a life-threatening arrhythmia. In randomized-controlled clinical trials, ICD therapy has been beneficial for patients with sudden death, symptomatic ventricular arrhythmias, and those with low ejection fraction from ischemic heart disease [106], independent of life threatening arrhythmias [107]. However, the available evidence does not support that similar benefits are likely in patients with idiopathic DCM. In the Cardiomyopathy Trial (CAT), a small randomized trial of DCM patients of recent onset and low ejection fraction (EF< 30%) showed that ICD implantation has a neutral effect on all cause mortality [108]. Owing to their adverse effects on mortality, the use of anti-arrhythmic therapy is currently not recommended for life-threatening ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy except in whom ICD is contraindicated. On the other hand, the use of β-blockers is underutilized [109] and can reduce the incidence of electric shocks for patients on ICD therapy with DCM [109].

VIII. PROGNOSIS

Complete recovery with an excellent prognosis can be expected in most cases of uncomplicated myopericarditis. The development of develop myocarditis in neonates in the first

month, often from nursery outbreak or from infected mothers can progress into multisystem illness with extension to the liver and central nervous system. Clinical signs such as feeding difficulty, lethargy, and fever are proceeded by either cardiac or respiratory distress syndrome, or both. The initial infection with myocardial involvement sets the stages for the multiple phases of myocarditis, which can, occasionally, be punctuated with re-infection and autoimmune reactivation of the disease. The older patient typically seeks medical attention for management of congestive heart failure and, perhaps, dilated cardiomyopathy [13]. In patients with DCM, the risk factors for sudden death are a positive signal-averaged ECG, low heart rate variability index, inducible ventricular tachycardia or fibrillation, nonsustained ventricular tachycardia, and left ventricular dysfunction.

In their recent study of 21 consecutive patients with viral myocarditis, Fuse and coworkers have suggested that the proinflammatory cytokines might accelerate a poor outcome [110]. Patients who succumbed to their illness showed elevation of pulmonary capillary wedge pressure, low systolic reserve, systemic hypotension, and higher requirements for mechanical support compared with when survivors of viral myocarditis. In particular, the biochemical abnormalities were greater in individuals with a fatal outcome that survivors for soluble Fas, sFas (13.93+/-4.77 versus 3.77+/- 0.52 ng/mL, respectively; $p< 0.001$) and its ligand, sFasL (611.4+/-127.7 versus 269.5+/-37.3 pg/mL, respectively; $p<0.05$) [111].

Implications of Fulminant vs Non-fulminant myocarditis on Natural History. In a recent study, McCarthy and coworkers reported on the clinical outcome of 147 patients consistent with myocarditis on endomyocardial biopsy and the Dallas histopathological criteria [112]. Among 15 patients who the clinical criteria for fulminant myocarditis (i.e., severe hemodynamic compromise, abrupt onset of symptoms, and fever), 93 % were alive without a heart transplant after 5.6 years follow-up compared with 45% with milder myocarditis [112]. Although the underlying etiology and mechanisms are still poorly understood, these dramatic findings and other studies underscore that aggressive management and supportive care such left ventricular-assist devices are appropriate for patients with fulminant myocarditis, given the excellent long-term prognosis [112].

IX. FUTURE DIRECTIONS IN BASIC RESEARCH

Genetically engineered animal models have emerged as powerful tools for molecular and genetic studies of human diseases. Dilated cardiomyopathy seen in patients after viral infection has been successfully recapitulated in different species (e.g., mice, hamsters). Both viral (e.g., Coxsackievirus) and nonviral (e.g., myosin) agents evoke myocarditis in susceptible murine models that mimic the histopathological changes of viral-induced lymphocytic myocarditis seen in humans. Cardiac myosin-induced model of myocarditis is mediated by T-cell activation and autoantigen presentation through a MHC-dependent pathway. Using this model, Bachmaier and coworkers have recently shown mice lacking the low MW p55 receptor for TNFα are less susceptible than wild-type strains to coxsackieviral infection, coincident with activation of 'autoaggressive' T and B lymphocytes and production of myosin-specific IgG autoantibodies [113], providing genetic evidence about the role inflammatory mediators play in human myocarditis.

In experimental murine models, efforts to suppress viral entry, attachment and replication have been shown to reduce the severity of viral myocarditis, suggesting that similar strategies might have a beneficial outcome in patients with suspected viral myocarditis.

Since steroid treatment against viral myocarditis can exacerbate the disease, Rose and coworkers at Johns Hopkins have pursued an alternative hypothesis that delivery of myosin through a

nasal route can produce antigen-specific tolerance and suppress autoimmune myocarditis in a murine model [114]. Pretreatment (3 days) with intranasal cardiac myosin (200 μg/mouse) significantly suppressed the histopathological and proinflammatory manifestation of myocarditis seen in A/J mice are administered two SQ injections emulsified in Freund's adjuvant compared to untreated controls [114]. Suppression of myocarditis after nasal challenge corresponded with decreased levels of TNF-α, IL-1β, but had not measurable effects on either TGF-β or IgG-specific levels, suggesting that immunological tolerance is mediated by deletion of Th1 and Th2 autoreactive T cells [114]. Recent studies from the Rose group have suggested that the mechanism of nasal tolerization requires induction of IL-10 during the effector phase, suggesting that direct inflammatory mediators play key roles in the disease process [115]. Taken together, these studies provide proof of concept that future efforts for the treatment of autoimmune disease might include immunomodulatory strategies directed to antigenic stimuli that trigger viral myocarditis.

Investigations of the genetic, molecular, immunological and clinical events of viral myocarditis have relied extensively on animal models in susceptible hosts. However, many promising results in murine models are not always reproducible in humans, indicating the need for caution in extrapolation of findings from animals to humans. The genetic background and effects of modifiers on either viral-mediated myocarditis and/or immunological response might explain some differences. Emerging technologies such as proteomics and genomics, both in experimental models and patients, might lend important insights into the pathogenesis of human viral myocarditis.

X. FUTURE DIRECTIONS IN CLINICAL RESEARCH

Although recognized for almost two centuries, there are no clinically proven effective therapies for viral myocarditis. Molecular aids using PCR and other serologic methods are likely to speed diagnosis with greater accuracy and specificity. Since completion of the US Myocarditis Treatment trial, the ongoing ESETCID trail in progress is next large scale effort to address the role of immunodulation therapies using immune globulin and interferon [103]. Meanwhile, opportunities for therapeutic advances are likely to focus on candidates such as T-cell tyrosine kinase, $p56^{lck}$, and the Coxsackie's-adenovirus receptor/co-receptor complex, which can elegantly target the site of viral entry.

Thus, considerable enthusiasm has been generated for potential agents that block viral entry at the coxsackieviral adenoviral receptor complex (CAR). Potential targets against CAR include the specific antiviral agents such as the nucleoside analogue, Ribavirin [116], while immune globulin and interferon function act by boosting the intrinsic immune system [102,117,118]. In parallel, medical providers must be alert to epidemiological shifts in the prevalence of cardiotropic agents such as hepatitis C that can contribute to new cases of viral myocarditis worldwide. Likewise, it is anticipated that the global effort in basic and clinical research on AIDS will yield spin-offs in pathogenesis, vaccine development, and other unforeseen benefits for the treatment and prevention of viral mediated diseases in humans.

Considerable recent attention has been paid to the development of effective vaccines. Populations at high risk such as children and young adults, the most susceptible segments of the population, might benefit from an effective vaccination program. Pathogenic T cells are potential targets for blockade since receptor-mediated autoimmunity has been implicated in viral myocarditis. Likewise, nasal tolerization against myosin, a common antigen after acute myocardial infarction, would have important therapeutic implications beyond non-viral-induced myocarditis [119].

XI. CONCLUSION

There is irrefutable evidence that, among human pathogens, viruses are important etiologic agents in the development of viral myocarditis leading to dilated cardiomyopathy. However, the majority of patients with dilated cardiomyopathy would have escaped medical attention since the onset of viral infection is often insidious and nonspecific, and complete recovery is usually expected. There is insufficient clinical evidence to recommend primary prevention strategies (e.g., vaccines) for viral-induced myocarditis. For symptomatic cases, therapy must be individualized since the etiologies are diverse and efficacy, in most instances, remains unproven. Cardiac imaging with MRI can be an effective screening tool, and with exclusion of other etiological factors, the subset of patients eligible for the immune suppression can be identified using available biochemical and immunological markers and treatment instituted. Most importantly, future efforts are needed to forge consensus for treatment of the inflammatory phases and prevention of viral sequalae, beckoning us to pursue the fundamental understanding into disease mechanisms, from the bench to the bedside.

XII. ACKNOWLEDGMENTS

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