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Foreword to special issue on "Myocarditis"

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There are three phases to treatment: diagnosis, diagnosis and diagnosis
William Osler W. (1892) Principles and practice of medicine

William Osler, with a very actual sentence, stated, back in year 1892, in its Medicine textbook: "There are three phases to treatment: diagnosis, diagnosis and diagnosis" [1]. This sentence clearly highlights that the best clinical management is based upon the most accurate diagnosis. Historically myocarditis has being considered a rare and poorly understood condition, a conundrum with polymorphic clinical presentation and variable prognosis ranging from spontaneous resolution to progressive heart failure and death. The first comprehensive review with a modern approach to etiopathogenesis was published in 1980 by Woodroof JF, who highlighted the possible etiological role of Coxsackie viruses and of the immune system in the progression of cardiac damage, with possible evolution to a dilated cardiomyopathy [2]. A major advance in diagnosis was the refinement of the endomyocardial biopsy technique using the King's bioptome by Richardson [3]. Another important step was the development of a consensus pathological classification and histological definition of myocarditis by endomyocardial biopsy, known as the Dallas criteria [4]. Meanwhile, the first experimental observations were made by several investigators, suggesting a possible involvement of autoimmune mechanisms to cardiac autoantigens; in particular, a mouse model for myosin-induced autoimmune myocarditis was described by the Neu et al. [5]. In addition, various groups in the late 80s and early 90s reported the presence of circulating anti-heart autoantibodies against myosin as well as other autoantigens in acute and chronic myocarditis or dilated cardiomyopathy, in keeping with the hypothesis of autoimmunity being involved in a subset of patients [6–14]. A retrospective multicenter registry from the USA coordinated by Cooper et al. [15] reported the efficacy of immunosuppressive therapy in a rare but lethal form of myocarditis, e.g., giant cell myocarditis. On these premises, the multicenter Myocarditis Treatment Trial was designed using the Dallas criteria to recruit myocarditis patients to 6 months immunosuppression; the therapy with azathioprine and prednisone or cyclosporine A and prednisone was well tolerated, and no significant effect on survival was observed, although the study was not powered to detect differences in survival [16]. The results of the trial had a profoundly negative effect in the next decade on the use of endomyocardial biopsy to detect and treat myocarditis. However, researchers developed new diagnostic tools to be added to standard histology, in particular immunohistochemistry, to increase sensitivity of endomyocardial biopsy particularly in focal and chronic myocarditis and characterize the number and type of infiltrating inflammatory cells, and molecular detection of genomic material of infectious agents mainly by polymerase chain reaction (PCR), to diagnose infectious, particularly viral myocarditis [17–24]. This work leads to another major step forward, e.g., the 1995 WHO classification of cardiomyopathies, with the acknowledgment that myocarditis is diagnosed on endomyocardial biopsy by established histological, immunological and immunohistochemical criteria; molecular techniques on EMB were recommended to identify viral etiology [25]. In the WHO classification, infectious, autoimmune and idiopathic forms of myocarditis are recognized that may lead to dilated cardiomyopathy [25]. Using serum cardiac autoantibody testing as well as histology, immunohistology and viral PCR on endomyocardial biopsy, it is nowadays possible to define distinct etiopathogenetic

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subsets of myocarditis, in particular infectious versus immune-mediated, e.g., infection-negative forms [26]. This characterization is a key to define who are the infection-negative cases in which immunosuppression and immunomodulation may be beneficial. Conversely, immunosuppression and immunomodulation are contraindicated in patients with active myocardial infection. In the last years, another fundamental step has been the development of cardiovascular magnetic resonance imaging (CMR) as noninvasive imaging tool in inflammatory heart muscle disease [27, 28]. CMR does not replace endomyocardial biopsy in the diagnosis of myocarditis, it is currently unable to differentiate between infectious and immune-mediated forms, but is a valuable tool to refine the clinical suspicion of myocarditis and for noninvasive follow-up [27–29]. Even more importantly, it is revealing a much more broader prevalence of clinically suspected and unsuspected myocarditis especially in patients with minor symptoms, e.g., young patients with unexplained arrhythmia, or troponin positive patients with normal coronary arteries [28].

In this Special issue, basic and clinical researchers who provided major contributions to the myocarditis field in the last 20 years give an expert overview of some hot issues, from definition and classification to diagnosis and treatment. This work would not have been possible without the serendipity and support of the Editor of Heart Failure Reviews, Dr Sidney Goldstein, who suggested dedicating a special issue to a rare and generally neglected cause of heart failure. The issue is addressed to clinicians as well as basic scientists with an interest in this fascinating disease that most frequently affects young people and is dedicated to our patients, the lucky ones, who underwent cardiac transplantation, and especially those, the unlucky ones, who died because of sudden cardiac death or waiting for a new heart. It is worth noting that many contributors to this Special issue were directly, as authors, or indirectly, as reviewers, members of a European Myocarditis Task Force that produced the first consensus document on myocarditis, that will hopefully facilitate the design of new multicentre trials of etiology-directed treatment in different myocarditis forms, e.g., infectious and immune-mediated, according to the consensus criteria [29]. We are after all following the inspiration of one of the giants in Medicine, William Osler, and hope that his approach will lead to new and effective treatments for our myocarditis patients.

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