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16.7 Diseases of heart muscle CONTENTS 16.7.1 Myocarditis 3459 Jay W. Mason and Heinz-Peter Schultheiss 16.7.2 The cardiomyopathies: Hypertrophic, dilated,
restrictive, and right ventricular 3468 Oliver P. Guttmann and Perry Elliott 16.7.3 Specific heart muscle disorders 3489 Oliver P. Guttmann and Perry Elliott 16.7.1 Myocarditis Jay W. Mason and Heinz-Peter Schultheiss ESSENTIALS Myocarditis can be acute, subacute, or chronic and may affect either focal or diffuse areas of the myocardium. It has many infectious and noninfectious aetiologies, but viral infections are the main cause in most regions, with notable exceptions such as Chagas myocarditis in South America. The condition often results in congestive heart failure and is a common cause of chronic dilated cardiomyopathy, also called in- flammatory cardiomyopathy. It can present with (a)typical chest pain, palpitations, ventricular arrhythmias, syncope, or even ful- minant heart failure. Patients with lymphocytic myocarditis are usu- ally young (average age in the forties) and often report an antecedent viral illness. The disease can be diagnosed by demonstration of lymphocyte infiltration and adjacent myocyte damage on endomyocardial bi- opsy, and molecularly by the detection of viral genomic material and tissue markers of immune

activation in biopsy specimens. MRI and other imaging techniques are helpful in making the diagnosis, but their sensitivity and specificity is not sufficient in the chronic phase; hence endomyocardial biopsy remains the gold standard for defini- tive diagnosis and the basis for guiding clinical management in un- explained heart failure. Adverse immune activation is the primary cause of myocardial damage in most cases, hence appropriately timed immunosup- pressive therapy, most commonly with a steroid (prednisolone) and azathioprine, improves outcome in a significant number of cases. Antiviral therapies with interferon β in coxsackie- and adenovirus positive myocarditis are promising, although prospective random- ized studies have not been done. Specific forms of myocarditis include peripartum myocarditis, Lyme carditis, cardiac sarcoidosis, giant cell myocarditis, eosinophilic myocarditis, and Chagas carditis, each of which requires specific diagnostic and therapeutic measures. Introduction Myocarditis has captured the interest of clinicians and scientists because of its varied aetiology, its diagnostic and therapeutic chal- lenges, and the possibility that myocarditis may be the primary cause of so-called dilated cardiomyopathy. Scientific study of myo- carditis is facilitated by the availability of numerous easily manipu- lated animal models of the disease and by new molecular probes. Epidemiology Myocarditis affects young people: the average age of patients in the United States Myocarditis Treatment Trial was 42 years. There was a slight male predominance (62%) in that trial, but other series have not demonstrated a gender predilection. The true incidence of myocarditis is unknown: autopsy studies have reported figures of up to 3%, but varying histological criteria were used, and myocar- ditis may occur as an incidental complication of other fatal illnesses. About 10% of patients with influenzal infections have electrocar- diographic abnormalities, but it is not known if these are the result of myocarditis. The incidence of fatal myocarditis was estimated in a retrospective review of United States Air Force recruits under- going boot camp training: there were eight such deaths over 1 606 167 person days, which yields an estimate of 4/100 000 per year in people aged 17–28 years, perhaps somewhat greater than would be expected in the general population in the United States of America, who would not be exposed to similar levels of intense exercise or high probability of transmission of viral illnesses. A recent study

section 16 Cardiovascular disorders 3460 using International Classification of Diseases Codes estimated the global prevalence of myocarditis to be 22 of 100 000 people annu- ally. Studies addressing the issue of sudden cardiac death in young people report a high but variable autopsy prevalence of myocarditis, ranging from 2% to 40% cases. Aetiology and pathogenesis The most common form of myocarditis in Europe and North America is known as lymphocytic myocarditis or autoimmune myocarditis. Other frequently applied terms are viral or post-viral myocarditis, because an antecedent viral infection is common (Table 16.7.1.1). Indeed, some experts believe that nearly all Table 16.7.1.1 Aetiologies of myocarditis Infection Viruses Adenovirus Arbovirus Arenavirus Coronavirus Coxsackievirus (A, B) Cytomegalovirus Dengue virus Echovirus Encephalomyocarditis Epstein–Barr Hepatitis B Hepatitis C Herpes simplex Human herpesvirus-6 Human immunodeficiency Influenza (A, B) Junin Metapneumovirus Mumps Parvovirus (B19, bocavirus-2) Polio Rabies Respiratory syncytial virus Rubella (German measles) Rubeola (measles) Vaccinia Varicella-zoster virus Variola Zika virus Bacteria, spirochaetes, and bacteria-like organisms β-Haemolytic streptococci Borrelia burgdorferi (Lyme disease) Brucella spp. Campylobacter jejuni Chlamydia (psittaci, trachomatis, pneumoniae) Clostridia spp. Corynebacterium diphtheriae Francisella tularensis (tularaemia) Gonococcus Haemophilus influenza Legionella pneumophila Leptospira spp. Listeria monocytogenes Mycobacterium spp. Mycoplasma pneumoniae Neisseria meningitides Salmonella (berta, typhi) Streptococcus pneumoniae Staphylococcus spp. Treponema

pallidum (syphilis) Tropheryma whipplei Rickettsia Coxiella burnetii (Q fever) Orientia tsutsugamushi (scrub typhus) Rickettsia rickettsii (Rocky Mountain spotted fever) Rickettsia prowazekii (typhus) Protozoa Entamoeba histolytica Leishmania spp. Plasmodium vivax Toxoplasma gondii Trypanosoma cruzi (Chagas disease) Helminths Cysticercus Echinococcus spp. Schistosoma spp. Toxocara spp. Trichinella spp. Fungi Actinomyces spp. Aspergillus spp. Blastomyces dermatitides Candida spp. Coccidioides immitis Cryptococcus neoformans Fusarium Oxysporum Histoplasma capsulatum Mucor Nocardia spp. Sporothrix schenckii

16.7.1 Myocarditis 3461 lymphocytic myocarditides are the result of viral infections, pre- sumed to be subclinical in those patients with no awareness of a viral prodrome. In the past, cardiotrophic enteroviruses including echoviruses and coxsackieviruses were the predominant aetiological agents, but new data has demonstrated the following genomic distribu- tion: parvovirus B19 (36.6%), enterovirus (32.6%), human herpes virus 6 (10.5%), and adenovirus (8.1%). However, dozens of viruses have been implicated and many more undoubtedly cause myocar- ditis in humans; hence in clinical practice it is impractical to exclude them all. However, the knowledge of a specific virus (e.g., influenza A, Coxsackie-, Adeno-, or HHV6 virus), as the cause in a given case of myocarditis may have significant therapeutic relevance if viricidal therapy is being considered. In animal models, enteroviruses such as coxsackie B3 can cause three phases of myocarditis. The first is the result of direct injury of myocytes by viral entry, resulting in activation of innate immunity. During the second phase, which can last several weeks to several months, viral replication and activation of the acquired immune response occur. Phase three is characterized either by recovery or development of dilated cardiomyopathy. The underlying mech- anisms are complex and incompletely understood, but most hy- potheses suggest that autoimmune phenomena play a major role. In some instances molecular mimicry may be involved, in which the similarity of a viral antigen to a myocardial protein triggers an autoimmune reaction. In others an autoimmune response to cellular proteins released during the viral replication phase may occur, and myosin has been implicated in this regard. Cytokines arising from immune activation and cellular necrosis probably play a role in some cases, bringing about further cellular damage, such as through activation of matrix metalloproteinases. Viral persist- ence appears to induce a chronic adverse immune response and, as a result, to correlate with a poor prognosis. However, although these mechanisms have been well delineated in murine models, they have not been proven to cause myocarditis in humans, nor has their delineation generated therapies proven to be effective by prospective randomized studies. It also has to be emphasized that some viruses can cause myocar- ditis by the infection of endothelial cells. For example, parvovirus B19 primarily infects endothelial progenitor cells which then leads to an infection of cardiac endothelial cells. This can increase the cor- onary resistance, trigger coronary vasospasm, and induce myocyte necrosis. Myocarditis may also result from a hypersensitivity reaction to a drug or other agent (see Table 16.7.1.1). In these cases, eosino- phils accompany the inflammatory lymphocytic infiltrate. A few patients, perhaps about 10%, present with a secondary form of myo- carditis: these special presentations are discussed next. Recently human-induced pluripotent stem cell-derived cardio myocytes were introduced as a way to model the cardiomyocyte’s interaction with cardiotropic viruses, which offers an opportunity to examine possible prevention and treatment candidates directly in the infected human cell, even though the immune system is excluded. Drugs and chemicals Toxicity 2-Interferon Amphetamines Animal and insect toxins Anthracyclines Arsenic Cannabis Catecholamines, endogenous and exogenous Cocaine 5-Fluorouracil Interleukin 2 Lithium Paracetamol Paraphenylene diamine (hair dye) Hypersensitivity Aminophylline 5-Aminosalicylic

acid Ampicillin Azithromycin Benzodiazepines Clozapine Dapsone Digoxin Ephedrine Furosemide Hydrochlorothiazide Methyldopa Olanzapine Penicillin Phenytoin Quetiapine Sulfasalazine Tetracycline Tricyclic antidepressants Autoimmunity Antigenic mimicry Autoimmune disease associated Cardiac myosin Checkpoint inhibitor therapy Cytokines Dolutegravir therapy Dressler's syndrome Post-cardiotomy syndrome Post-infection Post-radiation

section 16 Cardiovascular disorders 3462 Relationship to idiopathic dilated cardiomyopathy Classic lymphocytic myocarditis can resolve, with resultant im- provement in cardiac function over weeks or months: 50% of pa- tients presenting with significant left ventricular dysfunction will have complete recovery, but 25% will go on to have chronic systolic dysfunction and about 25% will progress towards end-stage heart failure. In the United States Myocarditis Treatment Trial, the mean left ventricular ejection fraction improved during the year after ini- tial presentation by more than 10 ejection fraction units (from 24% to 36%; normal >55%). However, residual cardiac dilatation and dysfunction were common, and mortality was high, reaching 55% at 5 years. In those patients who do not recover fully, the ensuing clin- ical picture cannot be distinguished from that of idiopathic dilated cardiomyopathy. The possibility that myocarditis may occur without an obvious viral prodrome therefore raises the interesting possibility that viral myocarditis may be a common covert cause of idiopathic dilated cardiomyopathy. In the United States trial, only 10% of patients with suspected myocarditis had positive biopsies according to the Dallas classification. The fact that the histological evaluation of endomyocardial biopsy usually does not reveal myocarditis in pa- tients with idiopathic dilated cardiomyopathy may be the result of timing of the biopsy after resolution of the lymphocytic infiltrate, sampling error, or the inability to detect the inflammatory process. Immunohistochemistry using a large panel of monoclonal anti- bodies for characterization and quantification of infiltrating immune cells provides additional information and is regarded as obligatory today. Retrospective analysis has shown that the characterization and quantification of different infiltrative cell types (e.g. perforin- positive cytotoxic cells) are of high prognostic value and essential for deciding whether or not a patient should be treated. The presence of viral genomic material in endomyocardial biopsies—particularly persisting viral genome in follow-up biopsies—was associated with progressive left ventricular dysfunction and a higher mortality rate, whereas spontaneous viral clearance was associated with a signifi- cant improvement of left ventricular dysfunction. Absence of viral genome does not, however, eliminate post-viral autoimmune pro- cesses, proceeding despite complete viral clearing, as a possible aetiology. The fact that immunomodulatory therapy can improve cardiac function in patients with inflammatory cardiomyopathy, and even in dilated cardiomyopathy without lymphocytic myocardial infil- trates, adds indirect evidence that dilated cardiomyopathy has an inflammatory origin in a significant percentage of cases. Even in patients with so-called genetic cardiomyopathy, a genetic predis- position can interact with intrinsic or environmental factors. In this context a robust proinflammatory response in dilated cardio- myopathy hearts, likely in response to cellular damage triggered by MYBPC3 mutation and resultant contractile dysfunction, could be shown. This explains why patients with the same genotype develop different phenotypes, and vice versa. Clinical features In Europe and North America most cases of myocarditis present with congestive heart failure of unknown cause. In many instances there is a history of recent upper respiratory tract infection or of a 'flu-like' illness. This is followed by symptoms of cardiac decom- pensation, usually fatigue, breathlessness, and cough. Chest pain occurs in a substantial minority of patients, and—when com- bined with regional ST-segment shifts on the electrocardiogram (ECG)—can mimic acute myocardial infarction. A few patients present with ventricular tachyarrhythmias and minimal

or no car- diac dilatation. The usual duration of symptoms due to infection is brief, less than 1 month in approximately 50% of patients and nearly always less than 1 year. Myocarditis should always be suspected when a pa- tient presents with unexplained congestive heart failure with a rapid onset, especially if there is a viral prodrome. In adults under the age of 40, the combination of typical chest pain and a significant rise in troponin I is more likely due to myocarditis than to myocardial in- farction, and fever or a viral prodrome are usually reported by those with myocarditis. Clinical examination typically reveals signs of cardiac failure. Investigation The ECG may show conduction abnormalities, ST/T-wave changes (including persistent ST-segment elevation that does not proceed to Q-wave development), or arrhythmias (atrial or ventricular). The chest radiograph shows cardiomegaly and—in acute fulminant cases—pulmonary oedema. The echocardiogram reveals four- chamber dilatation and reduced contractility, and is notable for the fact that valvular disease is absent or minimal. Speckle tracking imaging is a new and promising method which gives additional information regarding regional contractility. Global longitudinal strain and strain rate are significantly impaired in patients with biopsy-proven myocarditis. Cardiac scintigraphy with indium-111 antimyosin antibodies and single photon emission computed tom- ography (SPECT) have been used to detect myocarditis. Cardiac MRI is the most reliable noninvasive method for diag- nosis, and can be used to distinguish acute myocardial infarction, acute myocarditis, and healed myocarditis. Contrast-enhanced MRI allows assessment of the regional extent of myocardial involvement. Detection of a pericardial effusion on the MRI increases the prob- ability of a diagnosis of myocarditis, and injection of fluorine-19, which is taken up by inflammatory cells, is a promising method for MRI detection of localized inflammation due to myocarditis. However, it must be emphasized that the diagnostic performance of MRI is significantly worse in chronic myocarditis, with a sensi- tivity and specificity of around 50%. In this context, it also has to be underlined that MRI is not able to detect viral persistence, which is a prerequisite for deciding if and how the patient should be treated. Furthermore, the nature and intensity of the inflammatory pro- cess, which is important for estimation of the prognosis, cannot be analysed. Endomyocardial biopsies (which have a complication rate of below 1% in experienced centres) using the standardized histopathological, immunohistological, virological, and molecular methods therefore remain the gold standard by which the diagnosis of the different forms of myocarditis is made and by which thera- peutic decisions can be made. Should coronary angiography be per- formed, the vessels are normal or show only minor abnormalities.

16.7.1 Myocarditis 3463 Elevation of serum cardiac biomarkers (e.g., troponin, creatine phosphokinase) is common. Dozens of viruses can cause myocarditis in humans, and it is im- practical to exclude them all. Some patients may present in the acute phase of the viral illness, as has recently been described in patients with influenza A (H1N1), but they usually present a substantial length of time after the viral infection has cleared, making it diffi- cult or impossible to document an acute rise in titre. However, the knowledge of a specific virus (e.g., influenza A, coxsackie-, adeno-, or HHV6 virus), as the cause in a given case of myocarditis may have significant therapeutic relevance if viricidal therapy is being considered, and in this context it should be restated that negative titres for the common viral agents do not exclude a viral aetiology. Management Virus-negative lymphocytic myocarditis/autoimmune myocarditis/inflammatory dilated cardiomyopathy As stated earlier, lymphocytic myocarditis is believed by most to have a viral aetiology, even in the absence of a clinically apparent viral pro- drome. In the acute phase of viral myocarditis, the direct cytolytic effect of viral myocyte infection may lead to congestive heart failure, although this is uncommon. In this early phase, the immune

response is likely, on balance, to be beneficial. Thus, antiviral therapy might be expected to be helpful, but on theoretical grounds immunosup- pressive therapy would not. However, though antiviral therapies have shown promise, none have been adequately tested in humans with acute myocarditis, although it is routine practice to administer neur- aminidase inhibitors such as oseltamivir to those with influenza A. In the second stage of myocarditis, thought to result from an ad- verse immune response to previous infection, immunosuppressive therapy has appeared to be beneficial in several trials. However, no benefit was demonstrated in the United States Myocarditis Treatment Trial, a prospective randomized trial performed in pa- tients with myocarditis defined histologically. In that trial the 'Dallas' criteria defined myocarditis histologically as a lymphocytic infiltrate with associated myocyte necrosis (Fig. 16.7.1.1). However, it must be emphasized that neither immunohistology nor viral gen- omic analyses were performed, and we now recognize these as an essential prerequisite for the decision as to whether a patient should be treated. Notwithstanding these concerns, it has become increasingly clear that immunosuppressive treatment in cases of viral–positive myo- carditis is not beneficial. Treatment with prednisone combined with either ciclosporin or azathioprine does not improve outcome, as de- fined by change in left ventricular ejection fraction. It is therefore appropriate to consider other diagnostic criteria, such as presence of viral genomic material and human leucocyte antigen upregulation on biopsy, circulating antiheart antibodies, and imaging, in the diag- nosis and treatment of myocarditis. RNA microarray analysis on bi- opsy specimens has been found to be highly sensitive and specific in differentiation of myocarditis from idiopathic dilated cardiomyop- athy, myocardial infarction, and other myocardial disorders associ- ated with inflammation. An algorithm for the diagnosis and treatment of suspected myo- carditis is shown in Fig. 16.7.1.2. This algorithm differs somewhat from recently published recommendations of the European Society of Cardiology (ESC), primarily in the use of endomyocardial biopsy, which is more liberally applied in the ESC consensus statement. Spontaneous improvement in left ventricular function can be antici- pated in about 50% of the patients. Thus, in the beginning it is rea- sonable to use standard therapy for congestive heart failure, without performing a biopsy or administering steroids, and to observe the patient, using echocardiography to monitor left ventricular function. However, in patients who do not improve in 8–12 weeks or even de- teriorate, or who present with cardiogenic shock, an endomyocardial biopsy should be performed as early as possible. As many experts would base a diagnosis of myocarditis on proven imaging techniques, such as contrast-enhanced MRI, in combination with a circulating biomarker such as cardiac-specific antibodies, it has to be empha- sized that endomyocardial biopsies remain the current gold standard for the diagnosis of myocarditis. Beside histological examination, more sophisticated techniques of immunohistology and molecular biology/virology are essential for a clear-cut diagnosis and the deci- sion whether and how the patients should be treated. If chronic, virus-negative myocarditis is present in patients with heart failure, immunosuppressive therapy should be administered, typically beginning with prednisone at 1.25 mg/kg per day, and azathioprine (Fig. 16.7.1.3). It must be admitted, however, that the efficacy of such treatment has not been proved by multicentre, pro- spective randomized studies, although Frustaci et al. clearly showed in a randomized placebo-controlled trial the positive impact of immunosuppression on recovery of left ventricular dysfunction in biopsy-proven virus-negative inflammatory cardiomyopathy. These data were confirmed by Escher et al. who could show the effect- iveness and beneficial haemodynamic effects of immunosuppres- sive therapy after 6-months, and in a long-term follow-up period up to 10 years. If the patient worsens despite this therapy, then endomyocardial biopsy should be repeated because of the sampling error regarding viral persistence. Viral positive myocarditis and inflammatory cardiomyopathy An algorithm for

management after endomyocardial biopsy is shown in Fig. 16.7.1.3. Direct antiviral treatments that have been Fig. 16.7.1.1 An example of acute myocarditis, with lymphocytic infiltration adjacent to frayed myocytes.

section 16 Cardiovascular disorders 3464 tested or proposed include interferon β, aciclovir, ganciclovir, foscarnet, and amantadine. Using polymerase chain reaction (PCR) technology and in-situ hybridization, viral RNA and DNA— mainly parvovirus B19, entero- and adenovirus, and human herpes virus 6—can be detected in endomyocardial biopsies of patients with myocarditis and inflammatory cardiomyopathy. In cocksackie- and adenovirus infection it has been shown that spontaneous and treatment-related viral clearance with interferon Usual presentation Ventricular tachyarrhythmia cardiogenic shock Continue standard treatment of CHF Monitor with echo Aggressive therapy of arrhythmia if present (e.g., ICD) Endomyocardial biopsy Patient improves haemodynamically MRI Echo & HM CHF treatment observe Suspected viral myocarditis or post-viral autoimmunity/inflammatory dilated cardiomyopathy Patient does not improve or worsens haemodynamically Negative for myocarditis Positive for myocarditis Differential diagnosis and differential therapies–see Figures 16.7.1.3 and 16.7.1.4 Fig. 16.7.1.2 Algorithm for diagnosis and treatment of suspected myocarditis. CHF, congestive heart failure; echo, echocardiogram; HM, Holter monitor; ICD, implantable cardioverter–defibrillator; MRI, magnetic resonance imaging. Endomyocardial biopsy Inflammation +/− Virus + Inflammation + Virus − Inflammation− Virus− Healed myocarditis LVEF >55% LVEF <55% Symptomatic therapy Risk stratification and heart failure therapy Dilated cardiomyopathy Genetic testing

- CD3 >10 cells/mm2
- CD45R0 >45 cells/mm2 -Perforin + cytotoxic T-cells

> 2.9 cells/mm2 Characterization Quantification Immunosuppressive therapy: corticosteroids & azathioprine Repeat EMB after six months Coxsackie virus + Adenovirus + Antiviral therapy Interferon-β Parvovirus B19 + Telbivudine or new drugs Immunohistology ci HHV6 + Viral load+ mRNA − Viral load + mRNA + Ganciclovir or valganciclovir No therapy Repeat EMB after six months Viral load+ mRNA − Immunohistology + Immuno- suppressive therapy: corticosteroids & azathioprine Repeat EMB after six months Fig. 16.7.1.3 Differential diagnosis and therapeutic options for endomyocardial biopsy-proven chronic myocarditis, inflammatory dilated cardiomyopathy, and dilated cardiomyopathy. EMB, endomyocardial biopsy; HHV6, human herpes virus 6; LVEF, left ventricular ejection fraction.

16.7.1 Myocarditis 3465 β is associated with clinical and haemodynamic improvement, but a prospective randomized study of this treatment in parvovirus B19 in- fection found it not to be effective. Retrospective analyses regarding the prognosis of parvovirus B19 have shown that the viral load is not important, but that active replication (evidenced by mRNA posi- tivity) and an accompanying inflammation in mRNA-negative pa- tients seem to be important. However, it has to be emphasized that up to now there are no useable or proven clinical data for the specific treatment of parvovirus B19 indicated in Fig. 16.7.1.3. Regarding HHV6 infection, it has been

shown that chromo- somal integrated (ci) HHV6 reactivation causes symptomatic pro- gressive heart failure symptoms, and that antiviral treatment with ganciclovir abolished viral mRNA and ameliorated cardiac symp- toms. Although there are no large prospective randomized studies to establish the efficiency of antiviral treatment, the clinical data clearly show that chronic viral infections and virus-associated in- flammatory processes cause myocardial damage and consequently ventricular dysfunction. An early biopsy-based diagnosis and timely treatment may therefore prevent disease progression and improve the clinical outcome. Immunomodulatory treatments including the application of intravenous immune globulins or immunoadsorption show conflicting results. They might be an option in individual cases, but the routine use of these methods cannot be recommended. Management of ventricular tachyarrhythmias in patients with myocarditis Lymphocytic myocarditis, with or without a viral prodrome, may present with ventricular tachyarrhythmias and little or no cardiac dilatation and dysfunction. An endomyocardial biopsy should be considered in all cases of ventricular tachycardia of recent onset if no aetiology is apparent, because the presence of myocarditis can substantially change treatment strategy. Since myocarditis is often a self-limited disorder, the patient's risk of recurrent ventricular tachyarrhythmias may resolve, and it may be unnecessary to subject them to electrophysiological study and/or cardioverter–defibrillator implantation. If arrhythmia does not improve spontaneously, a trial of immunosuppressive therapy should be considered. In such cases it is difficult to know how long to continue with antiarrhythmic drugs. The risks of ventricular arrhythmia should not be under- estimated, but nor should those of long-term treatment with agents such as amiodarone. If 24-h ECG monitoring at 6 months shows no sinister abnormalities, then many would withdraw antiarrhythmic treatment at that point, but others advocate repeat endomyocardial biopsy to document complete resolution of myocarditis before taking this step. In the case of severe ventricular tachycardia and an endomyocardial biopsy-based therapeutic option—for ex- ample, immunosuppressive therapy—the indication for a Life-Vest should be discussed before the implantation of an implantable cardioverter–defibrillator. Specific forms of myocarditis Specific forms of myocarditis and their treatments are shown in Fig. 16.7.1.4. Peripartum myocarditis Dilated cardiomyopathy developing during the last trimester of pregnancy or within 6 months of delivery is known as peripartum or postpartum cardiomyopathy. In some series the dominant cause is myocarditis. When heart failure develops rapidly in the first few weeks after delivery, myocarditis is more likely to be found on endomyocardial biopsy than when the onset is insidious and de- layed, and patients with early, rapid onset are more likely to recover quickly and completely. While steroid therapy has been used and is recommended by some, its efficacy has not been proved, and spon- taneous resolution of peripartum cardiomyopathy is well docu- mented. Bromocriptine, a dopamine D2 receptor agonist which blocks prolactin, seems to be a disease-specific treatment for this condition in addition to standard heart failure therapy. The usual prohibition against future pregnancy has been debated; it is very clear that some women risk recurrent heart failure, while others Peripartum Lyme Sarcoid Giant cell Eosinophilic Chagas • CHF at term or within six months of delivery Steroids recommended by some, but unproven Bromocriptine Amoxicillin or tetracycline indicated, but may not alter course
• Tick exposure • Typical rash • AV block common • Dilatation rare • Pulmonary or systemic disease • Increased serum ACE Steroids unequivocally indicated
• Autoimmunity • Rapid course Steroids + Ciclosporin + Azathioprine • Autoimmunity • Rapid course Steroids + Azathioprine • Central or South American residence or travel
• Complement fixation test Nifurtimox or benznidazone (probably only effective in acute Chagas) Therapeutic options for specific forms of acute myocarditis Acute myocarditis Autoimmune/ viral

(Dallas criteria) Specific treatment – follow up biopsy
Fig. 16.7.1.4 Suspected specific forms of myocarditis and their treatments. ACE, angiotensin converting enzyme; CHF, congestive heart failure; Comp fix, complement fixation; EMB, endomyocardial biopsy; AHA, antiheart antibody; PCR, polymerase chain reaction.

section 16 Cardiovascular disorders 3466 do not. In those women in whom severe heart failure persists, car- diac transplantation is an appropriate therapy. After transplant- ation, successful pregnancies have occurred without recurrence of cardiomyopathy. Lyme carditis Borrelia burgdorferi, a spirochete, infects humans following Ixodes tick bites. Lyme disease, which results from this infection, has been reported in 48 of the 50 United States, as well as in Europe and Asia (see Chapter 8.6.33). It is characterized by an erythema migrans rash and flu-like symptoms, followed by arthritis, carditis, and neuro- logical disorders in some patients. Carditis is detected in approxi- mately 8% of cases. Both lymphocytic infiltration and the bacterium itself can be demonstrated by endomyocardial biopsy. The usual car- diac manifestation is varying degrees of atrioventricular block, with cardiac dilatation occurring infrequently. Atrioventricular block is usually transient, though permanent complete heart block has been reported. The site of block appears to be the atrioventricular node in most cases, but block within the His bundle has been docu- mented by electrophysiological study, and the common occurrence of intraventricular conduction delays suggests that bundle branch block may also occur. Temporary pacing is usually sufficient, though recovery of antegrade conduction may take a week or longer. Lyme carditis should be considered in any case of heart block of unknown cause, especially in young people. Antibiotic therapy is recommended in Lyme carditis, but it is not known if this alters the course of carditis and atrioventricular block. Cardiac sarcoidosis Less than 10% of patients with pulmonary or systemic sarcoid- osis have clinically manifest cardiac involvement, ranging from conduction disturbances and arrhythmias to cardiac dilatation. Endomyocardial biopsy reveals typical sarcoid granulomas. The most serious complications of cardiac sarcoidosis are complete heart block, ventricular tachyarrhythmias, and dilated cardiomy- opathy. Cardiac sarcoidosis accounts for as much as 19% of all cases of unexplained atrioventricular block requiring pacemaker implantation in adults under 55 years of age. The relatively high incidence of sudden death in patients with sarcoidosis is thought to result from sudden complete heart block or ventricular fibril- lation. Patients with sarcoidosis who develop significant conduc- tion disease, arrhythmias, or congestive heart failure should receive steroids. Occasionally, cardiac involvement will occur without detectable systemic manifestations of sarcoidosis; thus, cardiac sarcoidosis is in the differential diagnosis of any undiagnosed ven- tricular arrhythmia, dilated cardiomyopathy, or atrioventricular block. See Chapter 16.7.3 for further discussion. Giant cell myocarditis Early recognition of this rapidly progressive form of myocarditis is required as it has a prognosis considerably worse than that of non- specific lymphocytic myocarditis. The endomyocardial biopsy is dis- tinguished by the presence of multinucleated giant cells and scattered lymphocytic infiltrates with eosinophils, but matters are made diffi- cult by sampling error due to the focal appearance of multinuclear giant cells. A new molecular method—myocardial gene expression profiling—facilitates the prediction of the presence of giant cells in the myocardium, even without a direct histological proof in single small endomyocardial biopsy sections, and thus reduces the risk of a sampling error. The aetiology of giant cell myocarditis is unknown, but thought to be autoimmune given its association with myasthenia gravis, thymoma, Crohn’s disease, and other immune disorders. It should be suspected in patients—particularly those with a history of an auto- immune condition—who present with disease which progresses un- usually rapidly, without viral prodrome, and who do not respond to

standard therapy of congestive heart failure. Endomyocardial biopsy should be performed if giant cell myocarditis is suspected, because combined immunosuppressive therapy with antithyroglobulin, cyclosporine, and corticosteroid appears to be helpful. Patients with giant cell myocarditis should be considered for early cardiac trans- plantation if they do not respond to therapy. Giant cell infiltration can be isolated to the atria, producing atrial enlargement and ar- rhythmias; this form of the disease is more benign. Eosinophilic myocarditis Eosinophilic myocarditis is a rare form of myocardial inflammation. The aetiological factors are hypersensitivity or allergic reactions, in- fectious, malignancies, hypereosinophilic syndromes, and vasculitis, notably Churg–Strauss syndrome. The clinical presentation varies from asymptomatic forms to life-threatening conditions. Many pa- tients have significant increased eosinophilic cells in the peripheral blood, but diagnosis depends on endomyocardial biopsy. Treatment differs significantly regarding the underlying aetiology, but im- munosuppressive therapy represents the mainstay of treatment. Chagas disease Chagas disease, caused by Trypanosoma cruzi, is the leading cause of myocarditis and dilated cardiomyopathy in some Central and South American countries, but uncommon in the United States of America (see Chapter 8.8.12). Overt acute myocarditis with congestive heart failure, arrhythmias, and conduction disease may develop, but car- diac involvement in early Chagas disease is usually subclinical. Years later, chronic Chagas disease may develop and may involve the heart. In the chronic phase, right bundle branch block and biventricular failure are present, and right heart failure predominates. Myocarditis occurs in both the acute and chronic phases, when immune medi- ation of myocyte injury is well documented. Antiprotozoal treat- ment with nifurtimox or benznidazole is beneficial in the acute phase. These agents are also indicated in the chronic phase, but— while they do reduce or eliminate serological immune markers of disease—it is not known if they improve outcome. Likely future developments The use of endomyocardial biopsy for diagnosis of myocarditis is es- sential at present, with a combination of morphological, molecular, and genetic analyses necessary to improve prognosis by a specific causal treatment. In the future it might be replaced gradually by other methods, including molecular assessments of biopsy tissue and noninvasive methods. In addition to diagnosis, new techniques like microRNA cluster analysis, gene expression profiles, analysis of genetic predisposition, or other aspects of immune response, will identify more accurately subsets of patients likely to respond to specific therapies. Relevance of animal models to clinical forms of

 myocarditis will be improved by a fuller analysis and understanding of the disorder in humans. The most important advances will lead to prevention of the causative infections through vaccination and other prophylactic measures. These developments could profoundly re- duce the incidence of dilated cardiomyopathy throughout the world. FURTHER READING Aretz HT, et al. (1987). Myocarditis. A histopathologic definition and classification. Cardiovasc Pathol, 1, 3–14. Baughman KL (2006). Diagnosis of myocarditis: death of Dallas cri- teria. Circulation, 113, 593–5. Blauwet LA, Cooper LT (2010). Myocarditis. Prog Cardiovasc Dis, 52, 274–88. Caforio, AL, et al. (2013). Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a pos- ition statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Euro Heart J, 34, 2636–48. Cooper LT (2009). Myocarditis. N Engl J Med, 360, 1526–38. Cooper LT, Berry GJ, Shabetai R (1997). Idiopathic giant-cell myocarditis—natural history and treatment. N Engl J Med, 336, 1860–6. Corsten M, et al. (2015). The microRNA-221/-222 cluster balances the antiviral and inflammatory response in viral myocarditis. Eur Heart J, 36, 2909–19. Escher F, et al. (2014). Presence of perforin in endomyocardial biopsies of patients with inflammatory cardiomyopathy predicts poor out- come. Eur J Heart Fail 16, 1066–72. Escher F, et al. (2015). Aggravation of left ventricular dysfunction in

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