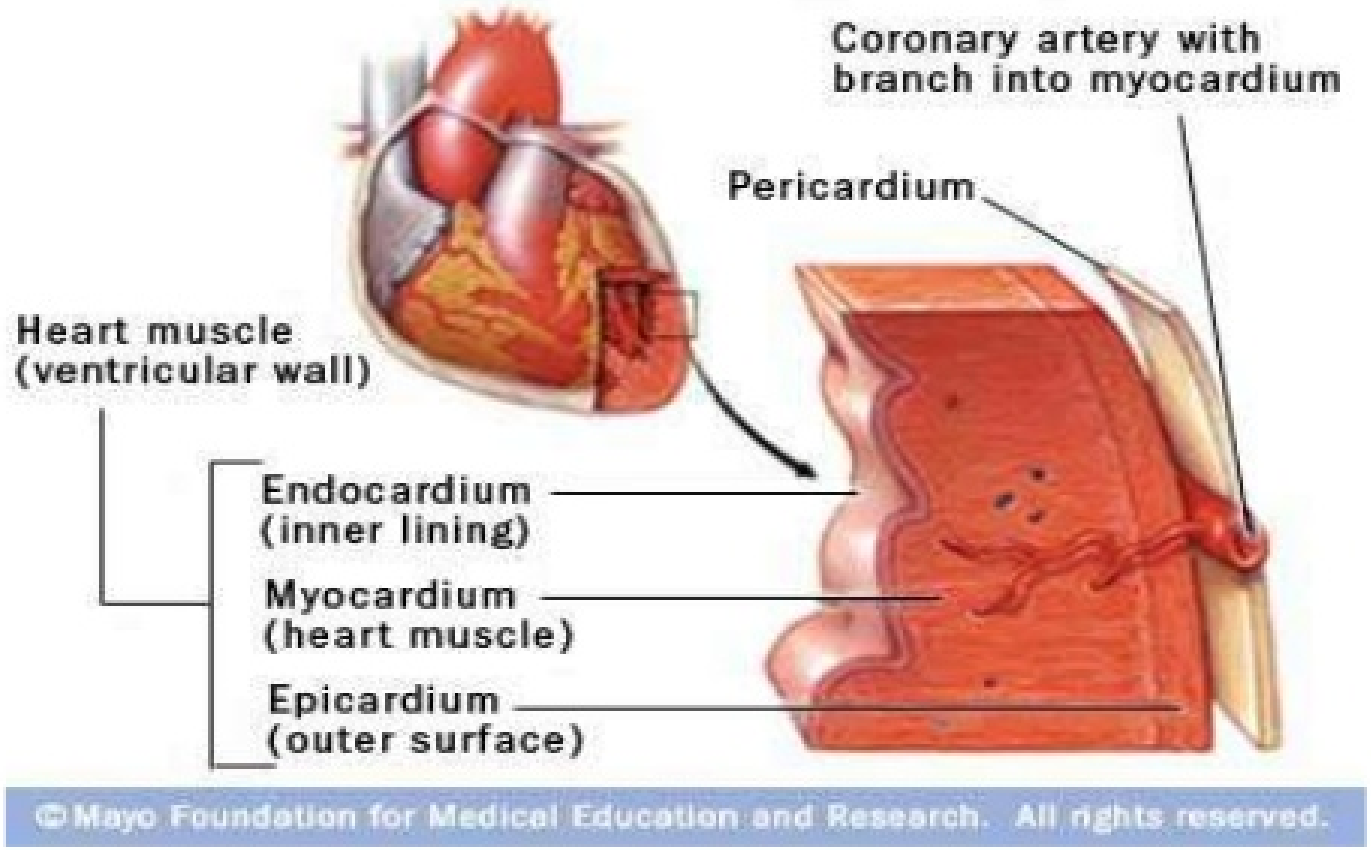
MYOCARDITIS

DR. RONAK MODI

Layers of the Heart Muscle



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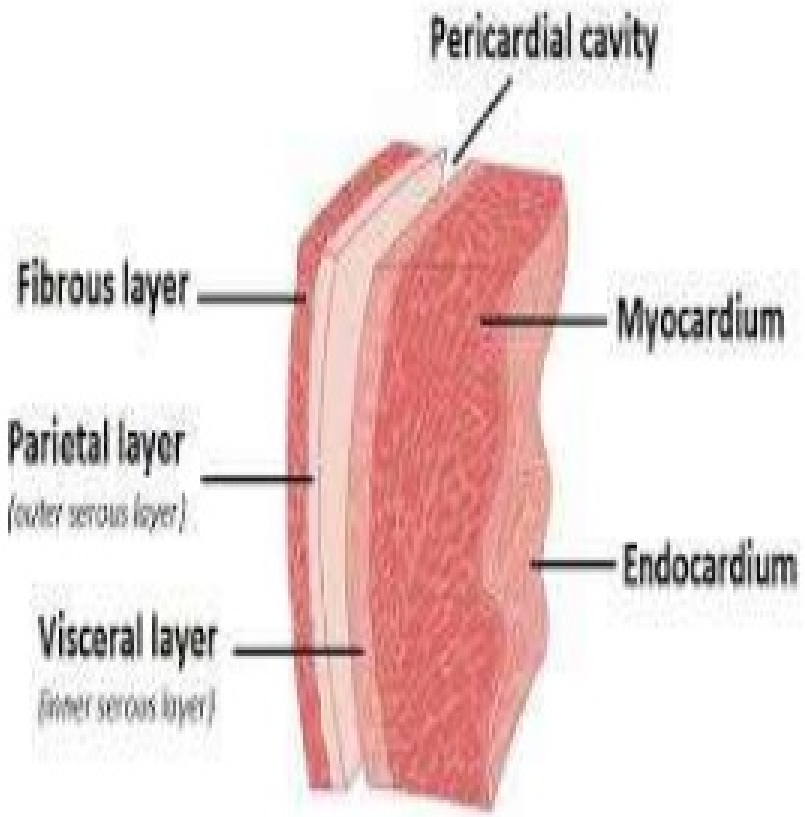
Inflammatory Disorders of the Heart

- Endocarditis
- Pericarditis
- Myocarditis



- Inflammation of myocardium.
- Inflammation – after any form of injury to heart – infection, ischemic damage, mechanical trauma, genetic cardiomyopathies.
- Classic myocarditis refers to inflammation to the heart muscle occurring as a result of exposure to either discrete external antigen such as virus, bacteria, protozoa, toxins or drugs, or internal trigger such as autoimmune activation against self antigens.

- Classic example of cardiac injury----immunologic response from the host.
- Overwhelming or inappropriate immune response may destroy the heart tissue.
- Chronically cardiac remodelling leads to DCM, heart failure, or death.
- Self limiting requires proper care.

- Differing histologic criteria used to define myocarditis
- Dallas criteria.
- Criteria criticized because of inter reader variability in interpretation, lack of prognostic value, and low sensitivity due in part to sampling error

TABLE 67-1 Endomyocardial Biopsy Diagnosis of Myocarditis: The Dallas Criteria

Definition

Idiopathic *myocarditis*: "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease"

Classification

First biopsy
- Myocarditis with/without fibrosis
- Borderline myocarditis (repeat biopsy may be indicated)
- No myocarditis

Subsequent biopsy
- Ongoing (persistent) myocarditis with or without fibrosis
- Resolving (healing) myocarditis with or without fibrosis
- Resolved (healed) myocarditis with or without fibrosis

Descriptors

	Inflammatory Infiltrate	Fibrosis
Distribution	Focal, confluent, diffuse	Endocardial, interstitial
Mild, moderate, severe	Mild, moderate, severe	
Type	Lymphocytic, eosinophilic, granulomatous, giant cell, neutrophilic, mixed	Perivascular, replacement

Modified from Leone O, Veinot JP, Angelini A, et al: 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 21:245, 2012.

Magnitude of the problem

- Global prevalence of myocarditis ≈22 of 100 000 patients annually-**I C D**--International Classification of Diseases.
- **I C D 10**---0.5% and 4% of cases of prevalent heart failure are due to myocarditis.

❑ **AHA**-myocarditis as the third leading cause of sudden cardiac death in competitive athletes.(*Maron et al*- **Circulation 2015**)

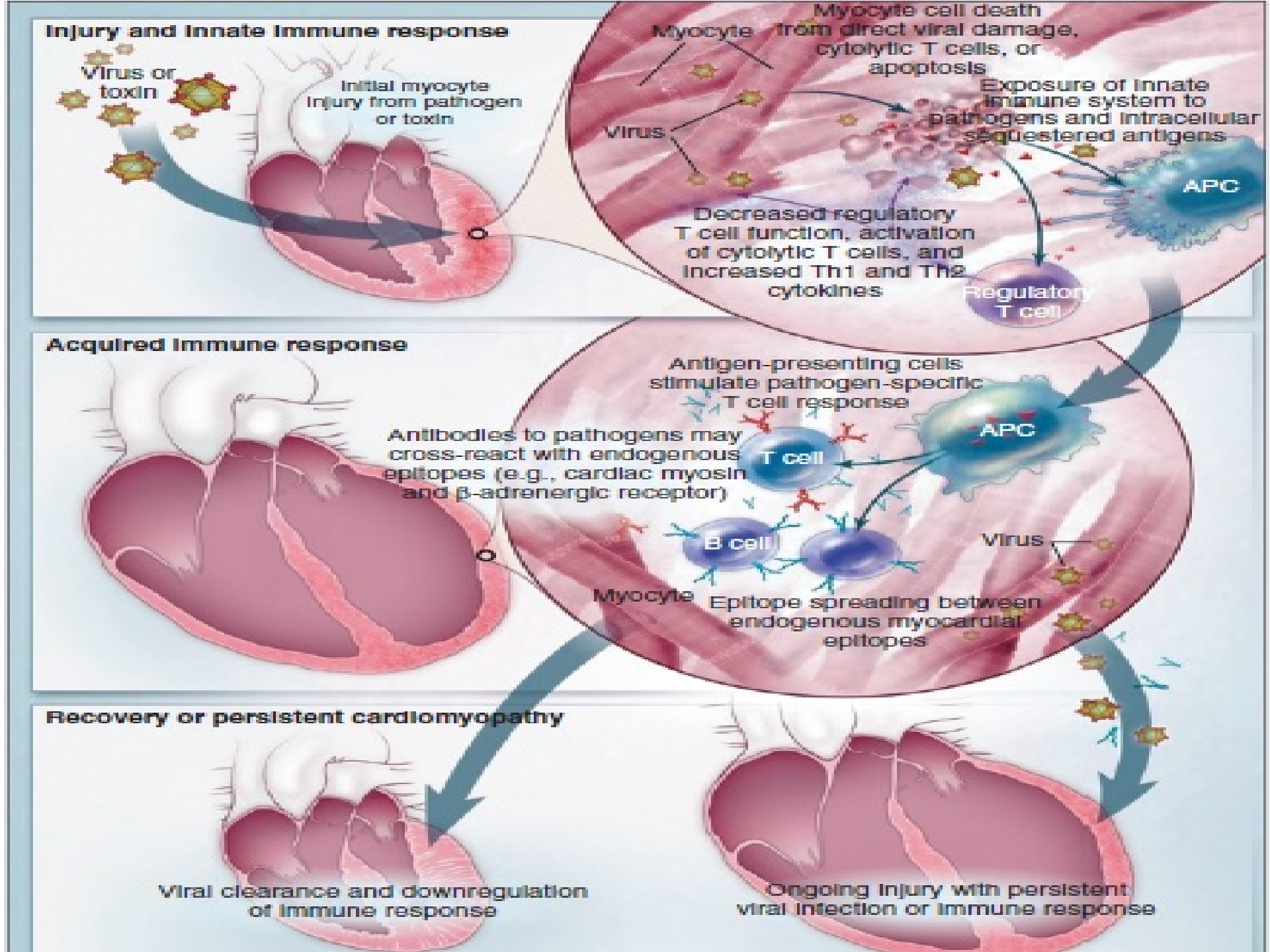
- Autopsy studies- myocarditis is responsible for 4-12% of SCD.

CAUSES

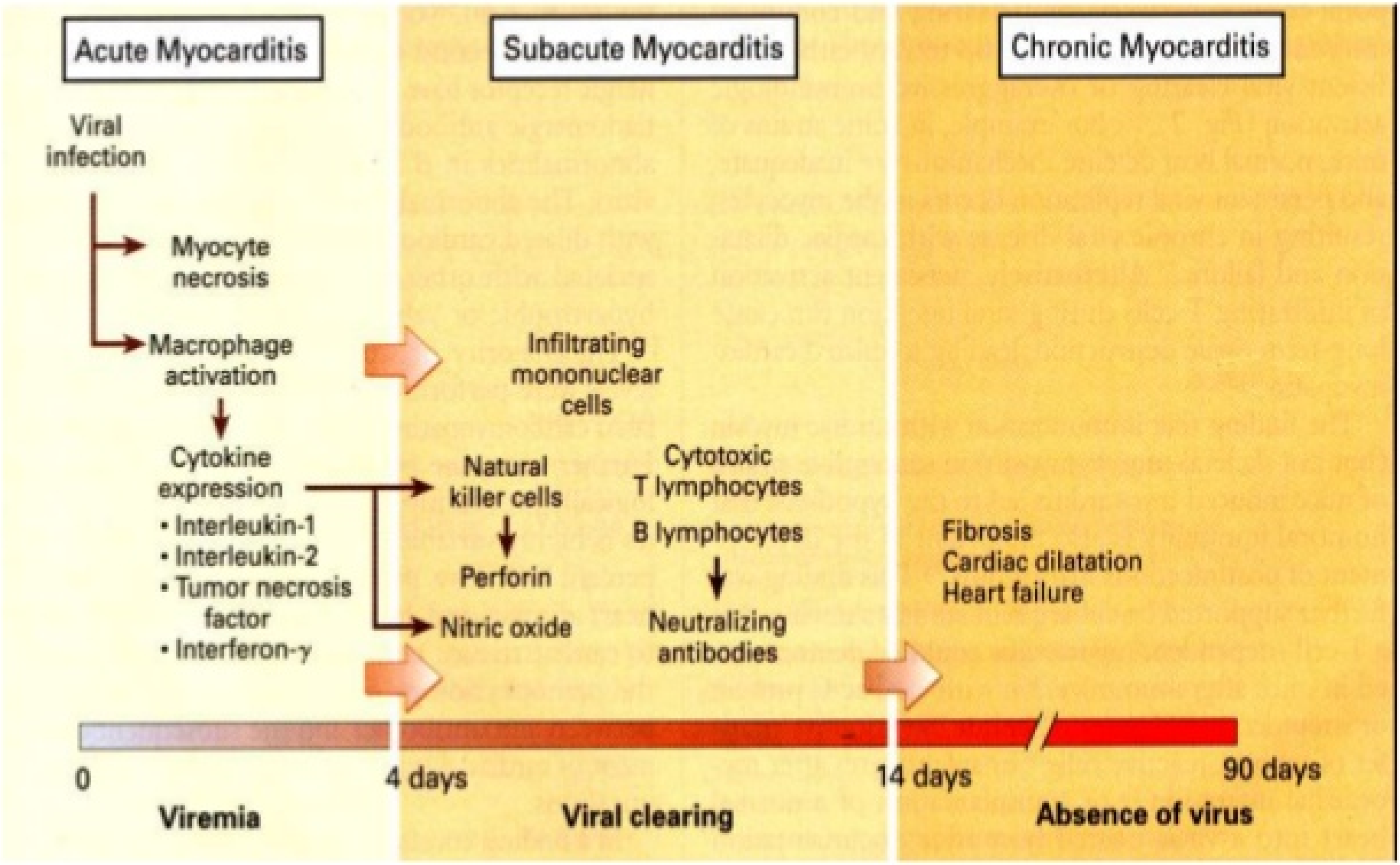
TABLE 35–1. Causes of Myocarditis
Infectious
Viruses: Coxsackievirus, echovirus, HIV, Epstein-Barr virus, influenza, cytomegalovirus, adenovirus, hepatitis A and B, mumps, poliovirus, rabies,
respiratory syncytial virus, rubella, vaccinia, varicella zoster, arbovirus
Bacteria: *Corynebacterium diphtheriae, Streptococcus pyogenes, Staphylococcus aureus, Haemophilus pneumoniae, Salmonella* spp., *Neisseria gonorrhoeae, Leptospira* spp., *Borrelia burgdorferi, Treponema pallidum, Brucella* spp., *Mycobacterium tuberculosis, Actinomyces* spp., *Chlamydia* spp., *Coxiella brunetti, Mycoplasma pneumoniae, Rickettsia* spp
Fungi: *Candida* spp., *Aspergillus* spp., *Histoplasma* spp., *Blastomyces* spp., *Cryptococcus* spp., *Coccidioidomycosis* spp.
Parasites: *Trypanosoma cruzii,Toxoplasma* spp., *Schistosoma* spp. *Trichina* spp.
Noninfectious
Drugs causing hypersensitivity reactions
Antibiotics: Sulfonamides, penicillins, chloramphenicol, amphotericin B, tetracycline, streptomycin
Antituberculous: Isoniazid, para-aminosalicylic acid
Anticonvulsants: Phenindione, phenytoin, carbamazepine
Anti-inflammatories: Indomethacin, phenylbutazone
Diuretics: Acetazolamide, chlorthalidone, hydrochlorothiazide, spironolactone
Others: Amitriptyline, methyldopa, sulfonylureas
Drugs not causing hypersensitivity reactions
Cocaine, cyclophosphamide, lithium, interferon-α
Nondrug causes
Radiation, giant cell myocarditis

Pathogenesis of myocarditis

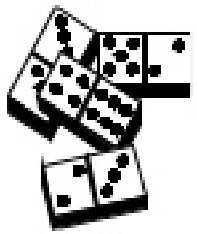
- Post viral and autoimmune myocarditis
- From acute injury to chronic DCM may be simplified into a **three-stage process**
- 1. Injury and Innate immune response
- 2. Acquired Immune response
- 3. Recovery and or Persistent cardiomyopathy.


Injury and Innate Immune response
Virus or toxin
Initial myocyte injury from pathogen or toxin
Myocyte
Myocyte cell death from direct viral damage, cytolytic T cells, or apoptosis
Virus
Exposure of innate immune system to pathogens and intracellular sequestered antigens
APC
Decreased regulatory T cell function, activation of cytolytic T cells, and increased Th1 and Th2 cytokines
Regulatory T cell
Acquired Immune response
Antigen-presenting cells stimulate pathogen-specific T cell response
APC
Antibodies to pathogens may cross-react with endogenous epitopes (e.g., cardiac myosin and β-adrenergic receptor)
T cell
B cell
Virus
Myocyte
Epitope spreading between endogenous myocardial epitopes
Recovery or persistent cardiomyopathy
Viral clearance and downregulation of immune response
Ongoing injury with persistent viral infection or immune response

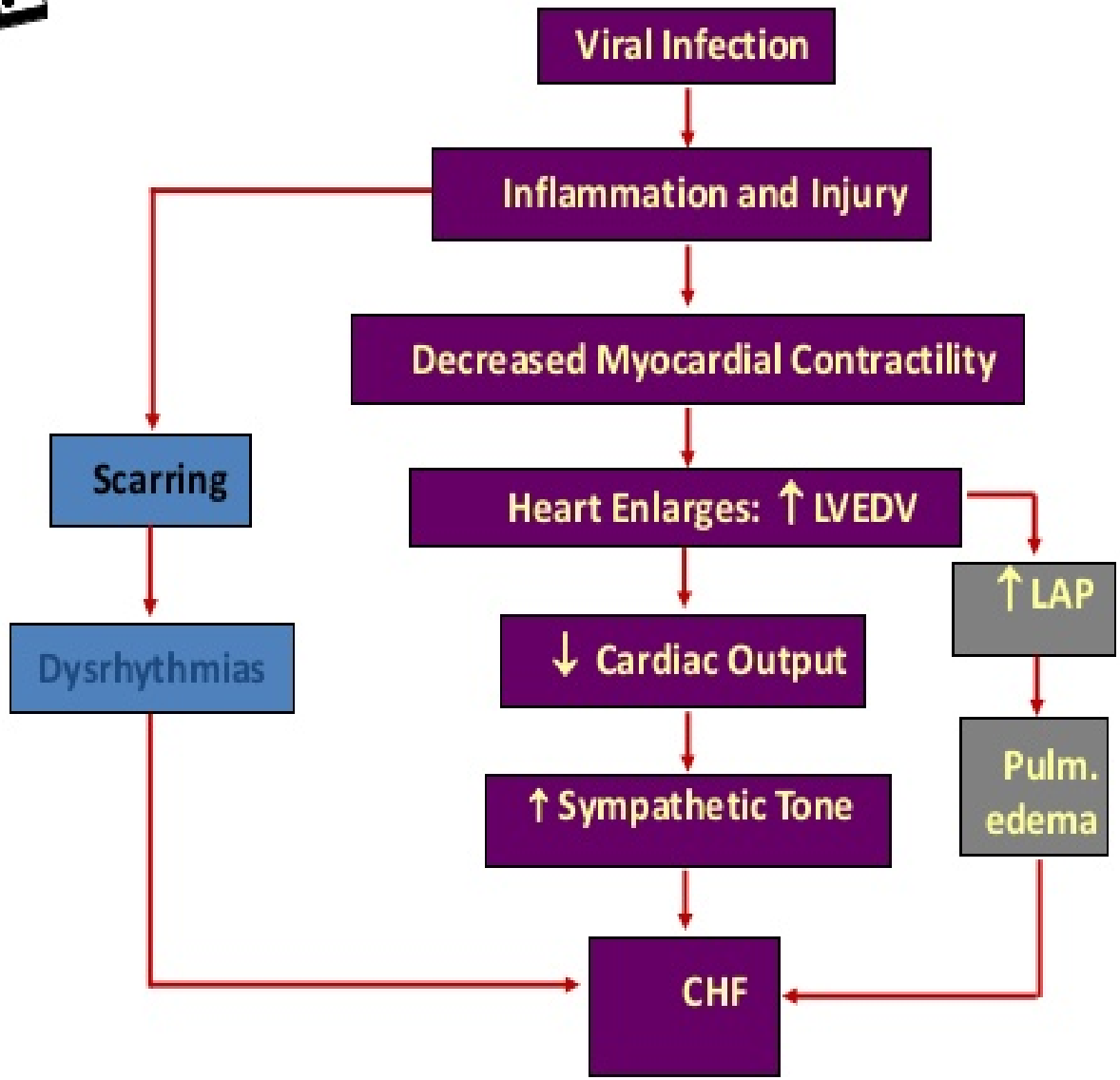
- Acute injury leads to cardiac damage, exposure of intracellular antigens such as cardiac myosin, and activation of the innate immune system.
- Over weeks, specific immunity that is mediated by T lymphocytes and antibodies directed against pathogens and similar endogenous heart epitopes cause robust inflammation.
- In most patients, the pathogen is cleared and the immune reaction is down regulated, with few sequelae.
- In other patients, however, the virus is not cleared and causes continued myocyte damage, and heart specific inflammation may persist because of mistaken recognition of endogenous heart antigens as pathogenic entities.



New England Journal of Medicine 343:1391 2000



PATHOPHYSIOLOGY OF MYOCARDITIS
THE DOMINO EFFECT



CARDIAC REMODELING

- Remodeling of the heart after cardiac injury can significantly affect cardiac structure and function, and the degree of such remodeling may mean the difference between appropriate healing and the development of DCM

Signs and symptoms

- **Chest pain** (often described as "stabbing" in character).
- **CHF**(leading to edema,breathlessness and hepatic congestion).
- Palpitations (due to **arrhythmias**).
- **Sudden death** (in young adults, myocarditis causes up to 20% of all cases of sudden death).
- **Fever** (especially when infectious)
- Since myocarditis is often due to a viral illness, many patients give a history of **symptoms consistent with a recent viral infection,** including fever, diarrhea, joint pains, and easy fatigueability.
- Myocarditis is often associated with **pericarditis**, and many patients present with signs and symptoms that suggest concurrent myocarditis and pericarditis.

Specific Clinical Presentations

Acute Myocarditis

- Nonspecific symptoms
- ❑ Kuhl et al- fatigue (82%), DOE (81%), arrhythmias (55%, both supraventricular and ventricular), palpitations (49%), and chest pain at rest (26%).
- Viral prodrome---20-80%.
- Diagnosis of exclusion.

Fulminant Myocarditis

- 10% biopsy proven.
- Abrupt onset(≤2 weeks).
- Haemodynamic compromise.
- Echo-Global LV dysfunction and myocardial oedema.
- EMB- diffuse myocarditis.
- Supportive treatment.

Giant Cell Myocarditis

- Subtle onset
- Present with heart failure, arrhythmia and heart block.
- Survival <6 months
- Improved with immuno suppressants.
- Discontinuation ---------- recurrence.
- EMB---- Giant cells and scar tissue.
- Cardiac transplantation+ mechanical circulatory support.

Chronic Active Myocarditis

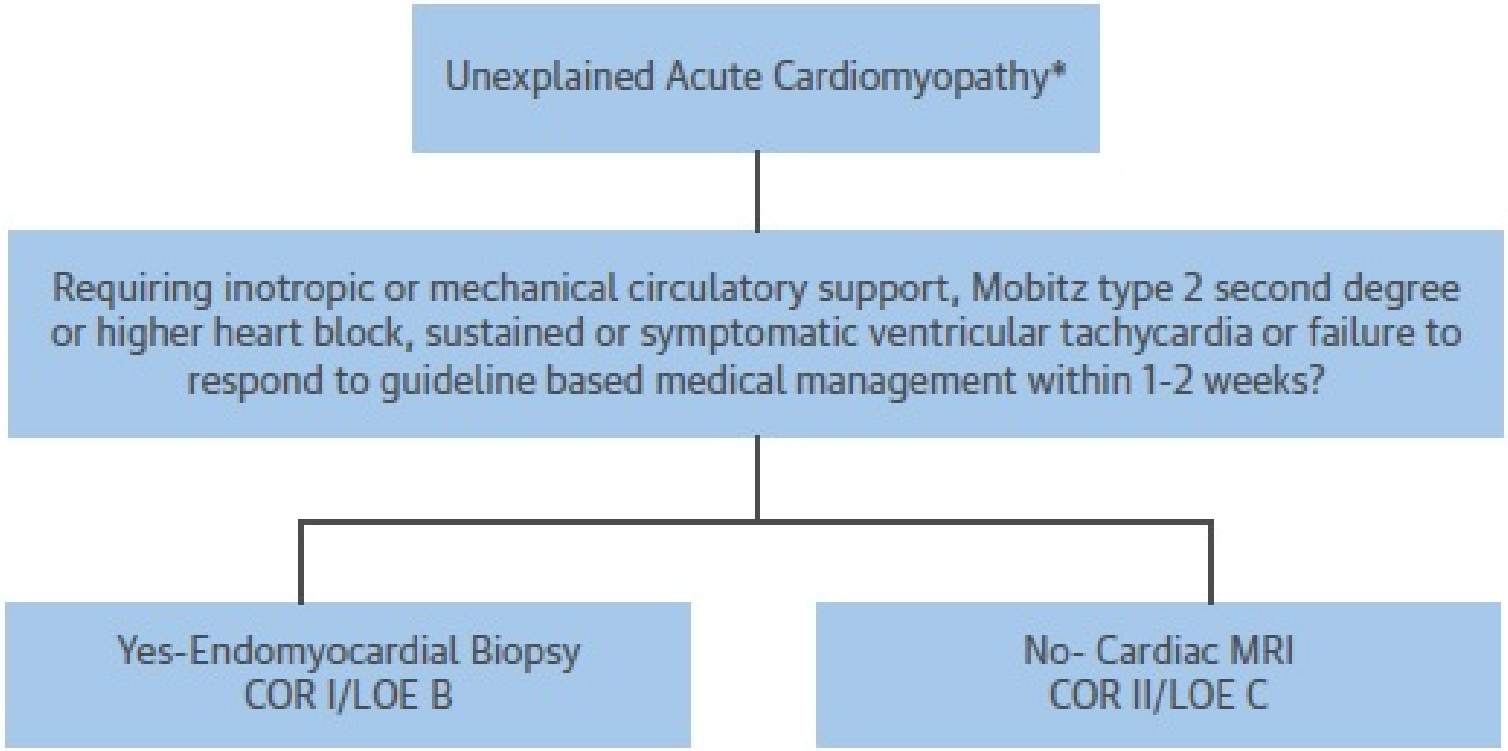
- Older
- Insidious
- Features of LV dysfunction.
- EMB---fibrosis and myocyte dropout.
- 60-70% of patients-----DCM with unknown aetiology.
- MRI, PET-CT, Immunohistochemistry

Differentials

- Ischaemic heart disease.
- Hypertrophic cardiomyopathy.
- Cardiac amyloidosis.
- Arrythmogenic right ventricular cardiomyopathy.

- Pieroni et al -patients with right ventricular myocarditis ---indistinguishable from ARVC ---- clinical features, presence, and severity of structural and functional right ventricle abnormalities (**J Am Coll Cardiol.2009**).

FIGURE 4 Algorithm for the Evaluation of Suspected Myocarditis



Endomyocardial biopsy (EMB) should be performed in those patients with clinically suspected unexplained acute myocarditis who require inotropic or mechanical circulatory support, Mobitz type 2 second degree or higher heart block, sustained or symptomatic ventricular tachycardia or failure to respond to guideline-directed medical management within 1 to 2 weeks. In other clinical scenarios of clinically suspected acute myocarditis, EMB may be helpful, but CMR may be considered as an initial diagnostic test to identify inflammation. Reprinted with permission from Bozkurt et al. (176). *Usually a dilated cardiomyopathy. Fulminant myocarditis may have normal end diastolic diameter with mildly thickened walls. Exclude ischemic, hemodynamic (valvular, hypertensive), metabolic, and toxic causes of cardiomyopathy as indicated clinically. CMR = cardiac magnetic resonance; COR = Class of recommendation; LOE = Level of Evidence; MRI = magnetic resonance imaging.

Clinical presentation

- Wide range of potential clinical presentation
- Clinical picture may be one of asymptomatic electrocardiographic or echocardiographic abnormalities or may include signs and symptoms of chest pain, cardiac dysfunction, arrhythmias or heart failure, and/or hemodynamic collapse.
- Transient electrocardiographic or echocardiographic abnormalities have been observed frequently during community viral outbreaks or influenza epidemics

Diagnostic Approaches

- Histologic diagnosis according to the classic Dallas criteria
- Myocarditis is severely under diagnosed.
- Clinical suspicion, together with hybrid clinical and laboratory criteria and new imaging modalities, may help secure the diagnosis without necessarily resorting to biopsy in all cases.
- One classification scheme divides patients into three categories

TABLE 67-2 Three-Tiered Clinical Classification for Diagnosis of Myocarditis by Level of Diagnostic Certainty

DIAGNOSTIC CATEGORY	CRITERIA	HISTOLOGIC CONFIRMATION	BIOMARKER, ECG, OR IMAGING ABNORMALITIES CONSISTENT WITH MYOCARDITIS	TREATMENT NEEDED
Possible subclinical acute myocarditis	In the clinical context of possible myocardial injury *without* cardiovascular symptoms but with at least one of the following: 1. Biomarkers of cardiac injury raised 2. ECG findings suggestive of cardiac injury 3. Abnormal cardiac function on echocardiogram or CMR	Absent	Required	Not known
Probable acute myocarditis	In the clinical context of possible myocardial injury *with* cardiovascular symptoms and at least one of the following: 1. Biomarkers of cardiac injury raised 2. ECG findings suggestive of cardiac injury 3. Abnormal cardiac function on echocardiogram or CMR	Absent	Required	Per clinical syndrome
Definite myocarditis	Histologic or immunohistologic evidence of myocarditis	Present	Not required	Tailored to specific cause

Laboratory Testing

- Biomarkers to screen for myocarditis
- Hypothesis that a diagnosis of heart damage in this setting indicate a greater risk of arrhythmias or cardiomyopathy
- So raised troponin confirms the suspected case.
- Also define severity and short term prognosis
- Fulminant myocarditis is associated with higher level of cardiac troponin than acute myocarditis and also associated with low LVEF.

Laboratory Testing

- **A variety of other biomarkers have demonstrated prognostic value in acute myocarditis.**

1. In fulminant myocarditis, higher sr creatitine, lactate, AST are associated with increase in hospital mortality
2. N- terminal pro- brain type natriuretic peptide is predictably associated with DCM due to myocarditis and decline rapidly once recover.
3. Higher IL-10 and soluble Fas are associated with increase risk of death or need for surgery.
4. Nonspecific biomarkers of inflammation, such as leukocyte count, C-reactive protein, erythrocyte sedimentation rate, and leukocyte count have low specificity.

E.C.G

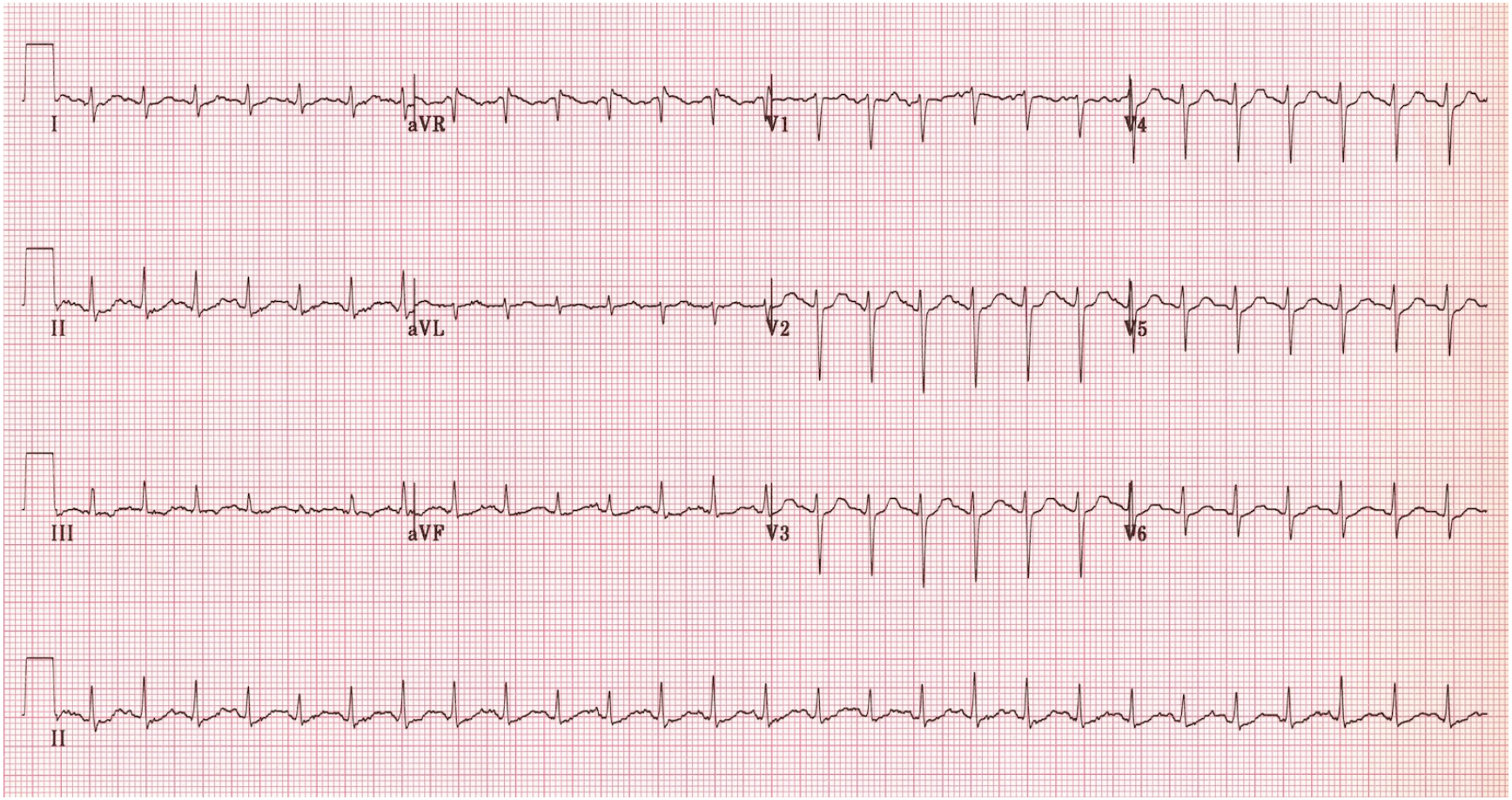
- ECG changes can be variable and include:
- Sinus tachycardia.
- QRS / QT prolongation.
- Diffuse T wave inversion.
- Ventricular arrhythmias.
- AV conduction defects.
- With inflammation of the adjacent pericardium, ECG features of pericarditis can also been seen (= myopericarditis).
- NB. The most common abnormality seen in myocarditis is sinus tachycardia with non-specific ST segment and T wave changes.

Myocarditis mimicking acute myocardial infarction:

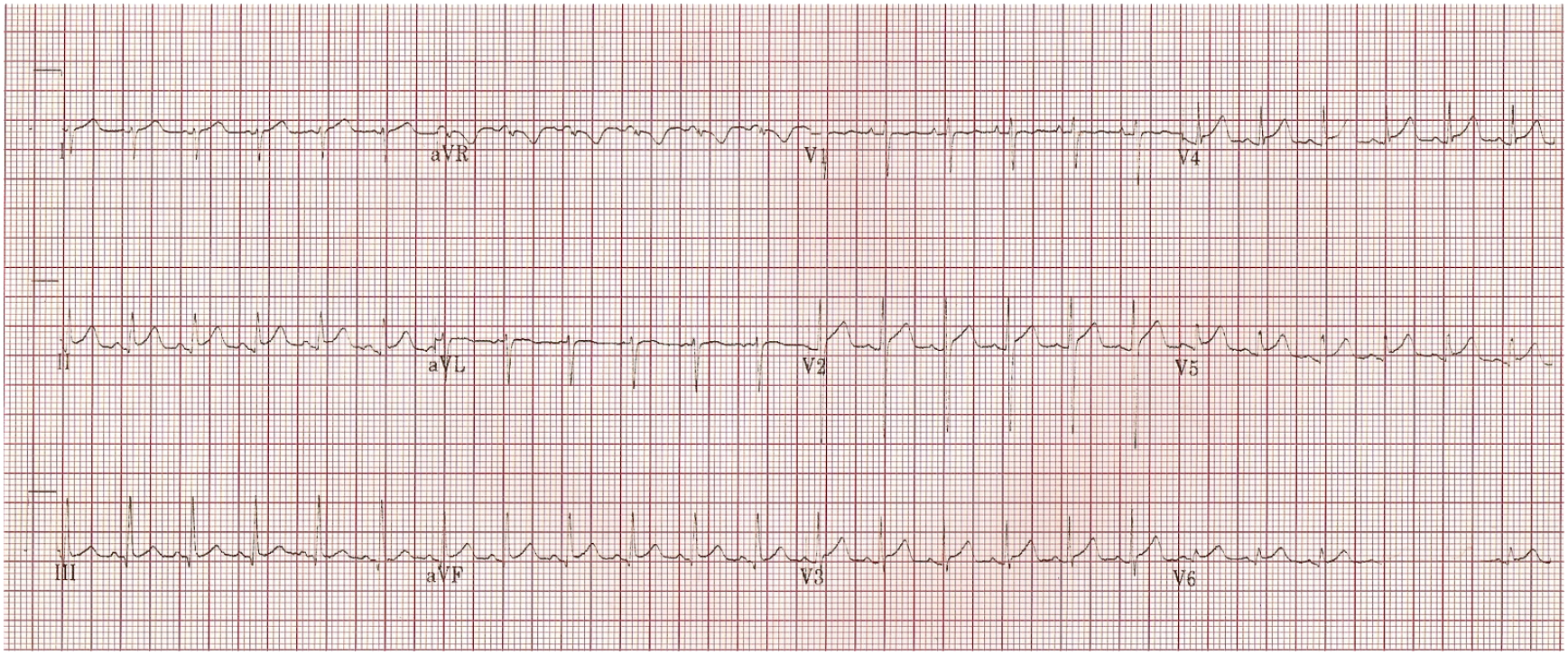
Occasionally, a pseudo infarct pattern and ischemic changes are seen.

ST segment elevation is commonly seen, but ST segment depression, T wave inversion, poor R wave progression,and Q waves have also been described

Example 1



Example 2



Cardiac Imaging

- An assessment of left ventricular function is essential in all cases of suspected myocarditis

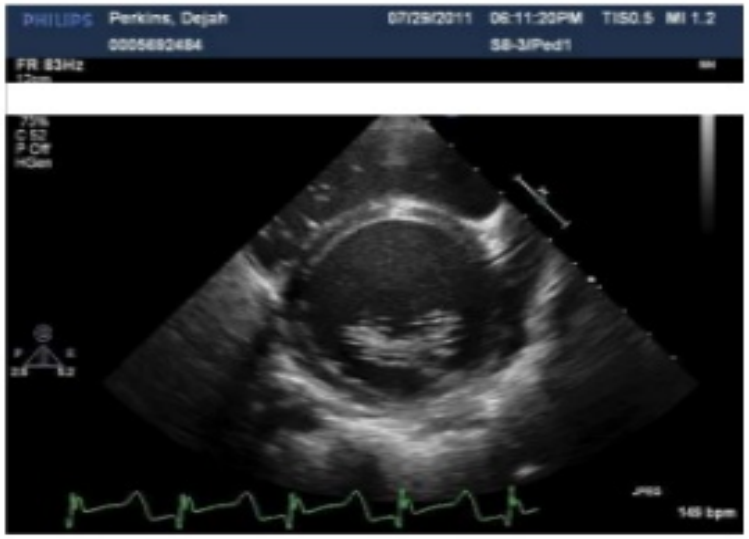
Echocardiography

•Echocardiography helps to rule out non-inflammatory cardiac disease such as valve disease and to monitor changes in cardiac chamber size, wall thickness, ventricular function, and pericardial effusions.

• Global ventricular dysfunction, regional wall motion abnormalities,and diastolic dysfunction with preserved EF may occur in myocarditis.

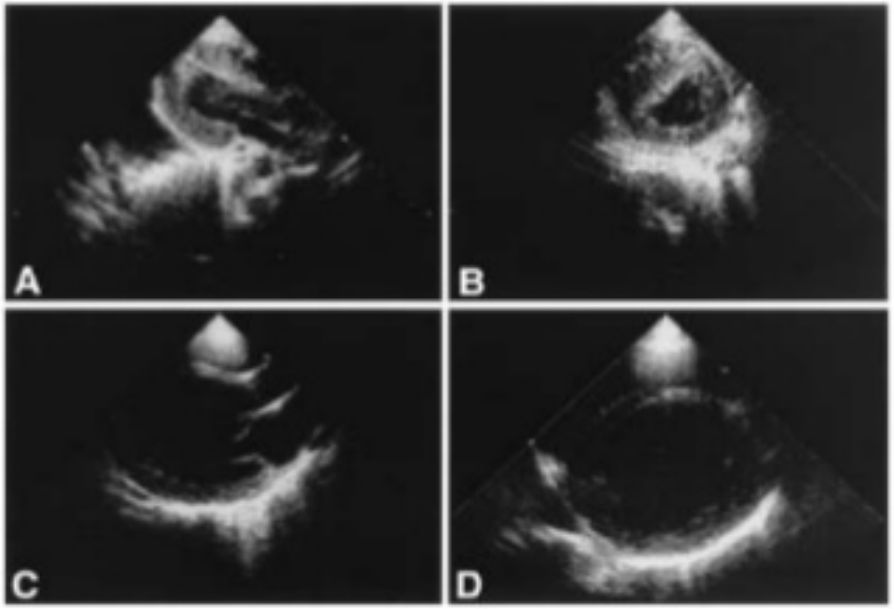
• Histologically proven myocarditis may resemble dilated, hypertrophic, and restrictive cardiomyopathy and can mimic ischaemic heart disease.

Echocardiogram



Echocardiogram
markedly dilated heart with ejection fraction of 15 %, mural thrombus was present

Echocardiographic Findings in Fulminant and Acute Myocarditis



Fulminant myocarditis

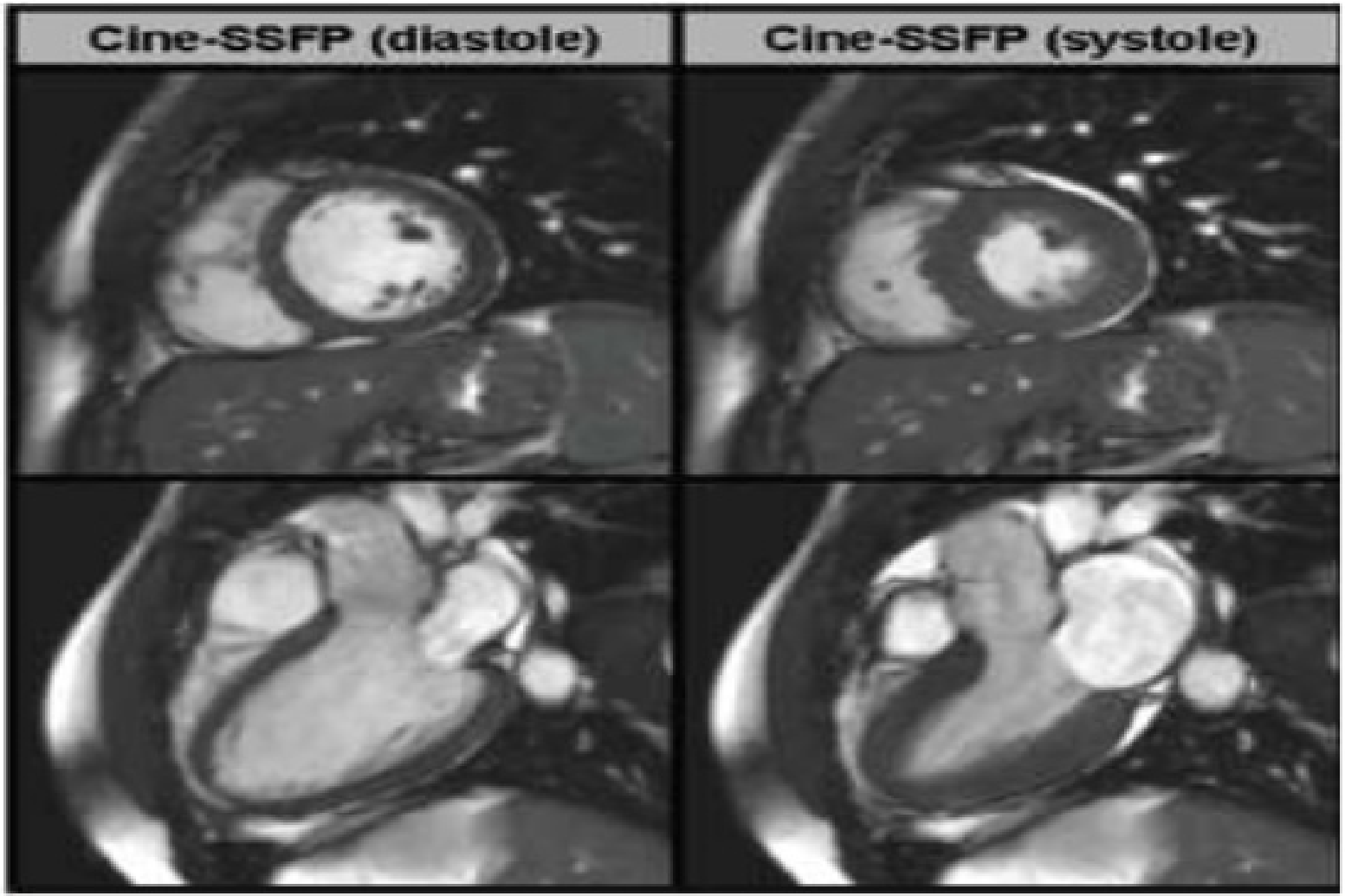
Acute myocarditis

Fulminant myocarditis often presents with a non-dilated, thickened, and hypocontractile left ventricle as the intense inflammatory response results in interstitial oedema and loss of ventricular contractility

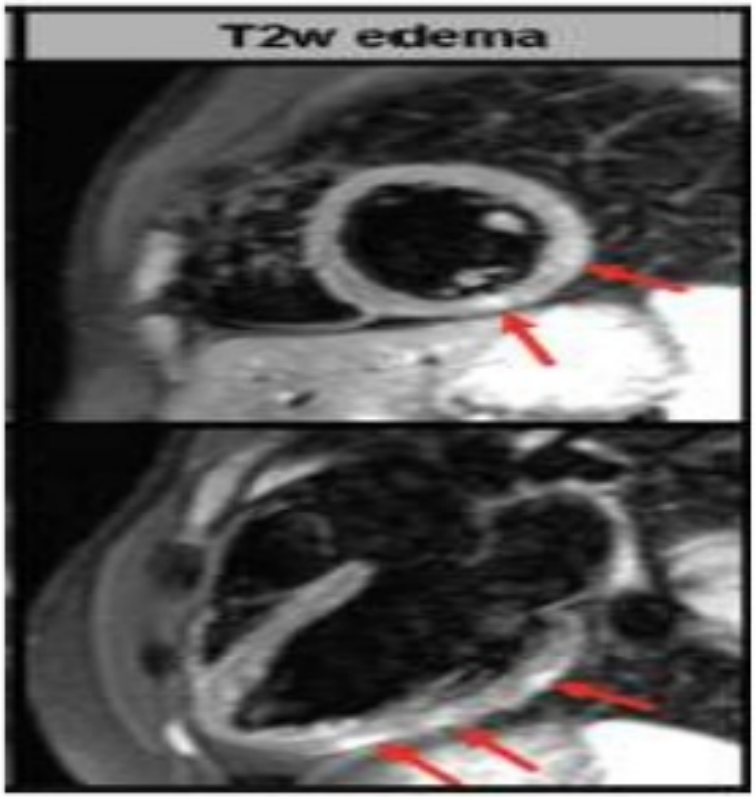
MRI

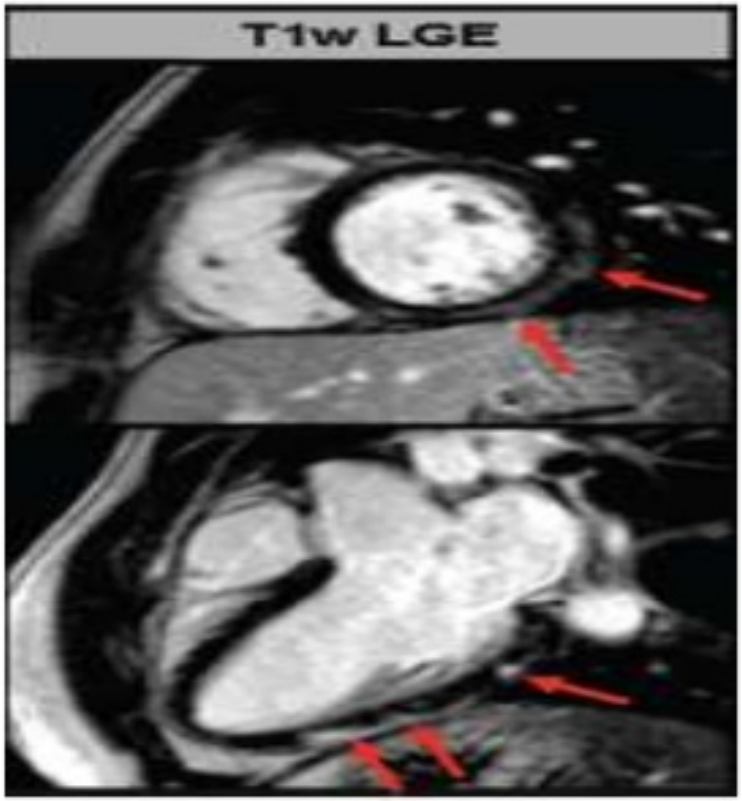
- MRI is emerging as an important tool for the diagnosis and follow-up of patients with acute myocarditis
- Distinguish most cases of ischemic from non ischemic
- The T1-weighted, myocardial delayed enhancement technique can quantitate regions of damage and possibly predict the risk of cardiovascular death and ventricular arrhythmias after myocarditis.
- The T2-weighted, short tau inversion recovery (STIR), and T1-weighted delayed post contrast signal abnormalities seen in acute myocarditis all decrease with time.

- sensitivity and specificity of CMR in suspected myocarditis more than 14 days after symptom onset were poor (sensitivity, 63%; specificity, 40%)
- CMR performs best in the setting of acute cardiomyopathy or chest pain with elevated troponin.
- Both T1- and T2-weighted sequences should be used, to optimize sensitivity and specificity.
- (PET) imaging remains useful to diagnose cardiac sarcoidosis.



cine-SSFP images are shown in diastole and systole and suggest absence of any wall motion abnormality





T2-weighted edema images demonstrate the presence of patchy focal edema in the subepicardium of the inferolateral wall

T1-weighted LGE images demonstrate presence of subepicardially distributed LGE which is typical for acute myocarditis.

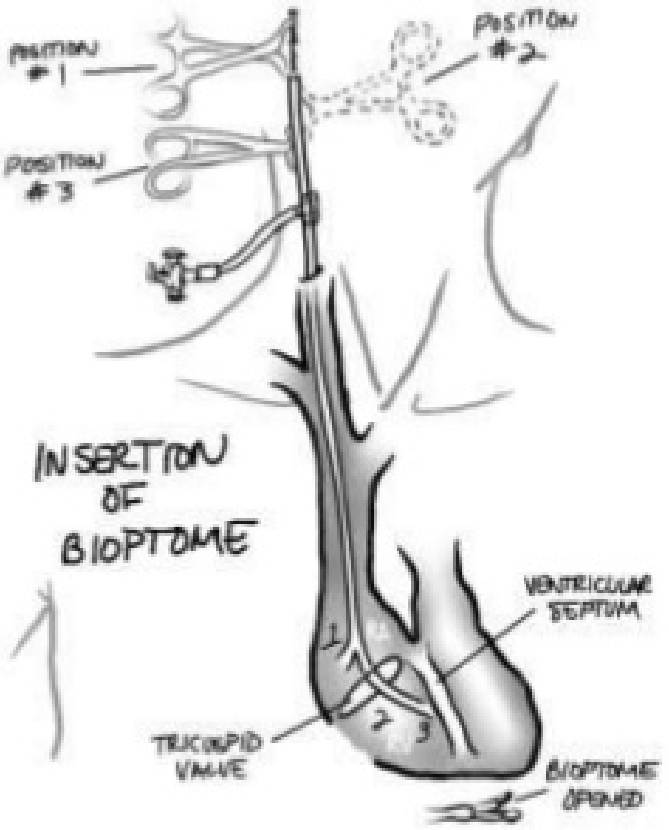
Endomyocardial Biopsy

- The gold standard in diagnosis of myocarditis is still the EMB.
- Lymphocytic infiltration in association with myocyte necrosis and death.
- Best method to differentiate between giant cell myocarditis and sarcoidosis.
- Eosinophilic myocarditis -myocyte necrosis---intra cavitary thrombi containing eosinophils----lumen of intra myocardial coronary vessels.

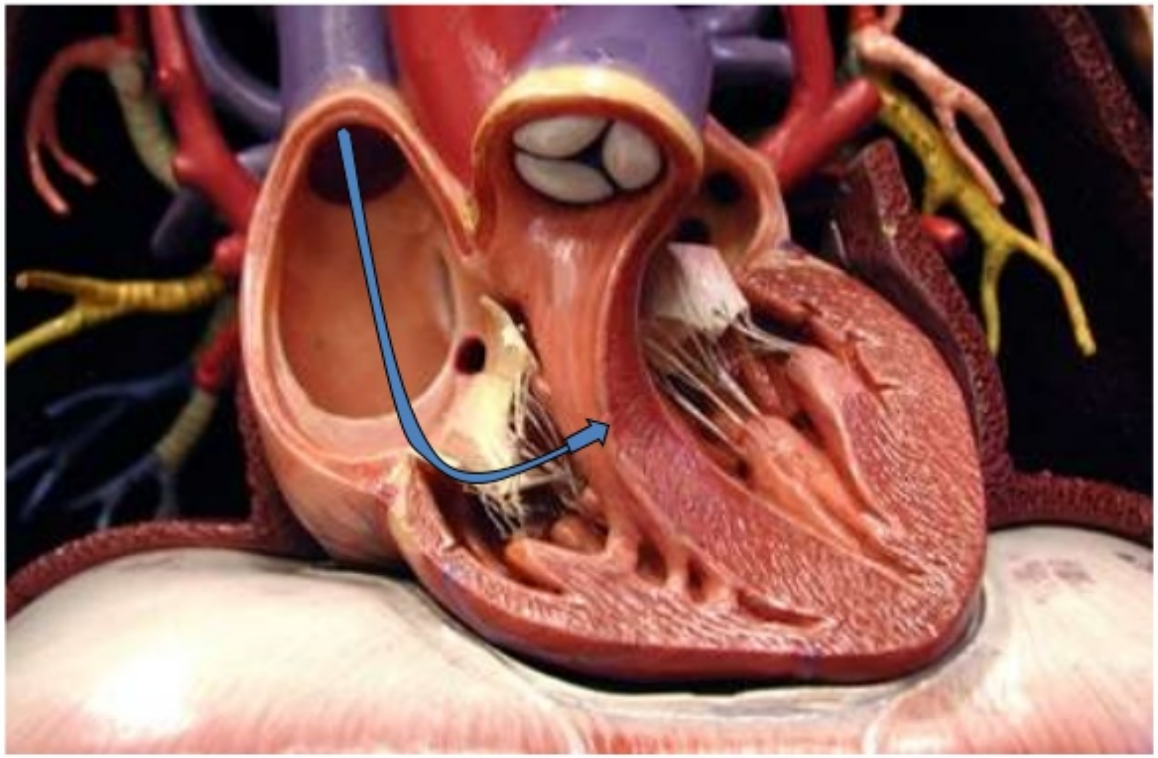
- ESC recommends EMB------ as early as possible.
- ACC/AHA recommends EMB based on 3 classes of comprehensive clinical presentations, risks, and measurements using non invasive techniques.

- Immunohistochemistry useful.

Endomyocardial Biopsy



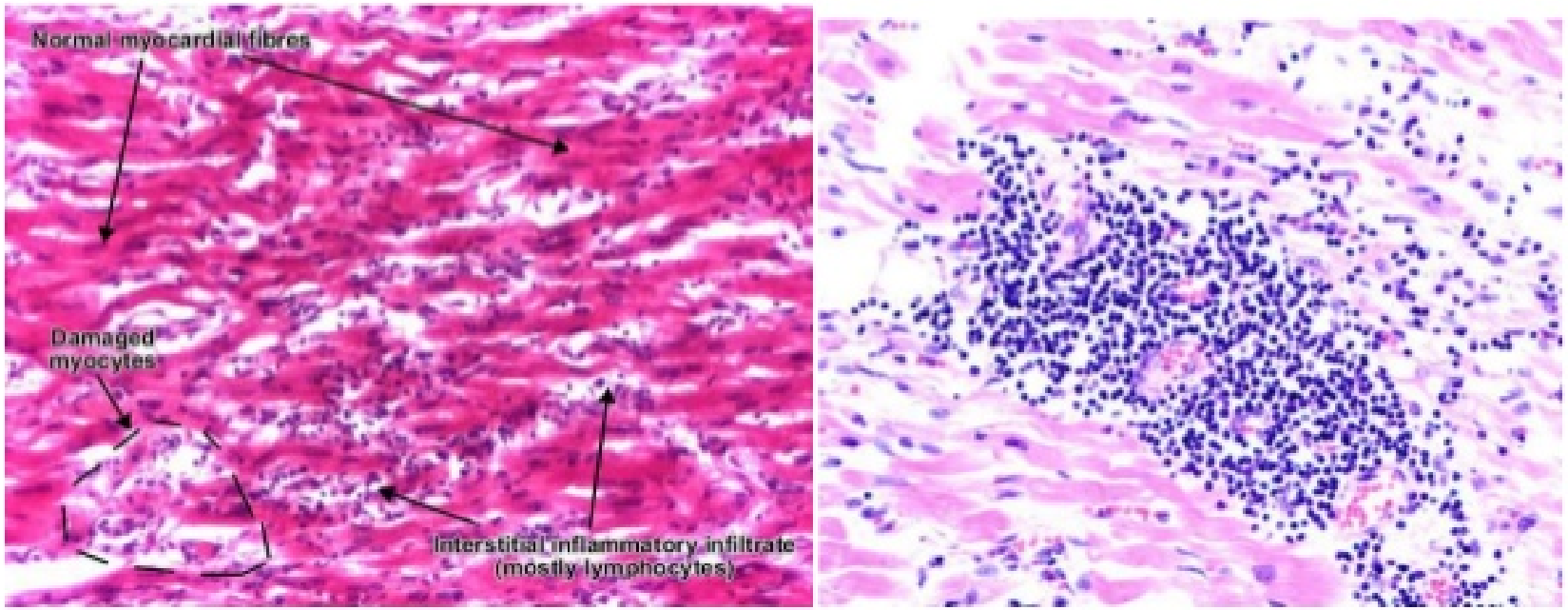
RV - EMB : THE TECHNIQUE (jugular approach)



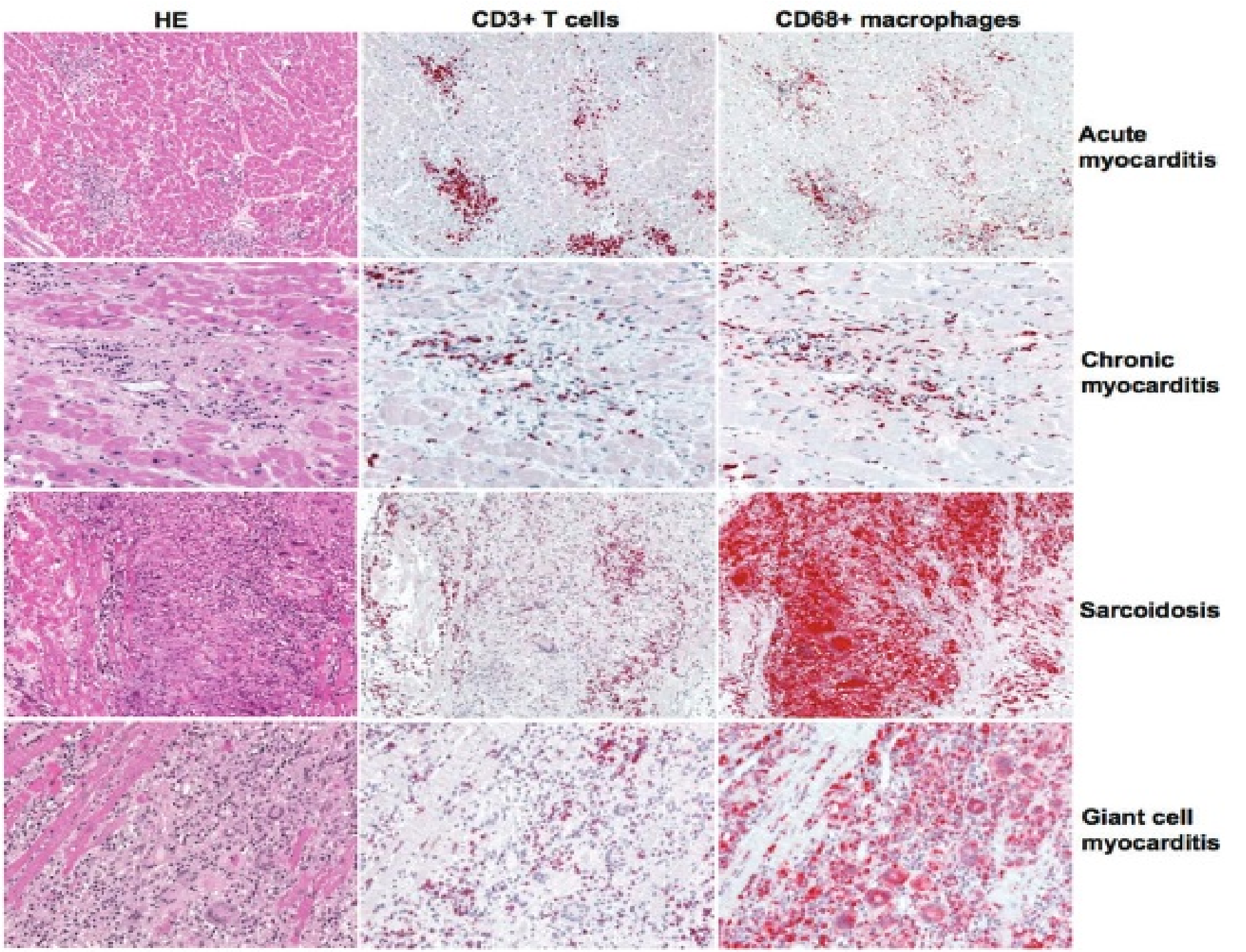
Recommendations

11. Tissue obtained from EMB should be analysed using histology, immunohistochemistry, and viral PCR (on heart tissue and a blood sample).
12. At least three myocardial samples, each 1–2 mm in size, should be taken (from the right or from the left ventricle) and immediately fixed in 10% buffered formalin at room temperature for light microscopy; additional samples should be taken, snap frozen in liquid nitrogen, and stored at −80°C, or stored in RNA later tubes at room temperature, for viral PCR[2,149]
13. Endomyocardial biopsy may be repeated if necessary to monitor response to aetiology-directed therapy, or if a sampling error is suspected in a patient with unexplained progression of heart failure.

Viral myocarditis:



*N.B. established histological **Dallas criteria** defined as follows:histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of nonischaemic origin


HE
CD3+ T cells
CD68+ macrophages
Acute myocarditis
Chronic myocarditis
Sarcoidosis
Giant cell myocarditis

INDICATION FOR EMB

- Endomyocardial biopsy is limited today to fulminant cases,
- To cases with conduction disturbances and malignant arrhythmias
- To rule out giant cell myocarditis
- To cases unresponsive to standard anti-failure therapy

Treatment

- Acute myocarditis resolves in about 50% of cases in the first 2–4 weeks, but about 25% will develop persistent cardiac dysfunction and 12–25% may acutely deteriorate and either die or progress to end-stage DCM with a need for heart transplantation. The core principles of treatment in myocarditis are optimal care of arrhythmia and of heart failure
- The first-line therapy for all patients with myocarditis and heart failure is supportive care. A very small proportion of patients will require hemodynamic support that ranges from

- Patients with LV dysfunction or symptomatic HF should follow current HF therapy guidelines,
- Diuretics and ACE inhibitors or ARBs
- Beta-blockers can be used cautiously in the acute setting.
- Digoxin should be avoided in patients suffering from acute HF induced by viral myocarditis

- Routine treatment of mild to moderately severe acute myocarditis with immunosuppressive drugs is not recommended for adults. These data are based on the U.S. Myocarditis Treatment Trial.
- There may be a role for a **short course of immunosuppression** in patients with chronic DCM who fail to respond to guideline-based heart failure management.
- In the Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC) trial, 85 patients with chronic inflammatory cardiomyopathy without persistent viral infection were randomly assigned to receive either prednisone and azathioprine or placebo.

- Immunosuppressive treatment was associated with an increase in left ventricular ejection fraction from 26% to 46% and improved quality of life.
- Patients with ventricular arrhythmias or heart block due to acute myocarditis should be hospitalized for electrocardiographic monitoring.
- Arrhythmias usually resolve after several weeks.
- Manage conventionally in the setting myocarditis for arrythmias.
- In the setting of GCM or cardiac sarcoidosis, the high rate of ventricular arrhythmias may warrant early consideration for an ICD.
- Lymphocytic myocarditis and nonsustained VT, use a temporary external defibrillator .

- Transplantation also is an effective therapy for patients with myocarditis who have refractory heart failure despite optimal medical therapy and mechanical circulatory support.
- Survival after transplantation for myocarditis is similar to survival for other causes of cardiac transplantation. However, the risk of graft loss may be greater in children who undergo transplantation.

- **Steroids**

- Mainstay in CS.
- Halt Progression of LV dysfunction

❑ Survival doubtful-------- (Blauwet -Heart Fail Rev 2012)

- Early initiation
- AV block recovery----20-30%
- GCM- cyclosporine based combined immunosuppression beneficial.

Table 2

Immunosuppression in acute giant cell myocarditis, chronic myocardis, and i cardiomyopathy

	Giant cell myocarditis
Oral stercids 3 (anti-CD3-antibodies)[*1]	5 mg/day i.v. for 7 days10 mg/kg body weight (3 days)
Ciclosporin[*2]	Targeted trough level: 100–120 µg/mL
Methylprednisolone[*3]	1 mg/kg body weight (1 week)Reduction: 10 mg/4 weeks
Chronic/autoimmune myocarditis, eosinophilic myocarditis, inflammatory	
Methylprednisolone[*3]	1 mg/kg body weight (2 weeks), then reduction by 10 mg each week for (duration of treatment 6 months)
Azathioprine[*2, 3, 4]	50–150 mg/day (6 months)
	Stomach protection
Pantoprazole	20 mg/die
Calcium substitution	1×1 g/die

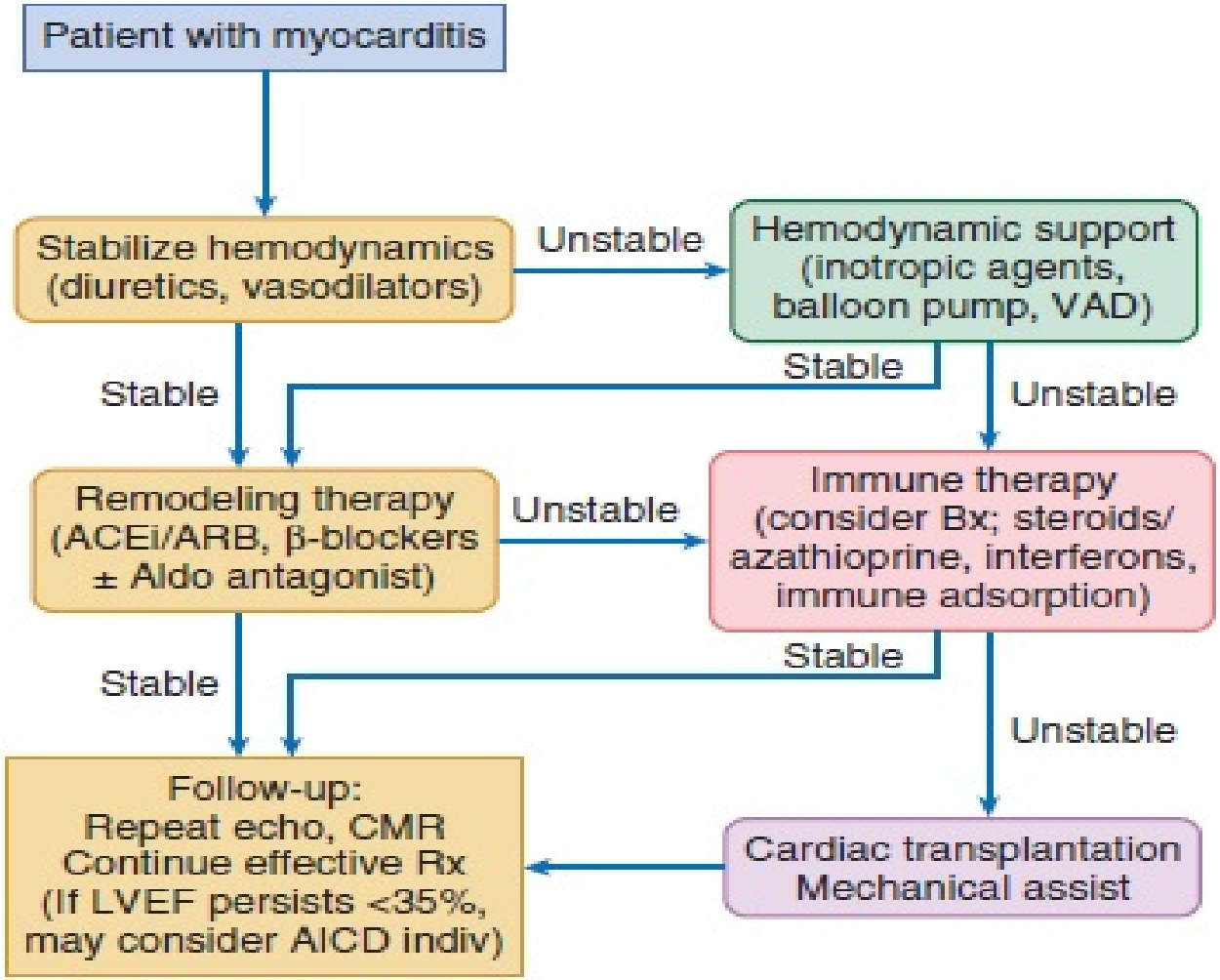


FIGURE 67-9 Treatment algorithms for patients with myocarditis, depending on hemodynamic stability and response to general supportive and remodeling treatment regimen at each step. All patients require aggressive support and appropriate follow-up. Immune therapy at present is still indicated mainly to support those who have failed to improve spontaneously. ACEi = angiotensin-converting enzyme inhibitor; AICD = automatic implantable cardioverter-defibrillator; Aldo = aldosterone; ARB = angiotensin receptor blocker; Bx = biopsy; CMR = cardiac magnetic resonance; echo = echocardiography; indiv = based on individual assessment of risk versus benefit; LVEF = left ventricular ejection fraction; VAD = ventricular assist device.

Key Messages:

- Viral infections are the most common triggers of inflammatory myocardiopathies.
- Non-specific symptoms are frequently identified and cardiologically evaluated only at an advanced stage.
- Pathophysiological processes in myocarditis take place at the cellular and subcellular levels, myocardial biopsy is the only method for confirmation of diagnosis.
- Clinical course of myocarditis is unpredictable, all patients with etiologically unexplained heart failure have to undergo myocardial biopsy.
- Numerous chronic viral infections and post infectious or autoimmune inflammations of the myocardium are treatable.