MYOCARDITIS

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MYOCARDITIS

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INFLAMMATORY DISEASE OF CARDIAC MUSCLE.

INFECTIOUS AND NON INFECTIOUS CAUSES

OFTEN SELF LIMITING

ACUTE , SUBACUTE OR CHRONIC (INHERITED CARDIOMYOPATHIES)

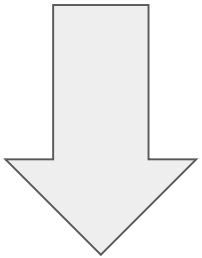
DEFINITION

- 1995, myocarditis was defined by the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) as

- Inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immuno histochemical criteria

INFLAMMATORY CARDIOMYOPATHY

MYOCARDITIS ACCOMPANIED BY CARDIAC DYSFUNCTION



DILATED CARDIOMYOPATHY

TABLE 55.3 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: Biomarkers of cardiac injury raised ECG findings suggestive of cardiac injury Abnormal cardiac function on echocardiogram or CMR	Absent	Required	Not known
Probable acute myocarditis	In clinical context of possible myocardial injury *with* cardiovascular symptoms and at least one of the following: Biomarkers of cardiac injury raised ECG findings suggestive of cardiac injury 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

CMR, Cardiac magnetic resonance imaging; *ECG*, electrocardiogram.
Modified from Sagar S, Liu PP, Cooper LT, Jr. Myocarditis. *Lancet*. 2012;379:738.

EPIDEMIOLOGY

FREQUENCY IS NOT WELL DEFINED

VARIED PRESENTATION

LACK OF NON INVASIVE TESTING

2019 Global Burden of Disease report,

Prevalance 9.21 / 1 lakh

MAGNITUDE OF PROBLEM

- **I C D 9—**

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.

PATHOGENESIS

CARDIAC INJURY FOLLOWED BY IMMUNE RESPONSE — INFLAMMATION

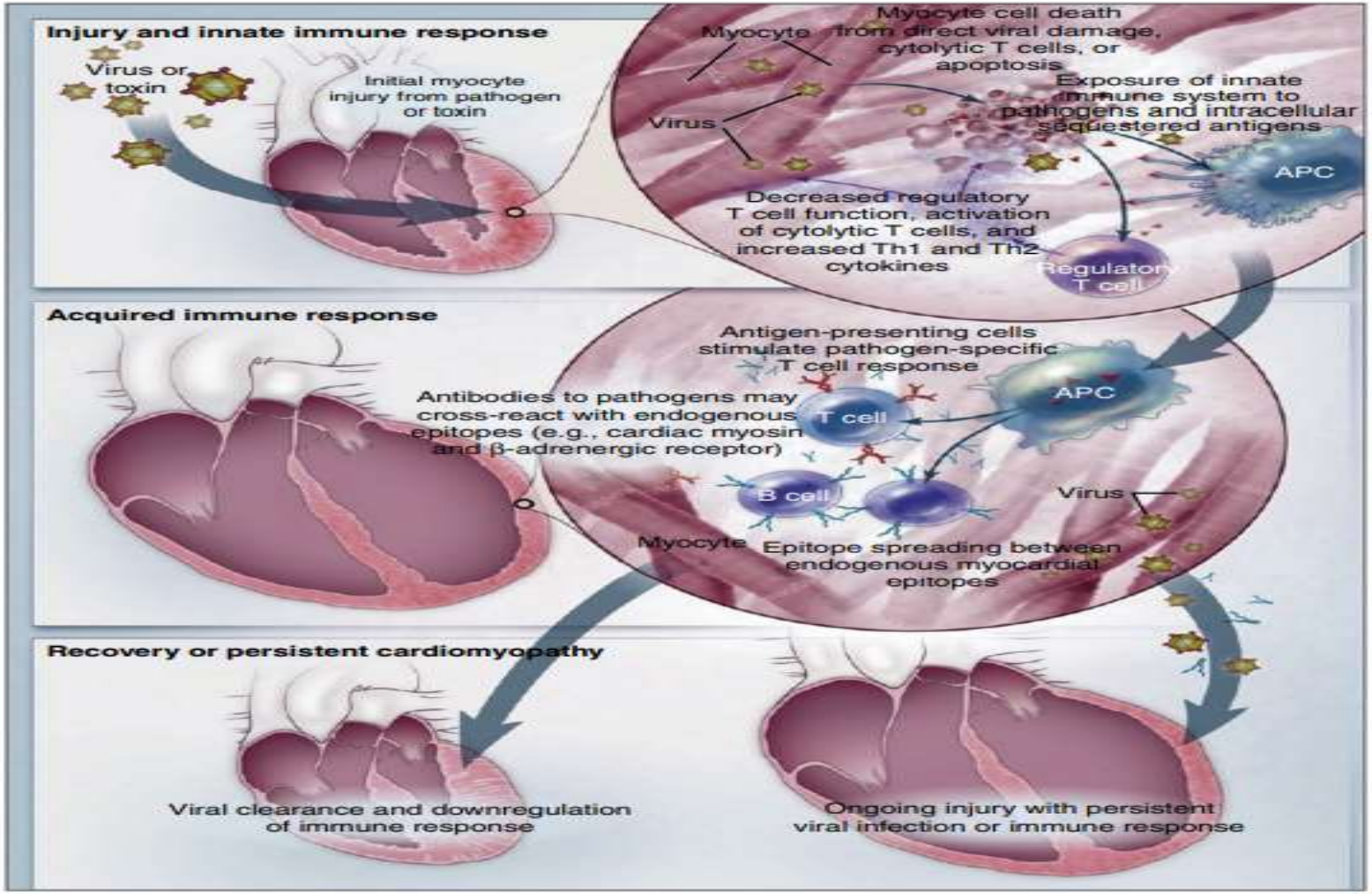
OFTEN SELF LIMITING

EXAGERRATED RESPONSE = DESTROY HEART TISSUE ACUTELY

CHRONIC INFLAMMATION → CARDIAC REMODELLING

↓

DCM , HEART FAILURE


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

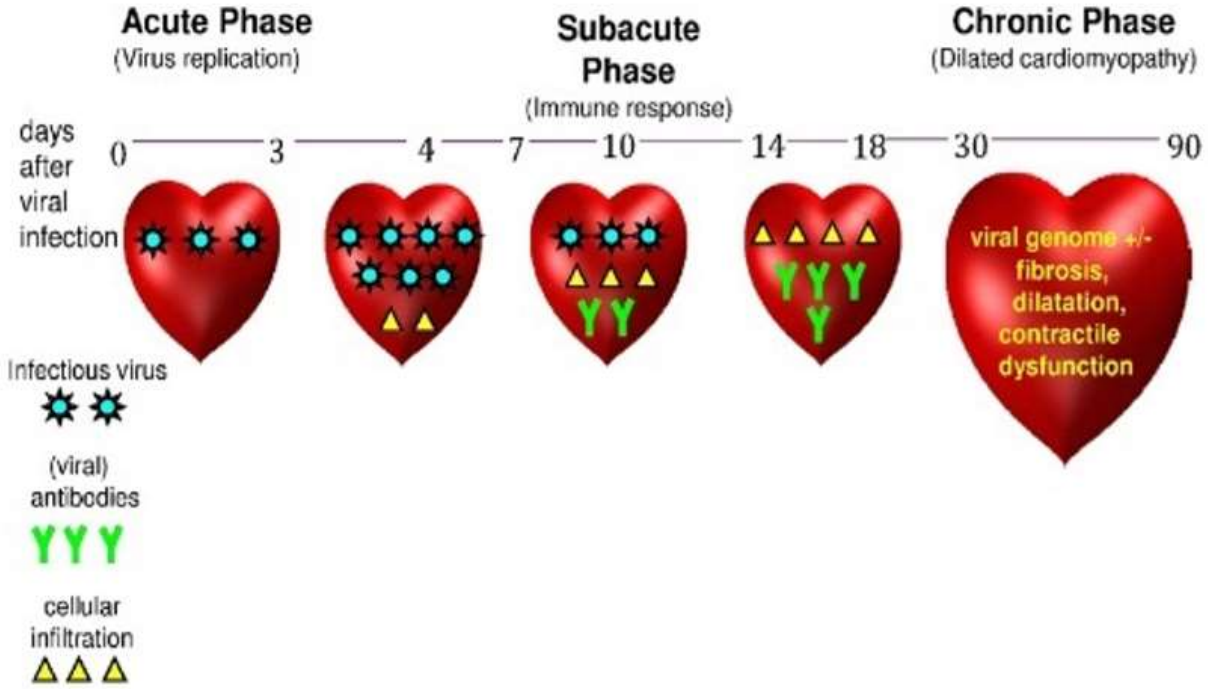
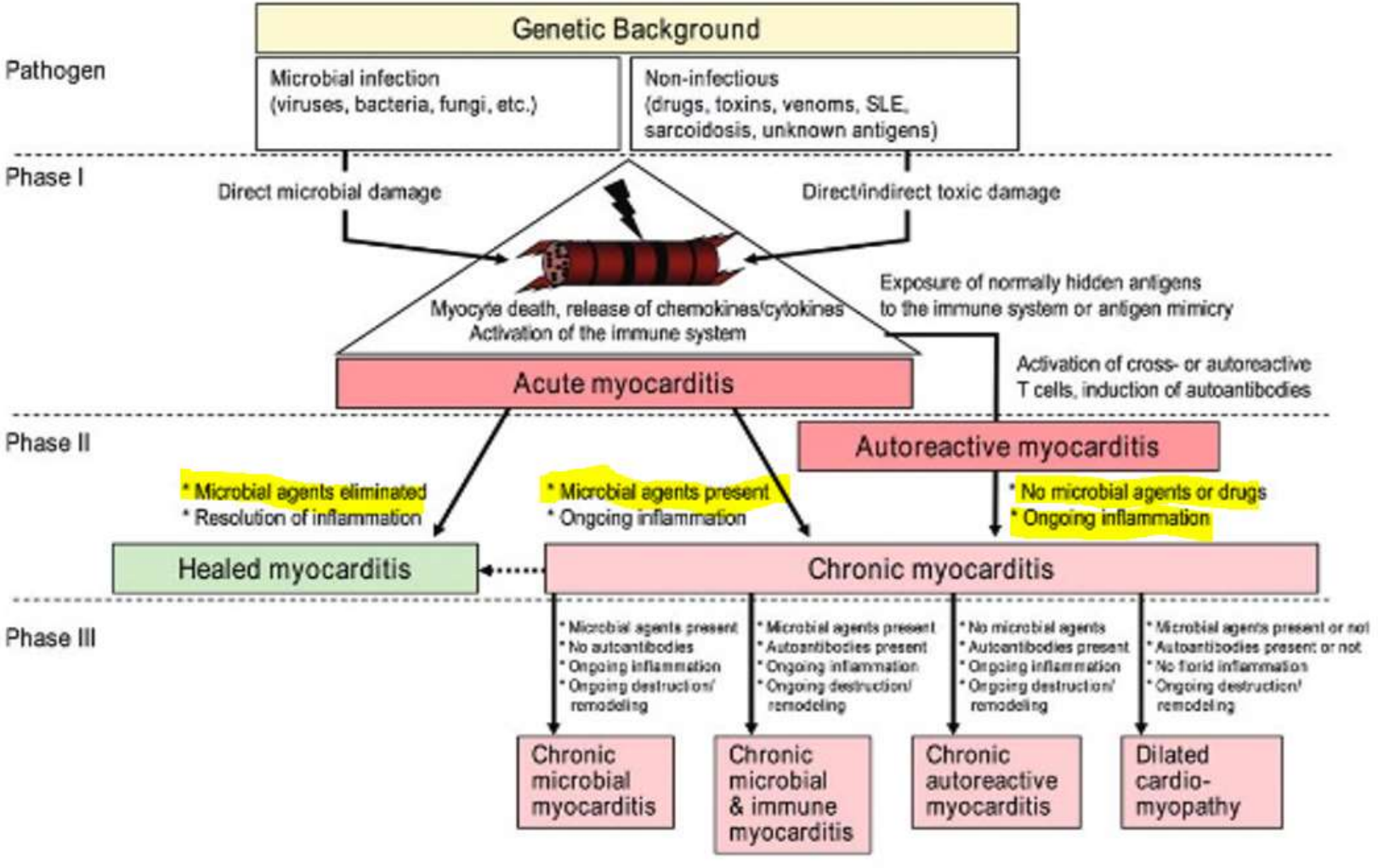


Figure 1 **Time Course of Viral Myocarditis**

Time course of viral myocarditis in 3 phases (derived from murine models). The acute phase of myocarditis takes only a few days, whereas the subacute and chronic phase covers a few weeks to several months. Modified from Kawai (22).


Genetic Background
Pathogen
Microbial infection
(viruses, bacteria, fungi, etc.)
Non-infectious
(drugs, toxins, venoms, SLE,
sarcoidosis, unknown antigens)
Phase I
Direct microbial damage
Direct/indirect toxic damage
Myocyte death, release of chemokines/cytokines
Activation of the immune system
Exposure of normally hidden antigens
to the immune system or antigen mimicry
Acute myocarditis
Activation of cross- or autoreactive
T cells, induction of autoantibodies
Phase II
Autoreactive myocarditis
* Microbial agents eliminated
* Resolution of inflammation
* Microbial agents present
* Ongoing inflammation
* No microbial agents or drugs
* Ongoing inflammation
Healed myocarditis
Chronic myocarditis
Phase III
* Microbial agents present
* No autoantibodies
* Ongoing inflammation
* Ongoing destruction/
remodeling
* Microbial agents present
* Autoantibodies present
* Ongoing inflammation
* Ongoing destruction/
remodeling
* No microbial agents
* Autoantibodies present
* Ongoing inflammation
* Ongoing destruction/
remodeling
* Microbial agents present or not
* Autoantibodies present or not
* No florid inflammation
* Ongoing destruction/
remodeling
Chronic
microbial
myocarditis
Chronic
microbial
& immune
myocarditis
Chronic
autoreactive
myocarditis
Dilated
cardio-
myopathy

Aetiology

Commonly viruses.

1950s to the 1990s- Entero viruses.

Last 2 decades- PCR and in situ hybridization led to other viruses.

Selected bacteria- diphtheria, Borrelia.

T. cruzi in Endemic areas

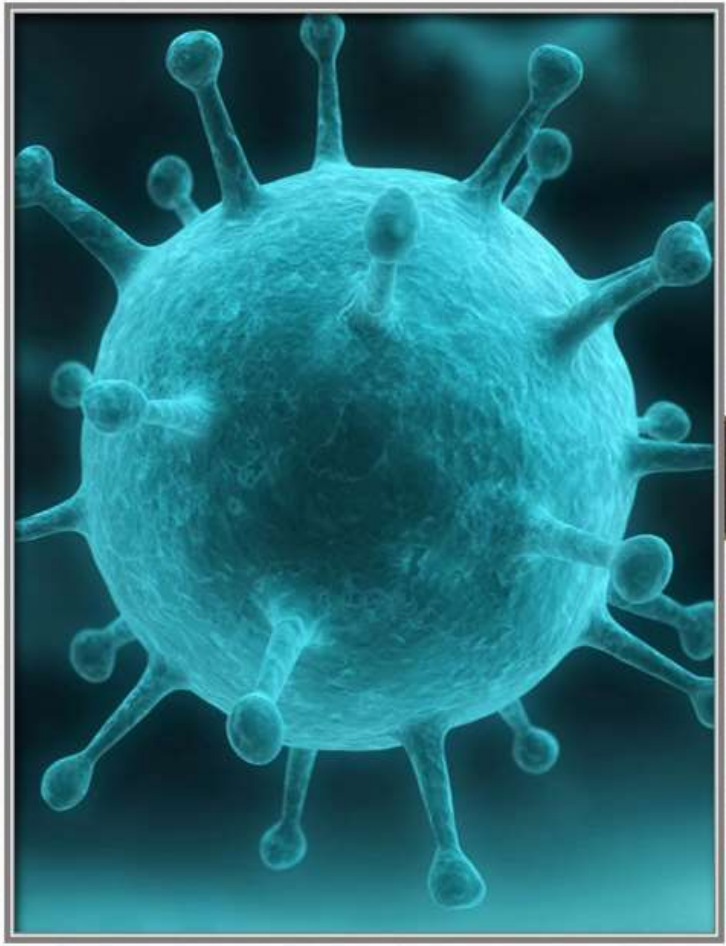
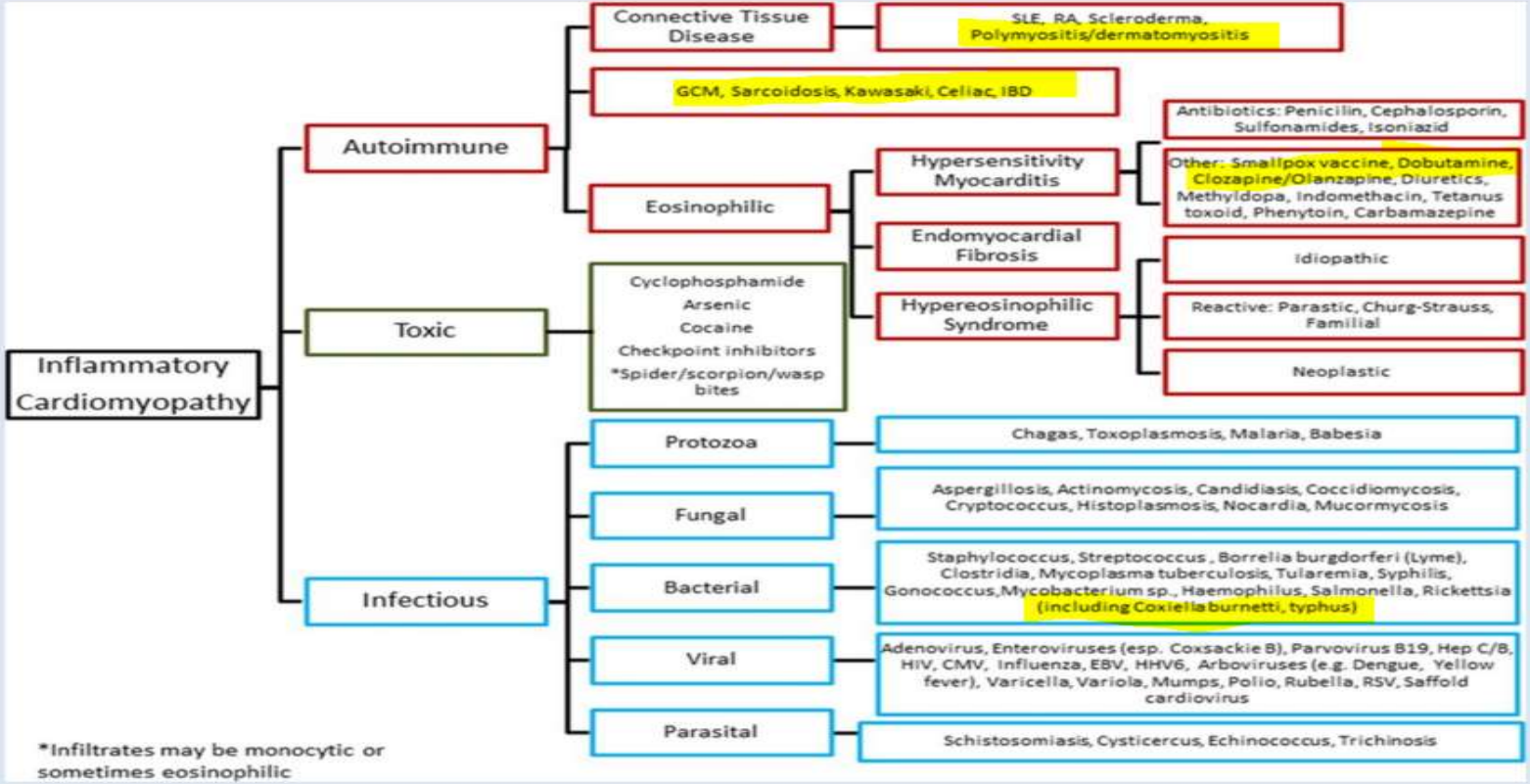


TABLE 55.4 Causes of Myocarditis

VIRUSES AND VIRAL DISORDERS	BACTERIA AND BACTERIAL DISORDERS	CARDIOTOXINS	HYPERSENSITIVITY MEDIATORS AND FACTORS
Adenovirus*	*Chlamydia*	Anthracycline drugs*	Cephalosporins
B19V	Cholera	Arsenic	Clozapine
Coxsackievirus B*	Leptospirosis	Carbon monoxide	Diuretics
Cytomegalovirus*	Lyme disease	Catecholamines	Hypereosinophilia
Epstein-Barr virus	*Mycoplasma*	Chagas disease	Insect bites
Hepatitis C virus	*Neisseria*	Cocaine*	Kawasaki disease
Herpes simplex virus	Relapsing fever	Copper	Lithium
HIV*	*Salmonella*	Ethanol*	Sarcoidosis
Influenza virus	Spirochete	Heavy metals	Snake bites
Mumps	*Staphylococcus*	Lead	Sulfonamides
Poliovirus	*Streptococcus*	Leishmaniasis	Systemic disorders
Rabies	Syphilis	Malaria	Tetanus toxoid
Rubella	Tetanus	Mercury	Tetracycline
SARS-CoV-2	Tuberculosis	Protozoa	Wegener granulomatosis
Varicella-zoster virus			
Yellow fever			

*Frequent cause of myocarditis.
HIV, Human immunodeficiency virus.
Modified from Elamm C, Fairweather D, Cooper LT. Pathogenesis and diagnosis of myocarditis. *Heart J.* 2012;98:835.

Pathogenesis of inflammatory cardiomyopathies



Trachtenberg et al Circ Res. 2017;121:803-818

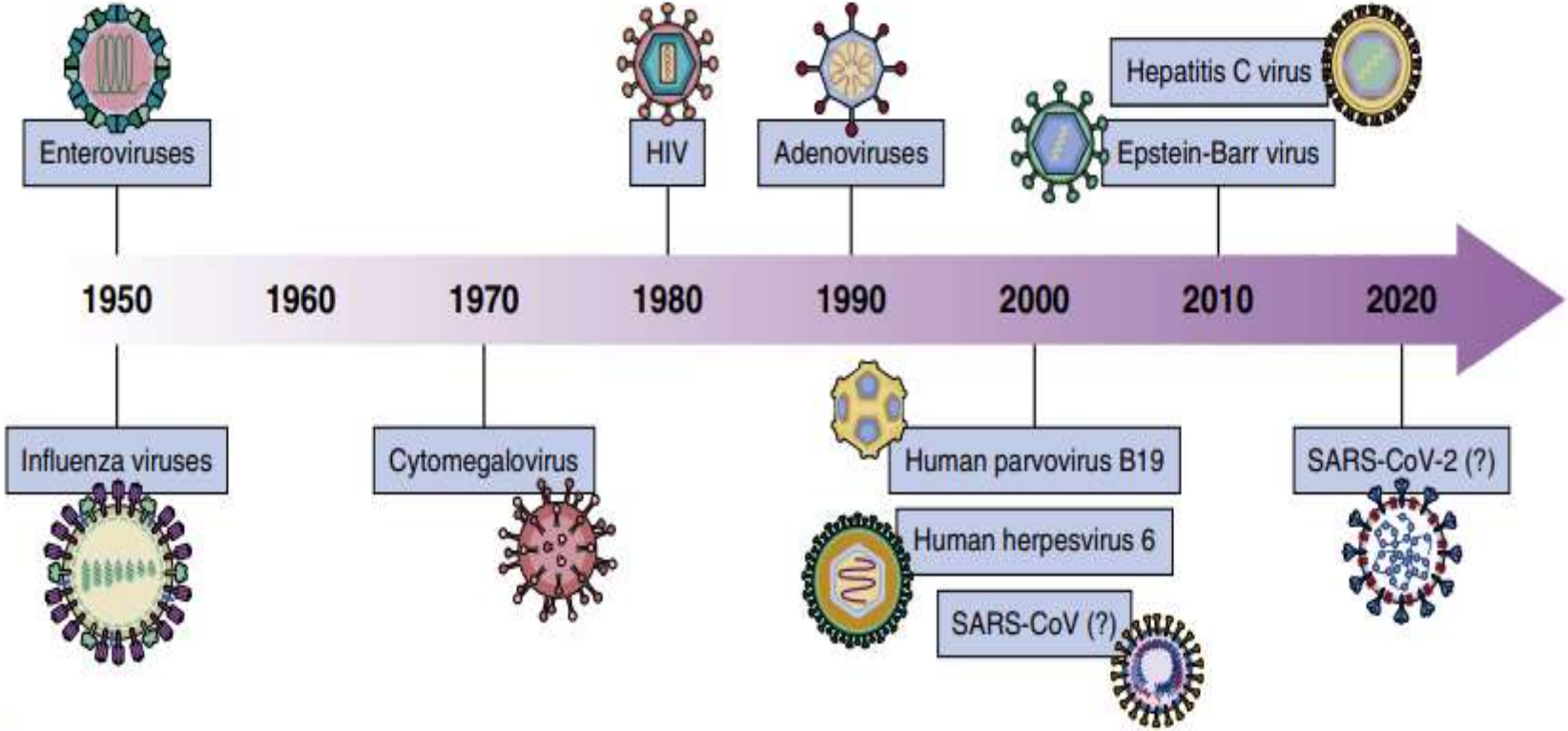


FIGURE 55.2 Prominent viruses associated with inflammatory cardiomyopathy over time. Over the years, the number of recognized viruses associated with inflammatory cardiomyopathy has grown. This evolution is partly influenced by the intentional detection of a broader repertoire of viruses over time as well as by the occurrence of novel viruses or virus genotypes in the heart. The association between severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 and inflammatory cardiomyopathy is not yet clear. "(?)" denotes unclear, needing further investigation; HIV, human immunodeficiency virus. (Adapted from Tschope C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol.* 2020;Oct 12:1–25. https://doi.org/10.1038/s41569-020-00435-x.)

Table 1. Studies Investigating Viral Prevalence in Myocarditis Patients

Study	Year	PVB, %	EV, %	AV, %	HSV, %	EBV, %	CMV, %	HHV, %	Notes
Kandolf et al[24]	1991	ND	24.2	ND	ND	ND	ND	ND	23/95 (24.2%) patients with suspected myocarditis, 10/33 (30.3%) patients with DCM
Griffin et al[25]	1995	ND	21	31	3.4	ND	3.4	ND	58 cases of fixed and frozen myocardial autopsy samples for PCR
Bowles et al[26]	2003	<1	14	23	<1	<1	3	ND	PCR using EMB samples from 624 patients with myocarditis
Kühl et al[27]	2005	36.6	32.6	8.1	ND	ND	ND	10.5	12% Dual infection in acute myocarditis, generally PVB+HHV in 172 patients
Caforio et al[19]	2007	3.0	12.5	5.0	ND	4.0	2.5	ND	174 confirmed viral myocarditis patients
Breinholt et al[28]	2010	82.6	ND	1	ND	19.8	2.5	ND	PCR using EMB samples of 99 children (3 wk to 18 y of age)
Gaaloul et al[29]	2014	ND	28	ND	ND	ND	ND	ND	Evaluated CVB genomes in hospitalized patients with inflammatory heart diseases. One case of CVB1 and 27 of CVB3
Cooper and Knowlton[29a]	2015	11–56	15–30	2–23	ND	ND	ND	ND	Chapter 67, Braunwald's Heart Disease, 10th edition

AV indicates adenovirus; CMV, cytomegalovirus; CV, coxsackievirus; DCM, dilated cardiomyopathy; EBV, Ebola virus; EMB, endomyocardial biopsy; EV, enterovirus; HHV, human herpes virus; HSV, herpes simplex virus; ND, not determined; PCR, polymerase chain reaction; and PVB, parvovirus B.

BIMODAL PRESENTATION

FULMINANT IN YOUNG CHILDREN AND TEENAGERS

WHEREAS INSIDIOUS WITH HEART FAILURE AND DCM IN ADULTS

RESPONSIBLE 10-15% OF NEW ONSET IDIOPATHIC DCM CASES.

CLINICAL FEATURES

- Chest pain and dyspnoea.
- Preceded by viral prodrome URI or GI.
- Chest pain resembles MI or pericarditis.

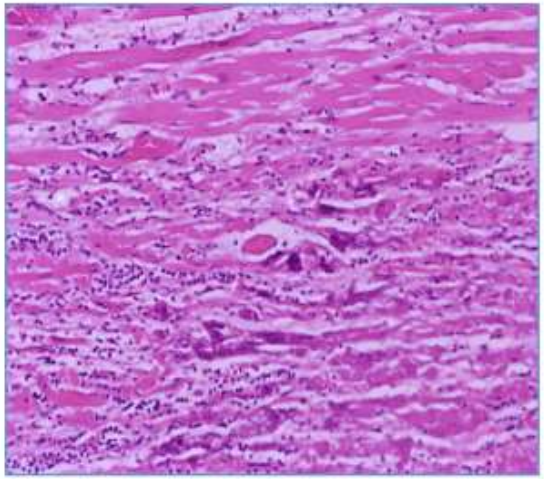
Myo-pericarditis in 11% (*Imazio et al*-circulation 2013)

- Angina Coronary vasospasm

  Micro vascular dysfunction
- Palpitations and syncope.
- Heart failure and sudden cardiac death.

Myocarditis

Clinical Presentations



- Myopericarditis/MINOCA
- Sudden Death
- Acute Dilated Cardiomyopathy
- Chronic Dilated Cardiomyopathy

Clinical features of myocarditis

Excessive fatigue or exercise intolerance
Chest pain
Unexplained sinus tachycardia
S3, S4, or summation gallop
Abnormal electrocardiogram
Abnormal echocardiogram
New cardiomegaly on chest radiograph
Atrial or ventricular arrhythmia
Partial or complete heart block, new-onset bundle branch block
New-onset or worsening heart failure
Acute pericarditis
Cardiogenic shock
Sudden cardiac death
Respiratory distress/tachypnea
Hepatomegaly

VIRAL CASES ESPECIALLY PARVOVIRUS PRESENT WITH CHEST PAIN DUE TO ENDOTHELIAL DYSFUNCTION

GIANT CELL MYOCARIDTIS = VENTRICULAR ARRYTHMIAS

RASH WITH ARTHRITIS= DRUG INDUCED HYPERSENSITIVITY

HILAR LYMPHADENOPATHY WITH POLYARTHRALGIA = LOFGREN SYNDROME.

ACUTE VIRAL 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 cases display this phenotype
- 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 immunosuppressants.
- 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

EOSINOPHILIC MYOCARDITIS

IN ASSOCIATION WITH OFFENDING AGENT

OR SECONDARY TO SYSTEMIC EOSINOPHILIC DISORDERS

LOFFLERS ENDOCARDITIS

WITHDRAWAL OF OFFENDING AGENTS AND STEROIDS

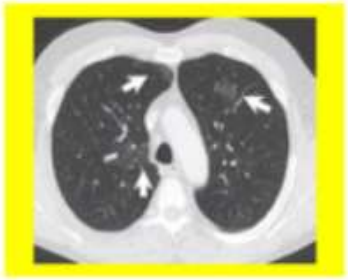
- FULMINANT NECROTIC MYOCARDITIS

POOR PROGNOSIS

AGGRESIVE IMMUNOSUPRESSION AND MECHANICAL CIRCULATORY SUPPORT

A

SYSTEMIC CONDITIONS ASSOCIATED WITH EOSINOPHILIC MYOCARDITIS

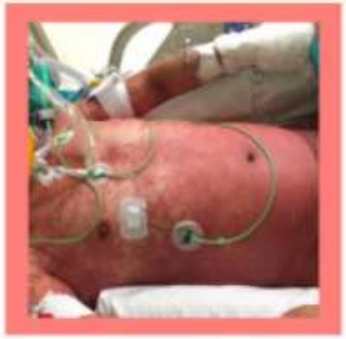


1. Eosinophilic granulomatosis with polyangiitis (EGPA)

2. Hypereosinophilic syndrome (HES)

3. Parasitic infections

4. Hypersensitivity reaction to drugs /DRESS

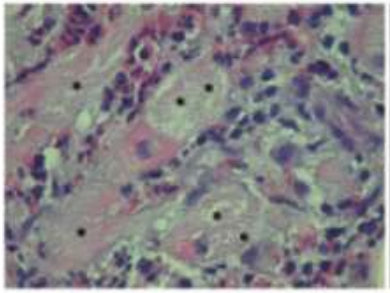


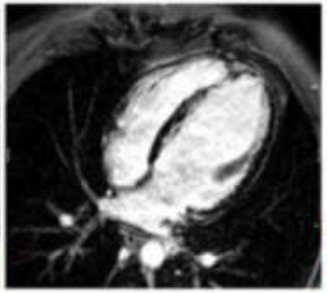
5. Solid cancer

EOSINOPHILIC MYOCARDITIS

B

ACUTE INTENSE EXPOSURE TO EOSINOPHILIA

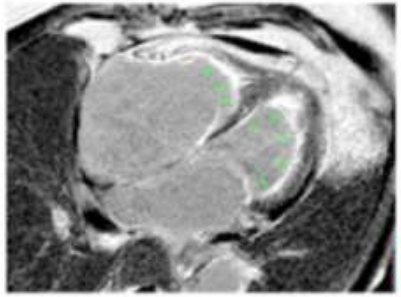




NECROTIC/INFLAMMATORY STAGE

EOSINOPHILIC MYOCARDITIS

CHRONIC EXPOSURE TO EOSINOPHILIA



LOEFFLER CARDIOMYOPATHY

THROMBOTIC/FIBROTIC STAGES

SPECIFIC SCENARIOS

DRUG INDUCED HYPERSENSITIVITY

WITHIN 8 WKS

SULFA DRUGS,ANTIMICROBIALS, ALLOPURINOL,CLOZAPINE

DOBUTAMINE CAN CAUSE EOSINOPHILIC MYOCARDITIS

STOP IF EOSINOPHILIA OR UNEXPECTED DECLINE IN LVEF

RADIATION

MOSTLY CAUSES CONCSTRICTIVE PERICARDITIS ,MYOCARDIAL FIBROSIS IN LONG TERM(5 - 20 YRS AFTER THERAPY)

OCCASIONALLY CAN PRESENT AS ACUTE PERICARDITIS WITH MILD LV SYSTOLIC DYSFUNCTION , SELF LIMITING

LABORATORY TESTING

CARDIAC TROPONINS

CKMB is elevated in only 7.5%-- biopsy-proven myocarditis,

whereas the cardiac troponin I or T is elevated in at least 50% of Patients with biopsy-proven myocarditis

(89% to 94% specificity and 34% to 53% sensitivity).

CBC = LEUCOCYTOSIS (LYMPHOCYTIC) , EOSINOPHILIA (EM)

NT PRO BNP

INFLAMMATORY MARKERS —--- NON SPECIFIC

NOVEL MARKERS(SOLUBLE FaS LEVELS, FaS LIGAND LEVELS) UNDER INV

VIRAL ANTIBODY TITRES = DOES NOT CORRELATE / NR

Anticardiac antibody titers. low specificity

(against sarcolemma, myosin, laminin, ADP/ATP translocator, or β-adrenergic receptors) is not indicated (only 62% of myocarditis cases have titers ≥1:40).

RHEUMATOLOGIC SCREENING WHEN INDICATED

ANA,DS DNA

ANTI JO1

C ANCA

ANTI SCL70

ECG

- Low sensitivity – used for screening.
- Nonspecific T waves and ST-segment changes including ST-segment elevation.

Sinus tachycardia disproportionate to degree of fever.

- BRADY OR TACHYARRYTHMIAS.
- PR segment depression with diffuse STE in myopericarditis.

Ukena et al - prolonged QRS duration is a significant independent predictor for cardiac death or heart transplantation (**Eur J Heart Fail. 2011**)

ECHO

LV FUNCTION , THROMBUS , DIMENSIONS , SEPTAL WALL THICKNESS

FULMINANT = NORMAL DIASTOLIC DIMENSIONS AND INCREASED SEPTAL WALL THICKNESS AND VICE VERSA IN ACUTE MYOCARDITIS

HCV= HCM PHENOTYPE

RULE OUT OTHER ETIOLOGIES OF SYSTOLIC DYSFUNCTION

RV DYSFUNCTION AT ONSET IS A/W POOR PROGNOSIS.

OTHER IMAGING MODALITIES

1. Antimyosin scintigraphy (indium III monoclonal antimyosin antibody) provides identification of myocardial inflammation,

high sensitivity (91% to 100%) NPV (93% to 100%)

low specificity (28% to 33%).

2. Gallium scanning identifies severe myocardial cellular infiltration with high specificity (98%)

low sensitivity(36%).

CORONARY ANGIOGRAPHY

TO RULE OUT CAD.

ESPECIALLY IN CASES WITH NEW ONSET HEART FAILURE,

ACS LIKE PRESENTATION,

PSEUDO INFARCT PATTERN ON ECG

RWMA.

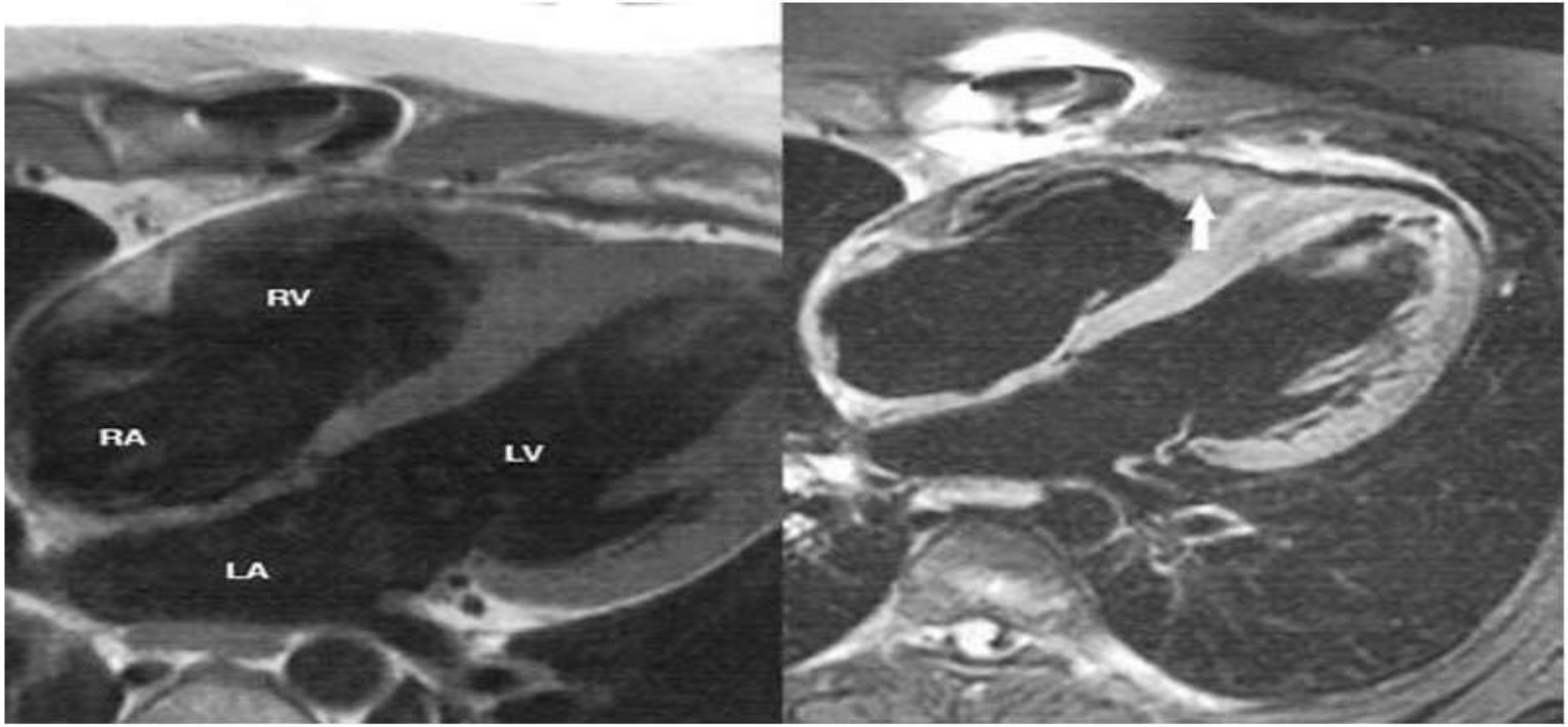
CARDIAC MRI

- cMRI sensitivity and specificity are as high as 100% and 90%.

- T2-weighted CMR -oedema visualised by signal intensity.

T1-weighted sequences -inflammation or fibrosis.

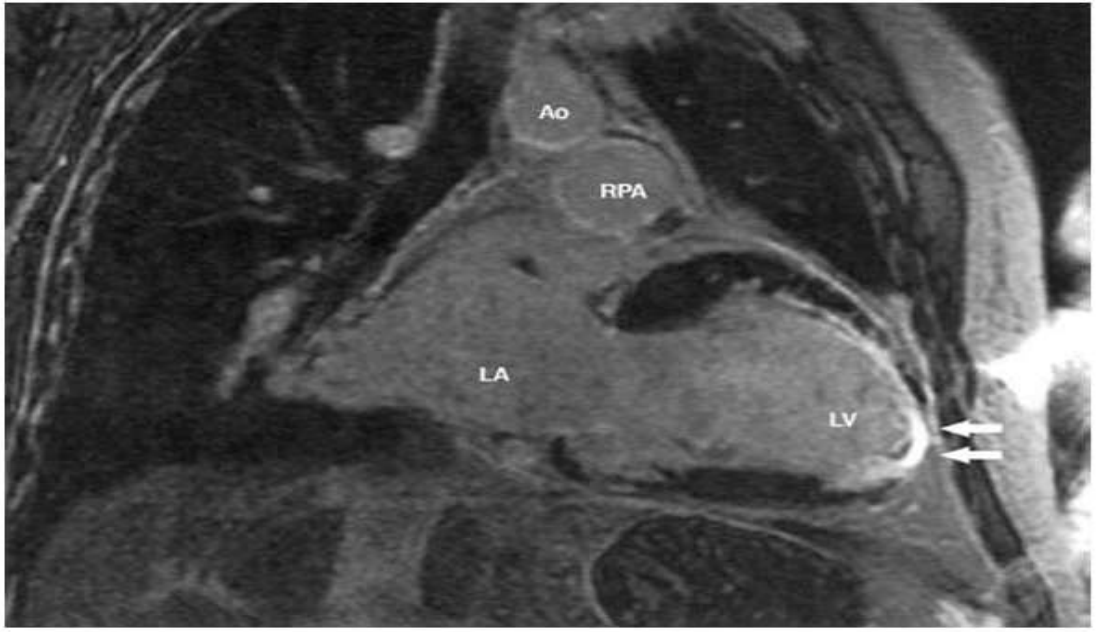
T1-weighted (left) and T2-weighted (right) images



Delayed hyperenhancement

- In areas where the myocardium is infarcted or fibrotic, there is delayed 'wash-in' and 'wash-out' of MRI contrast agents.
- show up as bright or 'hyperenhanced' areas of myocardium when 'delayed' images are taken, typically 10–20 minutes after injection of gadolinium DPTA

combination of delayed wash-in and wash-out kinetics of nonviable tissue
and diff volumes of distribution of Gd in viable and nonviable regions



Hyperenhancement patterns

CAD

A. Subendocardial infarct

B. Transmural infarct

Non-CAD

A. Mid-wall HE

- Dilated cardiomyopathy
- Myocarditis

- Hypertrophic cardiomyopathy
- Right ventricular pressure overload (eg, congenital heart disease, pulmonary HTN)

- Sarcoidosis
- Myocarditis
- Anderson-Fabry
- Chagas disease

B. Epicardial HE

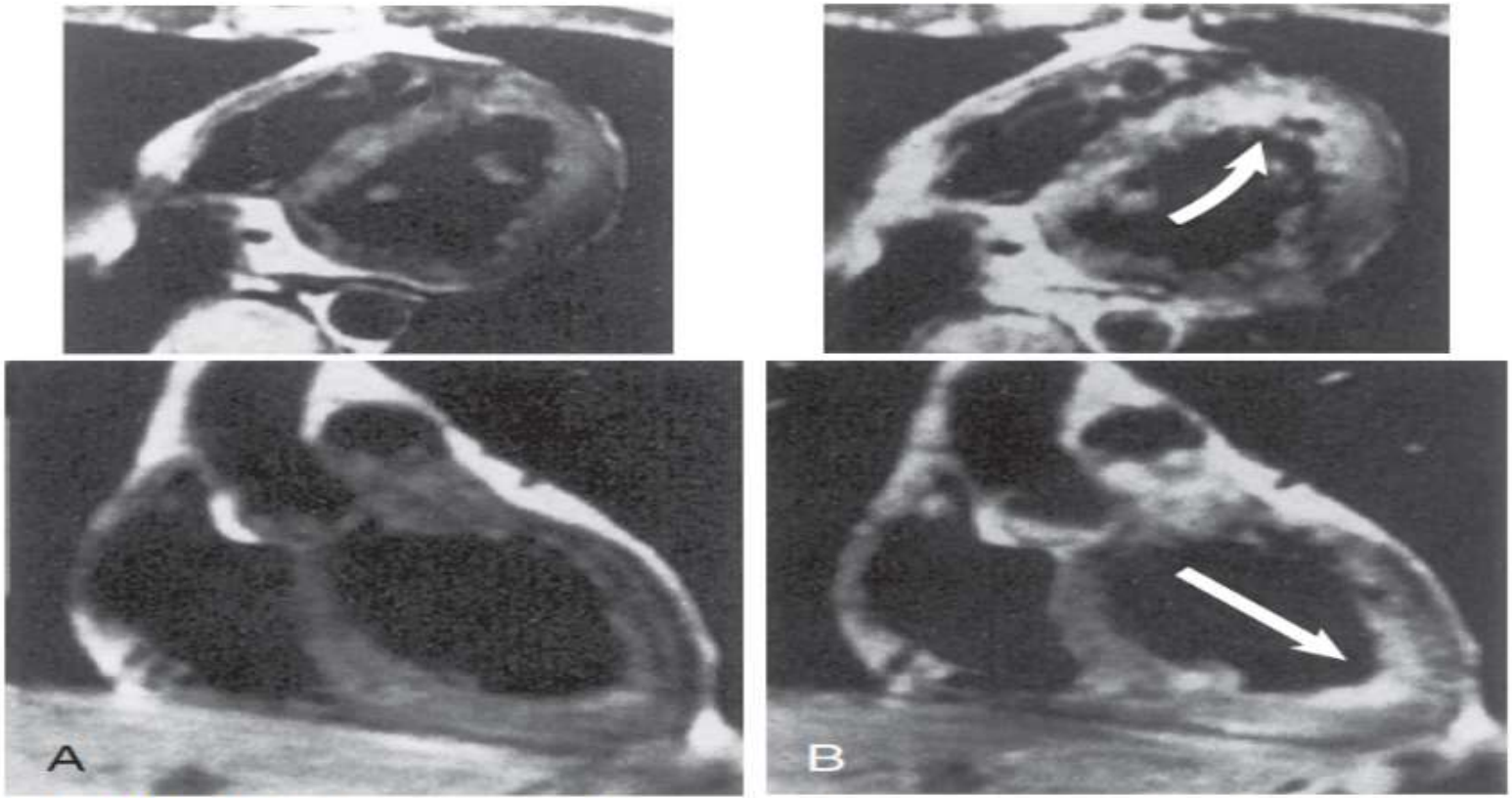
- Sarcoidosis, myocarditis, Anderson-Fabry, Chagas disease

C. Global endocardial HE

- Amyloidosis, systemic sclerosis, postcardiac transplantation

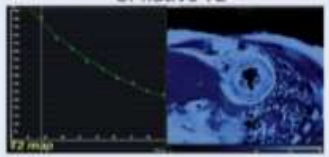
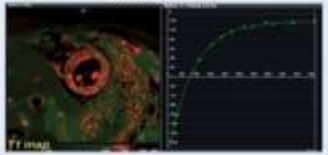
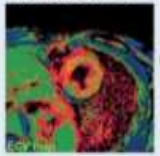
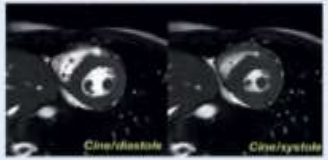
- Rim-like pattern --- septal wall or a sub epicardial distribution ----free LV lateral wall - PVB19.
- PVB19 ---- CE -lateral wall
- HHV 6 -----CE -mid wall ---- IVS .
- CE- CMR : Guidance for EMB sampling when necessary.
-
- Lacks the ability to determine the magnitude of inflammation.

c MRI is a reliable method of detecting myocardial fibrosis in DCM



EFIGURE 55.3 **A,** Precontrast T1-weighted transaxial *(upper)* and coronal *(lower)* magnetic resonance images through the left ventricle in a patient with myocarditis. **B,** Postcontrast magnetic resonance images at the same levels after injection of contrast material. Note enhancement of the myocardial signal in the septum and apical region *(arrows)*. (From Matsouka H, Hamada M, Honda T, et al. Evaluation of acute myocarditis and pericarditis by Gd-DTPA enhanced magnetic resonance imaging. *Eur Heart J.* 1994;15:283.)

MRI - Louise criteria for acute Myocarditis

	2018 Lake Louise Criteria	CMR Image Examples
Main Criteria	**Myocardial Edema** (T2-mapping or T2W images)	Regional or global increase of native T2  or Regional or global increase of T2 signal intensity 
	Non-ischemic Myocardial Injury (Abnormal T1, ECV, or LGE)	Regional or global increase of native T1  or Regional or global increase of ECV  or Regional LGE signal increase 
Supportive Criteria	**Pericarditis** (Effusion in cine images or abnormal LGE, T2, or T1) **Systolic LV Dysfunction** (Regional or global wall motion abnormality)	Pericardial effusion  Regional or global hypokinesis 

Ferreira et al JACC 72:3158-3176; 2018

ETABLE 55.1 Lake Louise Consensus Criteria Cardiac Magnetic Resonance Diagnosis of Myocarditis

In the setting of clinically suspected myocarditis,* CMR findings are consistent with myocardial inflammation, if at least two of the following criteria are present:

1. Regional or global myocardial SI increase in T2-weighted images.†
2. Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images.‡
3. There is at least one focal lesion with nonischemic regional distribution in IR-prepared gadolinium-enhanced T1-weighted images("late gadolinium enhancement"). A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation, if
   - criterion 3 is present.

A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended, if

- none of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation.
- one of the criteria is present.

The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis.

CMR, Cardiac magnetic resonance.
*The clinical suspicion for active myocarditis should be based on the criteria listed in Table 55.3.
†Images should be obtained using a body coil or a surface coil with an effective surface coil intensity correction algorithm; global SI increase has to be quantified by an SI ratio of myocardium over skeletal muscle of ≥2.0). If the edema is more subendocardial or transmural in combination with a co-localized ischemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported.
‡Images should be obtained using a body coil or a surface coil with an effective surface coil intensity correction algorithm; a global SI enhancement ratio of myocardium over skeletal muscle of ≥4.0 or an absolute myocardial enhancement of ≥45% is consistent with myocarditis.

Recommendations

5. Cardiovascular magnetic resonance findings consistent with myocarditis should be based on Lake-Louise criteria (*Table 5*).
6. Cardiovascular magnetic resonance may be considered in clinically stable patients prior to EMB. Cardiovascular magnetic resonance does not replace EMB in the diagnosis of myocarditis and should not delay EMB in life-threatening presentations.

MRI - Louise criteria for acute Myocarditis

CMR is recommended for the characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease (myocarditis), LV non-compaction, amyloid, sarcoidosis, iron overload/haemochromatosis.	I	C

- **MRI (Lake-Louise Criteria/T1/T2)**

- **High accuracy in the acute stage**
- **a negative result does not exclude a myocarditis**
- **a positive result does not clarify the etiology / viral situation**

ENDOMYOCARDIAL BIOPSY

GOLD STANDARD FOR DEFINITIVE DIAGNOSIS

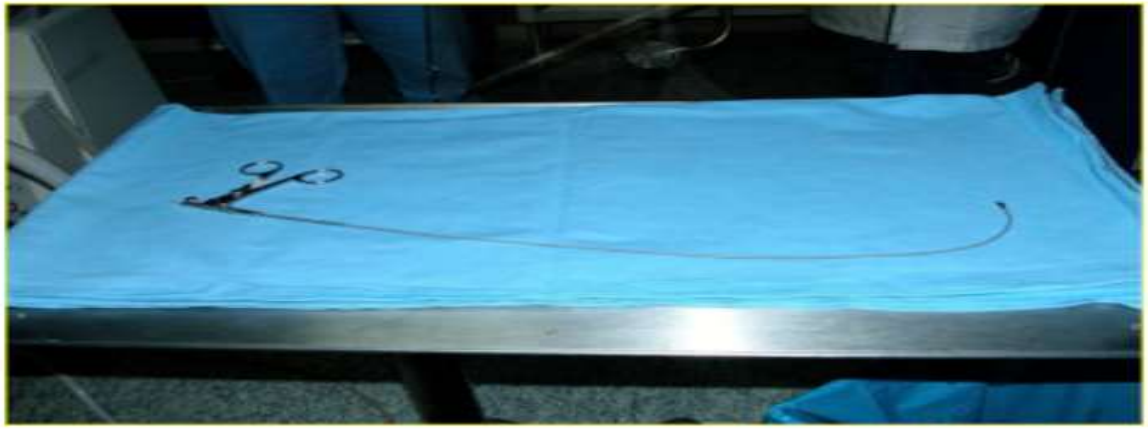
STIFF SHAFT OR FLEXIBLE SHAFT BIOPTOME

MAJOR COMPLICATIONS 1/1000 IN EXP CENTRES

- ACCESS RELATED
- CARDIAC PERFORATION
- VALVULAR REGURG
- TAMPONADE

Sign in to download hi-res image

Figure 9.8. *Cordis* disposable bioptome. Forceps jaws (*arrow*).



Endomyocardial Biopsy

CONTRAINDICATIONS

Absolute contraindications

- Routine use of EMB for detecting the etiology of heart failure
- LV thrombus (LV biopsy)
- Aortic valve mechanical prosthesis (LV biopsy)

Relative contraindications

- Uncorrected coagulopathies
- Anticoagulation therapy
- Thrombocytopenia
- Serious organ dysfunction (including renal dysfunction)
- Vascular anomaly
- Contrast agent allergy
- Anxious patients who cannot rest during the procedure

Seferović PM et al. EJHF 2020

AHA/ACCF/ESC SCIENTIFIC STATEMENT

The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease

A Scientific Statement From the American Heart Association, the American College of Cardiology, and the European Society of Cardiology

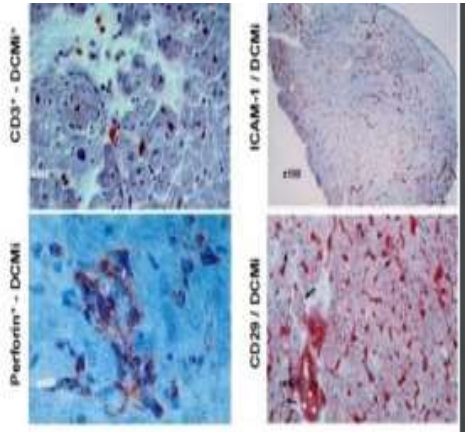
Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology

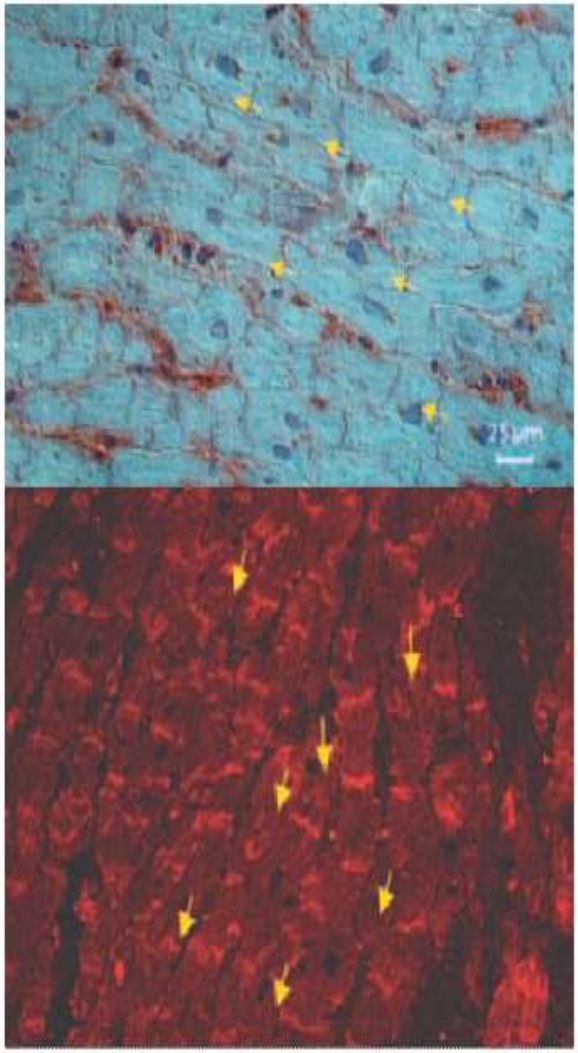
Cooper LT et al. JACC & Eur Heart J 2007

Scenario Number		Class of Recommendation (I, IIa, IIb, III)	Level of Evidence (A, B, C)
1	New-onset heart failure of *<2 weeks'* duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I	B
2	New-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	I	B
3	Heart failure of *>3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	IIa	C
4	Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa	C
5	Heart failure associated with suspected anthracycline cardiomyopathy	IIa	C
6	Heart failure associated with unexplained restrictive cardiomyopathy	IIa	C
7	Suspected cardiac tumors	IIa	C
8	Unexplained cardiomyopathy in children	IIa	C
9	New-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	B
10	Heart failure of *>3 months'* duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	C
11	Heart failure associated with unexplained HCM	IIb	C
12	Suspected ARVD/C	IIb	C
13	Unexplained ventricular arrhythmias	IIb	C
14	Unexplained atrial fibrillation	III	C

Diagnosis of Myocarditis

DEFINITION OF MYOCARDITIS





- Inflammatory disease of the myocardium diagnosed by established histological*, immunological and immunohistochemical criteria** and identification of viral genome in the myocardium (PCR)

*Dallas criteria: histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin

MARBURG CRITERIA 1996

**inflammatory infiltrate: ≥14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of CD 3 positive T-lymphocytes ≥7 cells/mm^2

Caforio, Pankuweit…Ristic et al. Eur Heart J 2013

TABLE 55.2 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 or without fibrosis
- Borderline myocarditis (repeat biopsy may be indicated)
- No myocarditis

Subsequent biopsy

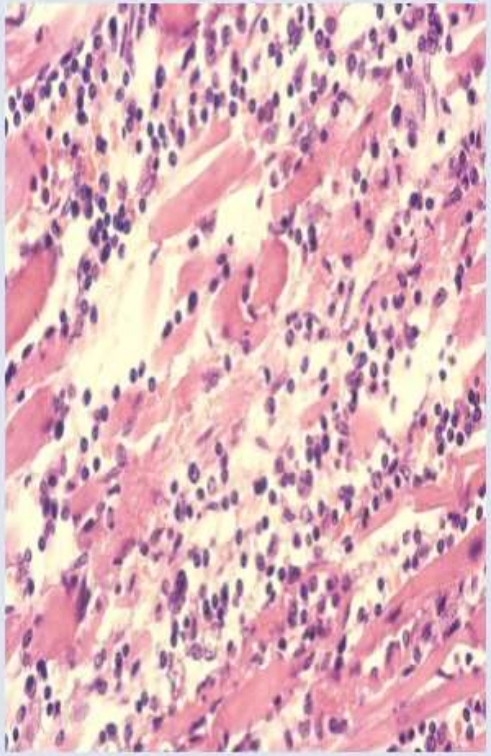
- Ongoing (persistent) myocarditis with or without fibrosis
- Resolving (healing) myocarditis with or without fibrosis
- Resolved (healed) myocarditis with or without fibrosis

	DESCRIPTORS	
	INFLAMMATORY INFILTRATE	FIBROSIS
Distribution	Focal, confluent, diffuse	Endocardial, interstitial
Extent	Mild, moderate, severe	Mild, moderate, severe
Type	Lymphocytic, eosinophilic, granulomatous, giant cell, neutrophilic, mixed	Perivascular, replacement

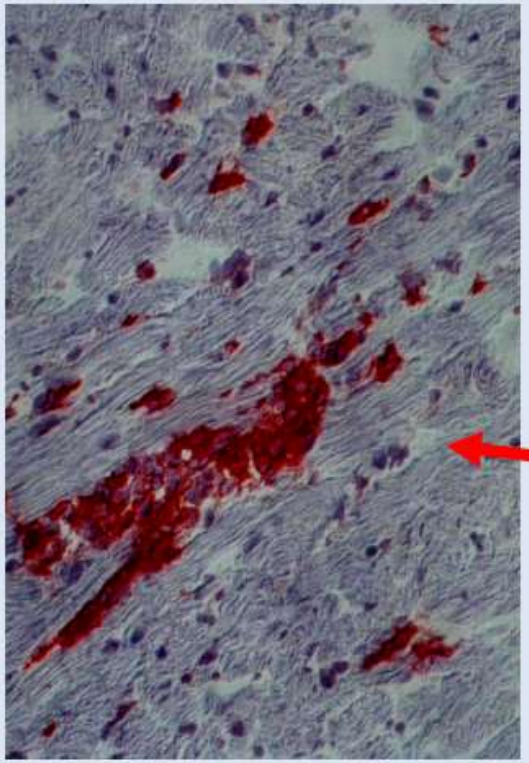
Modified from Leone O, Veinot JP, Angelini A, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol*. 2012;21:245.

The requirement for a specific treatment strategy for myocarditis is a comprehensive diagnostic by an endomyocardial biopsy

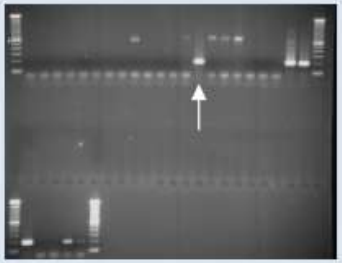
Histology



Immuno-Histology



Molecular-biology

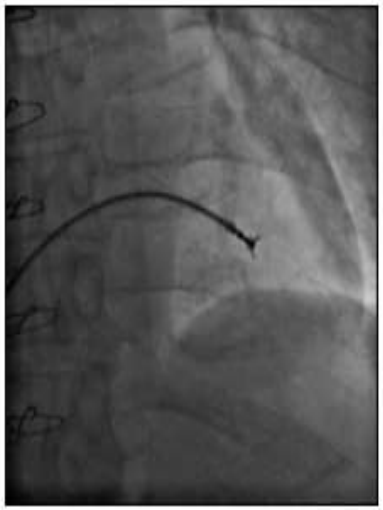


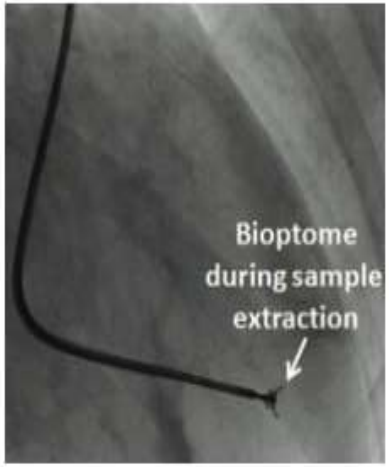
Coxsackie

Sampling error
(5-6 samples)

Caforio et al, Eur Heart J 2013
Noutsias et al 2011

TECHNICAL ADVANCES





Biopsy site

- RV EMB
- LV EMB
- BV EMB

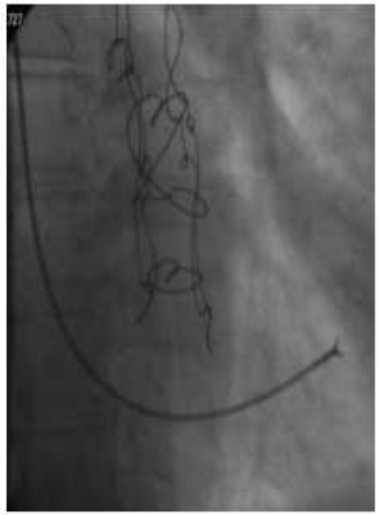
Approach

- Femoral
- Radial
- Jugular

Guidance

- MRI
- Electromechanical mapping
- Echocardiography

Pitfalls of endomyocardial biopsy
Diagnostic accuracy of EMB depends on: • Expertise of operator who performs the procedure • Timing of the procedure related to beginning of patient symptoms • Biopsy site (RV or LV) • Number of bioptic samples • Expertise of pathologist who analyses the samples • Patchy diseases



Endomyocardial biopsy[97,908,918–920]

Indication. In suspected phenotypes requiring specific treatments (i.e. giant cell myocarditis, eosinophilic myocarditis, sarcoidosis, vasculitis, SLE, other systemic, auto-immune inflammatory conditions, or storage diseases).

Number of samples. A minimum of 5 but possibly at least 7 samples: 3 for pathology, 2 for infection (DNA, PCR) and 2 for RNA viruses/viral replication.[919,920]

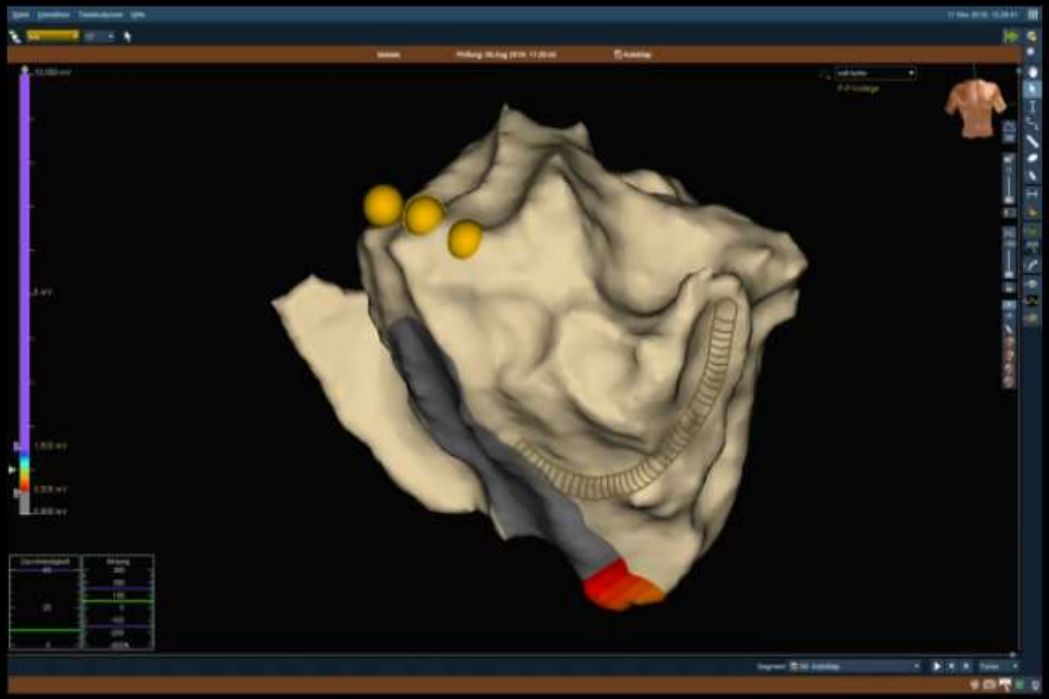
Aetiology. Search for common cardiotropic viruses (parvovirus B19, HHV4, HHV6, enteroviruses, adenovirus and coxsackie) by quantitative rtPCR when a viral aetiology is suspected. Viral mRNA for active viral replication should be assessed, if possible.

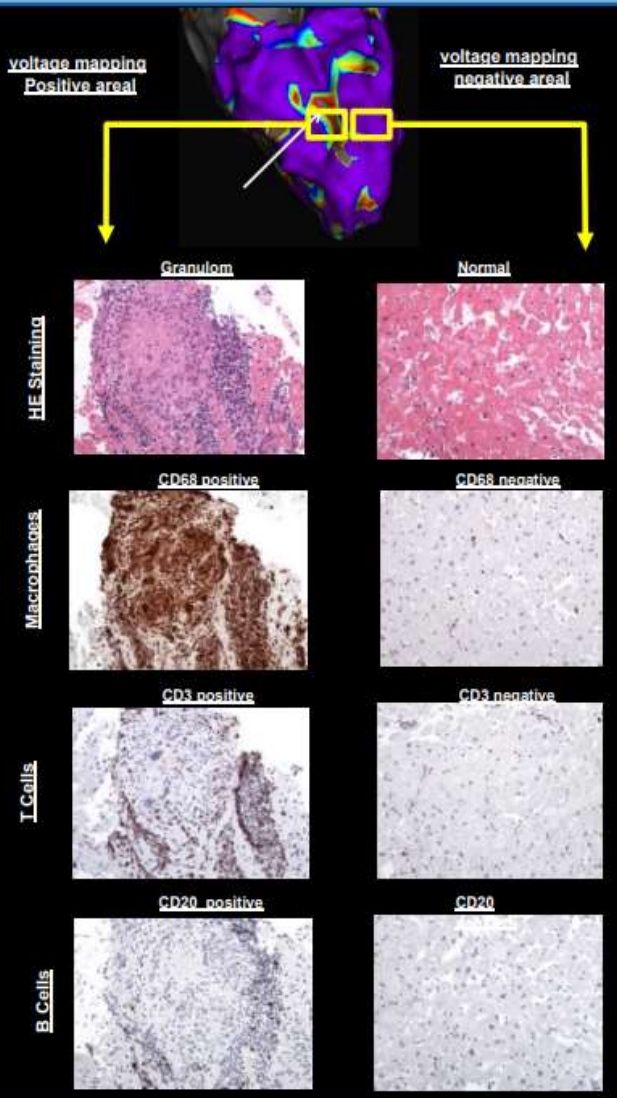
Further assessment if indicated: CMV, HIV, *Borrelia burgdorferi* (Lyme disease), *Coxiella burnetii* (Q-fever), *Trypanosoma cruzi* (Chagas disease) and SARS-CoV-2.

Immunohistochemistry. Quantification of CD3-, CD4-, CD8- or CD45- staining lymphocytes and CD68 macrophages per mm^2; anti-HLA-DR.

Histology. Haematoxylin and eosin staining, fibrosis assessment with Masson's Trichrome and Picrosirius Red, amyloid fibrils detection with Congo Red.

Electro-anatomic mapping-guided endomyocardial biopsies

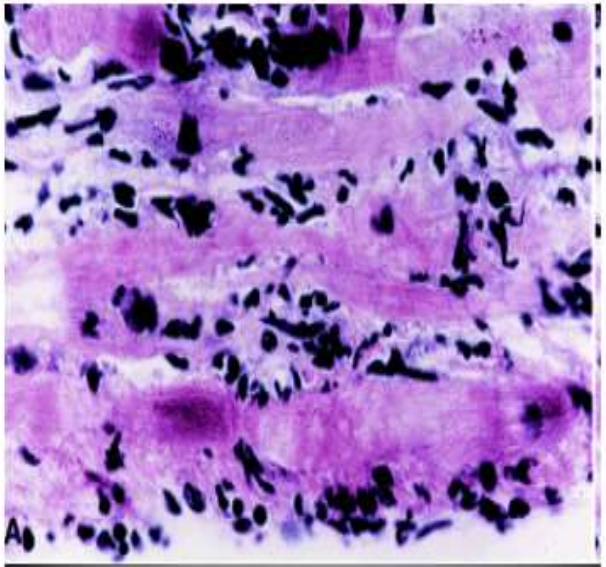


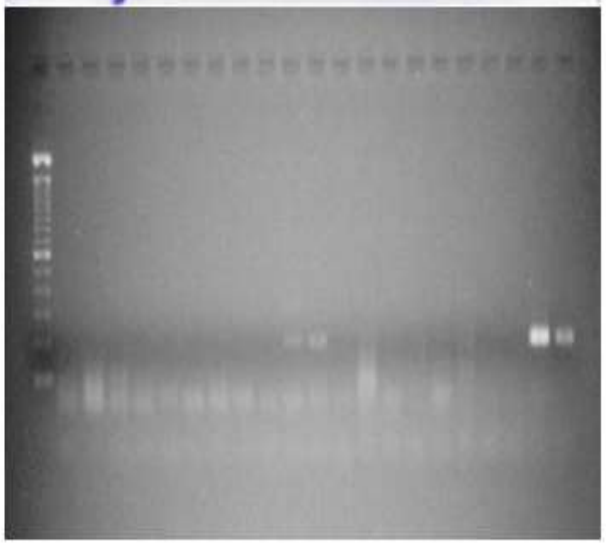


Tschöpe et al., Nat Rev Cardiology 2021

Dg & Treatment of Myocarditis: ESC Consensus 2013

IMPACT OF EMB FINDINGS ON TREATMENT





- **Immunosuppression** should be started **only after ruling out active infection on EMB by PCR**.
- Consideration of immunosuppression in proven autoimmune (infection-negative) myocarditis: **giant cell myocarditis, cardiac sarcoidosis** (regardless of the degree of ventricular dysfunction)**, and systemic autoimmune disease**.
- Infection-negative **eosinophilic or toxic myocarditis with heart failure and arrhythmia**.
- Immunosuppression may be considered, on an individual basis, in **infection-negative lymphocytic myocarditis refractory to standard therapy**.
- **Physical activity should be restricted** during the acute phase of myocarditis and for **at least 6 months**.

EMB should be considered in patients with rapidly progressive HF despite standard therapy when there is a probability of a specific diagnosis, which can be confirmed only in myocardial samples.[97,98]	IIa	C

1. Routine EMB confirmation of myocarditis is unnecessary

a. EMB can be considered in those patients with a rapid deterioration in cardiac function of unknown etiology

who do not respond to standard medical therapy.

IN CASES OF ACUTE DCM, FULMINANT MYOCARDITIS EMB IS MOST USEFUL

SUSPECTED CASES OF GCM WITH ARRHYTHMIAS WHERE IMMUNOSUPPRESSIVE THERAPY

IMPROVES SURVIVAL. GCM VS SARCOIDOSIS (GRANULOMA)

- A retrospective study of 112 consecutive patients with biopsy-confirmed myocarditis at the Massachusetts General Hospital demonstrated the following pathological distribution:

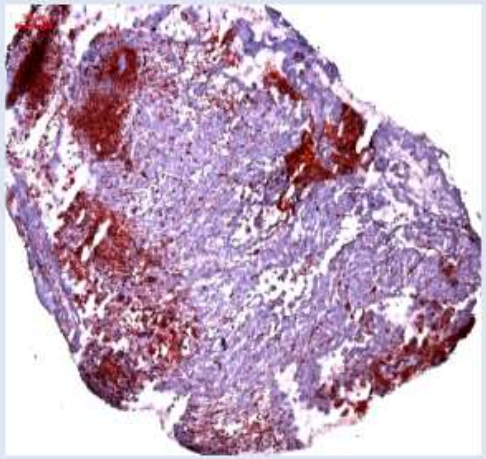
1. Lymphocytic 55%
2. Borderline 22%
3. Granulomatous 10%
4. Giant cell 6%
5. Eosinophilic 6%

Magnani JW, Suk-Danik HJ, Dec GW, DiSalvo TG *Am Heart J.* 2006

Initial defect size and type of inflammatory response

Severe unexplained acute new onset HF

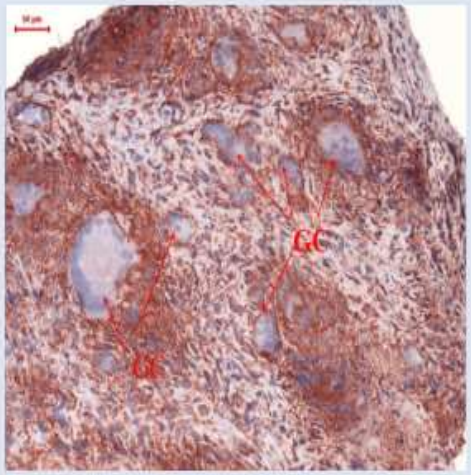
Fulminant Myocarditis



(EF: 32%)

Moderate Prognosis

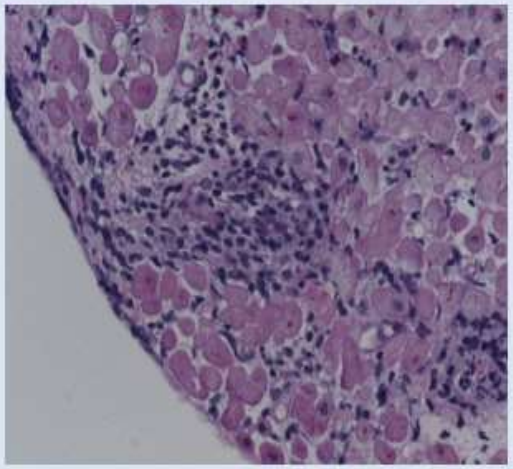
Giant cell Myocarditis



(EF: 32%)

Poor Prognosis

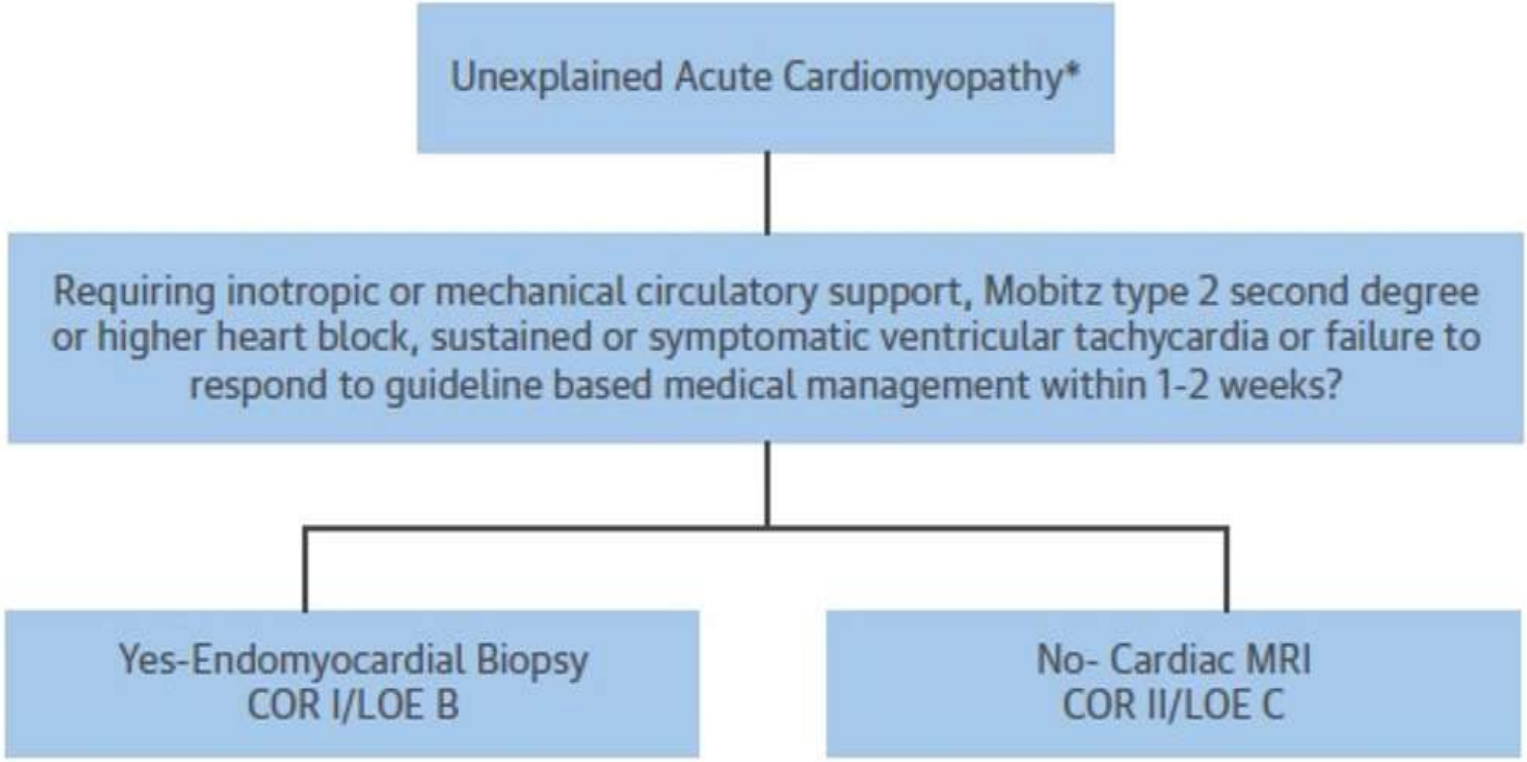
Eosinophilic Myocarditis



(EF: 30%,)

Poor Prognosis

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.

Diagnostics

	Sensitivity	Specificity
• ECG	high	low
• hsTroponin, CRP	intermediate	low
• Virus serology	low	low
• Echocardiography	high	low
• MRI (Lake-Louise Criteria)	high	intermediate
• Endomyocardial biopsy		

Gold standard for the identification of cardiac inflammation

McDonagh et al EHJ 2021

AHA 2019

Table 2. When to Perform Magnetic Resonance Imaging or Endomyocardial Biopsy? When Alone and When Together? (Following Consensus of the Authors, Which Is in Agreement With Other Experts in the Field)[12,18,19]

	cMRI	EMB
Shock	(–)	++
AMC without complications	+	–
AMC with unstable arrhythmia	(–)	+
DCMi (>3 mo)	+*	++†
Assess response to therapy	+	(+)‡

AMC indicates acute myocarditis; cMRI, cardiac magnetic resonance imaging; DCMi, inflammatory cardiomyopathy; and EMB, endomyocardial biopsy.

*A negative result does not exclude ongoing low-gradient inflammation.

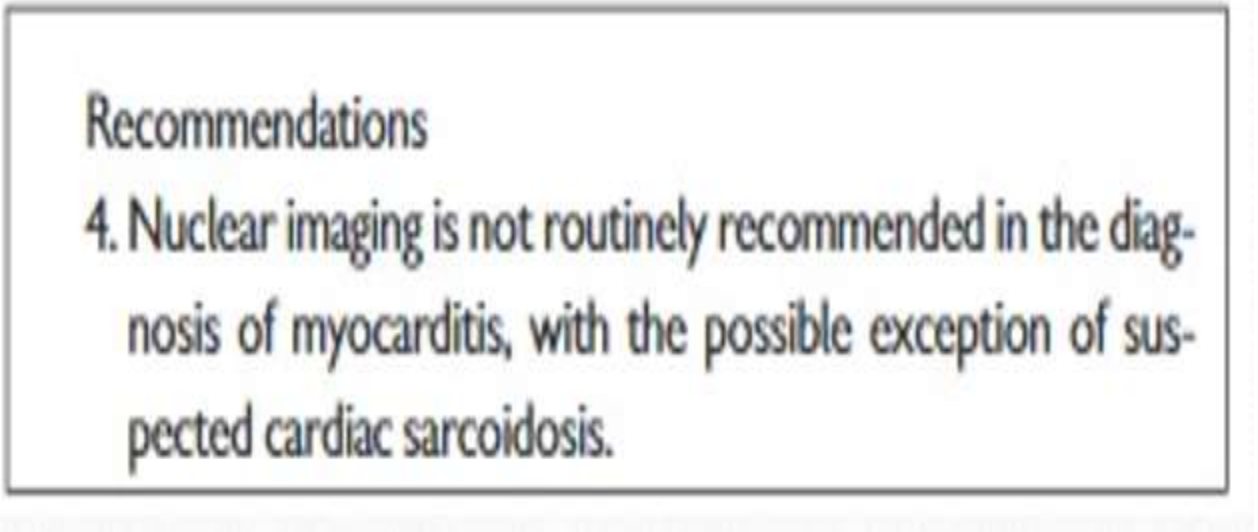
†Therapy selection/decision.

‡Therapy failure/nonresponder.

- FDG-PET----active myocardial inflammation----suspected CS.
- FDG-PET +Myocardial perfusion---- active inflammation and scarring.

- 18F-FDG-PET ---extra cardiac inflammation
- lymph nodes that are amenable to biopsy
-

Blankstein et al -------Mismatch of FDG and perfusion measurements predicts adverse cardiac events, and RV involvement is associated with high risk for arrhythmias



Recommendations

4. Nuclear imaging is not routinely recommended in the diagnosis of myocarditis, with the possible exception of suspected cardiac sarcoidosis.

TREATMENT

1ST LINE = SUPPORTIVE CARE

GDMT FOR HF AND ARRHYTHMIAS

ECM=STEROIDS WITH IMMUNOSUPPRESANTS DRUGS

MEPOLIZUMAB IN SOME CASES.

GCM= PREDNISONE WITH AZATHIOPRINE

2YRS . ABRUPT CESSATION —- RECURRENCE

Immunoglobulin therapy

- Ineffective in acute DCM.
- Chronic CMP with viral replication may benefit—*Dennert et al* (**Antivir Ther 2010**).

Specific Regimens

Table 2

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

	Giant cell myocarditis
Oral steroids 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

CARDIOGENIC SHOCK

INOTROPES (DOBUTAMINE,MILRINONE,LEVOSIMENDAN)

IMPELLA

VA ECMO

ECMELA

BIPELLA

PROPELLA

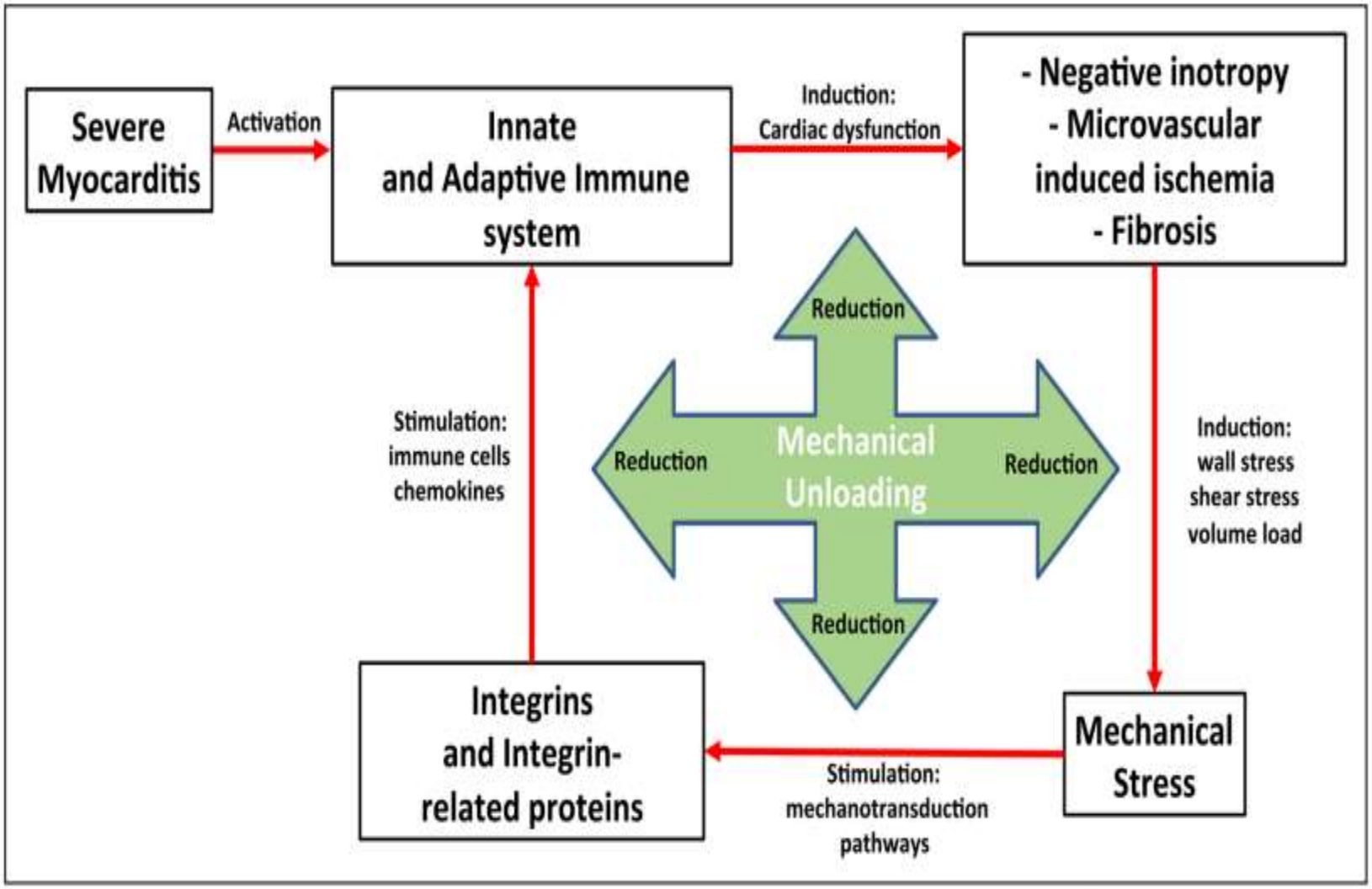


Figure 3. Hypothetical schematic presentation illustrating how mechanical unloading could abrogate pathogenic (inflammatory) processes in myocarditis. Hypothetical scheme illustrates how myocarditis via activation of the innate and adaptive immune system induces cardiac dysfunction (negative inotropy, microvascular-induced ischemia, and fibrosis), which leads to mechanical stress in terms of wall stress, shear stress, and volume load. Mechanical stress, in turn, induces mechanotransduction pathways involving integrins and integrin-related proteins, which stimulate chemokine production and activate immune cells, further boosting the inflammatory process. Therefore, mechanical unloading could be a novel treatment strategy for myocarditis.

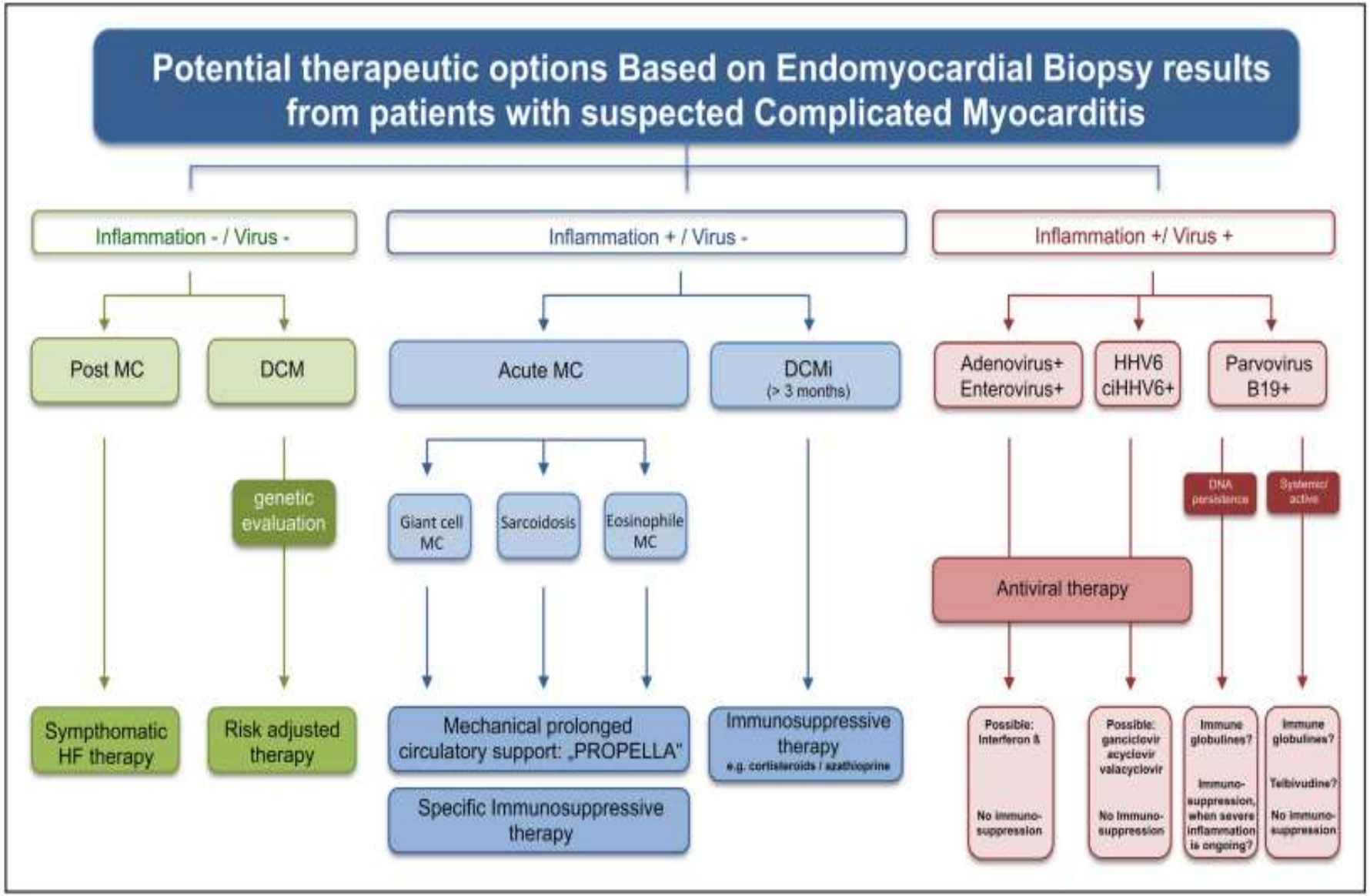


Figure 2. Proposed treatment options in complicated myocarditis according to endomyocardial biopsy results and clinical settings. Scheme represents treatment options for complicated myocarditis depending on endomyocardial biopsy results and clinical presentation, following expert-based recommendations and consensus,[2,11-16] which still need to be proven in large randomized clinical trials. Parvovirus B19+ (B19V) active: signs of active/acute B19V systemic infection; B19V DNA persistence: no signs of systemic B19V infection; low cardiac copy numbers (B19V DNA <500 genomic equivalents/µg).[17] + indicates positive; –, negative; ciHHV-6, chromosomally integrated human herpesvirus type 6; DCM, dilated cardiomyopathy; DCMi, inflammatory dilated cardiomyopathy; HF, heart failure; LV, left ventricle; MC, myocarditis; and PROPELLA, prolonged LV Impella.

Table 3. Use of Immunosuppressive Therapy in Virus-Negative Patients With Chronic Idiopathic Inflammatory Cardiomyopathy

RCT / Registry	No. of Patients	Patient Collective	Treatment	End Points
Wojnicz et al[47]	84	DCM patients with increased HLA expression	Immunosuppression for 3 mo	Primary end point: no significant differences in the primary end point (a composite of death, heart transplantation, and hospital readmission)
				Secondary end point: LV-EF increased significantly in the immunosuppression group compared with the placebo group after 3 mo of follow-up
				At the end of the follow-up period, 71.4% patients from the immunosuppression group vs 30.8% patients from the placebo group were improved (P=0.001)
Frustaci et al (TIMIC study)[27]	85	Myocarditis and chronic (>6 mo) heart failure patients, unresponsive to conventional therapy, with no evidence of myocardial viral genomes	Group 1 (43 patients) prednisone 1 mg/kg per day for 4 wk followed by 0.33 mg/kg per day for 5 mo and azathioprine 2 mg/kg per day for 6 mo in addition to conventional heart failure therapy	Improvement of LV-EF and decrease in LV dimensions and volumes compared with baseline
				No major adverse reactions
			Group 2 (42 patients): placebo in addition to conventional heart failure therapy	No improvement of LV-EF that significantly worsened compared with baseline
Escher et al[26]	114	Chronic myocarditis or inflammatory cardiomyopathy following Caforio et al[2] (≥14 infiltrating inflammatory cells/mm^2)	Prednisone and azathioprine for 6 mo	Improvement of LV-EF compared to baseline after 6-mo period (LV-EF rising from 44.6±17.3% to 51.8±15.5%; P=0.006)
Merken et al[29]	209	Inflammatory cardiomyopathy following Caforio et al[2] (≥14 infiltrating inflammatory cells/mm^2)	After 1:1 propensity score matching	Improved long-term outcome (eg, heart transplantation-free survival) as compared with standard heart failure therapy alone
			90: immunosuppressive therapy	
			90: placebo	A significant larger increase of LV-EF after a mean of 12-mo follow-up, as compared with patients receiving standard heart failure treatment only

DCM indicates dilated cardiomyopathy; EF, ejection fraction; HLA, human leukocyte antigen; LV, left ventricular; RCT, randomized clinical trial; and TIMIC, Tailored Immunosuppression in Inflammatory Cardiomyopathy.

EMB GUIDED TREATMENT IS LIMITED

AS VALIDATING CLINICAL TRIALS HAD SMALL SAMPLE SIZES

Current recommendations for immunosuppressive therapy from the ESC

1. Immunosuppression should be started only after ruling out active infection on EMB by PCR
2. Based on experience with noncardiac autoimmune disease, consideration of immunosuppression in proven autoimmune (for example, infection-negative) forms of myocarditis, should be made if no contraindications to immunosuppression are present, including giant-cell myocarditis, cardiac sarcoidosis, and myocarditis associated with known extracardiac autoimmune disease
3. Steroid therapy is indicated in cardiac sarcoidosis in the presence of ventricular dysfunction and/or arrhythmia and in some forms of infection-negative eosinophilic or toxic myocarditis with heart failure and/or arrhythmia
4. Immunosuppression can be considered, on an individual basis, in infection-negative lymphocytic myocarditis refractory to standard therapy in patients with no contraindications to immunosuppression
5. Follow-up EMB can be required to guide the intensity and the length of immunosuppression

Abbreviations: EMB, endomyocardial biopsy; ESC, European Society of Cardiology. Adapted from Caforio, A. L. P. *et al.* Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur. Heart J.* **34** (33), 2636–2648 © (2013), with permission from Oxford University Press and the European Society of Cardiology.

TABLE 11.3 Treatment Regimens for Myocarditis in Clinical Trials

Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) Study[a]

Intravenous immune globulin (Gamimune N, 10%): 1 g/kg/d IV × 2 d

Giant Cell Myocarditis Study[b]

Cyclosporine: 25 mg po bid, increase by 25 mg increments to target level

Monoclonal whole-blood immunoassay: 200–300 ng/mL

High-performance liquid chromatography assay: 150–250 ng/mL

Fluorescence polarization immunoassay serum-based polyclonal assay: 100–150 ng/mL

Dose reduction if renal dysfunction develops

Muromonab-CD3 (OKT-3): 5 mg IV qd × 10 d

Dose reduction if hypotension develops

Corticosteroid: methylprednisolone, 10 mg/kg IV qd × 3 d, followed by prednisone, 1–1.25 mg/kg with extended taper

Azathioprine: 200 mg po qd

Myocarditis Treatment Trial[c]

Corticosteroid/cyclosporine versus corticosteroid/azathioprine versus placebo (biopsy-proven myocarditis, LVEF < 45%, NYHA ≥ class II)

Oral prednisone: 1.25 mg/kg/d in divided doses × 1 wk; reduce oral dose by 0.08 mg/kg/wk until dose is 0.33 mg/kg/d at week 12; maintain oral dose until week 20, and then reduce dose by 0.08 mg/kg/wk until week 24; then off

Oral cyclosporine: 5 mg/kg bid to achieve level of 200–300 ng/mL × 1 wk; adjust oral dose to achieve level of 100–200 ng/mL from weeks 2 to 4; adjust oral dose to achieve level of 60–150 ng/mL from weeks 4 to 24

Immunosuppressive Therapy for Active Lymphocytic Myocarditis[d]

Prednisone 1 mg/kg/d for 4 wk; reduced to 0.33 mg/kg/d for 5 mo; azathioprine 2 mg/kg/d for 6 mo

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

[a]McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation*. 2001;103:2254–2259.

[b]Rosenstein ED, Zucker MJ, Kramer N. Giant cell myocarditis: most fatal of autoimmune diseases. *Semin Arthritis Rheum*. 2000;30:1–16.

[c]Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med*. 1995;333:269–275.

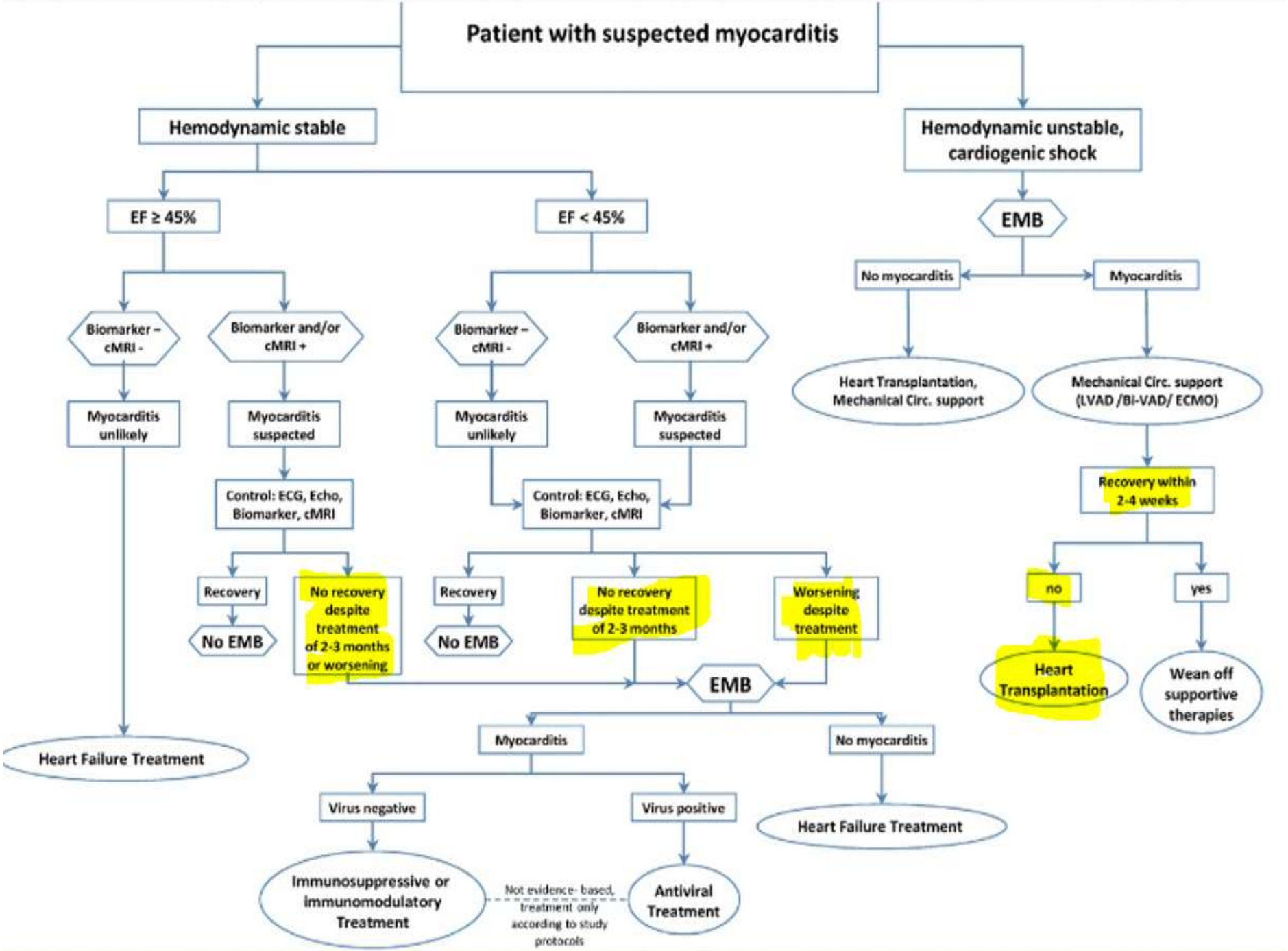

Patient with suspected myocarditis
Hemodynamic stable
Hemodynamic unstable, cardiogenic shock
EF ≥ 45%
EF < 45%
EMB
No myocarditis
Myocarditis
Biomarker – cMRI -
Biomarker and/or cMRI +
Biomarker – cMRI -
Biomarker and/or cMRI +
Heart Transplantation, Mechanical Circ. support
Mechanical Circ. support (LVAD /Bi-VAD/ ECMO)
Myocarditis unlikely
Myocarditis suspected
Myocarditis unlikely
Myocarditis suspected
Recovery within 2-4 weeks
Control: ECG, Echo, Biomarker, cMRI
Control: ECG, Echo, Biomarker, cMRI
Recovery
No recovery despite treatment of 2-3 months or worsening
Recovery
No recovery despite treatment of 2-3 months
Worsening despite treatment
no
yes
No EMB
No EMB
Heart Transplantation
Wean off supportive therapies
EMB
Heart Failure Treatment
Myocarditis
No myocarditis
Virus negative
Virus positive
Heart Failure Treatment
Immunosuppressive or immunomodulatory Treatment
Not evidence- based, treatment only according to study protocols
Antiviral Treatment

Table 4. Novel Promising Strategies for the Treatment of Myocarditis

Strategy	(Pre)clinical Evidence	Evidence of Target	Evidence of Therapy
IL-1β inhibitors			
Anakinra	acute MI,[126] acute decompensated heart failure,[127] HFpEF,[128] and idiopathic recurrent pericarditis fulminant myocarditis[129,130]	++	+++
Canakinumab	patients with previous MI and hs-CRP levels ≥2 mg/L (CANTOS)[131]	++	+++
Colchicine	pericarditis with pericardial effluent,[132–135] stable coronary artery disease,[136] and postpericardiotomy syndrome[137,138]	++	+++
HMGB1 inhibitors	patients suffering from acute myocarditis and troponin I–induced experimental autoimmune myocarditis[139]	++	++

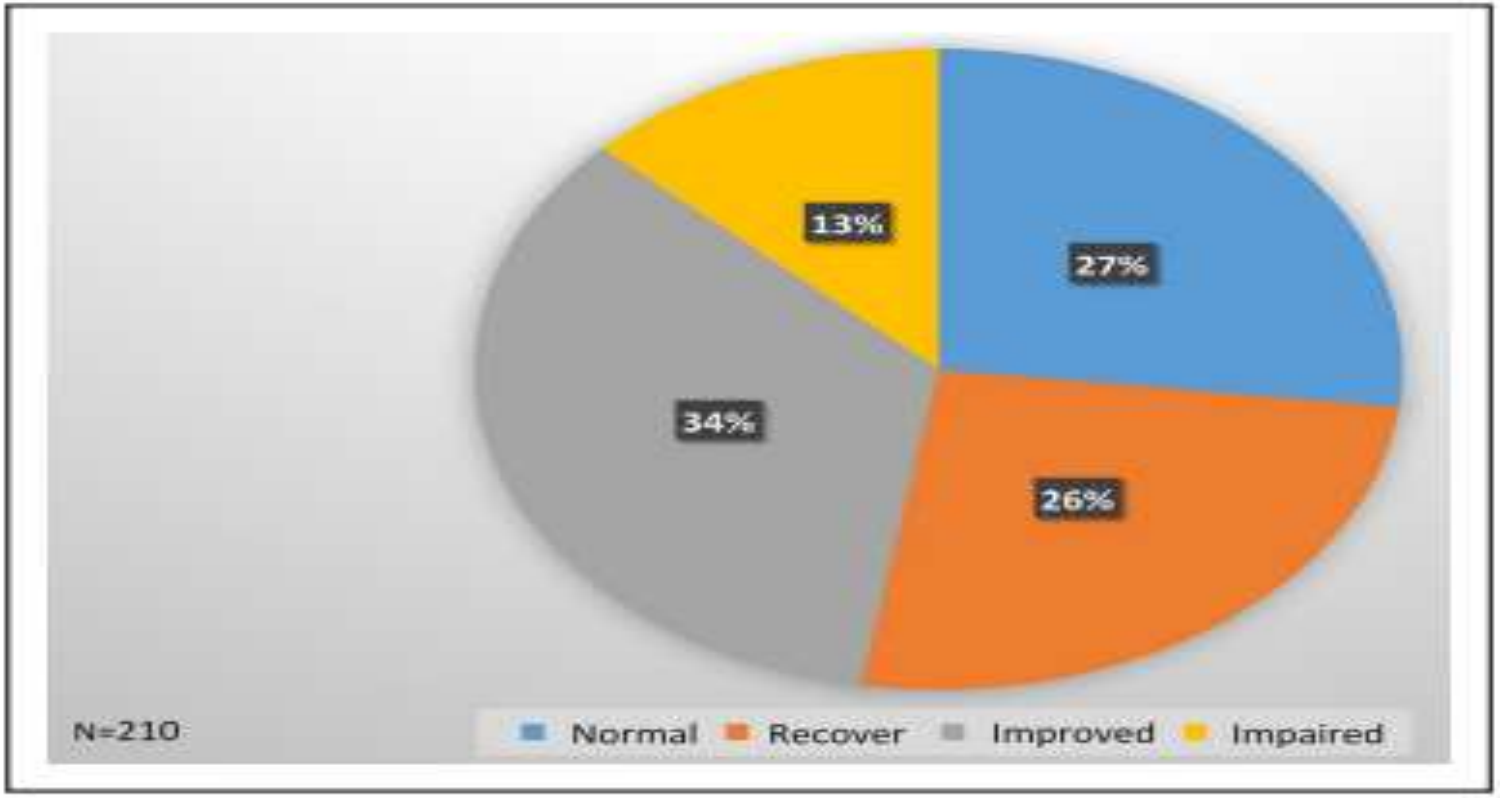
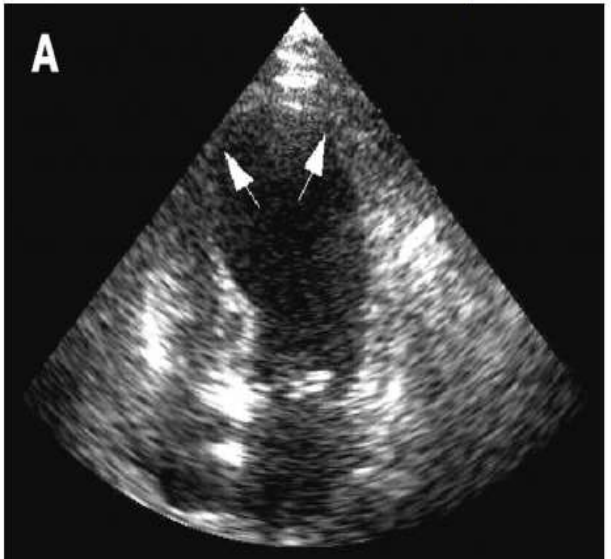


Figure 1. Spontaneous course of ejection fraction after standard heart failure medication in endomyocardial biopsy-proven myocarditis patients. Pie chart illustrates observations of our single-center registry (enrolled at Charité, Department of Cardiology, Berlin, Germany, from 2015 to 2018) illustrating the course of myocarditis in a 2-y follow-up. From 210 patients who had biopsy-proven myocarditis, and came to our hospital with ECG changes, elevated troponin levels and impaired ejection fraction (EF), we found that in 47% the cases, EF did not recover to normal (gray and yellow) after 2-y standard heart failure therapy. In 53% of the cases, EF was found to be normal: EF recovered in 26% of the cases (orange) after 2 y. In 27%, EF was initially not affected and stayed stable.

Myocarditis vs. Takotsubo cardiomyopathy

- Takotsubo cardiomyopathy may present with symptoms and signs similar to myocarditis
- However, the patterns of wall motion abnormality most commonly seen in stress cardiomyopathy (typically LV apical dysfunction, less commonly mid-ventricular or basal) are generally not seen in myocarditis



Myocarditis vs. Takotsubo cardiomyopathy

- Recovery of ventricular function with stress cardiomyopathy is generally more rapid (commonly within one week and generally within four weeks) than with myocarditis.

- CMR may be helpful since signs of myocardial inflammation and scar, which are typical for myocarditis, are generally absent in patients with Takotusob cardiomyopathy.

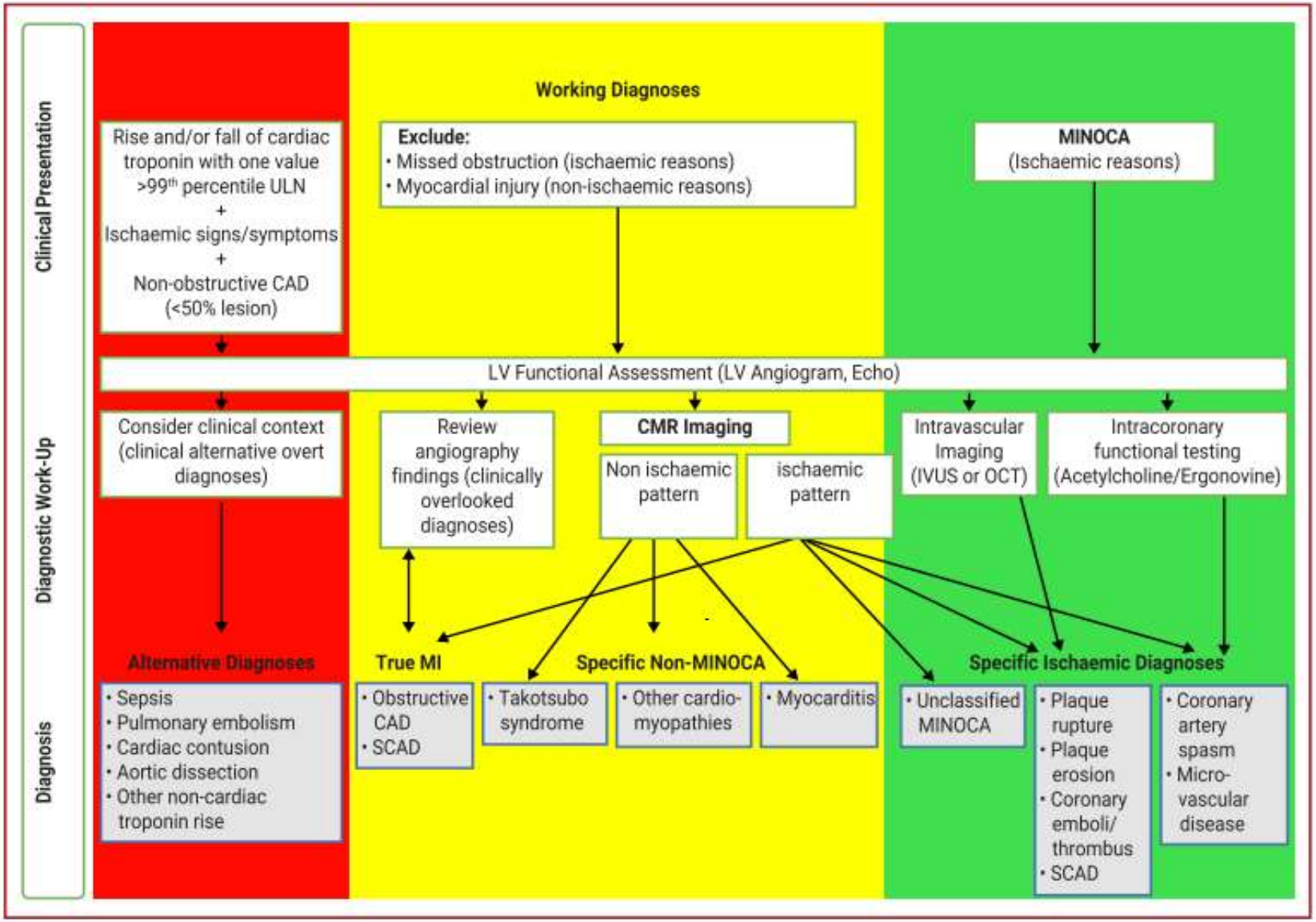


Figure 12 Diagnostic algorithm for myocardial infarction with non-obstructive coronary arteries using a traffic light scheme. Red indicates immediate alternative diagnosis without further additional testing. Yellow indicates initial working diagnosis that may lead to the final MINOCA diagnosis or alternative diagnoses. Green indicates final MINOCA diagnosis. CAD = coronary artery disease; IVUS = intravascular ultrasound; MINOCA = myocardial infarction with non-obstructive coronary arteries; CMR = cardiac magnetic resonance; Echo = echocardiogram; LV = left ventricular; OCT = optical coherence tomography; SCAD = spontaneous coronary artery dissection; ULN = upper limit of normal. *Listen to the audio guide of this figure online.*

COVID RELATED MYOCARDITS

VIRAL MYOCARDITIS

MILD LV SYSTOLIC DYSFUNCTION

MANAGED WITH GDMT

GOOD PROGNOSIS

MIS-A

DELAYED PRESENTATION. C. SHOCK

CYTOKINE STORM. NEEDS IV STEROIDS

POST VACCINATION MYOCARDITIS

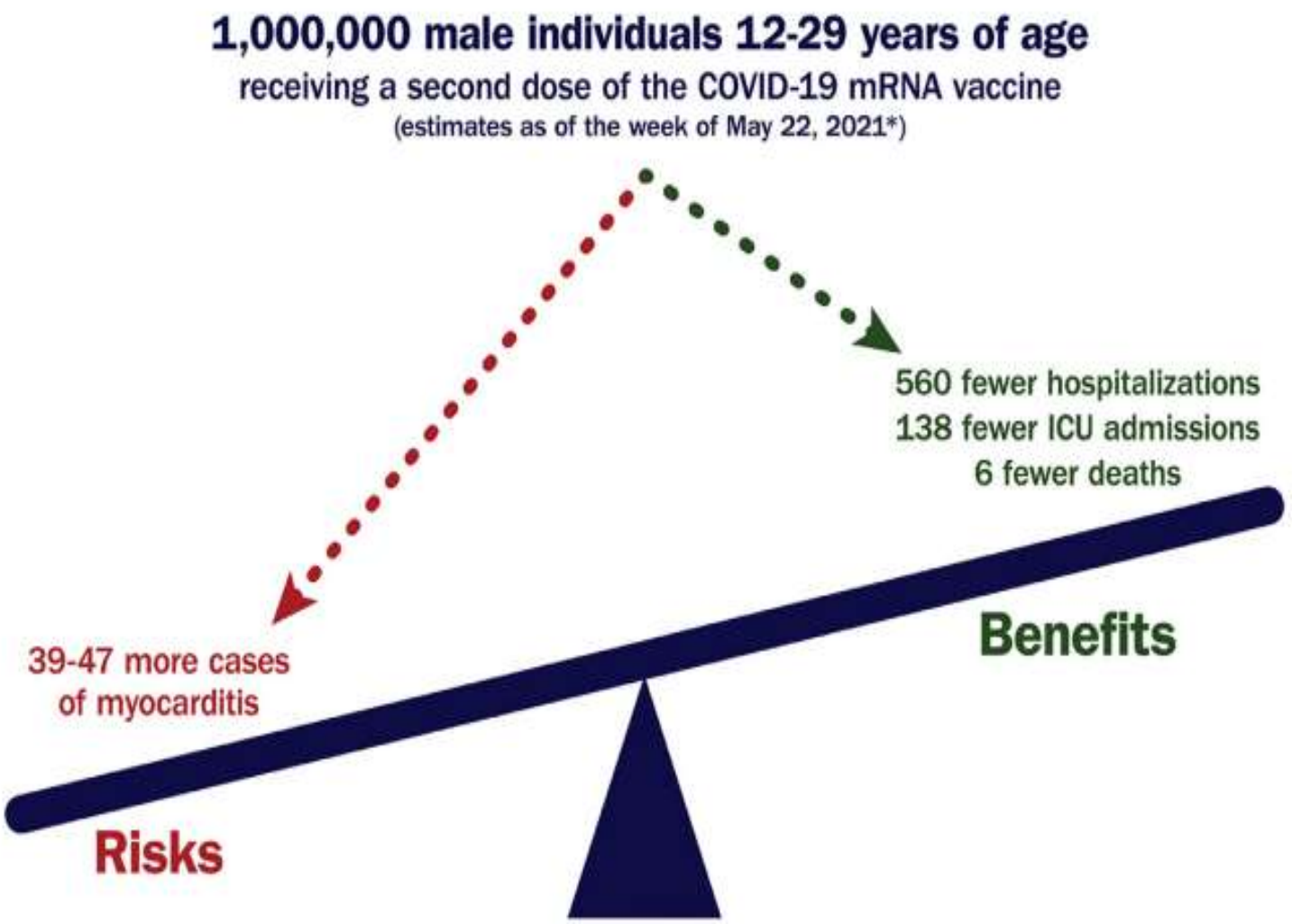
MRNA VACCINES

WITHIN 1 WEEK OF VACCINATION

NON FULMINANT COURSE.

FEW PTS DEVELOPED MILD LV DYSFUNCTION.

FIGURE 4 Favorable Benefit-to-Risk Ratio for COVID-19 mRNA Vaccination Among Those at Highest Risk for Postvaccination Myocarditis



*Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET).[12,141]
COVID-19 = novel coronavirus disease 2019; ICU = intensive care unit, mRNA = messenger RNA.

nature medicine

Article | Open Access | Published: 14 December 2021

Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection

Martina Patone, Xue W. Mei, Lahiru Handunnetthi, Sharon Dixon, Francesco Zaccardi, Manu Shankar-Hari, Peter Watkinson, Kamlesh Khunti, Anthony Harnden, Carol A. C. Coupland, Keith M. Channon, Nicholas L. Mills, Aziz Sheikh & Julia Hippisley-Cox ✉

Nature Medicine **28**, 410–422 (2022) | Cite this article

	Myocarditis							Pericarditis				
	1–28 days post first dose			1–28 days post second dose			1–28 days post test	1–28 days post first dose			1–28 days post second dose	
	ChAdOx1nCoV-19 vaccine	BNT162b2 mRNA vaccine	mRNA-1273	ChAdOx1nCoV-19 vaccine	BNT162b2 mRNA vaccine	mRNA-1273	Positive SARS-CoV-2 test	ChAdOx1nCoV-19 vaccine	BNT162b2 mRNA vaccine	mRNA-1273	ChAdOx1nCoV-19 vaccine	BNT162b2 mRNA vaccine
Total number of people	142	94	9	84	64	*	134	102	59	*	117	75
Sex												
Women	40.8 (58)	50.0 (47)	*	27.4 (23)	42.2 (27)	*	39.6 (53)	26.5 (27)	37.3 (22)	0	27.4 (32)	30.7 (23)
Men	58.5 (83)	50.0 (47)	*	71.4 (60)	57.8 (37)	*	60.4 (81)	72.5 (74)	62.7 (37)	*	72.6 (85)	69.3 (52)
Not recorded	0.7 (1)	0	0	1.2 (1)	0	0	0	1.0 (1)	0	0	0	0

Myocarditis

Of the 38,615,491 vaccinated individuals included in our study, 1,615 (0.004%) were admitted to hospital with, or died from, myocarditis at any time in the study period (either before or after vaccination); 397 (0.001%) of these occurred in the 1-28 days post any dose of vaccine. Of the 1,615 who were admitted or died, 359 (22.2%) had a SARS-CoV-2 positive test, with 287 (17.8%) of these being before vaccination. There were 114 deaths with myocarditis recorded on the death certificate as a cause of death (23 had a SARS-CoV-2 positive test). Of those who have been admitted with, or died from, myocarditis in the 1-28 days postvaccination, 12.7% (18) and 10.7% (9) had a positive SARS-CoV-2 test before the first and second dose ChAdOx1 vaccine, respectively, and 7.4% (7) before the first dose of BNT162b2 vaccine (Table 2).

There was an increased risk of myocarditis at 1–7 days following the first dose of ChAdOx1 (IRR 1.76; 95% CI 1.29, 2.42), BNT162b2 (IRR 1.45, 95% CI 0.97, 2.12) and mRNA-1273 (IRR 8.38, 95% CI 3.53, 19.91), and the second dose of BNT162b2 (IRR 1.75, 95% CI 1.13, 2.70) and mRNA-1273 (IRR 23.10, 95% CI 6.46, 82.56). There was an increased risk of myocarditis at 1–7 days (IRR 21.08, 95% CI 15.34, 28.96), 8–14 days (IRR 11.29, 95% CI 7.70, 16.57), 15–21 days (IRR 5.36, 95% CI 3.24, 8.89) and 21–28 days (IRR 3.08, 95%CI 1.65, 5.75) following a positive test.

ELSEVIER DOYMA

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
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EVIDENCED-BASED CARDIOLOGY

Cochrane Corner: Corticosteroids for viral myocarditis☆

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[b] Unidade de Farmacologia Clínica, Instituto de Medicina Molecular, Lisboa, Portugal
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Received 1 August 2014; accepted 16 August 2014
Available online 13 January 2015

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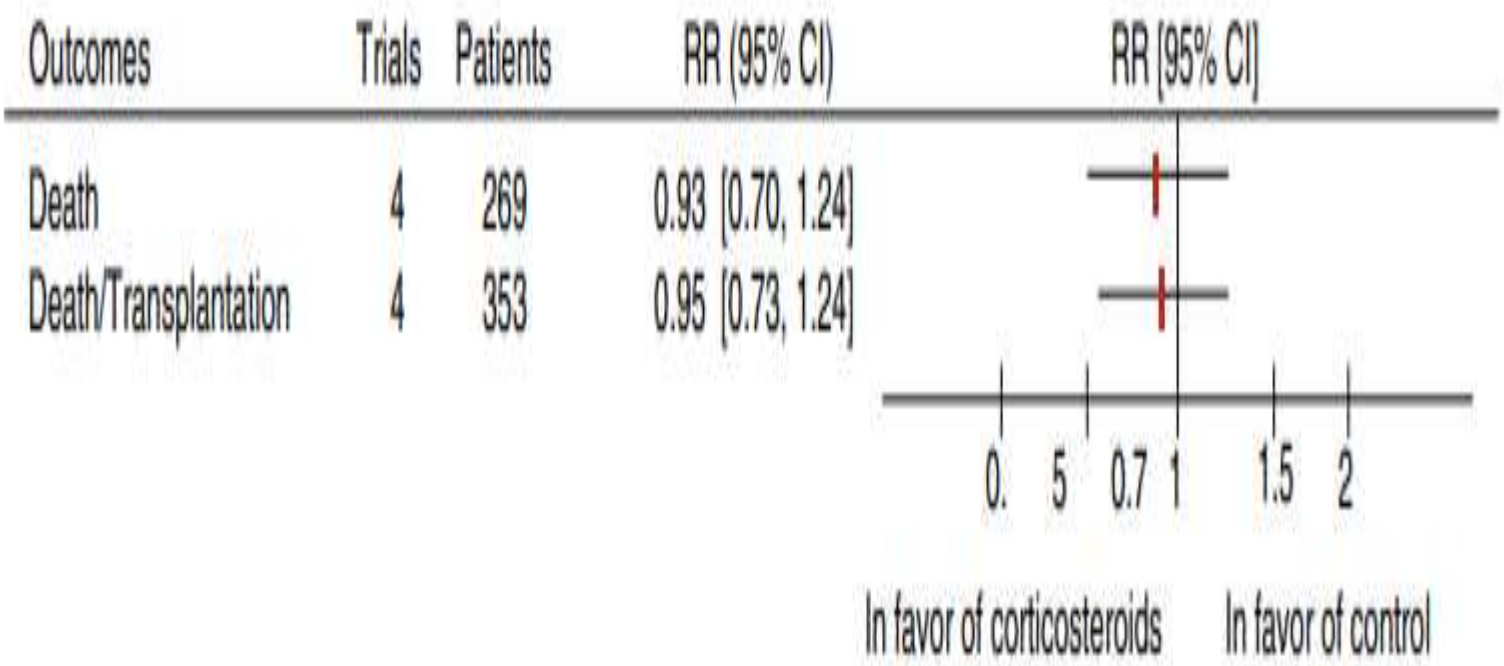
Outcomes
Trials
Patients
RR (95% CI)
RR [95% CI]
Death
4
269
0.93 [0.70, 1.24]
Death/Transplantation
4
353
0.95 [0.73, 1.24]
0.5
0.7
1
1.5
2
In favor of corticosteroids
In favor of control

CONCLUSION

- Viral infections are the most common triggers of MYOCARDITS

- 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 postinfectious or autoimmune inflammations of the myocardium are treatable.

MYOCARDITIS

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JUNIOR RESIDENT
DEPARTMENT OF MICROBIOLOGY
GOA MEDICAL COLLEGE

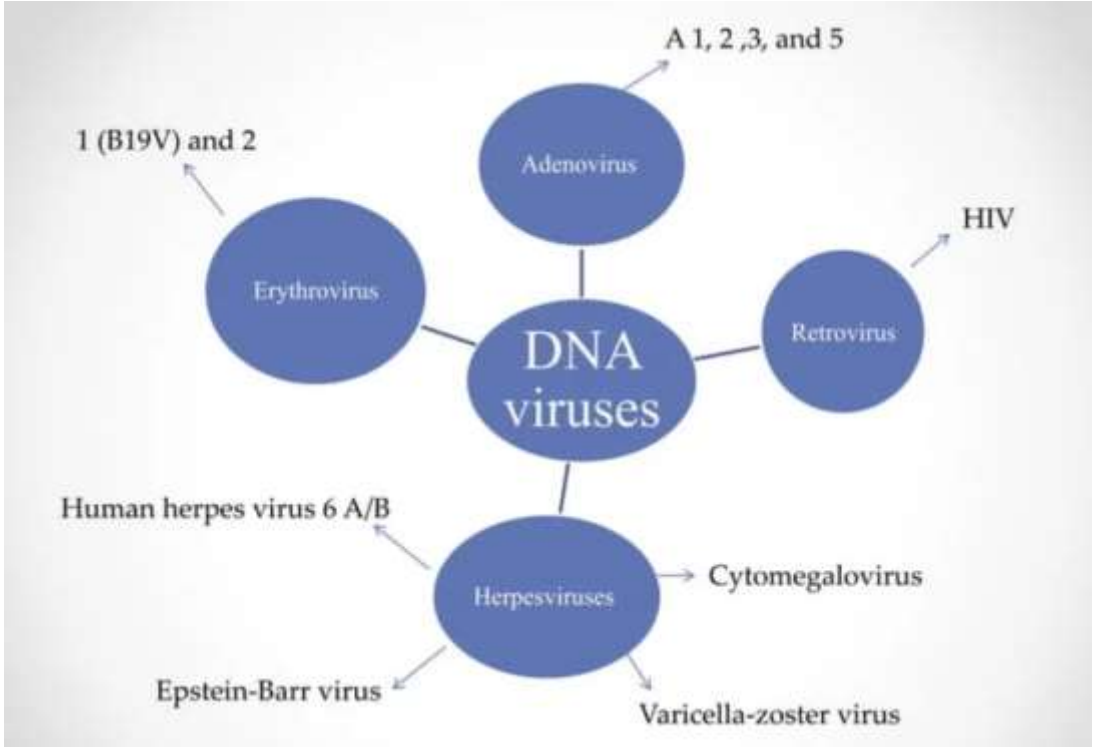
MYOCARDITIS

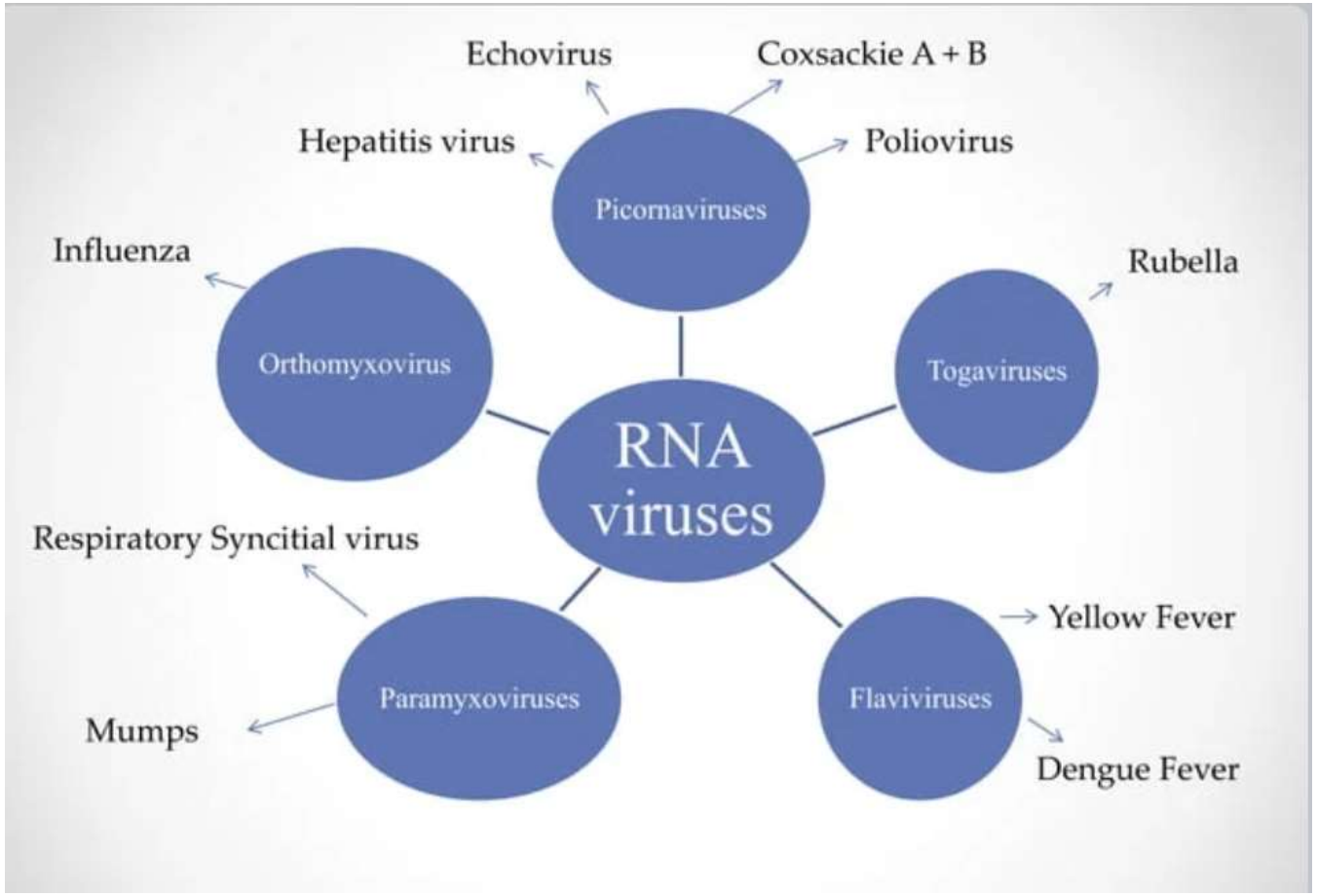
- Myocarditis is collection of diseases of infectious, toxic and autoimmune etiologies characterized by inflammation of the heart

- Subsequent myocardial destruction can lead to dilated cardiomyopathy

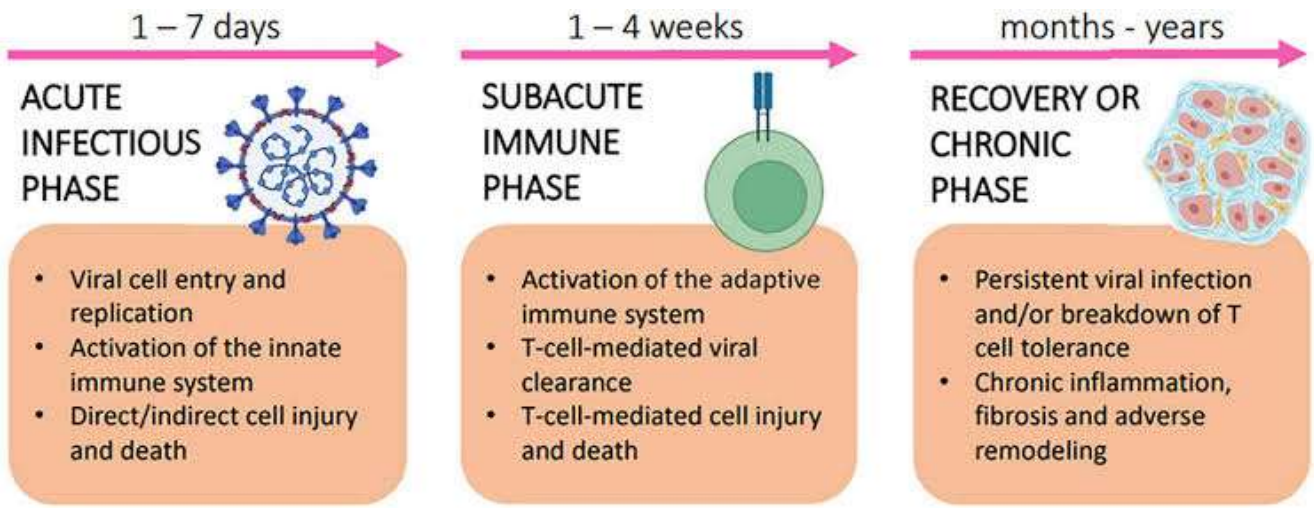
CAUSES

- Amongst the infectious causes, viral acute myocarditis is by far the most common




Echovirus
Coxsackie A + B
Hepatitis virus
Poliovirus
Picornaviruses
Influenza
Rubella
Orthomyxovirus
Togaviruses
RNA viruses
Respiratory Syncitial virus
Yellow Fever
Paramyxoviruses
Flaviviruses
Mumps
Dengue Fever

The 3 phases of viral myocarditis



- Coxsackie virus enter the system via CAR receptor
- Adenovirus also uses the CAR receptor and Integrin receptor
- Parvo virus causes endothelial dysfunction contributing to local inflammation and vasospasm
- Mixed infections- Multiple viruses can increase each other virus virulence. Seen in coxsackie and adenovirus infections

- Hepatitis C virus - symptoms of myocarditis seen in 3rd week of illness

- HIV related myocarditis is lymphocytic myocarditis
- The incidence was higher among patients with CD4 counts <400 cells/mm^3
- Ventricular dysfunction may be due to a) HIV infection itself

b)Immunologic dysregulation

c)Side effects of ART

- Influenza 5%-10% of infected patients
- The presence of pre existing cardiovascular disease greatly increases the risk of morbidity and mortality
- Cardiac involvement typicallly occurs within 4 days to 2 weeks of the onset of the illness

- Manifestations are age dependent
- In infants:

  -viral myocarditis can be fulminant
- In children:

  - acute, myopericarditis with congestive heart failure
- In older children and adolescents:

  - acute or chronic congestive heart failure

Molecular diagnosis

- In situ hybridization- Seeking the presence of viral genetic signatures in a pathologic sample

➢ PCR amplification of the RNA from the biopsy specimen itself, have increased the sensitivity of detecting virus signatures in the heart

➢The presence of viral genome is entirely independent of the presence or absence of inflammatory cells on the same biopsy specimen

BACTERIA

- Corynebacterium diphtheriae
- Neisseria meningococcus
- Borrelia (Lyme disease)

DIPHTHERIC MYOCARDITIS

- Myocarditis in patients with diphteria is a toxin mediated complication that sets in after one week of onset of respiratory illness

- Early administration of antidiphtheritic serum in patients with clinical diphtheria before the onset of myocarditis is of utmost importance to prevent this fatal complication

MENINGOCOCCAL MYOCARDITIS

- Meningococcal related acute myocarditis is probably an underdiagnosed complication of meningococcal disease.

- Indeed, myocarditis has been reported in 30% of adult patients suffering from the most severe forms of invasive meningococcal disease requiring ICU admission

- In these cases, left ventricular dysfunction may be due to direct bacterial injury to myocardium and to the meningococci induced inflammatory response, which may be cytotoxic for the myocardium

LYME CARDITIS

- Lyme disease(LD) is the most common tick borne multisystem infection in Europe and the USA
- Typical Borrelia strains include Borrelia burgdorferi and Borrelia afzelii
- Cardiac involvement in LD occurs in 0.3-10% of patients
- The most common cardiac manifestations is an acute presentation of Lyme Carditis(LC), which manifests as conduction disorder, pericarditis, and/ or myocarditis
- Endomyocardial biopsies(EMB)- It is the gold standard for definitive diagnosis of myocarditis

CHLAMYDIAE(CHLAMYDOPHILA PSITTACI)

- Psittacosis, a zoonotic disease caused by C. psittaci
- Aerosols from sick birds mainly infect humans
- C. psittaci may rarely affect the heart as the only manifestation of infection

- The possible explanation for the myocarditis may be that 1) C. psittaci infects myocytes and causes direct damage to cardiac tissues which usually presents with LDH release, superoxide production, and a reduced ATP level

2) myocarditis may be due to autoimmunity

- Meta genomic next generation sequencing(mNGS) may be a valuable tool for the diagnosis of C. psittaci infection

FUNGI

- Candida species
- Aspergillus species
- Cryptococcus species
- Histoplasma species

RICKETTSIAE

- Rickettsia typhi
- Typhus fever

PROTOZOA

- Trypanosoma cruzi(Chagas disease)
- Toxoplasmosis

- Chagas disease (CD) is caused by trypanosoma cruzi, a protozoan parasite that can cause acute myopericarditis as well as chronic fibrosing cardiomyopathy

- Symptomatic myocarditis is rare when the transmission is through the vector borne route

- In contrast, when patients are infected through the oral route myocarditis is often severe and carries a higher risk of mortality

- Diagnosis of acute Chagas myocarditis relies on the demonstration of the parasite and/or anti T cruzi IgM in a patient with the correct epidemiological background and clinical picture

- In developing countries diagnosis is usually performed by visualizing the trypomastigotes in fresh blood smears, thick drop preparations or buffy coat smears

HELMINTHS

Trichinellosis

- Caused by the nematode Trichinella spiralis and other Trichinella species and is common worldwide

- Humans become infected when eating undercooked meat cintaminated with cysts of Trichinella larvae

- Trichinella spiralis associated myocarditis is not caused by the direct larval invasion of the myocardium with encystation but is likely induced by an eosinophil enriched inflammatory response

- Inflammatory response typically occurs in the third week of infection
- Trichinosis myocarditis may initially manifest with chest pain and mimic an acute myocardial infarction
- Confirmation is based on serology and muscle biopsy specimens

ENZYMES IN MYOCARDITIS

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Cardiac biomarkers in myocarditis:

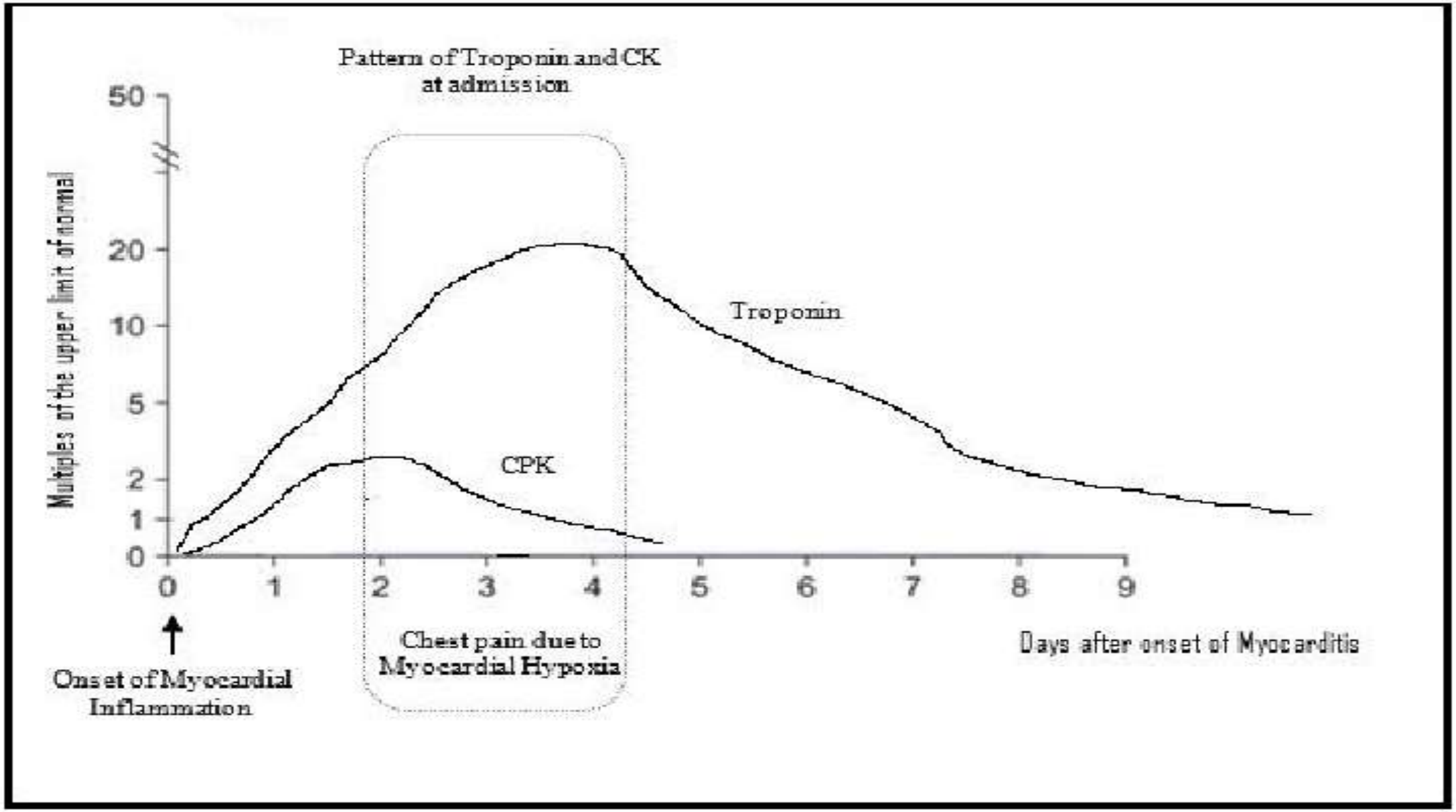
1. cTrop I/T
2. CK-MB
3. LDH
4. Myoglobin
5. AST/ALT

Other cardiac markers:

- N-terminal proBNP (NT-proBNP)
- C-reactive protein (CRP)
- Homocystein
- sera soluble ST2 (sST2)
- systemic immune–inflammatory index (SII)

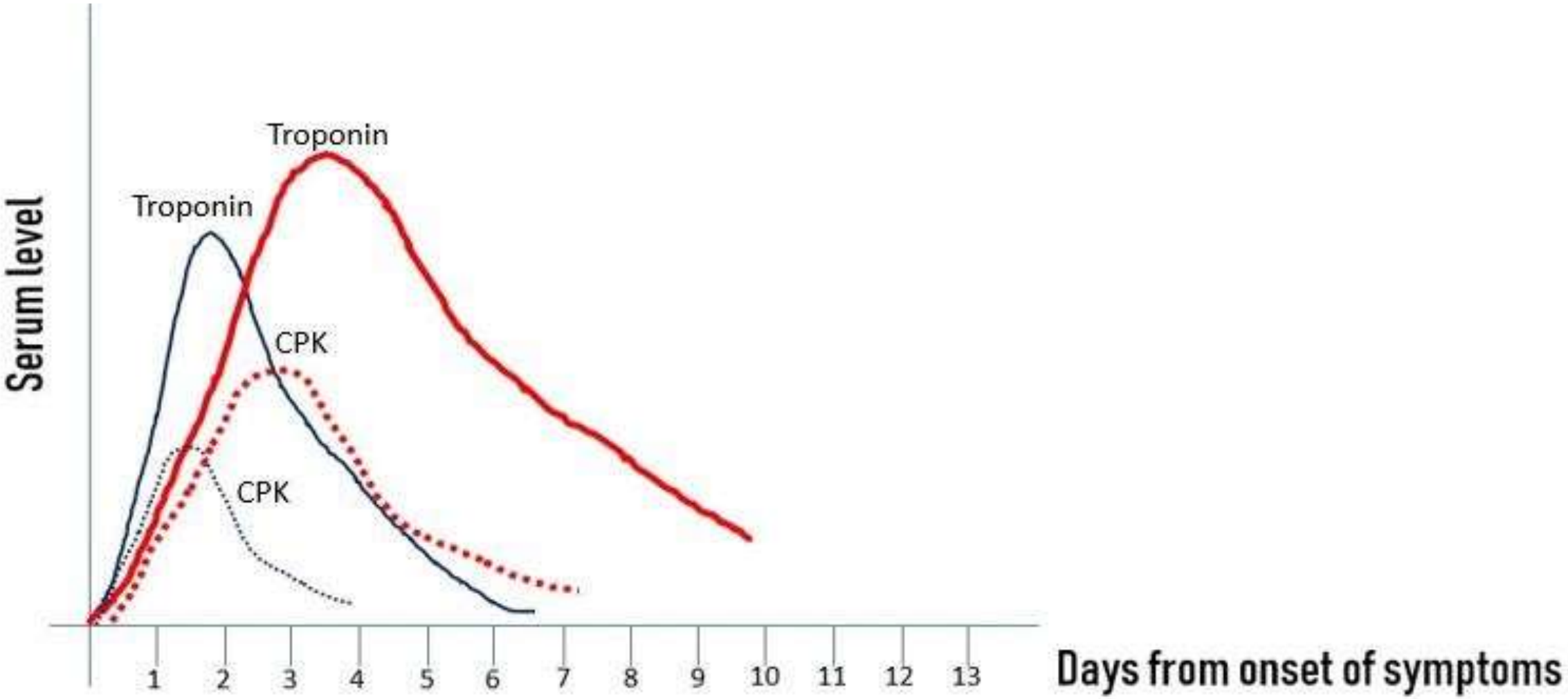
The following cardiac markers are often elevated in myocarditis, particularly early on in the course of the disease:

- Cardiac troponin I (cTnI) or T (cTnT)(34-53%)
- Creatine kinase (CK-MB)(2-6%)
- cTnI are elevated more frequently than CK-MB.
- cTnI is most likely to be elevated in patients with myocarditis early (within 1 week) after the onset of symptoms(marker for acute myocarditis)


Pattern of Troponin and CK
at admission
Multiples of the upper limit of normal
50
20
10
5
2
1
0
Troponin
CPK
0
1
2
3
4
5
6
7
8
9
Days after onset of Myocarditis
Onset of Myocardial
Inflammation
Chest pain due to
Myocardial Hypoxia

- Persistently elevated cTnT or CK-MB is suggestive of ongoing myonecrosis(MI).
- Cardiac enzymes may also be useful in differentiating myocarditis from dilated cardiomyopathy as CK-MB and cTnT levels are higher in myocarditis than dilated cardiomyopathy.
- cTnI is superior to CK-MB for detection of myocyte injury in myocarditis.
- Highly elevated cardiac markers and enzymes may help to rule in acute cases, but absence of them does not exclude myocarditis.

Troponin and CPK progression curve in myocarditis compared to acute non-ST myocardial infarction



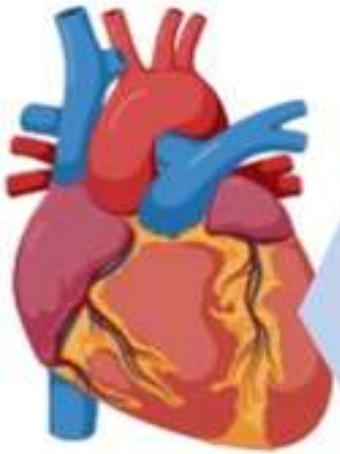
- Lactate dehydrogenase (LDH)(125-220 U/L)
- Alanine transaminase (ALT)
- Aspartate transaminase (AST)(5-34 U/L)
- AST is considered to be the most sensitive marker of myocarditis with the sensitivity of 85%. However, the specificities of AST and ALT are low in patients with myocarditis as they may be elevated secondary to other coexisting systemic or organ dysfunction.

Inflammatory Markers:

The following inflammatory markers are often elevated:

- CBC: leukocytosis or eosinophilia in hypersensitive myocarditis.
- C-reactive protein
- Erythrocyte sedimentation rate (ESR)

PROGNOSTIC MARKERS	INTERPRETATION
Fas and Fas ligand	CD95 Tumor Necrosis Factor receptor (TNF-R) family. has intracellular “death domain” troggers apoptosis. increased level indicates bad prognosis.
Antimyosin antibody	Increased levels indicate myocytes injury, associated with left ventricular systolic dysfunction. seen in chronic myocarditis,DCM,etc.
IL10	Anti-inflammatory cytokine High levels of interleukin 10 in fulminant myocarditis patients may be predictive of subsequent development of cardiogenic shock.



Genetic/ Genomics

MicroRNA: hsa-miR-Chr8:96, miR-4763-3p, miR-208b

Differentially expressed genes: Innate immunity (Irf7, Cxcl9), acquired immunity (Cd3g, H2-Aa), cardiac remodeling (Mmp12, Gpnmb)

Gene Variants: Desmoplakin (DSP), Titin (TTN), Filamin C (FLNC), RNA binding protein 20 (RBM20)

Mycardial Injury

Myocardial injury: high sensitivity Troponin I, NT-BNP

Cell Structure

Small molecule cell structure/adhesion proteins: VCAM-1, gelsolin, procollagen type III amino-terminal propeptide, tenascin-C

Immune Cells

Neutrophils: heparin binding proteins, serum alarmin S100A8/S100A9

T-cell pathways: T-reg/LAP+ T-reg, TH1 (IFN-γ, TNF-α), TH2 (IL-4, IL-5, IL-13), TH17 (IL-17), sST2 receptor (IL-33)

B-cell pathways/antibodies: immunoglobulin free light chains (FLC), beta-1 receptor/myosin heavy chain/cardiac troponin/Na/K ATPase antibodies

Myocarditis

From the eyes of a Pathologist

- Dr. R.G.W Pinto, Professor & H.O.D Pathology, Ex-Dean Goa University

- Dr. Shubhra S. Ghadi Amonkar , JR1 Pathology

- Myocarditis encompasses a diverse group of clinical entities in which an Infectious agent and/ or a inflammatory process targets the myocardium.
- Hence clinically it can have various presentation ranging from Asymptomatic to resembling other cardiac conditions such as Ischemic Heart disease and may even progress to CHF and Dilated cardiomyopathy in later stages.

Causes Of Myocarditis	
INFECTIVE	1. Viral- Coxsackie A and B, other enteroviruses > CMV, HIV, Influenza, COVID-19 2. Bacterial- *Mycobacteria*, Whipple's disease, *Coxiella, Bartonella, Borrelia* (Lyme's disease) 3. Parasitic- *Toxoplasma gondii*, helminthes like Trichinosis 4. Protozoan- *Trypanosoma cruzi* (Chagas Disease) 5. Fungal
AUTO IMMUNE	(1) SLE (2) Polymyositis (3) RHD(*Pancarditis)(4) (4) (4)Sarcoidosis
HPERSENSITIVITY MYOCARDITIS	
OTHERS	Secondary to :- !. Cardiotoxic drugs- Doxorubicin, Daunorubicin, Anthracycline (dose dependent) 2. Catecholamine Effect 3. Radiation 4. Transplant Rejection
IDIOPATHIC	

Pathogenesis

1. Viral Myocarditis

Viral myocarditis forms one of the most common causes world wide.

A) Most cases result from immune response directed against virally infected cells

B) In some cases, viruses trigger a reaction against cross- reacting proteins eg. Myosin heavy chin.

C) Some viruses cause a direct cell death

2. Non- viral Myocarditis :-

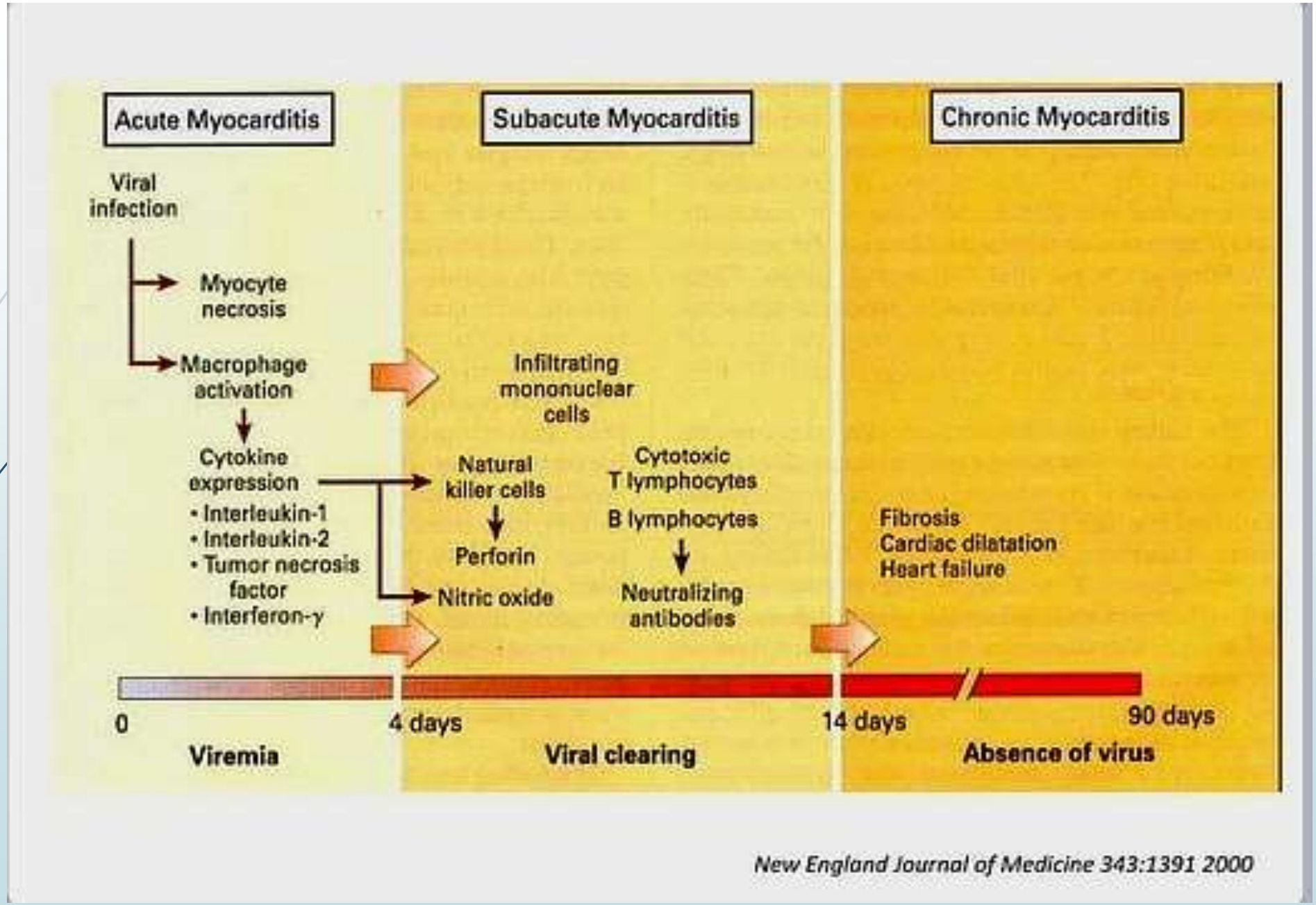
Includes

A) Protozoan- Includes Trypanosoma cruzi causing Chagas disease, which is most commonly seen in South America.

10% patients die during the acute attack. However the rest enter a chronic immune mediated phase with progressive development of signs of CHF, over 10- 20 yrs.

B) Toxoplasma gondii is seen as major cause of myocarditis in immunocompromised patients.

C) Lyme's diease- caused by Borrelia burgdarferri may cause myocarditis in 5% cases, manifesting as self- limiting conduction system diseases, and may require temporary pacemaker insertion in some cases.



New England Journal of Medicine 343:1391 2000

3. Non-infective Myocarditis

A) Hypersensitivity Myocarditis/ Drug Myocarditis

- It is the most common form of acute drug related myocardial injury, where the major contributors are Antibiotics, diuretics and anti- hypertensives.
- It is often non dose- related. Around 40 offending agents have been identified.
- It is also seen in patients undergoing Cardiac transplantation and is likely related to prolonged dopamine infusion.

B) **Secondary To Cardio-toxic drug**

- Most commonly seen in :-
- chemotherapy agents such as doxorubicin, Daunarubicin, Anthracycline (dose related), Targeted drugs of Tyrosine kinase, Immunotherapy agents and others eg. Lithium, phenothiazine, chloroquines
- Mechanism of injury includes Myofibre swelling , cytoplasmic vacuolization, lipid peroxidation of myocyte membranes.
- Removal of offending agents often leads to complete resolution without sequelae.
- Recurrent Myocarditis may be seen in patients with rapid tapering of immunosuppressant therapy.

C) **Secondary To Pheochromocytoma and "Catecholamine Effect" :-**

- **Pheochromocytoma**- due to release of catecholamine in circulation, it causes Focal areas of myocardial necrosis + contraction bands +/- sparse mononuclear inflammatory infiltrate.
- **"Catecholamine Effect"-** Various agents, that can be endogenous or exogenous, that produce effects like above.
- These include High dose of Ephedrine, vasopressors eg, Dopamine,

Intracranial lesions giving rise to intense autonomic stimulation, cocaine.

D) **Idiopathic**

Gross Findings

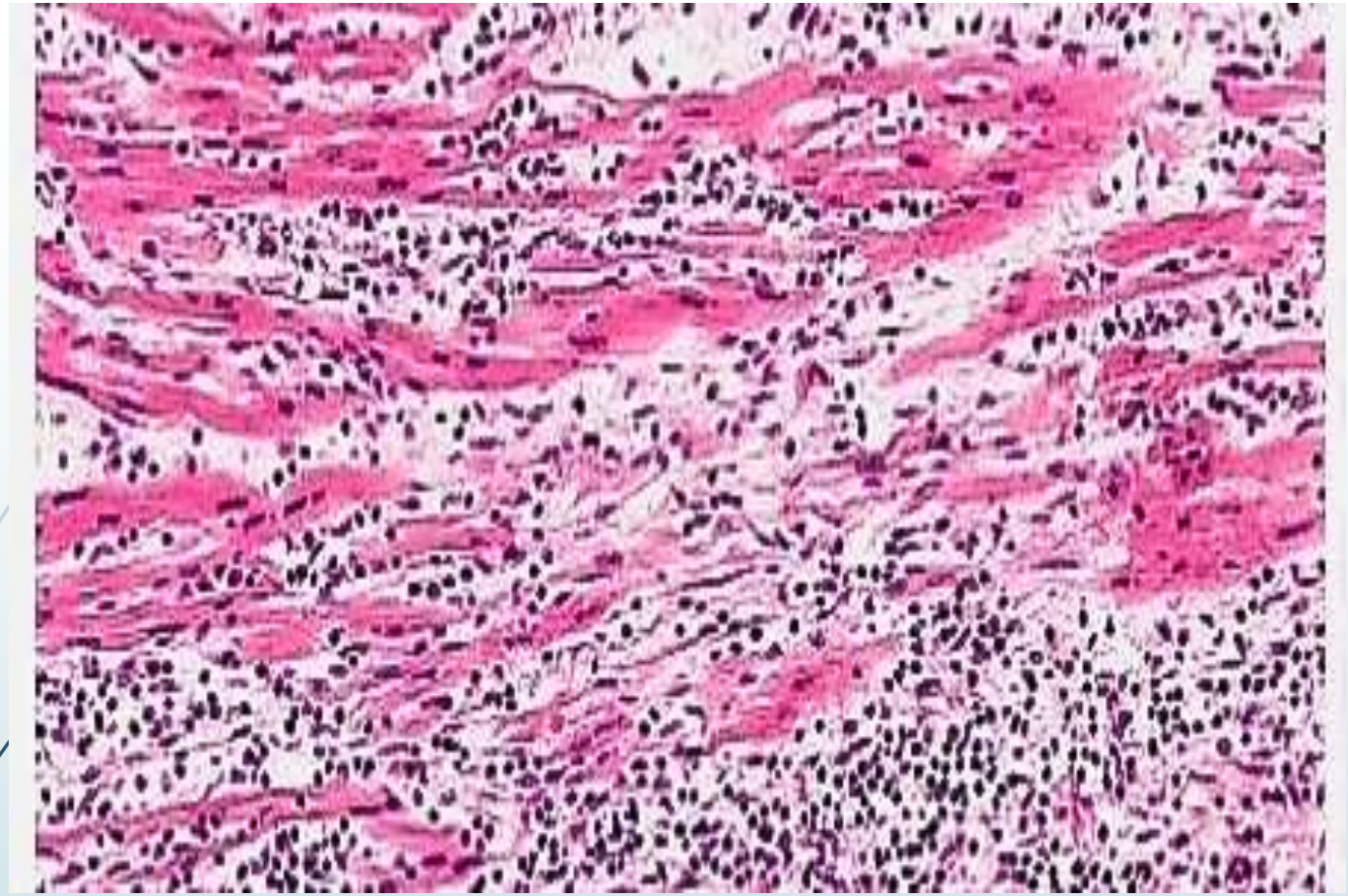
- Most cases have a **Normal** or slightly **dilated** heart.
- But in advanced stages, it can be Flabby, mottled with pale and hemorrhagic areas.

Microscopic Findings

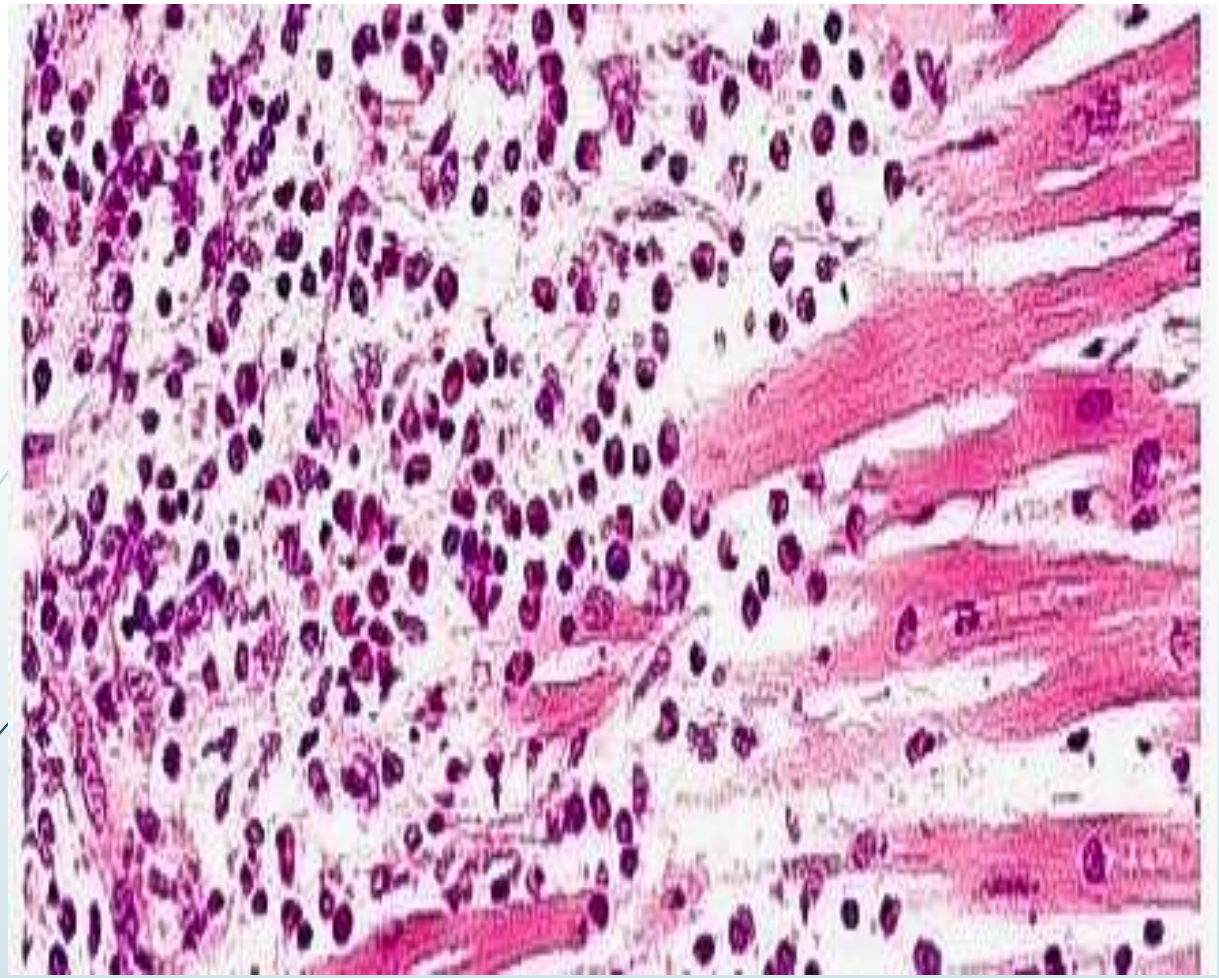
- Endomyocardial Biopsy, though not often done, remains the Gold-standard for diagnosis.
- **Dallas Criteria** :- Requires the presence of Inflammatory infiltrate **+** Myocyte necrosis/ degeneration of non- ischemic origin.
- **Diffuse lymphocytic infiltrates** are most commonly seen, but may also include histiocytes, neutrophils and occasionally eosinophil.
- However variations are found in other forms eg. **Giant Cell myocarditis, Hypersensitivity myocarditis, Chaga's myocarditis.**
- If the patient survives acute phases of myocarditis then,

  * the lesions may resolve without significant sequelae, or

  * heal progressively by Fibrosis.

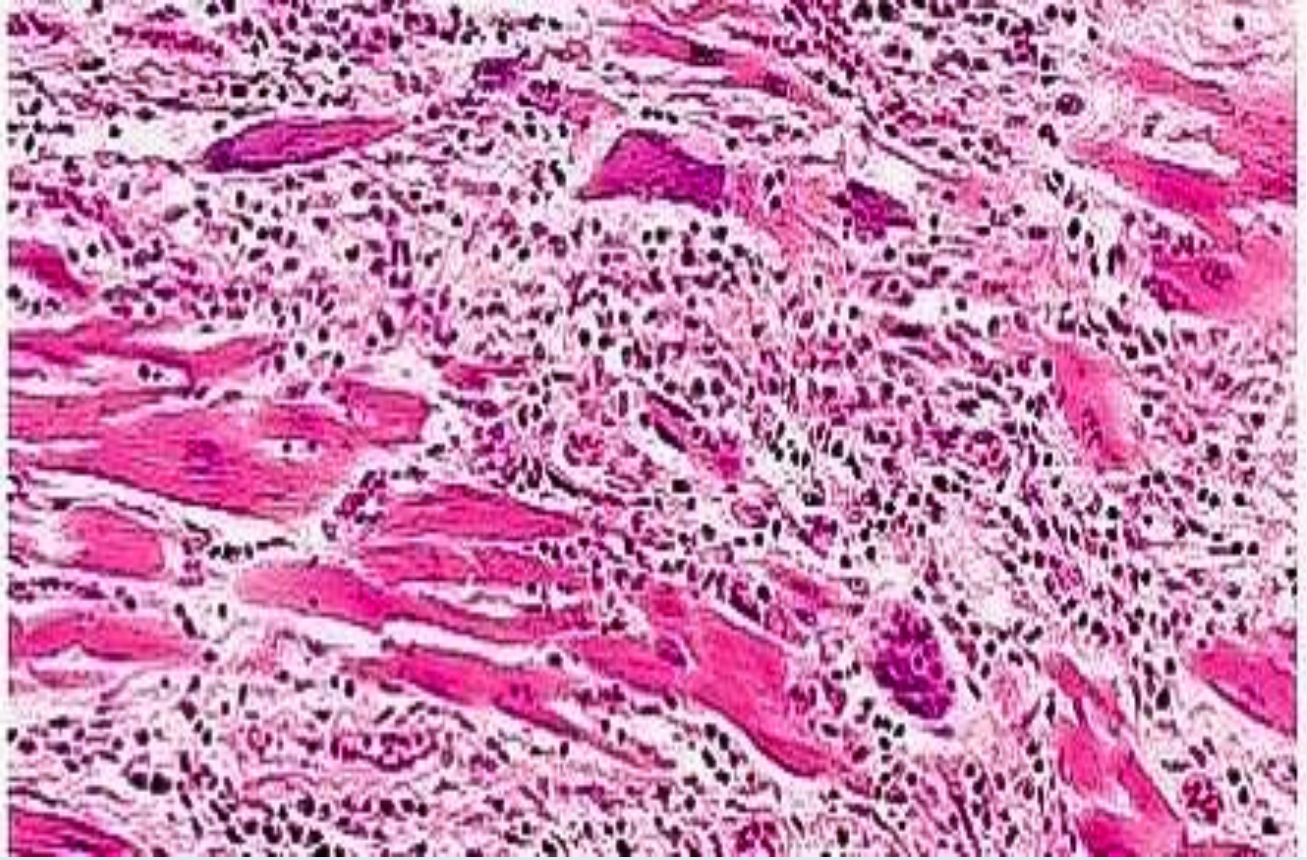


Lymphocytic Myocarditis : Characterized by edema associated with myocardial injury



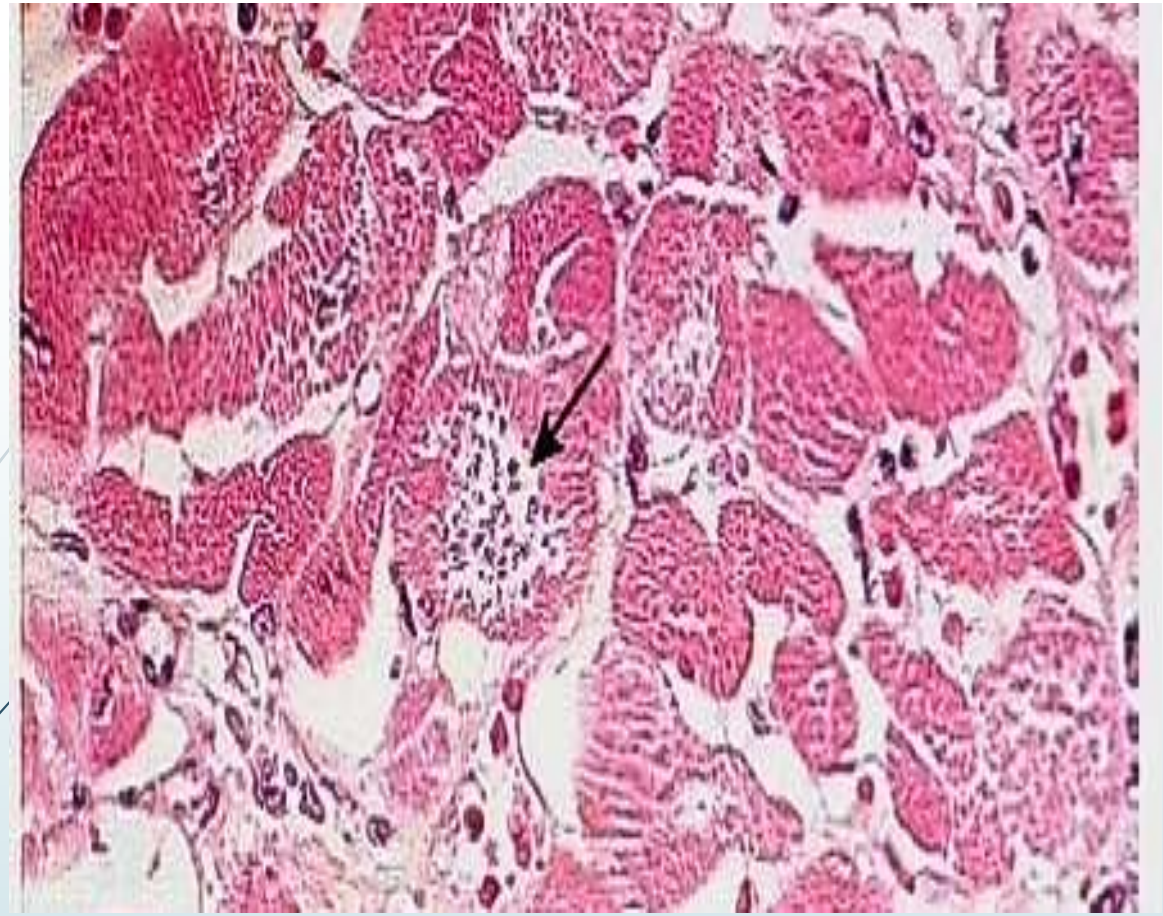
Hypersensitive Myocarditis :- Characterized by

1. Interstitial + Perivascular infiltrates with lymphocytes, macrophages and high proportion of eosinophil.
2. Lesser degree of myocardial injury is seen



Giant Cell Myocarditis:-

1. Morphologically distinct entity with widespread inflammatory infiltrate containing multinucleated giant cells.
2. Areas of focal – extensive necrosis seen
3. Well formed granulomas are not seen.
4. It represents the aggressive end of lymphocytic myocarditis spectrum and has poor prognosis.



Chaga's Myocarditis:-

1. Parasitizarion of scattered myofibres by Trypanosomes
2. Inflammatory infiltrates containing neutrophils, lymphocytes, macrophages, occasional eosinophils.

Advancements in Diagnosis/ troubleshooting

- Use of **Immunohistochemistry and special stains** like CD3, CD4, CD20, CD45, CD68. It increases the sensitivity and can aslo clarify nature of any ambiguous mononuclear cell.
- Difficult cases can be evaluated using leveled sections and masson trichrome stain.
- Some cases may only have patchy inflammatory infiltatres, therefore can be missed on biopsy. Therefore before ruling out the case as *no evidence of myocarditis*, deep sectioning of paraffin block should be considered.