Μυοκαρδίτιδα. Διαστρωμάτωση και αντιμετώπιση με βάση τις τρέχουσες οδηγίες.

Μαρία Παπαδημητρίου

Επιμελήτρια Α΄ Καρδιολογίας

Γενικό Νοσοκομείο Κιλκίς

European Heart Journal (2013) **34**, 2636–2648
doi:10.1093/eurheartj/eht210

ESC REPORT

Current state of knowledge on aetiology,diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Myocarditis (WHO /ISFC):
Inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria

Caforio et al, *European Heart Journal (2013) 34, 2636–2648*

Epidemiology

- affects relatively young patients

  median age of onset ranges between 30-45 years in most of the series

- affects men more than women

  male prevalence ranges between 60% and 80%

- has a wide spectrum of clinical presentations and trajectories, with most cases resolving spontaneously

Ammirati et al. An Expert Consensus Document
Circ Heart Fail. 2020;13:e007405

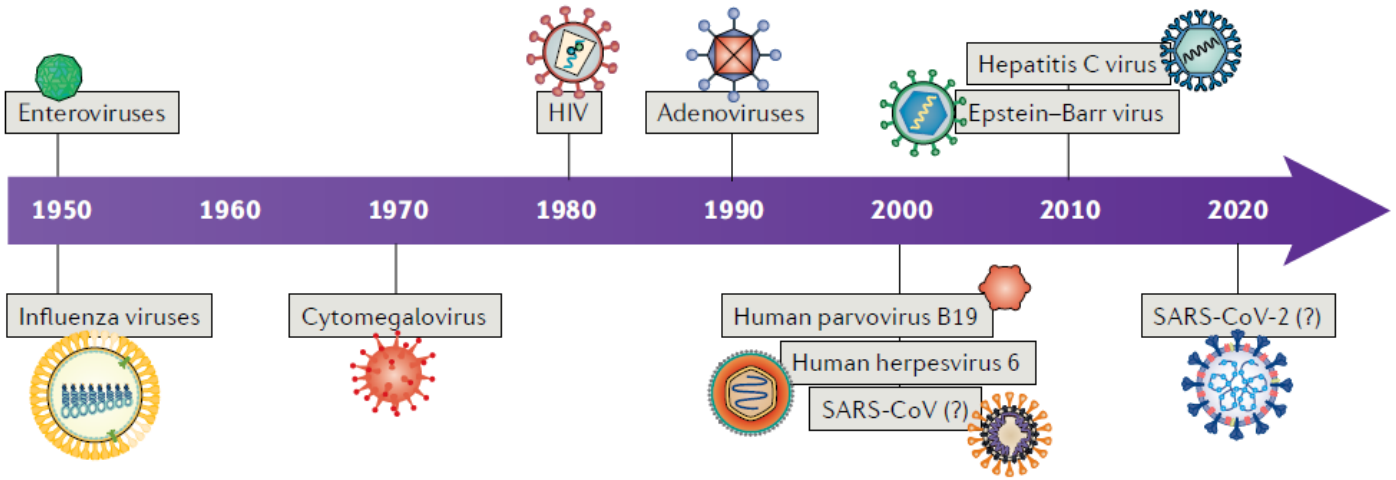
Causes of myocarditis

1. Infectious myocarditis	
Bacterial	*Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Meningococcus*, *Gonococcus*, *Salmonella*, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, *Mycobacterium* (tuberculosis), *Mycoplasma pneumoniae*, *Brucella*
Spirochaetal	*Borrelia* (Lyme disease), *Leptospira* (Weil disease)
Fungal	*Aspergillus*, *Actinomyces*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Mucormycoses*, *Nocardia*, *Sporothrix*
Protozoal	*Trypanosoma cruzi*, *Toxoplasma gondii*, *Entamoeba*, *Leishmania*
Parasitic	*Trichinella spiralis*, *Echinococcus granulosus*, *Taenia solium*
Rickettsial	*Coxiella burnetii* (Q fever), *R. rickettsii* (Rocky Mountain spotted fever), *R. tsutsugamuschi*
Viral	RNA viruses: Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1 DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus
2. Immune-mediated myocarditis	
Allergens	Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
Alloantigens	Heart transplant rejection
Autoantigens	Infection-negative lymphocytic, infection-negative giant cell Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever)
3. Toxic myocarditis	
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine
Heavy metals	Copper, iron, lead (rare, more commonly cause intramyocyte accumulation)
Miscellaneous	Scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide
Hormones	Phaeochromocytoma, vitamins: beri–beri
Physical agents	Radiation, electric shock

ESC Guidelines 2013
European Heart Journal 34, 2636–2648

Myocarditis and inflammatory cardiomyopathy: current evidence and future directions

Carsten Tschöpe[1,2,3]✉, Enrico Ammirati[4], Biykem Bozkurt[5,6], Alida L. P. Caforio[7], Leslie T. Cooper[8], Stephan B. Felix[9,10], Joshua M. Hare[11], Bettina Heidecker[12], Stephane Heymans[13,14], Norbert Hübner[2,15,16], Sebastian Kelle[2,3,17], Karin Klingel[18], Henrike Maatz[15], Abdul S. Parwani[3], Frank Spillmann[3], Randall C. Starling[19], Hiroyuki Tsutsui[20], Petar Seferovic[21] and Sophie Van Linthout[1,2]



Tschöpe et al, Nature Reviews Cardiology, https://doi.org/10.1038/ s41569-020-00435- x

Viruses associated with myocarditis and inflammatory cardiomyopathy

Viral tropism	Virus	Viral genome	Virulence	Treatment for associated heart disease
Cardiotropic	Adenoviruses	dsDNA	Virulent	IFNα or IFNβ (?); direct- acting antiviral therapy (?); intravenous immunoglobulins (?)
	Enteroviruses (coxsackieviruses, echoviruses)	(+)ssRNA		
Vasculotropic	Parvovirus B19	ssDNA	Bystander: latent; low viral DNA copy numbers in cardiac tissue; with or without cardiac inflammation	No need for antiviral therapy
			Virulent: high viral DNA copy numbers in cardiac tissue (>500 viral DNA copies per microgram cardiac DNA) with cardiac inflammation or systemic infection	Intravenous injection of immunoglobulins (?)
Lymphotropic	Cytomegalovirus; Epstein–Barr virus; human herpesvirus 6	dsDNA	Bystander: latent; low DNA copy numbers in cardiac tissue; with or without cardiac nflammation	No need for antiviral therapy
			Virulent: high cardiac DNA copy numbers; with cardiac inflammation	Anti- herpesvirus drugs
Cardiotoxic	Hepatitis C virus; HIV; Influenza viruses	(+)ssRNA	Virulent: cardiac inflammation with viraemia	Direct- acting antiviral therapy
ACE2- tropic; cardiotoxic (?)	Coronaviruses (MERS- CoV, SARS- CoV, SARS- CoV-2)	(+)ssRNA	Virulent: viraemia; cardiac inflammation (?)	Potential treatments currently under investigation: remdesivir; hydroxychloroquine and azithromycin; darunavir and cobicistat; lopinavir–ritonavir; favipiravir; ribavirin; IFNα; camostat mesylate

Tschöpe et al, *Nature Reviews Cardiology,* https://doi.org/10.1038/ s41569-020-00435- x

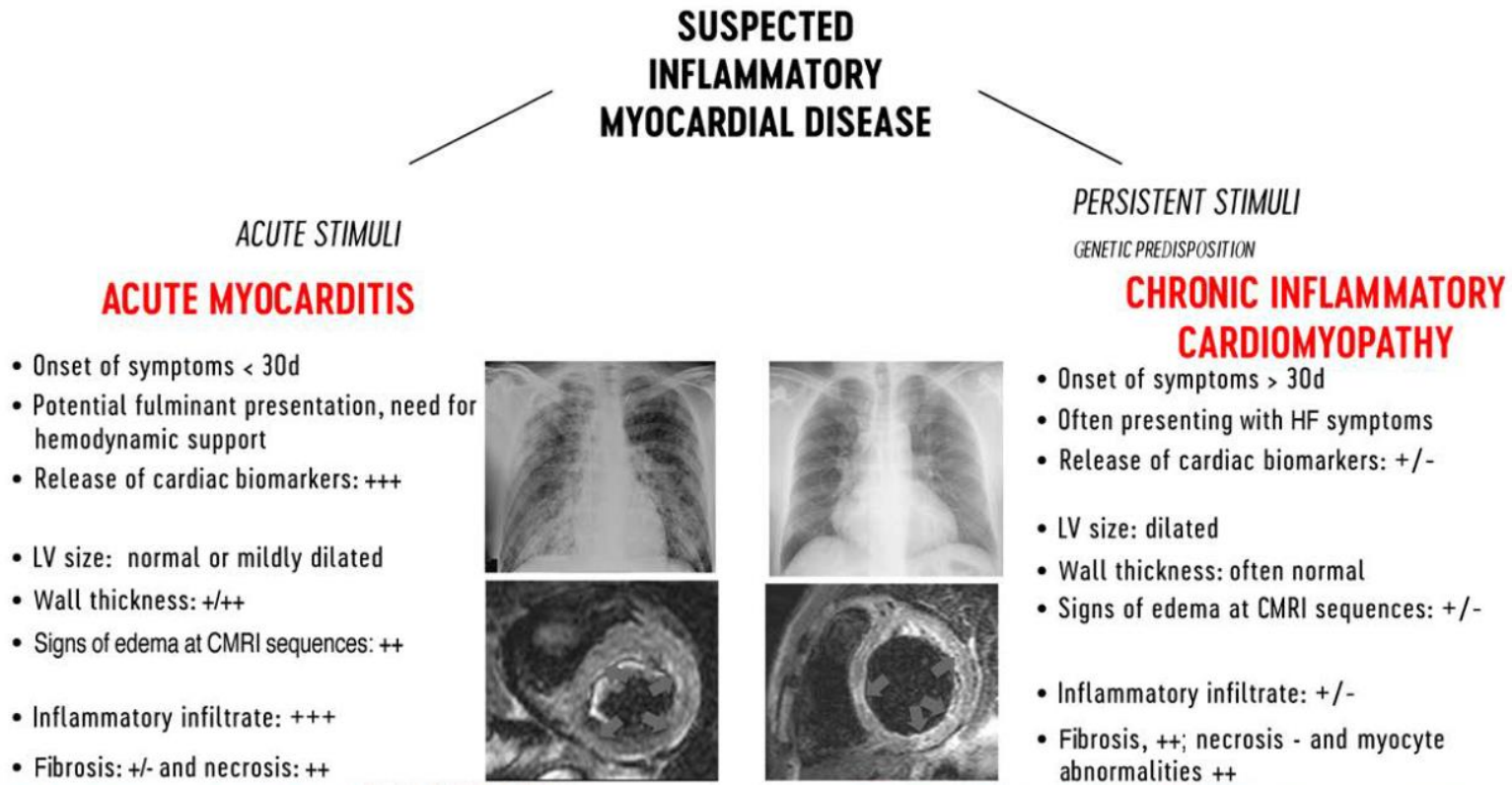
Circulation: Heart Failure

ADVANCES IN HEART FAILURE

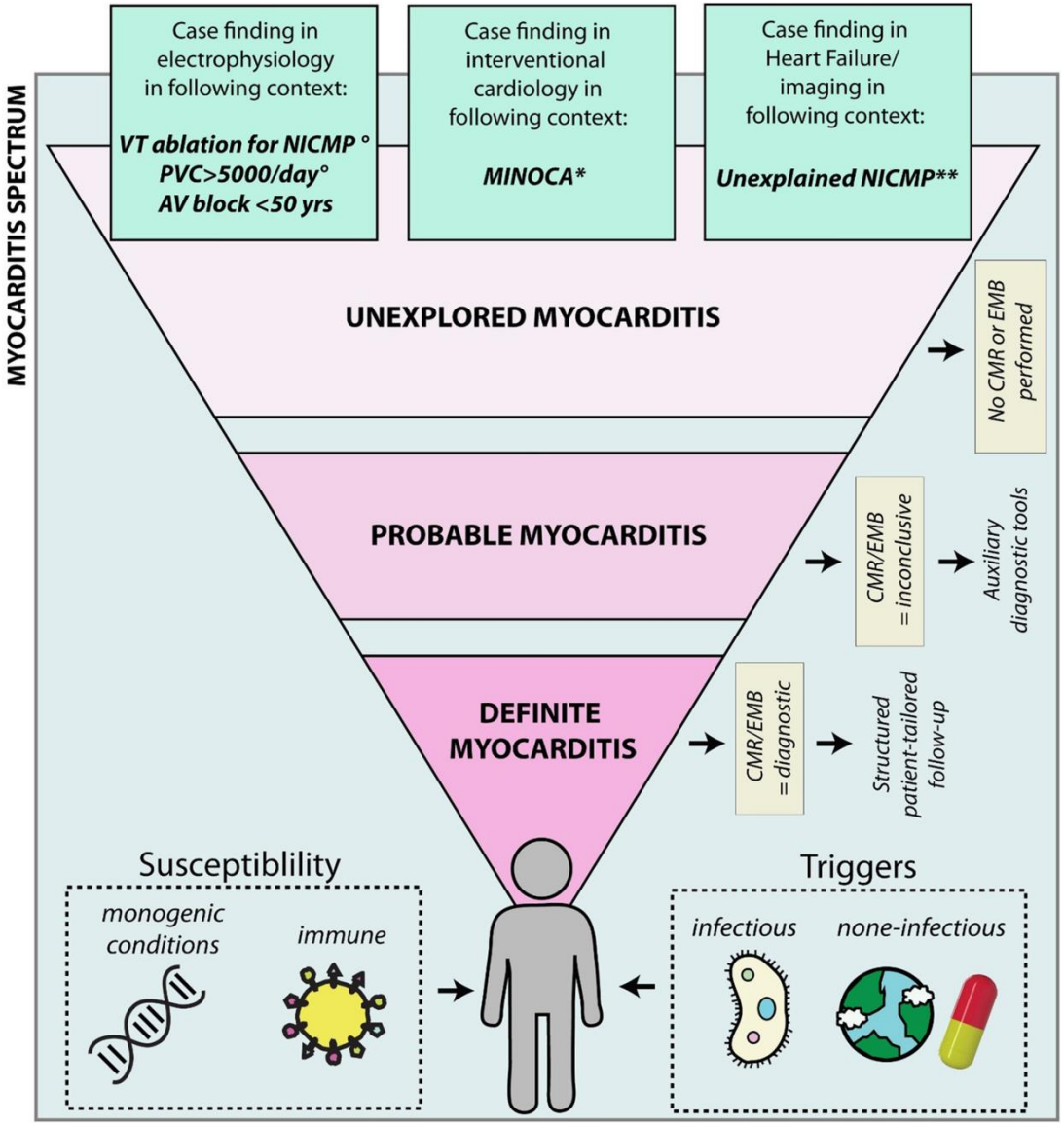
Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy

An Expert Consensus Document

Enrico Ammirati, MD, PhD*; Maria Frigerio, MD*; Eric D. Adler, MD; Cristina Basso, MD; David H. Birnie, MD; Michela Brambatti, MD, MS; Matthias G. Friedrich, MD; Karin Klingel, MD; Jukka Lehtonen, MD; Javid J. Moslehi, MD; Patrizia Pedrotti, MD; Ornella E. Rimoldi, MD; Heinz-Peter Schultheiss, MD; Carsten Tschöpe, MD; Leslie T. Cooper, Jr, MD†; Paolo G. Camici, MD†

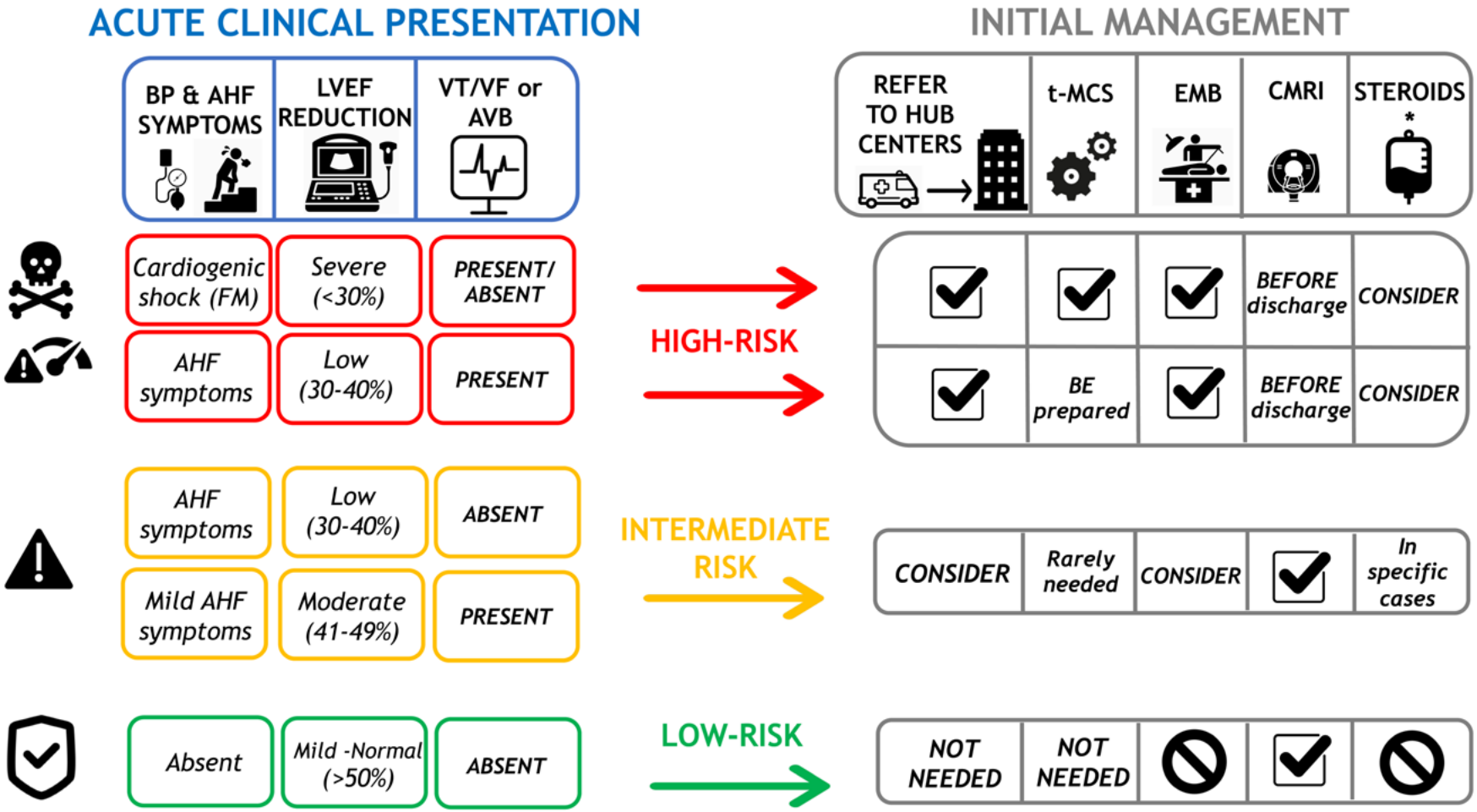


Clinical spectrum of myocarditis



Martens et al. *J Am Heart Assoc. 2023;12:e031454*

Proposed risk-based approach to acute myocarditis



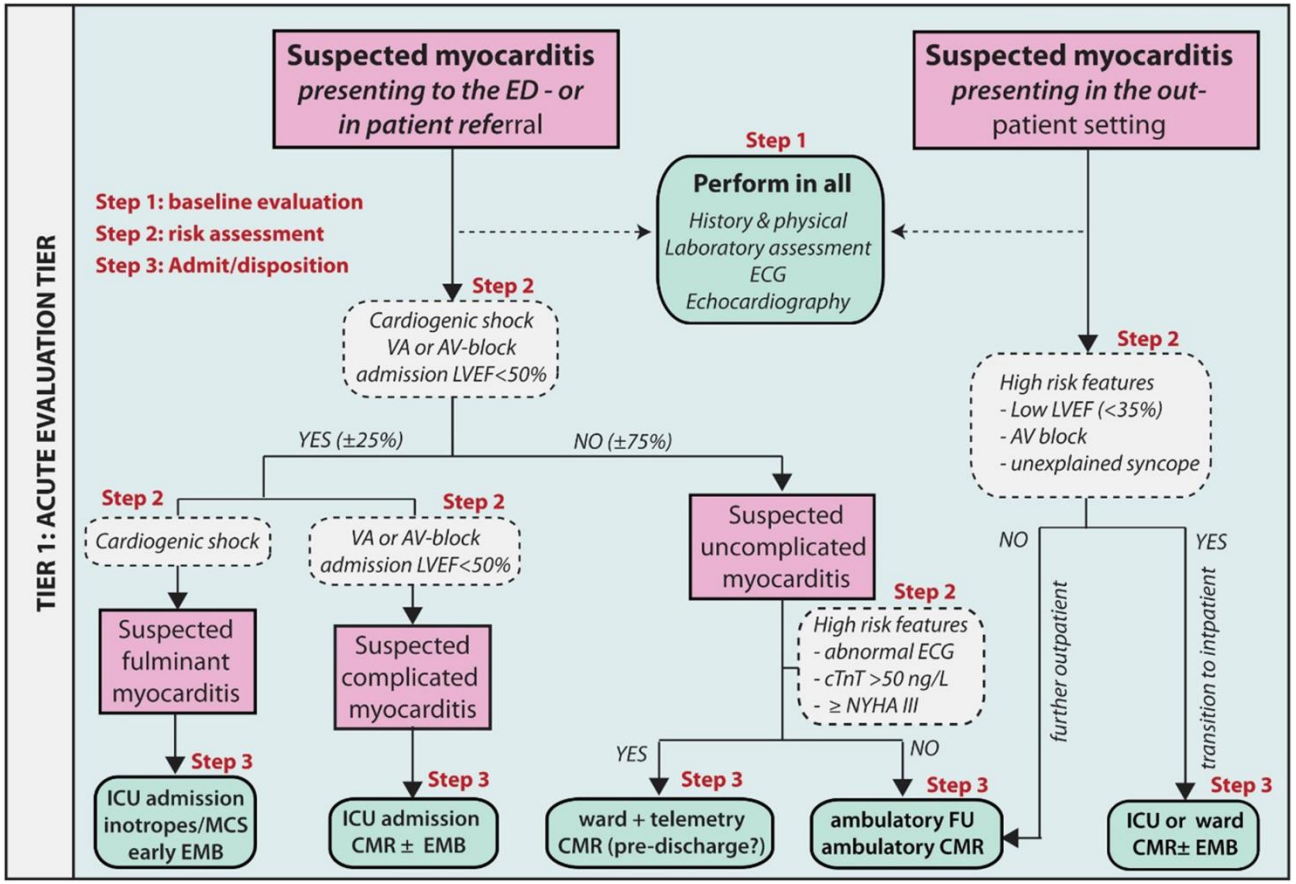
Ammirati et al. An Expert Consensus Document
Circ Heart Fail. 2020;13:e007405

Journal of the American Heart Association

CONTEMPORARY REVIEW

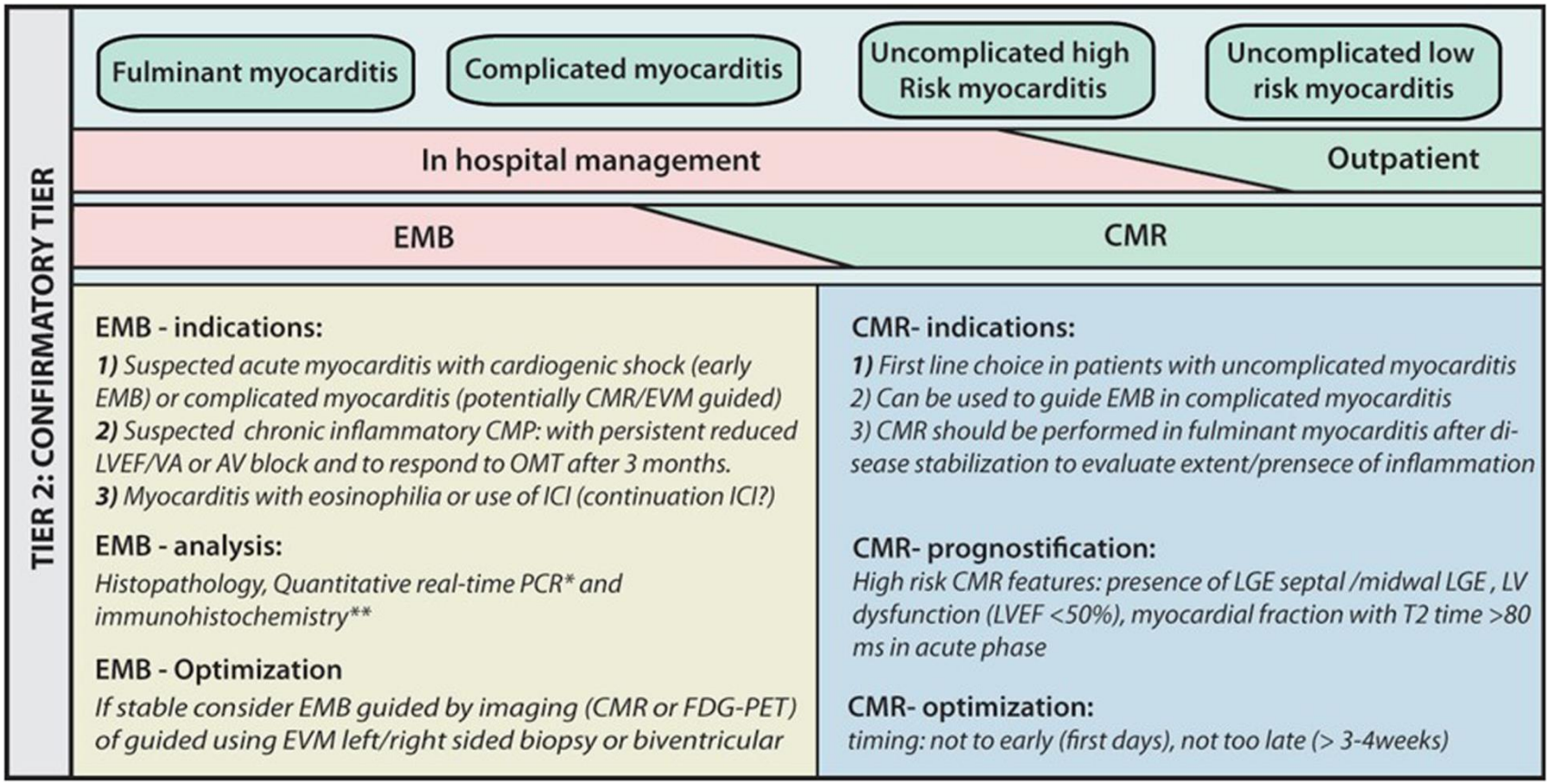
Diagnostic Approach for Suspected Acute Myocarditis: Considerations for Standardization and Broadening Clinical Spectrum

Pieter Martens, MD, PhD; Leslie T. Cooper, MD; W. H. Wilson Tang, MD



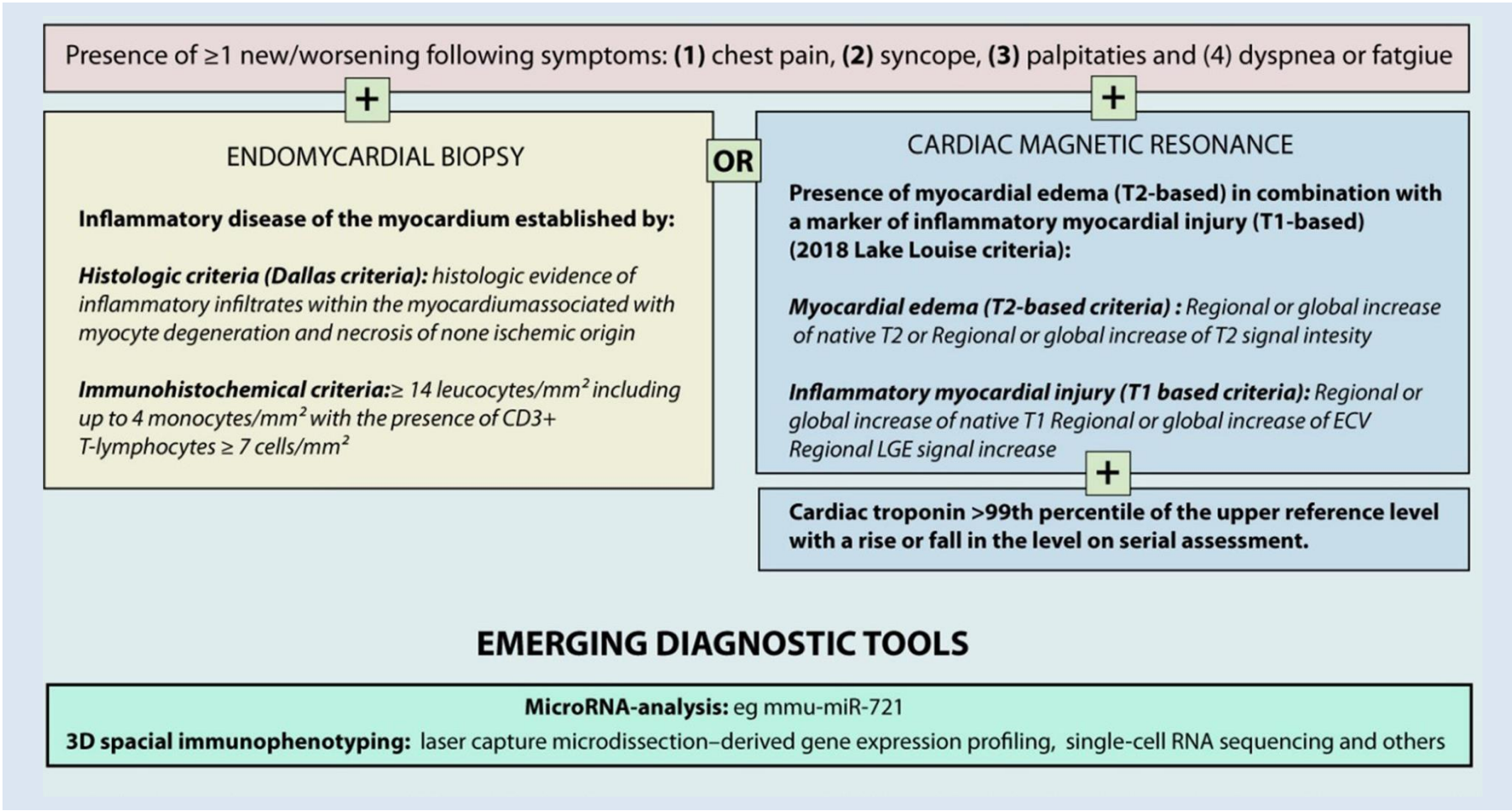
J Am Heart Assoc. 2023;12:e031454

Confirmation of myocarditis



Martens et al. *J Am Heart Assoc. 2023;12:e031454*

Definite myocarditis



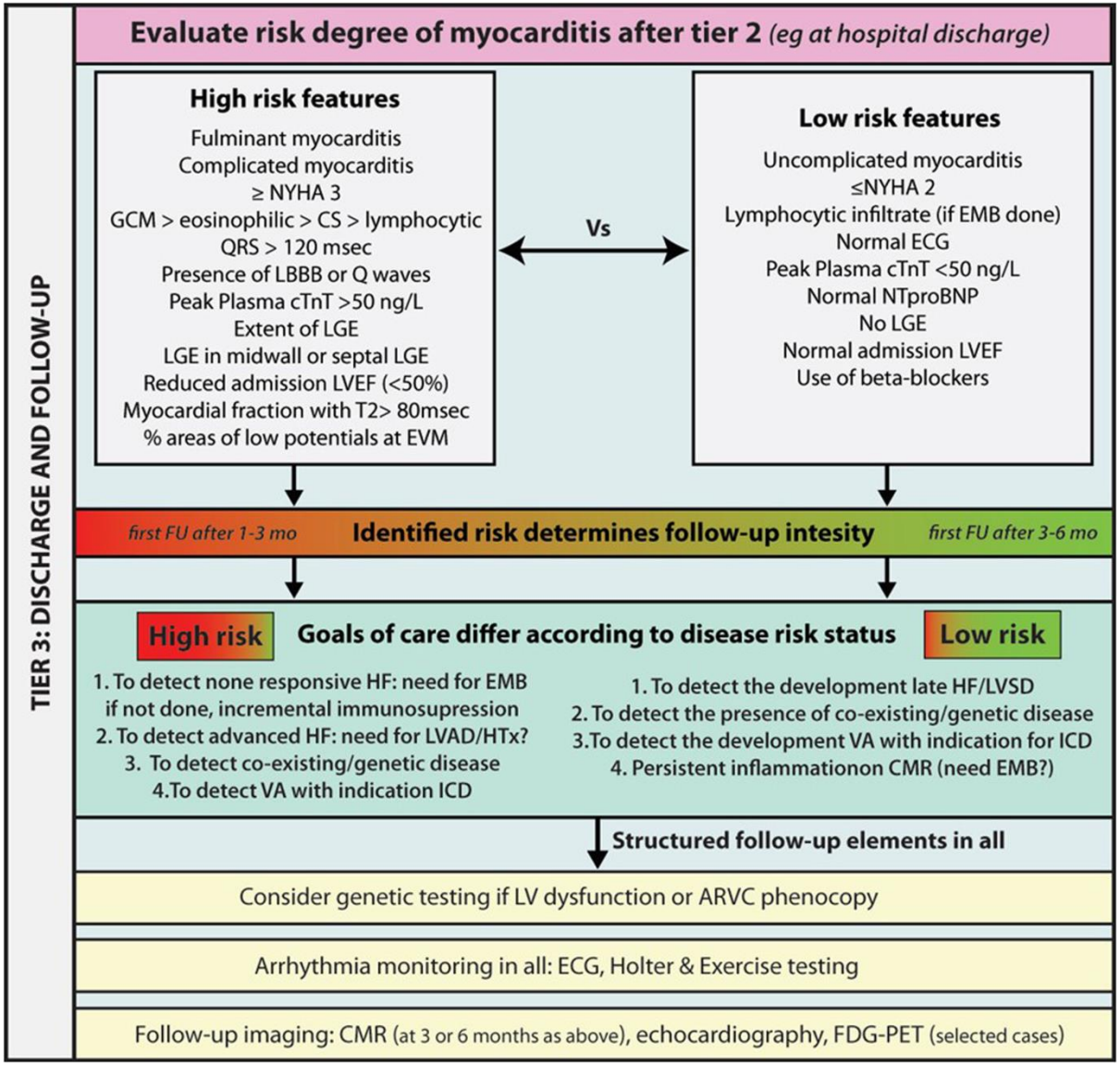
Martens et al. *J Am Heart Assoc. 2023;12:e031454*

Cardiac MRI versus endomyocardial biopsy in routine clinical practice

Clinical scenario	Characteristics	Cardiac MRI	Endomyocardial biopsy
Suspected acute myocarditis (disease onset ≤30 days)	Cardiogenic shock	–	++[a,b]
	Complicated, impaired ejection fraction or arrhythmias	++	
	Uncomplicated, stable, preserved ejection fraction and no arrhythmias	+	–/(+)[a,c]
Suspected inflammatory cardiomyopathy (disease onset > 30 days)	Persistent heart failure symptoms in preserved EF	++[c]	+[a,b]
	Persistent heart failure symptoms and reduced EF despite optimal medical therapy	++[c]	++[a,b]
	Significant arrhythmias despite optimal medical therapy	++[c]	++[a,b]
Suspected acquired dilated cardiomyopathy with a disease onset of months	Impaired EF and dilated LV of unknown etiology	++	+/++[a,b]
Ongoing clinical management	NA	+	–/+[d]

Tschöpe et al, Nature Reviews Cardiology, https://doi.org/10.1038/ s41569-020-00435- x

Post-diagnosis investigations and care



Martens et al. *J Am Heart Assoc. 2023;12:e031454*

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)
With the special contribution of the Heart Failure Association (HFA) of the ESC

Treatment and follow-up of acute myocarditis
HF therapy should be started if LV systolic dysfunction is present at presentation and should be continued for at least 6 months upon complete functional recovery (EF >50%)
Immunosuppression for at least 6-12 months is required in acute myocarditis with clinical or EMB evidence of auto-immune disease, including giant cell myocarditis, vasculitis or sarcoidosis.
Immunosuppression is not advised on a routine basis in acute myocarditis without clinical or EMB-based evidence of auto-immune disease. Initial empirical administration of i.v. corticosteroids may be taken into consideration in cases of high suspicion of immune-mediated myocarditis especially if complicated by acute HF, malignant arrhythmias and/or high degree AV block
Intense sporting activities should be avoided as long as symptoms, cardiac enzymes elevated or ECG/imaging abnormalities are present and last for at least 6 months since complete recovery.
Yearly follow-up for at least 4 years, with an ECG and echocardiography, is needed as acute myocarditis may lead to DCM in up to 20% of cases.

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 19–33
doi:10.1093/eurheartj/ehy730

SPECIAL ARTICLE
Sports cardiology

Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies,myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC)

Table 10 Recommendations for athletes with myocarditis

	Class/level of evidence
1. General consensus exists that athletes with diagnosis of myocarditis should be restricted from exercise programmes for a period of 3–6 months, according to the clinical severity and duration of the illness, LV function at onset, and extent of inflammation on the CMR. This time period is considered appropriate to ensure clinical and biological resolution of the disease.[3,4,105,118–120]	Class IIb/Level C
2. Individuals with previous myocarditis have an increased risk for recurrence and silent clinical progression of the disease. Therefore, athletes with previous myocarditis should undergo a periodical re-assessment, particularly within the first 2 years.	Class IIa/ Level C
3. It is reasonable for athletes to resume training and competition after a myocarditis if all of the following criteria are met: (1) LV systolic function has returned to the normal range. (2) Serum biomarkers of myocardial injury have normalized. (3) Clinically relevant arrhythmias, such as frequent or complex repetitive forms of ventricular or supraventricular arrhythmias are absent on 24-h ECG monitoring and exercise test.	Class IIa/ Level C
4. The clinical significance of persistent LGE in an asymptomatic athlete with clinically healed myocarditis is unknown, however, myocardial scar is a potential source of ventricular tachyarrhythmias.[111–113] At present, it seems reasonable for these athletes to resume training and participate in competitive sport if LV function is preserved and in the absence of frequent or complex repetitive forms of ventricular or supraventricular arrhythmias during maximal exercise and on 24-h ECG monitoring (including session of training/competition). Asymptomatic athletes with LGE, however, should remain under annual clinical surveillance.	Class III/ Level C

ESC European Society of Cardiology
European Heart Journal (2022) 43, 3997–4126
https://doi.org/10.1093/eurheartj/ehac262

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC)
Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC)

Recommendations for sudden cardiac death prevention and treatment ofventricular arrhythmias in myocarditis

Recommendations	Class	Level
General recommendations		
In confirmed or clinically suspected acute myocarditis, it is recommended that patients who present with life-threatening VAs are referred to a specialized centre	I	C
Secondary prevention of SCD and treatment of VA		
In patients with haemodynamically not-tolerated SMVT occurring in the chronic phase of myocarditis, an ICD implantation is recommended	I	C
In patients with haemodynamically not-tolerated sustained VT or VF during the acute phase of myocarditis, ICD implantation before hospital discharge should be considered	IIa	C
AADs should be considered (preferably amiodarone and beta-blockers) in patients with symptomatic non-sustained or sustained Vas during the acute phase of myocarditis.	IIa	C
In post-myocarditis patients with recurrent, symptomatic VT, AAD treatment should be considered.	IIa	C
Catheter ablation, performed in specialized centres, should be considered in post-myocarditis patients with recurrent, symptomatic SMVT or ICD shocks for SMVT in whom AADs are ineffective, not tolerated, or not desired	IIa	C
In patients with haemodynamically tolerated SMVT occurring in the chronic phase of myocarditis, ICD implantation should be considered.	IIa	C

ESC European Society of Cardiology

European Journal of Heart Failure (2021) 23, 854–871
doi:10.1002/ejhf.2190

POSITION PAPER

Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy

Disease	EMB processing/staining	Possible findings
Myocarditis DCM	**Histopathology** Haematoxylin and eosin, Mason or Mallory trichrome, Elastic van Gieson, PAS, Heidenhein's AZAN, and Methylene blue stain (Trypanosoma cruzii)	**Dallas criteria for myocarditis:** inflammatory infiltrates associated with myocyte degeneration and necrosis of non-ischaemic origin (active orborderline).
		Lymphocytic myocarditis: patchy or diffuse inflammatory infiltrate mostly of lymphocytes and macrophages [viral infections, immune-mediated myocarditis (systemic lupus erythematosus, polymyositis/dermatomyositis, rheumatoid arthritis, organ-specific autoimmune disorders, etc.)].
		Giant cell myocarditis: myocyte necrosis and diffuse or multifocal inflammatory infiltrates, with T lymphocytes, macrophage-derived multinucleated giant cells and eosinophilic granulocytes.
		Granulomatous myocarditis: non-necrotizing granulomas with macrophages and multinucleated giant cells, surrounded by fibrosis and a lymphocytic infiltrate (sarcoidosis).
		Eosinophilic myocarditis: interstitial inflammatory infiltrate dominated by eosinophils, often without myocyte damage, frequently accompanied by peripheral eosinophilia (hypersensitivity, parasitic infection, Churg–Strauss syndrome, endomyocardial fibrosis).
	Quantitative real-time PCR for enteroviruses, adenoviruses, herpesviruses (cytomegalovirus, herpes simplex, Epstein–Barr, human herpesvirus 6), parvovirus B19, influenza A and B, and SARS-CoV-2 virus + Borrelia	**Infection confirmed or not by (RT-) PCR**
	Immunohistochemistry CD3 (T cells), CD68 (macrophages), MHC II, alpha SM-myofibroblasts	**Myocarditis confirmed by immunohistochemistry:** ≥14 leucocytes/mm2 including up to 4 monocytes/mm2 with the presence of CD3+ T-lymphocytes ≥7 cells/mm2

Immune Checkpoint Inhibitor Associated Myocarditis

- Immune Checkpoint Inhibitors (ICIs) have transformed cancer treatment and include monoclonal antibodies which block immune brakes

- By activating the immune system, ICI can also lead to immune-related adverse events which can affect any organ

- Initially described in 2016, ICI-myocarditis is now considered an infrequent but potentially lethal complication of ICIs

- ICI-myocarditis is especially arrhythmogenic.
  Systolic HF occurs in about half of patients.

- ACHLYS trial
  Abatacept for theTreatment of Immune-Checkpoint Inhibitors Induced Myocarditis

Ammirati et al, 2022, doi: 10.3389/fmed.2022.838564

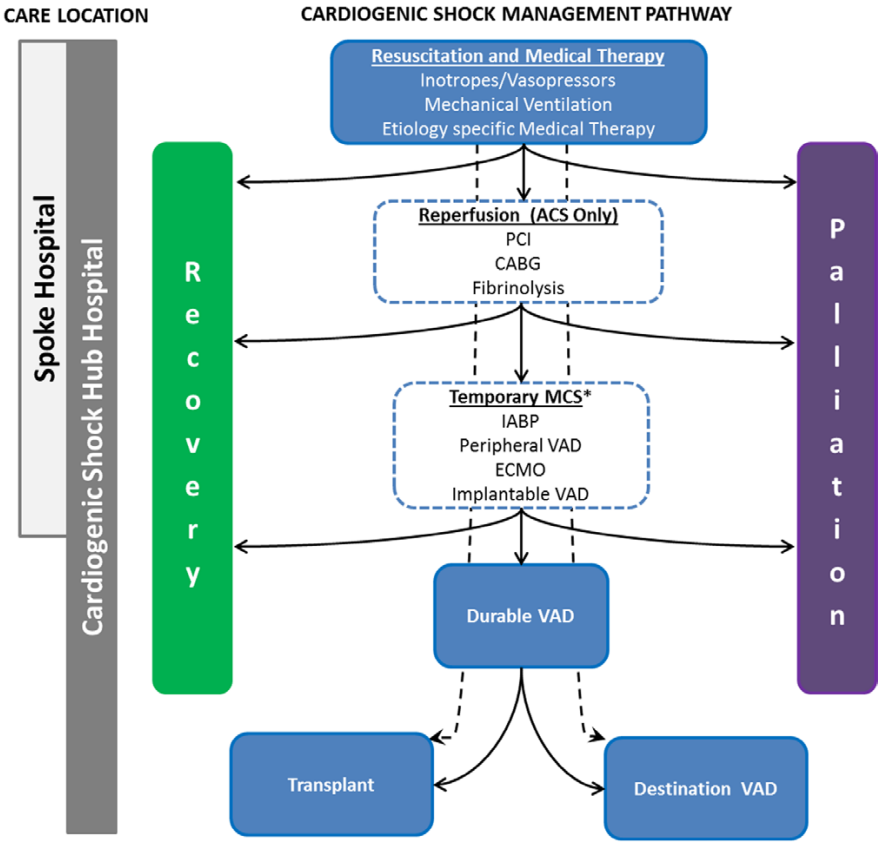
Circulation

AHA SCIENTIFIC STATEMENT

Recognition and Initial Management of Fulminant Myocarditis

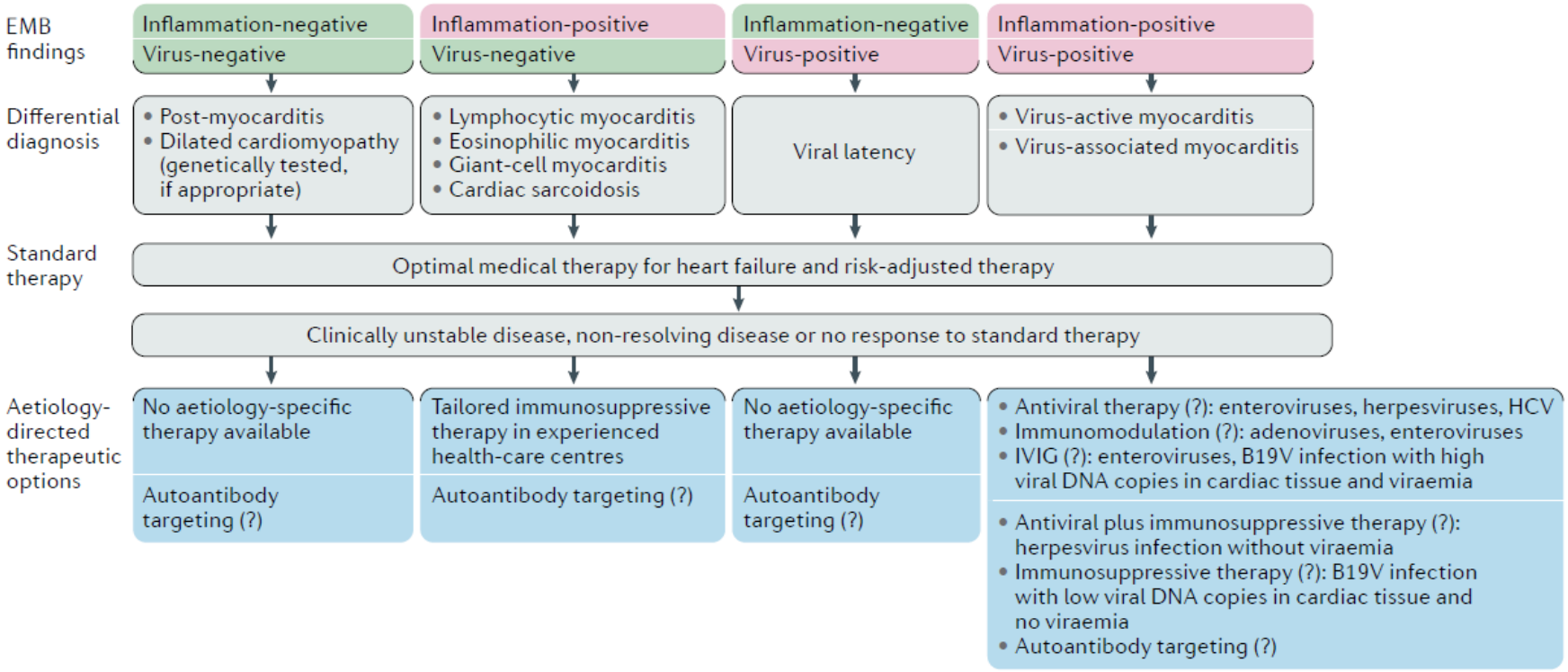
A Scientific Statement From the American Heart Association

Endorsed by the Heart Failure Society of America and the Myocarditis Foundation.



Kociol et al, *Circulation. 2020;141:e69–e92*

Endomyocardial biopsy-guided therapy in myocarditis and inflammatory cardiomyopathy



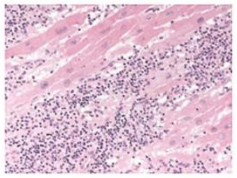
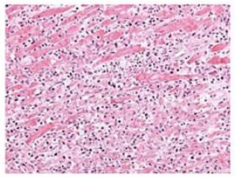
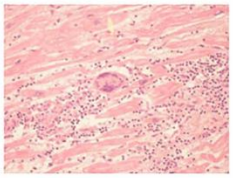
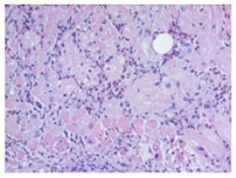
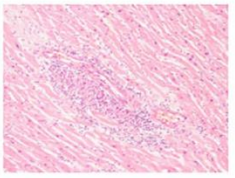
Tschöpe et al, Nature Reviews Cardiology, https://doi.org/10.1038/ s41569-020-00435- x

Immunosuppressive treatment strategies used for fulminant myocarditis or complicated acute myocarditis

SUSPECTED FULMINANT OR COMPLICATED ACUTE MYOCARDITIS

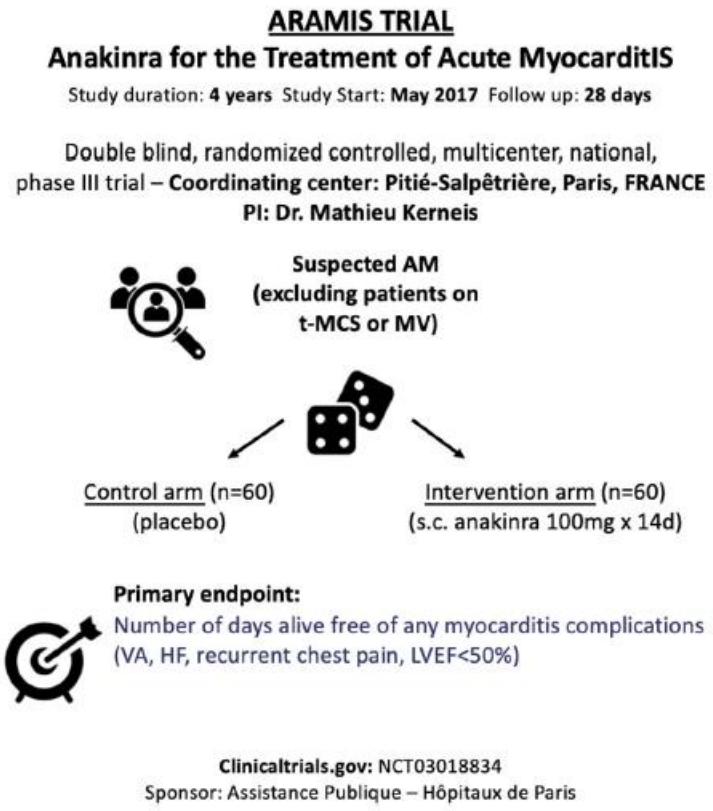
↓

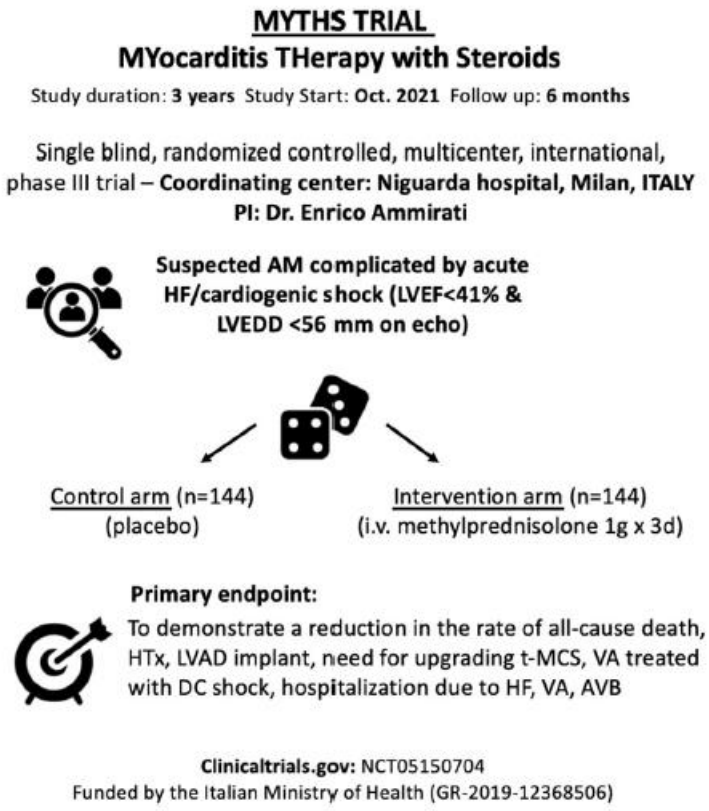
FIRST-LINE: **i.v. pulse methylprednisolone 7–14 mg/kg/day for 3 d, then 1 mg/kg/day**

	 **LYMPHOCYTIC**	 **ICI-ASSOCIATED**	 **GIANT CELL**	 **EOSINOPHILIC**	 **SARCOIDOSIS**
ADDITIONAL	- If associated systemic autoimmune disorders (eg. SLE and APS): add aggressive treatment of associated conditions	**Hold ICI** therapy Confirm ICI-myocarditis via definitive imaging and/or endomyocardial biopsy	- If hemodynamically unstable pts: **ATG**, from 1 mg/kg, usually single-dose to 300 mg in 3 days or (alternative) i.v. **alemtuzumab** (anti-CD52 antibody) single dose of 30 mg plus oral **CyA**, BID, target through levels 150–250 ng/mL - If hemodynamically stable pts: only oral **CyA**, BID, target trough levels 150–250 ng/mL	- If EGPA: consider i.v. **cyclophosphamide** (especially in ANCA-positive pts), 600 mg*m² at days 1, 15, and 30 - If clonal (myeloproliferative) HES: **imatinib** 100–400 mg OD - If helminthic infection: **albendazole** 400 mg BID for 2–4 wk - If hypersensitivity reaction: **withdraw suspected drug**	
SECOND-LINE	**IVIG** (2 g/kg), single continuous infusion in 24–48 h or divided in 4 d or **plasmapheresis**, 3–5 sessions in 5–10 d	i.v. **abatacept** (a CTLA- 4 agonist) or **ATG**, 1 mg/kg, usually single dose or i.v. **alemtuzumab** (anti-CD52 antibody), 30 mg, single dose	i.v. **rituximab** 375 mg×m² (BSA) mg (once a wk for 4 wk and then every 4 mo as maintenance therapy) for 1 yr	- If DRESS, EGPA or idiopathic HES: anti-IL5 agents (e.g., **benralizumab** 30 mg s.c./4–8wk or **mepolizumab** 100-300 mg/4wk)	s.c. **methotrexate** 15–20 mg/wk or i.v. **infliximab** 5 mg/kg (up to 500 mg) at time 0 and after 2 and 4 wk and then every 6–8 wk or s.c. **adalimumab** 40 mg/2wk

Ammirati et al, 2022, doi: 10.3389/fmed.2022.838564

Trials in the setting of acute myocarditis evaluating the use of immunosuppressive drugs





Ammirati et al, 2022, doi: 10.3389/fmed.2022.838564

Conclusions

- Myocarditis remains a challenging diagnosis because of the heterogeneity in the clinical manifestation and severity of the disease.

- The true incidence of myocarditis remains uncertain.

- Using a structured diagnostic approach of the patients with suspected myocarditis allowing to titrate the diagnostic and therapeutic process to the patients' individualized needs.