Early biopsy for all myocarditis – PRO

session: Cardiogenic shock 2024

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Nothing to disclose

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ESC REPORT

Myocardial and Pericardial Diseases
ESC Working Group

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

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1) Do we have a typical clinical presentation? NO

2) Can we reach the diagnosis of certainty and of aetiology without a biopsy? NO

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Myocarditis:clinical presentation

Mild symptoms
- **Palpitation, atypical chest pain, SOB**

Minor ECG abnormalities
- **Conduction disturbances, ST-T changes**

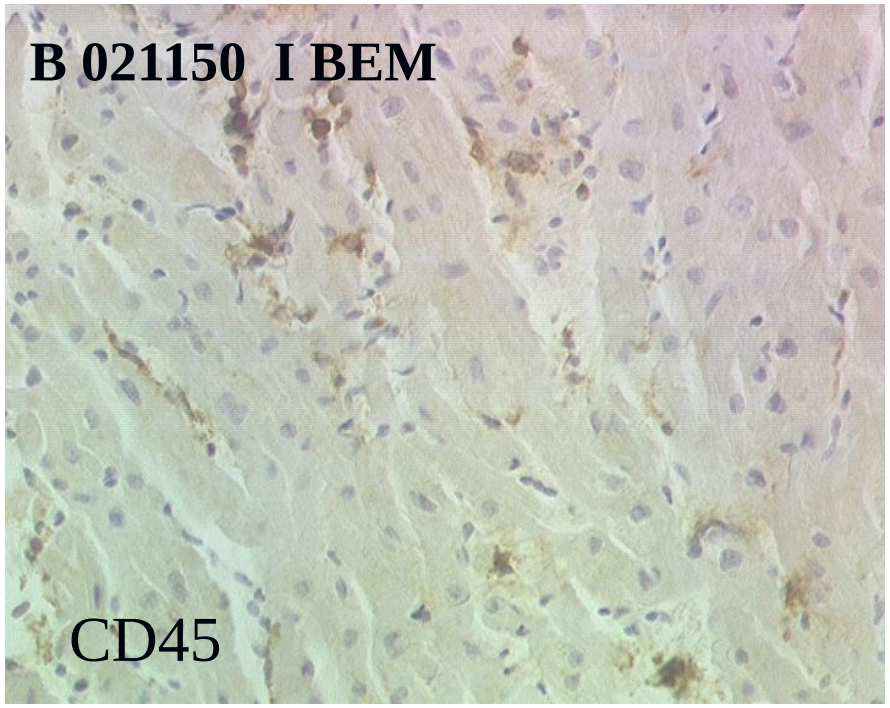
Major arrhythmia
- **SVT, complete A-V block, VT-VF**

Syncope, sudden cardiac death

Cardiogenic shock
- **Fulminant myocarditis**

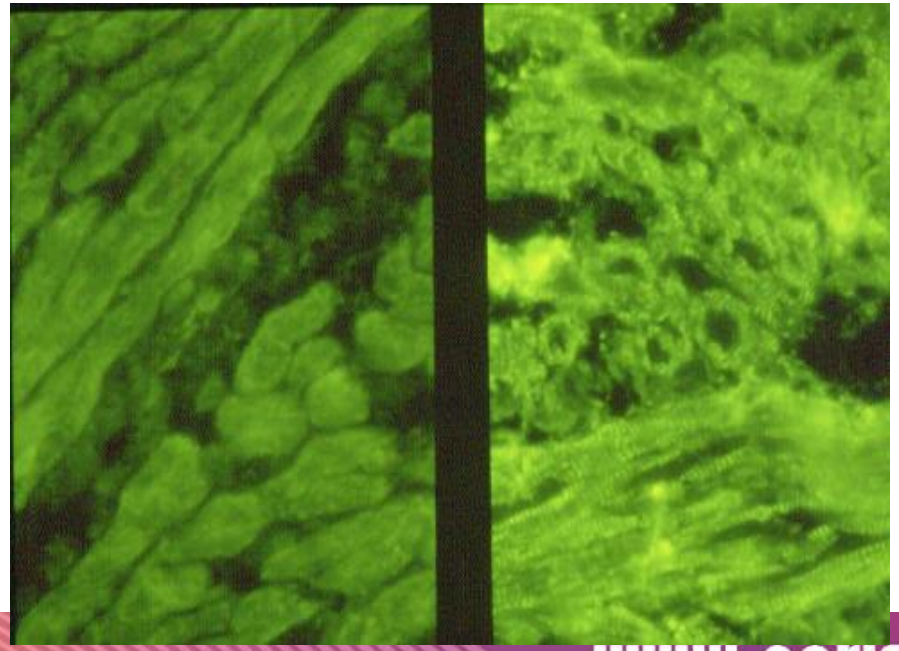
Unexplained heart failure with or without DCM features
- **Onset of symptoms: days or up to several years**
- **Peri-partum**

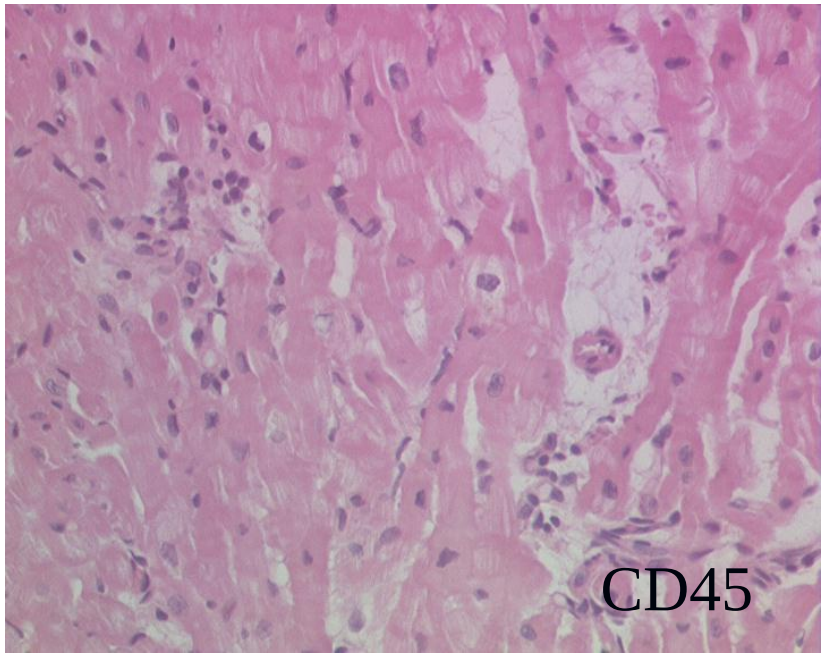
Infarct-like with normal coronary arteries



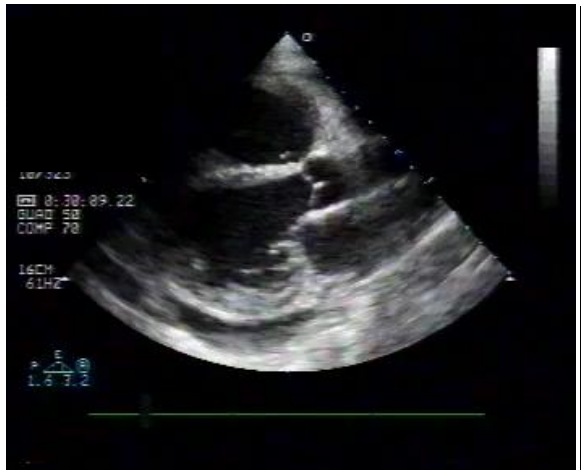
32 yr-old clinically suspected peri-partum DCM, cardiogenic shock

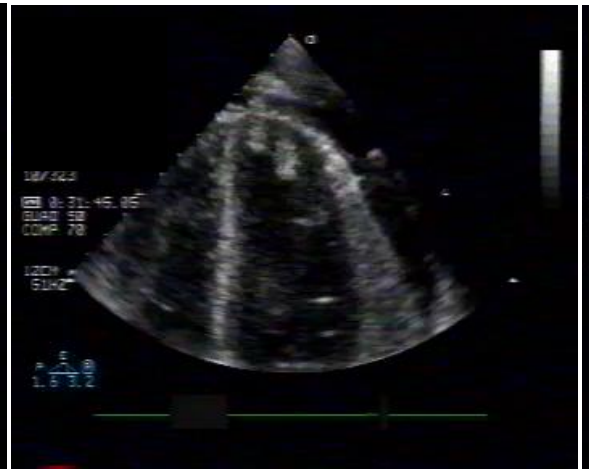
- **Active Autoimmune lymphocytic Myocarditis** (T Lymphocytes, few B cells)
- **Virus negative by PCR**
- **AHA pos**

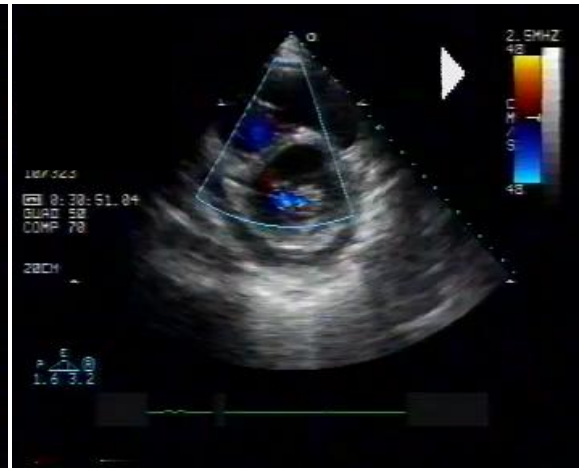




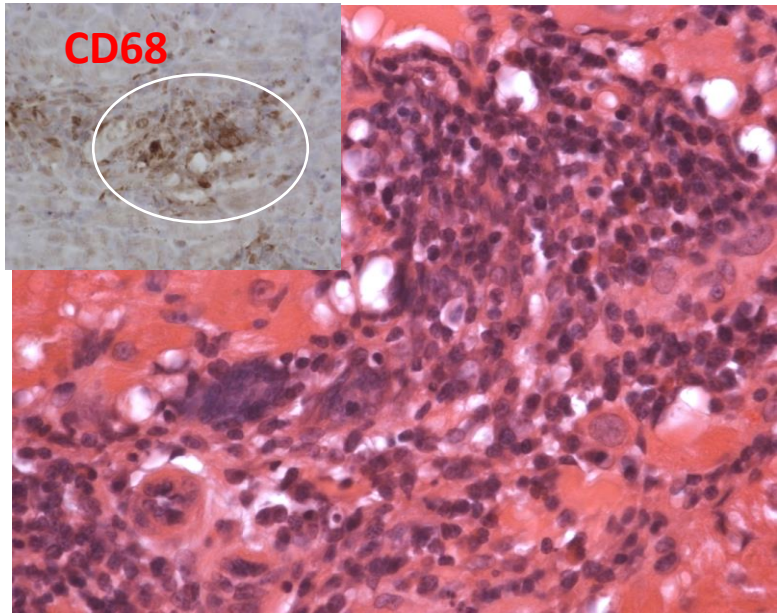
36-year woman with acute clinically suspected DCM, normal coro's and giant cell myocarditis





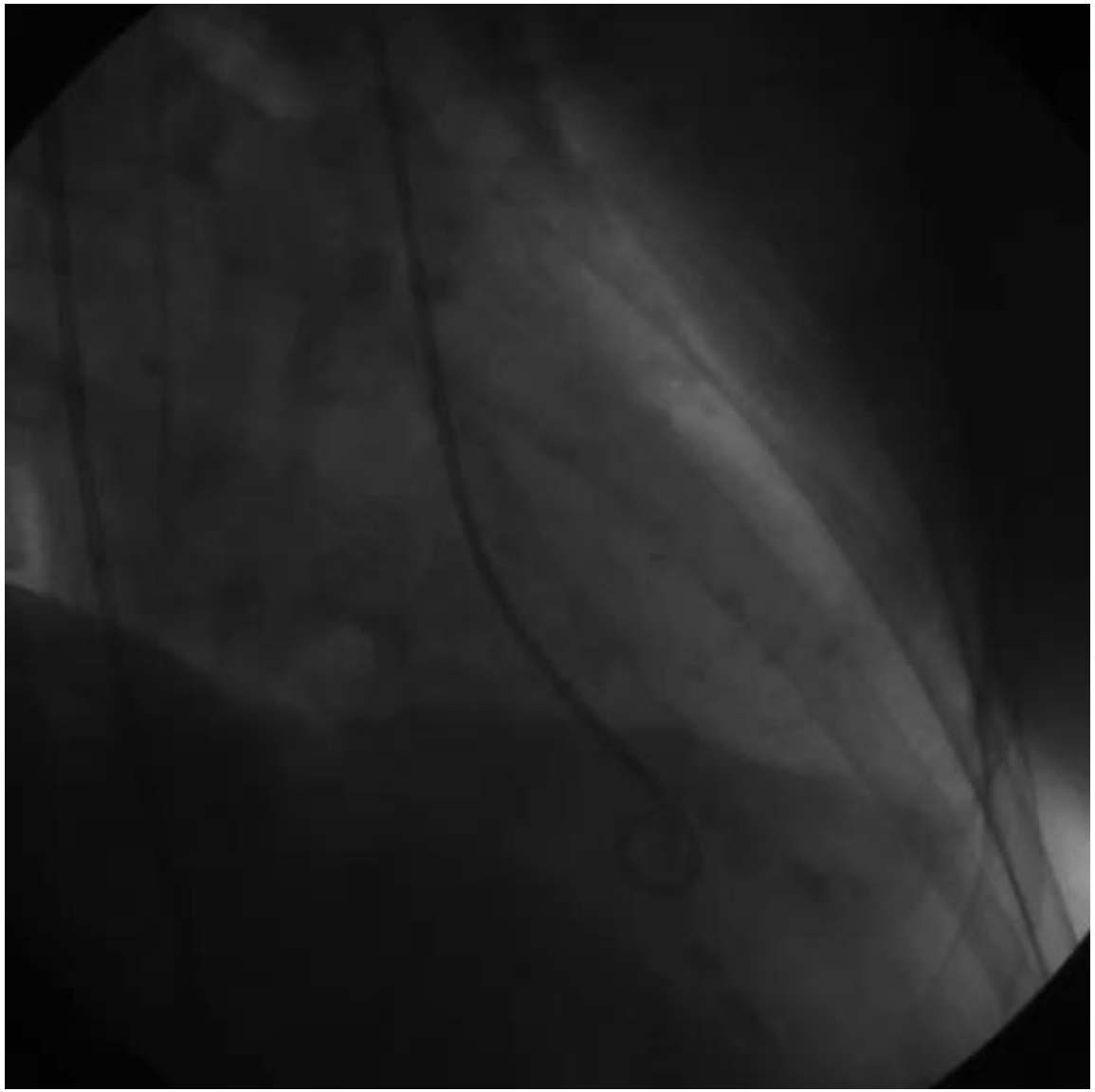


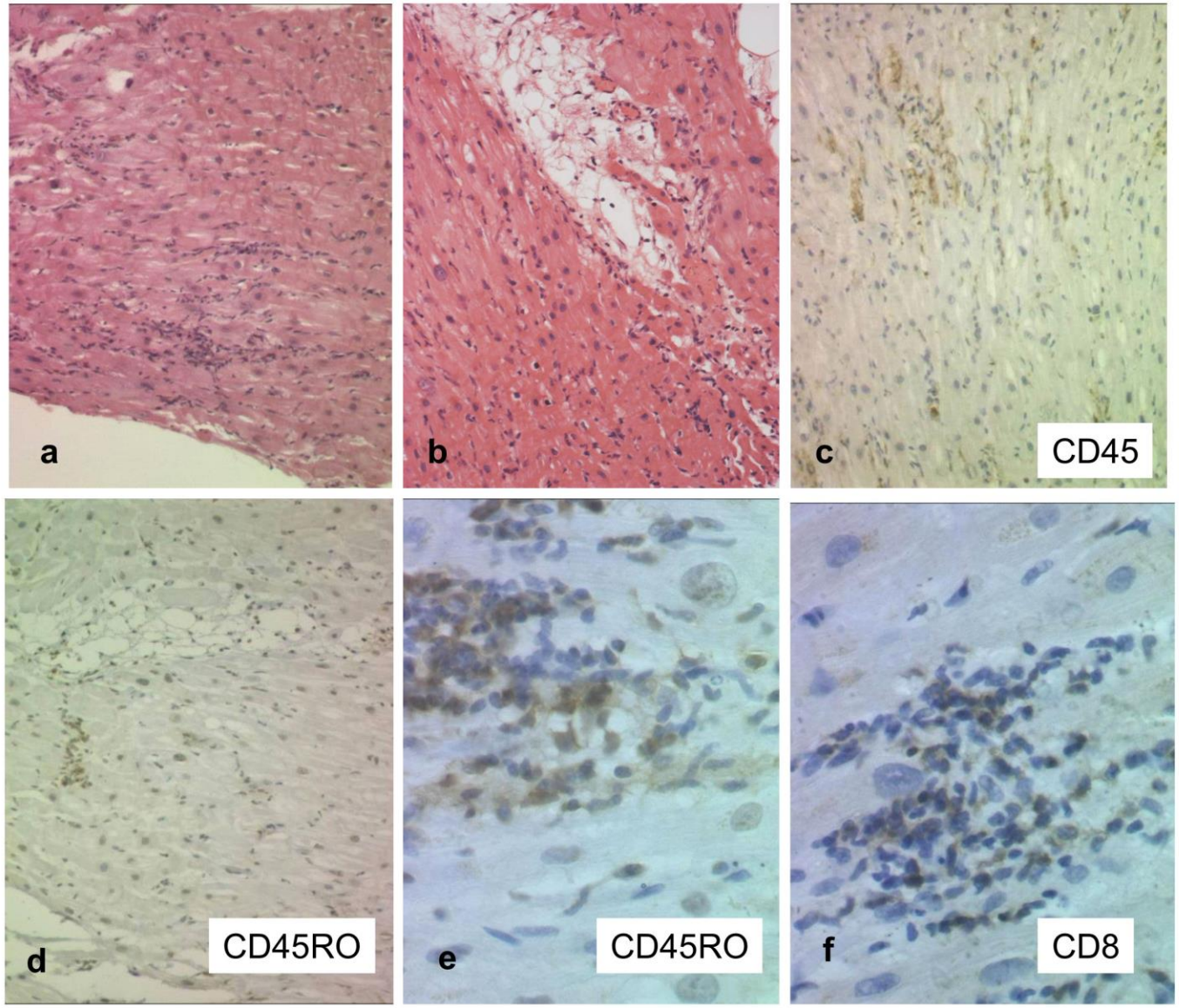
- *diffuse LV and RV hypokinesis*
- *moderate dilation of both ventricles,*
- *severe biventricular systolic dysfunction (LVEF 20%, RV FAC 20%)*
- *mild diffuse pericardial effusion,*
- *apical thrombus in the LV.*



Courtesy of Prof A Angelini, Cardiac Pathology, University of Padova, Italy

Lymphocytic virus-negative myocarditis, mimicking Takotsubo syndrome

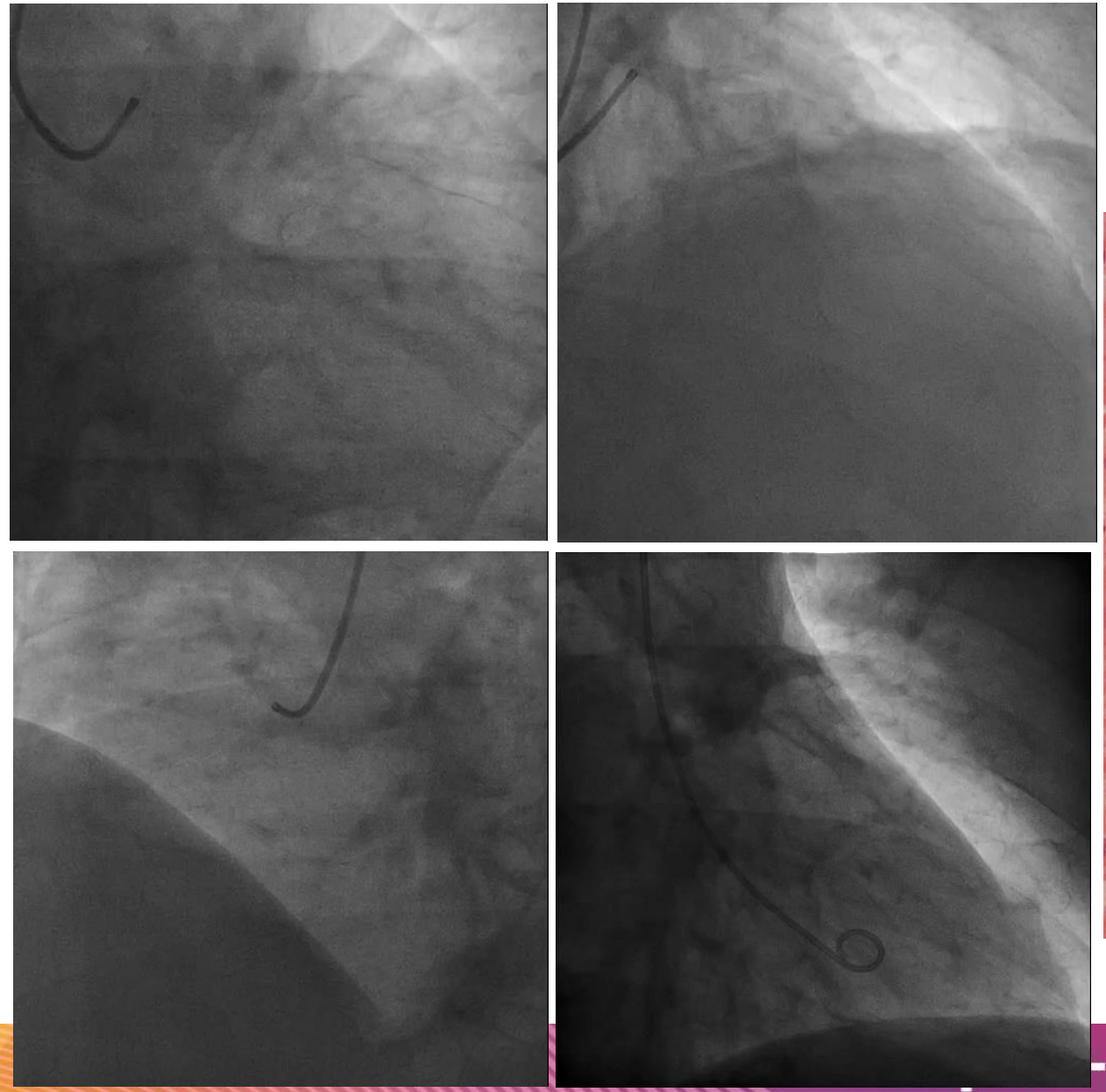


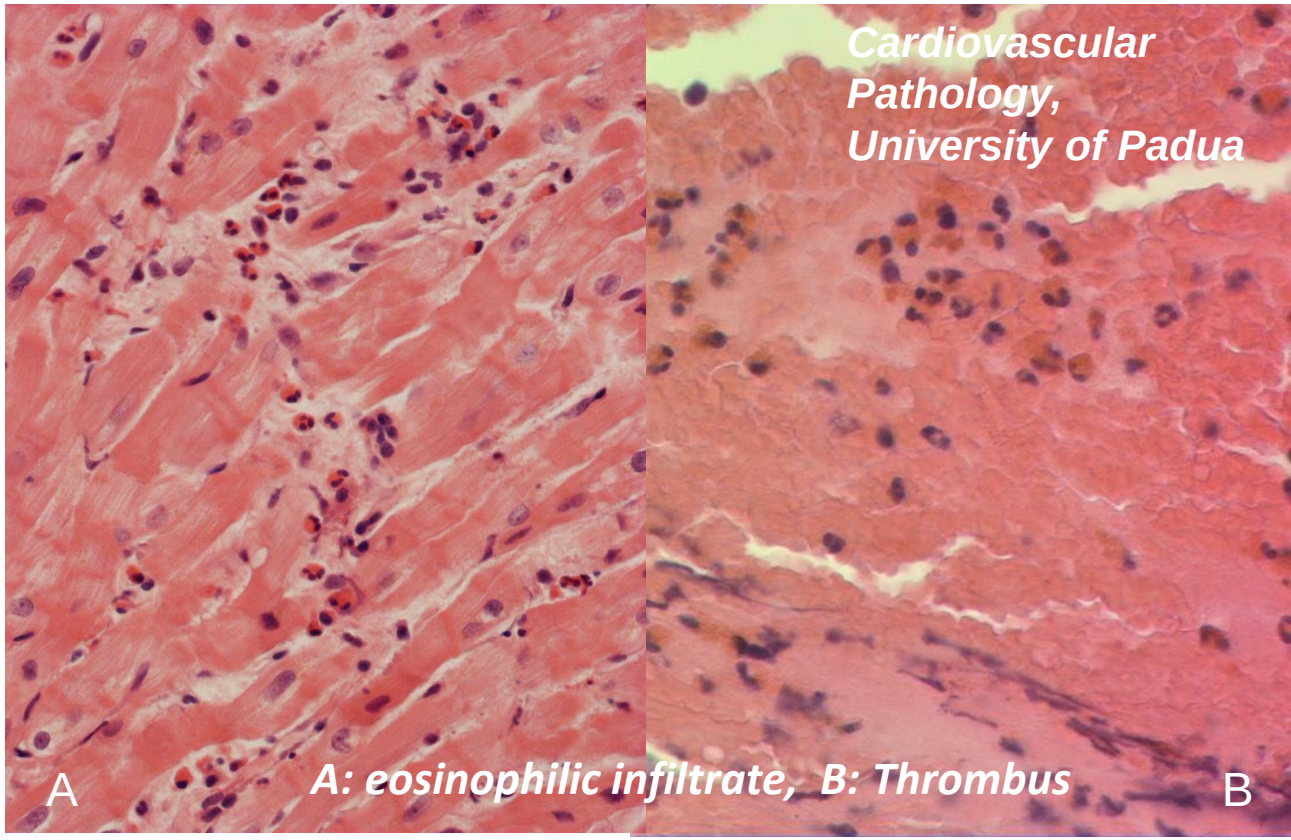


Caforio et al, Eur J Heart Fail 2009

a, b: inflammation and necrosis (HE); c,d=positive T lymph. activated (CD45RO); f=positive cytotoxic T lymph

65 yr, male, pseudo-infarct presentation, preserved LVEF, normal coro's, eosinophilic virus-negative myocarditis





Clinically suspected myocarditis – *ESC 2013 Task Force diagnostic criteria*

Table 4 Diagnostic criteria for clinically suspected myocarditis

Clinical presentations[a]
Acute chest pain, pericarditic, or pseudo-ischaemic
New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Subacute/chronic (>3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
Unexplained cardiogenic shock
Diagnostic criteria
I. ECG/Holter/stress test features
Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia
II. Myocardiocytolysis markers
Elevated TnT/TnI
III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)
New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
IV. Tissue characterization by CMR
Oedema and/or LGE of classical myocarditic pattern (see text)

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.
[a]If the patient is asymptomatic ≥2 diagnostic criteria should be met.

Caforio A et al., Eur Heart J 2013;34:2636-2648

Table 3 Diagnostic criteria for clinically suspected myocarditis

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: *- 1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%) –2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.* ***If the patient is asymptomatic ≥2 diagnostic criteria should be met.**

Recommendation

10. All patients with clinically suspected myocarditis should be considered for selective coronary angiography and EMB.

Caforio et al. Eur Heart J 2013; 34:2636-48

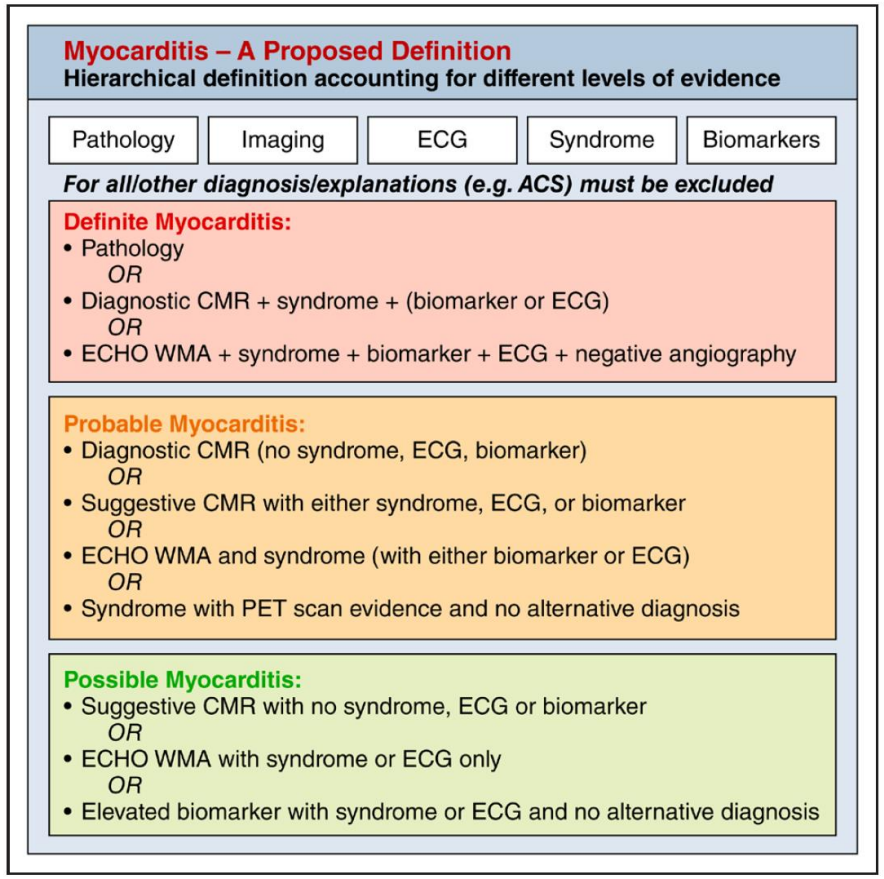


Figure 3. A proposed definition of myocarditis to be applied in clinical trials..
ACS indicates acute coronary syndrome; CMR, cardiac magnetic resonance imaging; PET, positron emission tomography; and WMA, wall motion abnormality.

Bonaca et al. 2019;140:80–91.

Myocarditis: definition

- Definition (Circulation, 1995 WHO/ISFC classification; Eur Heart J, 1999; AHA statements 2006, 2016; ESC 2008, Eur Heart J 2013, ANMCO/SIC 2020, HFA-ESC/HFSA/JHFS 2021, ESC chronic HF guidelines 2021)
  - Myocarditis is an inflammatory disease of the myocardium and is diagnosed by established histological, immunological and immunohistochemical criteria
- Histological features (Dallas criteria on EMB)
- Myocarditis forms
  - idiopathic, Infectious (mainly viral) and/or autoimmune

Etiological forms of biopsy-proven myocarditis

https://doi.org/10.1038/s41569-020-00435-x

NATURE REVIEWS | CARDIOLOGY

Viral myocarditis

Histological evidence for myocarditis associated with positive viral polymerase chain reaction (PCR) (*Table 1*).

Autoimmune myocarditis

Histological myocarditis with negative viral PCR, with or without serum cardiac autoantibodies (aabs) (*Table 2*).

N.B. There are autoimmune diseases (e.g. Hashimoto's thyroiditis) where aabs are mainly biomarkers, autoantibody-mediated forms (e.g. Graves' disease), in which aabs are pathogenic, and cell-mediated autoimmune diseases, which are negative for aabs. In all cases, autoimmune diseases are negative for infectious agents.

Viral and immune myocarditis

Histological myocarditis with positive viral PCR and positive cardiac aabs (*Table 2*).

N.B. A follow-up EMB may document persistent viral myocarditis, histological and virological resolution, or persistent virus-negative myocarditis, with or without serum cardiac aabs, e.g. post-infectious autoimmune disease.

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- Antiviral therapy first, if available, to achieve viral clearance (off –label)
- Immunosuppression if clinically indicated (LV dysfunction, arrhythmia), viral clearance and persistent myocarditis at follow-up biopsy

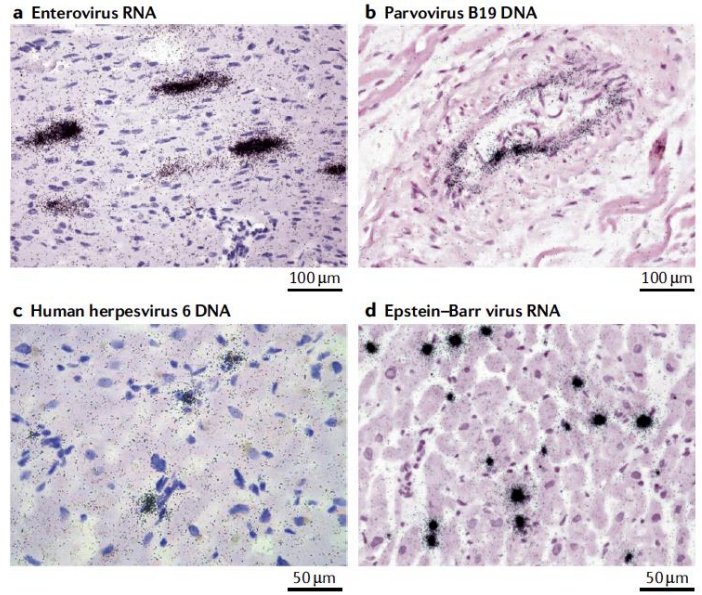

Fig. 4 | **Visualization of viral nucleic acids in acute myocarditis.** Viral nucleic acids in heart tissue samples from patients with acute myocarditis can be detected with radioactive in situ hybridization (black spots). Cell nuclei (purple) and cell cytoplasm and extracellular matrix (pink) are visualized with haematoxylin and eosin staining. Enteroviruses (panel **a**) infect and lyse cardiomyocytes, parvovirus B19 (panel **b**) infects endothelial cells, and human herpesviruses (panel **c**) and Epstein–Barr viruses (panel **d**) replicate in immune cells. Panels **a** and **b** ×400, panels **c** and **d** ×630.

Calabrese et al.,Diagn Mol Pathol 2002; 11(4):212-21

Etiological forms of biopsy-proven myocarditis

Viral myocarditis

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Viral and immune myocarditis

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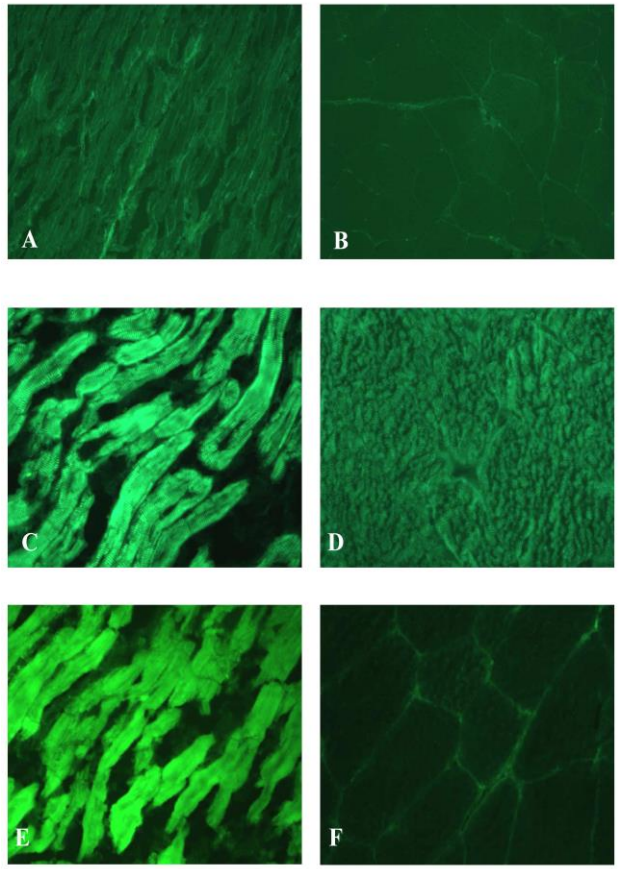
Caforio et al. Eur Heart J 2013; 34:2636-48

Autoimmune biopsy-proven myocarditis (60-81%): AHA pos, virus PCR neg

Efficacy of immunosuppression/ immunomodulation in patients with proven non infectious immune-mediated/autoimmune disease

Why treating?
-To stop the immunopathological response that is causing myocardial damage

-to prevent the deterioration of myocardial function, fibrosis and life-threatening arrhythmia



Eur Heart J 2007; 28:1326-33

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

Leslie T. Cooper, MD, FAHA, FACC; Kenneth L. Baughman, MD, FAHA, FACC; Arthur M. Feldman, MD, PhD, FAHA, FACC; Andrea Frustaci, MD; Mariell Jessup, MD, FAHA, FACC; Uwe Kuhl, MD; Glenn N. Levine, MD, FAHA, FACC; Jagat Narula, MD, PhD, FAHA; Randall C. Starling, MD, MPH; Jeffrey Towbin, MD, FAHA, FACC; Renu Virmani, MD, FACC

Table 1. Risks Associated With Endomyocardial Biopsy in 546 Procedures

Overall 33 complications (6%)
Sheath insertion 15 (2.7%)
12 (2.0%) arterial puncture during local anesthesia
2 (0.4%) vasovagal reaction
1 (0.2%) prolonged venous oozing after sheath removal
Biopsy procedure 18 (3.3%)
6 (1.1%) arrhythmia
5 (1.0%) conduction abnormalities
4 (0.7%) possible perforation (pain)
3 (0.5%) definite perforation (pericardial fluid)
2 of 3 patients with definite perforation died

Data derived from Deckers et al (20).

Jacc 2007

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

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Endomyocardial biopsy

Endomyocardial biopsy confirms the diagnosis of myocarditis and identifies the underlying aetiology and the type of inflammation (e.g. giant cell, eosinophilic myocarditis, sarcoidosis) which imply different treatments and prognosis (*Figure 1*).[1–3,11,14–16] Importantly, EMB is also the basis for safe (infection negative) immunosuppression and antiviral treatment. If EMB is performed by experienced teams, its complication rate is low (0–0.8).[9,18,139,148]

The recent scientific statement on EMB gave highest levels of recommendations in the life-threatening clinical presentations.[120] However, the diagnostic, prognostic, and therapeutic value of EMB was based on the Dallas histopathologic criteria and did not include immunohistochemistry and viral genome analysis (*Figure 1*).

Eur Heart J 2013; 34:2636-48

3) Is EMB dangerous for the patient? NO

Table 1 Major and minor complications of endomyocardial biopsy

Major complications	Minor complications
Death (0–0.07%)	Chest pain (transient) (0–1.8%)
Cardiac perforation/haemopericardium/tamponade (0–6.9%)	Deep vein thrombosis (0.23–3.8%)
Pneumothorax/air embolism (0–0.8%)	Puncture site haematoma/nerve palsy (0–0.64%)
Thromboembolism (0–0.32%)	Hypotension/vaso-vagal syncope (0–4.3%)
Valvular trauma (0.02–1.1%)	Arterial trauma/vascular damage/fistulae (0.32–2.8%)
Severe arrhythmias/atrioventricular block (0–11%)	

Detailed description of complications according to the centre volume, access site, type of endomyocardial biopsy procedure and patient characteristics as well as references are provided in online supplementary *Table S1*.

3) Is EMB dangerous for the patient? NO

Circulation: Heart Failure

ORIGINAL ARTICLE

Safety of Endomyocardial Biopsy in New-Onset Acute Heart Failure Requiring Veno-Arterial Extracorporeal Membrane Oxygenation

Robert M.A. van der Boon, MD, PhD; Wijnand K. den Dekker, MD, PhD; Christiaan L. Meuwese, MD, PhD; Roberto Lorusso, MD, PhD; Jan H. von der Thüsen, MD, PhD; Alina C. Constantinescu, MD, PhD; Olivier C. Manintveld, MD, PhD; Thijs S.R. Delnoij, MD, PhD; Joris. J. van der Heijden, MD; Nicolas M.D.A. van Mieghem, MD, PhD; Corstiaan A. den Uil, MD, PhD

BACKGROUND: Endomyocardial biopsy (EMB) has an important role in determining the pathogenesis of new-onset acute heart failure (new-AHF) when noninvasive testing is impossible. However, data on safety and histopathologic outcomes in patients requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is lacking.

METHODS: A retrospective, multicenter cohort of patients undergoing EMB while requiring VA-ECMO for new-AHF between 1990 and 2020 was compared with a cohort of nontransplant related biopsies not requiring VA-ECMO. Primary end point of the study was to determine the safety of EMB. Additionally, we describe the underlying pathogenesis causing new-AHF based on histopathologic examination of the samples obtained.

RESULTS: A total of 23 patients underwent EMB while requiring VA-ECMO (10.0%), 125 (54.3%) during an unplanned admission, and 82 (35.7%) in elective setting. Major complications occurred in 8.3% of all procedures with a significantly higher rate in patients requiring VA-ECMO (26.1% versus 8.0% versus 3.7%, P=0.003) predominately due to the occurrence of sustained ventricular tachycardia or need of resuscitation (13.0% versus 3.2% versus 1.2%, P=0.02). EMB led to a histopathologic diagnosis in 78.3% of the patients requiring VA-ECMO which consisted primarily of patients with myocarditis (73.9%).

CONCLUSIONS: EMB in patients requiring VA-ECMO can be performed albeit with a substantial risk of major complications. The risk of the procedure was offset by a histopathologic diagnosis in 78.3% of the patients, which for the majority consisted of patients with myocarditis. The important therapeutic and prognostic implications of establishing an underlying pathogenesis causing new-AHF in this population warrant further refinement to improve procedural safety.

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Short communication

Safety and usefulness of left ventricular endomyocardial biopsy in new-onset acute heart failure requiring mechanical support by an Impella® device

Carsten Tschöpe [a,b,c,d,*,1], Vivian Nelki [b,1], Tobias Daniel Trippel [b,c,1], Karin Klingel [e,1], Dawud Abawi [b,c,1,2], Alessio Alogna [b,c,d,1,2]

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ARTICLE INFO

Keywords:
Acute heart failure
Mechanical circulatory support
Endomyocardial biopsy
Myocarditis
Impella

ABSTRACT

Background: In patients with de novo acute heart failure (AHF) requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO), endomyocardial biopsy (EMB) has been recently shown to be feasible and a helpful method to clarify differential diagnoses, including acute myocarditis. This study aimed to evaluate the feasibility and safety of EMB in patients with a left ventricular (LV) implanted Impella® device.
Methods and results: This retrospective, single-center study involves 22 cardiogenic shock patients [SCAI shock stage: C (91%)] requiring mechanical circulatory support (MCS) either by Impella® axial pumps [20 patients (91%)] alone or in combination with VA-ECMO [2 patients (9%)] between December 2017 and January 2022. Coronary artery disease (CAD) or severe valvular heart disease were excluded. The study's primary endpoint was to verify the safety of EMB during MCS. Furthermore, histopathological analysis of the EMB samples was described. 30 LV-EMB procedures were performed. No major complications were reported (death, sustained ventricular tachycardia, need for cardiopulmonary resuscitation, cardiac tamponade, stroke, major bleeding). In 14 patients (64%), EMB-derived histology/immunohistology led to the definitive diagnosis of acute myocarditis.
Conclusions: EMB can be safely performed in patients suffering from cardiogenic shock requiring an Impella®-based MCS without the risk of major complications. In about 50% of the patients, relevant inflammatory heart disease could be detected, which required a change in treatment decisions.

3) Is EMB dangerous for the patient? NO

Structured Graphical Abstract

Key Question

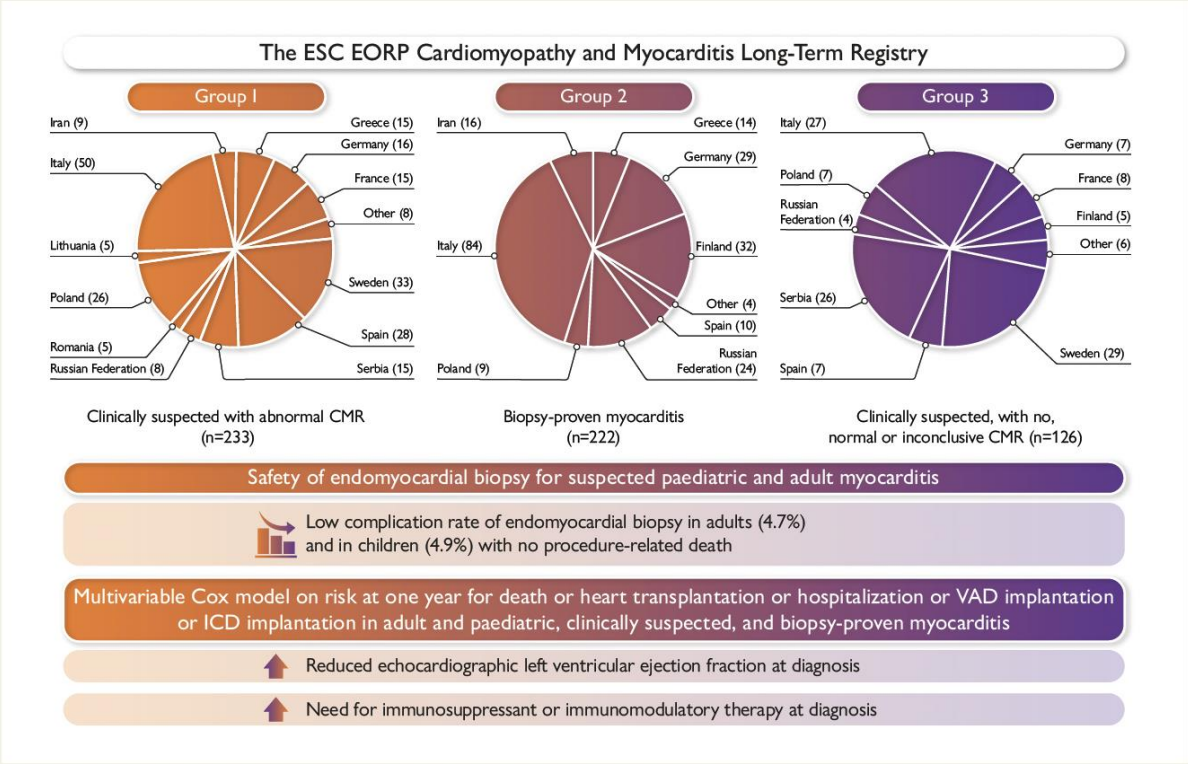
What is the safety and value of endomyocardial biopsy in paediatric and adult patients with suspected myocarditis? What are the predictors of worse outcome in patients with proven myocarditis?

Key Finding

Endomyocardial biopsy was safe in adults and children. Myocarditis on cardiac magnetic resonance was found in 31.3% of children and in 57.9% of adults with biopsy-proven myocarditis. Lower left ventricular ejection fraction and need for immunosuppression at diagnosis were independent predictors of unfavourable outcomes at one-year follow-up.

Take Home Message

In clinically suspected myocarditis endomyocardial biopsy is safe while cardiac magnetic resonance using Lake Louise criteria is less sensitive than endomyocardial biopsy. Lower left ventricular ejection fraction and need for immunosuppression at diagnosis are independent predictors of unfavourable outcomes at follow-up.



The top panel shows the distribution of patients of Group 1 (left piechart), Group 2 (middle piechart), and Group 3 (right piechart) recruited in different ESC countries. At the bottom, the main study results are summarized. CMR, cardiac magnetic resonance; ESC EORP, European Society of Cardiology EURObservational Research Programme; ICD, implantable cardioverter defibrillator; VAD, ventricular assist device.

ESC European Society of Cardiology
European Heart Journal (2024) **00**, 1–22
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Endomyocardial biopsy: safety and prognostic utility in paediatric and adult myocarditis in the European Society of Cardiology EURObservational Research Programme Cardiomyopathy and Myocarditis Long-Term Registry

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3) Is EMB dangerous for the patient? NO

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Table 3 Indications for endomyocardial biopsy

Clinical presentation	Endomyocardial biopsy finding
• Suspected fulminant myocarditis or acute myocarditis with acute HF, LV dysfunction and/or rhythm disorders. • Suspected myocarditis in haemodynamically stable patients.	Myocarditis type: • Lymphocytic myocarditis • Eosinophilic myocarditis • Giant cell myocarditis • Granulomatous myocarditis
Dilated cardiomyopathy with recent onset HF, moderate-to-severe LV dysfunction, refractory to standard treatment (following exclusion of specific aetiologies).	Myocyte abnormalities, focal or diffuse fibrosis and inflammatory infiltrates (inflammatory cardiomyopathy).
Suspected ICI-mediated cardiotoxicity: acute HF with/without haemodynamic instability early after drug initiation (~ first 4 cycles)	ICI-mediated myocarditis
High-degree atrioventricular block, syncope and/or unexplained ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia, frequent multifocal premature ventricular complexes), refractory to treatment, without obvious cardiac disease or with minimal structural abnormalities.	• Myocarditis • Arrhythmogenic right ventricular cardiomyopathy • Cardiac sarcoidosis
Autoimmune disorders with progressive HF unresponsive to treatment with/without sustained ventricular arrhythmias and/or conduction abnormalities.	• Autoimmune myocarditis • Viral myocarditis • Vasculitis/vasculopathy
MINOCA/takotsubo syndrome with progressive LV dysfunction and HF with/without ventricular arrhythmias or conduction abnormalities.	Differential diagnosis of myocarditis

3) Is EMB dangerous for the patient? NO

ACUTE MYOCARDITIS: DIAGNOSTIC AND MANAGEMENT PROTOCOL

History, Examination, ECG, Echo, Laboratory tests: Troponin, CRP, ESR, Blood Cell Count, BNP, CMR; if Available, Serum Cardiac Autoantibodies

Clinically Suspected Myocarditis

Consider coronary angiography and EMB

No coronary disease

Haemodynamically stable
LV function Preserved
No eosinophilia
No significant rhythm or conduction disturbances
Not associated with systemic immune disease#

Haemodynamically unstable, Decreased LV Function, Cardiogenic Shock

Pharmacological & if needed Mechanical support (ECMO, LVAD/Bi-VAD, Bridge to heart transplant or to recovery)

Lymphocytic

Giant cell, Eosinophilic, Sarcoidosis (acute decompensation)

General Supportive Therapy

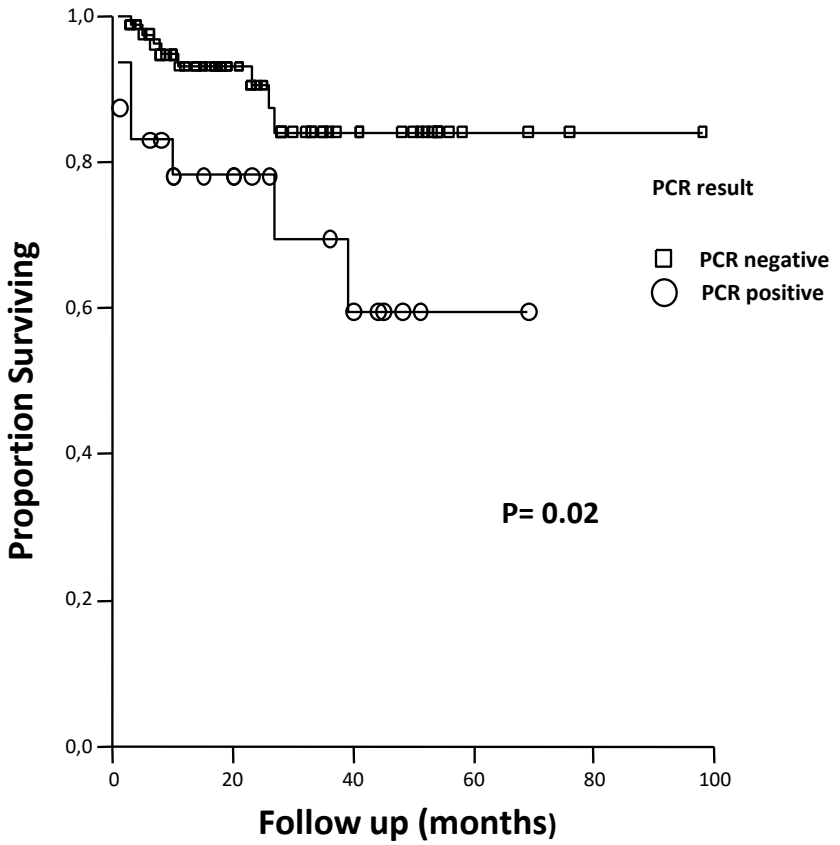
General Supportive Therapy Immunosuppression if unresponsive & virus negative EMB

Immunosuppression if infection negative EMB

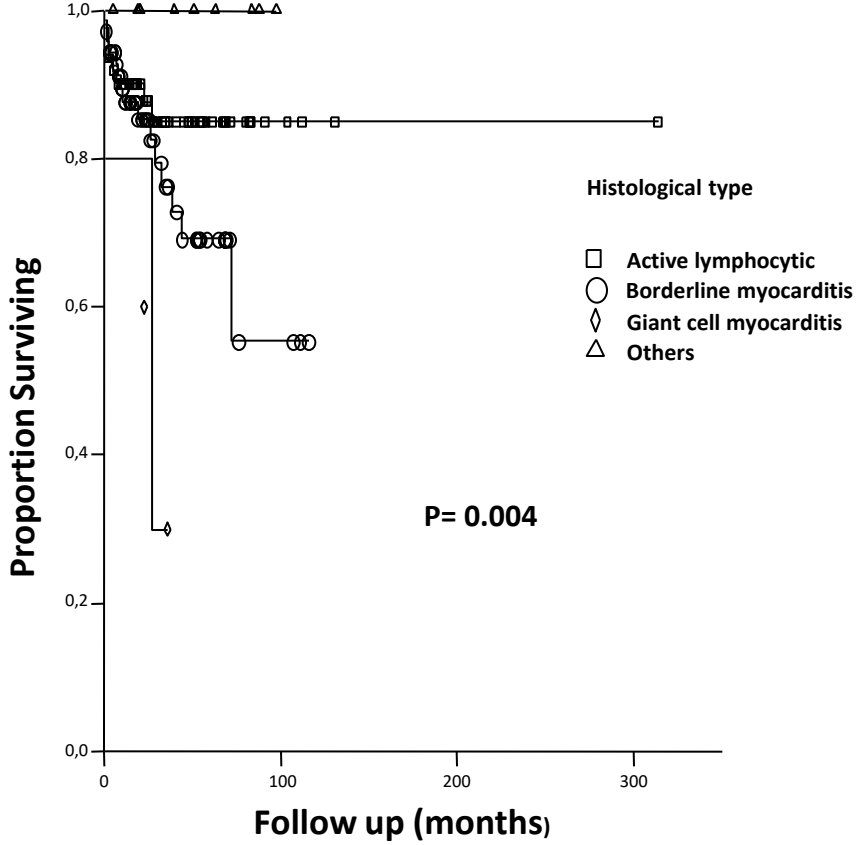
4) Is EMB needed for all patients? NO

If myocarditis is associated with systemic immune disease exacerbation, therapy overlaps with treatment of the background disease (usually immunosuppression).

AM: Actuarial survival and PCR result



AM: Actuarial survival and histology type



4) Is myocarditis etiology prognostically relevant? YES

Caforio et al, Eur Heart J 2007; 28:1326-33

Predictors of relapse, death or heart transplantation in myocarditis before the introduction of immunosuppression: negative prognostic impact of female gender, fulminant onset, lower ejection fraction and serum autoantibodies

Anna Baritussio[1], Alessandro Schiavo[1], Cristina Basso[2], Andrea Silvio Giordani[1], Chun-yan Cheng[1], Elena Pontara[1], Maria Grazia Cattini[1], Elisa Bison[1], Nicoletta Gallo[3], Monica De Gaspari[2], Elisa Carturan[2], Gaetano Thiene[2], Giuseppe Tarantini[1], Mario Plebani[3], Stefania Rizzo[2], Dario Gregori[4], Sabino Iliceto[1], Renzo Marcolongo[5], and Alida Linda Patrizia Caforio[1]*

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ESC European Society of Cardiology

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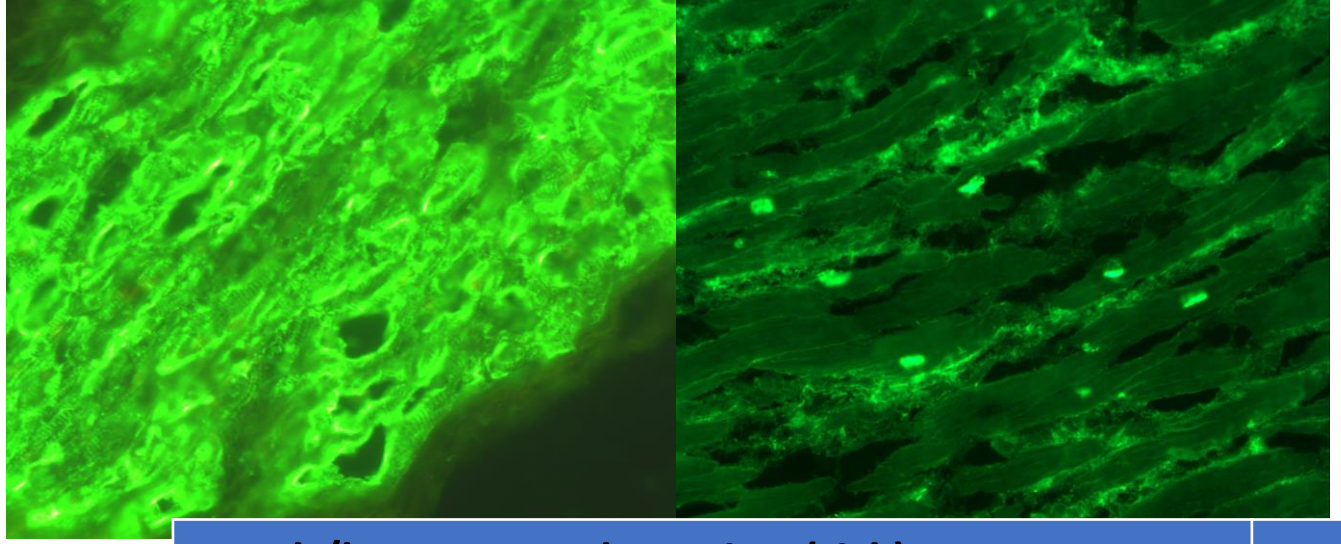
4) Is myocarditis etiology prognostically relevant?
YES

Aims Outcome predictors in myocarditis are not well defined; we aimed at identifying predictors of death, heart transplantation (HTx) and relapse before the introduction of immunosuppression.

Methods and results From 1992 to 2012, 466 consecutive patients (68% male, mean age 37 ± 17 years, single centre recruitment, median follow-up 50 months) were included, of whom 216 had clinically suspected and 250 biopsy-proven myocarditis. Serum anti-heart (AHA) and anti-intercalated disk (AIDA) autoantibodies were measured by indirect immunofluorescence. Univariable and multivariable analyses of clinical and diagnostic features at diagnosis were performed. Survival free from death or HTx at 10 years was 83% in the whole study population and was lower in biopsy-proven versus clinically suspected myocarditis (76% vs. 94%, $p < 0.001$). Female gender (hazard ratio [HR] 2.7, 95% confidence interval [CI] 1.1–6.5), fulminant presentation (HR 13.77, 95% CI 9.7–261.73), high-titre organ-specific AHA (HR 4.2, 95% CI 1.2–14.7) and anti-nuclear antibodies (ANA) (HR 5.2, 95% CI 2.1–12.8) were independent predictors of death or HTx; higher echocardiographic left ventricular ejection fraction (LVEF) at diagnosis was protective, with a 0.93-fold risk reduction for each 1% LVEF increase (95% CI 0.89–0.96). History of myocarditis at diagnosis (HR 8.5, 95% CI 3.5–20.7) was an independent predictor of myocarditis relapse at follow-up; older age was protective (HR 0.95, 95% CI 0.91–0.99). Predictors of death, HTx and relapse did not differ in biopsy-proven versus clinically suspected myocarditis.



4) Is myocarditis etiology prognostically relevant? YES

Left: Organ-specific antiheart autoantibody (AHA) strong positive (high titer) serum on human heart (x400)

Right: AHA negative, antinuclear autoantibody (ANA) positive serum on human heart: negative (x400)

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Death/heart transplantation (risk)	Hazard ratio (HR); 95% confidence intervals (CI)
Female gender ⬆	HR 2.69; CI 1.1-6.4
Fulminant presentation ⬆	HR 13.77; CI 0.72-261.73
High-titre organ-specific AHA ⬆	HR 4.1; CI 1.16-14.7
ANA positive ⬆	HR 5.1; CI 2.0-12.7
Higher echocardiographic LVEF ⬇	For each % increase, risk reduced by 0.93 times (CI 0.89- 0.96)

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Take-home message: Female gender, fulminant onset, lower LVEF at presentation and high-titre organ-specific AHA and ANA were independent predictors of death and heart transplantation, suggesting that autoimmune features predict worse prognosis.

Table 2 Sample processing, analysis and characteristic findings according to clinical presentation

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 or borderline). **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/mm^2 including up to 4 monocytes/mm^2 with the presence of CD3+ T-lymphocytes ≥7 cells/mm^2

Caforio A et al., Eur Heart J 2013;34:2636-2648

- ***Center expertise***
- ***Multidisciplinary teams***
- ***Hub and spoke myocarditis network***

5) Do we have a common aetiology and similar treatment? NO

6) Do we have non-invasive alternative tools to identify aetiology? NO

European Journal of Heart Failure (2021) doi:10.1002/ejhf.2190

Usefulness of Immunosuppression for Giant Cell Myocarditis

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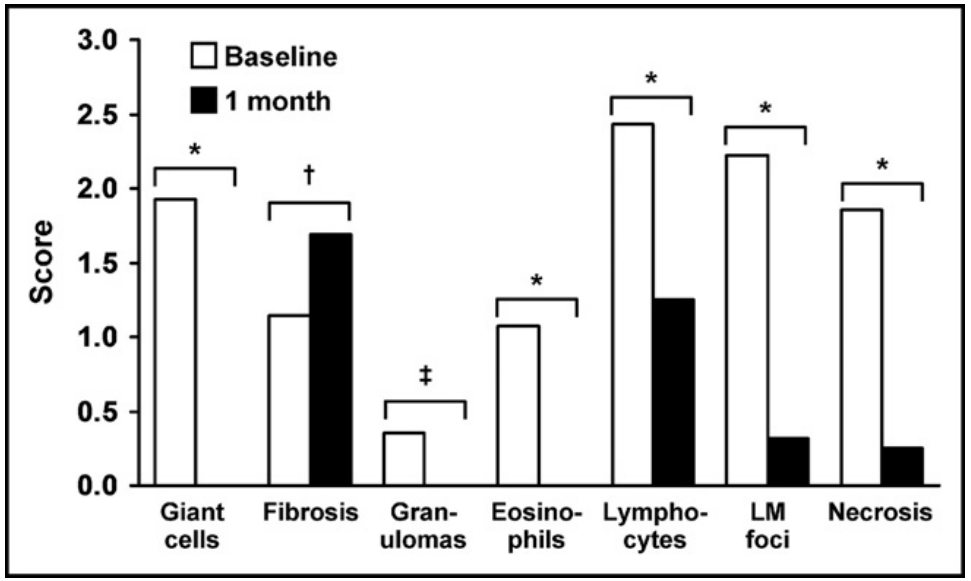


Figure 1. Average histologic scores by blinded analysis at baseline and day 30 in subjects enrolled in the GCM Treatment Trial. *p <0.001, †p = 0.43, ‡p = 0.01. LM = lymphocytic myocarditis.

Table 2
Serum antibody titers in acute giant cell myocarditis

Subject ID	Antihuman Cardiac Myosin	Anti-β1 Adrenergic Receptor	Anti-β2 Adrenergic Receptor
1	1:100	1:400	1:400
2	1:100	1:3,200	1:1,600
3	1:200	1:6,400	1:3,200
4	1:1,600	1:1,600	1:1,600
5	<1:100	1:3,200	1:3,200
8	1:800	1:6,400	1:3,200
10	1:6,400	1:25,600	1:12,800
11	1:100	1:3,200	1:3,200
Positive control	1:6,400	1:25,600	1:25,600
Negative control	1:100	1:800	1:800

5) Do we have a common aetiology and similar treatment? NO

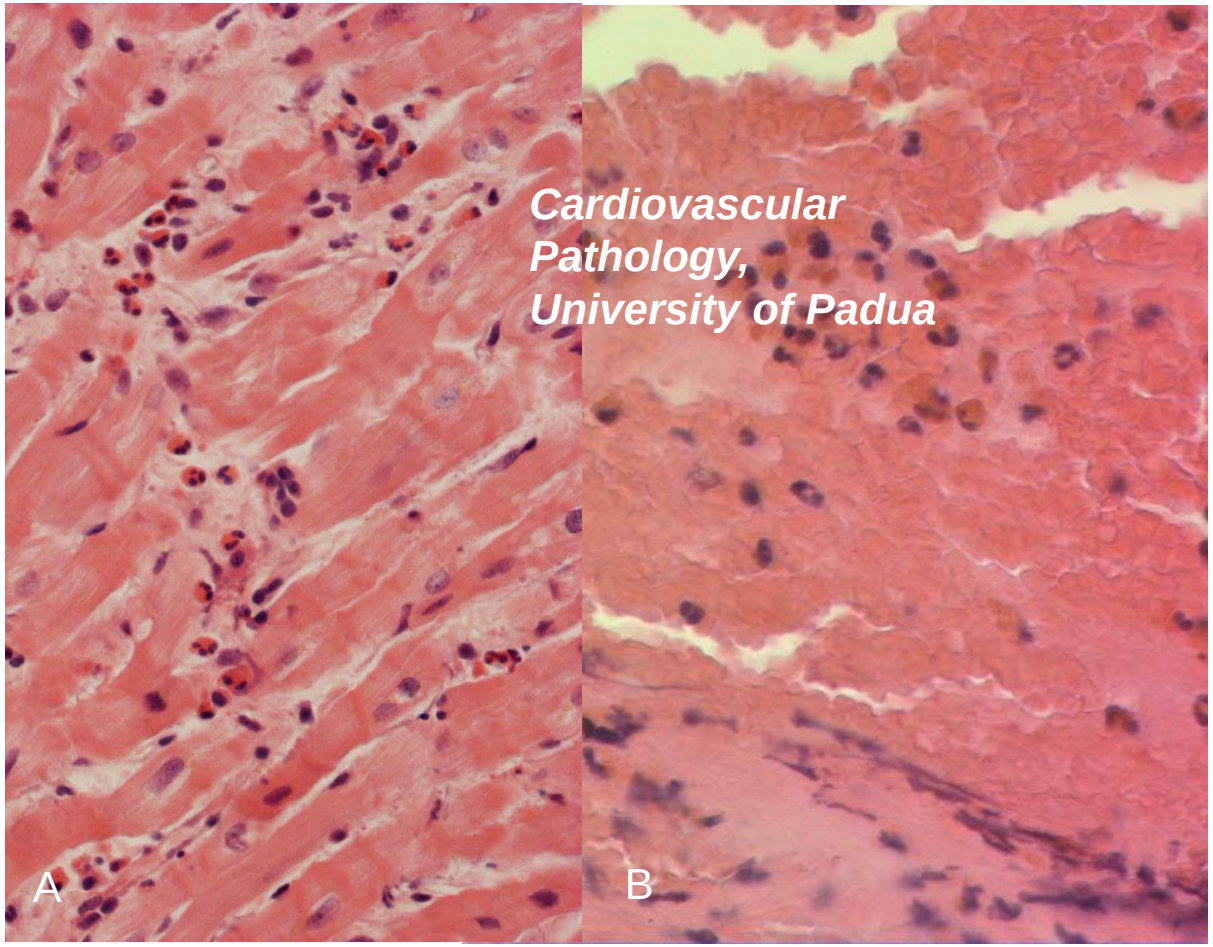
Etiology and immumodulation/immunosuppression (IS):

- Triple IS (steroid+CsA or Tacrolimus+azathioprine or MMF)
- Biological agents for refractory/relapsing disease
- Life-long

EMB: eosinophilic myocarditis

Etiology and immunosuppression (IS):

- Exclude
  - infectious(parasitic/fungal)
  - hematological/neoplastic
- Treat
  - Hypersensitivity/toxic
  - SIDs (e.g. EGPA)
- How
  - Stop offending drug (e.g. ICI, clozapine)
  - acutely: i.v Steroids
  - Maintainance: steroid taper to lower effective dose +IS sparing drugs



5) Do we have a common aetiology and similar treatment? NO

Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study

Andrea Frustaci[1,2*], Matteo A. Russo[3,4], and Cristina Chimenti[1,2,4]

European Heart Journal (2009) 30, 1995–2002
doi:10.1093/eurheartj/ehp249

EMB: lymphocytic myocarditis

Etiology and immumodulation/IS:

- double IS (steroid+azathioprine or MMF)
- Duration: at least 6 months ; longer?

Aims To evaluate the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy.

Methods and results This randomized, double-blind, placebo-controlled study included 85 patients with myocarditis and chronic (>6 months) heart failure unresponsive to conventional therapy, with no evidence of myocardial viral genomes. Patients received either prednisone 1 mg kg^{-1} day^{-1} for 4 weeks followed by 0.33 mg kg^{-1} day^{-1} for 5 months and azathioprine 2 mg kg^{-1} day^{-1} for 6 months (43 patients, Group 1) or placebo (42 patients, Group 2) in addition to conventional therapy for heart failure. Primary outcome was the 6 month improvement in left-ventricular function. Group 1 showed a significant improvement of left-ventricular ejection fraction and a significant decrease in left-ventricular dimensions and volumes compared with baseline. None of Group 2 patients showed improvement of ejection fraction, that significantly worsened compared with baseline. No major adverse reaction was registered as a result of immunosuppression.

Conclusion These data confirm the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy. Lack of response in 12% of cases suggests the presence of not screened viruses or mechanisms of damage and inflammation not susceptible to immunosuppression.

5) Do we have a common aetiology and similar treatment? NO

Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy: 20-year follow-up of the TIMIC trial

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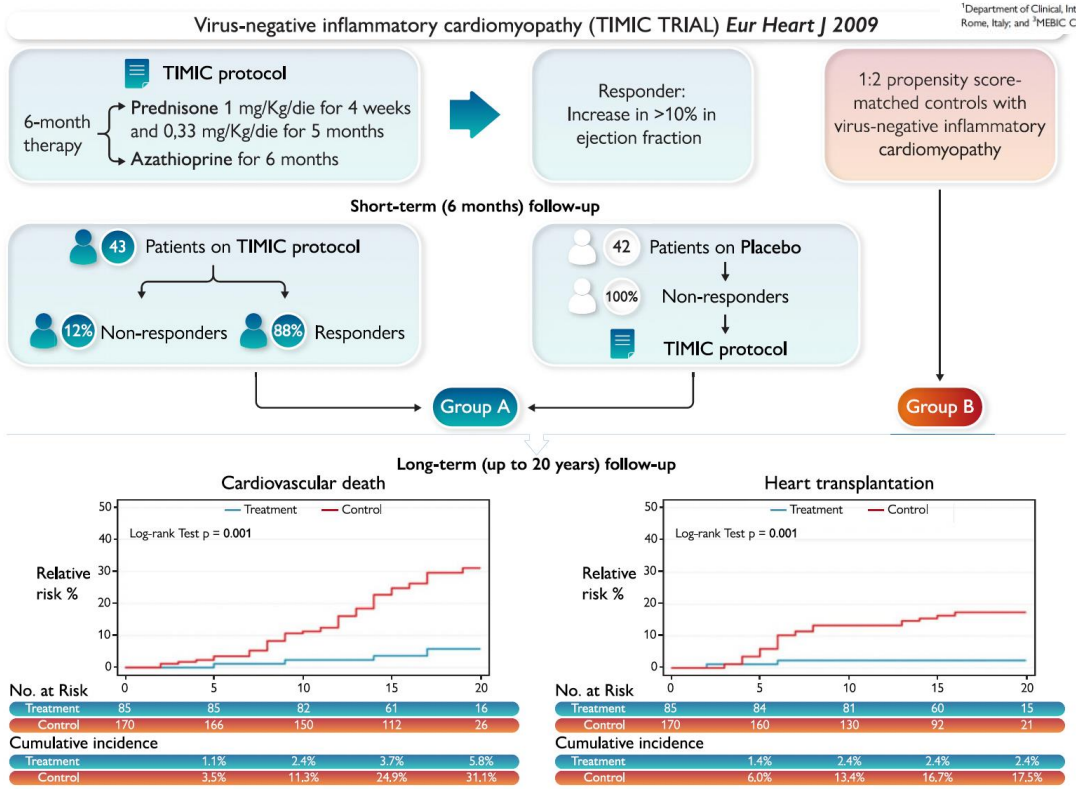

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https://doi.org/10.1093/eurheartj/ehac348

Box plots of the distribution of left ventricular ejection fraction and left ventricular end-diastolic volume at baseline, short-term (6 months), and long-term follow-up in patients on TIMIC protocol (blue) and control patients (green) are presented in the left upper panel. The composite endpoint of cardiovascular death and heart transplantation (primary outcome) during follow-up in patients on TIMIC protocol (blue line) and control patients (red line) is shown in the left lower panel. The incidence of cardiovascular death (right upper panel) and heart transplantation (right lower panel) during follow-up in patients on TIMIC protocol (blue line) and controls (red line) is also presented.

5) Do we have a common aetiology and similar treatment? NO

Long-term efficacy and safety of tailored immunosuppressive therapy in immune-mediated biopsy-proven myocarditis: a single center propensity weighted study

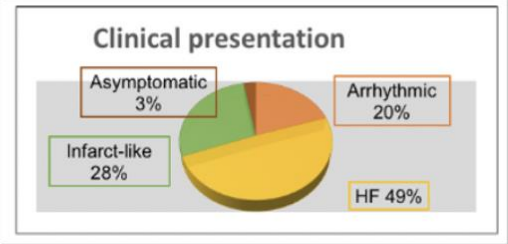
Caforio A.L.P.[1], Giordani A.S.[1], Baritussio A.[1], Marcolongo D.[1], Vicenzetto C.[1], Tarantini G.[1], Napodano M.[1], Toscano G.[2], Gregori D.[3], Brigiari G.[3], Bartolotta P.[3], De Gaspari M.[4], Basso C.[4], Iliceto S.[1], Marcolongo R.[1]

[1] Cardiology [2] Cardiac Surgery [3] Cardiovascular Pathology, Department of Cardiac Thoracic Vascular Sciences and Public Health, University of Padova, Padova, Italy [4] Statistics, Department of Statistical Sciences, University of Padova, Padova, Italy

358 BP myocarditis patients
Age 40 years (27-52)
64% ♂

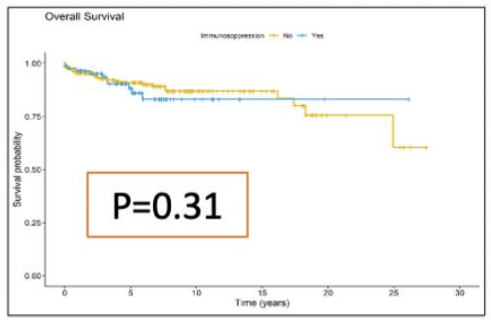
→ 267 Non-IT

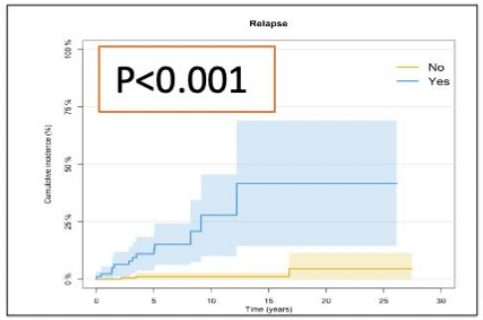
→ 91 IT

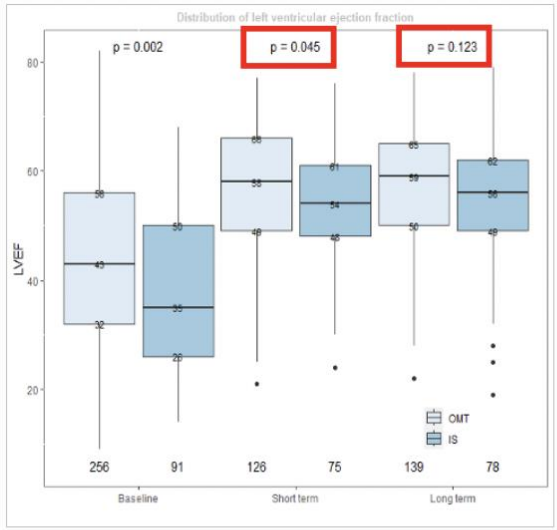


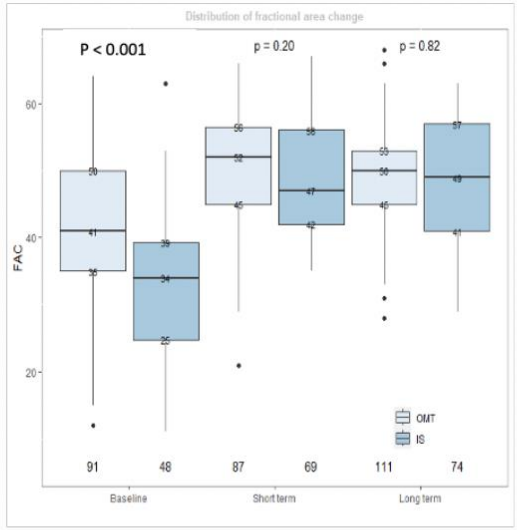
IT: long standing and tailored
- **Safety** check list
- **1st line**: 61% PDN+AZA
- **2nd line**: 62% PDN+MMF

Propensity score weighting → Age, gender, LVEF, NYHA, histological type









Conclusions: For the first time, the efficacy and safety of **prolonged tailored IS** in BP **lymphocytic and non-lymphocytic** autoimmune myocarditis, **with or without HF** and/or **biventricular dysfunction**, has been proved.
IS patients, despite having lower biventricular function and a higher risk profile at baseline as well as a higher frequency of relapses, at long-term follow up showed normalized biventricular function and a similar survival compared to their propensity-score weighted controls.

7) Do biopsy data change clinical management? YES

Caforio et al, Eur J Heart Fail 2024 (in press) DOI:10.1002/ejhf.3220

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

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Table 32 Endomyocardial biopsy in patients with suspected myocarditis

Indication (see also Section 4.3). Progressive or persistent severe cardiac dysfunction and/or life-threatening ventricular arrhythmias and/or Mobitz type 2 second-degree or higher AV block with lack of short-term (<1-2 weeks) expected response to usual medical treatment. The aim is to identify aetiology and to indicate specific treatment (e.g. giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, systemic inflammatory disorders).[97,98,917,918,958]
Number and sites of the samples A minimum of 5 but possibly at least 7 samples, 3 for pathology, 2 for infections (DNA, PCR) and 2 for RNA viruses/viral replication. Left and/or right ventricle. CMR or PET guided sampling may be considered.[919]
Aetiology Quantitative PCR viral genome analysis for common cardiotrophic viruses (parvovirus B19, HHV4, HHV6, enteroviruses, adenovirus and coxsackievirus) by rtPCR. Viral mRNA for active viral replication may be assessed although it has low sensitivity. On indication, search for CMV, HIV, *Borrelia, Coxiella burnetii* (Q-fever) and SARS-CoV-2.
Diagnosis of inflammation Immunohistochemistry with staining for anti-CD3-, CD4-, CD8- or CD45 antibodies for lymphocytes and anti-CD68 antibodies for macrophages and anti-HLA-DR antibodies.[907,917,918,959]
Therapeutic implications **Immunosuppressive therapy** may be indicated based on the results of EMB as in giant cell myocarditis or eosinophilic myocarditis and, possibly, also in sarcoidosis, vasculitis or selected patients with increased cardiac inflammation of unknown origin based upon multidisciplinary counselling.[98,917–919,954] **Antibiotics:** *Borrelia* (Lyme disease). **Antiviral therapy:** HIV, CMV, HHV6 pending on load and viral replication (mRNA).

- ***Aim of EMB in suspected myocarditis in HF presentation: to identify etiology and specific treatment , i.e. antiviral or immunosuppression based upon multidisciplinary counselling***

5) Do we have a common aetiology and similar treatment? NO

6) Do we have non-invasive alternative tools to identify aetiology? NO

7) Do biopsy data change clinical management? YES

Structured Graphical Abstract

Key Question

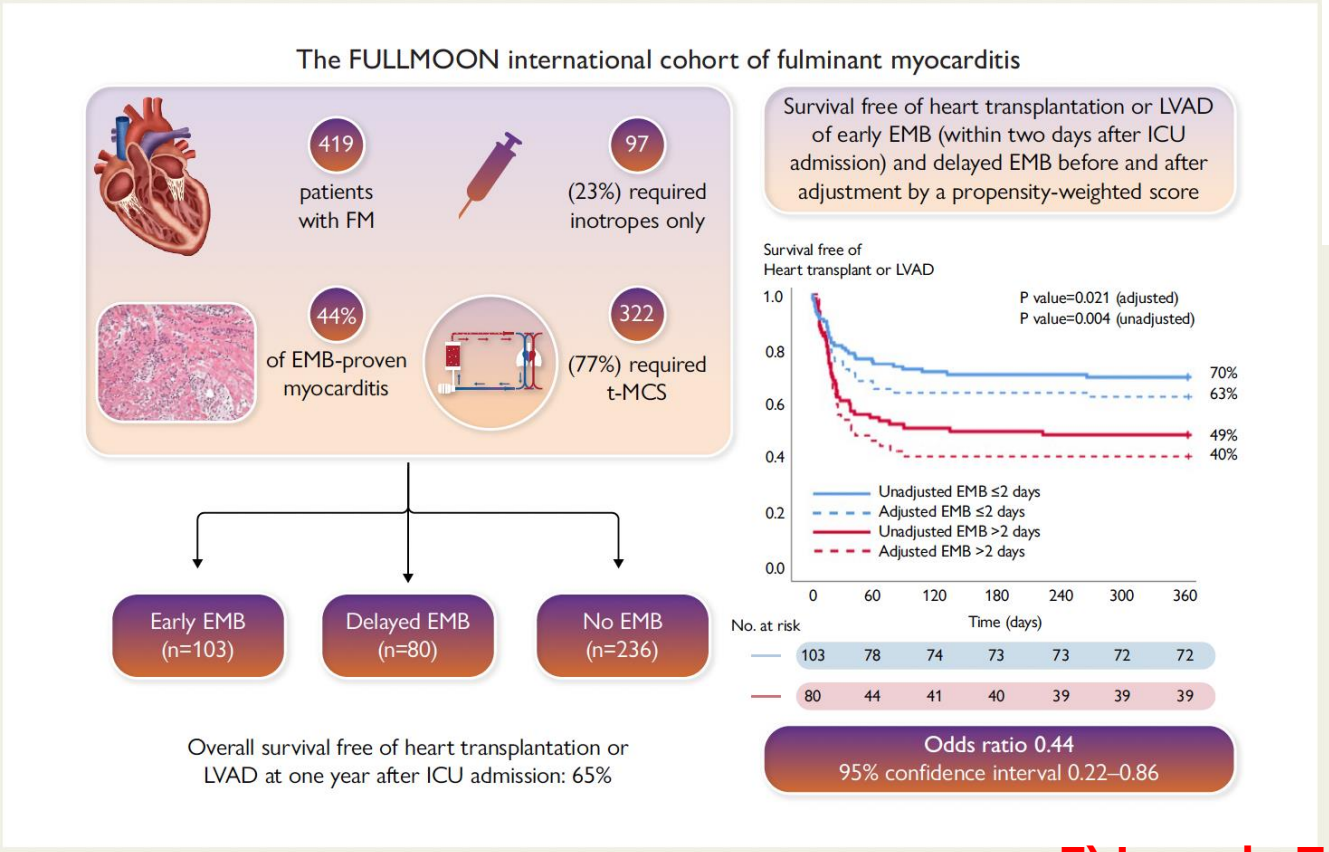
Does endomyocardial biopsy (EMB) at early stage (i.e. within two days after intensive care unit admission) improve outcomes in adult patients with fulminant myocarditis?

Key Finding

Among patients with EMB-proven fulminant myocarditis (n=183), early EMB was independently associated with a better survival free of heart transplantation or left ventricular assist device, when compared to delayed EMB (63% vs 40%, p=0.021).

Take Home Message

EMB should be used promptly in patients admitted to an intensive care unit for clinically suspected fulminant myocarditis.



The FULLMOON international cohort of clinically suspected and biopsy-proven fulminant myocarditis. EMB, endomyocardial biopsy; FM, fulminant myocarditis; ICU, intensive care unit; LVAD, left ventricular assist device; t-MCS, temporary mechanical circulatory support.

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https://doi.org/10.1093/eurheartj/ehad707
CLINICAL RESEARCH
Acute cardiovascular care

Fulminant myocarditis proven by early biopsy and outcomes

Florent Huang [1,2], Enrico Ammirati[3], Maharajah Ponnaiah [4], Santiago Montero [5], Victor Raimbault[2], Darryl Abrams[6], Guillaume Lebreton [7], Vincent Pellegrino[8], Joshua Ihle[8], Maurizio Bottiroli[3], Romain Persichini[9], Marisa Isabel Barrionuevo-Sánchez[10], Albert Ariza-Solé[10], Pauline Yeung Ng[11], Simon Wai Ching Sin[12], Raj Ayer[13], Hergen Buscher[13], Slimane Belaid[14], Clément Delmas[14], Rita Ferreira[15], Roberto Roncon-Albuquerque Jr[15], Teresa López-Sobrino[16], Jeroen J. H. Bunge[17], Christoph Fisser[18], Guillaume Franchineau[19], Jamie McCanny[20], Shinichiro Ohshimo[21], Alessandro Sionis [22], Francisco José Hernández-Pérez[23], Eduardo Barge-Caballero[24], Martin Balik[25], Henrique Muglia[26], Sunghoon Park[27], Dirk W. Donker[28,29], Beatriz Porral[30], Nadia Aïssaoui[31], Armand Mekontso Dessap[32], Virginia Burgos[33], Mathieu Lesouhaitier[34]*, Justin Fried[35], Jae-Seung Jung[36], Sandra Rosillo[37], Vincent Scherrer[38], Saad Nseir[39], Hadrien Winszewski[40], Pablo Jorge-Pérez[41], Antoine Kimmoun[42], Rodrigo Diaz[43], Alain Combes[2,44], and Matthieu Schmidt [2,44]; for the FULLMOON Study Group†

7) Is early EMB associated with better outcome? YES

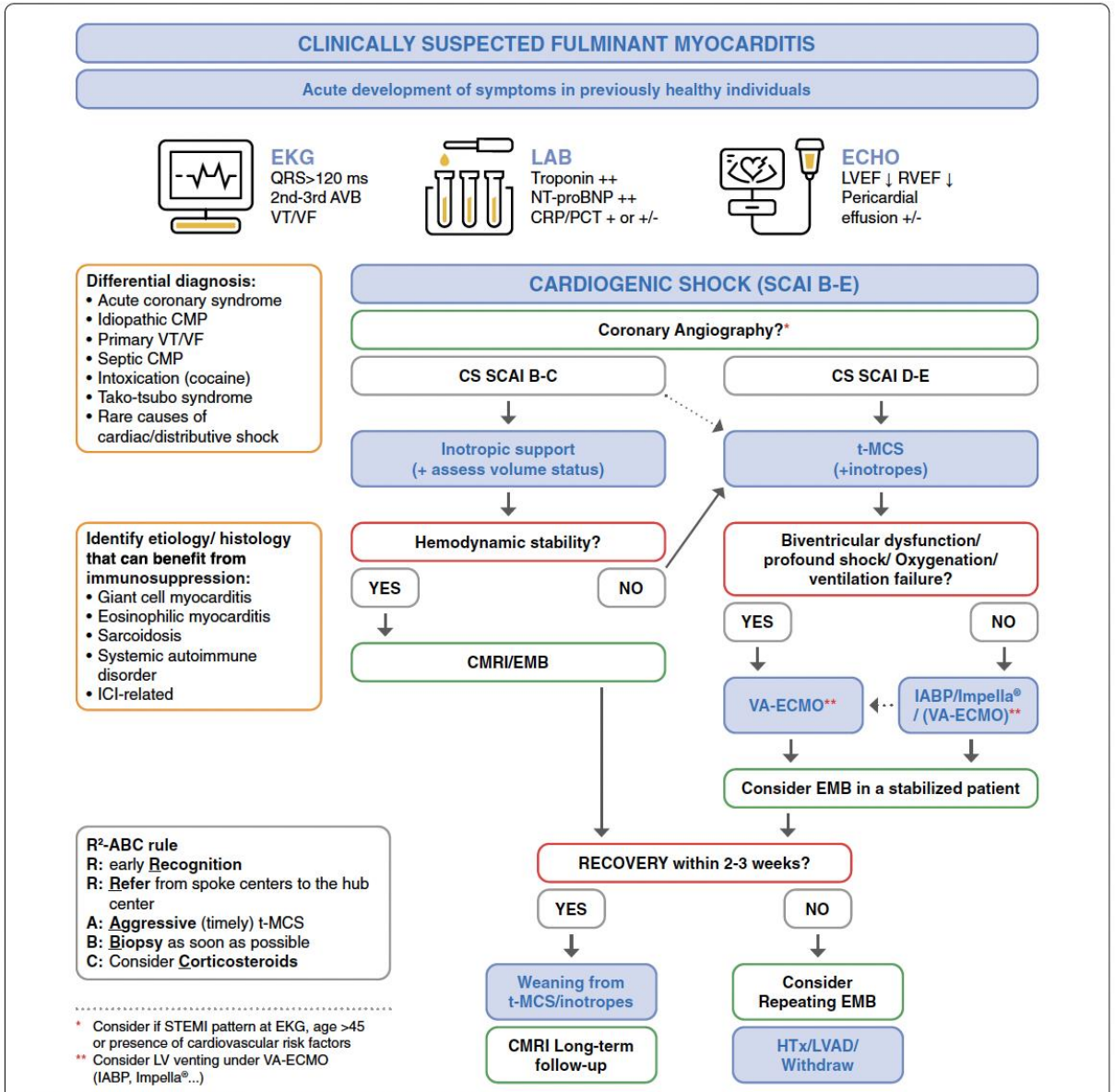

Fig. 1 Suggested management of patients with fulminant myocarditis.
AVB, atrioventricular block; CMP, cardiomyopathy; CRP, C-reactive protein; ECHO, echocardiography; HTx, heart transplantation; IABP, Intra-aortic balloon pump; ICI, immune checkpoint inhibitor; LAB, laboratory tests; LV, left ventricular; LVEF, left ventricular ejection fraction, LVAD, left ventricular assist device; PCT, procalcitonin; RVEF, right ventricular ejection fraction; SCAI, Society for Cardiovascular Angiography and Interventions clinical expert consensus statement on the classification of cardiogenic shock (A, at risk/B, beginning/C, classic/D, deteriorating/E, extremis); t-MCS, temporary-mechanical circulatory support; VA-ECMO, venoarterial extracorporeal membrane oxygenator; VF, ventricular fibrillation; VT, ventricular tachycardia

Myocarditis: a primer for intensivists

Enrico Ammirati[1,2*], Esther Vorovich[3] and Alain Combes[4,5]

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Take-home messages

In conclusion, to improve the outcome of patients with suspected FM, early recognition and referral to tertiary centers that provide timely t-MCS, have capabilities for EMB if indicated, and have dedicated expertise in myocarditis
is recommended. R2-
ABC (Recognition, Refer, Aggressive circulatory support, Biopsy as soon as possible, and consider Corticosteroids; Fig. 1).

7) Is early EMB associated with better outcome? YES

Early EMB for all myocarditis – PRO

- Do we have a typical clinical presentation? NO
- Can we reach the diagnosis of certainty and aetiology without EMB? NO
- Is EMB dangerous for the patient? NO
- Do we have a common aetiology and similar treatment? NO
- Do we have non-invasive alternative tools to identify aetiology? NO
- Is aetiology prognostically relevant? YES
- Do we have effective etiology-directed therapy ? YES
- Is an early biopsy associated with better outcome in biopsy-proven fulminant myocarditis? YES
- Do we need an early biopsy for all clinically suspected myocarditis? NO
- Do we need an early biopsy for high risk clinically suspected myocarditis? YES

  e.g. fulminant onset, reduced LVEF, hemodynamic instability, sustained arrhythmia

- *Take-home message: Time is muscle also in inflammatory-induced myocardial damage/necrosis*

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Biopsy-proven pediatric and adult giant cell and other rare immune-mediated forms of myocarditis: creation

of a prospective multicenter Italian registry and a biobank network to identify clinical, immune and genetic predictors of dismal prognosis, relapse and response to immunosuppressive therapy

Patients, relatives and care-givers: AMICAV (Associazione Malattie Infiammatorie Cardio-vascolari)

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European Reference Network
for rare or low prevalence complex diseases
Network Heart Diseases (ERN GUARD-HEART)

"There are three phAses to treatment: diagnosis, diagnosis and diagnosis."

William Osler. Principles and Practice of Medicine, 1892