Aspetti controversi e gestionali sulle miocarditi

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OSPEDALI RIUNITI DI TRIESTE

Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

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Although the cause of myocarditis often remains unknown, a large variety of infections, systemic diseases, drugs and toxins have been associated with this disease. In most cases, myocarditis is induced by cardiotropic viruses and often evolves silently without discernible prognostic impact. However, in some patients, the lack of complete viral clearance and/or the association of a heart-specific inflammation can cause persistent myocyte damage, ultimately leading to progressive myocardial dilation and dysfunction or life-threatening arrhythmias. Spontaneous improvement of left ventricular function is described for 40-50% of patients.

The diagnostic work-up and prognostic assessment of myocarditis should be multiparametric and all available resources should be employed, i.e. biomarkers of myocardial damage and ventricular dysfunction (troponin I, brain natriuretic peptide), advanced echocardiography, cardiac magnetic resonance and, in selected cases, endomyocardial biopsy (with histopathologic, immunohistochemical and virological analyses). These are the necessary prerequisites for an evidence-based and personalized management of myocarditis, which may require in some cases specific immunoactive treatments.

However, controversial issues regarding diagnosis (such as role and timing of cardiac magnetic resonance imaging, role of endomyocardial biopsy) and therapy of myocarditis still remain unsolved. The purpose of this review is to analyze these crucial features in order to provide useful instructions for clinical practice.

Key words. Cardiomyopathies; Endomyocardial biopsy; Immunosuppression; Myocarditis.

G Ital Cardiol 2013;14(7-8):504-516

Miocarditi: aspetti controversi e gestionali

- In quali ambiti clinici è da sospettare una miocardite?
- Quale ruolo diagnostico e prognostico ha l'imaging di I° livello con l'ecocardiografia?
- Qual' è il ruolo della risonanza magnetica e con quali protocolli di acquisizione?
- Quando è indicata la biopsia?
- Quando utilizzare un trattamento specifico con immunosoppressori o antivirali?

"Myocarditis, one of the most challenging diagnoses in cardiology."

- Rarely recognized
- Pathophysiology: poorly understood
- No commonly accepted diagnostic gold standard
- All current treatments are controversial

Miocardite
Difficoltà nella diagnosi clinica

- Polimorfismo nella presentazione clinica
- Eterogeneità negli standard diagnostici
  (BEM – RMN – clinica – amministrativa)
- Probabilmente frequentemente sottodiagnosticata
  - **0,5%** dei ricoveri per causa cardiovascolare

Kytö V, Sipilä J, Rautava P.
The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood.
Heart 2013;99(22):1681–4.

  - **5%** di autopsie non selezionate (causa di morte in 1/4 di questi casi)

Carniel E, Sinagra G, Bussani R, et al.
Fatal myocarditis: morphologic and clinical features.
Ital Heart J 2004;5(9):702–6.

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

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In this position statement of the ESC Working Group on Myocardial and Pericardial Diseases an expert consensus group reviews the current knowledge on clinical presentation, diagnosis and treatment of myocarditis, and proposes new diagnostic criteria for clinically suspected myocarditis and its distinct biopsy-proven pathogenetic forms. The aims are to bridge the gap between clinical and tissue-based diagnosis, to improve management and provide a common reference point for future registries and multicentre randomised controlled trials of aetiology-driven treatment in inflammatory heart muscle disease.

Definitions

Myocarditis (WHO /ISFC[1]):

Inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria**.*

N.B. established histological Dallas criteria[12] defined as follows:

'histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin [12]'.

N.B. unspecified immunohistochemical criteria[1], we propose an abnormal inflammatory infiltrate to be defined as follows:

'$\geq$ 14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of CD 3 positive T-lymphocytes $\geq$ 7 cells/mm^2'.[15,18,19]

Inflammatory Cardiomyopathy (WHO /ISFC[1]):

Myocarditis in association with cardiac dysfunction.

N.B. Inflammatory cardiomyopathy, involved in the pathogenesis of DCM, includes idiopathic, autoimmune and infectious subtypes.[1]

Dilated Cardiomyopathy (ESC[13]; WHO /ISFC[1]):

DCM is a clinical diagnosis characterized by dilation and impaired contraction of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease.

N.B. DCM includes idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic subtypes.[1]

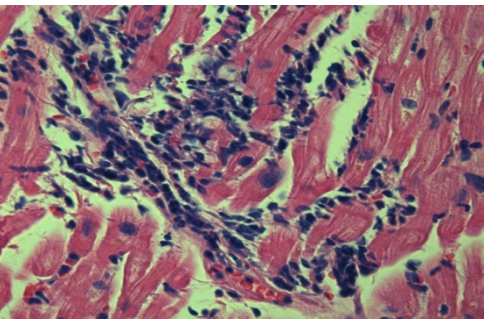
Table 1 **Causes of myocarditis/inflammatory cardiomyopathy**

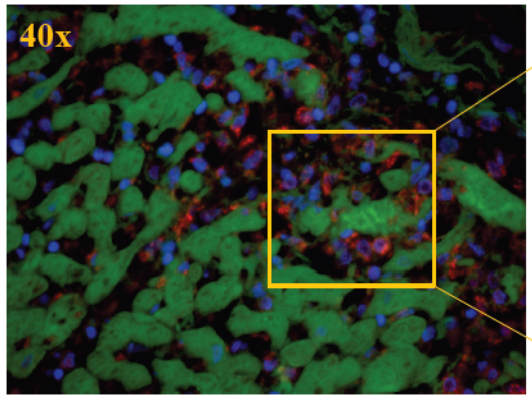
1. Infectious myocarditis	
Bacterial	*Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Meningococcus*, *Gonococcus*, *Salmonella*, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, *Mycobacterium* (tuberculosis), *Mycoplasma pneumoniae*, *Brucella*
Spirochaetal	*Borrelia* (Lyme disease), *Leptospira* (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

Miocarditi …….

- **<u>Miocardite Linfocitaria</u>**
- **M.di Lyme** (Borrelia Burgdorferi): zone endemiche, puntura di zecca, BAV
- **M.di Chagas (Tripanosoma Cruzii)**: viaggi in America centro-meridionale, aneurismi apicali, BBD +EAS
- **Miocardite in HIV** (50% in autopsie)
- **Sarcoidosi**: M.granulomatosa
- **Miocardite eosinofila**: r. ipersensibilità, s. ipereosinofiliche sistemiche, **Churg-Strauss, Loeffler**, reaz. a **farmaci**, parassiti, protozoi, vaccini, M.eosinofilica necrotizzante acuta
- **M. a cellule giganti**:autoimmune/ipersensibilità, acuta/fulminante

Fisiopatologia della “Miocardite”





First phase

Direct virus mediated myocardial damage

Second phase

Secondary viral mediated autoimmune myocardial injury

Third phase

Myocardial remodeling leading to DCM

Acute viral infection

Myocarditis

Genetic susceptibility

Fulminant

Asymptomatic

Chronic

Death

Recovery (complete or incomplete)

DCM

Dennert R, Crijns HJ, Heymans S. Acute viral myocarditis. Eur Heart J 2008;29:2073-82

Table 3 Clinical presentations of patients with biopsy-proven inflammatory heart muscle disease

(1) Acute coronary syndrome-like
- (a) Acute chest pain
  - Frequently starting within 1–4 weeks of a respiratory or gastrointestinal infection
  - Frequently associated with severe and recurrent symptoms
  - In the absence of angiographic evidence of CAD
- (b) ST/T wave changes
  - ST-segment elevation or depression
  - T-wave inversions
- (c) With or without normal global or regional LV and/or RV dysfunction on echocardiography or CMR
- (d) With or without increased TnT/TnI that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months

(2) New onset or worsening heart failure in the absence of CAD and known causes of heart failure
- (a) New onset or progressive heart failure over 2 weeks to 3 months
  - Dyspnoea
  - Peripheral oedema
  - Chest discomfort
  - Fatigue
- (b) Impaired systolic LV and/or RV function, with or without an increase in wall thickness, with or without dilated LV and/or RV on echocardiography or CMR
- (c) Symptoms possibly started after a respiratory or gastrointestinal infection, or in the peri-partum period
- (d) Non-specific ECG signs, bundle branch block, AV-block, and/or ventricular arrhythmias

(3) Chronic heart failure in the absence of CAD and known causes of heart failure (see point 2 above)
- (a) Heart failure symptoms (with recurrent exacerbations) of >3 months duration
- (b) Fatigue, palpitation, dyspnoea, atypical chest pain, arrhythmia in an ambulant patient
- (c) Impaired systolic LV and/or RV function on echocardiography or CMR suggestive of DCM or non-ischaemic cardiomyopathy
- (d) Non-specific ECG signs, sometimes bundle branch block and/or ventricular arrhythmias and/or AV-block

(4) 'life-threatening condition', in the absence of CAD and known causes of heart failure comprising
- (a) Life-threatening arrhythmias and aborted sudden death
- (b) Cardiogenic shock
- (c) Severely impaired LV function

Heart 2001;85:499–504 499

REVIEW

The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review

A D'Ambrosio, G Patti, A Manzoli, G Sinagra, A Di Lenarda, F Silvestri, G Di Sciascio

Assenza di sintomi

Dolore toracico

Aritmie ipocinetiche/ ipercinetiche

Scompenso cardiaco

Forma fulminante

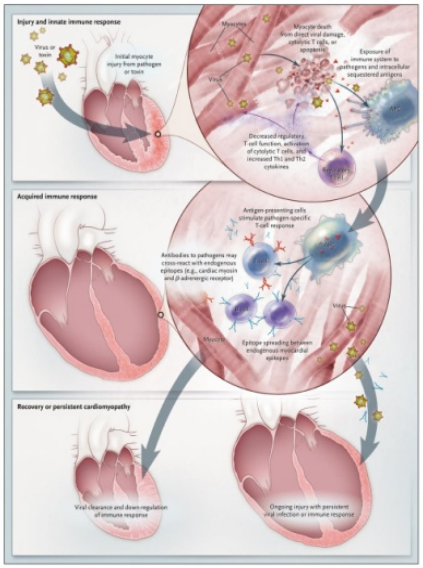
Guarigione completa o incompleta

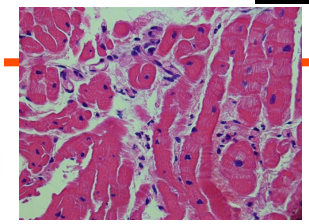
CMPD

Morte improvvisa

Morte in shock e MOF

-·-·-·- evoluzione possibile





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Facoltà di Medicina e Chirurgia – Università degli Studi di Trieste

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.

CRITERI DIAGNOSTICI RMN MIOCARDITE (Lake-Louise criteria)
Friedrich et al. A JACC white paper. 2009;53:1475

Table 5 Diagnostic cardiac magnetic resonance criteria for myocarditis

In the setting of clinically suspected myocarditis (*Tables 3–4*), CMR findings are consistent with myocardial inflammation, if at least two of the following criteria are present:

(1) Regional or global myocardial signal intensity increase in T2-weighted oedema images[a]
(2) Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images[b]
(3) There is at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement)[c]

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

Table reprinted with permission from (20).
[a]Global signal intensity (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 colocalized ischaemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported.
[b]A global SI enhancement ratio of myocardium over skeletal muscle of ≥ 4.0 or an absolute myocardial enhancement of $\geq 45\%$ is consistent with myocarditis.
[c]Images should be obtained at least 5 min after gadolinium injection; foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is colocalized with a transmural regional edema, acute myocardial infarction is more likely and should be reported.

Myocarditis should be suspected in the presence of:
1 or more of the clinical presentations in *Table 4*, with or without ancillary features (see below),
and
1 or more of the diagnostic criteria from different categories (I to IV) in *Table 4*
or
when the patient is asymptomatic, 2 or more diagnostic criteria from different categories (I to IV).

Ancillary features which support the clinical suspicion of myocarditis include:

- Fever $\geq$38.0°C at presentation or within the preceding 30 days with or without evidence of a respiratory (chills, headache, muscle aches, general malaise) or gastrointestinal (decreased appetite, nausea, vomiting, diarrhoea) infection;
- peri-partum period[121];
- previous clinically suspected or definite myocarditis (according to the criteria set in *Table 4*);
- personal and/or family history of allergic asthma, other types of allergy, extra-cardiac autoimmune disease, toxic agents;
- family history of DCM, myocarditis (according to the present criteria).

Work-up diagnostico in sospetta miocardite (Caforio et al.)

Recommendations

7. Troponins, erythrocyte sedimentation rate, reactive C protein levels should be assessed in all patients.
8. Routine viral serology testing is not recommended.
9. Serum samples should be assessed, if possible, for cardiac aabs, if one (or more) of the published tests is available (*Table 2*), according to specific centre expertise. Disease-specific aabs should preferably be tested.

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.

Recommendation

1. Standard 12-lead electrocardiogram should be performed in all patients with clinically suspected myocarditis.

Recommendations

2. All patients with clinically suspected myocarditis should undergo a standard trans-thoracic echocardiogram at presentation.
3. Trans-thoracic echocardiogram should be repeated during hospitalization if there is any worsening of haemodynamics.

Recommendation

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

Recommendations

26. All patients with myocarditis should be followed, with clinical assessment, ECG, and echocardiography.
27. Long-term follow-up for patients that have experienced myocarditis is recommended.

Sospetta miocardite: test diagnostici di imaging

Ecocardiografia (I):

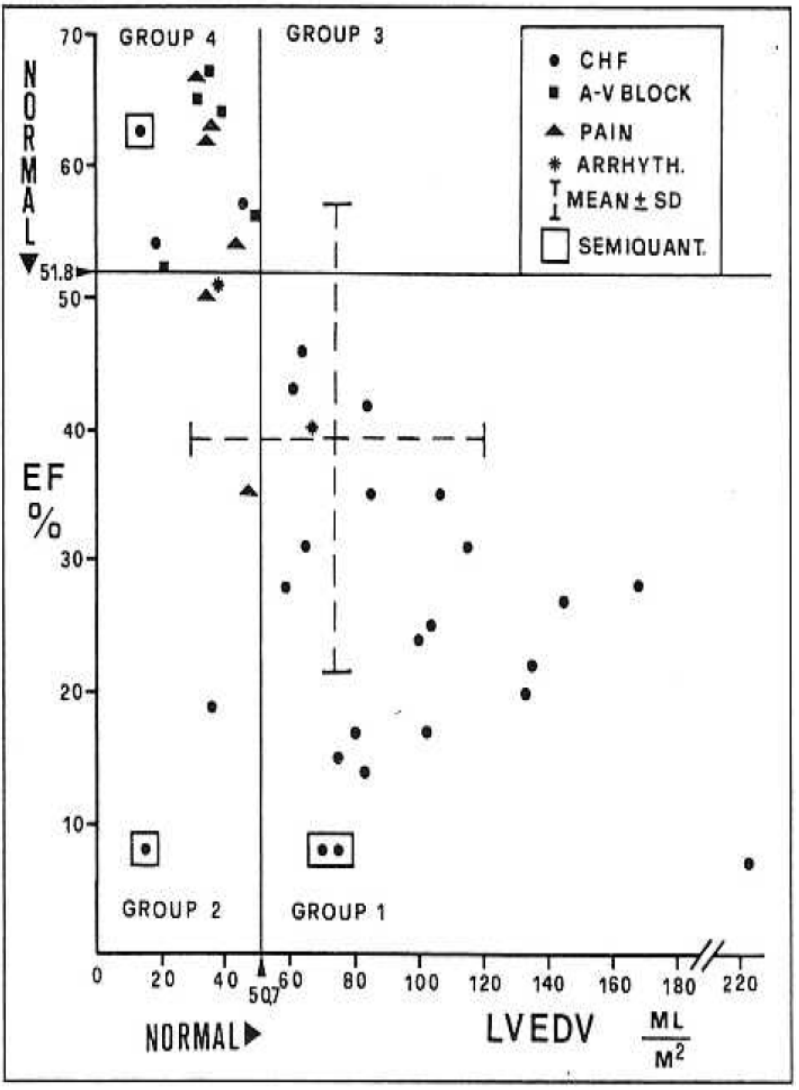
Non noti reperti eco specifici di miocardite, ma:

- Eco fondamentale per identificare disfunzione ventricolare
- Utile nella diagnosi differenziale con altre cause di scompenso cardiaco
- Importante per stratificare la prognosi
- Utile nel follow-up

Pinamonti B, Alberti E, Cigalotto A, Dreas L, Salvi A, Silvestri F, Camerini F.

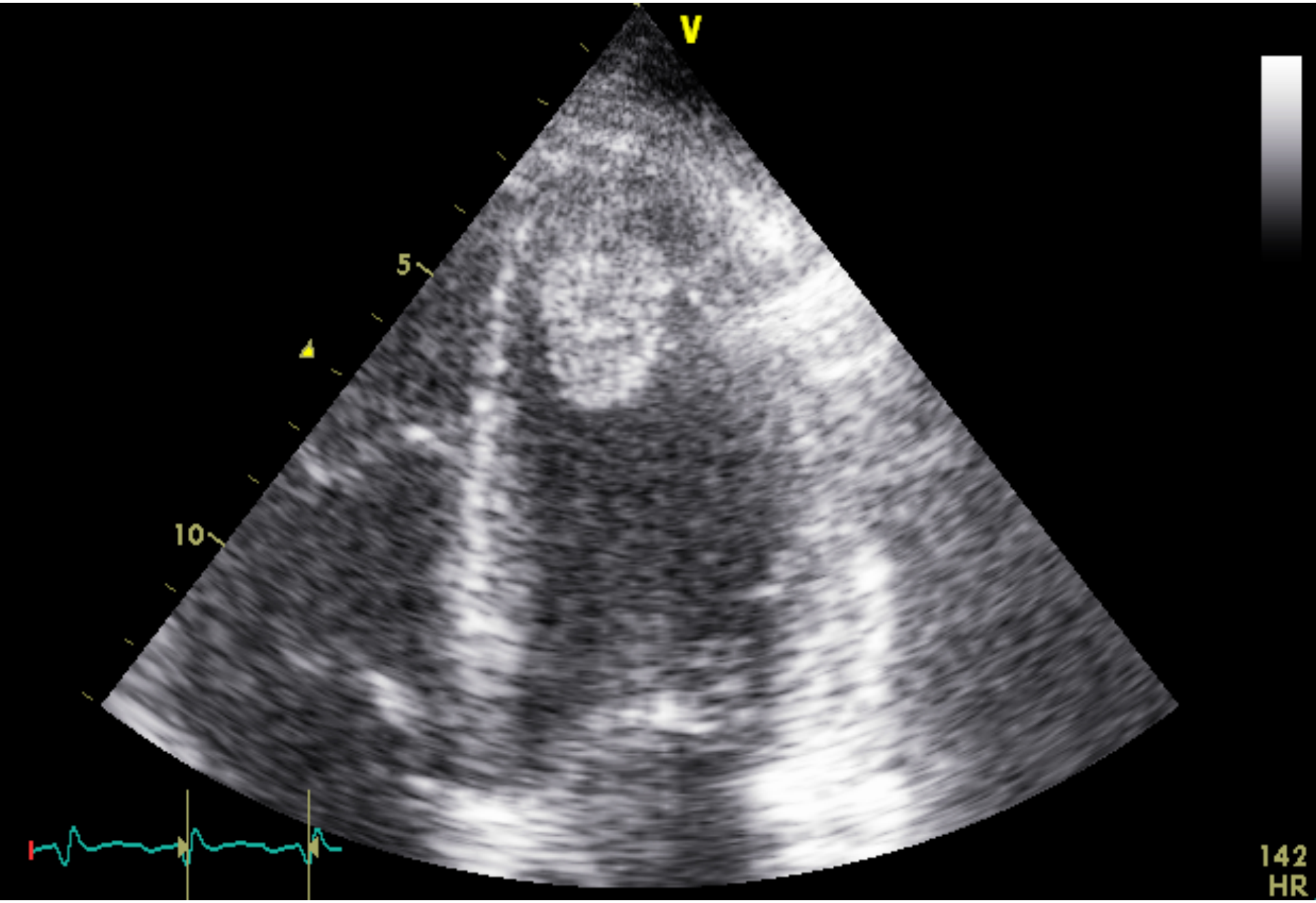
ECHOCARDIOGRAPHIC FINDINGS IN MYOCARDITIS.

***Am J Cardiol*. 1988;62:285–291.**



Correlazione clinico-ecocardiografica

Asinergie a distrettualità non-coronarica
Pseudoipertrofia
Iper-riflettenza della trama miocardica
Trombosi ventricolare
Disfunzione diastolica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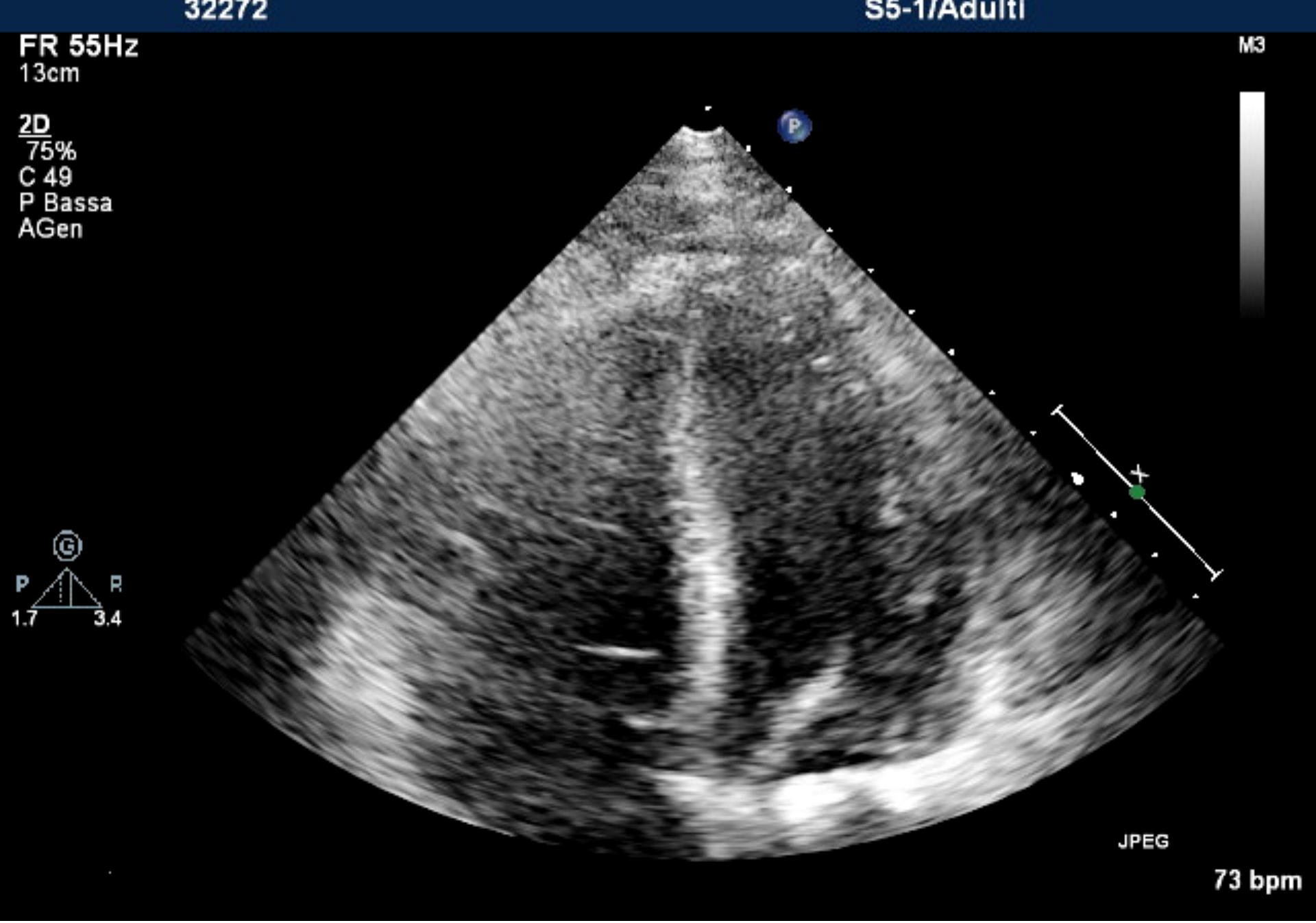
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13cm
2D
75%
C 49
P Bassa
AGen
M3
P
G
P
R
1.7
3.4
JPEG
73 bpm

Echocardiographic Findings in Fulminant and Acute Myocarditis

JACC Vol. 36, No. 1, 2000
July 2000:227–32

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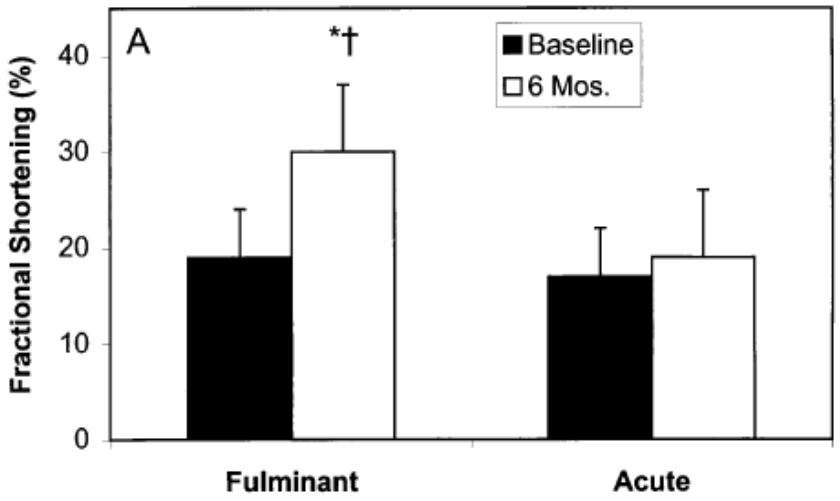
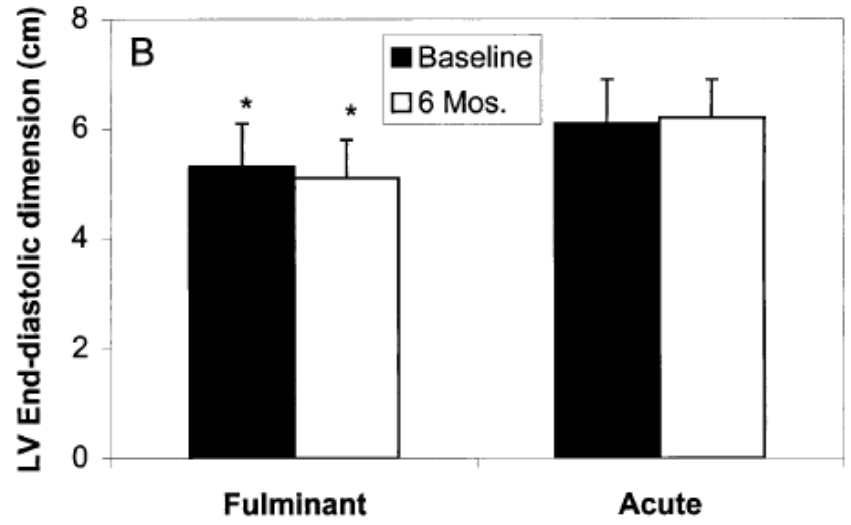
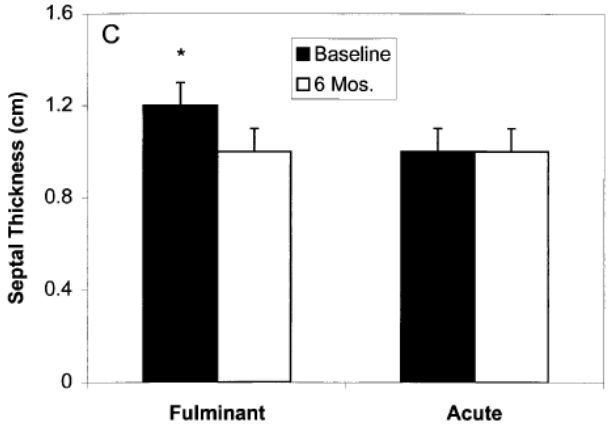
Grover M. Hutchins, MD,† Edward K. Kasper, MD, FACC,* Kenneth L. Baughman, MD, FACC,*
Joshua M. Hare, MD, FACC*







	Fulminant (n = 11)	Acute (n = 43)	p Value
Histology			
Myocarditis	100% (11)	77% (33)	NS
Borderline myocarditis	0% (0)	23% (10)	
Inflammation			
Severe	55% (6)	5% (2)	< 0.01
Moderate	45% (5)	14% (6)	
Mild	0% (0)	81% (35)	
Hemodynamics			
Right atrial pressure	11 ± 8	4 ± 3	< 0.01
Mean pulmonary artery pressure	28 ± 11	21 ± 9	0.03
Pulmonary artery wedge pressure	21 ± 11	14 ± 9	0.03
Mean blood pressure	79 ± 11	90 ± 12	< 0.01
Heart rate (beats/min)	109 ± 21	91 ± 21	< 0.01
Cardiac index (L/min/m^2)	2.8 ± 0.9	2.5 ± 0.6	NS
SVRI (dynes·sec·cm^{-5}·m^2)	2,072 ± 440	2,939 ± 752	< 0.01
PVRI (dynes·sec·cm^{-5}·m^2)	244 ± 242	218 ± 150	NS
LVSWI (g-m/m^2)	21 ± 11	31 ± 14	NS

Sospetta miocardite: test diagnostici di imaging (II)

TECNICHE RADIOISOTOPICHE

Scintigrafia con Gallio-67:

- marcatore di flogosi cronica;
- MA bassa specificità, non più utilizzato

Anticorpi antimiosina marcati con Indio-111:

- identificazione di necrosi miocardica
- utile metodo per screening; elevata sensibilità ed elevato valore predittivo negativo.
- MA poco specifico, scarsamente disponibile, esposizione a dose di radiazioni, ritardo nella risposta

Sospetta miocardite: test diagnostici di imaging

RISONANZA MAGNETICA NUCLEARE

- Sequenze spin eco T2 pesato > aumento segnale > edema
- Gadolinio sequenze precoci > global relative enhancement (GRE) > aumento segnale > iperemia
- Gadolinio sequenze tardive (LE) > aumento segnale (LE) > identificazione necrosi/fibrosi
- Elevata sensibilità e specificità (anche se non assoluta), specie se considerate tutte e 3 le tecniche
- Metodica diagnostica non invasiva ottimale nella sospetta miocardite
- Utile nell'indirizzare i pazienti alla diagnosi con BEM e nell'orientare la sede del prelievo BEM

JACC White Paper

Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper

J. Am. Coll. Cardiol. 2009;53;1475-1487

Proposed Diagnostic CMR Criteria (Lake Louise Consensus Criteria) for Myocarditis

- presence of at least 2 of the following criteria
  - edema in T2-weighted images
  - early gadolinium enhancement, in T1-weighted images
  - late gadolinium enhancement, in T1-weighted images
- LV dysfunction and/or pericardial effusion (supportive evidence)
- A repeat CMR study between 1 and 2 weeks after the initial CMR (if there is strong clinical evidence for myocardial inflammation)

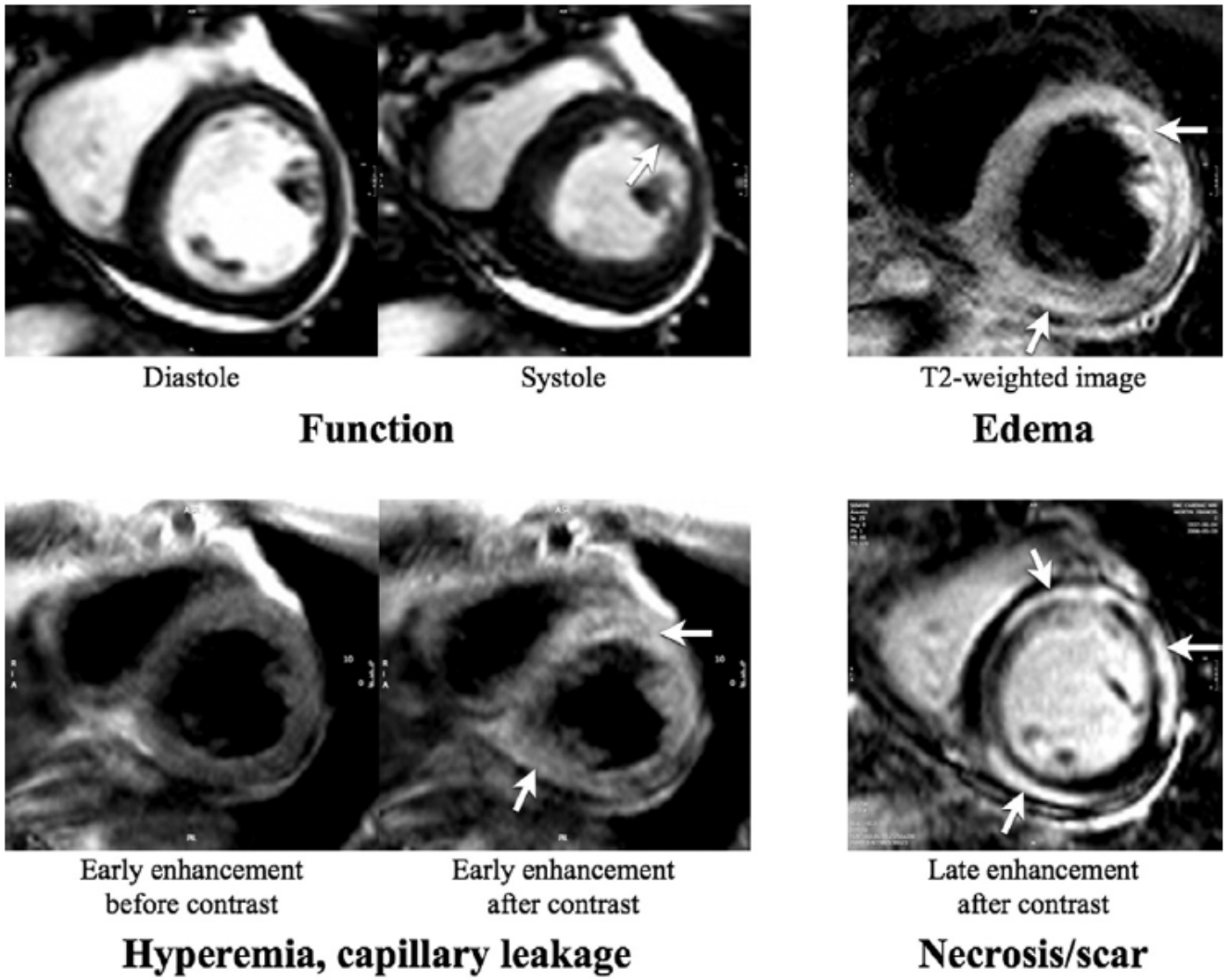
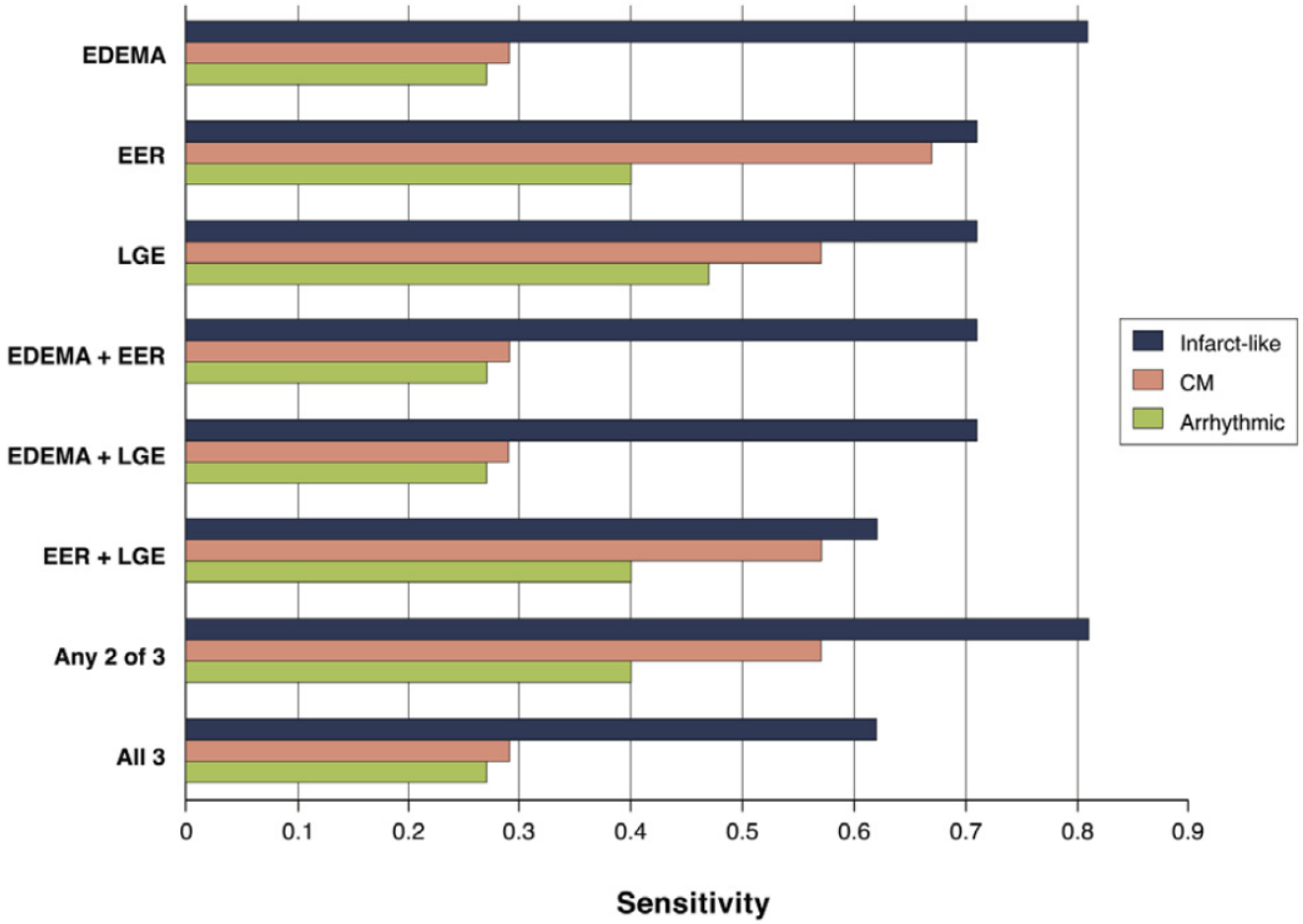


Figure 2. Short-axis cardiac magnetic resonance images of the same anatomical regions with pathological findings in a patient with acute myocarditis. **(Upper row, left)** Steady-state free precession images in diastole **(left)** and systole **(right)**, showing anterior hypokinesis **(arrow)** and a small pericardial effusion. **(Upper row, right)** Triple-inversion-recovery prepared T2-weighted spin echo image showing regional edema of the anteroseptal, anterior, anterolateral, and inferior segments with predominant subepicardial involvement. **(Lower row, left)** T1-weighted fast spin echo images before **(left)** and after **(right)** application of gadolinium. Note the diffuse signal intensity increase. The quantitative evaluation showed a pathological signal change. **(Lower row, right)** T1-weighted inversion-recovery prepared gradient echo image obtained 5 min after application of gadolinium. There are extensive areas with high signal intensity (late enhancement), predominantly involving subepicardial regions **(arrows)**. A small artifact is noted, which should not be interpreted as pathology.

CMR Sensitivity Varies With Clinical Presentation and Extent of Cell Necrosis in Biopsy-Proven Acute Myocarditis



Francone M, Frustaci A et al;

JACC: CARDIOVASCULAR IMAGING, VOL. 7, NO. 3, 2014
MARCH 2014:254–63

ELSEVIER

International Journal of Cardiology 127 (2008) 17–26

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Review

Myopericarditis: Etiology, management, and prognosis

Massimo Imazio *, Rita Trinchero

Myopericarditis: Etiology, management, and prognosis

Massimo Imazio *, Rita Trinchero

MIOPERICARDITE/PERIMIOCARDITE

Criteri diagnostici:

1) Criteri per pericardite acuta: almeno 2 criteri tra: - dolore toracico tipico con incremento inspiratorio; - sfregamenti pericardici; - alterazioni ST diffuse; - versamento pericardico.
2) Segni di interessamento miocardico: - incremento enzimi cardiaci (troponina) E/O - disfunzione VS globale/segmentaria.
3) Presenza di marker di infiammazione (PCR)

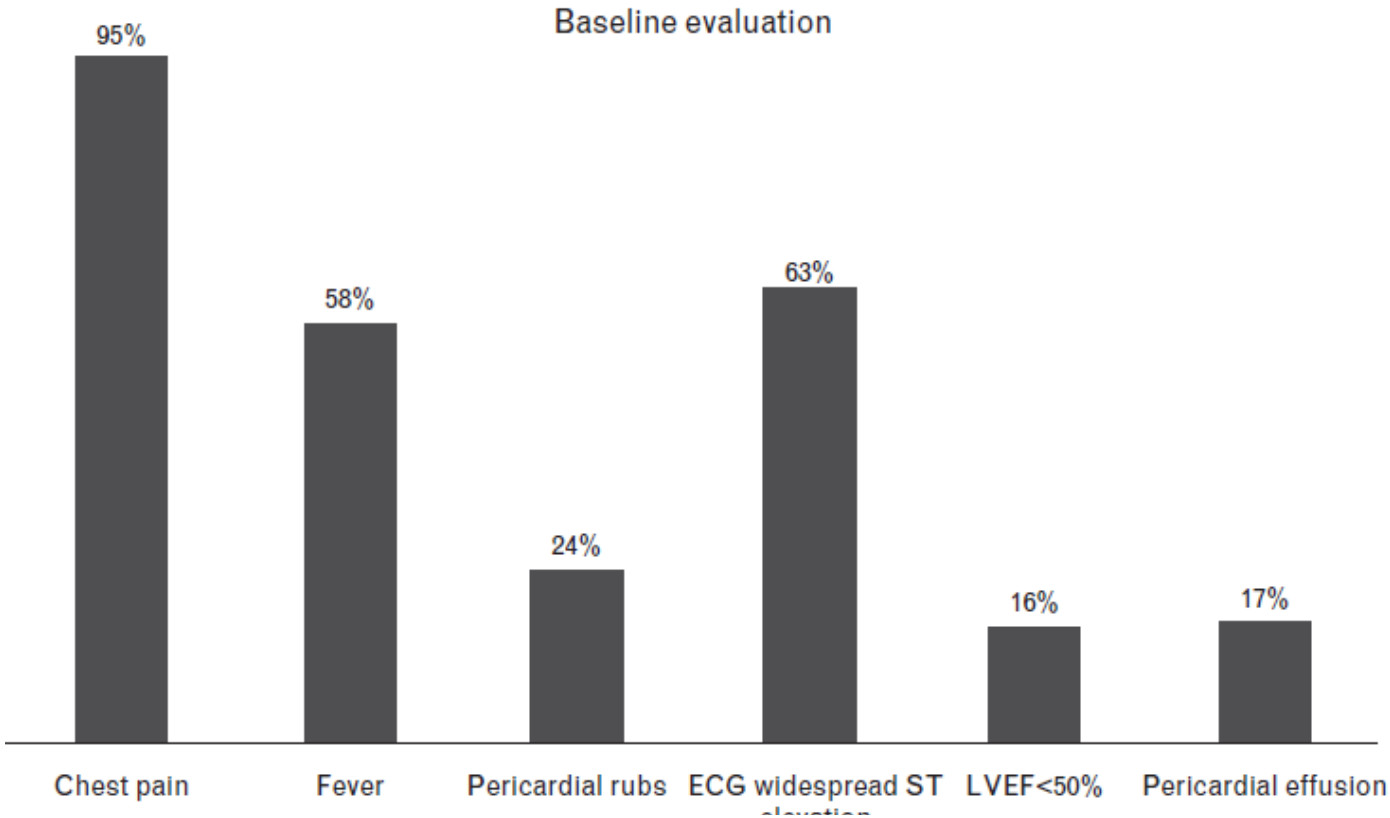
FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Clinical presentation and long-term follow-up of perimyocarditis

Alessandra Buiatti[a], Marco Merlo[a], Bruno Pinamonti[a], Marzia De Biasio[b], Rossana Bussani[c] and Gianfranco Sinagra[a]

Methods We enrolled 62 consecutive patients (men 79%, aged 38 ± 18 years) with PMY (84% idiopathic, 8% autoimmune, 8% infective) from August 2002 to July 2010. The diagnosis has been made according to clinical and laboratory data (significant increase of troponin I in all patients). After at least 1 year (mean follow-up: 1635 ± 298 days), 59 patients (95%) had available data.

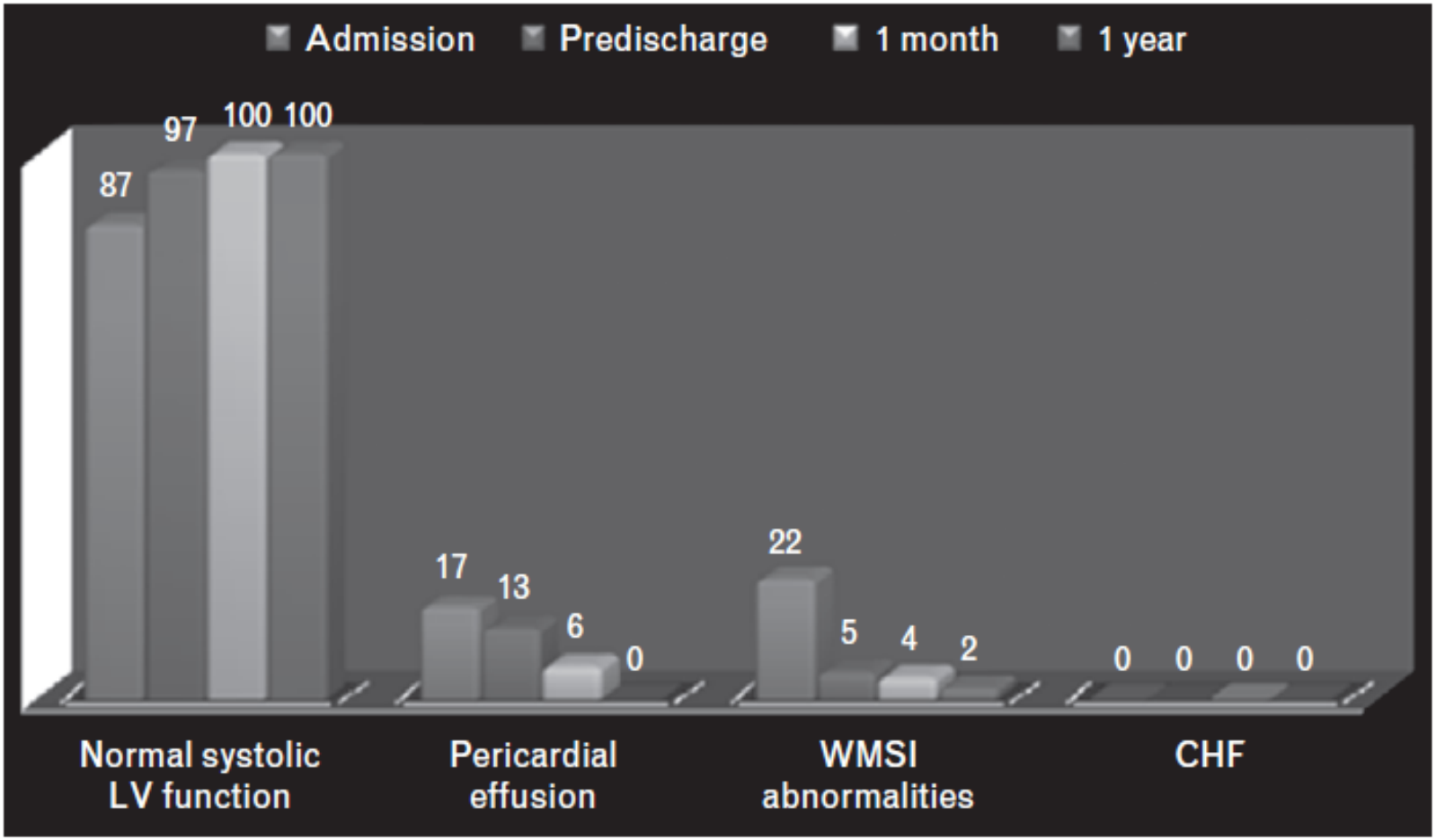
Results Chest pain was present in 59 patients (95%), flu-like syndrome in 36 (58%) and pericardial rubs in 15 (24%). None of the patients showed heart failure at presentation. At admission, eight patients (13%) presented mild–moderate left ventricular systolic dysfunction, 13 (22%) showed wall motion abnormalities, and 10 (17%) showed mild pericardial effusion. At 1 year no patients died, developed heart failure or showed abnormal echocardiogram.



Clinical presentation of perimyocarditis Buiatti *et al.*

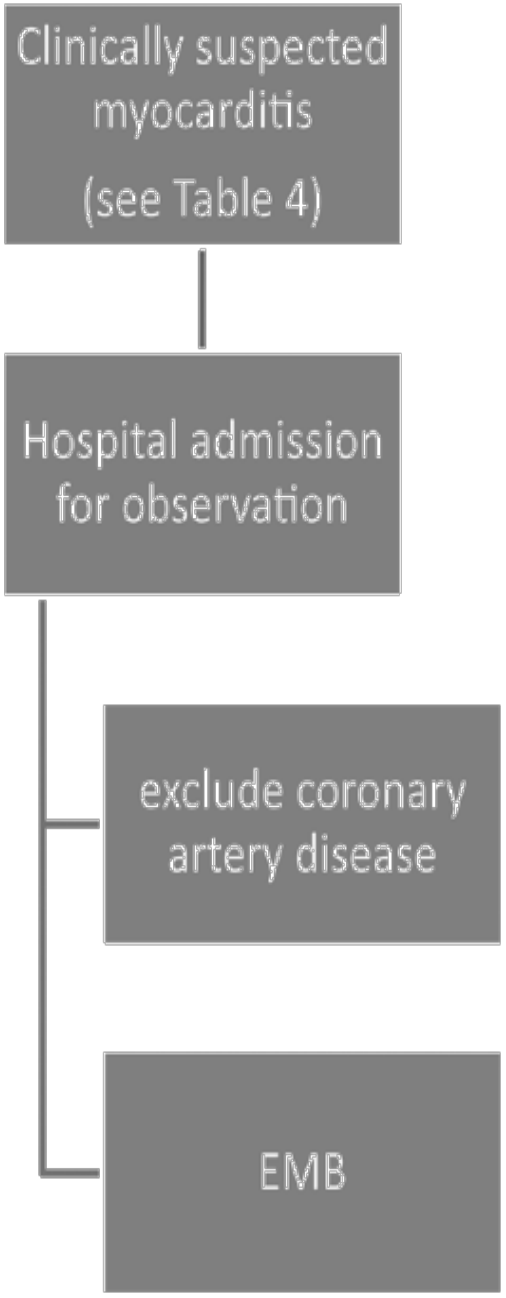
Clinical presentation and long-term follow-up of perimyocarditis

Alessandra Buiatti[a], Marco Merlo[a], Bruno Pinamonti[a], Marzia De Biasio[b], Rossana Bussani[c] and Gianfranco Sinagra[a]



Mid–long-term temporal evolution of some relevant clinical laboratory features in perimyocarditis. Numbers over bars refer to percentage (%) of cases. CHF, congestive heart failure; LV, left ventricular; WMSI, wall motion score index.

ESC 2013 suggested flow chart for definite diagnosis of myocarditis



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

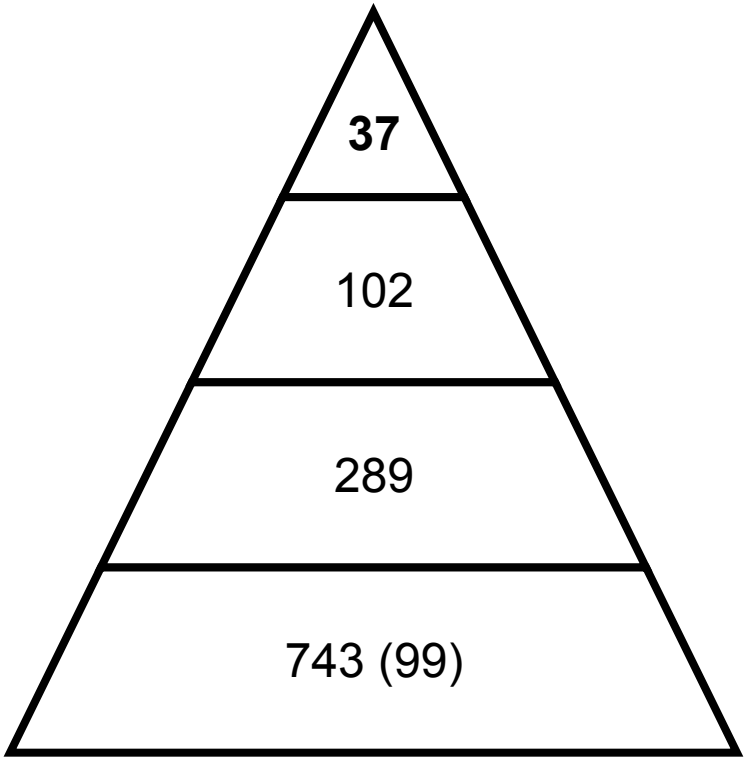
In patients fulfilling the diagnostic criteria for clinically suspected myocarditis, we recommend selective coronary angiography and EMB.

This recommendation also applies to patients with an acute coronary syndrome-like presentation with or without features suggestive of myocarditis on CMR.

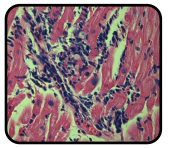
Therefore, in the absence of robust prospective data (in suspected myocarditis with pseudo-infarct presentation and normal coronary arteries), **the definitive diagnosis of myocarditis should still be based on EMB**.

Caforio ALP et al. *Eur Heart J*. 2013;39 (epub ahead of print 3.7.2013)

Cardiomiopatie infiammatorie a Trieste (2004-2014)

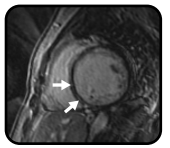


BEM con miocardite attiva
(2004-2014)

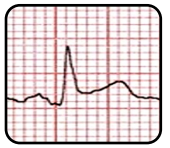


BEM effettuate
(2004-2014)

Nuove CMPD
(2004-2014)



Pericarditi/Perimiocarditi
(2004-2014)

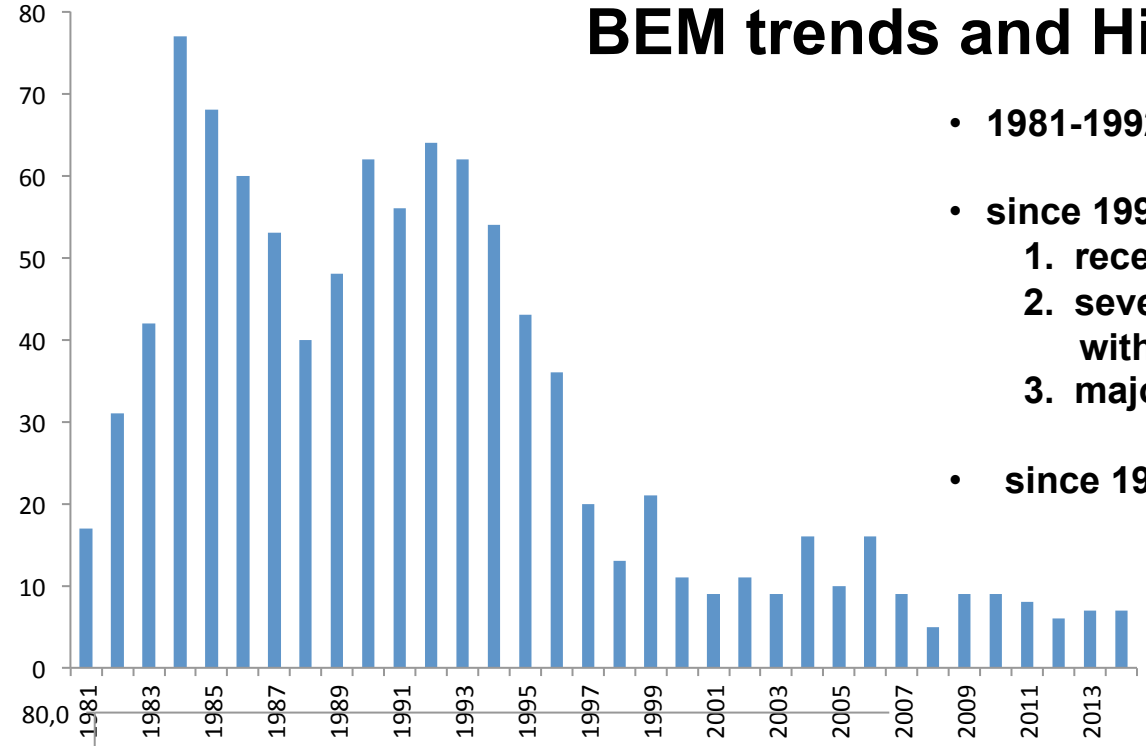


registro miocarditi bioptiche: 104 pazienti
registro perimiocarditi, dal 2004: 99 pazienti
registro aritmiocarditi: in definizione (16 pazienti)

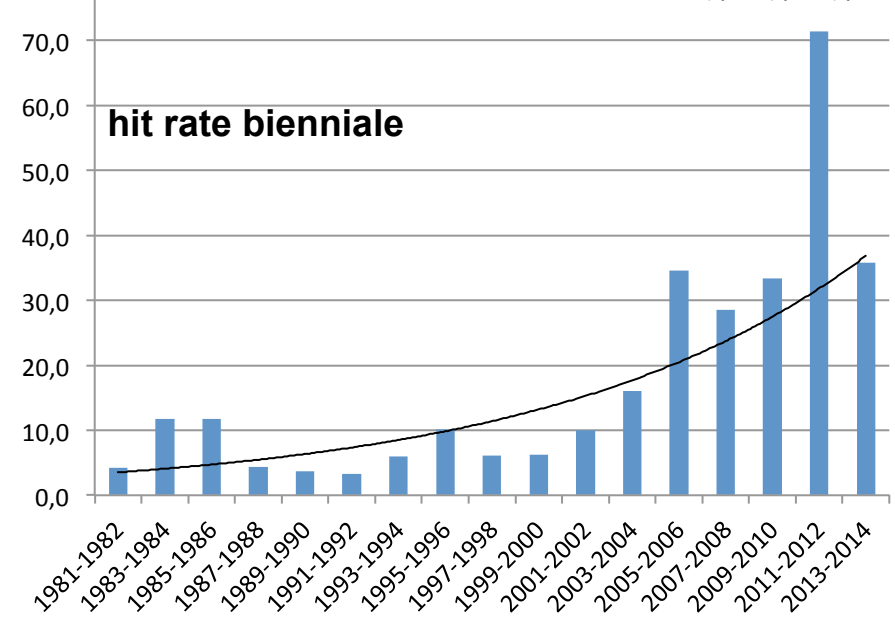
endomyocardial biopsy - complication rate

	Total	Major Complications	Minor Complications
Jang, JKMS 2013	9,2% (21/228)	1,3% (3/228)	7,9% (18/228)
Chimenti, Circulation 2013	1,78% (75/4221)	0,62% (26/4221)	1,16% (49/4221)
Bennet, Circ Heart Fail 2013	1,9% (16/851)	0,95% (8/851)	0,95% (8/851)
Yilmaz, Circulation 2010	6,2% (47/755)	1,1% (8/755)	5,2% (39/755)
Holzmann, Circulation 2010	1,1% (33/3048)	0,1% (3/3048)	1% (30/3048)
Felker, N Engl J Med 2000	8% (1230)	0,2% deaths (2/1230)	
Trieste, 2005-2015	7,5% (5/67)	3% (2/67)	4,8% (3/67)

BEM trends and Hit-Rate



- 1981-1992 all pts with unexplained LV dysfunction
- since 1993, in those who presented with
  1. recent onset HF
  2. severe LV dysfunction (LVEF <40%) without ventricular remodeling,
  3. major ventricular arrhythmias
- since 1993: immunohistochemical analysis



Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

Marco Anzini, Michele Moretti, Marco Merlo, Andrea Perkan, Rossana Bussani, Gianfranco Sinagra

Tabella 1. Fasi patologiche delle miocarditi e ruolo delle indagini diagnostiche sierologiche, molecolari e bioptiche.

	Fase 1 - Acuta	**Fase 2 - Subacuta**	**Fase 3 - Cronica**
Caratteristiche patogenetiche	Lisi diretta dei miociti dal virus o mediata dalla risposta immunitaria innata	Distruzione dei miociti mediata dalla risposta immunitaria specifica	Sostituzione dei miociti distrutti da fibrosi
Indagini sierologiche su sangue	Due prelievi a distanza di 10-15 giorni per eventuale sieroconversione	Singolo controllo della sierologia completa	Non rilevanti
Ricerca di genoma virale mediante RT-PCR	Ricerca su campioni biologici (sangue, feci, tampone faringeo)	Ricerca su sangue (potenzialmente utile, soprattutto se in associazione a BEM)	Ricerca su sangue (potenzialmente utile, soprattutto se in associazione a BEM)
BEM	Le indicazioni alla BEM sono poste sulla base della severità clinica e sull'impatto atteso sulla terapia. Con tale premessa l'indagine è potenzialmente utile in tutte le fasi della malattia in pazienti selezionati, valutando l'impatto atteso su terapia e prognosi.		

Indicazioni alla biopsia endomiocardica

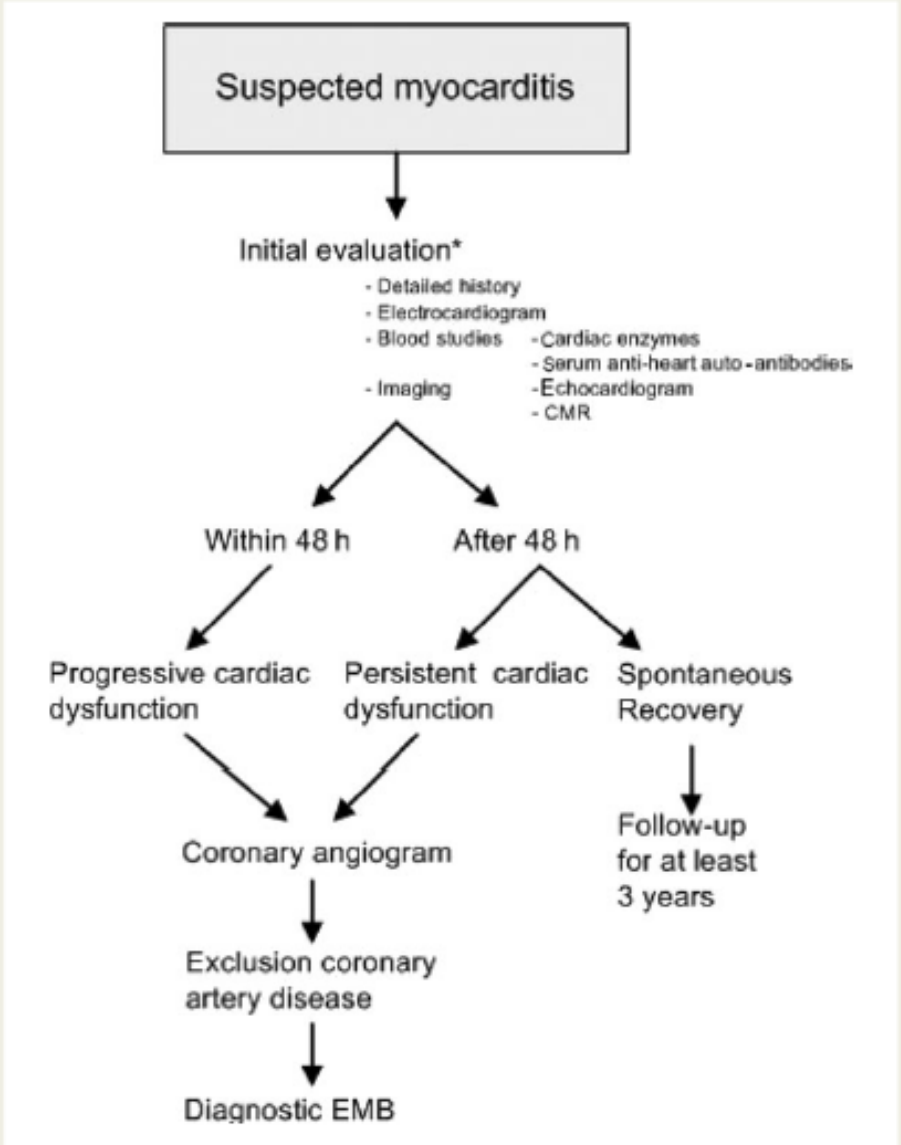
- Nel sospetto di miocardite:
  - ✓FEVsin < 40% persistente e/o scompenso cardiaco e/o aritmie VE maggiori persistenti nonostante terapia convenzionale (1-2 settimane)
  - ✓Intervallo esordio diagnosi ≤ 3-6 mesi
  - ✓Contesto anamnestico suggestivo

Necessità di approccio integrato mediante valutazione istopatologica, immunoistochimica e virologico-molecolare.

European Heart Journal (2008) **29**, 2073–2082
doi:10.1093/eurheartj/ehn296

Acute viral myocarditis

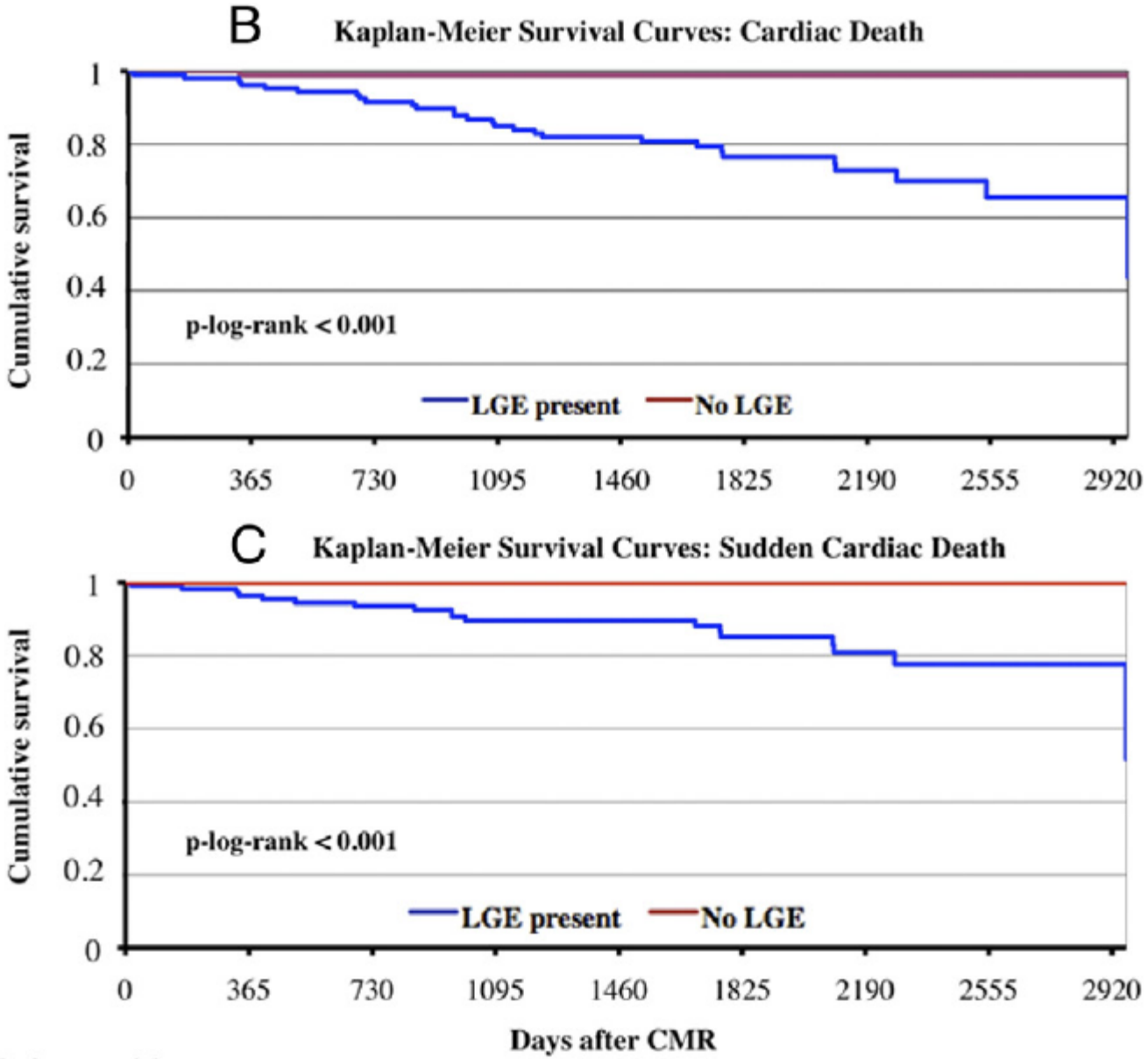
Robert Dennert, Harry J. Crijns, and Stephane Heymans*

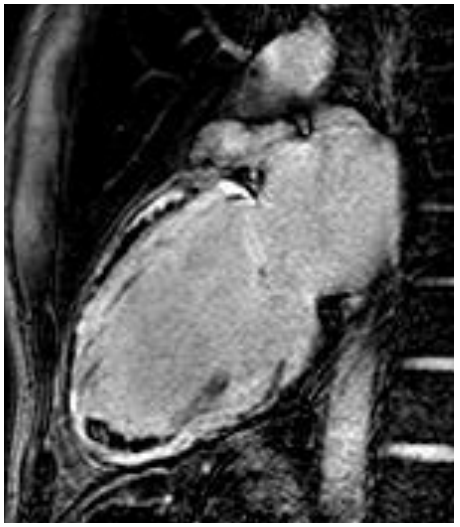


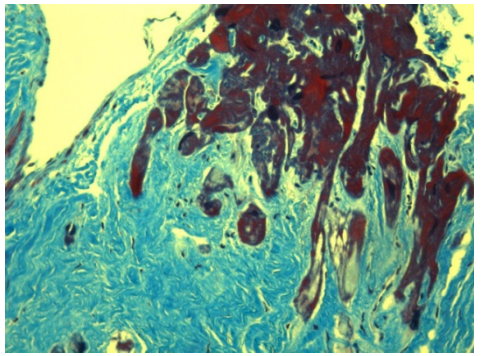
Long-Term Follow-Up of Biopsy-Proven Viral Myocarditis

Predictors of Mortality and Incomplete Recovery

JACC Vol. 59, No. 18, 2012
May 1, 2012:1604–15







Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

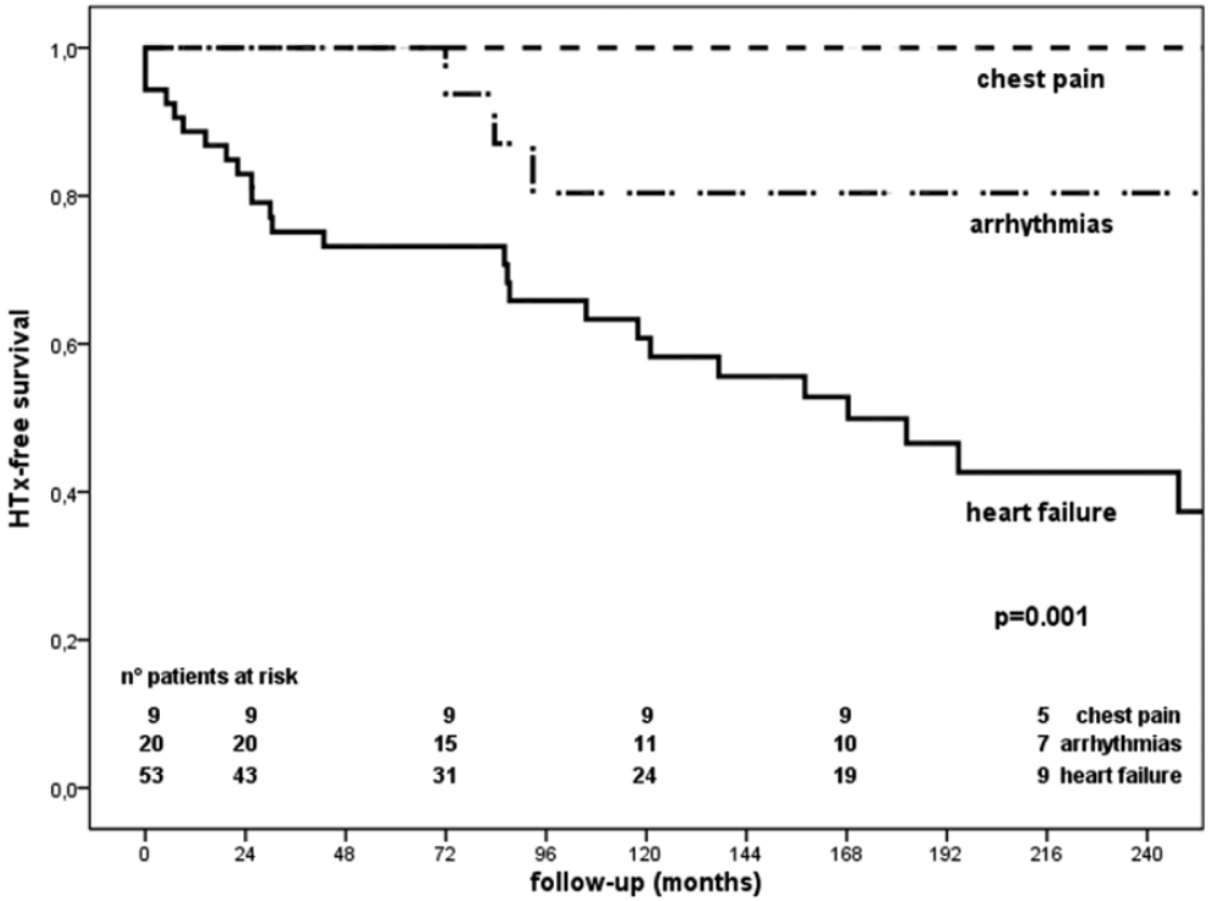
American Heart Association®

Long-Term Evolution and Prognostic Stratification of Biopsy-Proven Active Myocarditis

Marco Anzini, Marco Merlo, Gastone Sabbadini, Giulia Barbati, Gherardo Finocchiaro, Bruno Pinamonti, Alessandro Salvi, Andrea Perkan, Andrea Di Lenarda, Rossana Bussani, Jozef Bartunek and Gianfranco Sinagra

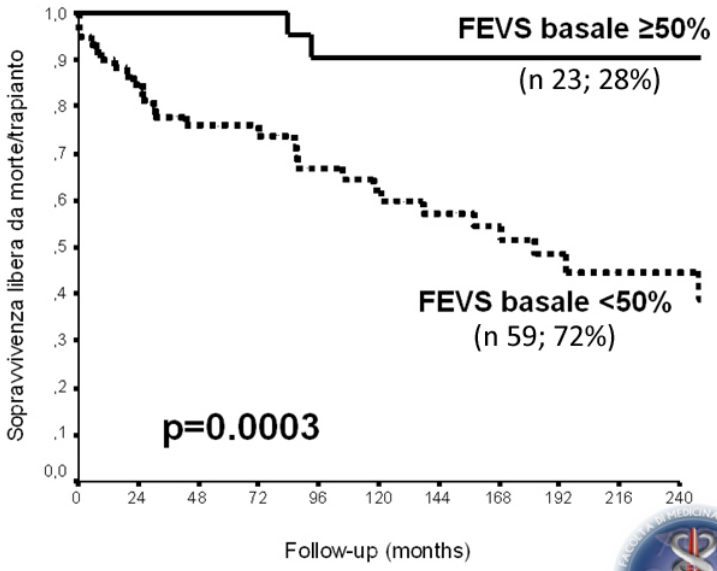
Circulation. 2013;128:2384-2394; originally published online October 1, 2013;
doi: 10.1161/CIRCULATIONAHA.113.003092

82 pts; f.up 147 mo;
6 mo improv/norm
LVEF: 53%



Active Myocarditis: presentation and prognosis – Predittori Basali

	Univariable Analysis			Multivariable Analysis		
	HR	CI 95%	P Value	HR	CI 95%	P Value
Age < 13 y	3.554	1.226–10.301	0.020	**3.316**	**0.965–11.389**	**0.057**
NYHA functional class III–IV	2.941	1.391–6.220	0.005			
Heart failure	7.192	2.172–23.820	0.001			
NSVT	2.330	1.078–5.032	0.031			
LADI, mm/m (1 mm/m increase)	1.205	1.092–1.330	<0.001	**1.141**	**1.022–1.274**	**0.019**
LVEDDI, mm/m (1 mm/m increase)	1.069	1.021–1.119	0.005			
LVEF, % (5-U decrease)	1.271	1.108–1.458	<0.001			
LVEF < 50%	9.088	2.148–38.458	0.003	**8.029**	**1.010–63.860**	**0.049**
RVFS < 33%	2.130	1.038–4.371	0.039			
RAP (for 1-mm Hg increase)	1.231	1.099–1.380	<0.001			
Mean PAP (for 1-mm Hg increase)	1.056	1.008–1.107	0.021			
PCWP (for 1-mm Hg increase)	1.099	1.049–1.152	<0.001			
Cardiac index (500 mL/min/m^2 decrease)	1.649	1.634–1.663	0.003			
Diuretics	3.365	1.434–7.897	0.005			
Digoxin	4.266	1.816–10.021	0.001			
Inotropes	4.155	1.664–10.374	0.002			



Active Myocarditis: presentation and prognosis – Ruolo del follow-up

Caratteristiche clinico-strumentali della popolazione a 6 mesi

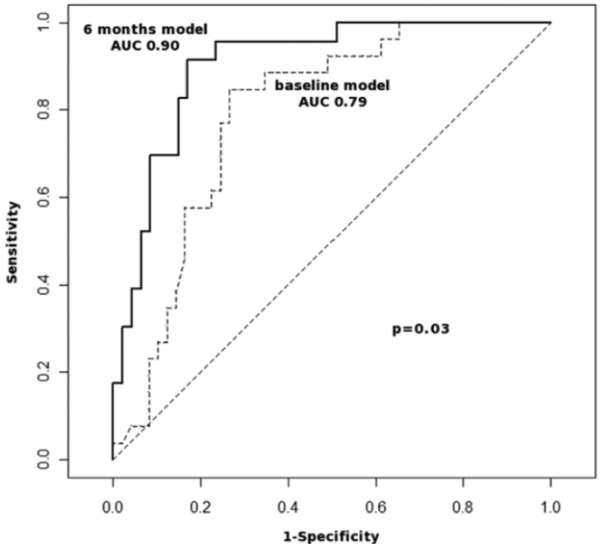
	Pop. totale (77; 100%)	SCC (49; 64%)	Aritmie (19; 24%)	DoloreToracico (9; 12%)	p value
NYHA III-IV – no. (%)	4(5)	4(8)	0(0)	0(0)	0.320
DAS N – mm/m	21±3	22±3	20±4	20±3	0.128
DTD VS N – mm/m	35±7	38± 6	30±4	29±4	<0.001
FE VS – %	46±14	40±13	54±11	61±6	<0.001
FE VS < 50 % – no. (%)	40(52)	35(71)	5(26)	0(0)	<0.001
Miglioramento/normalità – no. (%)	**41(53)**	18(34)	14(70)	9(100)	<0.001

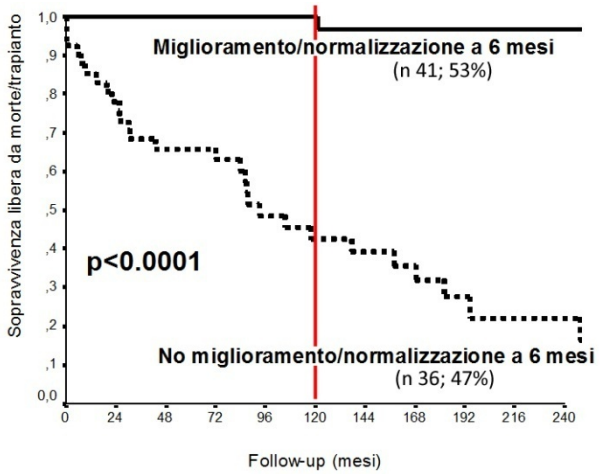
Predittori Prognostici alla rivalutazione a 6 mesi

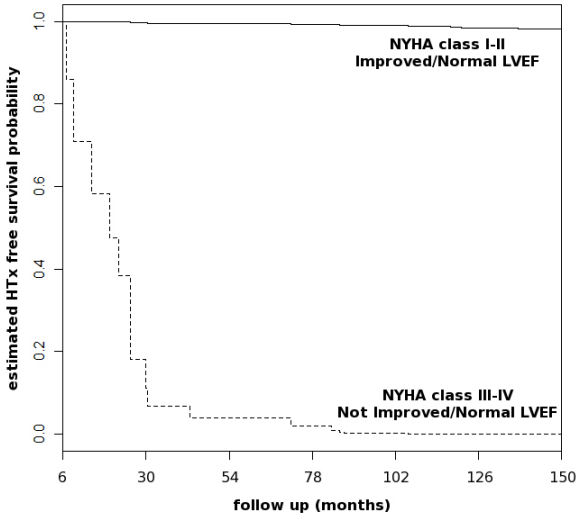
	Univariable Analysis			Multivariable Analysis		
	HR	CI 95%	p Value	HR	CI 95%	p Value
NYHA functional class III–IV	37.15	7.362–187.507	<0.001	**16.24**	**3.193–30.572**	**0.001**
LADI, mm/m (1 mm/m increase)	1.23	1.081–1.397	0.002	**1.18**	**1.030–1.348**	**0.017**
LVEF, % (5-U decrease)	1.56	1.347–1.808	<0.001			
LVEF < 50%	41.17	5.523–304.625	<0.001			
LVEDDI, mm/m (1 mm/m increase)	1.09	1.037–1.148	0.001			
Improved/normal LVEF	0.02	0.003–0.152	<0.001	**0.03**	**0.004–0.213**	**0.001**

Active Myocarditis: presentation and prognosis – Ruolo del follow-up

multivariable analysis – 6 months	HR	CI 95%	p
NYHA III-IV a 6 mesi	**16.237**	**3.19-30.57**	**0.001**
DAS N a 6 mesi – mm/m (per incremento 1 mm/m)	**1.178**	**1.03-1.34**	**0.017**
Miglioramento / normalità	**0.028**	**0.004-0.213**	**0.001**







Ospedali Riuniti di Trieste

Miocardite: indicazioni al trattamento immunosoppressivo
Linee guida utilizzate nel centro cardiologico di Trieste

Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

Marco Anzini, Michele Moretti, Marco Merlo, Andrea Perkan, Rossana Bussani, Gianfranco Sinagra

Nella pratica clinica del nostro centro, in accordo con quanto affermato, l'immunosoppressione viene praticata nei casi di miocardite con severità clinica di presentazione o decorso, bioptica mente accertata, in presenza di immunoattivazione del tessuto miocardico all'indagine immunoistochimica ed in assenza di genoma virale alla PCR su sangue e su miocardio, qualora nel breve termine sia evidente la refrattarietà del quadro clinico alla terapia convenzionale per lo scompenso cardiaco o per le aritmie ventricolari maggiori (Tabella 3, Figura 4).

G Ital Cardiol 2013;14(7-8):504-516

Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

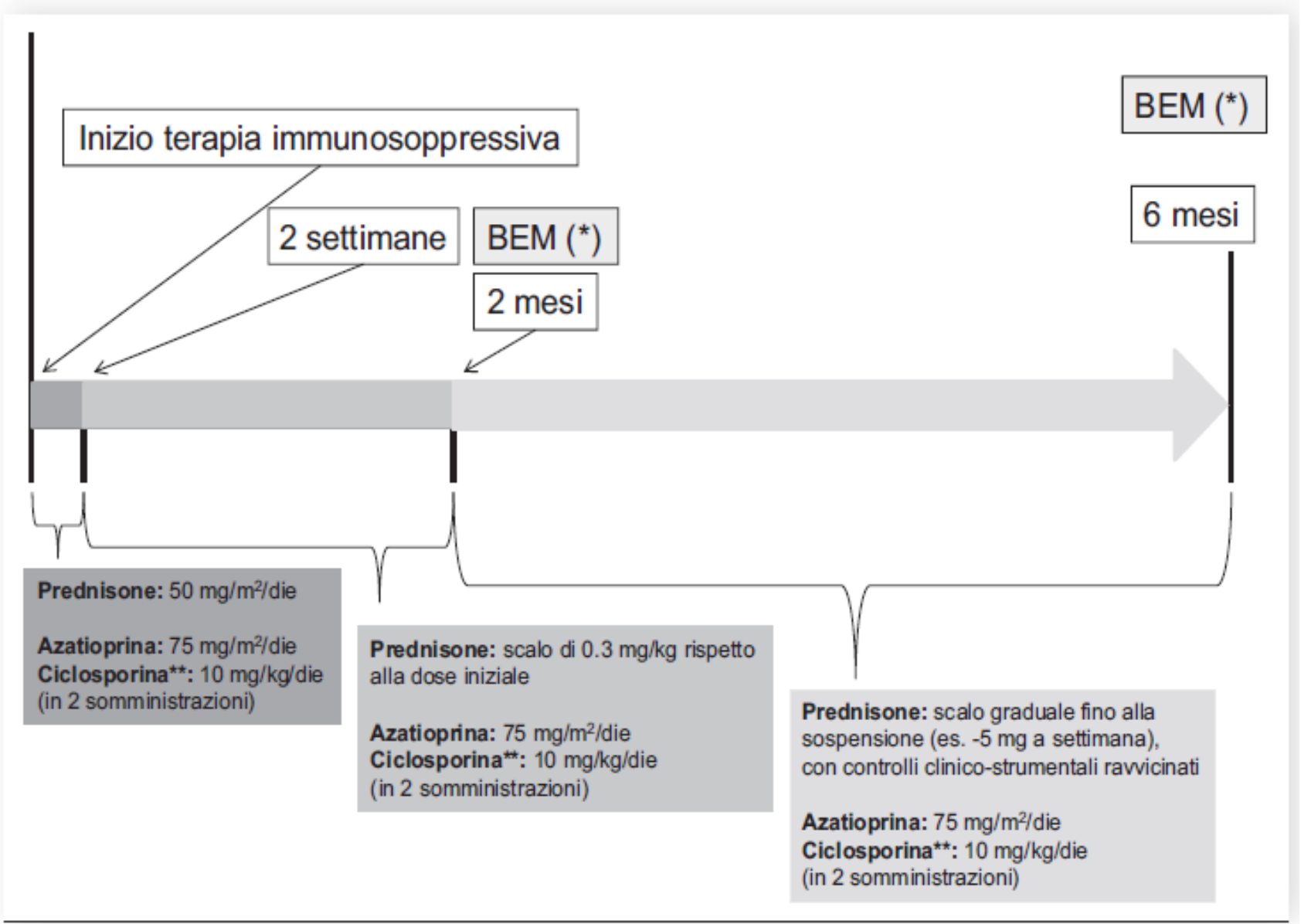
Marco Anzini, Michele Moretti, Marco Merlo, Andrea Perkan, Rossana Bussani, Gianfranco Sinagra

Tabella 3. Protocolli di terapia immunosoppressiva nelle miocarditi.

Farmaco	Dosaggio
Protocollo utilizzato da Wojnicz et al.[56]	
Prednisone	1 mg/kg/die per 12 giorni, quindi riduzione della dose di 5 mg/die ogni 5 giorni fino alla dose di 0.2 mg/kg/die, per un totale di 90 giorni
Azatioprina	1 mg/kg/die per un totale di 100 giorni
Protocollo utilizzato da Frustaci et al.[57]	
Prednisone	1 mg/kg/die per 4 settimane, quindi 0.33 mg/kg/die per 5 mesi
Azatioprina	2 mg/kg/die per 6 mesi
Protocollo utilizzato presso la S.C. di Cardiologia di Trieste[4]	
Prednisone	50 mg/m^2/die per 2 settimane indi scalo di 0.3 mg/kg per 2 mesi, quindi scalo gradualmente fino allo stop (6 mesi)
Azatioprina	75 mg/m^2/die per 6 mesi
Ciclosporina[a]	10 mg/kg/die (2 somministrazioni) per 6 mesi

[a]in casi selezionati (es. miocardite a cellule giganti) o in caso di persistente attività infiammatoria nonostante terapia con prednisone.

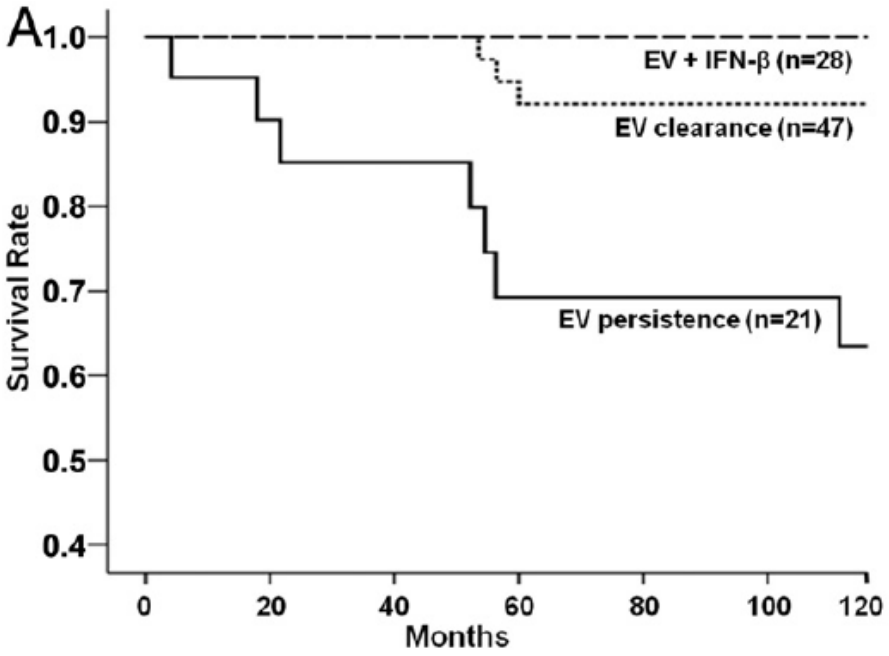
Protocollo di trattamento immunosoppressivo utilizzato nelle miocarditi presso il Dipartimento Cardiovascolare dell'Azienda Ospedaliero-Universitaria di Trieste

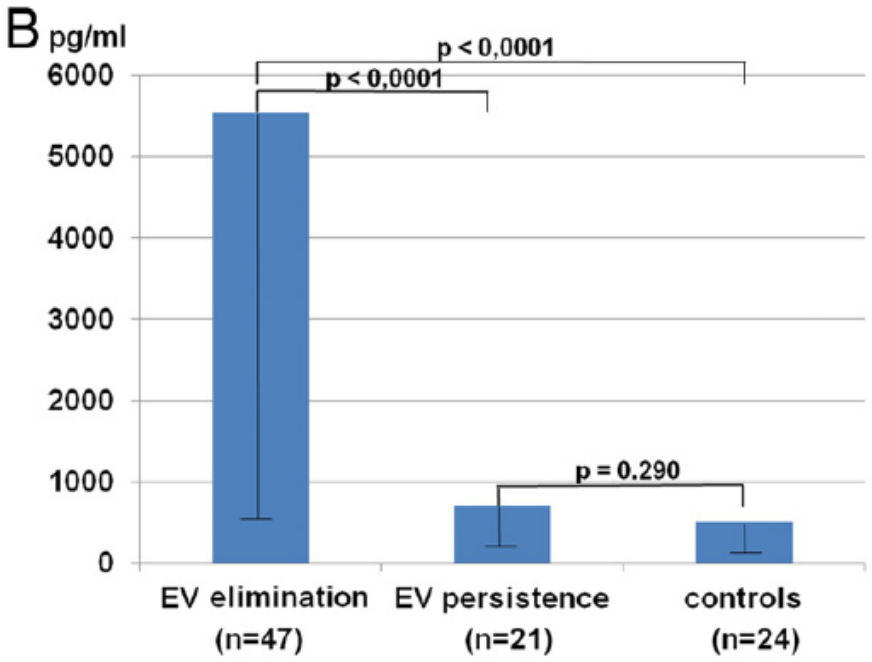


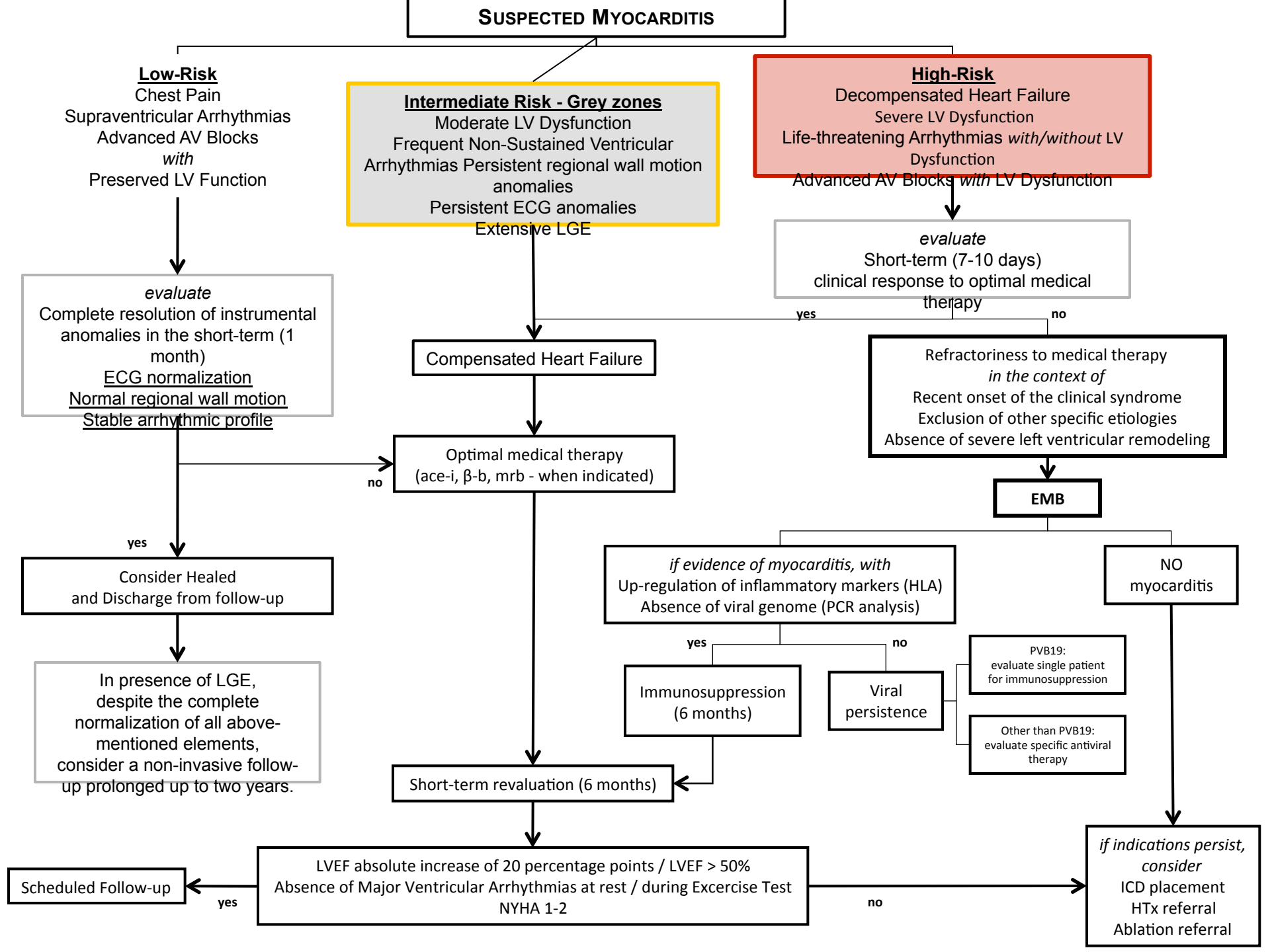
Research Correspondence

JACC Vol. 60, No. 14, 2012
October 2, 2012:1295–6

Interferon-Beta Improves Survival in Enterovirus-Associated Cardiomyopathy






SUSPECTED MYOCARDITIS
Low-Risk
Chest Pain
Supraventricular Arrhythmias
Advanced AV Blocks
with
Preserved LV Function
Intermediate Risk - Grey zones
Moderate LV Dysfunction
Frequent Non-Sustained Ventricular Arrhythmias Persistent regional wall motion anomalies
Persistent ECG anomalies
Extensive LGE
High-Risk
Decompensated Heart Failure
Severe LV Dysfunction
Life-threatening Arrhythmias with/without LV Dysfunction
Advanced AV Blocks with LV Dysfunction
evaluate
Complete resolution of instrumental anomalies in the short-term (1 month)
ECG normalization
Normal regional wall motion
Stable arrhythmic profile
evaluate
Short-term (7-10 days)
clinical response to optimal medical therapy
yes
no
Compensated Heart Failure
Refractoriness to medical therapy
in the context of
Recent onset of the clinical syndrome
Exclusion of other specific etiologies
Absence of severe left ventricular remodeling
Optimal medical therapy
(ace-i, β-b, mrb - when indicated)
no
EMB
yes
Consider Healed
and Discharge from follow-up
if evidence of myocarditis, with
Up-regulation of inflammatory markers (HLA)
Absence of viral genome (PCR analysis)
NO
myocarditis
yes
no
Immunosuppression
(6 months)
Viral
persistence
PVB19:
evaluate single patient for immunosuppression
Other than PVB19:
evaluate specific antiviral therapy
In presence of LGE,
despite the complete normalization of all above-mentioned elements,
consider a non-invasive follow-up prolonged up to two years.
Short-term revaluation (6 months)
LVEF absolute increase of 20 percentage points / LVEF > 50%
Absence of Major Ventricular Arrhythmias at rest / during Excercise Test
NYHA 1-2
yes
no
Scheduled Follow-up
if indications persist,
consider
ICD placement
HTx referral
Ablation referral

A proposal for the scheduled follow-up for patients with myocarditis

	Low-risk	Grey zones	High-risk
Time of clinical revaluations	1 month 6 months 2 years	3 months 6 months 12 months, then yearly	3 months 6 months 12 months, then yearly
Non invasive testing	Assess ECG and echocardiograpy normalization between 1 and 6 months. Cardiac RMN recommended.	Periodic evaluation of LVEF and LV remodeling (echocardiography). Periodic evaluation of the arrhythmic burden (Holter-ECG). Annual evaluation of arrhythmias induction during exercise test. Cardiac RMN with LGE evaluation, if not assessed at disease presentation.	
Exercise restriction	Yes, for 2 years	Yes, lifetime	Yes, lifetime
Life-time follow-up	No, if normalization at 2 years	Yes	Yes
Life-time therapy	No, if normalization at 2 years	Yes	Yes

Aspetti controversi e gestionali nelle miocarditi
Conclusioni (I)

- La miocardite è una malattia di difficile riconoscimento clinico, per la presentazione aspecifica e multiforme e per la sensibilità e specificità non ottimali delle indagini strumentali non invasive attualmente disponibili
- In presenza di quadro di presentazione clinica suggestivo di miocardite, le indagini diagnostiche di primo livello (es.ematochimici, ECG, Eco) hanno lo scopo di incrementare il livello di probabilità di malattia, di valutare la severità del quadro e sono utili per la diagnosi differenziale

Aspetti controversi e gestionali nelle miocarditi
Conclusioni (II)

- In casi selezionati di sospetta miocardite e grave profilo di rischio clinico è utile un approfondimento diagnostico con RM cardiaca che va eseguita in centri specializzati utilizzando approcci multipli.
- E' da tener presente tuttavia che nei casi di miocardite anche la RM, pur essendo discretamente specifica, non ha un'elevata sensibilità. Se persiste quindi un elevato sospetto pur con RM non diagnostica, è indicato approfondimento con CGF e BEM, che è da considerare il GOLD STANDARD diagnostico

Aspetti controversi e gestionali nelle miocarditi
Conclusioni (III)

- Nei pazienti con diagnosi di miocardite è utile uno stretto follow-up clinico-strumentale (es.bioumorali, ECG, ECO), importante per la gestione del paziente e dal punto di vista prognostico.
- Il trattamento specifico delle miocarditi con farmaci immunosoppressori o antivirali va deciso in casi selezionati e gestito in centri di riferimento