Management of myocarditis: Update 2018

J. Parissis
Athens, GR
Myocarditis: A short story...

- **1980**: First review on etiopathogenesis (Coxsackie viruses, immune system)
- **1985**: Dallas criteria
- **1987**: Cardiac autoantibodies in mouse model of autoimmune myocarditis
- **1995**: Myocarditis Treatment Trial
- **1995**: WHO definition
- **2009**: CMR imaging for suspected myocarditis
- **2013**: ESC first position paper on myocarditis

- **1974**: King’s endomyocardial biotome

Caforio, Heart Fail Rev 2013
Definition

- **Myocarditis (WHO):** inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immunohistochemical criteria

- **Inflammatory cardiomyopathy (WHO):** myocarditis and cardiac dysfunction

Richardson et al, Circulation 1996
Definition

- **Myocarditis (WHO):** inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immunohistochemical criteria

- **Inflammatory cardiomyopathy (WHO):** myocarditis and cardiac dysfunction

- **Viral myocarditis:** histological evidence of myocarditis and positive viral PCR

- **Autoimmune myocarditis:** histological evidence of myocarditis and negative viral PCR, (with or without serum cardiac autoantibodies)

Richardson et al, Circulation 1996
Caforio et al, Eur Heart J 2013
Epidemiology: key points

- Responsible for 9-12% of sudden death cases in young adults (post-mortem)
- Leads to DCM in 21% of patients over 3 years
- Biopsy-proven viral myocarditis bears a 19% mortality in 5 years

Fabre et al, Heart 2006
D’Ambrosio et al, Heart 2001
Grun et al, JACC 2012
Biopsies from 245 patients with “idiopathic” DCM

Kühl et al, Circulation 2005
## Etiology

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
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<tr>
<td><strong>Infectious</strong></td>
<td>viral, bacterial, fungal, parasitic, protozoal, rickettsial, spirochetal</td>
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<td><strong>Immune-mediated</strong></td>
<td>- auto-antigens (Giant cell, sarcoidosis, SLE etc)</td>
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<td>- allo-antigens (transplant rejection)</td>
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<td>- allergens (penicillin etc)</td>
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<td><strong>Toxic</strong></td>
<td>chemotherapy, heavy metals, scorpion sting, radiation, pheochromocytoma</td>
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</tbody>
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Caforio et al, Eur Heart J 2013
Pathophysiology: key points

- Viral trigger *plus* immune response

Kindermann et al, JACC 2012
Shi et al, JACC 2009
Noutsias et al, Circulation 2001
Pathophysiology: key points

Kindermann et al, JACC 2012
Pathophysiology: key points

- Human cardiomyocyte CAR (coxsackie and adenovirus receptor) expression may be a **predisposing factor** for facilitating viral myocarditis.

Shi et al, J Am Coll Cardiol 2009
Noutsias et al, Circulation 2001
Pathophysiology: key points

Ιογενής λοίμωξη  →  Γενετική προδιάθεση

Αρχική προσβολή

Ανοσολογική απάντηση

Δυσλειτουργία

Απουσία συμπτωμάτων  →  Καρδιακή ανεπάρκεια  →  Αρρυθμίες

Χρόνια φάση

Ιάση  →  Μυοκαρδιοπάθεια

Farmakis, HJC 2012
## Diagnosis: Key points

### Table 4  Diagnostic criteria for clinically suspected myocarditis

**Clinical presentations**
- 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. Myocardciotolysis markers
   - Elevated TnT/Tnl

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 endocarditary thrombi

IV. Tissue characterization by CMR
   - Oedema and/or LGE of classical myocarditic pattern (see text)

_Caforio et al, Eur Heart J 2013_
Diagnosis: Key points

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Diagnostic criteria for clinically suspected myocarditis</th>
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Clinical presentations
- Acute chest pain, pericarditic, or pseudo-ischaemic
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≥1 clinical presentations and
≥1 diagnostic criteria or
≥2 diagnostic criteria

Caforio et al, Eur Heart J 2013
Diagnosis: Key points 1

- **Biomarkers**: not specific, but troponins elevated more frequently than CKMB

- **Virus serology**: low diagnostic value (only 4% agreement with biopsy PCR) due to: delay in testing, cross-reactions, past exposure to highly prevalent viruses (70% PRVB19 IgG+) - not to be routinely performed

  Mahfoud F et al, Eur Heart J 2011

- **ECG**: low sensitivity for diagnosis, but useful for risk stratification (QRS >120 ms, QTc >440 ms, abnormal QRS axis, PVCs indicate poor outcome)

  Ukena et al, Eur J Heart Fail 2011
Echocardiography:
• assess geometry and function
• rule-out other causes of HF
• useful tips (fulminant: no LV dilatation & increased wall thickness due to edema vs acute: LV dilatation & normal wall thickness)

Ukena et al, Eur J Heart Fail 2011
CMR

- Highly in agreement with biopsy
- **LGE**, the best predictor of mortality in biopsy-proven viral myocarditis

Grun et al, JACC 2012
Endomyocardial biopsy

- **Dallas criteria** alone have low diagnostic/prognostic value (variation in interpretation, inability to detect noncellular mediated inflammation)

Kindermann et al, Circulation 2008
Endomyocardial biopsy

- **Immunohistology** to detect inflammation and **molecular studies** to detect viral genome enhance diagnostic & prognostic value and may guide therapy

Kindermann et al, Circulation 2008
Endomyocardial biopsy

ESC Guidelines

• New-onset HF <2w and hemodynamic compromise (IB)
• New-onset HF 2w-3m, dilated LV and new arrhythmias or no response to therapy (IB)
Endomyocardial biopsy

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

Recommendations
11. Tissue obtained from EMB should be analysed using histology, immunohistochemistry, and viral PCR (on heart tissue and a blood sample).
13. Endomyocardial biopsy may be repeated if necessary to monitor response to aetiology-directed therapy, or if a sampling error is suspected in a patient with unexplained progression of heart failure.

Caforio et al, Eur Heart J 2013
Therapy: key points

- No standard therapy for the majority of cases
- General heart failure therapy & physical rest
- Mechanical support & transplantation for severe HF
- Immunosuppression for specific types
- Immune/anti-viral therapies not yet established
Therapy: key points

Farmakis, HJC 2012
Heart failure therapy

• Standard HF regimens (RAASi, β-blockers, MRA) according to current guidelines

• Data on myocarditis mainly from animal models

• **Duration of HF therapy?**
ACEi & ARBs

- Captopril, losartan and olmesartan reduced inflammation, necrosis, fibrosis and LV remodelling in animal models

Seko, Clin Sci (Lond) 2006
Bahk et al, Int J Cardiol 2008
Sukumaran et al, Exp Biol Med (Maywood) 2010
• Lack of β-blocker treatment is associated with poor outcome (along with NYHA and immunohistology)

Kindermann et al, Circulation 2008
β-blockers

- Should be avoided in acute severe HF

- Type of β-blocker:
  - **Carvedilol** was cardioprotective in rats (anti-inflammatory properties) but metoprolol and propranolol were not
  - **Metoprolol** increased inflammation, necrosis and mortality in mice

Yuan et al, Am J Physiol Heart Circ Physiol 2004
Aldosterone antagonists

- **Eplerenone** improved survival, reduced inflammation and suppressed expression of genes related to fibrosis and remodeling in rats

Xiao et al, Eur J Heart Fail 2009
Diuretics

• **Torsemide** reduced progression to DCM in rats

Veeraveedu et al, Eur J Pharmacol 2008
Physical activity

- may worsen outcome in acute/subacute phase but beneficial in chronic HF
- should be restricted during the acute phase and for **at least 6 months** in athletes and non-athletes
- return to training and competition if LV function and cardiac dimensions return to normal and no clinically relevant arrhythmias exist

36th Bethesda Task Force, Maron et al, JACC 2005
ESC WP Position Paper, Cadorio et al, Eur Heart J 2013
Device therapy

- **Temporary pacemaker** in symptomatic AV block II or III (often in Chaga's & Lyme diseases)

- **ICD** after VF or symptomatic VT

- Avoid **premature implantation** of ICD/CRT-D as LV function may improve with medical HF therapy (but early in **giant-cell or sarcoidosis**)

- How long can we wait for improvement?

- Is there a role for EPS?  

Kindermann et al, JACC 2012
Mechanical support

- VADs or ECMO
- Bridge to recovery or transplantation
- Considered early for patients with fulminant acute myocarditis when maximal medical therapy fails
  - Despite severe initial presentation, good overall prognosis (>60-80% survival, high rate of LV function recovery)

Mirabel et al, Crit Care Med 2011
Rajagopal et al, Crit Care Med 2010
ECMO use in AHF: National registry of Finland

- 53% weaned directly, 9% bridged to ventricular assist device, 11% bridged to transplantation
- Cumulative one year survival 61%
- According to indication of ECMO:
  - ACS 42%
  - Myocarditis 71%
  - Cardiomyopathy 62%
  - Primary graft failure 50%
  - Postcardiotomy shock 62%
  - Other 50%

ESC HF Congress 2017
Immunomodulatory therapies

- Immunosuppression
- Immunoglobulin
- Immunoabsorption
- Antiviral
Immunomodulatory therapies

• ≥20 treatment trials with immune or anti-inflammatory therapy

• Limitations:
  – Use of Dallas criteria only - lack of immunohistochemistry and molecular analysis (eg, viral myocarditis treated with immunosuppression)
  – Spontaneous remission is high and not considered: in ESETCID study, inflammation was eradicated in 60% of immunosuppression arm and in 40% of placebo arm
  – Lack of control groups

Hufnagel et al, Herz 2000
Immunosuppression

- Prednisone, cyclosporine, azathrioprine

- Clear role in giant cell myocarditis, sarcoidosis and other immune conditions (eg. SLE)

- Conflicting evidence in other forms

- Is the a role for blind immunosuppression in non-responding cases?

- Only after ruling out active infection on EMB by PCR

Caforio et al, Eur Heart J 2013
Immunosuppression

- **Giant cell myocarditis:**
  - corticosteroids, cyclosporine, azathioprine combinations
  - survival, 12 months vs 3 months if untreated

- **Sarcoidosis:**
  - high-dose corticosteroids
  - 5-year survival, 60-90%

Cooper et al, Am J Cardiol 2008
Kim et al, Am Heart J 2009
Nunes et al, Semin Respir Crit Care Med 2010
Immunosuppression
Myocarditis Treatment Trial

- N=111
- Prednisone with azathioprine or cyclosporine vs placebo for 6 months
- No difference in survival or LVEF improvement

Immunosuppression
Myocarditis Treatment Trial

- No immunohistology for the detection of inflammatory cells and no molecular biological analyses for viral exclusion
- Patients with viral infection treated with immuno-suppression

n=85
Prednisone & azathiprine vs placebo for 6 months
Significant improvement in LVEF and LV dimensions

Frustaci et al, Eur Heart J 2009
Immunosuppression
TIMIC Trial

- All biopsies studied with histology and immunohistology and viral infection ruled out by molecular methods

Frustaci et al, Eur Heart J 2009
Immunoglobulin

- High dose intravenous immunoglobulin
- Antiviral and immunomodulating actions
- Conflicting evidence (no benefit in adults, benefit in children)
- No benefit in IMAC trial (recent-onset DCM, only 15% biopsy-proven myocarditis of non-specified cause)

McNamara et al, Circulation 2001
Elimination of anticardiac antibodies

Small studies in DCM, improved LV function and decreased myocardial inflammation

Ongoing trial in 200 pts in Europe

Mobini et al, I Autoimmun 2003
Felix et al, J Am Coll Cardiol 2000
Antiviral therapy

• Viral infection a common cause

• Encouraging results with IFN-β
LV dysfunction and viral persistence (adenovirus/enterovirus) – 2 studies

IFN-β induced:

• Viral elimination
• Improved NYHA
• Improved LVEF
• Improved survival

Kuhl et al, Circulation 2003
Kuhl et al, J Am Coll Cardiol 2012 (letter)
IFN-\(\beta\): BICC trial

- 143 patients, inflammatory DCM and confirmed viral infection (adeno/enterovirus, PRVB19)
- Betaferon for 6 months:
  - Viral elimination (*not complete for PVB19*)
  - Improved NYHA and PGA

Schultheiss et al, Circulation 2008 (abstract)
TREATMENT ALGORITHM

Inflammatory Cardiomyopathy—Pathophysiological Mechanisms and Treatment

Myocarditis/Inflammatory Cardiomyopathy

Virus positive

Antivirale therapy

Virus negative
Inflammation negative

Mutation-screening

Risc-stratification

Perforin + >2.9/mm²

or

Elevated infil. cells >10 CD3

Perforin neg CD3 <10 cells

Sympt. therapy

Control biopsy

Choronic inflammation

Immunosupr. therapy

Coxsackie/Adeno virus

Parvo Virus B19 mRNA pos

Interferon β

Telbivudine?

New drugs?

Immunosupr. therapy

Figure 4. Flow chart of inflammatory cardiomyopathy: Pathophysiological mechanisms and treatment.
Conclusions I

• Despite advances, standard therapy remains limited to \textit{general HF therapy} in most cases

• Several clinical trials on immune therapies suffer \textit{methodology problems}

• \textbf{Biopsy} may guide therapy if classical histology is combined with immunohistochemistry staining for inflammation and molecular studies for viral genome detection
Conclusions II

• **Immunosuppression**
  – indicated for acute giant cell myocarditis, sarcoidosis and acute myocarditis associated with autoimmune diseases (eg SLE)
  – may be beneficial in virus-negative inflammatory cardiomyopathy

• **Antiviral therapy** may be beneficial in proven viral inflammatory cardiomyopathy
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, Sabine Pankuweit, Eloisa Arbustini, Cristina Basso, Juan Gimeno-Blanes, Stephan B. Felix, Michael Fu, Tiina Heliö, Stephane Heymans, Roland Jahns, Karin Klingel, Ales Linhart, Bernhard Maisch, William McKenna, Jens Mogensen, Yigal M. Pinto, Arsen Ristic, Heinz-Peter Schulteiss, Hubert Seggewiss, Luigi Tavazzi, Gaetano Thiene, Ali Yilmaz, Philippe Charron, and Perry M. Elliott
Πανελλήνια καταγραφή μυοκαρδίτιδας
ΕΜΕΚΑ – ΟΕ Καρδιακής Ανεπάρκειας ΕΚΕ

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<th>Visit 1 (1 month)</th>
<th>Visit 2 (3 months)</th>
<th>Visit 3 (6 months)</th>
<th>Visit 4 (12 months)</th>
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