Myocardites aigües

71ème Journée Française de Médecine

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MYOCARDITIS

Plain definition:

" inflammation of the myocardium"

But numerous classification schemes:

Chronology

- Boikan WJ. Virchow Arch 1931;282:46
- Burch GE. Bull Tulane Medical Faculty 1948;8:1
- Dec GW. N Engl J Med 1985;312:885
- Fenoglio JJ. N Engl J Med 1983;308:12
- Lustock MJ. Dis Chest 1955;28:243
- Lieberman EB. J Am Coll Cardiol 1991;18:1617

Etiology

- Saphir O. Arch Pathol 1941;32:1000
- Gore I. Am Heart J 1947;34:827

Morphology

- Baandrup U.Br Heart J 1981;45:475
- Edwards WD. Mayo Clin Proc 1982;57:419
- Hammond EH. Circulation 1983;68:3A
- Maisch B. Am J Cardiol 1983;52:1072
- Unverferth DV. Circulation 1983;68:1194
- Mills AS. Circulation 1984;70(suppl II):401
- Cassling RD. Am Heart J 1985;110:713
- Linder J. Arch Pathol 1985;109:917
- Oliveira JSM. Am Heart J 1985;110:1092
- Sanderson JE. Am J Cardiol 1985;55:755
- Waller BF. J Am Coll Cardiol 1986;7:120
- Aretz HT. Am J Cardiovasc Pathol 1987;1:3
- Kurnick JT. Eur Heart J 1987;(suppl E):14
- Southern JF. Eur Heart J 1987;7(suppl E):23
- Lieberman EB. J Am Coll Cardiol 1991;18:1617

HISTOPATHOLOGY: DALLAS CLASSIFICATION

inflammation of the myocardium with or without associated myocyte necrosis

	Active	Borderline	Persistent	Healing	Healed
Inflammatory infiltrate	++	+ scattered	unchanged	decrease	resolved
Myocyte damage	++ necrosis, vacuolization irregularities disruption	absent	unchanged	decrease	resolved
Interstitial fibrosis	±		±	±	±
Remarks	endocardial and subendocardial layers	second EMB or re-examination	refers to previous EMB	refers to previous EMB	refers to previous EMB

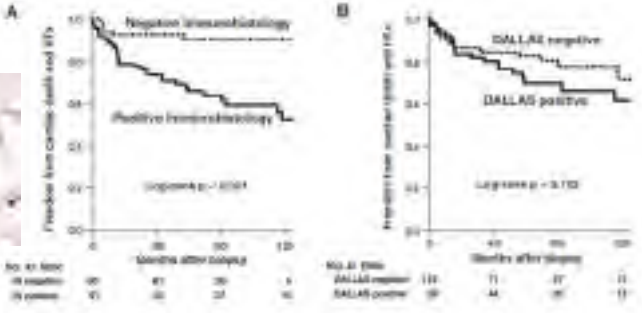
varibility of the interpretation, lack of prognostic value, low sensitivity, no impact on the treatment

Aretz HT et al. Am J Cardiovasc Pathol 1987;1:3

Predictors of Outcome in Patients With Suspected Myocarditis

Ingrid Kindermann, MD; Michael Kindermann, MD; Reinhard Kandolf, MD; Karin Klingel, MD; Burkhard Bültmann, MD; Thomas Müller; Angelika Lindinger, MD; Michael Böhm, MD

- 181 pts, 42±15 years with clinically suspected viral myocarditis, 59 ± 42 months FU.
- primary end point was time to cardiac death or heart transplantation



Circulation. 2008;118:000-000

Clinical scenarios

Clinical Scenario	Duration of Illness	Pathological Correlates	Prognosis	Treatment
Acute myocardial infarction-like syndrome with normal coronary arteries	Several hours or days	Active lymphocytic myocarditis or, rarely, necrotic eosinophilic myocarditis or giant-cell myocarditis	Good if lymphocytic myocarditis is present on biopsy	Supportive
Heart failure with normal-sized or dilated left ventricle and hemodynamic compromise	Less than 2 wk	Active lymphocytic myocarditis or, less commonly, necrotizing eosinophilic myocarditis or giant-cell myocarditis	Good in fulminant lymphocytic myocarditis, but acute care often requires inotropic or mechanical circulatory support	Supportive; possible use of corticosteroids or IVIG in children
Heart failure with dilated left ventricle and new ventricular arrhythmias, high-degree heart block, or lack of response to usual care within 1 to 2 wk	A few weeks to months	Giant-cell myocarditis, eosinophilic myocarditis, or lymphocytic myocarditis	Poor; high likelihood of death or need for cardiac transplantation if giant-cell myocarditis is found on biopsy	Variable therapy according to histopathological results
Heart failure with dilated left ventricle without new ventricular arrhythmias or high-degree heart block	A few weeks to months	Nonspecific changes most likely, with the presence of viral genomes in 25 to 35% of patients and of lymphocytic myocarditis (Dallas criteria) in about 10%	Good in the first several years, but a risk of late disease progression with heart failure and cardiomyopathy	Supportive; definition of genomic predictors of risk under investigation

Copper LT. NEJM 2009;360:1526-38.

Role of endomyocardial biopsy ?

The role of EMB in 14 clinical scenarios

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

Cooper LT AHA/ACCF/ESC scientific statement JACC 50 2007

Recommendation I level of evidence B

1 New-onset heart failure of <2 *weeks'* duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise

2 New-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks

Cooper LT AHA/ACCF/ESC scientific statement JACC 50 2007

Clinical scenarios

Clinical Scenario	Duration of Illness	Pathological Correlates	Prognosis	Treatment
Heart failure with eosinophilia	Any duration	Eosinophilic or hypersensitivity myocarditis or eosinophilic endomyocarditis	Poor	Supportive, including identification and treatment of underlying cause; possible use of corticosteroids for hypersensitivity myocarditis
Heart failure with dilated left ventricle and new ventricular arrhythmias, high-degree heart block, or lack of response to usual care in 1 to 2 wk	More than several months	Cardiac sarcoidosis, idiopathic granulomatous myocarditis, or specific infection (e.g., Trypanosoma cruzi and Borrelia burgdorferi); nonspecific changes most likely	Increased risk or need for pacemaker or implantable cardioverter-defibrillator if sarcoidosis is confirmed on biopsy	Supportive; corticosteroids for biopsy-proven cardiac sarcoidosis
Heart failure with dilated left ventricle without new ventricular arrhythmias or high-degree heart block	More than several months	Nonspecific changes most likely; increased number of inflammatory cells shown by sensitive immunostaining in up to 40% of patients and the presence of viral genomes in 25 to 35%	Depends on functional class, ejection fraction, and the presence or absence of inflammation and viral genomes on biopsy	Supportive; antiviral treatment and immunosuppression under investigation

Copper LT. NEJM 2009;360:1526-38.

Realization of EMB

- Strict conditions of realization to avoid complications
- Learning curve

Risks associated with EMB 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

Deckers JACC 1992 19 43

Complication Rate of Right Ventricular Endomyocardial Biopsy via the Femoral Approach

A Retrospective and Prospective Study Analyzing 3048 Diagnostic Procedures Over an 11-Year Period

Table 2. Major Complications of 2505 Retrospective and 543 Prospective EMB Procedures

Major Complications of EMB Procedures	Retrospective, Absolute/%	Prospective, Absolute/%
Pericardial tamponade with pericardiocentesis	2/0.08	0/0
Persistent complete AV block with permanent pacemaker required	1/0.04	0/0
Urgent cardiac surgery	0/0	0/0
Advanced cardiac life support	0/0	0/0
Hemothorax or pneumothorax	0/0	0/0
Death	0/0	0/0

right femoral vein approach
under biplane fluoroscopic control

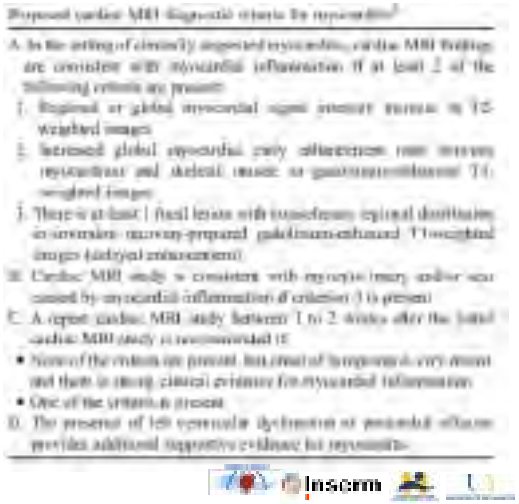
Table 3. Minor Complications of 2505 Retrospective and 543 Prospective EMB Procedures

Minor Complications of EMB Procedures	Retrospective, Absolute/%	Prospective, Absolute/%
Small pericardial effusions	...	4/0.74
New	...	3/0.55
Increase	...	1/0.18
Conduction abnormalities	[illegible]	20/3.7
RBBB sustained (>24 h)	...	2/0.37
RBBB temporary (<24 h)	...	6/1.10
AV block II Mobitz, 2:1 periprocedural (<10 min) requiring 0.5 to 1 mg atropine	...	2/0.37
AV block III periprocedural (<10 min) requiring 0.5 to 1 mg atropine	...	2/0.37
AV block III temporary (<24 h) requiring atropine+temporary pacemaker	5/0.20	[illegible]
Arrhythmias	...	[illegible]
Nonsustained ventricular tachycardia (<10 ventricular complexes)	...	0/0
Episodes (<12 h) of atrial fibrillation	...	[illegible]
Persistent atrial fibrillation with cardioversion	...	1/0.18

Holzmann Circulation. 2008;118:

Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper

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



Freidrich JACC 2009 53, 1475–87

Proposal cardiac MRI diagnostic criteria for myocarditis[5]

A. In the setting of clinically suspected myocarditis, cardiac MRI findings are consistent with myocardial inflammation if at least 2 of the following criteria are present:
1. Regional or global myocardial signal intensity increase in T2-weighted images
2. Increased global myocardial early enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
3. There is at least 1 focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (delayed enhancement)

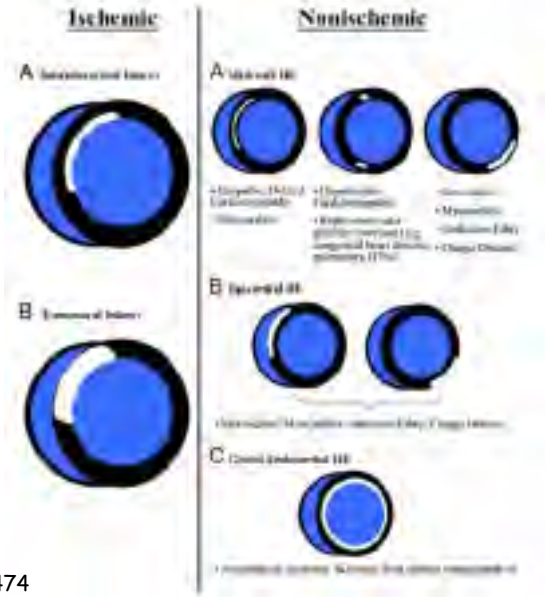
B. Cardiac MRI study is consistent with myocyte injury and/or scar caused by myocardial inflammation if criterion 3 is present

C. A repeat cardiac MRI study between 1 to 2 weeks after the initial cardiac MRI study is recommended if
- None of the criteria are present, but onset of symptoms is very recent, and there is strong clinical evidence for myocardial inflammation
- One of the criteria is present

D. The presence of left ventricular dysfunction or pericardial effusion provides additional supportive evidence for myocarditis

Myocardial tissue characterization

- T1- or T2-weighted sequences enable myocardial tissue characterization because of different relaxation properties of fat, muscle, inflammation
  - viability / post-myocardial infarction scarring
  - highly specific patterns of fibrosis and scarring described for many nonischemic cardiomyopathic processes
- Diagnostic, pathophysiology
- Viability: with/without stress



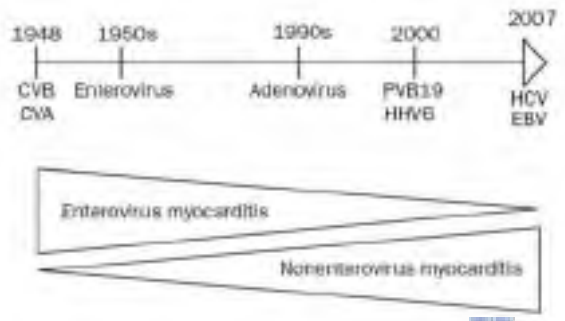
Mahrholdt Eur Heart J 2005;26: 1461–1474

Etiologies

Infectious	Toxins
Viral: adenovirus, coxsackie B, Hepatitis C, HV6, HIV, Parvovirus B19	**Drugs**: aminophylline,anthracyclines, cocaine
Bacterial: diphteria, tuberculosis, streptococcus A, pneumoniae	**Environmental**: arsenic, CO
Ricketsial: Q fever	**Hypersensitivity reactions**: benzodiazepines, cephalosporins, dobutamine, penicilins, smallpox vaccination
Fungal	**Venoms**: bee, spiders, scorpion, snake
Protozoal: Chagas, toxoplamosis	**Autoimmune diseases**: GCM, systemic lupus, Wegener's granulomatous
Helminthic	**Systemic disease**: Celiac disease, Churg Strauss, HES, sarcoidosis
	Other: cardiac rejection

Etiologies

- Viral and post viral myocarditis: major cause of acute and chronic DCM
- Seroepidemiologic and molecular studies:
  - linked coxsackievirus B from 1950s to 1990s
  - With EMB shifted from coxsackievirus B to adenovirus in the late 1990s
  - and then to parvovirus B19 and other viruses

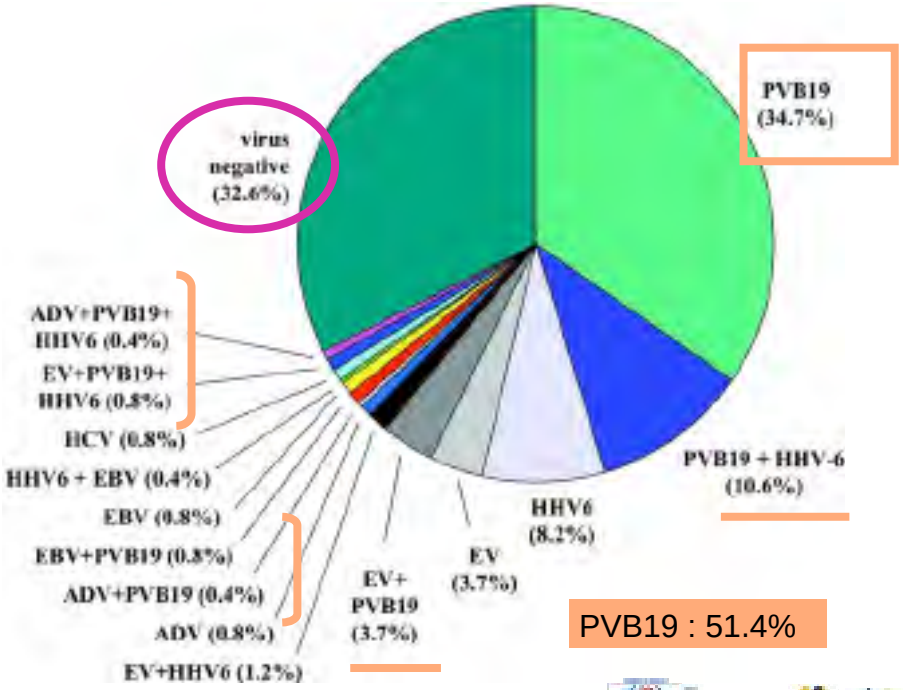


Tracking for the virus

Diagnosis	# Samples	# of Samples PCR+	PCR Amplimer (#)*
Myocarditis	624	239 (38%)	Adenovirus 142 (23%) Enterovirus 85 (14%) CMV 18 (3%) Parvovirus 6 (<1%) Influenza A 5 (<1%) HSV 5 (<1%) EBV 3 (<1%) RSV 1 (<1%)
DCM	149	30 (20%)	Adenovirus 18 (12%) Enterovirus 12 (8%)
Total	773	269 (35%)	
Controls	215	3 (1.4%)	Enterovirus 1 (<1%) CMV 2 (<1%)

*In 26 samples from myocarditis patients, two viruses were detected.

Bowles, N. E. et al. JACC 2003;42:466-472



Kühl et al. Circulation 2005; 111: 887.

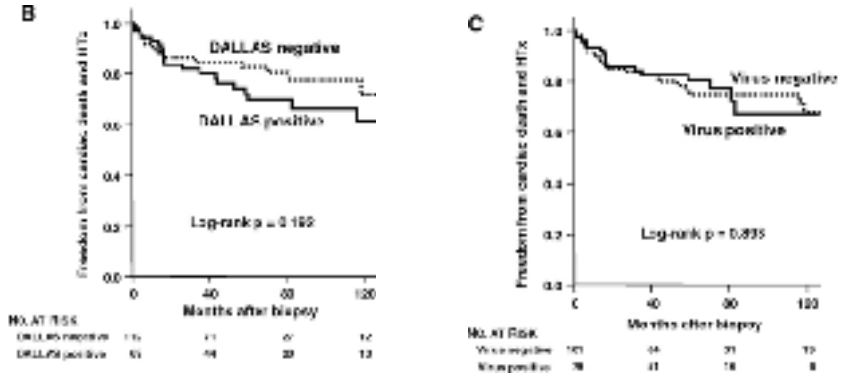
Prognostic signification?

Baseline Characteristics of the 181 Patients with suspected myocarditis

• Age, y		42.4±15.3, men 122 (67.4)
• NYHA functional class		
	I	39 (21.5)
	II	52 (28.7)
	III	73 (40.3)
	IV	17 (9.4)
• LV end-diastolic dimension index, mm/m		36.2±6.90
• LV ejection fraction, %		37.7±18.5
• LV end-diastolic pressure, mm Hg		15.6±7.40
• Endomyocardial biopsy results		
•		
• Immunohistology positive		91 (50.3)
• Immunohistology negative		90 (49.7)
•		
• Acute myocarditis		5 (2.8)
• Borderline myocarditis		64 (35.4)
• No myocarditis		112 (61.9)
•		
• Detection of viral genome		79 (43.9)

Kindermann, I. et al. Circulation 2008;118:639-648

Baseline Characteristics of the 181 Patients with suspected myocarditis



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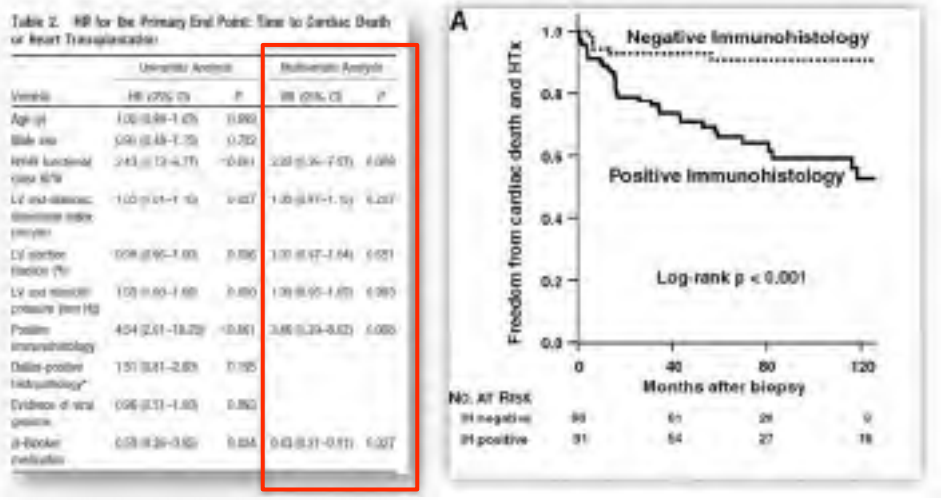

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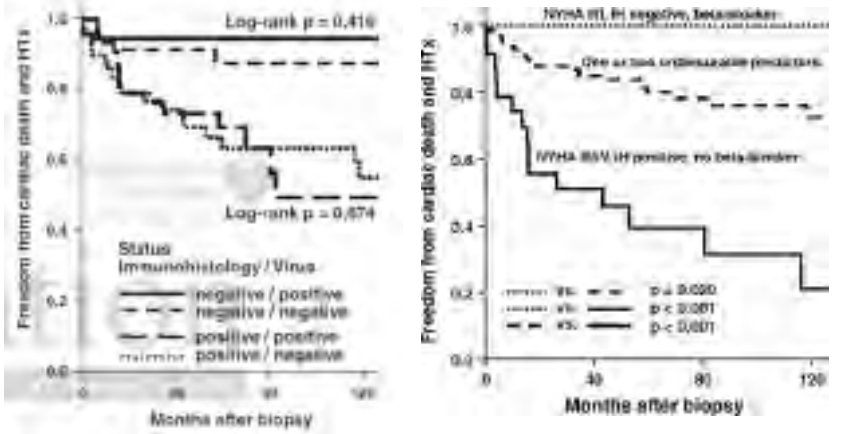


Kindermann, I. et al. Circulation 2008;118:639-648

Therapeutic implication?

Treatment

- Supportive therapy for LV dysfunction.
  - patients will improve with ACEI, BB, diuretics,
- When deterioration despite optimal medical management:
  - mechanical circulatory support LVAD or extracorporeal membrane oxygenation, as a bridge to transplantation or recovery
- Refrain from aerobic activity for a period of months after the clinical onset of the disease
  - reintroduction of aerobic activities depends on the severity of LV dysfunction and the extent of recovery

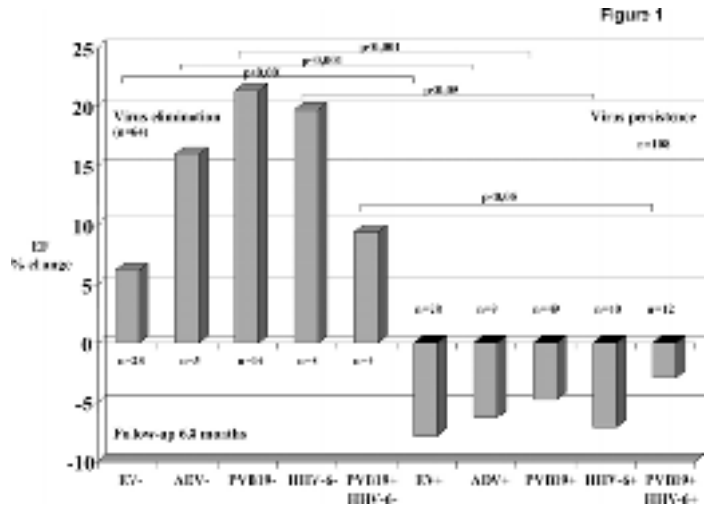
Arrhythmias

- Should be managed conventionally
- Acute myocarditis:
  - temporary pacemakers may be required for symptomatic bradycardia or complete heart block.
- Patients with symptomatic or sustained ventricular arrhythmias:
  - amiodarone
  - possibly an ICD, even if active inflammation is still present.
- The prognostic importance and treatment of nonsustained VT in acute myocarditis
  - not evaluated.

Antiviral therapy

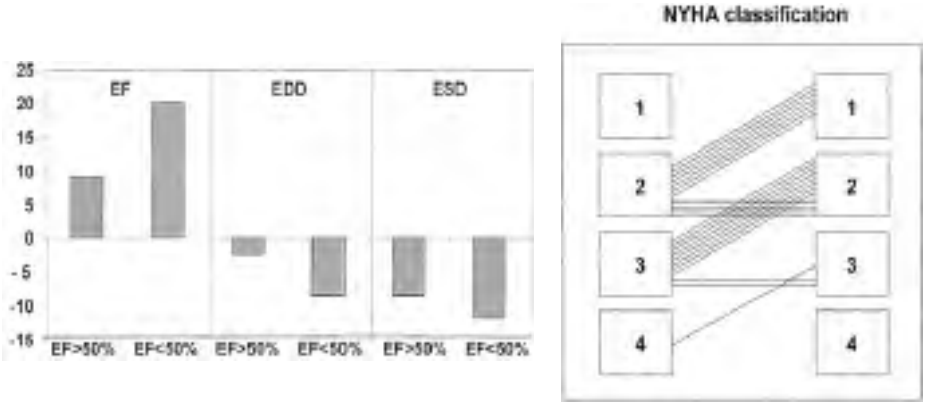
- Acute myocarditis are diagnosed weeks after viral infection:
  - it is unlikely that antiviral therapy would be provided early enough to be of benefit in acute viral myocarditis
  - successful antiviral therapy or vaccines would need to be tailored to current viruses (changes in seroepidemiology)
- Interferon beta:
  - patients with viral persistence in chronic, stable dilated cardiomyopathy
  - viral clearance achieved, significant increase in LV function in the treatment group

Hemodynamic course in 172 patients during a median follow-up of 6.8 months BICC study

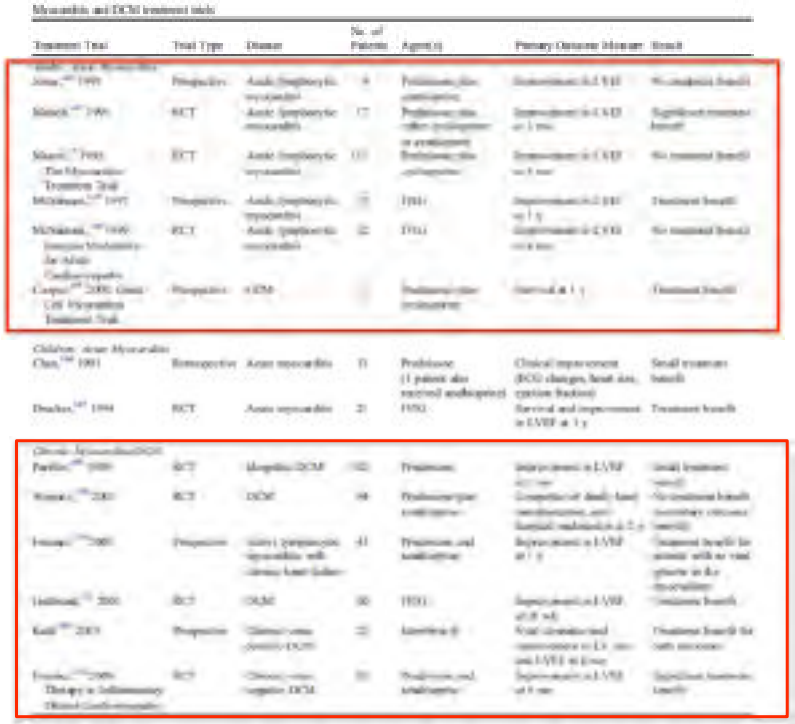


Kuhl, U. et al. Circulation 2005;112:1965-1970

Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction.22 pts



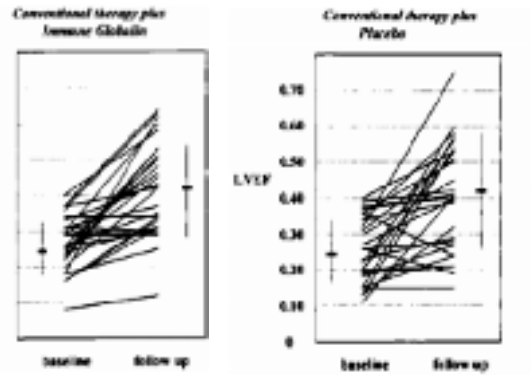
Kuhl et al Circulation 2003;107:2793-8



Controlled Trial of Intravenous Immune Globulin in Recent-Onset Dilated Cardiomyopathy

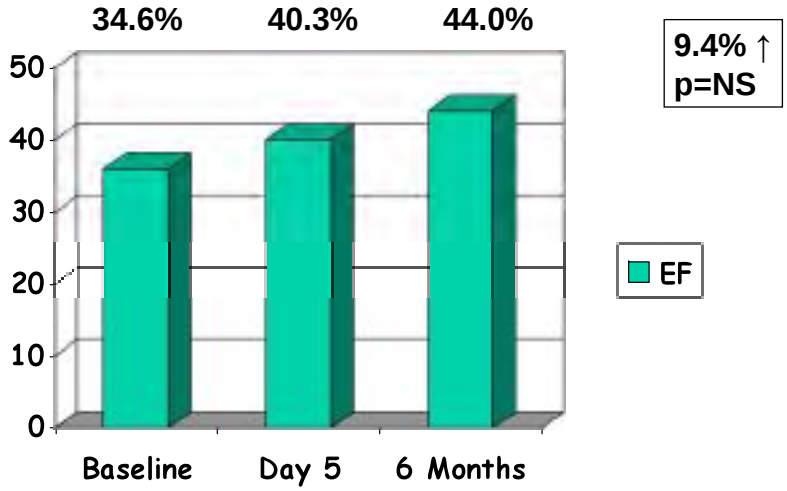
Dennis M. McNamara, MD; Richard Holubkov, PhD; Randall C. Starling, MD; G. William Dec, MD; Evan Loh, MD; Guillermo Torre-Amione, MD; Alan Gass, MD; Karen Janosko, RN, MSN; Tammy Tokarczyk, RN, BSN; Paul Kessler, MD; Douglas L. Mann, MD; Arthur M. Feldman, MD, PhD; for the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) Investigators

- 62 pts MCD < 6 months
- IVIG did no better than those given placebo.
- The use of IVIG for acute myocarditis in adults is not recommended.
- IVIG has not been evaluated rigorously for the treatment of chronic dilated cardiomyopath with inflammation or viral persistence.



Circulation 2001;103:2254-9

Immuno-adsorption



Cooper, LT et al J Clin Apheresis 2007

Immunosuppressive treatment

- **Acute lymphocytic myocarditis**
  - RCT were negative or only marginally positive
  - immunosuppression is not beneficial in the routine treatment of acute lymphocytic myocarditis.
  - future trials involving patients with acute myocarditis are probably not feasible since the disease affects so few patients, has a highly variable clinical prognosis, and is associated with substantial improvement in left ventricular function with usual care.
- **Giant-cell myocarditis**
  - transplant-free survival in patients with may be prolonged with a combination of cyclosporine and corticosteroids.
- **Chronic, moderate-to-severe cardiomyopathy**
  - May be broader role for immunosuppression
  - condition is unlikely to improve further after optimal care has been given for 6 to 12 months.
  - In one trial involving 84 patients with chronic DCM and HLA expression on cardiomyocytes, the use of azathioprine and prednisone was associated with improvement in cardiac function and in NHYA

Conclusion

- Lots of question are unsolved
  - heterogeneity of clinical scenarios
  - echocardiography
  - role of the endomyocardial biopsy
    - necessity of histologic confirmation
  - cardiac MRI:
    - does not respond to all the diagnostic and prognostic issues
  - transcriptomics, proteomics, genetics ?
  - specific treatment:
    - ?