Myocarditis & Inflamatory Cardiomyopathy

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DEFINITIONS

MYOCARDITIS: inflamatory infiltrate of the myocardium (- acute/active, - chronic)

INFLAMATORY CM: Myocarditis in association with cardiac dysfunction

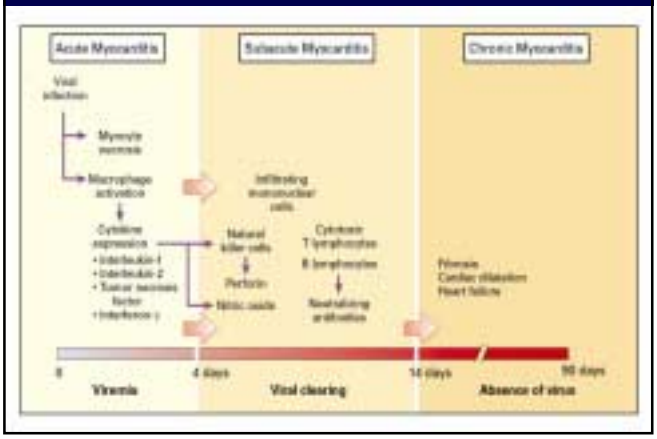
VIRAL CARDIOMYOPATHY: Viral persistence in a dilated heart (without inflamation)

WHO / WHF task force, 1995

Pathophysiology

Time course of experimental myocarditis in mice, Kawai Circ 1999

Modified by Feldman AM, Mcnamara D. Myocarditis. NEJM 2000;343:1388



Natural Course of Viral Heart Disease

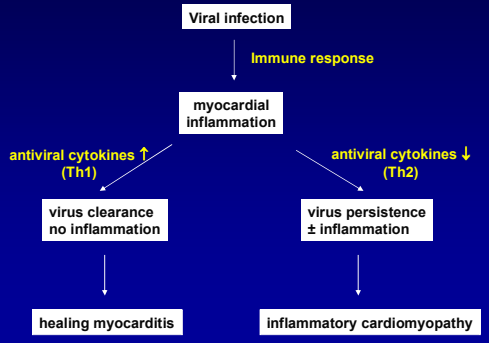


Table 1. Table Illustrating the TH1/TH2 Paradigm Indicating the Characteristics of TH1 and TH2 T Cell Subsets

TH1	TH2
Activate macrophages (delayed-type hypersensitivity)	Activate B cells (humoral immunity)
IL-12 and IFN- Induces TH1 Subset	IL-4 induces TH2 subset
Secrete IFN- and IL-2 that inhibit TH2	Secrete IL-4 and IL-10 which inhibit TH1
IgG 2a (mice), IgG1, IgG3 (humans)	IgE, IgG1 (mice), IgG4 (humans)

Recent evidence suggests that both B and T cells are involved in polarized cytokine production[71] and $CD4^+$ and $CD8^+$ T cells as well as natural killer and dendritic cells may also be involved in production of polarizing cytokines.

Cunningham MW Am J Pathol 2001;159:5-12

MYOCARDITIS

Etiology & Clinical Features

INFLAMMATORY CARDIOMYOPATHY -

Definition: myocarditis in association with cardiac dysfunction:

Idiopathic

Autoimmune

Infectious

VIRAL INFECTION and MYOCARDITIS and DCM

Hufnagel, Herz 2000;25:279-285

- Using PCR and in-situ hybridization techniques in endomyocardial biopsies viral genomes could be detected
- **Most common viral genome** is **enterovirus RNA** in most cases **coxsackievirus B**
- **Other RNA viruses:** hepatitis C, influenza
- **DNA virus genome:** adenovirus, cytomegalic virus, and Epstein-Barr virus.

MYOCARDITIS: Diagnosis

Clinical features:

1)asymptomatic + ECG abnormalities

2) CHF with ventricular dilatation

3) Fulminant heart failure/collapse with severe LV dysfunction,dilatation

Recent history of flu-like symptoms

Tzivoni D

MYOCARDITIS: Diagnosis

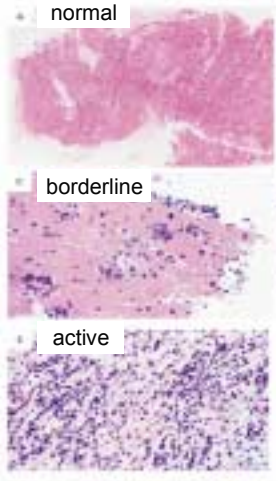
ECG: ventricular arrhythmias, heart block, ST-T changes, sinus bradycardia, changes similar to pericarditis or acute myocardial infarction.

Lab: leukocytosis, elevated ESR, eosinophilia, elevated cardiac enzymes, CK, troponin,

testing for the presence of viral genome in endocardial biospy by PCR

Antimyosin scintigraphy can identify myocardial inflammation in the absence of histologic evidence.

Tzivoni D



Myocarditis Dallas criteria

- inflamatory infiltrate without necrosis

- inflamatory infitrate with necrosis

Feldman AM, Mcnamara D. Myocarditis. NEJM 2000;343:1388

Limitation of EMB in myocarditis

- Once considered the gold standard for Dg
- Low rate of positive histologic findings
- Sampling error
- Variability in histological evaluation

THE WORLD HEART FEDERATION (WHF), COUNCIL ON CARDIOMYOPATHIES, FOUNDED

2 EXPERT COMMITTEES:

1. On histopathology and immunohistochemistry

2. On molecular diagnosis of infective or viral cardiomyopathies

Maish B et al. Herz 2000

IMMUNOHISTOLOGY

Diagnosis and Quantification (/mm^2) of Inflamation

- Leucocytes, lymphocytes(CD3$^+$ /CD2$^+$, CD4), macrophages
- Cytotoxic T lymphocites (perforin)
- Cell adhesion mollecules (CAMs)
- Cytokines

Molecular Diagnosis of Myocardial Viral Presence

- PCR
- Reverse trancriptase PCR
- Nested PCR
- In situ hybridization

Therapy of Acute Myocarditis

Fulminant

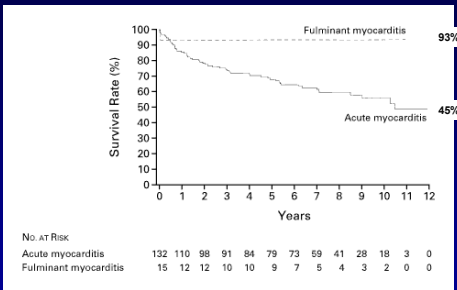
Giant Cell

FULMINANT MYOCARDITIS

McCarthy RE, NEJM 2000;342:690-696.

- 147 patients with myocarditis by Dallas criteria
- **Fulminant myocarditis**: severe hemodynamic compromise, rapid onset of symptoms and fever
- **Acute (non-fulminant) myocarditis**: indistinct onset of CHF, hemodynamically stable, no fever

Transplantation Free Survival in Fulminant Myocarditis



Fulminant n=15, Acute n=132

McCarthy RE, NEJM 2000;342:690-696

Treatment of Fulminant Myocarditis

McCarthy RE, NEJM 2000;342:690-696

Pts were critically ill & initially needed
"Aggressive hemodynamic support"

- vasopressors
- antifailure therapy

2 pts required LVAD

Despite the severe presentation, long term prognosis was excellent

Conclusions
Fulminant Myocarditis

- This condition needs aggressive initial hemodynamic support
- Despite the severe presentation, long term prognosis is excellent

Mechanical Support in Fulminant Myocarditis

Acker AM, Ann Thorac Surg 2001

- 146 pts with circulatory collapse had:
  - extracorporeal devices (EMO*, VAD)
  - intracorporeal VAD (25%)
- Survival:
  - 70% of external devices (20% HTx)
  - 50% of intracorporeal devices (40% HTx)

• Mechanical support served as bridge to HTx or to Recovery without HTx in 50-70% of cases

Idiopathic Giant-Cell Myocarditis — Natural History and Treatment

Leslie T. Cooper, M.D., Gerald J. Berry, M.D., Ralph Shabetai, M.D., for The Multicenter Giant Cell Myocarditis Study Group Investigators, NEJM 1997;336:1860-1866

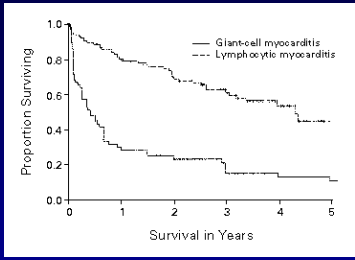
IDIOPATHIC GIANT CELL MYOCARDITIS (IGCM)

Cooper LT et al, NEJM 1997;336:1860-1866

IGCM is a rare and frequently fatal disease

- 63 patients- IGCM proven by Bx (33male, 42.6 ys)
- Death or cardiac transplant - 89%
- Median survival - 5.5 months
  - 3 mo's without immunosuppression.
  - 12 mo's with <u>combined</u> immunosuppr.

Kaplan–Meier Survival Curves for Patients with Giant-Cell Myocarditis From the Onset of Symptoms



Rx of choice: initially Immunosuppression±VAD, heart transplant

Cooper LT et al, NEJM 1997;336:1860-1866

TREATMENT of Acute Myocarditis

Current Therapy of Viral Myocarditis

- Mainly symptomatic
- Bed rest, avoid exercise
- ACE inhibitors
- β blockers?
- Diuretics
- Digitalis ?
- Aldospirone
- Other vasodilators

- Antiarrhythmics, ICD
- Anticoagulants
- Vasopressors
- Mechanical support
- Transplantation

Therapy : Special Aspects Learned from Murine Myocarditis

- **Digoxin – not indicated –increased expression of proinflamatory cytokines and mortality**
- **β blockers can induce CHF due to suppression of tachycardia**
- **NSAI's, Prednisone – potentiate myocardial necrosis Cyclosporine, Cyclophosphamide increased mortality**

ANTIVIRAL AGENTS

- **Ribavirin, Gancyclovir, Acyclovir – in RSV pneumonitis, post-transplant CMV infection**
- **IFN (Interferon) used in MS, under experimental evaluation in Inflamatory CM**

"No specific therapy had been approved yet for therapy of entero or adenoviral infections"
(Bowles NE, Towbin JA et al. JACC, August 6, 2003)

INFLAMATORY CARDIOMYOPATHY

Inflamatory CM - etiology

A - chronic myocarditis, increase in number of inflammatory cells (T-cells or activated macrophages)

B - viral persistence (by PCR of myocardial tissue)

C – neither A or B, Many cases show increased expression of class II antigens in the myocardium and circulatory auto AB to components of myocytes. It is unknown whether these AB are the cause of myocyte death or are secondary phenomenon

MAJOR CLINICAL THERAPEUTIC TRIALS

- Immune supression
- Imune modulation

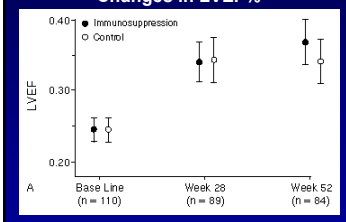
Immune supression

Randomized Immunosuppressive Trials

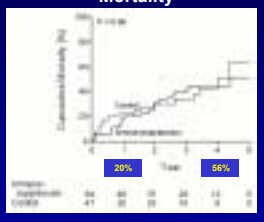
Reference	Agent	Pts	Enroll criteria	Outcome measure	Benefit
Parillo JE 1989	PRED, 3mo	102	CHF, DCM	LVEF 3-6 mo	NO (6mo)
Mason JW 1995, (MTT)	PRED +CSP/AZA 6mo	111	CHF<24mo, LVEF <0.45 Lymphocytic infiltrate	LVEF 6 mo Survival	NO

Myocarditis Treatment Trial (MTT)

Changes in LVEF%



Mortality



CONCLUSION: Routine immunosupessive therapy is not indicated in histologically proven myocarditis

Lessons Learned From the MTT
Looking Beyond Conventional Histology

- Immunohistochemical Markers
  - histochemical T cell staining
  - major histocompatibility Ag's
  - activated macrophages, B cells, cytokines, adhesion mollecules
- Viral presence/persistence
- Immune response to viral Ag's

Mc Kenna WJ, Davies MJ. NEJM 1995

Randomized Immunosuppressive Trials

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Wojnicz R 2001	PRED + AZA 3mo	84	CHF>6mo, LVEF<0.40 HLA^{++}	Survival, LVEF, LV size NYHA	NO YES (3mo, 2years)

Immune modulation:

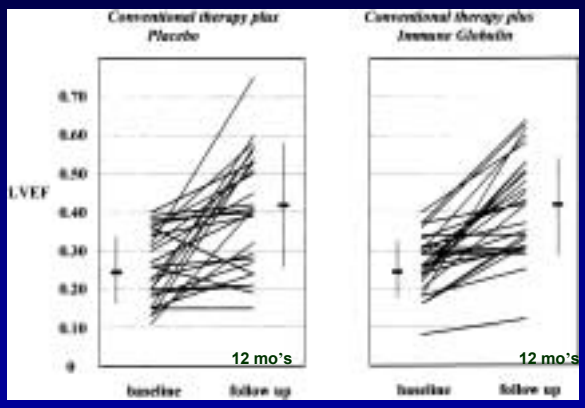
- immune gloguline
- immune adsorbtion
- anti viral therapy

Immunomodulatory trials (randomized)

Reference	Agent	Pts	Enrollment criteria	End points	Benefit
McNamara 2001 (IMAC)	IVIG	62	CHF <6mo, Myoc/DCM, LVEF<0.40	LVEF 6&12 mo	NO

Immunomodulatory trials (non-randomized)

IV IMMUNE GLOBULIN: the IMAC Trial



LVEF over time by treatment

Immunomodulatory trials (randomized)

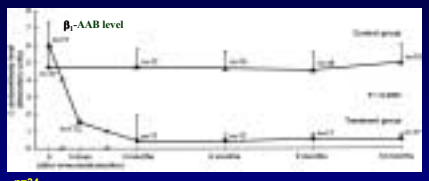
Reference	Agent	Pts	Enrollment criteria	End points	Benefit
McNamara 2001	IVIG	62	CHF <6mo, Myoc/DCM, LVEF<0.40	LVEF 6&12 mo	NO

Immunomodulatory trials (non-randomized)

* Immunoadsorbtion trials (for subtraction of β_1-AAB's, IgG-3) - phase 2, case control trials

* Wallukat G Int J Cardiol 1996; Muller J Circulation 2000; Felix SB JACC 2000; Staudt A, Circulation 2002

Follow-up (1 year) After Immunoadsorbtion

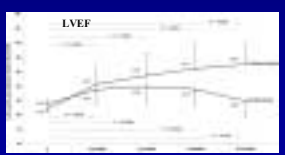


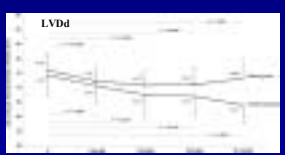
n=34

NYHA at 1 y (mean):

1.5-IA / 2.7-control

P<0.001





Muller J, Circulation 2000;101:385

Immunoadsorbtion-Conclusions

Immunoadsorbtion *with/without IgG substitution improved LV performance and functional class in DCM

This is a promising method which has to be further investigated

Wallukat G Int J Cardiol 1996, Muller J Circulation 2000, *Felix SB JACC 2000, *Staudt A, Circulation 2002;106:2448

Viral Presence in the Myocardium

- Viruses invade, can persist and replicate in the myocardium* (inducing chronic myocite damage)
- Clinical outcome is probably worse in pts with enteroviral RNA in the myocardium#
- Genetic defense mechanisms are important in susceptibility to viral infection (like abundance of CAR^)

* Bowles NE Lancet 1986, Kandolf R Proc Natl Acad Sci USA 1987, Wessely R Circulation 1998, Kaway C Circulation 1999, Paushinger M Circulation1999. # Why HJ Ciculation 1994, FigulaHR, JACC 1995, Fuijoka S JACC 2000, Frustaci A Circulation 2003 ^ Bergelson J Science 1997, Roelvink P Science1999, Bewley M Science1999, Noutsias M Circulation 2001

Reference	Agent	Pts	Enrollment criteria	End points	Benefit
Immunomodulatory trials (randomized)					
McNamara 2001	IVIG	62	CHF <6mo, Myoc/DCM, LVEF<0.40	LVEF 6&12 mo	NO
Immunomodulatory trials (non-randomized)					
*Kuhl U 2003 (phase 2)	Interferon-β 6 mo	22	CHF >12 mo,No myoc. on histology, Viral persistence on PCR	Safety, Viral clearance, NYHA, LVEF	YES

*Miric M et al. Heart 1996. Open label randomized in DCM . Viral genomes not evaluated. Administration of IFN-α improved LV fct in 77% vs 66% in conventional Rx.

Kuhl U e al. Circulation 2003;107:2793-2798

CONCLUSIONS

Kuhl U e al. Circulation 2003;107:2793-2798

By indings of this phase 2 pilot study in pts with >12 mo's of symptoms and viral persistence:

- IFN-β therapy was safe
- Resulted in virus elimination and prevented progression of LV dysfuntion
- The promising results will be evaluated in BICC (Betaferon in Chronic Viral Cardiomyopathy)

Kuhl U, Schultheiss HP et al. Circulation 2003

Action of Interferon-β in Viral Myocarditis

- Virostatic
- Virus clearance achieved by:
  - Antigen specific T lymphocites
  - Natural killer cells
  - Cytokines

EUROPEAN STUDY OF EPIDEMIOLOGY AND TREATMENT OF CARDIAC INFLAMMATORY DISEASE (ESETCID)

Active/Healing myocarditis by histology or immunohistochemistry, LVEF<45%

Specific therapies

1. Entero, Adenovirus, CMV – Immunomodulation
2. Virus negative (autoreactive myocarditis) Prednisone +Azathioprine

Maisch B et al Eur Heart J 1995, Hufnagel G et al. Herz 2000

Responders & Nonresponders to Immunossupressive Rx in Active Myocarditis

- 41 pts (29 M, 12F, mean age 42.9±13.5 ys)
- with CHF > 6 months (NYHA class III/IV, LVEF<40%) despite Rx
- positive EMB for active lymphocytic myocarditis - (histological and histochemical dg)
- Prednisone and Azathioprine for 6 mo's in ALL

Frustaci A, Circulation 2003;107: 857-63

Responders & Nonresponders to Immunossupressive Rx in Active Myocarditis

- 20 non-responders:
  - Myocardial viral genome in 17 pts (85%)
  - No cardiac autoantibodies
- 21 Responders:
  - Myocardial viral genome in 3 pts (HCV)
  - Cardiac autoantibodies in 19 pts (90%)

Frustaci A, Circulation 2003;107: 857-63

Conclusions Viral myocarditis

✓ Currently, cardiovascular supportive measures are the standard Rx of viral myocarditis

✓ Immunosuppression is recommended only for giant cell, granulomatous, eosinophilic forms and myocarditis associated with connective tissue diseases

Conclusions Inflamatory CM

✓ Potentially very promising therapies were applied and found effective in well defined* patient categories with Inflamatory CM

✓ These "patient-type tailored" approaches are under investigation in large- scale, randomized, multicenter trials