Miocarditi ed Insufficienza Cardiaca:

Inquadramento eziopatogenetico e sospetto diagnostico

ECOCARDIOCHIRURGIA 2010
HOTEL EXECUTIVE MILANO

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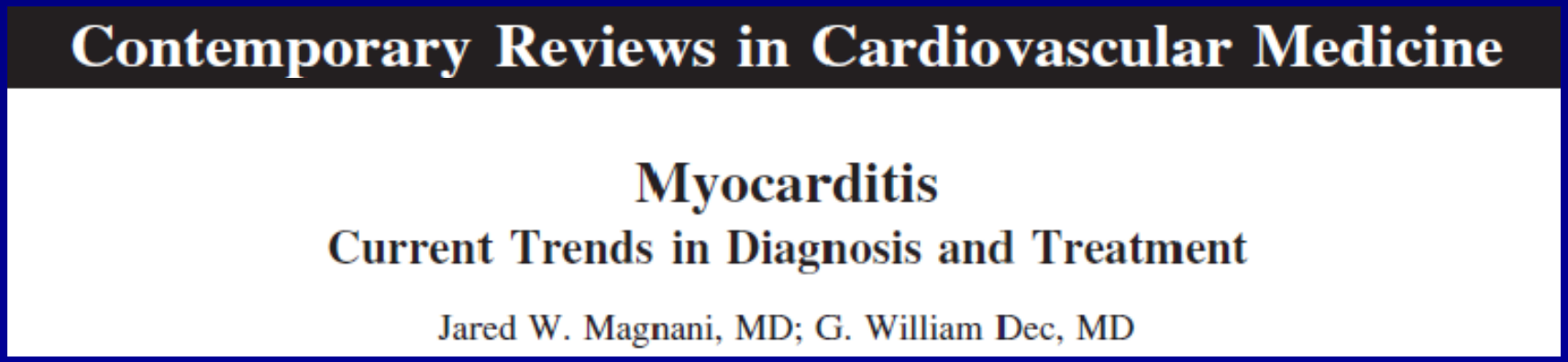
DEFINITION: 1

"Myocarditis is clinically and pathologically defined as "inflammation of the myocardium."

Despite its rather clear-cut definition, the classification, diagnosis, and treatment of myocarditis continue to prompt considerable debate."



DEFINITION 2

The Dallas criteria were proposed in 1986 to provide a histopathologic classification for the diagnosis of myocarditis. These criteria require that an inflammatory cellular infiltrate with or without associated myocyte necrosis be present on conventionally stained myocardial tissue sections.

These criteria are limited by:

- variability in expert interpretation;
- lack of prognostic value;
- discrepancy with other markers of viral infection and immune activation in the myocardium;
- low sensitivity that is at least partly due to sampling error

PROGRESS IN CARDIOVASCULAR DISEASE 2010 Leslie T. Cooper

DEFINITION 3
Newer Histopatologic Criteria

Newer histologic criteria rely on cellspecific immunoperoxidase stains for surface antigens such as:

- anti-CD3,
- anti-CD4,
- anti-CD20,
- anti-CD28,
- Antihuman leukocyte antigen

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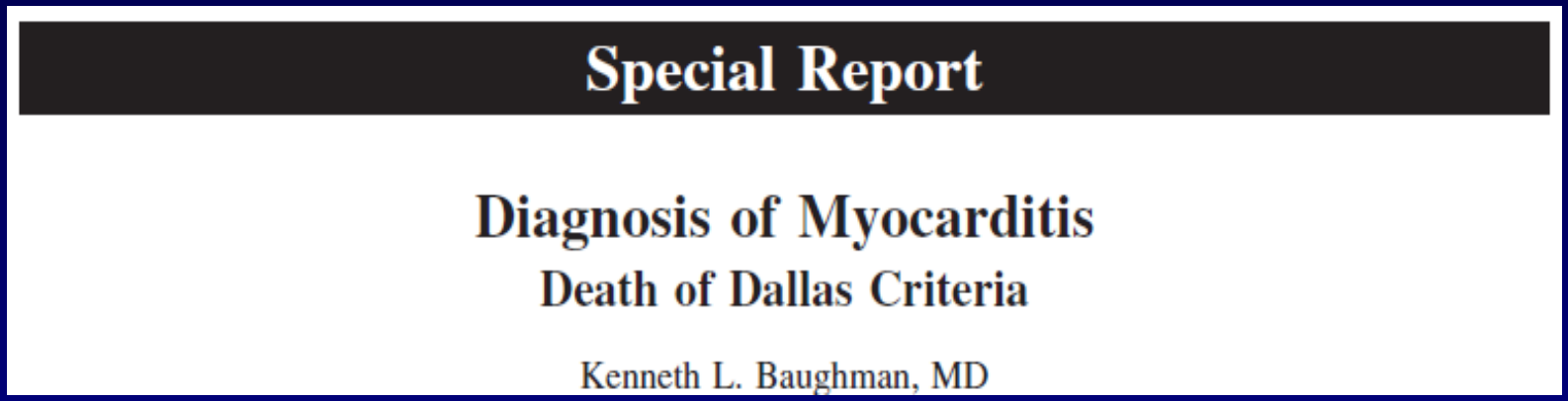
DEFINITION : WORK IN PROGRESS



Special Report

Diagnosis of Myocarditis

Death of Dallas Criteria

Kenneth L. Baughman, MD

- The time has come to redefine viral and autoimmune heart disease with the use of methodologies available in the 21° century.
- Clinicians, pathologists, immunologists, and molecular cardiologists must contribute to the new criteria, which should include clinical presentation, histopathology, immunohistochemistry,viral polymerase chain reaction, cardiac antibody assessment, and imaging results.

EBM : indications
AHA/ACC GL for Heart Failure

Rapidly progressive CMP refractory to optimal medical therapies

Unexplained CMP associated with progressive conduction system disease or life-threatening ventricular arrhythmias

New onset heart failure with rash, fever or eosinophilia

Suspicion of Giant Cell M.
(young age, newsubacute HF, progressive arrhythmias)

- NB EMB RMN GUIDED !!!

EPIDEMIOLOGY

The true incidence of myocarditis has been difficult to determine because clinical presentations vary widely, and EMB is rarely used due to perceived risks and lack of a widely accepted and sensitive histologic standard.

Autopsy report revealed varying % of incidence according to population studied:

RANGE 0.12-12%

- MTT (Ptz with unexplained HF) : 9.6% EMB (EHJ 1995)
- Male prevalence / Mean age 20 to 51 years (HUM PAT 2005)
- Young athletes : 12% of cases of SD < 40 years (Circ 2009)

BUT

High prevalence of viral genomes in DCM Pts suggest substantial disease burden in the community

CLINICAL PRESENTATION: 1

The clinical presentation of acute myocarditis in adults is highly variable, ranging from subclinical disease to fulminant heart failure.

1. Viral prodrome syndrome (27%):

Fever, rash, myalgias, arthralgias, fatigue, and respiratory or gastrointestinal symptoms frequently precedes the onset of myocarditis by several days to a few weeks (2-3 days to 20 days)

2. “New rapid onset” unexplained HF (72%):

Patients may present with chest pain, dyspnea, palpitations, fatigue, decreased Exercise tolerance, or syncope.

3. Ptz with “Acute Coronary like” syndrome (18%):

Chest pain in acute myocarditis may mimic typical angina and be associated with electrocardiographic changes, including ST-segment elevation.

CLINICAL PRESENTATION: 2

Highly variable clinical presentation

4. Ptz with “AMI like” syndrome (1.5%)

Chest pain associated with coronary artery vasospasm may occur in Patients with myocarditis.

5. Ptz with Peri-Myocarditis (53%):

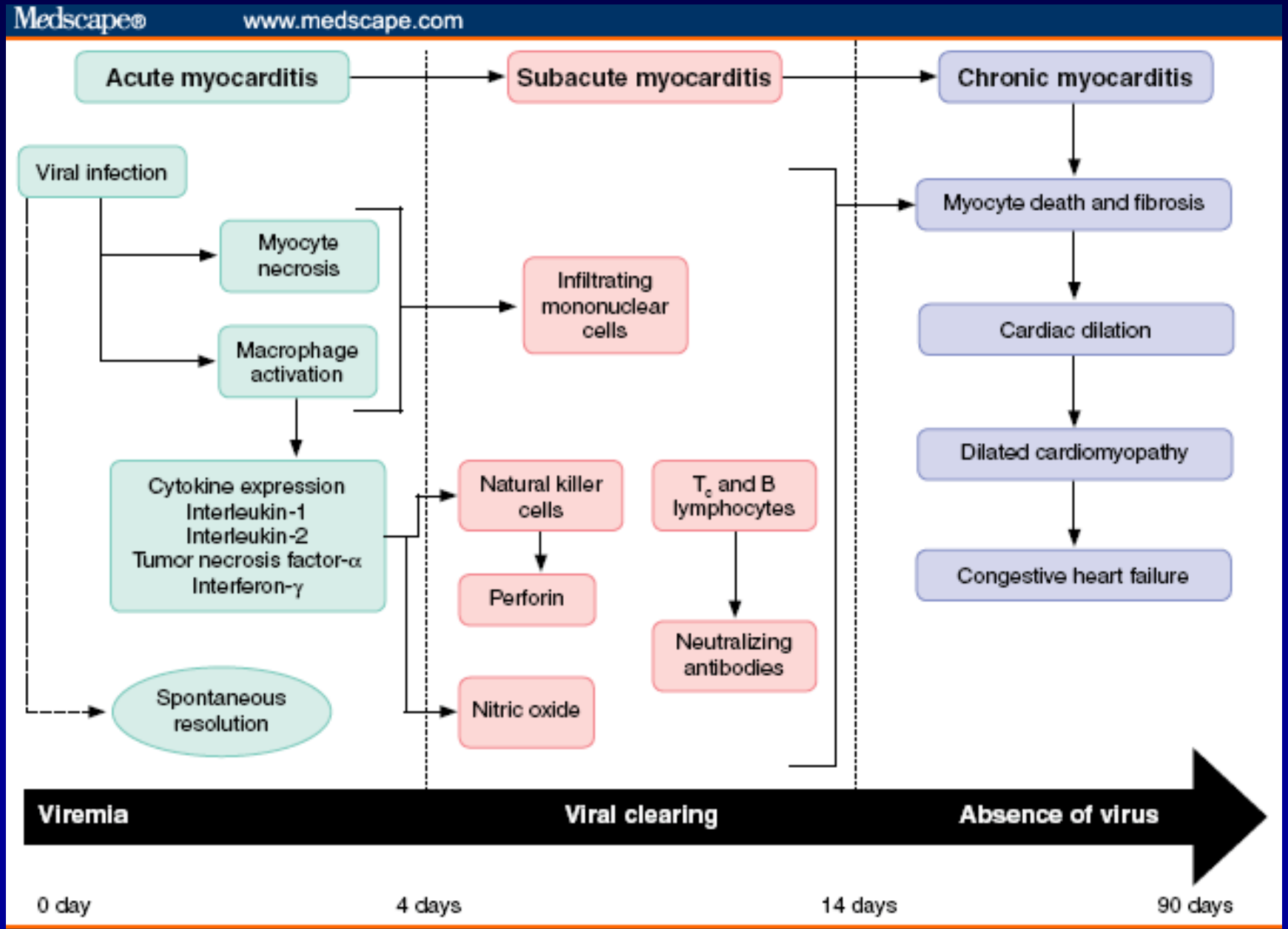
Chest pain may be more typical for pericarditis, suggesting pericardial involvement.

6. Ptz with Cardiac rhythm disturbances (18%):

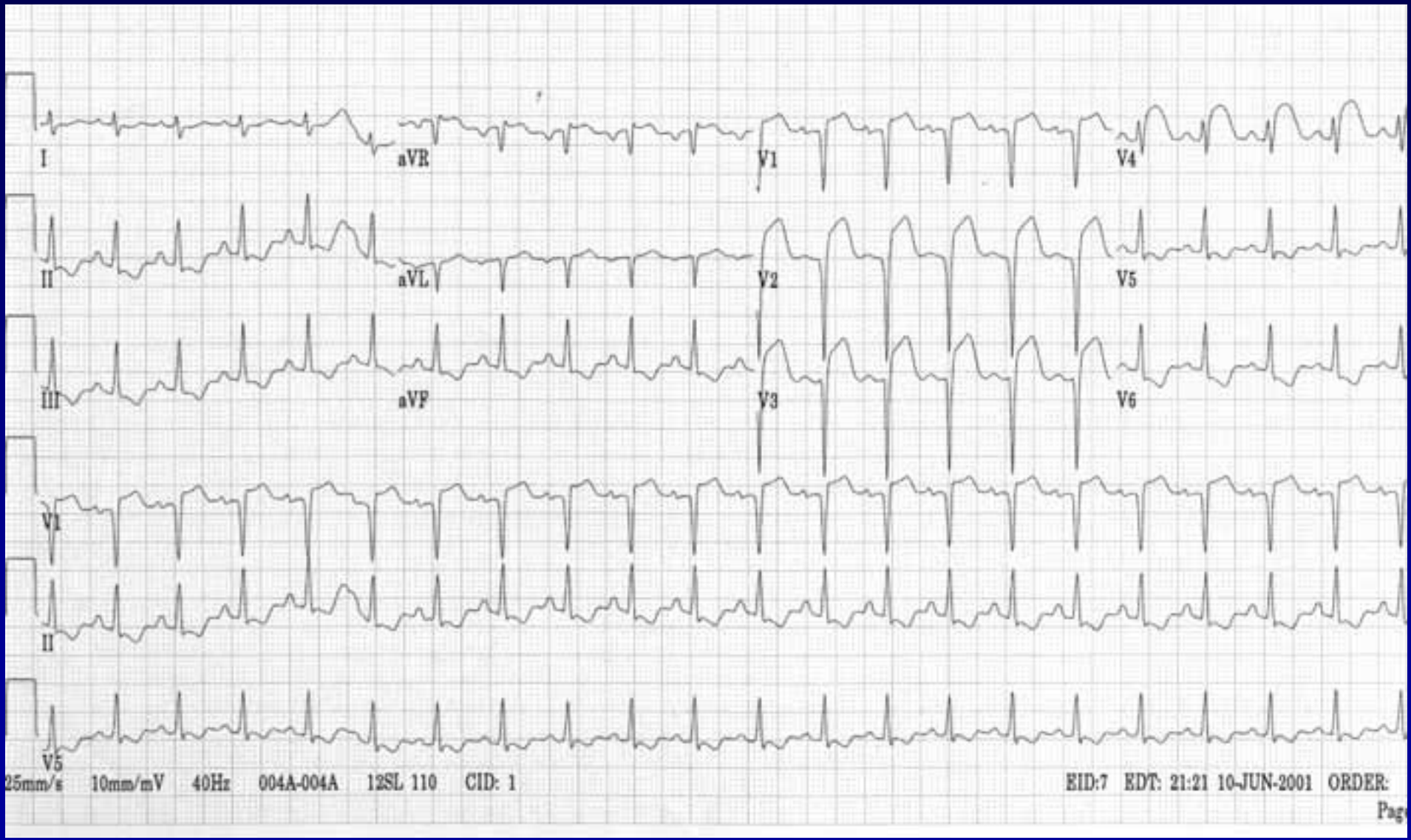
New-onset atrial or ventricular arrhythmias or high-grade atrioventricular (AV) block.

** Data from “European Study of Epidemiology of inflammatory Heart Disease (ESETCID)”

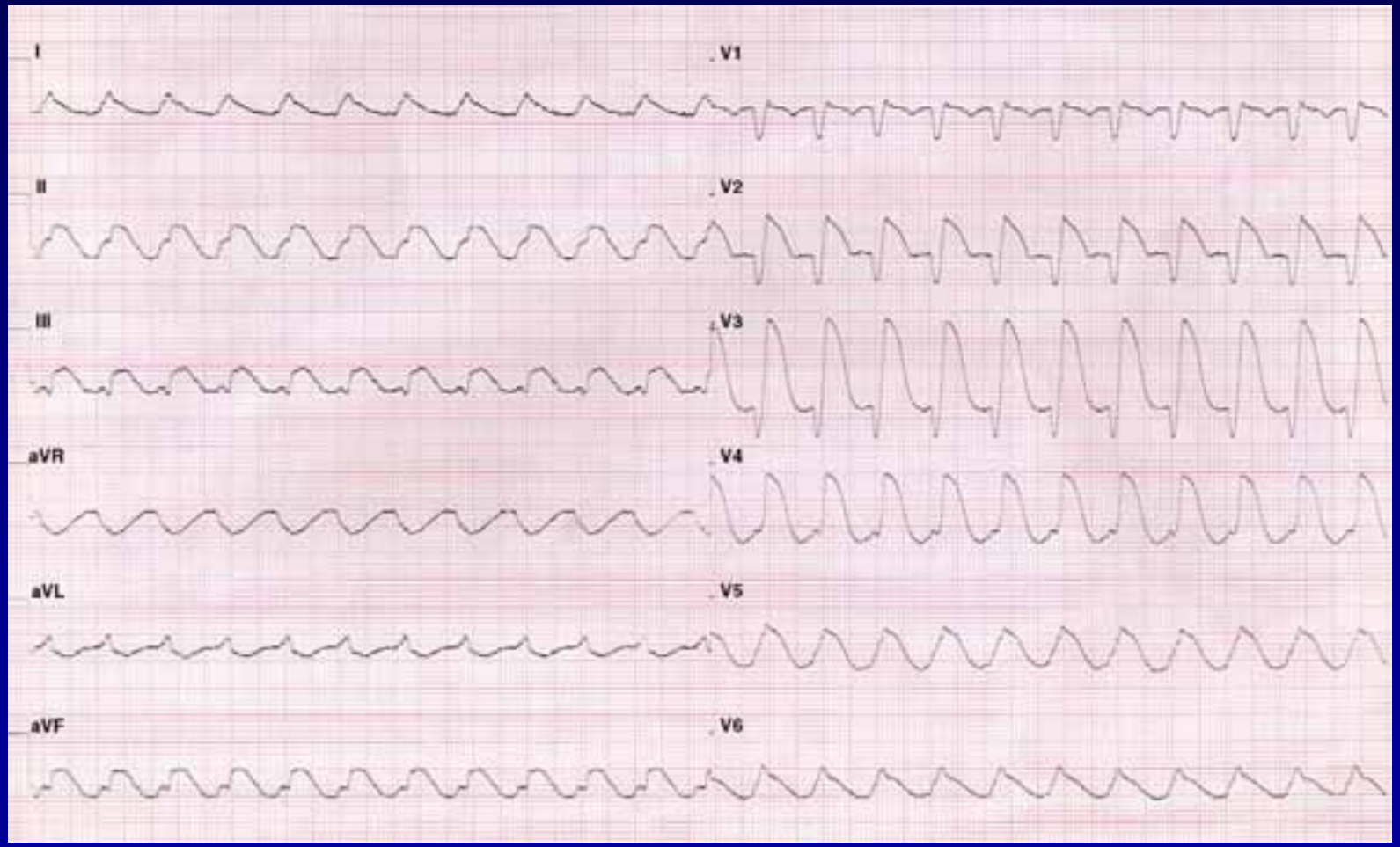
CLINICAL PRESENTATION: 3



15 Y MALE, HIGH FEVER, HYPOTENSION, generalized skin RASH : Rickettsial Infection



42 YEARS MALE,CHEST PAIN, FEVER, HYPOTENSION, SYNCOPE: HIV Infection



ETIOLOGIES

Etiologies

Infectious	Toxins
Viral: **adenovirus**, arbovirus, Chikungunya virus, Cytomegalovirus, echovirus, Enterovirus (**Coxsackie B**), Epstein-Barr virus, Flavivirus (dengue fever and yellow fever), hepatitis B virus, **hepatitis C virus**, herpes viruses (**human herpesvirus-6**), **HIV/AIDS**, influenza A and B viruses, Parvovirus (**parvovirus B-19**), mumps virus, poliovirus, rabies virus, respiratory syncytial virus, rubeola virus, rubella virus, varicella virus, variola virus (smallpox)	Drugs: aminophylline, amphetamines, **anthracyclines**, catecholamines, chloramphenicol, **cocaine**, cyclophosphamide, doxorubicin, ethanol, 5-flurouracil, imatinib mesylate, interleukin-2, methysergide, phenytoin, trastuzumab, zidovudine
Bacterial: *Burkholderia pseudomallei* (melioidosis), *Brucella*, *Chlamydia* (especially *Chlamydia pneumonia* and *Chlamydia psittacosis*), ***Corynebacterium diphtheriae*** (**diphtheria**), *Francisella tularensis* (tularemia), *Haemophilus influenzae*, gonococcus, *Clostridium*, *Legionella pneumophila* (Legionnaire disease), ***Mycobacterium*** (**tuberculosis**), *Neisseria meningitidis*, *Salmonella*, *Staphylococcus*, **Streptococcus A** (**rheumatic fever**), ***Streptococcus pneumoniae***, syphilis, tetanus, tularemia, *Vibrio cholera*	Environmental: arsenic, carbon monoxide, copper, iron, lead
Spirochetal: ***Borrelia burgdorferi*** (**Lyme disease**), *Borrelia recurrentis* (relapsing fever), leptospira, *Treponema pallidum* (syphilis)	Hypersensitivity reactions Drugs: azithromycin, benzodiazepines, clozapine, cephalosporins, dapsone, dobutamine, gefitinib, lithium, loop diuretics, methyldopa, mexiletine, nonsteroidal antiinflammatory drugs, penicillins, phenobarbital, **smallpox vaccination**, streptomycin, sulfonamides, tetanus toxoid, tetracycline, thiazide diuretics, tricyclic antidepressants
Rickettsial: ***Coxiella burnetii*** (**Q fever**), *Orientia tsutsugamushi* (scrub typhus), *Rickettsia prowazekii* (typhus), *Rickettsia rickettsii* (Rocky Mountain spotted fever)	Other: bee venom, wasp venom, black widow spider venom, scorpion venom, snake venom
Fungal: *Actinomyces*, *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Mucor* species, *Nocardia*, *Sporothrix schenckii*, *Strongyloides stercoralis*	
Protozoal: *Balantidium*, *Entamoeba histolytica* (amebiasis), *Leishmania*, *Plasmodium falciparum* (malaria), *Sarcocystis*, ***Trypanosoma cruzi*** (**Chagas disease**), *Trypanosoma brucei* (African sleeping sickness), ***Toxoplasma gondii*** (toxoplasmosis)	Autoimmune diseases Dermatomyositis, **GCM**, inflammatory bowel disease, rheumatoid arthritis, Sjögren syndrome, **systemic lupus erythematosus**, Takayasu's arteritis, Wegener's granulomatosis
Helminthic: *Ascaris*, *Echinococcus granulosus*, *Heterophyes*, *Paragonimus westermani*, *Schistosoma*, *Strongyloides stercoralis*, *Taenia solium* (cysticercosis), *Toxocara canis* (visceral larva migrans), *Trichinella spiralis*, *Wuchereria bancrofti* (filariasis)	Systemic diseases **Celiac disease**, Churg-Strauss syndrome, collagen-vascular diseases, **hypereosinophilic syndrome with eosinophilic endomyocardial disease**, Kawasaki disease, **sarcoidosis** (**idiopathic granulomatous myocarditis**), scleroderma
	Other Heart stroke, hypothermia, rejection of the posttransplant heart, radiation therapy

Most common etiologies are rendered in **bold**.

Viral Myocarditis

Incidence (?): (90% Mahrholdt 2006; 26% Caforio EHJ 2007)

Adenovirus and Enterovirus (including Coxsackievirus) historically being the most frequently identified viruses

- Recently, the most commonly detected viral genomes in EMB samples were Parvovirus B-19 and Human Herpesvirus-6

- HIV Myocarditis : before HAART more than 50% Ptz
  Direct myocardial damage by HIV is infrequent
  Hypotesis:
  Coinfections /Antiretroviral Medications (HAART) /Tipe 1 Glycopretein 120

NB Elimination of virus genomes in treated Pts better prognosis (soft data)

NB : Co-infection in 25% of cases / worse prognosis

NB: Sierology only diagnostic tool for HIV, HCV, CMV

Toxins and Hypersensitivity Myocarditis

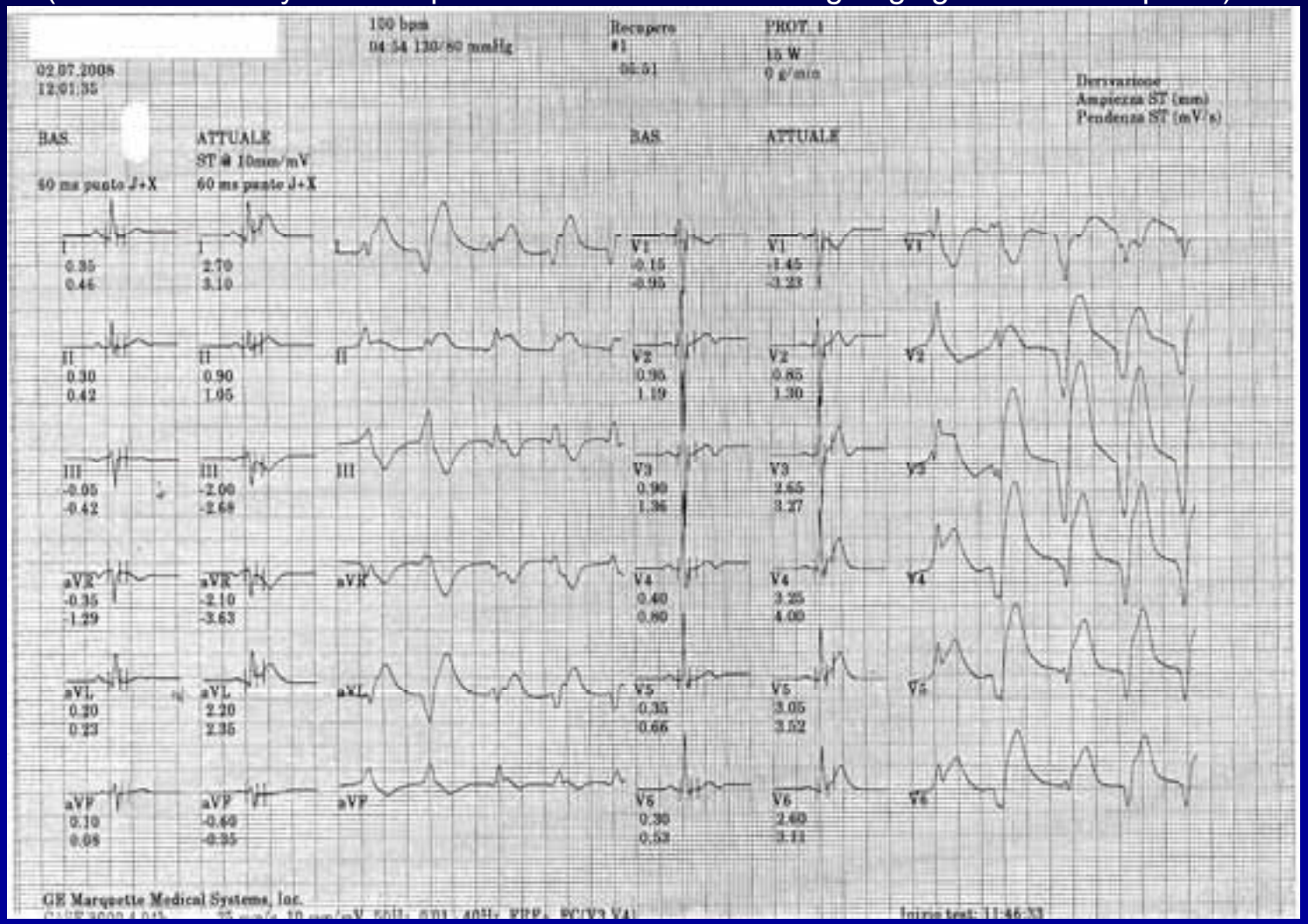
Drugs:

Aminophylline
Amphetamines
Anthracyclines ++
Catecholamines,
Chloramphenicol
Cocaine, ↑ ↑
Cyclophosphamide, doxorubicin, ethanol
5-flurouracil, imatimib mesylate, interleukin-2,
Methysergide, Phenytoin,
Trastuzumab, Zidovudine

53 year-old man, Angina new onset

Capecitabine (Xeloda) 3500mg/die (3th day).

(Normal coronary vessels /persitent ST elevation during angiogram without spasm)



Hypersensitivity reactions

Antibiotics

Azithromycin,
Cephalosporins,
Penicillins,
Streptomycin,
Tetracycline,

Sulfonamides,FANS, tricyclic antidepressants

Cardiovascular Drugs

- Dobutamine, Loop diuretics, Mexiletine, Thiazide diuretics,

The possibility of drug-induced hypersensitivity myocarditis should be considered in any patient taking either prescription or over the counter medications, particularly if eosinophilia or eosinophilic myocardial infiltration is present.

Idiophatic GCM

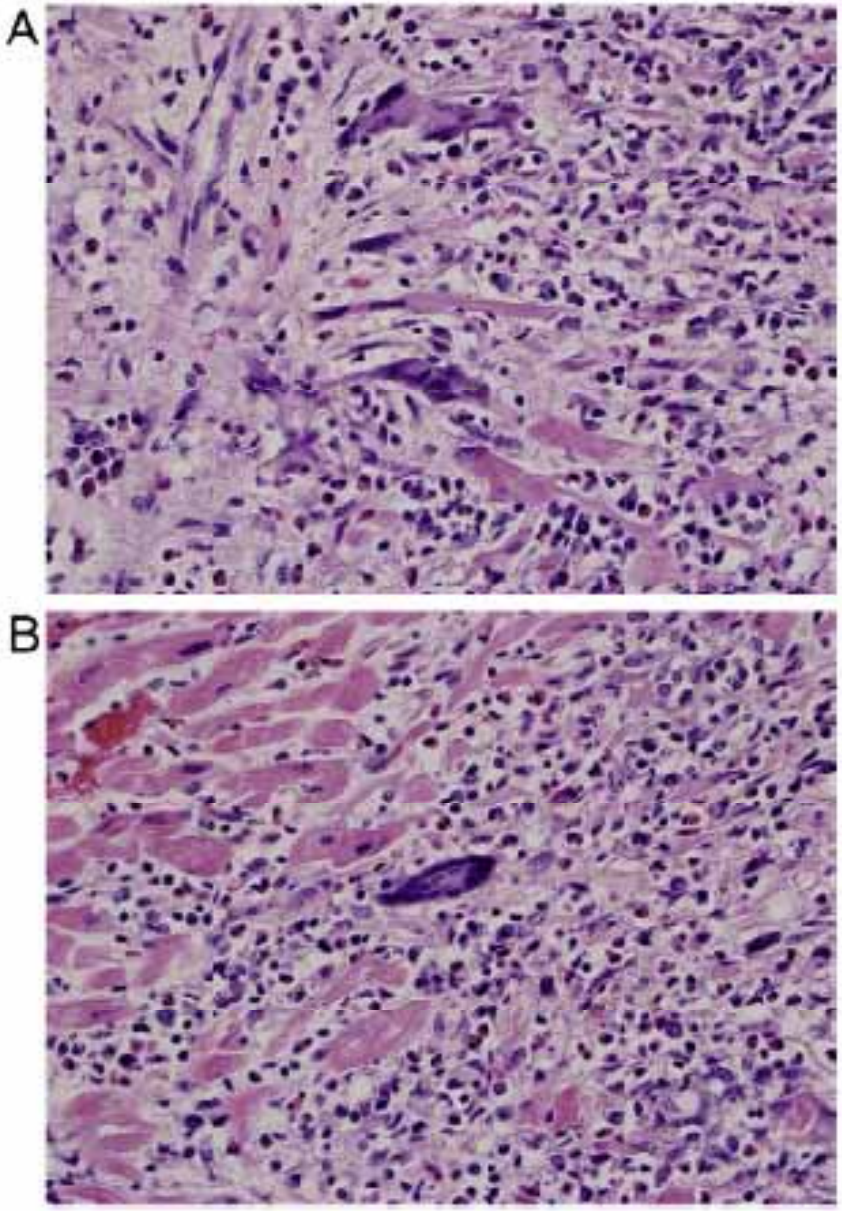


Fig 1. Giant cell myocarditis. A and B. Endomyocardial biopsy specimen demonstrates widespread lymphocytic infiltrate, myocyte necrosis, numerous eosinophils, and several giant cells (hematoxylin and eosin). Images provided courtesy of Dr. Wendy Gunther.

Idiopathic GCM is a rare, virulent, autoimmune form of myocarditis histologically defined by the presence of multinucleated giant cells, a lymphocytic inflammatory infiltrate, and myocyte necrosis (Fig 1A and B).[94] This disease usually occurs in young adults and carries a high risk of death unless cardiac transplantation is performed. It is considered to be autoimmune because of its association with other autoimmune disorders,[23] thymoma,[95] and drug hypersensitivity.[96] Rare in adults, GCM is rarer still in children and is associated with immune-mediated disease in other organs.[23]

Pathophysiology: Experimental Myocarditis

Viral Mediated (CAR)

Cells Immuno-mediated effect

Immune response due to cardiac auto-antibodies

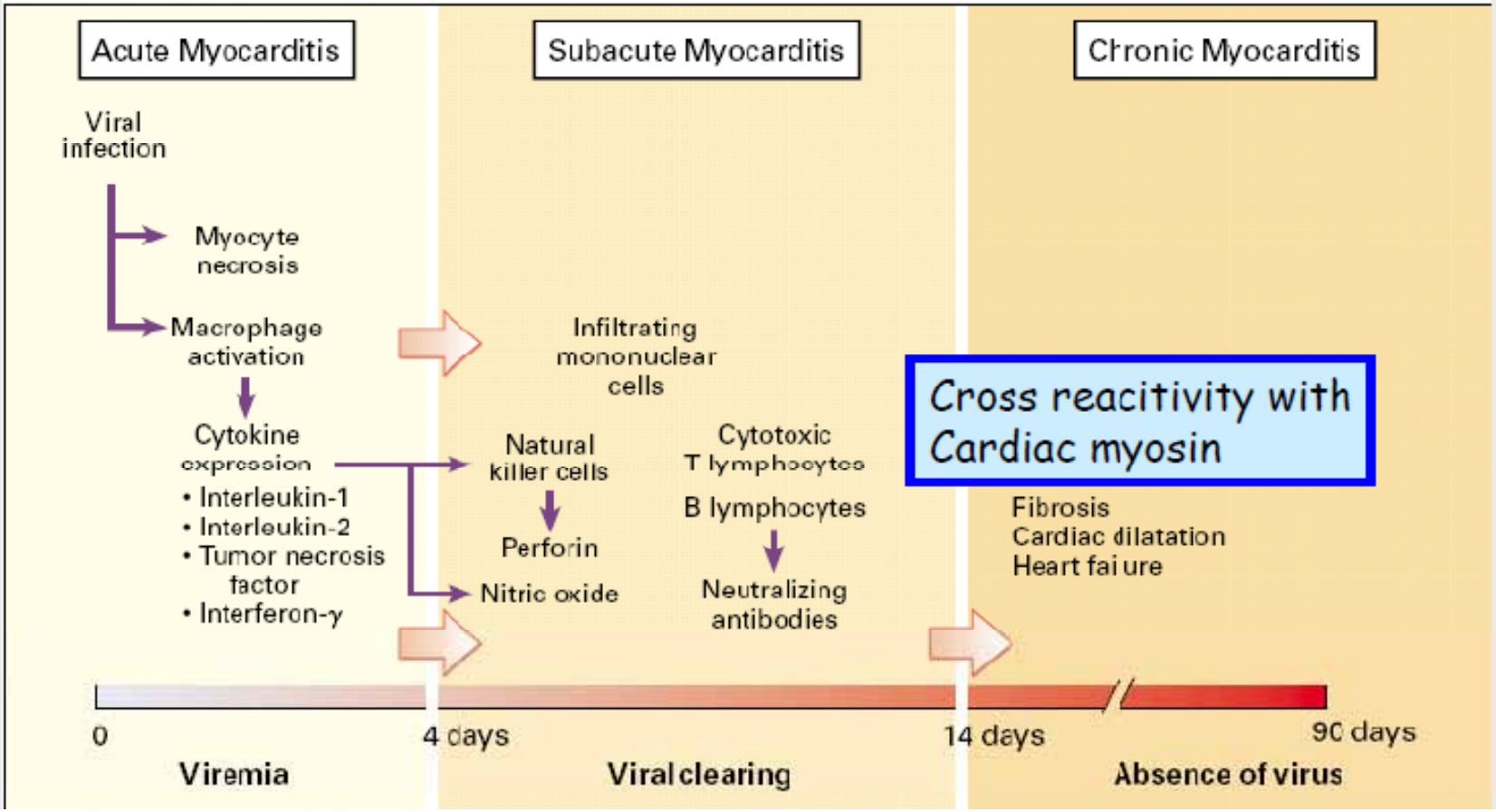


Figure 1 Pathophysiological process of virus myocarditis.

Pathogenesis of Viral Myocarditis

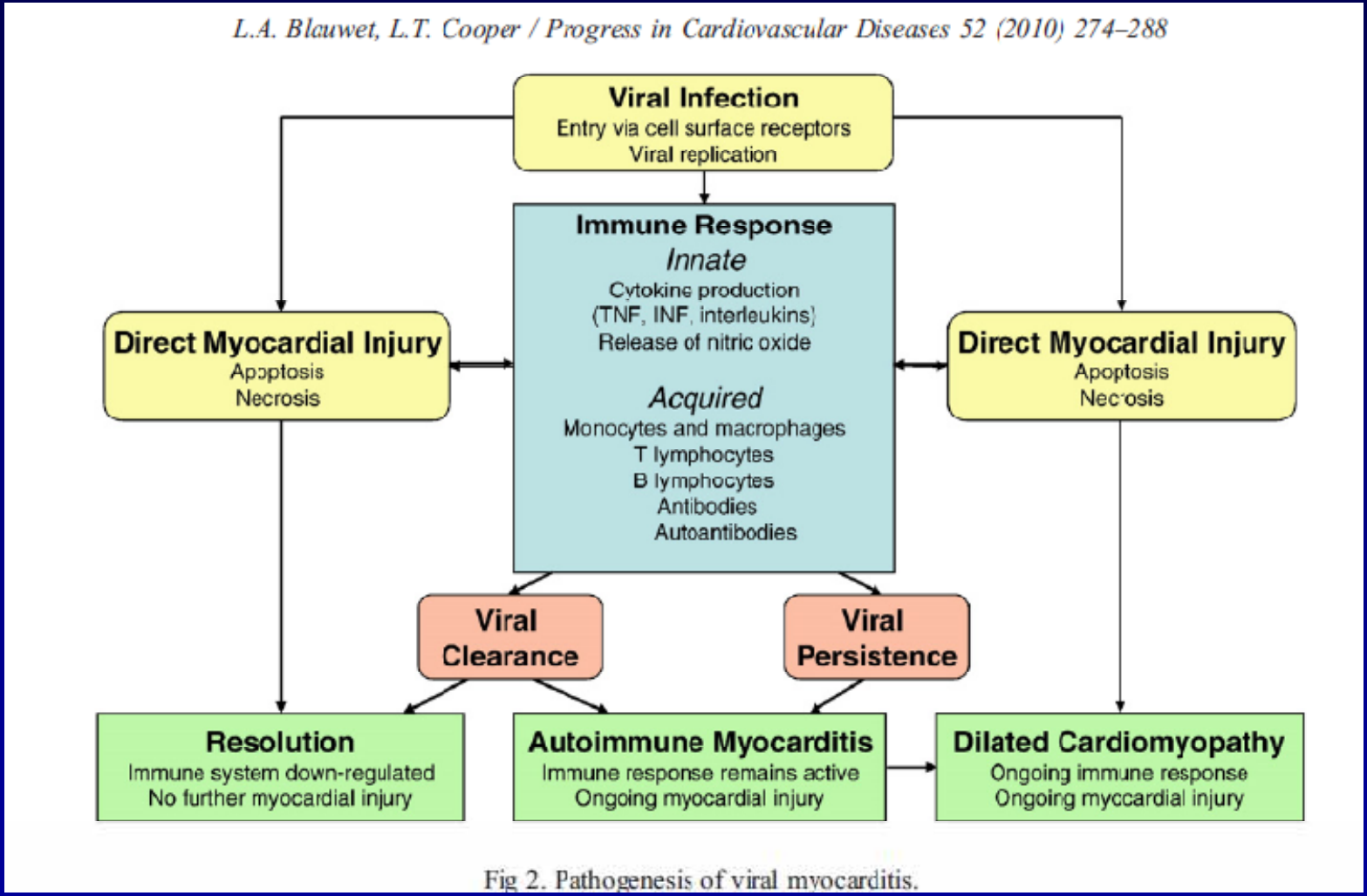
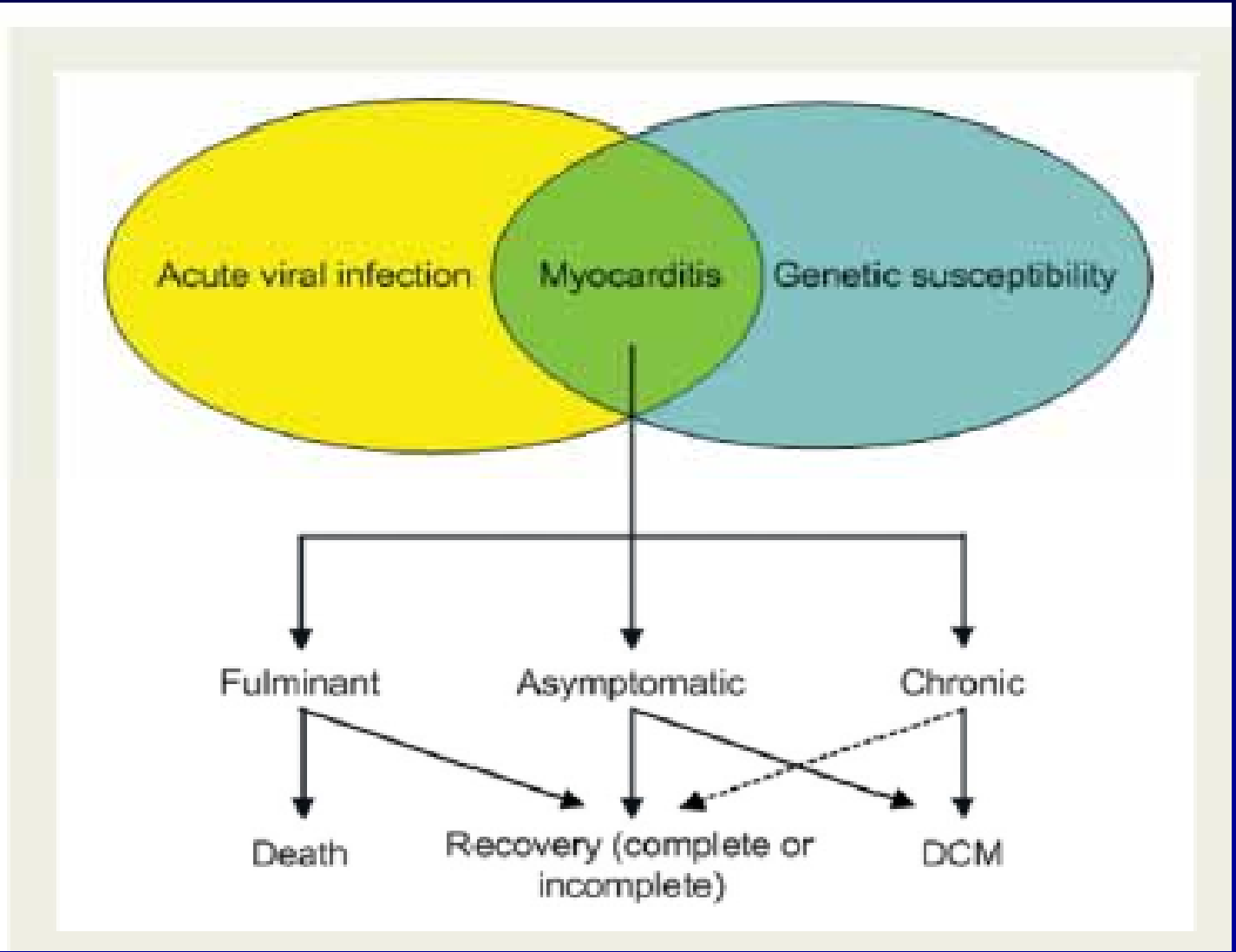
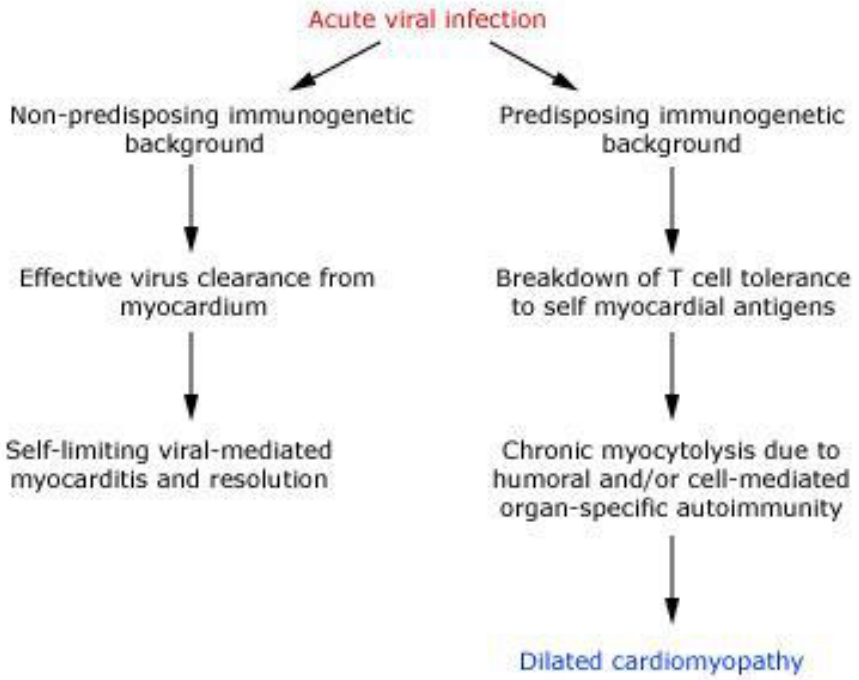


Fig 2. Pathogenesis of viral myocarditis.

Why not all ?


Acute viral infection
Myocarditis
Genetic susceptibility
Fulminant
Asymptomatic
Chronic
Death
Recovery (complete or incomplete)
DCM

Virus-immune hypothesis in dilated cardiomyopathy



Following acute viral myocarditis, subjects who are not genetically predisposed to autoimmunity develop a self-limited disease and recover completely. In contrast, in individuals with a genetic predisposition to autoimmunity, a viral infection may initiate a chronic autoimmune myocarditis leading to dilated cardiomyopathy.

Data from Caforio, ALP, Baboonian, C, McKenna, WJ, Eur Heart J 1997; 18:1053

Treatment of Myocarditis

HF Standard Therapy

1. Discontinued offending agents (cardiotoxic drugs, toxic agents etc)
2. ACEi, Diuretics, β-blockers, RAS inhibithors
3. Digoxin (CAUTION) : increase mortality (exper. data)
4. Calcium Channel blockers (CAUTION) : no data
5. FANS (CAUTION) : ↑ inflammation and mortality (exper.data)
6. Inotropic medication, mechanical ciirculatory support and transplanatation : fulminant myocarditis / acute phase non responders to optimal medical treatment

NB CAUTION : information from sperimental study of viral M.

Treatment of Myocarditis

Antiviral Therapy

As viral infection is the most common cause of myocarditis, it would seem plausible that treatment with antiviral medications or antiviral vaccines would be beneficial. It is clear that viral genomes are present in a subset of patients with acute myocarditis,[154] but it remains uncertain whether this affects mortality or the need for cardiac transplantation.[5,47] Data regarding antiviral treat-

Antiviral therapy with ribavirin e/o interferon in humans with fulminant myocarditis: NOT PROVED EFFECTIVE

(Ray Inf.Dis.1997 Khul Circ. 2003)

IMMUNOSUPPRESSIVE TREATMENT

Treatment with immunosuppressants such as prednisone, cyclosporin, and azathioprine showed little or no treatment effect.

In patients with GCM, however, long-term survival is improved with treatment with cyclosporin and corticosteroids, and in fact, withdrawal of immunosuppression in this population has at times resulted in increased risk of recurrent, occasionally fatal, GCM

Myocarditis and DCM treatment trials

Treatment Trial	Trial Type	Disease	No. of Patients	Agent(s)	Primary Outcome Measure	Result
Adults: Acute Myocarditis						
Jones,[161] 1991	Prospective	Acute lymphocytic myocarditis	9	Prednisone plus azathioprine	Improvement in LVEF	No treatment benefit
Maisch,[162] 1995	RCT	Acute lymphocytic myocarditis	17	Prednisone plus either cyclosporine or azathioprine	Improvement in LVEF at 3 mo	Significant treatment benefit
Mason,[17] 1995: The Myocarditis Treatment Trial	RCT	Acute lymphocytic myocarditis	111	Prednisone plus cyclosporine	Improvement in LVEF at 6 mo	No treatment benefit
McNamara,[163] 1997	Prospective	Acute lymphocytic myocarditis	10	IVIG	Improvement in LVEF at 1 y	Treatment benefit
McNamara,[164] 1999: Immune Modulation for Acute Cardiomyopathy	RCT	Acute lymphocytic myocarditis	62	IVIG	Improvement in LVEF at 6 mo	No treatment benefit
Cooper,[155] 2008: Giant Cell Myocarditis Treatment Trial	Prospective	GCM	11	Prednisone plus cyclosporine	Survival at 1 y	Treatment benefit
Children: Acute Myocarditis						
Chan,[166] 1991	Retrospective	Acute myocarditis	13	Prednisone (1 patient also received azathioprine)	Clinical improvement (ECG changes, heart size, ejection fraction)	Small treatment benefit
Drucker,[167] 1994	RCT	Acute myocarditis	21	IVIG	Survival and improvement in LVEF at 1 y	Treatment benefit
Chronic Myocarditis/DCM						
Parrillo,[168] 1989	RCT	Idiopathic DCM	102	Prednisone	Improvement in LVEF at 3 mo	Small treatment benefit
Wojnicz,[169] 2001	RCT	DCM	84	Prednisone plus azathioprine	Composite of death, heart transplantation, and hospital readmission at 2 y	No treatment benefit (secondary outcome benefit)
Frustaci,[170] 2003	Prospective	Active lymphocytic myocarditis with chronic heart failure	41	Prednisone and azathioprine	Improvement in LVEF at 1 y	Treatment benefit for patients with no viral genome in the myocardium
Gullestad,[171] 2001	RCT	DCM	40	IVIG	Improvement in LVEF at 26 wk	Treatment benefit
Kuhl,[160] 2003	Prospective	Chronic virus-positive DCM	22	Interferon-β	Viral clearance and improvement in LV size and LVEF at 6 mo	Treatment benefit for both outcomes
Frustaci,[172] 2009: Therapy in Inflammatory Dilated Cardiomyopathy	RCT	Chronic virus-negative DCM	85	Prednisone and azathioprine	Improvement in LVEF at 6 mo	Significant treatment benefit

Abbreviations: LVEF indicates left ventricular ejection fraction; RCT, randomized controlled trial.

IMMUNOSUPPRESSIVE TREATMENT

Immunosuppression may be beneficial in treating patients with chronic DCM unresponsive to standard heart failure therapy.

The recently completed Therapy in Inflammatory Dilated Cardiomyopathy trial, have shown that the use of azathioprine and prednisone results in significant improvement in left ventricular ejection fraction and New York Class

(TIMIC STUDY Frustaci et Al. EHJ 2009)

Myocarditis Prognosis: 1

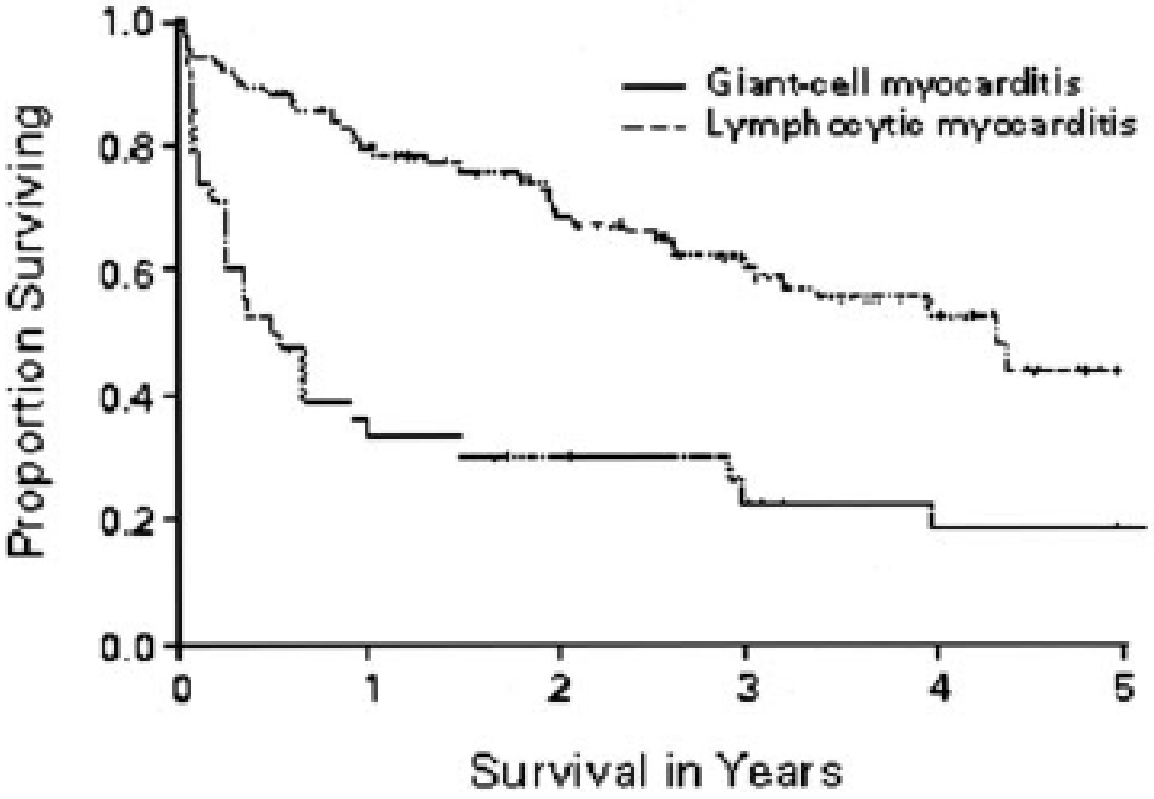


Figure 5. Kaplan-Meier survival curves for 38 patients with biopsy-proven myocarditis and 111 patients with lymphocytic myocarditis enrolled in the Myocarditis Treatment Trial. Duration refers to the time from biopsy diagnosis. $P<0.001$ by log-rank test. Reproduced with permission from Cooper et al.[70]

Myocarditis Prognosis: 2

- Excellent for adult with ALM with EF preserved
- Mortality (4 y follow-up) 56% if EF < 45% baseline and HF symptoms (data obtained in population study without β-blockers therapy)
- Adults with Fulminat Myocarditis (survive to acute phase) have an excellent long-term prognosis
- Patients with GCM have a median survival < 6 months