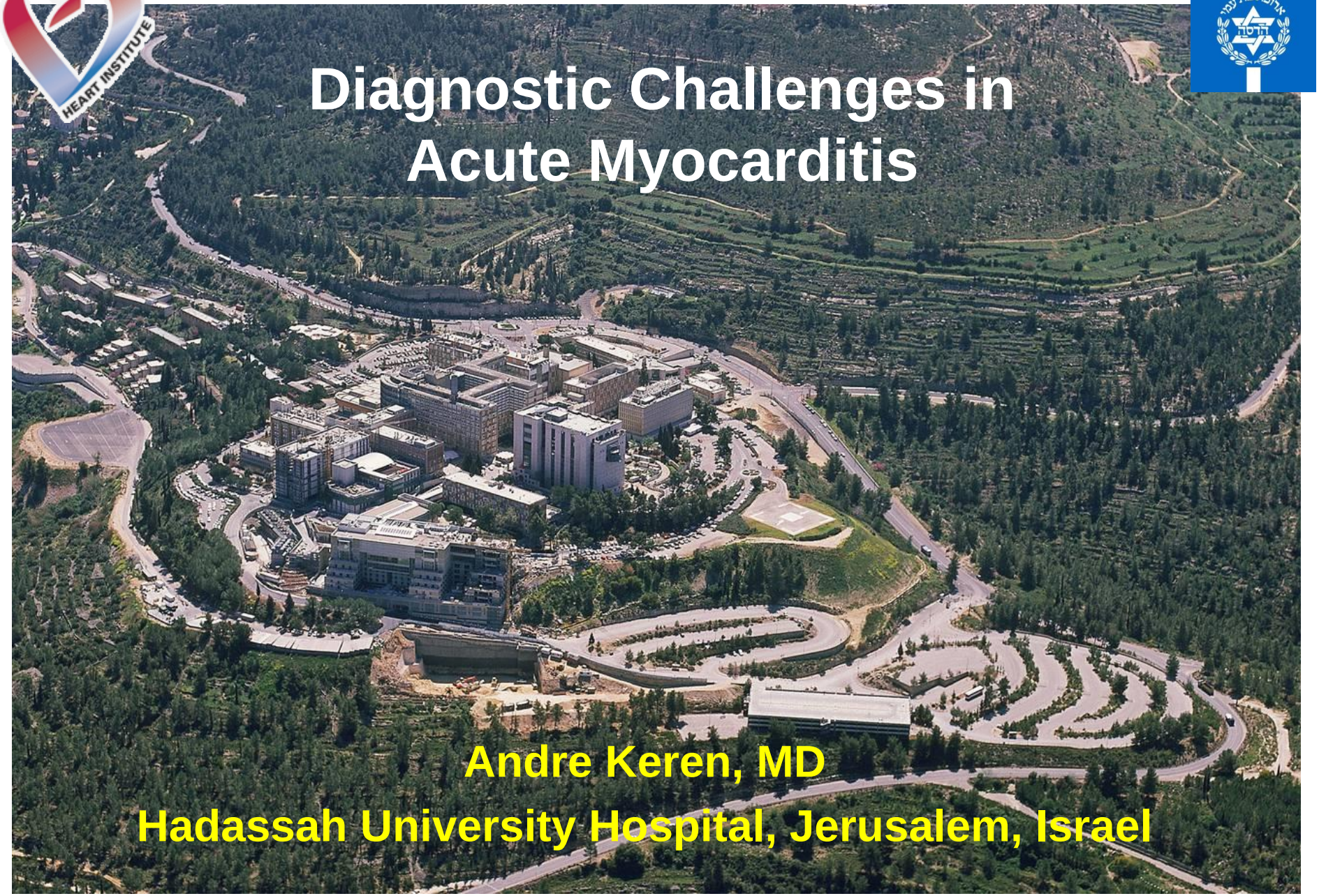
Diagnostic Challenges in Acute Myocarditis



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ACUTE MYOCARDITIS

- **Myocarditis is an infectious, toxic or autoimmune process causing inflammation of the heart**
- **The most common etiology appears to be the viral infection**

European Heart Journal (2008) **29**, 270–276
doi:10.1093/eurheartj/ehm342

ESC REPORT

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*

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Table 1 Examples of different diseases that cause cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations ß myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α-myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β3 (TGFβ3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP α-dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

Elliott P et al. Eur Heart J 2008;29:270-276

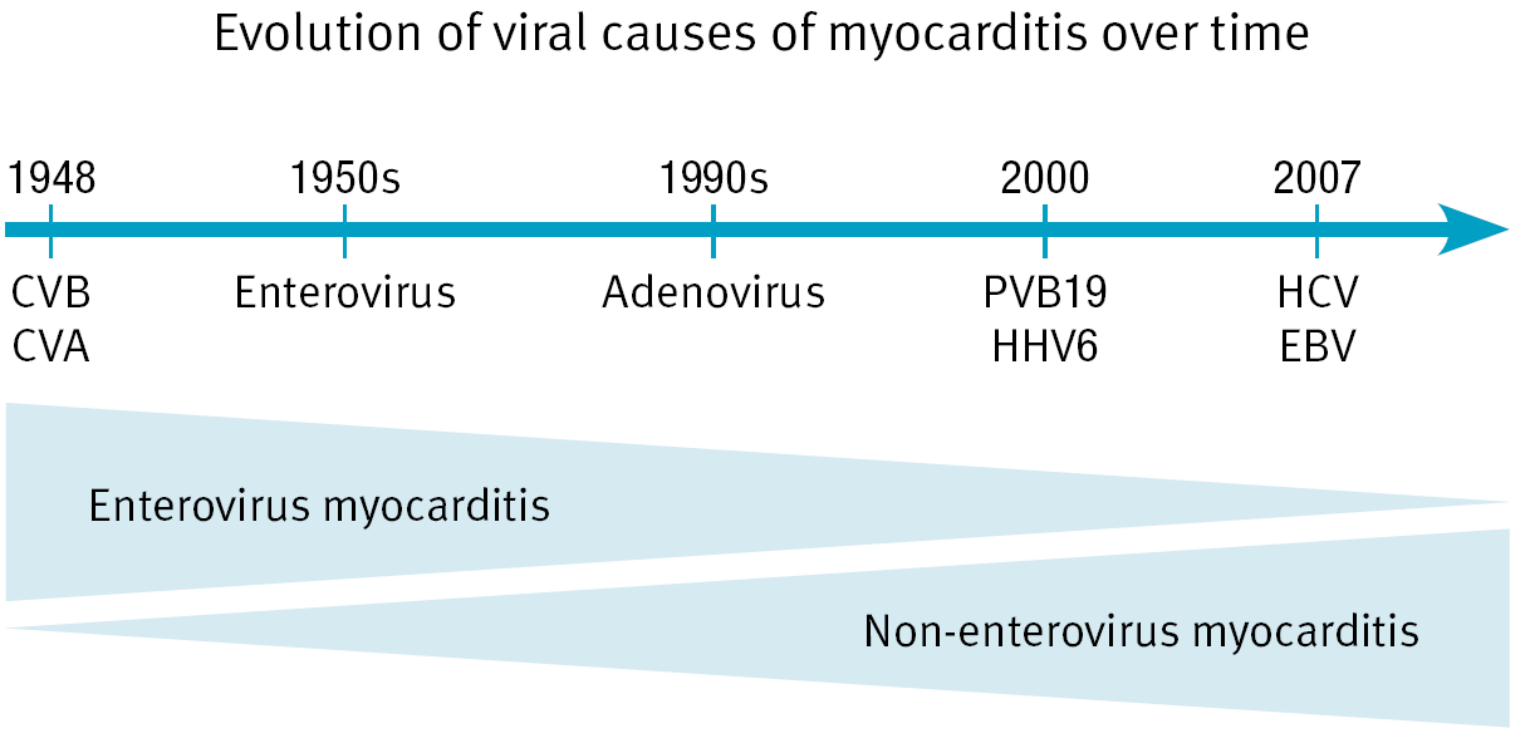
Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010

Rafael Lozano, Mohsen Naghavi, Kyle Foreman, Stephen Lim, Kenji Shibuya, Victor Aboyans, Jerry Abraham*, Timothy Adair*, Rakesh Aggarwal*, Stephanie Y Ahn*, Mohammad A AlMazroa*, Miriam Alvarado*, H Ross Anderson*, Laurie M Anderson*, Kathryn G Andrews*, Charles Atkinson*, Larry M Baddour*, Suzanne Barker-Collo*, David H Bartels*, Michelle L Bell*, Emelia J Benjamin*, Derrick Bennett*, Kavi Bhalla*, Boris Bikbov*, Aref Bin Abdulhak*, Gretchen Birbeck*, Fiona Blyth*, Ian Bolliger*, Soufiane Boufous*, Chiara Bucello*, Michael Burch*, Peter Burney*, Jonathan Carapetis*, Honglei Chen*, David Chou*, Sumeet S Chugh*, Luc E Coffeng*, Steven D Colan*, Samantha Colquhoun*, K Ellicott Colson*, John Condon*, Myles D Connor*, Leslie T Cooper*, Matthew Corriere*, Monica Cortinovis*, Karen Courville de Vaccaro*, William Couser*, Benjamin C Cowie*, Michael H Criqui*, Marita Cross*, Kaustubh C Dabhadkar*, Nabila Dahodwala*, Diego De Leo*, Louisa Degenhardt*, Allyne Delossantos*, Julie Denenberg*, Don C Des Jarlais*, Samath D Dharmaratne*, E Ray Dorsey*, Tim Driscoll*, Herbert Duber*, Beth Ebel*, Patricia J Erwin*, Patricia Espindola*, Majid Ezzati*, Valery Feigin*, Abraham D Flaxman*, Mohammad H Forouzanfar*, Francis Gerry R Fowkes*, Richard Franklin*, Marlene Fransen*, Michael K Freeman*, Sherine E Gabriel*, Emmanuela Gakidou*, Flavio Gaspari*, Richard F Gillum*, Diego Gonzalez-Medina*, Yara A Halasa*, Diana Haring*, James E Harrison*, Rasmus Havmoeller*, Roderick J Hay*, Bruno Hoen*, Peter J Hotez*, Damian Hoy*, Kathryn H Jacobsen*, Spencer L James*, Rashmi Jasrasaria*, Sudha Jayaraman*, Nicole Johns*, Ganesan Karthikeyan*, Nicholas Kassebaum*, Andre Keren*, Jon-Paul Khoo*, Lisa Marie Knowlton*, Olive Kobusingye*, Adofo Koranteng*, Rita Krishnamurthi*, Michael Lipnick*, Steven E Lipshultz*, Summer Lockett Ohno*, Jacqueline Mabweijano*, Michael F MacIntyre*, Leslie Mallinger*, Lyn March*, Guy B Marks*, Robin Marks*, Akira Matsumori*, Richard Matzopoulos*, Bongani M Mayosi*, John H McAnulty*, Mary M McDermott*, John McGrath*, Ziad A Memish*, George A Mensah*, Tony R Merriman*, Catherine Michaud*, Matthew Miller*, Ted R Miller*, Charles Mock*, Ana Olga Mocumbi*, Ali A Mokdad*, Andrew Moran*, Kim Mulholland*, M Nathan Nair*, Luigi Naldi*, K M Venkat Narayan*, Kiumarss Nasseri*, Paul Norman*, Martin O'Donnell*, Saad B Omer*, Katrina Ortblad*, Richard Osborne*, Doruk Ozgediz*, Bishnu Pahari*, Jeyaraj Durai Pandian*, Andrea Panozo Rivero*, Rogelio Perez Padilla*, Fernando Perez-Ruiz*, Norberto Perico*, David Phillips*, Kelsey Pierce*, C Arden Pope III*, Esteban Porrini*, Farshad Pourmalek*, Murugesan Raju*, Dharani Ranganathan*, Jürgen T Rehm*, David B Rein*, Guiseppe Remuzzi*, Frederick P Rivara*, Thomas Roberts*, Felipe Rodriguez De León*, Lisa C Rosenfeld*, Lesley Rushton*, Ralph L Sacco*, Joshua A Salomon*, Uchechukwu Sampson*, Ella Sanman*, David C Schwebel*, Maria Segui-Gomez*, Donald S Shepard*, David Singh*, Jessica Singleton*, Karen Sliwa*, Emma Smith*, Andrew Steer*, Jennifer A Taylor*, Bernadette Thomas*, Imad M Tleyjeh*, Jeffrey A Towbin*, Thomas Truelsen*, Eduardo A Undurraga*, N Venketasubramanian*, Lakshmi Vijayakumar*, Theo Vos*, Gregory R Wagner*, Mengru Wang*, Wenzhi Wang*, Kerrianne Watt*, Martin A Weinstock*, Robert Weintraub*, James D Wilkinson*, Anthony D Woolf*, Sarah Wulf*, Pon-Hsiu Yeh*, Paul Yip*, Azadeh Zabetian*, Zhi-Jie Zheng*, Alan D Lopez†, Christopher J L Murray†‡*

Lancet 2012;380:2095-2128

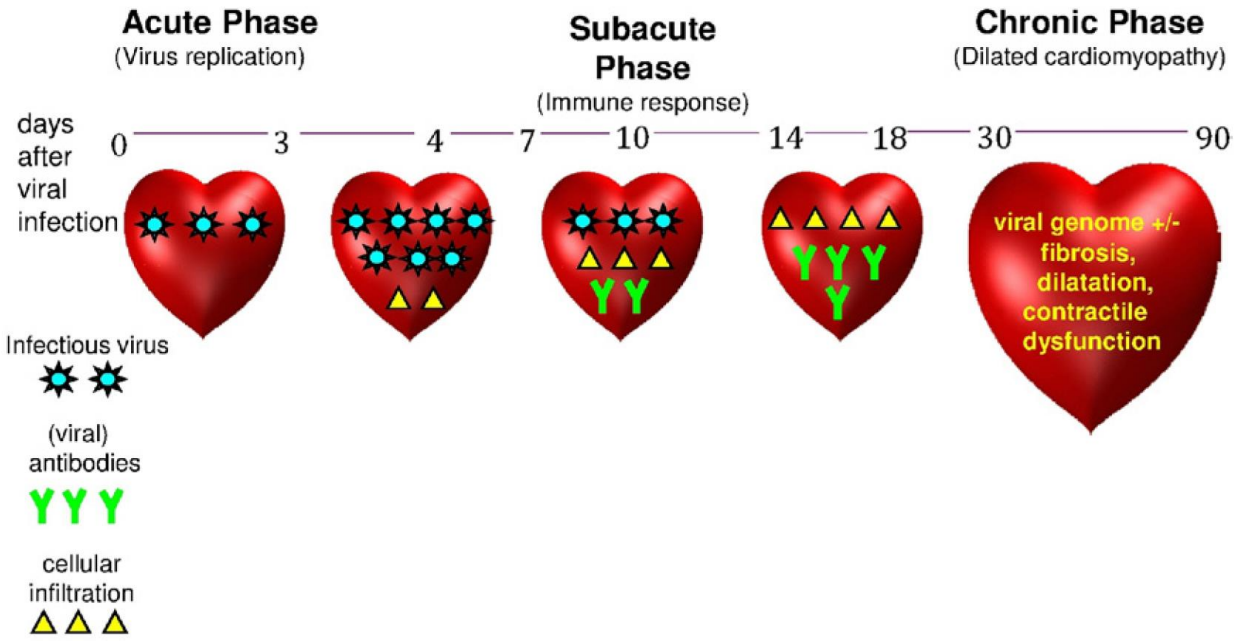
	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
(Continued from previous page)						
Mouth cancer	81·9 (68·6–88·3)	123·9 (104·2–136·3)	51·2%	2·0 (1·7–2·2)	1·9 (1·6–2·1)	–5·9
Nasopharynx cancer	45·2 (29·9–59·6)	64·9 (42·3–83·3)	43·6%	1·1 (0·7–1·4)	1·0 (0·6–1·3)	–8·2
Cancer of other part of pharynx and oropharynx	74·0 (43·8–90·9)	102·4 (59·5–128·5)	38·3%	1·8 (1·1–2·2)	1·6 (0·9–2·0)	–12·9
Gallbladder and biliary tract cancer	97·4 (66·1–136·0)	151·7 (100·4–206·8)	55·7%	2·4 (1·6–3·4)	2·3 (1·5–3·1)	–4·7
Pancreatic cancer	200·0 (154·1–261·5)	310·2 (231·7–393·1)	55·1%	5·0 (3·8–6·5)	4·7 (3·5–6·0)	–4·8
Malignant melanoma of skin	31·0 (20·3–46·6)	49·1 (29·9–69·5)	58·4%	0·8 (0·5–1·1)	0·7 (0·5–1·1)	–1·5
Non-melanoma skin cancer	20·5 (12·5–32·7)	30·6 (17·5–46·3)	49·6%	0·5 (0·3–0·8)	0·5 (0·3–0·7)	–10·7
Ovarian cancer	113·6 (82·9–138·8)	160·5 (115·9–200·6)	41·2%	2·8 (2·0–3·4)	2·4 (1·8–3·1)	–12·1
Testicular cancer	6·5 (3·8–8·3)	7·7 (4·8–10·0)	18·6%	0·1 (0·1–0·2)	0·1 (0·1–0·1)	–18·9
Kidney and other urinary organ cancers	85·1 (62·0–112·9)	162·1 (125·5–219·8)	90·6%	2·1 (1·5–2·7)	2·5 (1·9–3·3)	19·4
Bladder cancer	123·4 (100·2–148·5)	170·7 (131·1–201·2)	38·3%	3·1 (2·5–3·7)	2·6 (2·0–3·0)	–16·3
Brain and nervous system cancers	131·5 (88·7–188·3)	195·5 (115·1–239·3)	48·7%	3·0 (2·1–4·4)	3·0 (1·7–3·6)	–2·5
Thyroid cancer	24·0 (18·0–29·9)	36·0 (26·4–43·2)	50·2%	0·6 (0·4–0·7)	0·5 (0·4–0·7)	–6·7
Hodgkin's disease	18·9 (11·8–26·2)	17·7 (11·6–25·5)	–6·0%	0·4 (0·3–0·6)	0·3 (0·2–0·4)	–36·7
Non-Hodgkin lymphoma	143·2 (119·4–158·9)	210·0 (166·0–228·5)	46·7%	3·3 (2·8–3·7)	3·2 (2·5–3·4)	–5·0
Multiple myeloma	49·3 (34·5–71·2)	74·1 (48·9–102·2)	50·4%	1·2 (0·9–1·8)	1·1 (0·7–1·6)	–7·5
Leukaemia	218·3 (175·7–269·2)	281·3 (219·6–328·0)	28·9%	4·7 (3·8–5·9)	4·2 (3·3–4·9)	–11·5
Other neoplasms	412·7 (319·5–521·9)	608·4 (441·2–737·3)	47·4%	9·8 (7·6–12·4)	9·2 (6·7–11·2)	–5·7
Cardiovascular and circulatory diseases	11 903·7 (11 329·4–12 589·3)	15 616·1 (14 542·2–16 315·1)	31·2%	298·1 (283·9–314·9)	234·8 (218·7–245·2)	–21·2
Rheumatic heart disease	462·6 (431·5–517·7)	345·1 (305·8–374·3)	–25·4%	11·1 (10·3–12·4)	5·2 (4·6–5·6)	–53·1
Ischaemic heart disease	5211·8 (5014·5–5643·9)	7029·3 (6577·2–7431·1)	34·9%	131·3 (126·4–142·2)	105·7 (98·8–111·9)	–19·5
Cerebrovascular disease	4660·4 (4436·1–5154·9)	5874·2 (5304·7–6280·1)	26·0%	105·7 (98·8–111·9)	88·4 (79·8–94·4)	–24·6
Ischaemic stroke	2241·1 (2088·0–2494·9)	2835·4 (2657·0–3262·8)	26·5%	57·6 (53·7–64·0)	42·3 (39·6–48·7)	–26·6
Haemorrhagic and other non-ischaemic stroke	2419·4 (2050·9–2827·9)	3038·8 (2643·4–3496·9)	25·6%	59·7 (50·6–69·7)	46·1 (40·1–53·1)	–22·7
Hypertensive heart disease	590·7 (481·0–740·6)	873·2 (715·5–1074·1)	47·8%	14·9 (12·1–18·6)	13·1 (10·8–16·2)	–11·5
Cardiomyopathy and myocarditis	286·8 (250·5–316·8)	403·9 (361·5–450·4)	40·8%	6·7 (5·9–7·4)	6·1 (5·4–6·8)	–9·8
Atrial fibrillation and flutter	34·4 (27·9–43·1)	114·7 (92·7–144·7)	233·9%	0·9 (0·7–1·1)	1·7 (1·4–2·1)	89·6
Aortic aneurysm	131·9 (94·6–173·3)	191·7 (140·3–249·2)	45·3%	3·3 (2·4–4·3)	2·9 (2·1–3·8)	–12·7
Peripheral vascular disease	18·6 (12·2–28·7)	49·8 (32·9–74·8)	167·0%	0·5 (0·3–0·7)	0·7 (0·5–1·1)	53·3
Endocarditis	35·8 (30·0–44·4)	48·3 (39·3–55·4)	34·8%	0·8 (0·7–1·0)	0·7 (0·6–0·8)	–8·0
Other cardiovascular and circulatory diseases	470·6 (446·3–489·9)	685·9 (664·0–705·3)	45·7%	11·5 (11·0–11·9)	10·3 (9·9–10·5)	–10·9

Lancet 2012;380:2095-2128



Schultz JC, Hilliard AA, Cooper LT. Mayo Clin Proc 2009;84:1001-1009

Time Course of Viral Myocarditis



Kindermann I, Bohm M, et al. J Am Coll Cardiol 2012;59:779-792

Panel: Selected classifications for myocarditis

Cause

- Viral, such as enteroviruses (eg, Coxsackie B), erythroviruses (eg, Parvovirus B19), adenoviruses, and herpes viruses
- Bacterial, such as *Corynebacterium diphtheriae*, *Staphylococcus aureus*, *Borrelia burgdorferi*, and *Ehrlichia* species
- Protozoal, such as *Babesia*
- Trypanosomal, such as *Trypanosoma cruzi*
- Toxic: alcohol, radiation, chemicals (hydrocarbons and arsenic), and drugs, including doxorubicin
- Hypersensitivity: sulphonamides and penicillins

Histology

- Eosinophilic
- Giant cell
- Granulomatous
- Lymphocytic

Immunohistology (not mutually exclusive)

- World Heart Federation: 14 or more CD3+ or CD68+ cells per high power field
- Increased expression of human leucocyte antigens (eg, HLA-DR)
- Increased expression of adhesion molecules (eg, intracellular adhesion molecule 1)

Clinicopathological

- Fulminant
- Acute
- Chronic active
- Chronic persistent

Clinical (not mutually exclusive)

- Acute heart failure
- Syncope
- Chest pain resembling an acute myocardial infarction
- Myopericarditis

Sagar S, Liu PP, Cooper LT. Lancet 2012;379:738-747

MYOCARDITIS: Diagnosis

Clinical features:

1) Asymptomatic + ECG abnormalities
2) Chest pain, ACS like presentation
3) CHF, ventr dysfct ± ventricular dilatation
4) Fulminant heart failure/collapse with severe LV dysfunction, dilatation
5) Syncope, sudden death due to brady/ tachyarrhtythmias

Recent history of flu-like symptoms

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.

Table 1: A three-tiered clinical classification for the diagnosis of myocarditis on the basis of level of diagnostic certainty

	Criteria	Histological confirmation	Biomarker, ECG, or imaging abnormalities consistent with myocarditis	Treatment
Possible subclinical acute myocarditis	In the clinical context of possible myocardial injury without cardiovascular symptoms but with at least one of the following: 1 Biomarkers of cardiac injury raised 2 ECG findings suggestive of cardiac injury 3 Abnormal cardiac function on echocardiogram or cardiac MRI	Absent	Needed	Not known
Probable acute myocarditis	In the clinical context of possible myocardial injury with cardiovascular symptoms and at least one of the following: 1 Biomarkers of cardiac injury raised 2 ECG findings suggestive of cardiac injury 3 Abnormal cardiac function on echocardiogram or cardiac MRI	Absent	Needed	Per clinical syndrome
Definite myocarditis	Histological or immunohistological evidence of myocarditis	Needed	Not needed	Tailored to specific cause

ECG=electrocardiogram.

Sagar S, Liu PP, Cooper LT. Lancet 2012;379:738-747

JACC White Paper

Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper

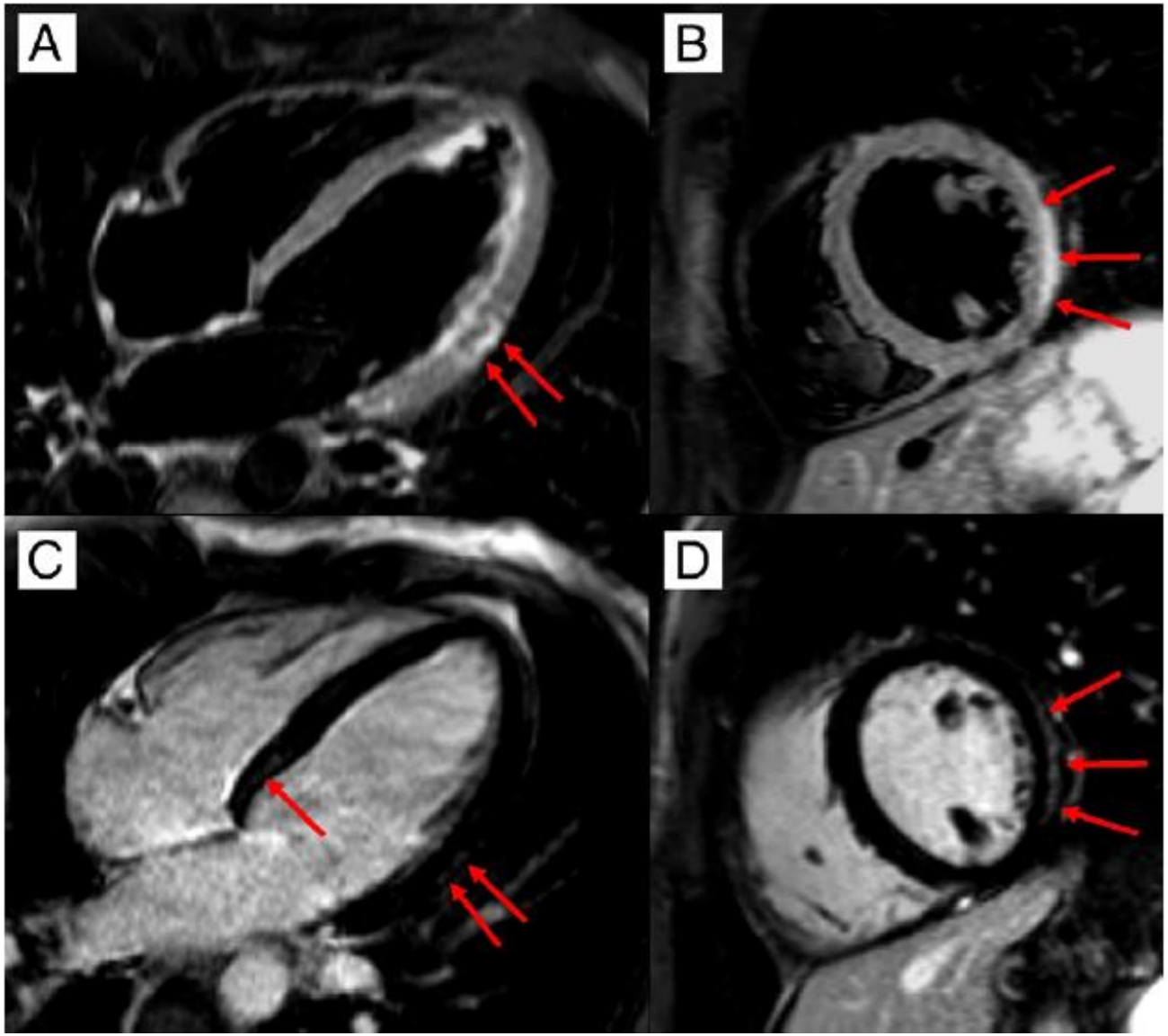
Matthias G. Friedrich, MD,* Udo Sechtem, MD,‡ Jeanette Schulz-Menger, MD,§ Godtfred Holmvang, MD,‖ Pauline Alakija, MD,† Leslie T. Cooper, MD,¶ James A. White, MD,# Hassan Abdel-Aty, MD,§ Matthias Gutberlet, MD,** Sanjay Prasad, MD,†† Anthony Aletras, PHD,‡‡ Jean-Pierre Laissy, MD,§§ Ian Paterson, MD,‖‖ Neil G. Filipchuk, MD,* Andreas Kumar, MD,* Matthias Pauschinger, MD,¶¶ Peter Liu, MD,## for the *International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis*

J Am Coll Cardiol 2009;53:1475-1487

	Validation	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)
T2 and LGE	Clinical histology	25	95	56	86
T2, LGE, or both	Clinical histology	60	66	62	79
Any 1 of 3	Clinical histology	88	48	70	68
Any 2 of 3	Clinical histology	67	91	78	91

PPV=positive predictive value. T2=T2-weighted MRI. LGE=late gadolinium enhancement. Adapted with permission from Friedrich and colleagues.[79]

Table 2: **Accuracy of several combinations of cardiac MRI tissue criteria for the diagnosis of myocarditis**



Kindermann I, Bohm M, et al. J Am Coll Cardiol 2012;59:779-792

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AHA/ACCF/ESC SCIENTIFIC STATEMENT

The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease

A Scientific Statement From the American Heart Association, the American College of Cardiology, and the European Society of Cardiology

Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology

Leslie T. Cooper, MD, FAHA, FACC; Kenneth L. Baughman, MD, FAHA, FACC; Arthur M. Feldman, MD, PhD, FAHA, FACC; Andrea Frustaci, MD; Mariell Jessup, MD, FAHA, FACC; Uwe Kuhl, MD; Glenn N. Levine, MD, FAHA, FACC; Jagat Narula, MD, PhD, FAHA; Randall C. Starling, MD, MPH; Jeffrey Towbin, MD, FAHA, FACC; Renu Virmani, MD, FACC

Clinical Scenario	Class of Recommendation (I, IIa, IIb, III)	Level of Evidence (A, B, C)
New-onset heart failure of *<2 weeks'* duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I	B
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
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
Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa	C

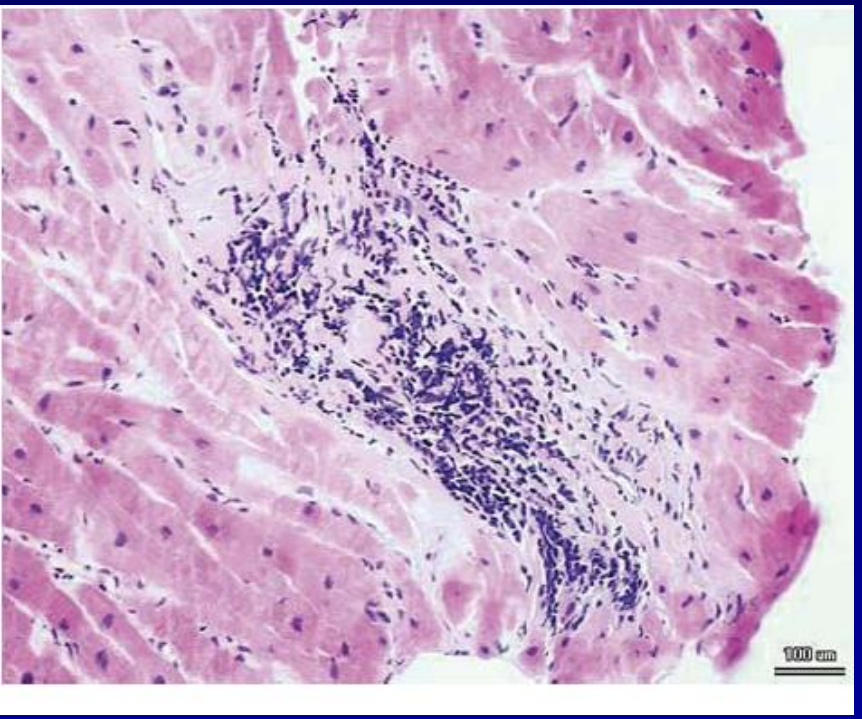
Special Report

Diagnosis of Myocarditis

Death of Dallas Criteria

Kenneth L. Baughman, MD

Circulation 2006;113;593-595

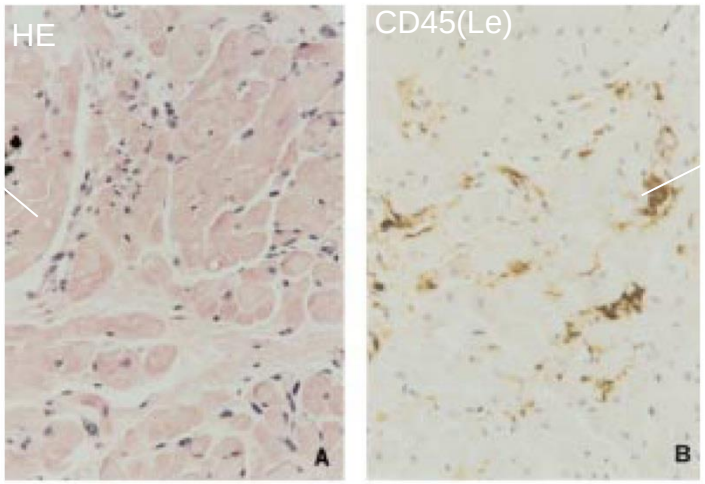


- **"Dallas" criteria proposed in 1986: cellular infiltrate with myocyte necrosis**
- **Sampling error; sensitivity- 35%**
- **High inter-observer variability in pathological interpretation**
- **No correlation with outcome**

Immunohistologic analysis (CD3; CD68, HLA) increase biopsy sensitivity and decrease sampling error

Histological and immunohistological findings in 12 pts with acute myocarditis mimicking AMI

7 (58%) +ve



11 (92%) +ve

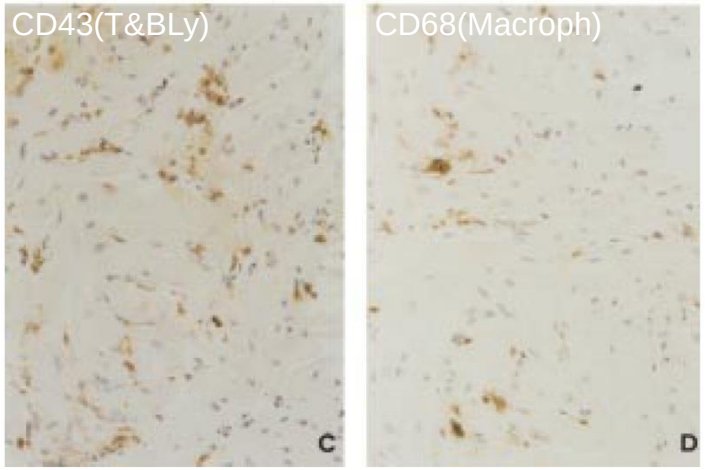
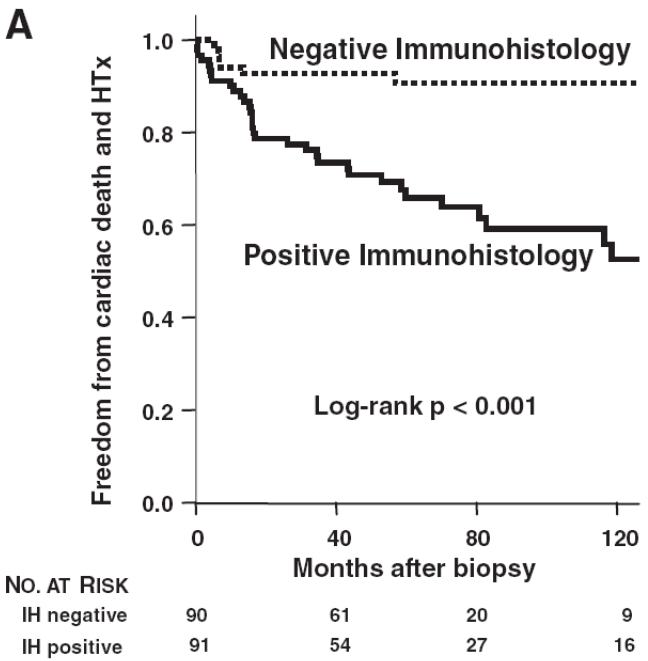
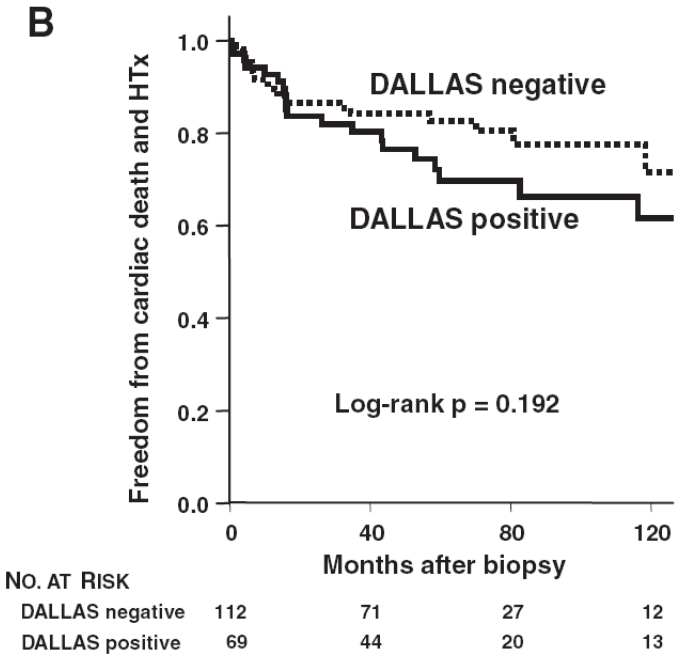


Figure 3 Patient 9: active lymphocytic myocarditis. Haematoxylin and eosin stain. (A) Inflammatory infiltrate surrounding a few necrotic myocytes. Immunohistochemical staining for CD45 (leucocytes) (B), for CD43 (lymphocytes) (C), and for CD 68 (macrophages) (D) confirmed the presence of inflammatory cells within the myocardium.

Angelini A et al. Heart 2000;84:245-50

EMB Predictors of Outcome in Myocarditis





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

Clinical Scenarios

Table 1. Clinical Scenarios for the Diagnosis of Myocarditis.*

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, necrotizing 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 or 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 or 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
Heart failure with eosinophilia	Any duration	Eosinophilic or hypersensitivity myocarditis, 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 of 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

Cooper LT, NEJM 2009;360:1526-1538

Case 1: 76yo female with CIHD, S/A AMI, NIDDM, CAF

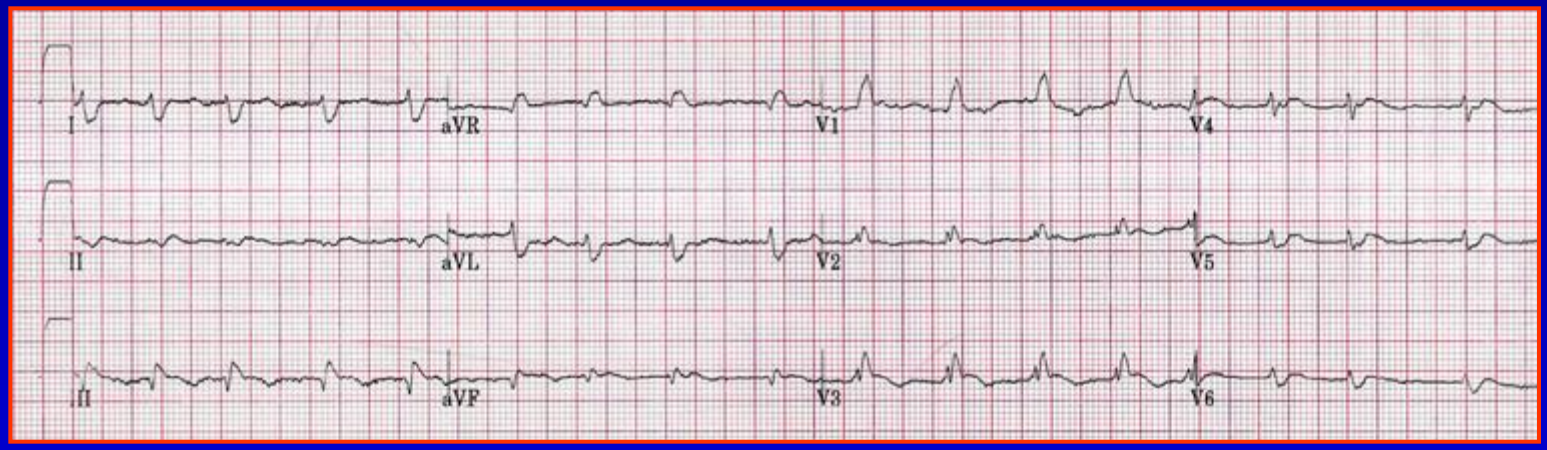
March 2007

- Admission for: dyspnea, chest discomfort and fatigue
- 2w earlier – transient Bells palsy followed by ptosis of right eyelid

Case 1: 76yo female with CIHD, S/A AMI, NIDDM, CAF

- Physical exam on admission:
  - Weak with mild dyspnea
  - BP 111/75 pulse 102
  - Temp 36 O^2 Sat 92%
  - Distant irregular heart sounds
  - Lungs clear to auscultation
  - Extremities without edema
  - Clinically stable condition

ECG



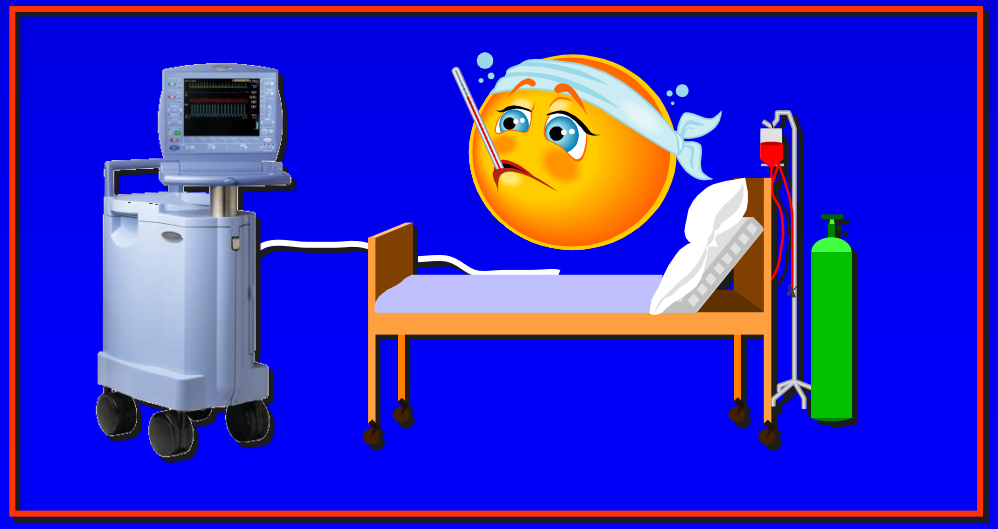
Atrial Fibrillation, RBBB, Q waves & ST-T changes in Inferior leads

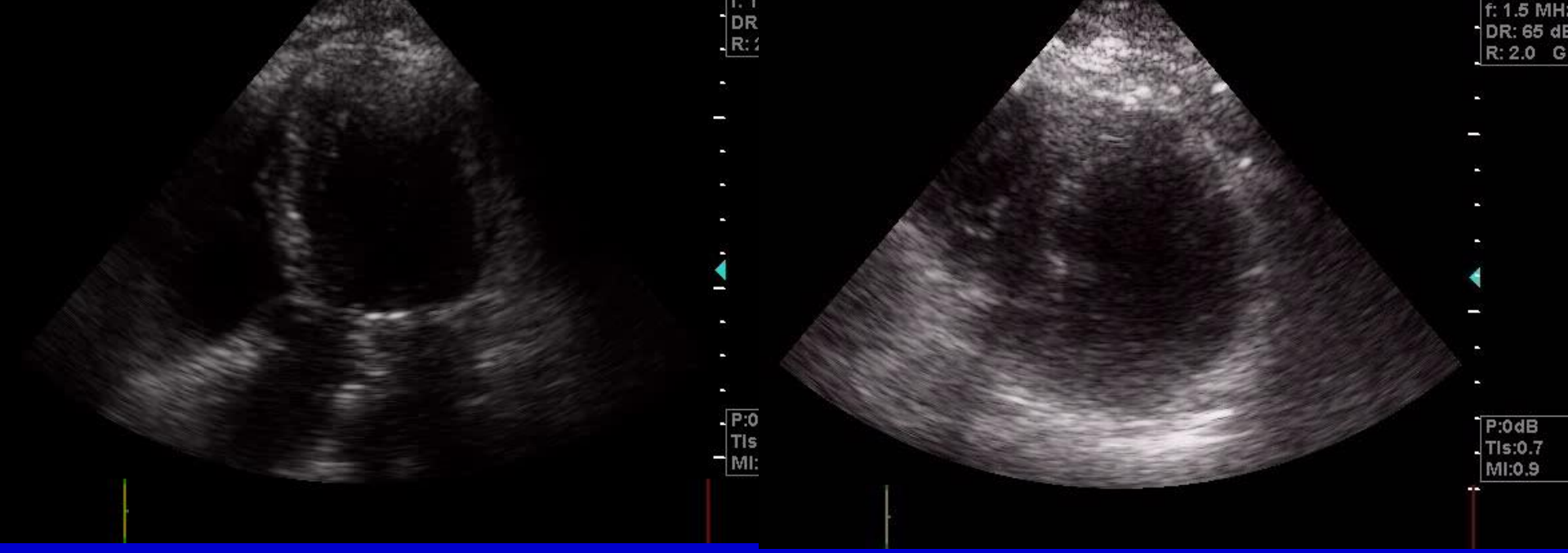
Positive CRP 3.5, TropT 5.5 ng/ml CPK 346 U/L

Dg: ACS, NSTEMI

Within a Few Hours

- Developed Cardiogenic shock:
  Dyspnea, congestion on X-ray, no Δ ECG
- Treated with IABP and IV diuretics

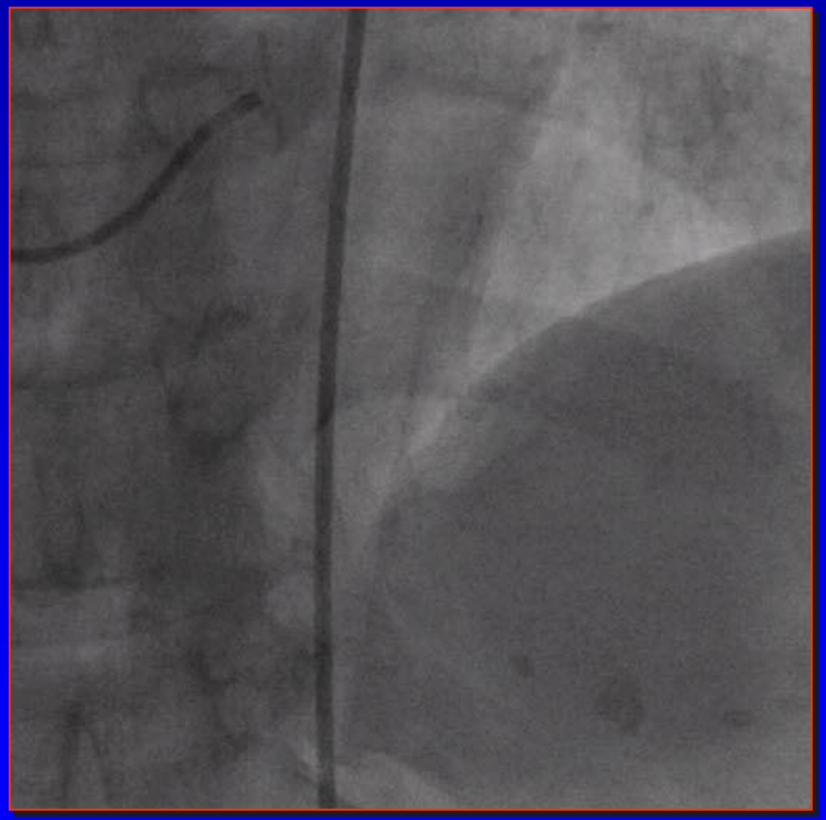




Decreased LV function. No significant valvular disease. No PHT

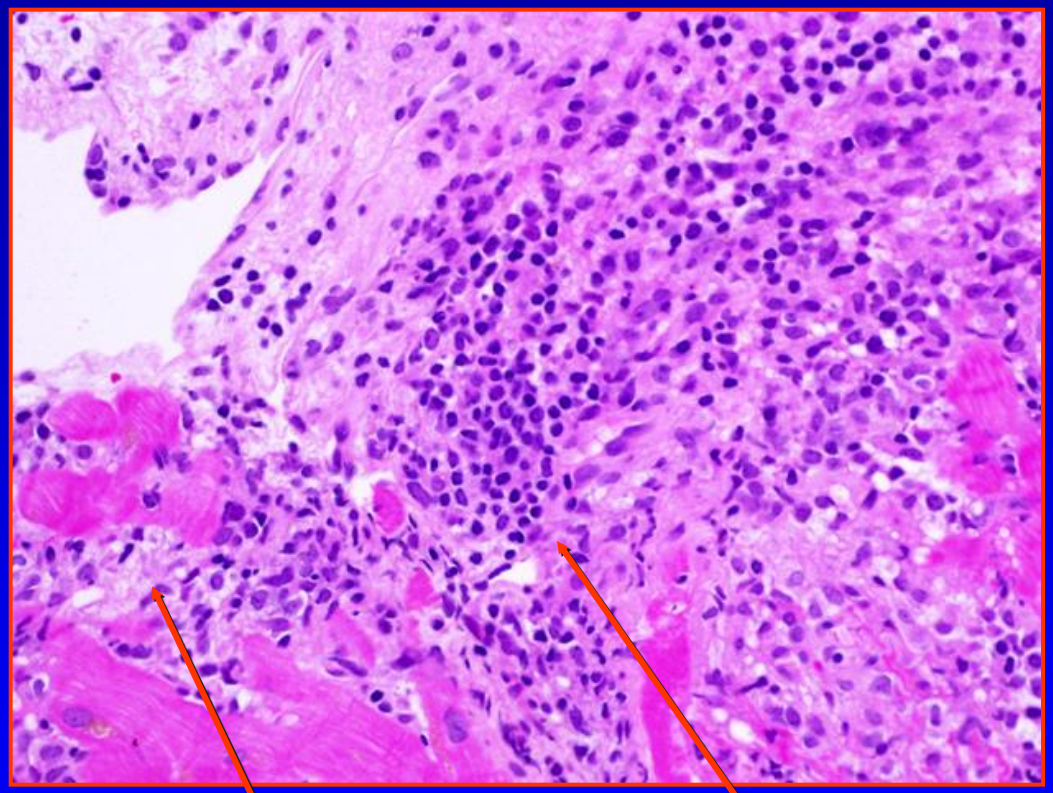
Catheterization

- Mid-LAD 100%
- No change from previous Cath
- No PHT (33/23) CI 1.5 l/min/m2
- No branch cutoff on pulmonary angio



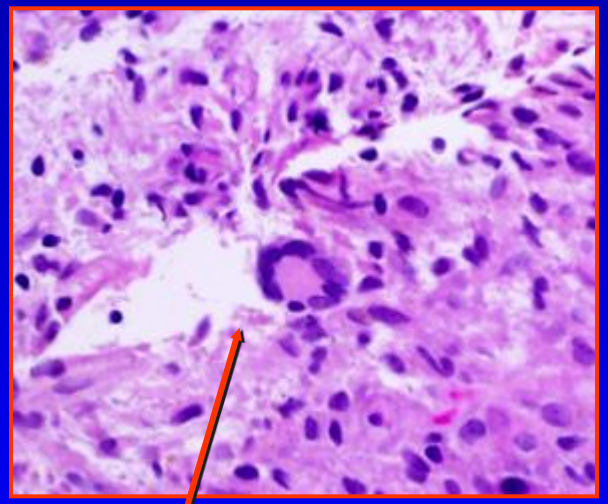
- Endomyocardial biopsy performed

Endomyocardial Biopsy



Myocyte Necrosis

Lymphocytic Infiltrate

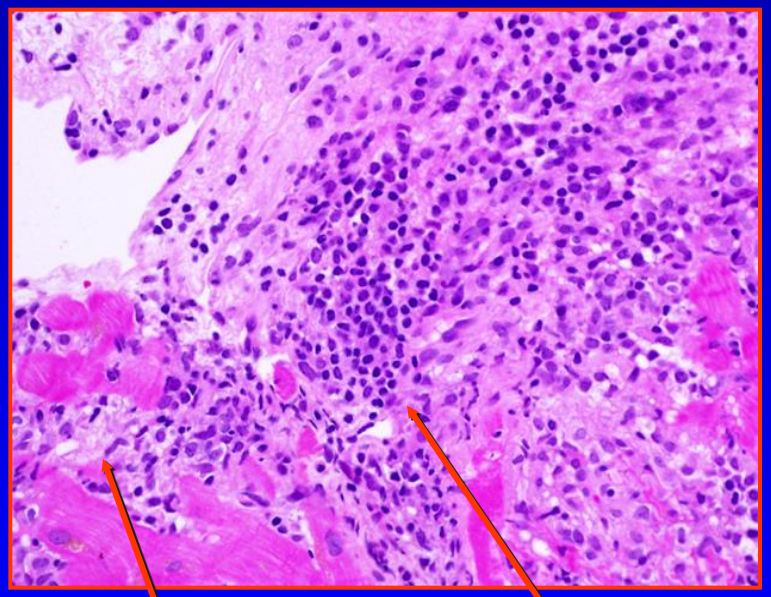


Giant Cell

Gotsman I, Keren A, Admon D. IMAJ 2011;13:773-775

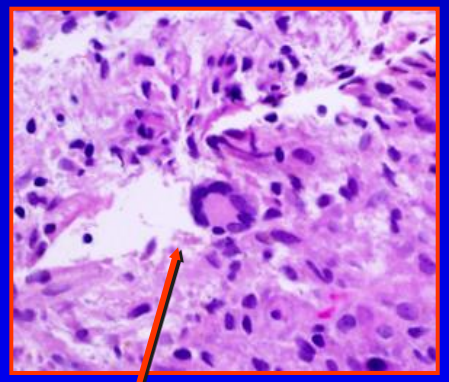
Diagnosis

- Giant Cell Myocarditis ? **Immunosuppression**
- Lymphocytic Myocarditis? **Supportive Rx**



Myocyte Necrosis

Lymphocytic Infiltrate



Giant Cell

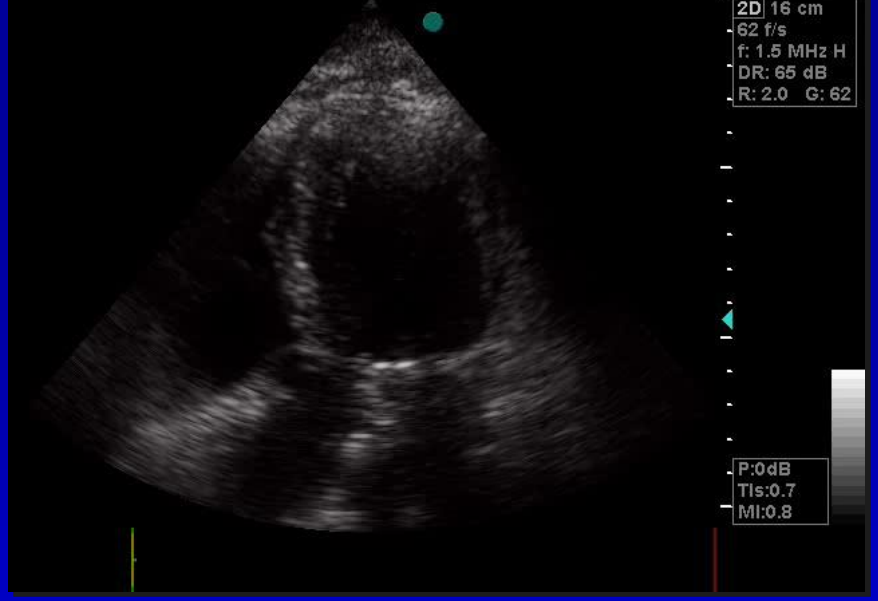
Hospital Course

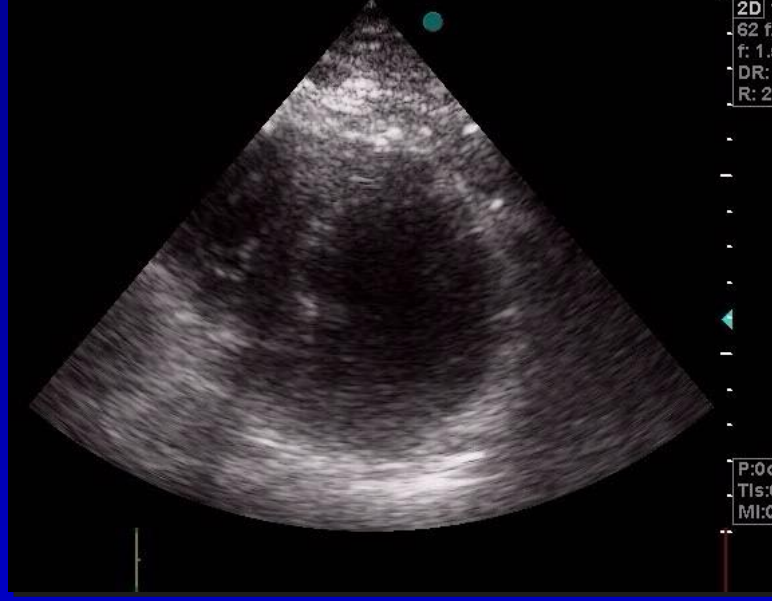
- Treated with ACE-I, BB, Diuretic
- On going decision for - possible Giant Cell myocarditis
- Significant improvement: Conservative therapy
- Weaned from IABP after 3 days

Pathological Dx:

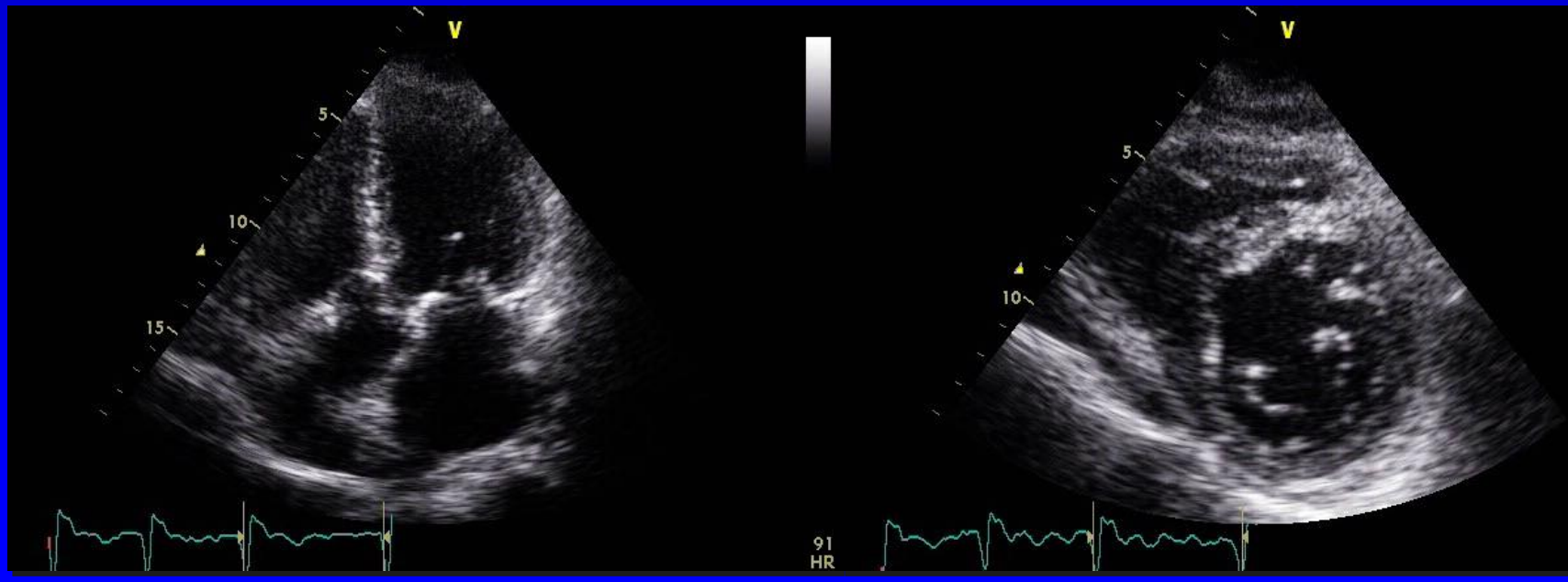
Severe, diffuse necrotizing lymphocytic myocarditis

29.3.07


2D 16 cm
62 f/s
f: 1.5 MHz H
DR: 65 dB
R: 2.0 G: 62
P:0dB
TIs:0.7
MI:0.8



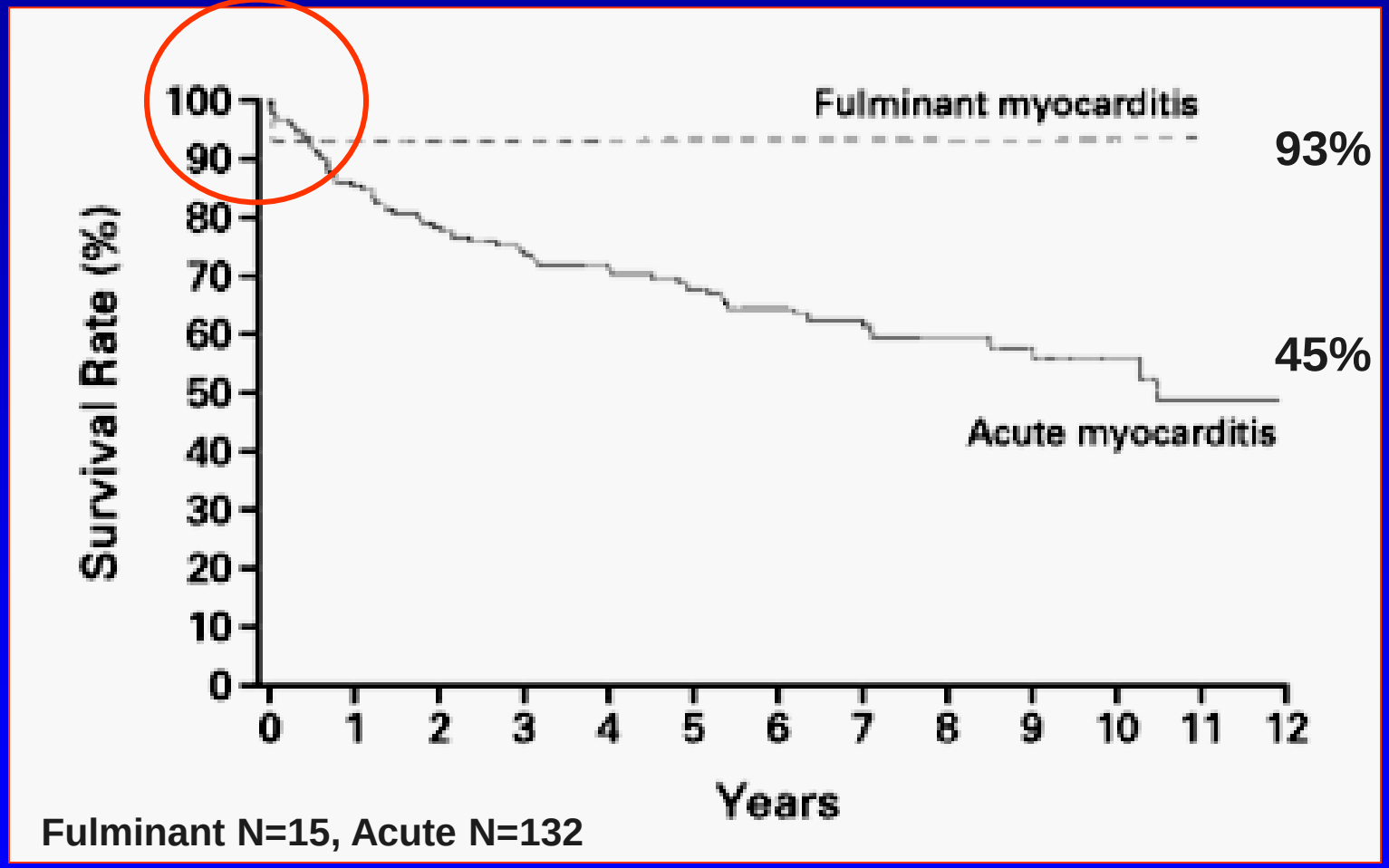
12.4.07


V
5
10
15
V
5
10
91
HR

Lymphocytic Myocarditis

- Acute/Subacute myocarditis are less ill initially but might have a progressive course that leads to death or the need for cardiac transplantation
- Fulminant myocarditis is characterized by critical illness at presentation, but good long-term survival

Transplantation Free Survival in Fulminant Myocarditis



McCarthy RE, NEJM 2000;342:690-696; Mason JW NEJM 1995;333:269-275

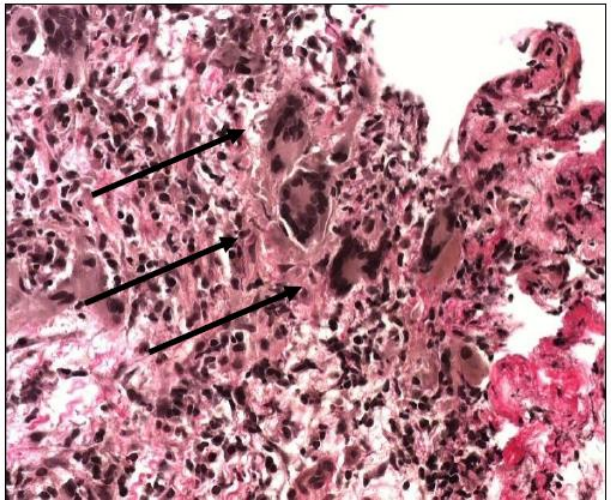
Case 2: 53yo female, acute heart failure and ventricular fibrillation

- **March 2007**
  - **Worsening heart failure, LVEF 35%**
  - **Ventricular fibrillation**
  - **Supportive therapy, ICD, Transfer to Charite**
  - **EMB**

Courtesy Schultheiss HP, Charite, Berlin

Case 2: 53yo female, acute heart failure and ventricular fibrillation

Biopsy diagnosis: giant cell myocarditis



Heart Failure Rx + Immunosuppressive Rx with Cyclosporine150mg/day, Prednisone 80mg/day

Case 2: 53yo female, acute heart failure and ventricular fibrillation

May 2007 – June 2008
Improvement of left ventricular function (EF : 56%
and further clinical improvement (NYHA II)

Control biopsies (June 2008):
no giant cells,
healing myocarditis,
no viral infection

Reduction of immunosuppressive therapy:
Ciclosporin 100mg/day
Prednisolon 5 mg/day

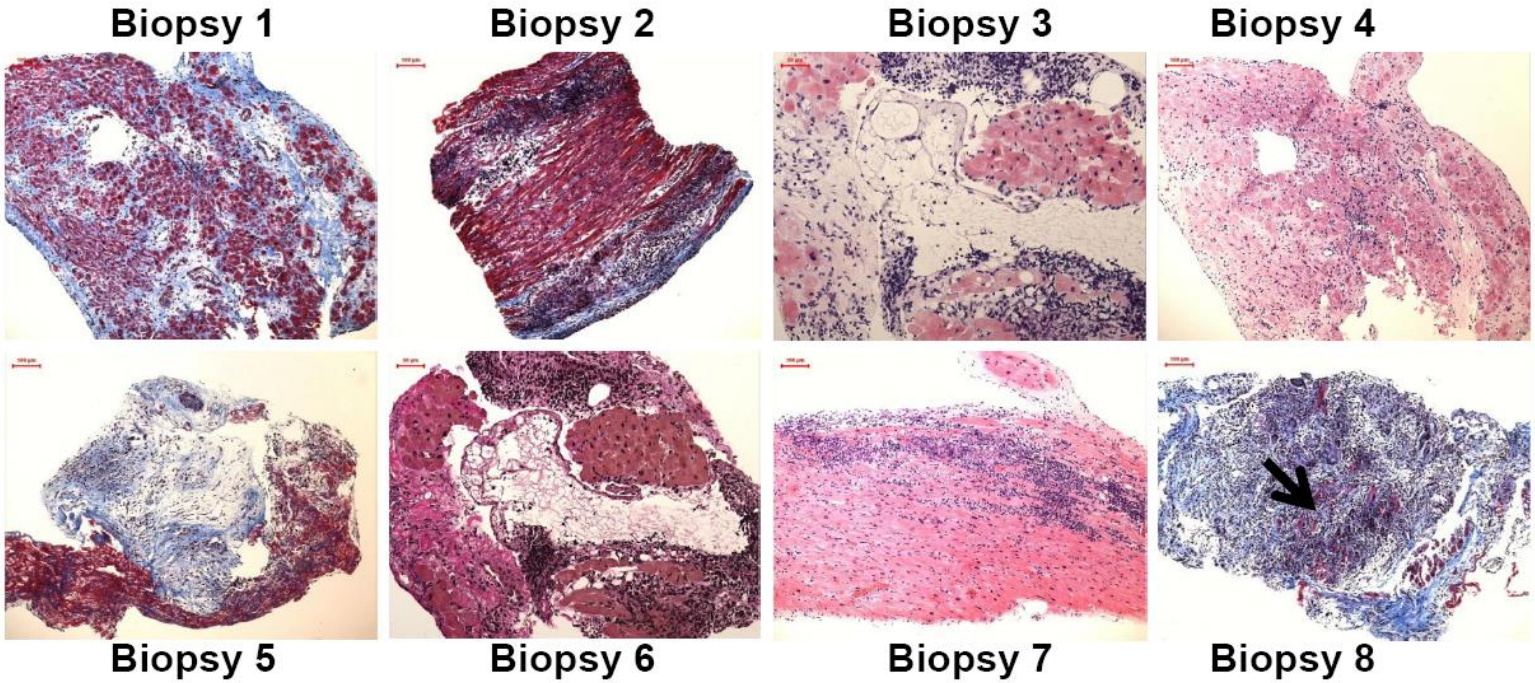
Case 2: 53yo female, acute heart failure and ventricular fibrillation

July 2008:

Fever 39°C,
NYHA III
VT, appropropriate ICD shock
Troponin T : 0.6
proBNP: 35,000 pg/ml
Left ventricular function: EF 19%

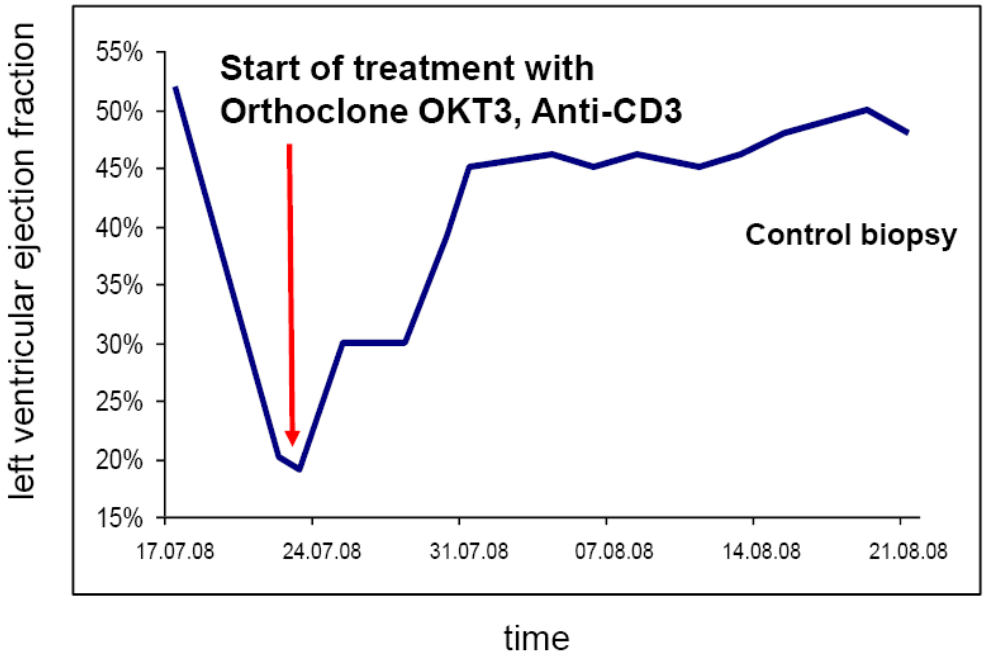
Again: myocardial biopsy

July 23, 2008: Re-biopsy



Diagnosis: Giant cell myocarditis

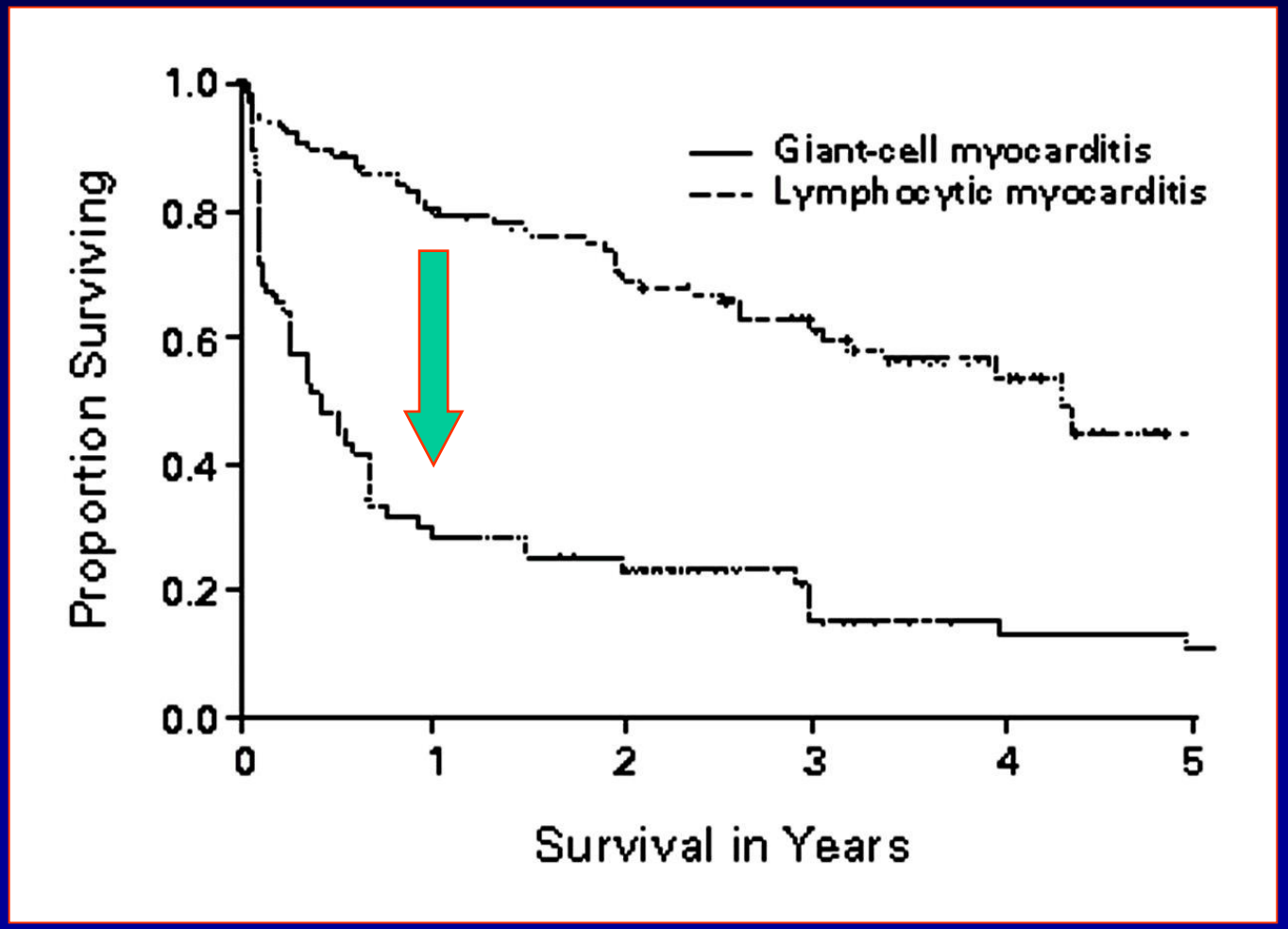
A 53 year old female with recurrence of giant cell myocarditis



Chronic Rx: Stable, with LVEF of 63% on 15.6.2011

- Cyclosporine (through level100-140ng/ml)
- Prednisone 15mg/day

Giant-Cell Myocarditis



Cooper, et al, NEJM 1997

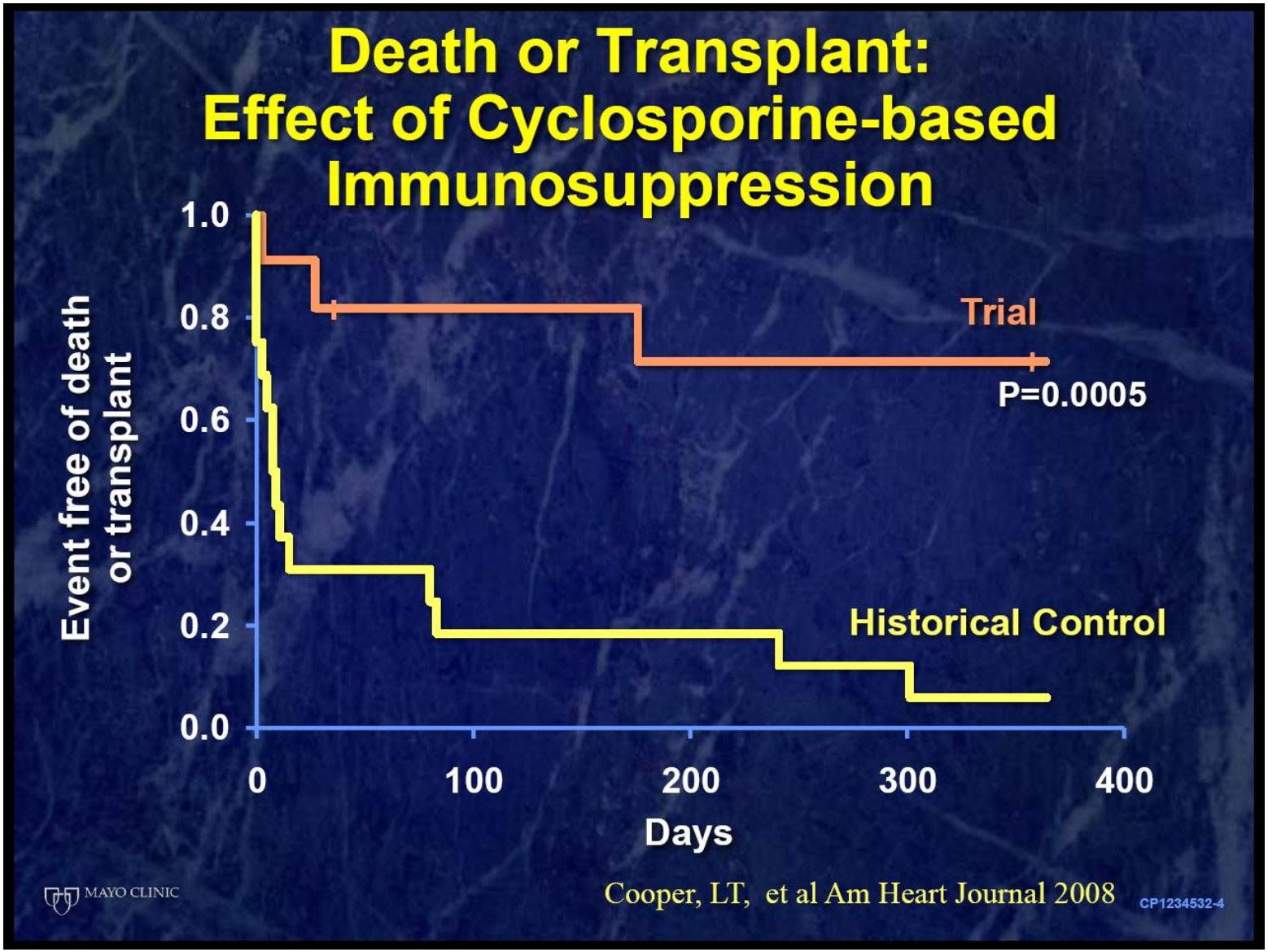
1 year Outcome in the GCM Treatment Trial

Table 1
Demographics, treatment, and outcome of 11 subjects with giant cell myocarditis

Subject Number	Gender	Age at Entry	Duration of Symptoms (days)	Treatment	Baseline LVEF (Percentage)	Outcome
1	M	49	64	OKT3, C, S	25	Transplant
2	M	51	4	OKT3, C, S	48	Alive
3	F	70	40	OKT3, C, S	54	Alive
4	M	39	19	OKT3, C, S	47	Alive
5	F	79	5	C, S	19	Alive
6	M	71	1	C, S	17	Died
7	F	58	1	OKT3, C, S	43	Alive
8	F	76	24	OKT3, C, S	67	Alive
9	F	45	4	OKT3, C, S	50	Alive
10	F	48	6	OKT3, C, S	15	Transplant
11	F	81	1	OKT3, C, S	68	Alive

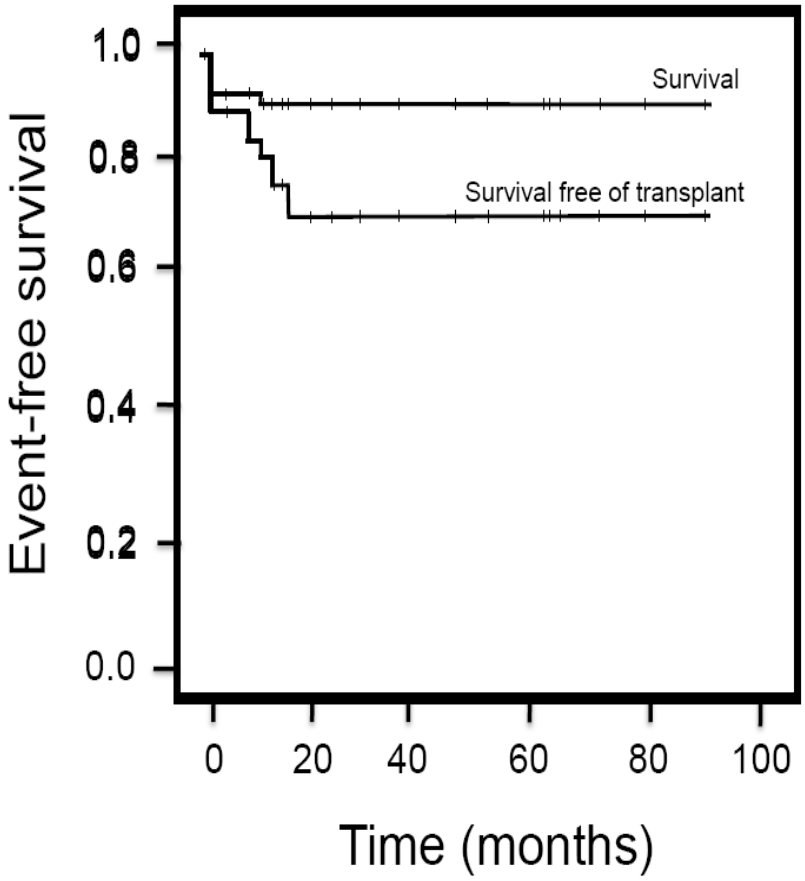
C = cyclosporine; F = female gender; M = male gender; OKT3 = muromonab-CD3; S = corticosteroids.

Cooper LT et al. Am J Cardiol 2008;102:1535-1539



By courtesy of Cooper LT

- Kaplan-Meier curves for survival free of death and death/transplantation in 26 pat. treated with immunosuppressive medication



Lessons Learned from Recent Studies/Registries of GCM

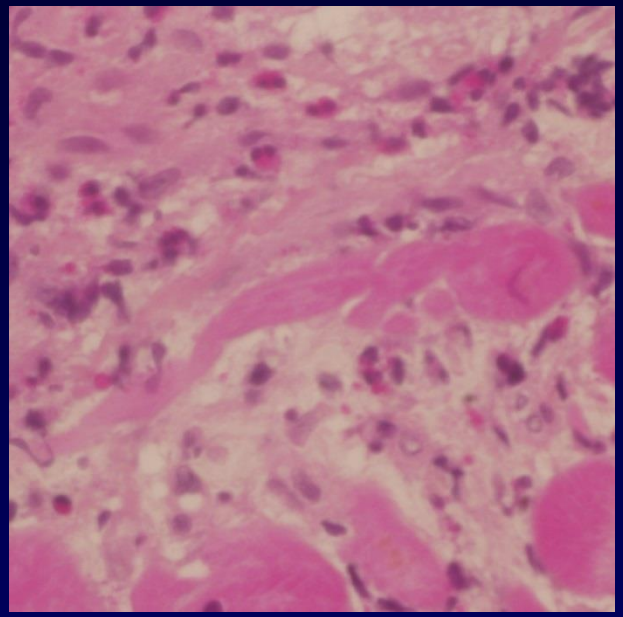
- Immunosuppressive Rx improves survival and probably has to be given life long
- Withdrawal of immunosuppression can result in recurrence and fatal GCM
- Ventricular arrhythmias frequently recurred during follow up in a Finish registry of 26 pts with GCM and immunosuppressive Rx

When to Suspect GCM

- Rapidly progressive course
- Failure to respond to usual care
- Ventricular tachycardia
- High-grade heart block

Cooper LT, Am Heart J 2008

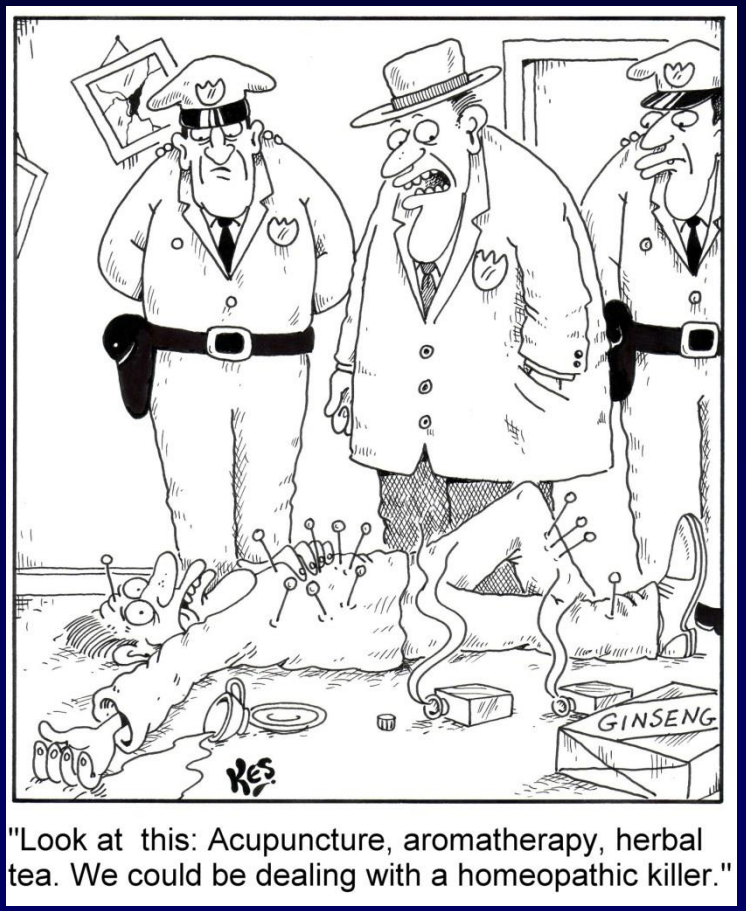
Cse 3: 44yo male, Cyclist, Asthma for 3years, Eosinophilia, Homeopathic Rx



Pancarditis, Churg Strauss Syndr, Steroids & Cyclophospamide

By courtesy of Dr Marc Klutstein, Shaare Zedek Hospital, Jerusalem

Homeopathic treatment including garlic , teea extracts , spiroline, bee sting, etc



"Look at this: Acupuncture, aromatherapy, herbal tea. We could be dealing with a homeopathic killer."

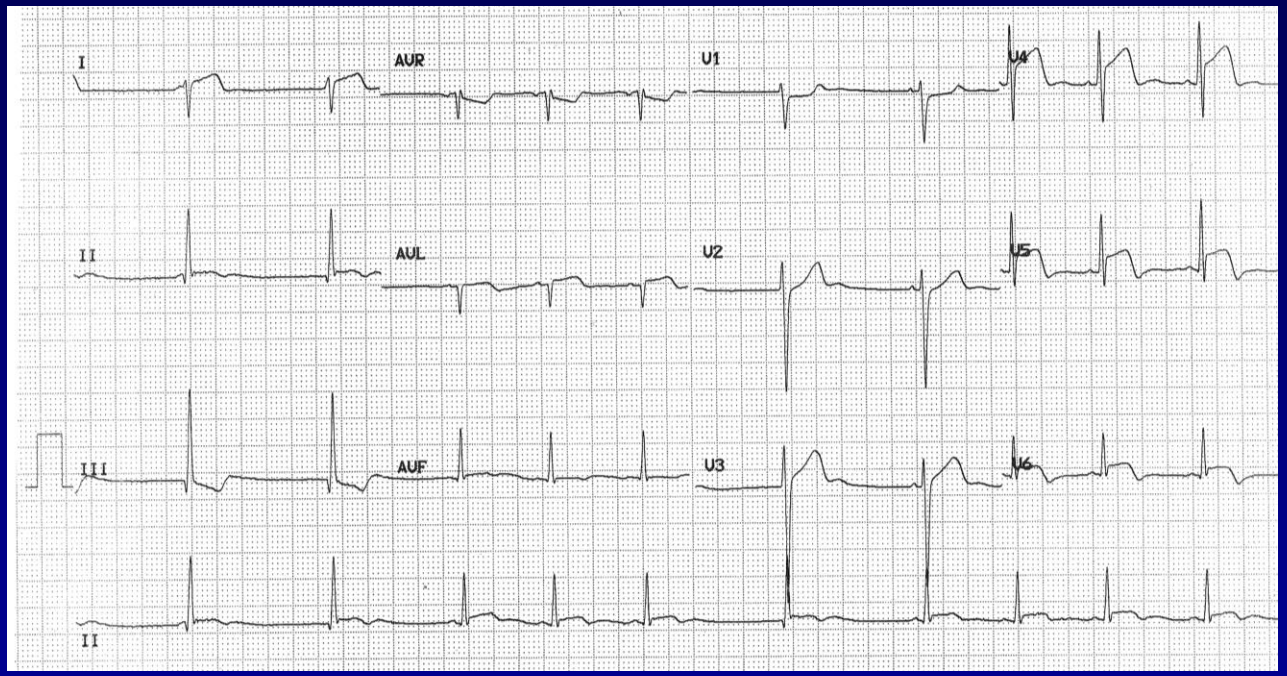
By courtesy of Dr Marc Klutstein, Shaare Zedek Hospital, Jerusalem

Eosinophilic Myocarditis

- Idiopathic
- Allergic/hypersensitivity: drugs, parasites, vaccines, venomes
- Systemic disease: Loffler, Churg Strauss, etc (myocardial, endocardial, valvular involvement)
- Fulminant necrotizing myocarditis

- Immunosuppressive Rx required for periods related to etiology

Case 4: 32yo, Obese, AHT, severe chest pain, ECG changes, +ve enzymes



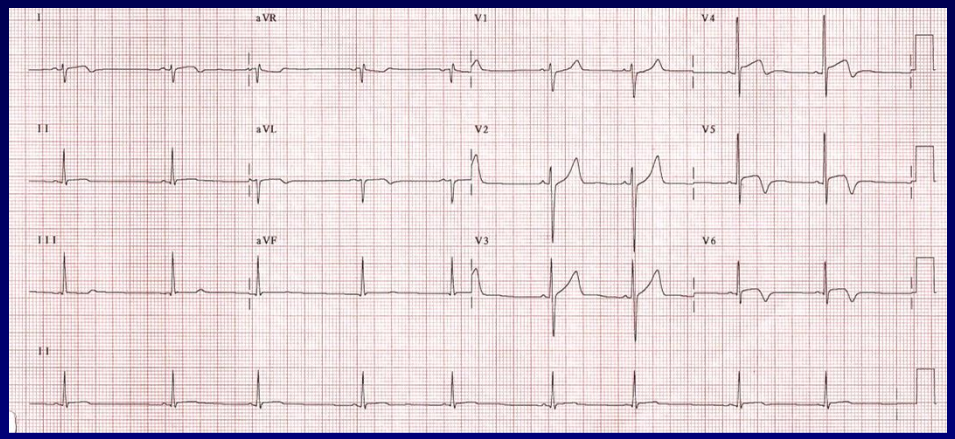
Admission ECG

Echocardiogram, Coronary angiogram: NORMAL

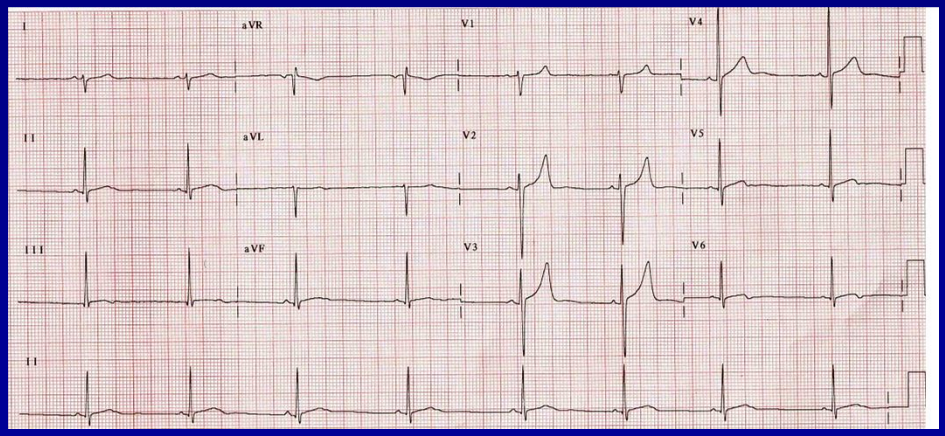
Max enzyme levels reached: CK 1242 IU/L (N<200); Troponin T: 2.73 ug/L (N<0.01)

Case 4: 32yo, Obese, AHT, severe chest pain, ECG changes, +ve enzymes

Day 2



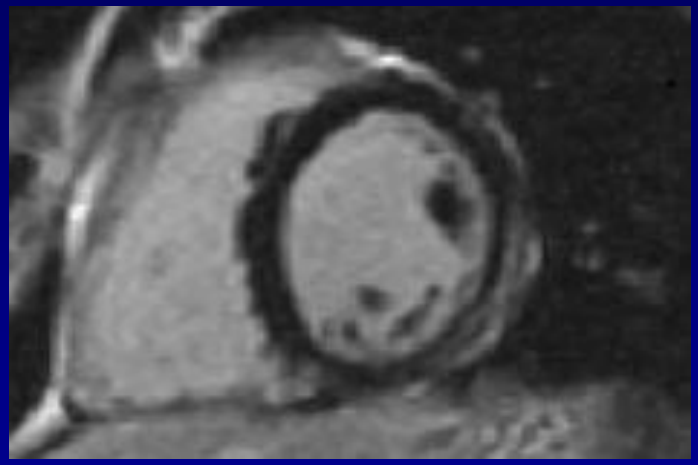
Discharge

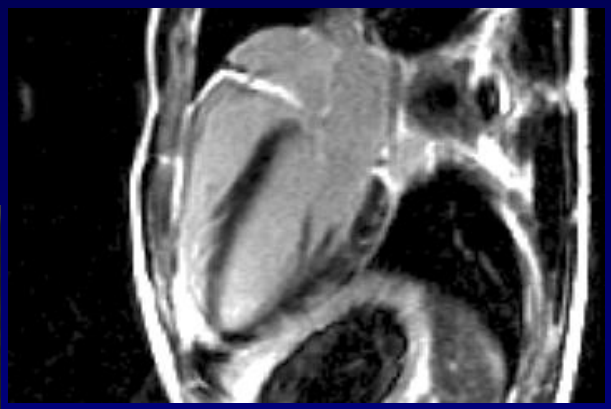


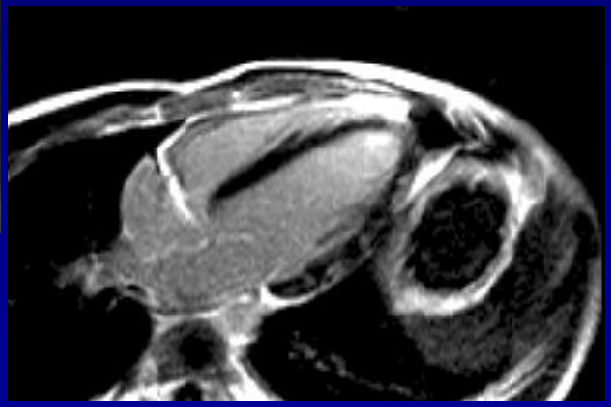
Discharge diagnosis: Acute myocarditis masquerading ACS

Case 4: 32yo, Obese, AHT, severe chest pain, ECG changes, +ve enzymes

2 weeks later







Parvovirus B19 Infection Mimicking Acute Myocardial Infarction

Uwe Kühl, MD, PhD; Matthias Pauschinger, MD; Thomas Bock, MD; Karin Klingel, MD; C. Peter Lothar Schwimmbeck, MD; Bettina Seeberg; Lars Krautwurm; Wolfgang Poller, MD; Heinz-Peter Schultheiss, MD; Reinhard Kandolf, MD, PhD

PCR, n (%)	
PVB19	12 (50)
EV	3 (12.5)
ADV	2 (8.3)
No virus	7 (29.2)

PVB19 targets endothelial cells and might lead to an AMI picture by inducing endothelial dysfunction

Circulation 2003;108:945-50

Management of Myocarditis Masquerading AMI

- Diagnostic challenge
- Avoid inadequate therapy
- Urgent coronary angiogram
- Usual therapy for acute myocarditis
- The role of PVB19 in etiology merits further evaluation

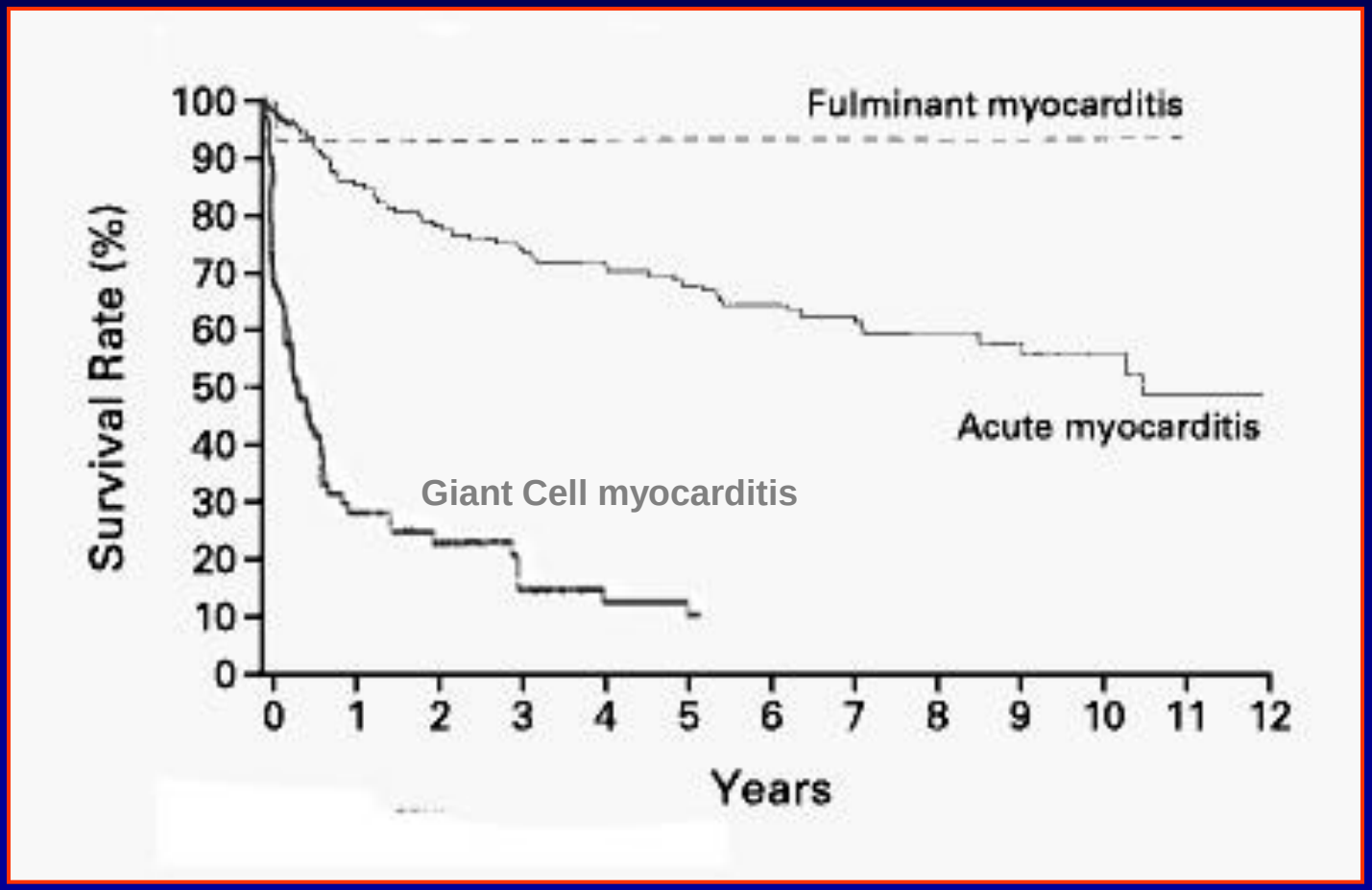
Current state of knowledge on aetiology, diagnosis, management and therapy of myocarditis.

A Position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Alida LP Caforio[1]*, Sabine Pankuweit [2]*, Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M Pinto[15], Arsen Ristic[16], Heinz Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], Perry M Elliott[13]

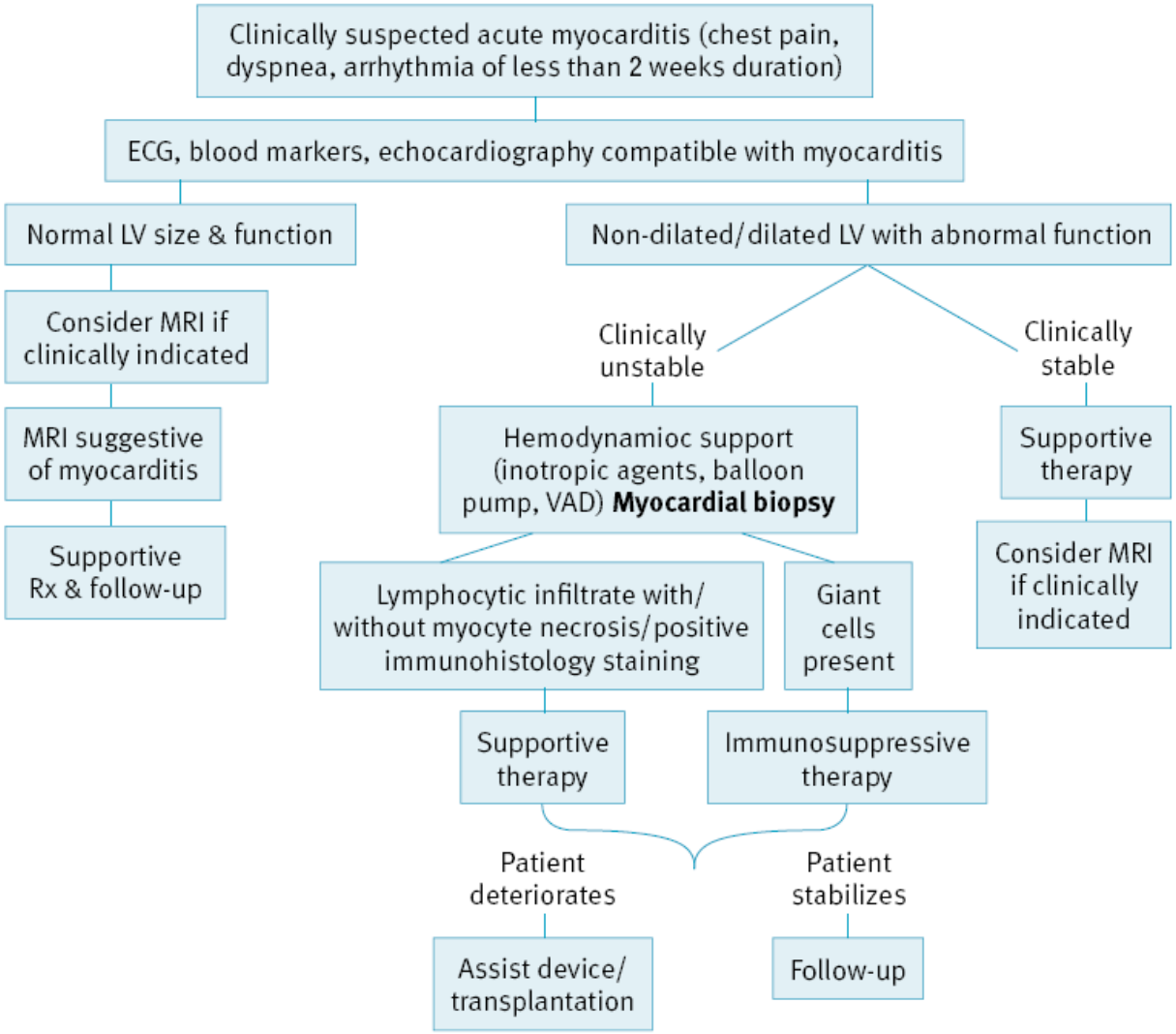
European Heart J, *in press*

Challenges in Management of Myocarditis



Mason JW N Engl J Med 1995;333:269-275; Cooper LT N Engl J Med 1997;336:1860-1866; McCarthy RE NEJM 2000;342:690-696;

Figure 4. Flow chart for evaluation and treatment of patients with suspected acute myocarditis



Shauer A, Gotsman I, Keren A et al. IMAJ 2013;15:180-185

Myocarditis is an underdiagnosed cause of acute heart failure, sudden death and dilated cardiomyopathy

Sagar S, Liu PP, Cooper LT. Lancet 2012;379:738-747

Thank You