Myocarditis in Children

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The patient

- 5 months old previously healthy child comes to the ER with respiratory distress

- History of respiratory illness 2 weeks ago

The patient

- RR 60/min, HR 170, BP 80/40
- Pale and cold
- Severe respiratory distress
- 1/6 systolic murmur
- No organomegaly
- Pulses palpable

The patient

- Chest X ray cardiomegaly
- Echocardiogram: Mildly dilated LV and severe dysfunction. Mitral regurgitation
- ECG: Sinus tachycardia. Inverted T waves in the lateral leads

- Diagnosis
- Myocarditis
- Dilated cardiomyopathy

Clues to myocarditis

- Acute disease, normal growth, history of viral illness

Clues to DCM

- Chronic symptoms, fatigue and SOB, FTT, family hx, other organs involvement

Etiology

- Infectious
- Immune-mediated
- Toxic

Etiology

Infectious

- Enteroviruses, especially coxsackie virus B
- Adenovirus
- Cytomegalovirus
- Influenza, parainfluenza
- Parvovirus
- Measles, rubella, Mumps, arboviruses, Epstein-Barr virus, HIV and hepatitis C virus

Etiology

INFECTIOUS

- **Bacterial**: brucella, Corynebacterium diphtheriae, gonococcus, Haemophilus influenzae, meningococcus, mycobacterium, Mycoplasma pneumoniae , pneumococcus, salmonella, Serratia marcescens, staphylococcus, Streptococcus pneumoniae, Strep. pyogenes, Treponema pallidum, Tropheryma whippelii, and Vibrio cholerae
- **Spirochetal**: borrelia and leptospira
- **Fungal:** actinomyces, aspergillus, blastomyces, candida, coccidioides, cryptococcus, histoplasma, mucormycoses, nocardia, and sporothrix
- **Protozoal:** Toxoplasma gondii and Trypanosoma cruzi
- Parasitic: ascaris, Echinococcus granulosus, Paragonimus westermani, schistosoma, Taenia solium, Trichinella spiralis, visceral larva migrans, and Wuchereria bancrofti
- **Rickettsial:** Coxiella burnetii, Rickettsia rickettsii, and Rick. tsutsugamushi
- **Viral**: coxsackievirus, cytomegalovirus, dengue virus, echovirus, encephalomyocarditis, Epstein–Barr virus, hepatitis A virus, hepatitis C virus, herpes simplex virus, herpes zoster, human mmunodeficiency virus, influenza A virus, influenza B virus, Junin virus, lymphocytic choriomeningitis, measles virus, mumps virus, parvovirus, poliovirus, rabies virus, respiratory syncytial virus, rubella virus, rubeola, vaccinia virus, varicella–zoster virus, variola virus, and yellow fever virus

Myocarditis. Arthur M. Feldman and Dennis McNamara. NEJM. 19.1388-1398

Etiology

IMMUNE-MEDIATED

- **Allergens:** acetazolamide, amitriptyline,cefaclor, colchicine, furosemide,isoniazid, lidocaine,methyldopa, penicillin, phenylbutazone, phenytoin, reserpine, streptomycin, tetanus toxoid, tetracycline, and thiazides
- **Alloantigens:** heart-transplant rejection
- **Autoantigens:** Chagas' disease, Chlamydia pneumoniae, Churg–Strauss syndrome, inflammatory bowel disease, giant-cell myocarditis, insulin dependent diabetes mellitus, Kawasaki's disease, myasthenia gravis, polymyositis, sarcoidosis, scleroderma, systemic lupus erythematosus, thyrotoxicosis, and Wegener's granulomatosis

Myocarditis. Arthur M. Feldman and Dennis McNamara. NEJM. 19.1388-1398

Etiology

TOXIC MYOCARDITIS

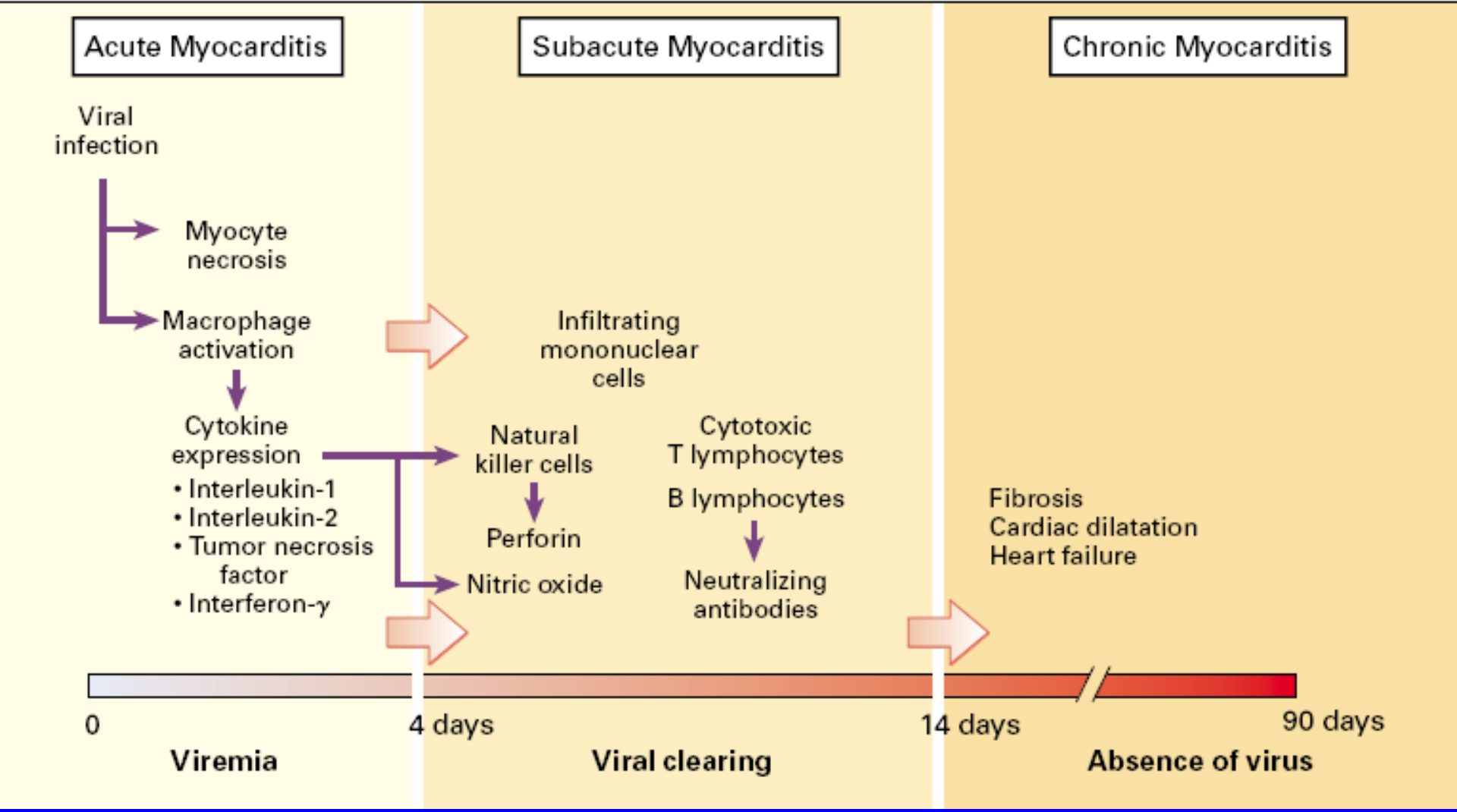
- **Drugs:** amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, ethanol, fluorouracil, hemetine, interleukin-2, lithium, and trastuzumab
- **Heavy metals:** copper, iron, and lead
- **Physical agents:** electric shock, hyperpyrexia, and radiation
- **Miscellaneous:** arsenic, azides, bee and wasp stings, carbon monoxide, inhalants, phosphorus, scorpion bites,snake bites, and spider bites

Myocarditis. Arthur M. Feldman and Dennis McNamara. NEJM. 19.1388-1398

Pathophysiology

- The virus spreads via the blood stream to the myocardium
- Lymphocytic infiltration and myocyte necrosis ensue
- The myocardium is infiltrated with T lymphocytes and macrophages while the B lymphocytes and natural killer cells are absent.
- Viral damage is minimized both by a direct cardioprotective effect of these substances and by enhanced recruitment/activation of mononuclear cells.
- Viral invasion of the myocardium is associated with direct destruction of myocytes, but it is the release of cytokines into the circulation which results in decreased myocardial performance. Cytokines such as tumor necrosis factor-α (TNFα), interleukin-1α and interleukin-1β are produced in large quantities by immune cells and the myocardium.

Chow LH, Ye Y, Linder J, et al. Phenotypic analysis of infiltrating cells in humanmyocarditis: an immunohistochemical study in paraffin-embedded tissue. ArchPathol Lab Med 1989; 113 (12): 1357-62.
Matsumori A, Yamada T, Suzuki H, et al. Increased circulating cytokines in pa-tients with myocarditis and cardiomyopathy. Br



Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflam-mation and cell death: learning from the past for the future. Circulation 1999;99:1091-100.

Signs & Symptoms

- Flu-like illness (fever, rhinorrhea, or GI disturbance)
- After the subsidence of symptoms of a systemic illness, patients frequently present with symptoms of acute heart failure, arrhythmias, syncope and sudden death
- Respiratory distress or GI symptoms may be the most prominent signs

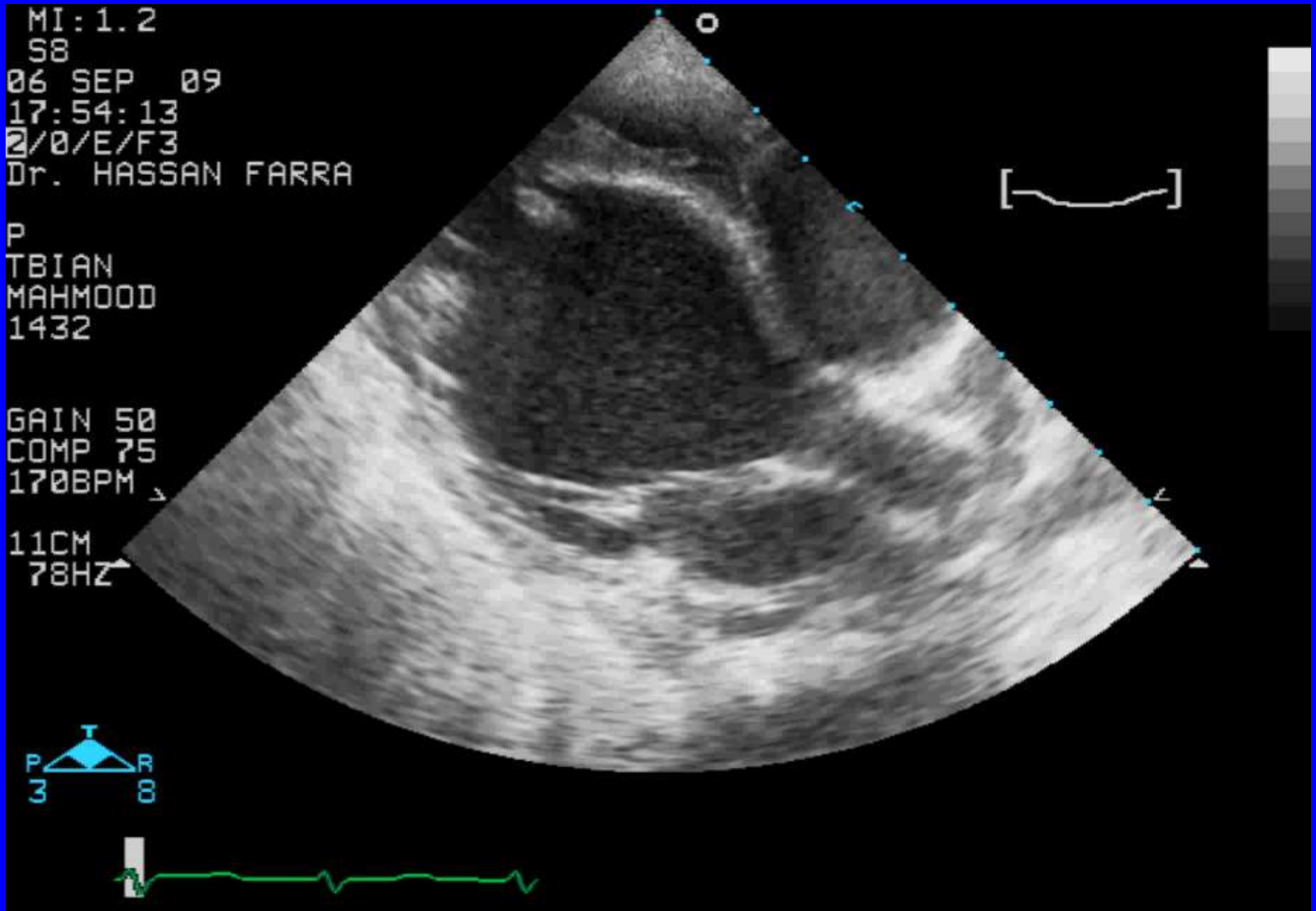
Signs & Symptoms

- Resting tachycardia
- Third heart sound
- Murmur of mitral regurgitation
- CXR shows cardiomegaly and edema but in acute fulminant myocarditis the heart size can be normal
- ECG changes are ST segment flattening and T wave inversion, with low QRS

Echocardiogram

- Depressed ejection fraction
- Increased left ventricular end-diastolic dimension
- Increased wall thickness
- Mitral regurgitation

Desmond Bohn and Lee Benson.
Diagnosis and Management of Pediatric Myocarditis.
Pediatric Myocarditis. Pediatr Drugs 2002; 4 (3): 171-181.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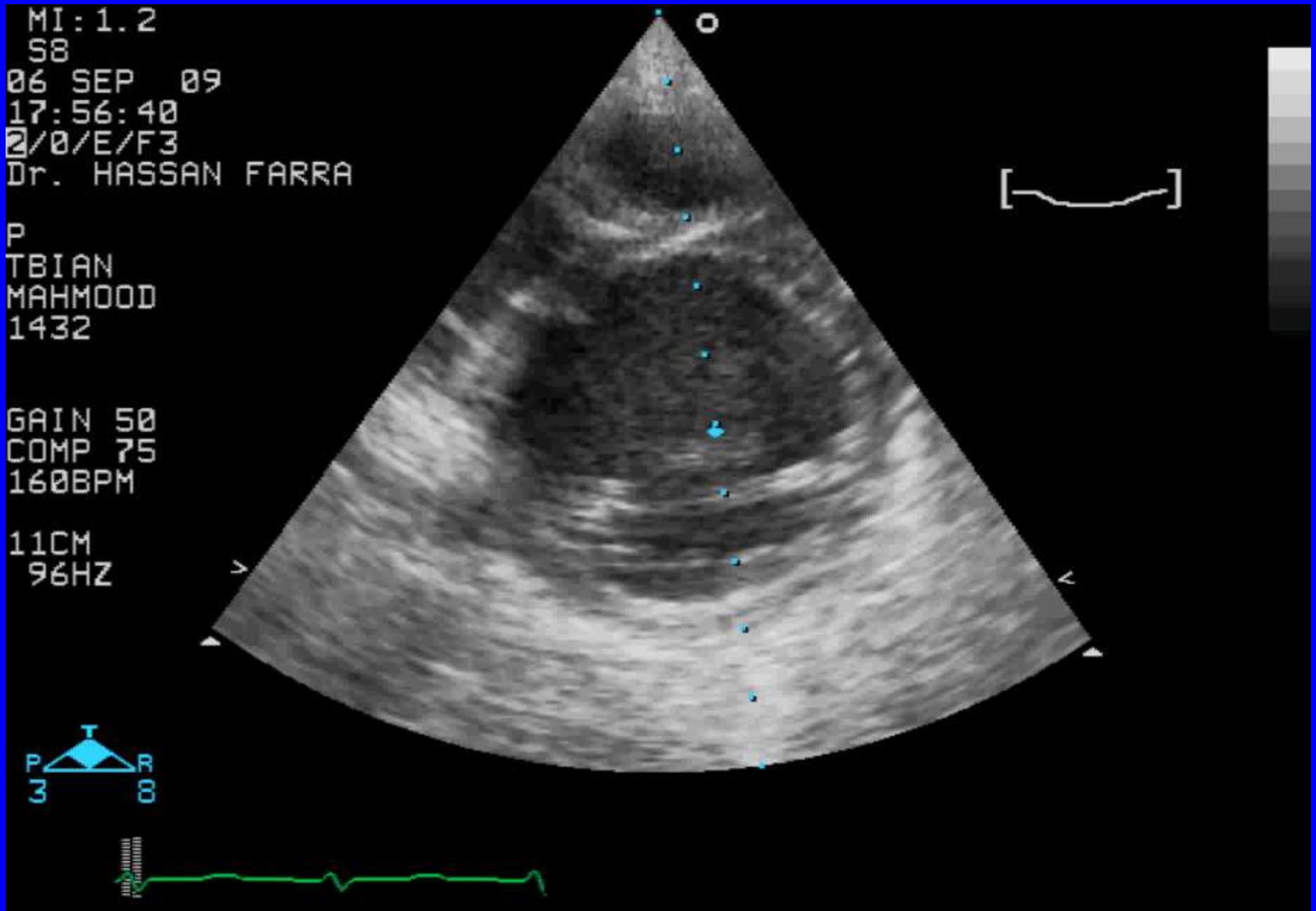
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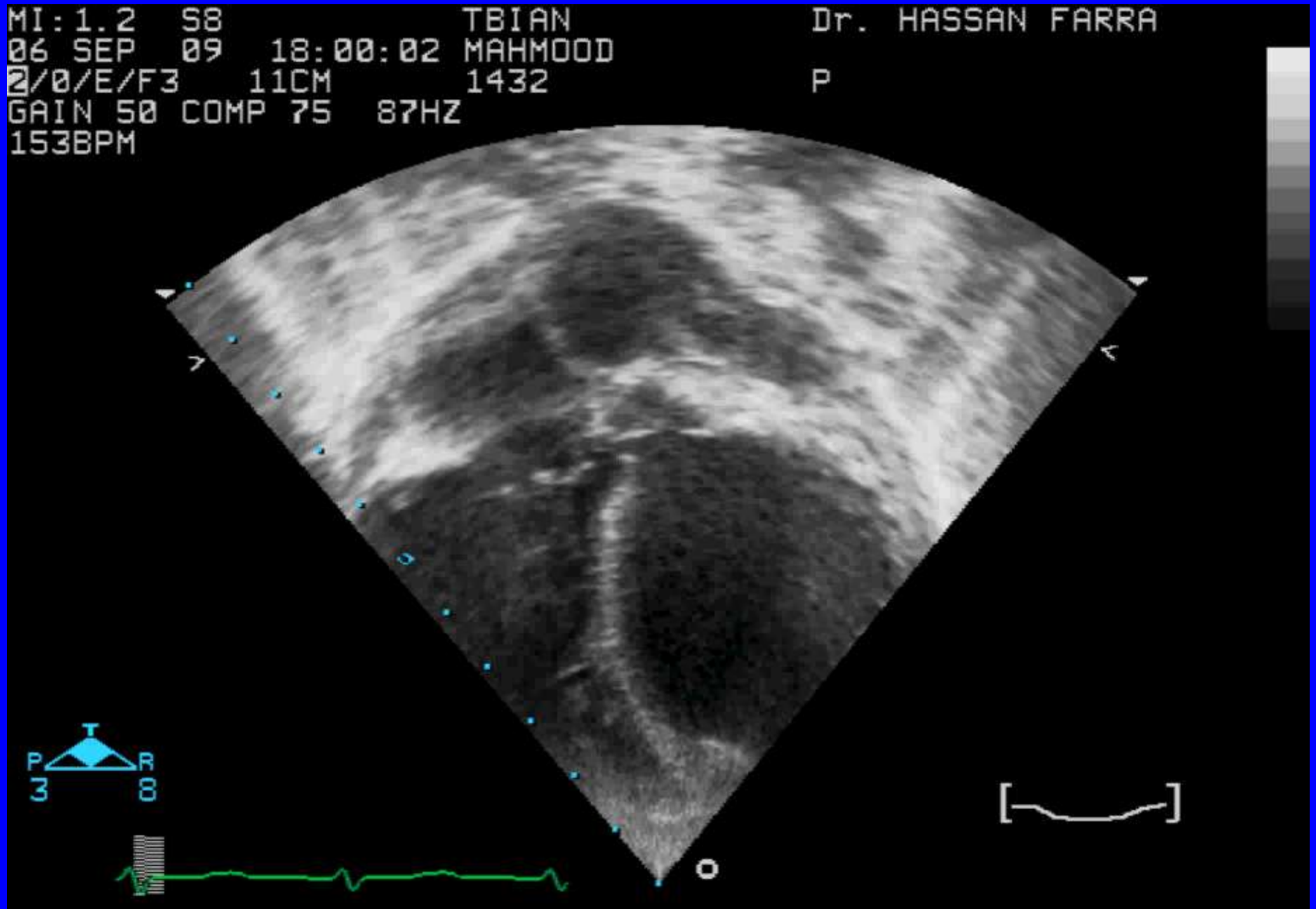
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Labs

- ABG: Metabolic acidosis and compensatory respiratory alkalosis
- Elevated liver enzymes
- Borderline urea and creatinin
- Elevated CPK and Troponin

Labs

- Viral serologies and cultures
- Recovery of virus from myocyte culture, in situ hybridization or by PCR

DCM labs

- CBC, lytes, urea, creatinin, glucose, LFTs, cholesterol, BNP
- Alk Phos, Calcium, phosphorus, Mg
- Thyroid, Uric acid, ABG, gap, troponin , CPK
- UA, ketones in the urine
- **Metabolic :**
  - Lactate, Pyruvate, Ammonia, Total free carnitine and acylcarnitine. Urine organic acid screen

Diagnosis

- Endomyocardial biopsy
- MRI with contrast

Pathology

- Gold standard
- Dallas criteria
  - Definitive: lymphocytic infiltration with myocyte necrosis
  - Borderline: lymphocytic infiltration with interstitial edema

Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis: a histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1 (1): 3-14

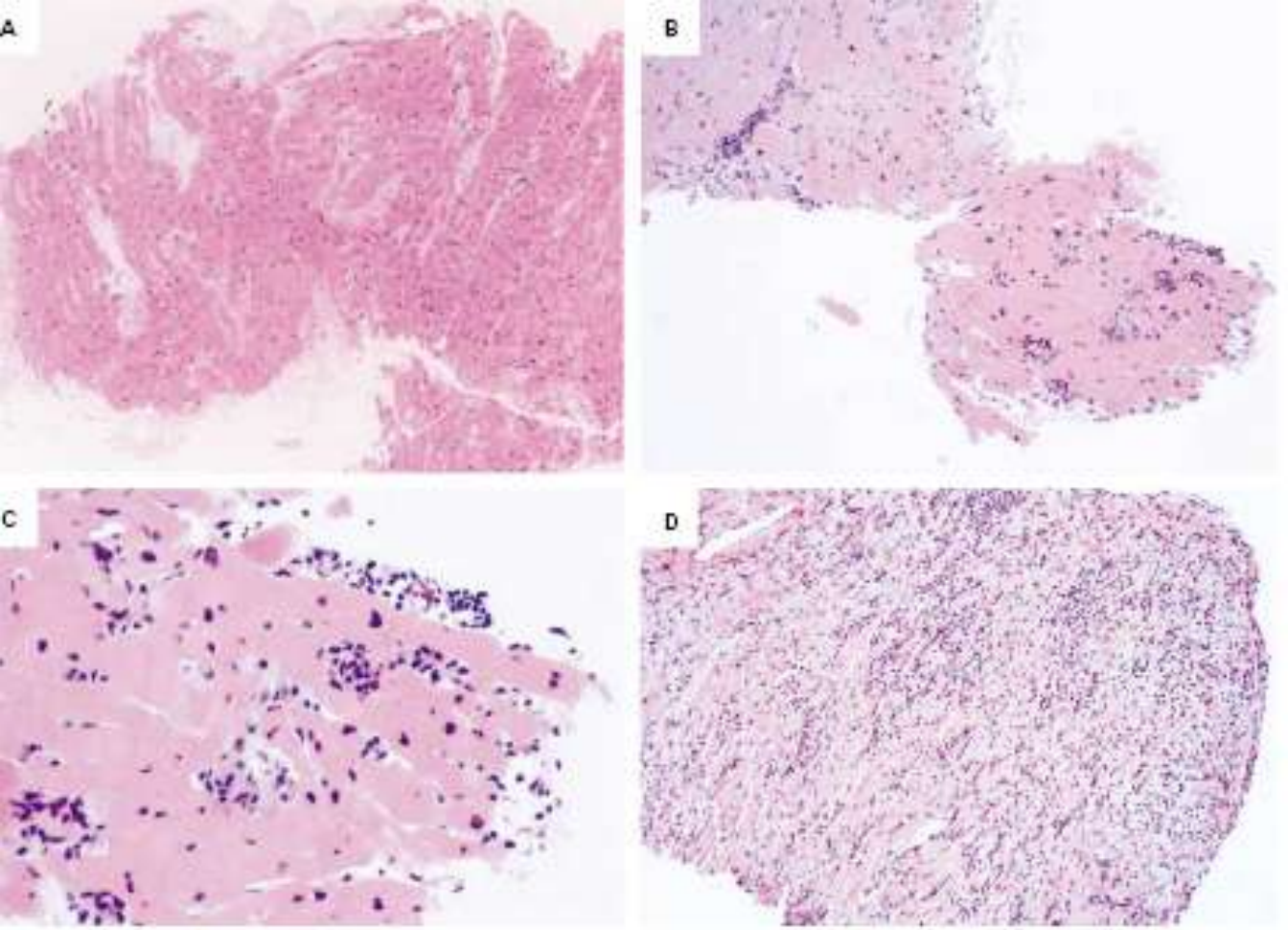
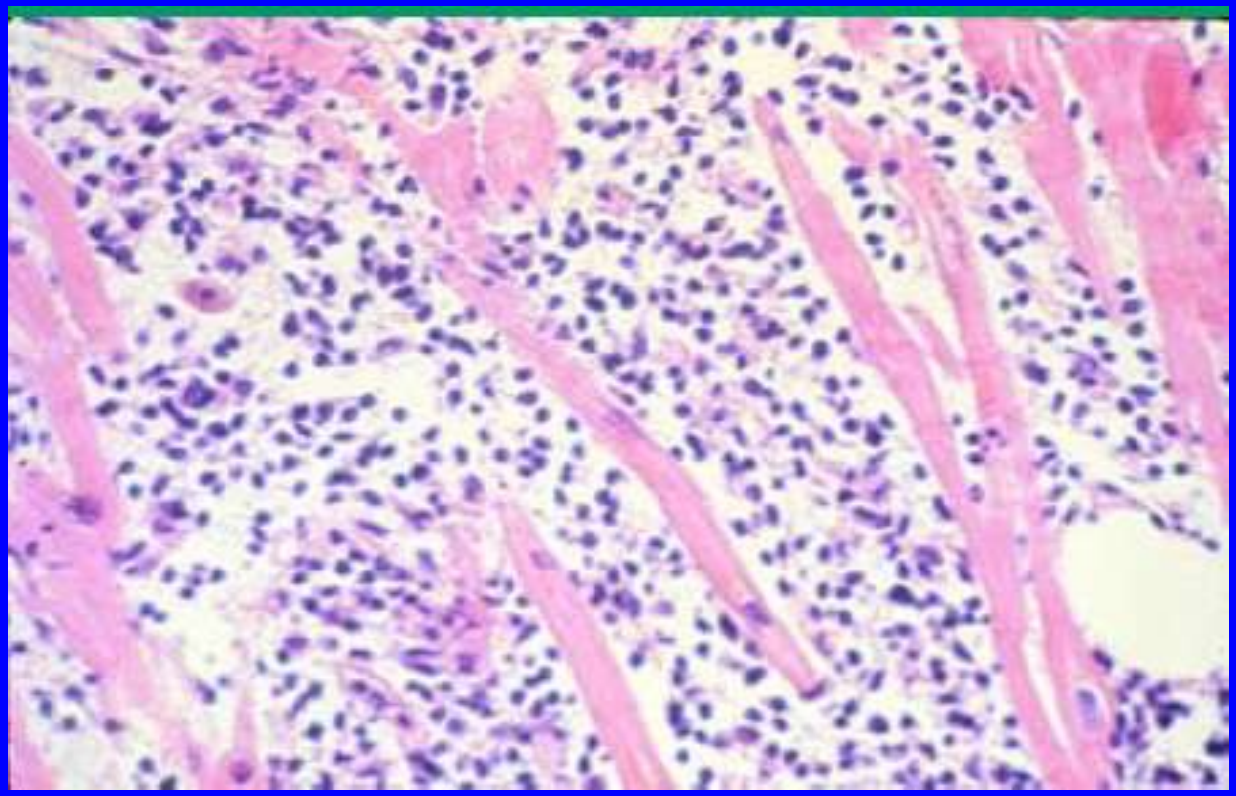


Figure 1. Histopathological Appearance of Normal Myocardium (Panel A, ×100), Borderline Myocarditis (Panel B, ×100; Panel C, ×350), and Active Myocarditis (Panel D, ×100; Panel E, ×300), According to the Dallas Criteria,[23] on Staining with Hematoxylin and Eosin.

Myocarditis. Arthur M. Feldman and Dennis McNamara. NEJM. 19.1388-1398



Endomyocardial biopsy of the right ventricle showing acute diffuse yocarditis. There is prominent myofiber necrosis and loss in association with a high-grade mononuclear infiltrates.

Pathology

- Eosinophilic
- Giant cell myocarditis

Kenneth L. Baughman, MD. Diagnosis of Myocarditis Death of Dallas Criteria. Circulation. 2006;113:593-595.

Pathology

Eosinophilic myocarditis

- May be attributed to eosinophilic syndromes or allergic reactions
- Responds to treatment of the eosinophilic disorder and/or withdrawal of the offending agent

Giant cell myocarditis

- Poor prognosis
- May respond to aggressive immunosuppressive therapy

Kenneth L. Baughman, MD. Diagnosis of Myocarditis Death of Dallas Criteria. Circulation. 2006;113:593-595.

Biopsy

Arguments in Favor of Biopsy

- Diagnosis and treatment:
  - To differentiate between viral myocarditis and cardiomyopathy.
- Prognosis:
  - The outcome with viral myocarditis is better than that with dilated cardiomyopathy, especially in children.
- Decision algorithm for Transplant and/or Mechanical Circulatory Support:

Desmond Bohn and Lee Benson.
Diagnosis and Management of Pediatric Myocarditis.
Pediatric Myocarditis. Pediatr Drugs 2002; 4 (3): 171-181.

Biopsy

Arguments Against Biopsy

- High Incidence of False-Negative Results:
  - The disease may be focal.
  - variability (disagreement of 40%) amongst expert pathologists evaluating the same biopsy specimens.
- Potential Risk:
  - myocardial perforation and arrhythmias
- Lack of Evidence for Immunosuppressive Therapy Efficacy:
  - Immunosuppressive therapy is not a proven therapy

Desmond Bohn and Lee Benson.
Diagnosis and Management of Pediatric Myocarditis.
Pediatric Myocarditis. Pediatr Drugs 2002; 4 (3): 171-181.

The patient

- Intubated and ventilated
- Sedated and muscle relaxed
- Central venous line, arterial line and Foley catheter inserted
- Milrinone and Furosemide started

Treatment

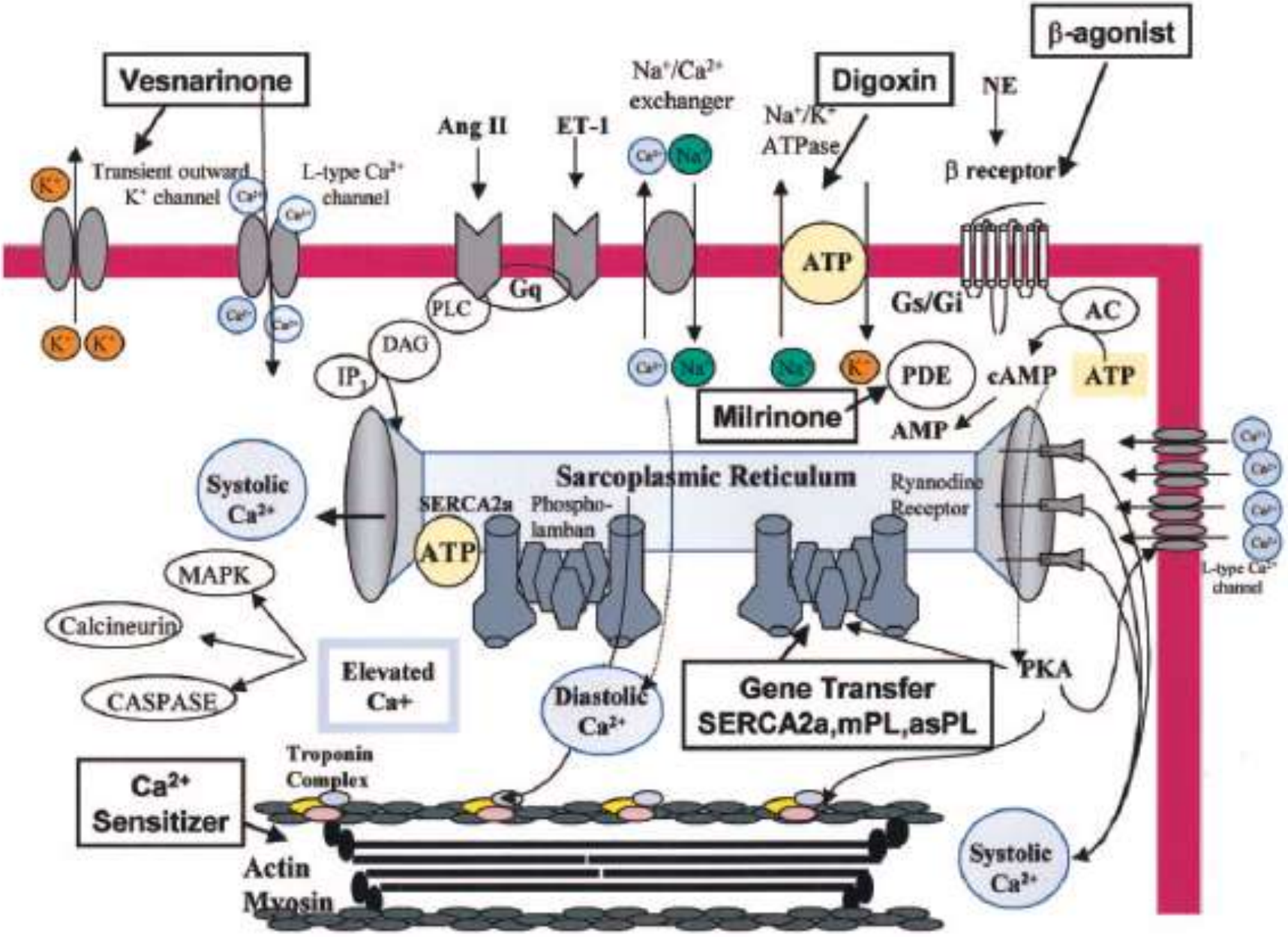
- Mechanical Ventilation
- Sedation/Muscle relaxation
- Inotropes
- Reduce preload and after load

Ventilation

- Raised intrathoracic pressure reduces transmural myocardial wall tension and left ventricular afterload

Hemodynamics

- Low cardiac index
- Elevated pulmonary wedge pressure
- High systemic vascular resistance



(Circulation. 2003;108:367-372.)

Phosphodiesterase inhibitors

- Amrinone, milrinone, and enoximone
- Decrease the rate of cAMP degradation
- Enhanced calcium influx into the cell
- Increased contractility
- Systemic arterial and venous dilation
- Improves relaxation
- Less arrhythmias
- Can be given peripherally
- Safer on the floor

The patient

- Started to develop renal failure
- Elevated urea and creatinin and decreased UOP
- Electrolytes normal
- Nephrology consultation
- ATN: Increase diuretics, fluid restriction, electrolytes monitoring

Diuretics

Furosemide, Bumetanide

Chlorothiazide, Hydrochlorothiaziade

Metolazone

Spironolactone

Mannitol

Neseritide

- Recombinant human BNP Natriuretic peptide
- Diuresis and natriuresis
- Vasodilator
- Suppress the neurohormonal activation
- Indirect increase in cardiac output
- Potential adverse impact on mortality rate and a potential risk of worsening renal function

The patient

- Had an episode of ventricular fibrillation
- Shocked once successfully and started on Amiodarone

The patient

- Renal failure peaked and then started to improve
- The patient was extubated after 1 week
- IV meds were changed to oral

The patient

- Discharged home on Digoxin, Enalapril, Lasix and Amiodarone after 2 weeks

Treatment

- Carnitine
- Anticoagulation
- Immunomodulators
- Antivirals
- Interferons
- Mechanical Support

Immunosupression

- Randomized 111 patients to receive either conventional medical therapy alone or combined with prednisone and either azathioprine or cyclosporin
- No difference in the left ventricular ejection fraction
- No difference in survival

Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppres-sive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. NEngl J Med 1995; 333 (5): 269-75

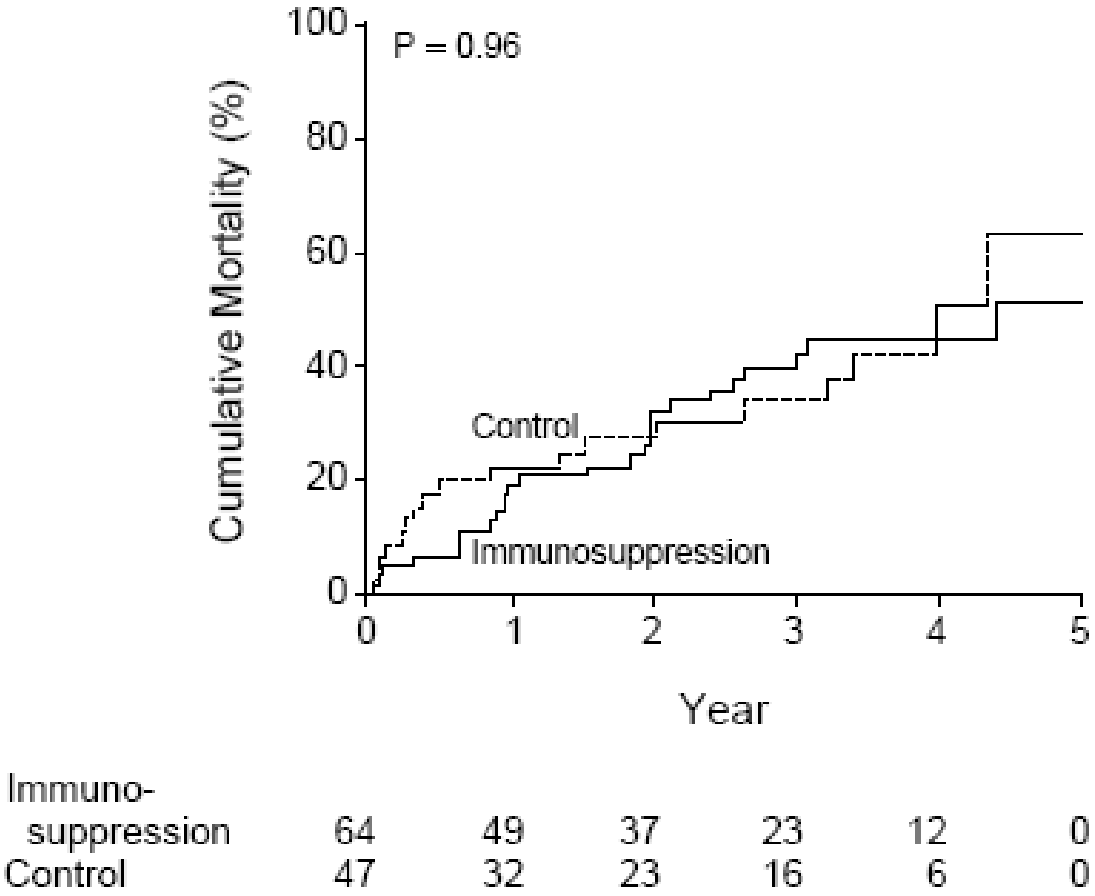


Figure 2. Actuarial Mortality (Defined as Deaths and Cardiac Transplantations) in the Immunosuppression and Control Groups.

The numbers of patients at risk are shown at the bottom. There was no significant difference in mortality between the two groups.

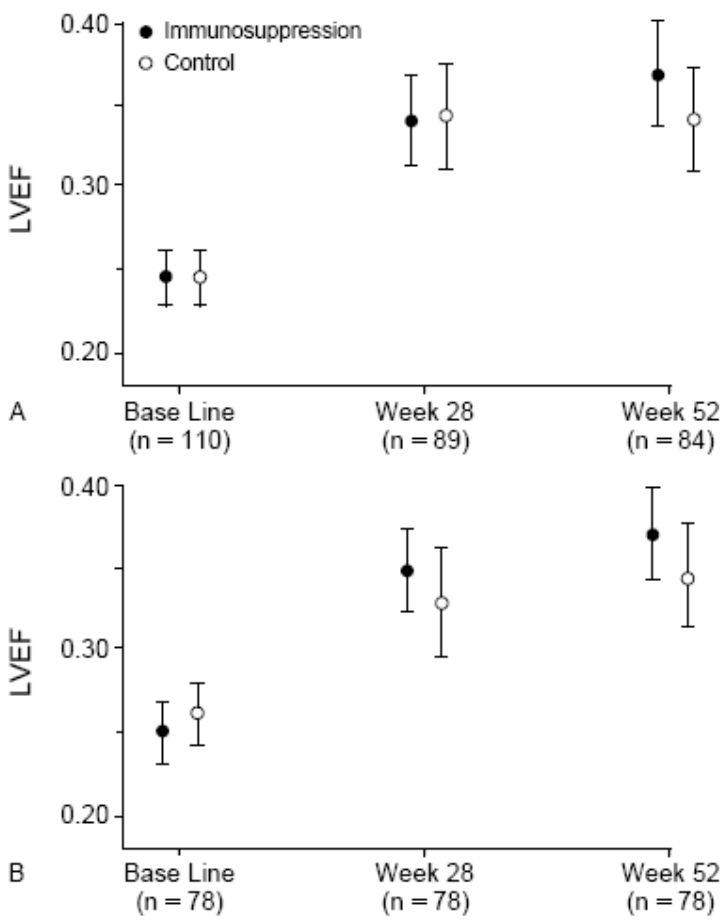


Figure 1. Mean (±SE) Left Ventricular Ejection Fraction (LVEF) in the Immunosuppression and Control Groups at Base Line, Week 28, and Week 52.

Panel A shows the mean values for all available studies at each time, with the numbers of patients indicated at the bottom of the panel. There was no difference between the two groups in the mean LVEF at base line, week 28, or week 52 (P = 0.97, P = 0.95, and P = 0.45, respectively). Panel B shows the mean values for the 78 patients in whom data were available at all three times. Again, there was no significant difference between the groups (P = 0.51, P = 0.60, and P = 0.50, respectively).

IVIG

- Enhancement of viral clearance or down-regulation of inflammation
- Only one trial randomized 62 patients to a therapy with gammaglobulin or control
- No change in EF was seen after 12 months

McNamara DM, Starling RC, Dec GW, et al. Intervention in myocarditis and acute cardiomyopathy with immune globulin: results from the randomized placebo controlled IMAC trial [abstract]. Circulation 1999; 100 Suppl. I: I-21

IVIG

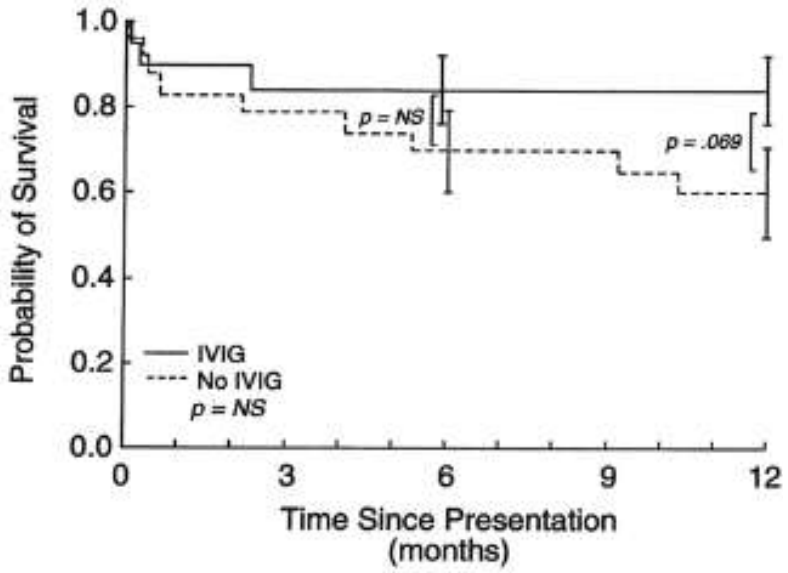
- One case-control trial
- Improved recovery of LV function with IVIG and a trend to a better survival at 1 year

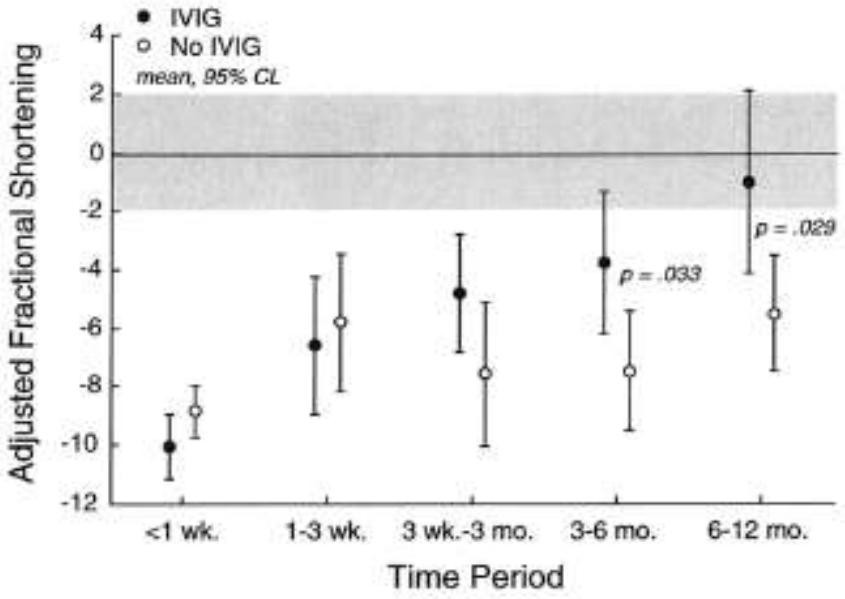
Feldman AM, et al. *N Engl J Med 2000;343:* 1388–1398.

Drucker NA, et al. *Circulation 1994;89:252–257*.

Drucker NA, Colan SD, Lewis AB, Beiser AS, Wessel DL, Takahashi M, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. Circulation 1994; 89:252–7

IVIG





- Probably beneficial in neonatal and pediatric myocarditis

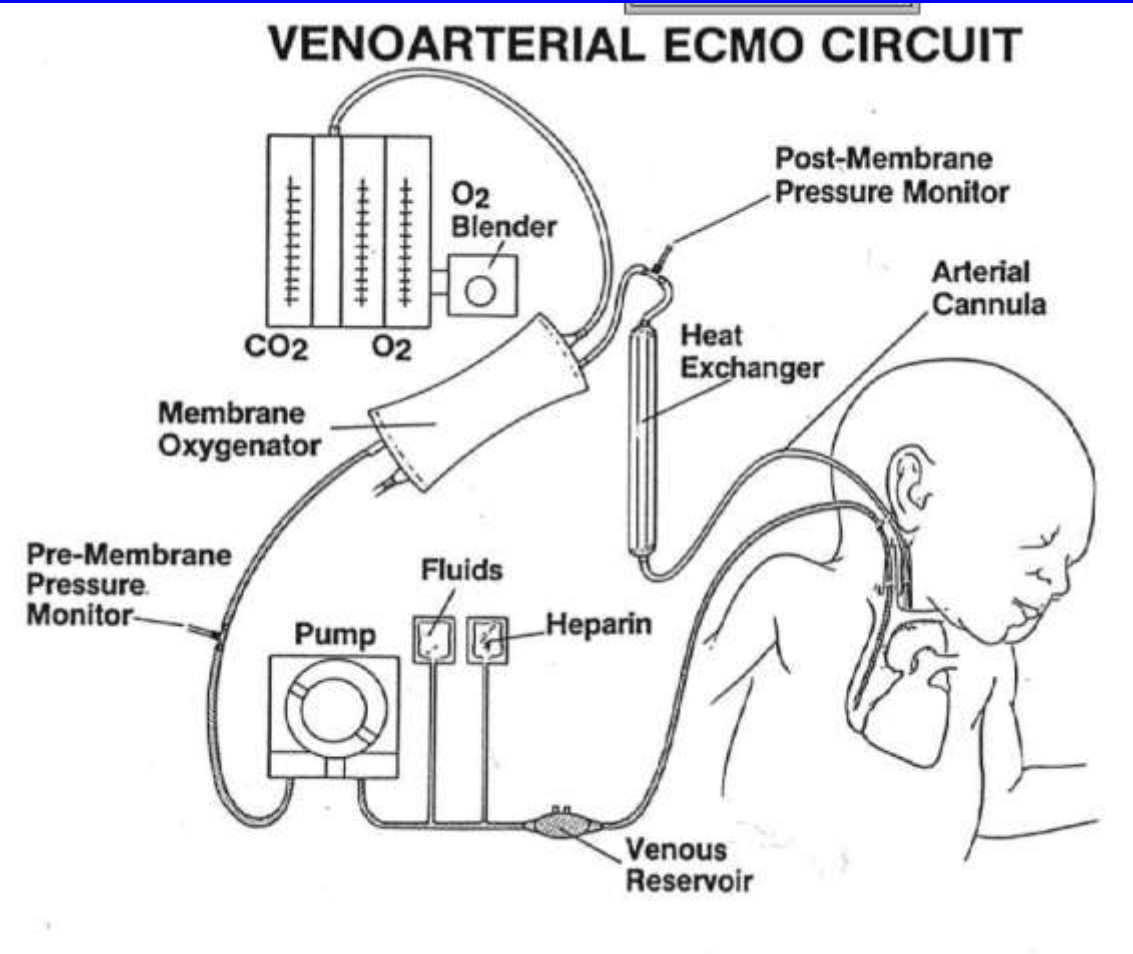
Antivirals

- Pleconaril for enteroviruses
- Cidofovir for adenoviruses
- Neuraminidase inhibitors for influenza viruses
- Gancyclovir for cytomegalovirus

ECMO

- Pump and oxygenator
- Most common device in children
- Cannulation from the neck or the groin
- Risk of bleeding, thrombosis and infection
- Not a long term therapy
- Needs a highly trained team

ECMO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O2
Blender
Arterial
Cannula
CO2
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Oxygenator
Pre-Membrane
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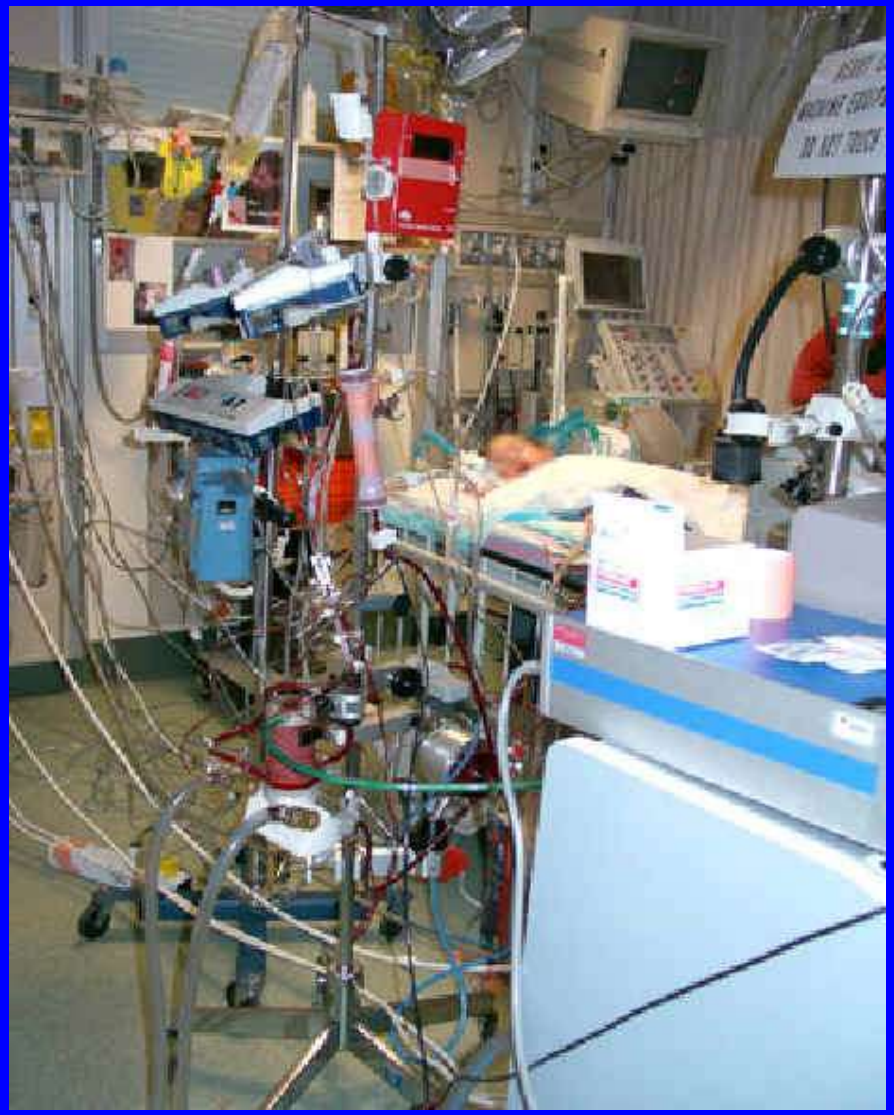
Fluids
Pump
Heparin
Venous
Reservoir

ECMO



VAD

- Only pump
- Most common device in adults
- Cannulation from the chest
- Same risks as in ECMO
- Long term therapy in adults
- Limited to older children
- Smaller devices are available in Europe

VAD

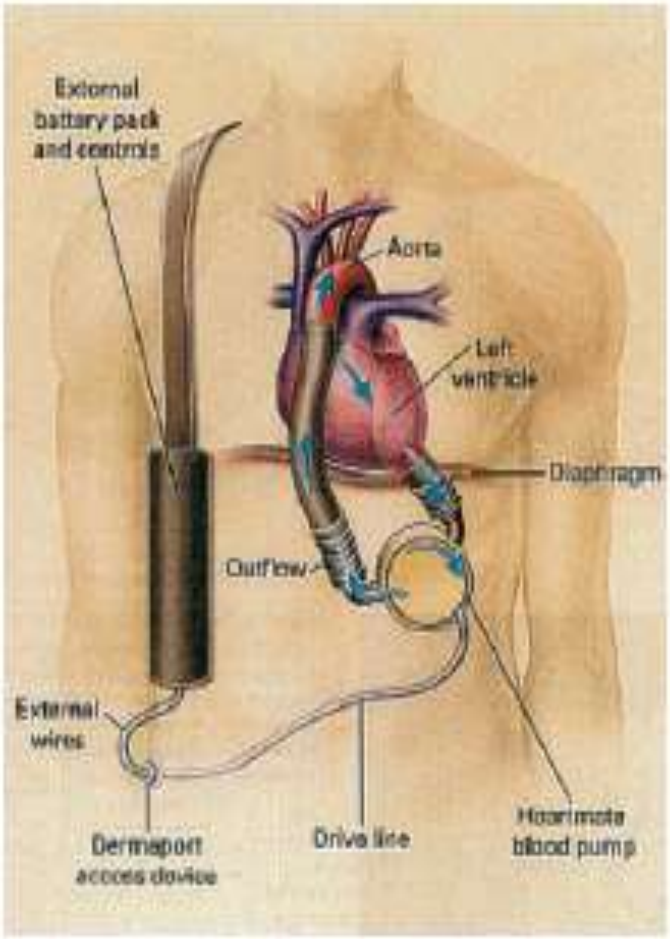


Figure 2. The HeartMate left ventricular assist device.

(Circulation 2002;106:2040-2050.)

VAD

VAD

(*Circulation*. 2006;113:147-155.)

Heart Transplant

- 1-year survival after heart transplantation in children is 85%

- Survival 20 years after transplantation is 40%

Circ Heart Fail. 2009;2:490-498

The patient

- Cardiac function improved gradually over the next few months
- By 6 months the cardiac evaluation was normal and the patient off meds

Prognosis

- The natural history is better in children
- Most of the patients who survive the acute phase seem to have restoration of normal cardiac function

Chan KY, Iwahara M, Benson LN, et al. Immunosuppressive therapy in the management of acute myocarditis in children: a clinical trial. J Am Coll Cardiol1991; 17 (2): 458-60.
Drucker NA, Colan SD, Lewis AB, et al. Gamma-globulin treatment of acutemyocarditis in the pediatric population. Circulation 1994; 89 (1): 252-7.
Lee KJ, McCrindle BW, Bohn DJ, et al. Clinical outcomes of acute myocarditis in childhood. Heart 1999; 82 (2): 226-33

Prognosis

- The overall survival in children with acute myocarditis who reach hospital alive can be as high as 80%

Jin O, Sole MJ, Butany JW, et al. Detection of enterovirus RNA in myocardial biopsies from patients with myocarditis and cardiomyopathy using gene amplification by polymerase chain reaction. Circulation 1990; 82 (1): 8-16


THANK YOU