Myocarditis
Bugs, Drugs, and the Role of Mechanical Circulatory Support

Matthew J. Bock, M.D.
Assistant Professor, Division of Pediatric Cardiology
Pediatric Heart Failure & Transplantation
Loma Linda University Children’s Hospital
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Disclosures:

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Objectives:

1. Identify common “bugs” associated with myocarditis
2. Discuss the role of drug therapy to treat myocarditis
3. Identify patients at risk for requiring mechanical circulatory support
Myocarditis

Inflammation of heart muscle
Definitions and Pathophysiology

- **Myocarditis:** Inflammation of heart muscle

- **Mechanism of Injury:**
  - Direct cytotoxicity by Chemical/Infectious Agents
  - Auto-antibody formation due to rheumatic process or “molecular mimicry”
Definitions and Pathophysiology

- Myocardial death leads to **systolic dysfunction** and rhythm disturbances

- Remaining viable myocytes hypertrophy leading to **diastolic dysfunction**

- Remodeling (healing) occurs through **fibrosis** (scar formation)
Mechanism of Disease

VIRAL INFECTION
- Myocyte destruction
- Immune activation
  - Early

VIRAL ERADICATION
- T-cell
- B-cell
- Mononuclear cell
- Cytokines
- Recovery

Ongoing myocardial damage
- Fibrosis
- Remodeling
- Dysfunction
- Late
Fig. 1. The immune response to viral myocarditis. Beneficial effects of the host immune response are represented by black arrows, and potentially deleterious effects are represented by grey arrows. Cells infected with virus are shaded dark blue, noninfected cells are white, and fibrotic changes are represented by light blue cells.\textsuperscript{[23]} $\text{IFN} = \text{interferon}; \text{IL} = \text{interleukin}; \text{NK} = \text{natural killer}; \text{NO} = \text{nitric oxide}; \text{TNF} = \text{tumor necrosis factor}$. 
Pathogenesis of Viral and Inflammatory Cardiomyopathy

- **Viral Infection**
  - Antiviral immune response
  - Antivirus cytokines ↑
  - Viral elimination healed inflammation
    - No/minor myocardial injury
    - Healed myocarditis
  - Viral elimination persistent inflammation
    - Severe myocardial injury
    - Dilated cardiomyopathy
  - Chronic viral infection ± inflammation
    - With or without myocardial injury
    - Inflammatory cardiomyopathy
    - Viral heart disease

- **Antiviral Treatment**
  - Inhibition of host receptor attachment
  - Inhibition of virus entry
  - Inhibition of virus uncoating
  - Inhibition of virus replication

- **Standard Heart Failure Medication**
- **Immunosuppression**
  - Cellular immune response
  - Humoral immune response
- **Antiviral Treatment**
  - Immunomodulation
  - Inhibition of virus replication
### Etiologies

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td>Viral: adenoviruses, echoviruses, enteroviruses (eg, coxsackieviruses), herpesviruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus, influenza A virus, parvovirus B19</td>
</tr>
<tr>
<td></td>
<td>Fungal: actinomyces, aspergillus, candida, cryptococcus</td>
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<tr>
<td></td>
<td>Helminthic: <em>Echinococcus granulosus</em>, <em>Trichinella spiralis</em></td>
</tr>
<tr>
<td></td>
<td>Protozoal: <em>Toxoplasma gondii</em>, <em>Trypanosoma cruzi</em></td>
</tr>
<tr>
<td></td>
<td>Rickettsial: <em>Coxiella burnetti</em>, <em>Rickettsia typhi</em></td>
</tr>
<tr>
<td></td>
<td>Spirochetal: <em>Borrelia burgdorferi</em>, leptospira, <em>Treponema pallidum</em></td>
</tr>
<tr>
<td><strong>Autoimmune diseases</strong></td>
<td>Celiac disease, Churg-Strauss syndrome, Crohn disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematoses, lymphohfollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis</td>
</tr>
<tr>
<td><strong>Hypersensitivity reactions</strong></td>
<td>Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamids, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methylpoda, smallpox vaccine, tetanus toxoid, tricyclic antidepressants</td>
</tr>
<tr>
<td><strong>Toxic reactions to drugs</strong></td>
<td>Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab</td>
</tr>
<tr>
<td><strong>Toxic</strong></td>
<td>Ethanol</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Arsenic, copper, iron, radiotherapy, thyrotoxicosis</td>
</tr>
</tbody>
</table>
### Etiologies

Table 1. Aetiologies of myocarditis.

<table>
<thead>
<tr>
<th>Viral</th>
<th>Bacterial</th>
<th>Other infectious</th>
<th>Immune</th>
<th>Autoimmune</th>
<th>Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td><em>Borrelia</em> sp.</td>
<td><em>Ascaris</em> sp.</td>
<td>Alloantigen (cardiac transplant recipient)</td>
<td>Polymyositis</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Coxsackie viruses</td>
<td><em>Brucella</em> sp.</td>
<td><em>Aspergillus</em> sp.</td>
<td>Chagas' disease</td>
<td>Rheumatoid arthritis</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>CMV</td>
<td><em>Clostridia</em> sp.</td>
<td><em>Blastomyces</em> sp.</td>
<td>Giant cell myocarditis</td>
<td>Rheumatic fever</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Dengue</td>
<td><em>Corynebacterium diptheriae</em></td>
<td><em>Candida</em> sp.</td>
<td>Systemic Lupus Erythematosus</td>
<td>Sarcoïdosis</td>
<td>Arsenic, cannabis</td>
</tr>
<tr>
<td>Æchovirus</td>
<td><em>Coxiella burnetti chaffeensis</em></td>
<td><em>Coccidioides</em></td>
<td>Scleroedema</td>
<td>Scleroedema</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Encephalo-myocarditis</td>
<td><em>Haemophilus influenzae</em></td>
<td><em>Cryptococcus</em> sp.</td>
<td>Cysticercosis</td>
<td>Systemic Lupus Erythematosus</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Epstein-Barr</td>
<td><em>Klebsiella</em> sp.</td>
<td><em>Cysticeriosis</em></td>
<td>Entamoeba sp.</td>
<td>Ulcerative colitis</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Hepatitis</td>
<td><em>Legionella pneumophilia</em></td>
<td><em>Echinococcus granulosus</em></td>
<td></td>
<td>Wegener's granulomatosis</td>
<td>Copper, clozapine</td>
</tr>
<tr>
<td>Human Herpes Virus-6</td>
<td><em>Legionspira</em> sp.</td>
<td><em>Entamoeba sp.</em></td>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Human Immunodeficiency Virus</td>
<td><em>Mycoplasma pneumoniae</em></td>
<td><em>Heterophyes</em></td>
<td></td>
<td></td>
<td>Electric shock</td>
</tr>
<tr>
<td>Influenza A including H1N1</td>
<td><em>Neisseria meningitidis</em></td>
<td><em>Histoplasma</em> sp.</td>
<td></td>
<td></td>
<td>Ethanol</td>
</tr>
<tr>
<td>Influenza B</td>
<td><em>Rickettsia</em> sp.</td>
<td><em>Nocardia</em></td>
<td></td>
<td></td>
<td>Furosemide</td>
</tr>
<tr>
<td>Herpes Simplex Virus-1</td>
<td><em>Salmonella</em> sp.</td>
<td><em>Rickettsia</em> sp.</td>
<td></td>
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<td>Hymenoptera</td>
</tr>
<tr>
<td>Mumps</td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Schistosoma</em> sp.</td>
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<td>Hyperpyrexia</td>
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<tr>
<td>Parvovirus B-19</td>
<td><em>Streptococcus nonll lifinis</em></td>
<td><em>Taenia solium</em></td>
<td></td>
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<td>Iron, isoniazid</td>
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<tr>
<td>Rabies</td>
<td><em>Trypanosoma pallidum</em></td>
<td><em>Toxocara canis</em></td>
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<td>Lead, lidocaine</td>
</tr>
<tr>
<td>Rhabdovirus</td>
<td><em>Vibrio cholerae</em></td>
<td><em>Toxoplasma gondii</em></td>
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<td>Loxoscelism</td>
</tr>
<tr>
<td>Respiratory syncitial virus</td>
<td></td>
<td><em>Trichinella spiralis</em></td>
<td></td>
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<td>Methyldopa</td>
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<tr>
<td>Rubella</td>
<td></td>
<td><em>Trypanosoma cruzi</em></td>
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<td>Neomercazole</td>
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<tr>
<td>Vaccinia (smallpox vaccine)</td>
<td></td>
<td><em>Wuchereria bancrofti</em></td>
<td></td>
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<td>Nonsteriodal anti-inflammatories</td>
</tr>
<tr>
<td>Varicella Zoster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Penicillin, Phenytioin</td>
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<tr>
<td>Variola</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Snake or scorpion venom</td>
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<tr>
<td>Yellow fever</td>
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<td>Sulfonamides</td>
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<td></td>
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<td></td>
<td>Tetracycline, Thiazides</td>
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<td>Trastuzumab</td>
</tr>
</tbody>
</table>
Infectious Etiologies

- **Viral**
  - Coxsackie Virus (A&B)
  - Echovirus
  - Adenovirus
  - Parvovirus
  - CMV

- **Rickettsial (RMSF, scrub typhus)**

- **Protozoal (T Cruzi/Chagas)**

- **Parasitic (Trichinosis, Toxoplasmosis)**
Non-Infectious Etiologies

- Drug Hypersensitivity
  - antibiotics, anti-inflammatories, anticonvulsants
- Drug Toxicity
  - cocaine, alcohol, Cytoxan, anthracyclines
- Immune mediated systemic diseases
  - JIA, ARF, HUS, SLE, Kawasaki, Giant Cell Myocarditis
Natural History

- A spectrum of disease manifestations:
  - Asymptomatic and self-limited
  - URI or GI illness with chest pain, palpitations, cough
  - Heart failure following a viral illness
  - Fulminant with cardiogenic shock
  - Sudden death
Presentation

- **Acute Myocarditis:**
  - Chest pain, tachycardia, fever, shortness of breath, viral symptoms
  - Normal to mildly depressed cardiac function
  - Minimal symptoms

- **Fulminant Myocarditis**
  - Presents in cardiogenic shock
  - Recent history of febrile/viral illness

- “Burned-out” Myocarditis (Dilated Cardiomyopathy)
Age Distribution in U.S.
Evaluation

- Labs:
  - **Cardiac:** Troponin, CK, (pro-)BNP, ESR, CRP, Venous Blood Gas with lactate
  - **Rheum:** ANA, RF, C3/C4, dsDNA (consult rheumatology)
Evaluation

Labs:

**ID:** Serum PCR for Adenovirus, enteroviruses (includes coxsackie virus, echovirus, rhinovirus, enterovirus), parvovirus B19, human herpesvirus 6, EBV, CMV, Influenza

- Consider blood culture, HIV, HBV, HCV, Rickettsia (Coxiella burnetti, Rickettsia typhi), Lyme disease (Borrelia burgdorferi)
- Respiratory viral panel or stool viral/bacterial culture if symptomatic
- Consult Infectious Disease specialists
Evaluation

- Imaging, Other testing:
  - **EKG**: sinus tachycardia, low-voltage QRS, AV block, BBB
  - Diffuse ST elevation if pericardial involvement (myopericarditis)
Evaluation

- Imaging, Other testing:
  - **EKG**: sinus tachycardia, low-voltage QRS, AV block, BBB
    - Diffuse ST elevation if pericardial involvement (myopericarditis)
  - **Chest X-ray**: Cardiomegaly, pulmonary edema, pneumonia
Evaluation

- **Imaging, Other testing:**
  - **EKG:** sinus tachycardia, low-voltage QRS, AV block, BBB
    - Diffuse ST elevation if pericardial involvement (myopericarditis)
  - **Chest X-ray:** Cardiomegaly, pulmonary edema, pneumonia
  - **Echocardiogram:** Systolic/Diastolic function, ventricular size, valve function, pericardial/pleural effusions
Evaluation

- Imaging, Other testing:
  - Cardiac MRI (with gadolinium):
    - Systolic function, ventricular size, valve function, pericardial/pleural effusions
    - Fibrosis (LGE-late gadolinium enhancement)
    - Edema (extracellular fluid volume by T1-Mapping)
Lake Louise cMRI Criteria

Table 2. Lake Louise Cardiac MRI Diagnostic Criteria for Suspected Myocarditis

Cardiac MRI finding are consistent with myocardial inflammation if at least 2 of the following criteria are present:

- Regional or global myocardial signal intensity increase in T2-weighted images
- Increased global myocardial early enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
- There is at least 1 focal lesion with nonischemic regional distribution in inversion-recovery prepared gadolinium-enhanced T1-weighted images (delayed enhancement)

Cardiac MRI study is consistent with myocyte injury or scar caused by myocardial inflammation if the third criterion is present.

A repeat cardiac MRI study between 1 and 2 wk 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

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

MRI indicates magnetic resonance imaging.
Cardiac MRI
Evaluation

- **Imaging, Other testing:**
  - **Cardiac MRI (with gadolinium):**
    - Systolic function, ventricular size, valve function, pericardial/pleural effusions
    - Fibrosis (LGE-late gadolinium enhancement)
    - Edema (extracellular fluid volume by T1-Mapping)

- **Catheterization:** Cardiac pressures, outputs, saturations, resistances, angiography,
  - Endomyocardial biopsy
Diagnosis – Endomyocardial Biopsy
Treatment of active myocarditis

- Supportive – Heart Failure Management
- Antiarrhythmic agents
- Antiviral agents

No clinical trial data to suggest immunotherapy:
- IVIG (Drucker, et al.)
- Immunosuppression (CSA, AZA, MMF)
- Steroids
- Except in some systemic autoimmune processes (SLE, MCTD)
γ-Globulin Treatment of Acute Myocarditis in the Pediatric Population
Drucker, et al. 1993

![Graph showing probability of survival over time with IVIG and no IVIG treatment.](image)
γ-Globulin Treatment of Acute Myocarditis in the Pediatric Population
Drucker, et al. 1993

![Graph showing the probability of recovery of left ventricular function over time since presentation with IVIG and no IVIG treatments.](image)
Management

Mild Cases: chest pain, mildly elevated troponin and CRP/ESR, normal echo function (LV EF >55%)

- No heart failure symptoms with normal echo = no cardiac meds
Management

Mild Cases: chest pain, mildly elevated troponin and CRP/ESR, mildly depressed echo function (LV EF 45-55%)

No heart failure symptoms with abnormal echo = start ACE inhibitor
Management

Moderate Cases: chest pain, shortness of breath, very elevated troponin and CRP/ESR, moderately depressed echo function (LV EF 35-45%), elevated pro-BNP, pulmonary edema

- Heart failure symptoms with abnormal echo = start ACE inhibitor and beta-1 antagonist slowly

- Diuretics may be needed until euvolemic (pulmonary edema/SOB resolved, pro-BNP improved)
Management

Moderate Cases: chest pain, shortness of breath, very elevated troponin and CRP/ESR, moderately depressed echo function (LV EF 35-45%), elevated pro-BNP, pulmonary edema

- IV inotropic support and afterload reduction (milrinone) may be needed initially if symptoms are moderate to severe.
- Avoid vasopressor agents (dopa, epi, norepi, AVP) unless hypotensive
Management

Fulminant Myocarditis:

- Active myocarditis leading to severe acute-onset heart failure
- Can present in cardiogenic shock – hypotension and inadequate tissue perfusion due to cardiac dysfunction
  - Associated pulmonary edema

Rule of Thirds:

- 1/3 Recover Function Completely (not on cardiac meds)
- 1/3 Recover Some Function (remain on cardiac meds)
● Management

● Fulminant Myocarditis:
  ● Initial stabilization via PALS algorithms
  ● Begin IV inotropic support (milrinone, dopa, epi, dobutamine)
  ● Begin IV diuretics when BP allows (may need initial fluid resuscitation)
Management

Fulminant Myocarditis:

Emergent LVAD placement or ECMO cannulation if:

- continued decline, despite increasing/maximal medical therapy (≥2 inotropes; end-organ dysfunction)

Elective LVAD is now an option as a bridge to transplant for those who do not recover function early
Mechanical Circulatory Support

» ECMO – Extracorporeal Membrane Oxygenation
» VAD – Ventricular Assist Device
Extracorporeal Membrane Oxygenation (ECMO)
ECMO

![Bar chart showing mortality rates for different cardiac diagnoses involving ECMO. The chart compares mortality rates among patients who died on ECMO, those who died on the waiting list, and those who died prior to discharge. The diagnoses include Myocarditis (N=61), CMP (N=218), CHD-2V (N=263), and CHD-1V (N=231).]
Waitlist Outcomes on ECMO

Myocarditis

- 45% Alive
- 30% Transplanted
- 14% Death
- 10% Recovered

Proportion of Patients

Days on Waitlist
Post-transplant Survival after ECMO

![Survival Curve Graph](image-url)
Mechanical Circulatory Support

» VAD – Ventricular Assist Device

~ Temporary VAD –
  • <2 wks, Bridge to Transplant, Recovery, Decision
  • Continuous Flow – Pedi-Mag, RotaFlow

~ Durable VAD –
PediMag VAD

Full magnetic levitation requires no bearings
Open flow path allows for optimum pump washing
Mechanical Circulatory Support

VAD – Ventricular Assist Device

~ Temporary VAD –
  • <2 wks, Bridge to Transplant, Recovery, Decision
  • Continuous Flow – Pedi-Mag, RotaFlow

~ Durable VAD –
  • >2wks, Bridge to Transplant/Recovery
  • Pulsatile – Berlin Heart, Thoratec PVAD
  • Continuous Flow – HeartMate II, HeartWare HVAD
Berlin EXCOR VAD
HeartMate II/III HeartWare H/MVAD
Heartware MVAD
Jarvik 2000 Series VADs
# Ventricular Assist Device Support

## Table 2: Patient Characteristics Before Implant of a Durable Device

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All (n = 200)</th>
<th>Pulsatile flow (n = 91)</th>
<th>Continuous flow (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>146 (73.0)</td>
<td>56 (61.5)</td>
<td>90 (82.6)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>17 (8.5)</td>
<td>10 (11.0)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>35 (17.5)</td>
<td>24 (26.4)</td>
<td>11 (10.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.0)</td>
<td>1 (1.1)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Patient age</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


Mechanical Support & Transplant (2006-2011)

A

% of patients that received care

Year 1 Year 2 Year 3 Year 4 Year 5

- Myocardial biopsy (p = 0.03)
- ECMO (p = 0.65)
- Cardiac MRI (p < 0.01)
- VAD (p = 0.53)
- Heart transplant (p = 0.2)
Outcomes – Biopsy Confirmed (PCMR)
Outcomes after Heart Transplant

![Graph showing survival rates for transplanted patients with and without myocarditis.](image)

- Transplanted patients: n=209
- No Myocarditis (n=186, deaths=31)
- Myocarditis (n=23, deaths=9)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myo</td>
<td>23 17 13 7 5 3 1</td>
</tr>
<tr>
<td>No Myo</td>
<td>186 135 98 62 37 15 4</td>
</tr>
</tbody>
</table>
Outcomes after Heart Transplant

Transplanted patients: n=209
Rejection Deaths=10

- No Myocarditis (n=186, rejection deaths=6)
- Myocarditis (n=23, rejection deaths=4)

Freedom from Rejection Death

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<td>No Myo</td>
<td>186 135 98 62 37 15 4</td>
</tr>
</tbody>
</table>
Management

“Burned-Out” Myocarditis (Dilated Cardiomyopathy)

- History of recent URI/viral illness (several weeks earlier)
- Present as DCM without evidence of inflammation or elevated troponin
Management

“Burned-Out” Myocarditis (Dilated Cardiomyopathy-DCM)

- Evaluation is necessary for all causes of DCM
  - Inherited/genetic, metabolic, neuromuscular, myocarditis
  - Age and patient risk factors determine work-up
- Treatment remains supportive, as for fulminant myocarditis
  - Inotropic support and diuretics, Mechanical Circulatory Support
  - Listing for heart transplant
QUESTION #1

In a previously well seven month old baby with tachypnea, hepatomegaly, diaphoresis, and tachycardia, which of the following conditions is most likely responsible:
QUESTION #1

In a previously well seven month old baby with tachypnea, hepatomegaly, diaphoresis, and tachycardia, which of the following conditions is most likely responsible:

Which of the following is the best answer?
A. Unobstructed total anomalous pulmonary venous return (TAPVR)
B. Anomalous origin of the left coronary artery (ALCAPA)
C. Viral Myocarditis
D. Tricuspid Atresia and VSD without P.S.
E. Pulmonary arteriovenous malformation
A 7 yo girl with chest pain, elevated troponin and CRP, diffuse ST-elevation on EKG and a concurrent URI is admitted to the CICU due to mildly diminished left ventricular function without heart failure symptoms for serial troponin monitoring. She is diagnosed with viral myocarditis.
A 7 yo girl with chest pain, elevated troponin and CRP, diffuse ST-elevation on EKG and a concurrent URI is admitted to the CICU due to mildly diminished left ventricular function without heart failure symptoms for serial troponin monitoring. She is diagnosed with viral myocarditis.

What is the most appropriate initial treatment?
A. Start IV milrinone and diuretics
B. Give IVIg alone
C. Supportive care only
D. Start enalapril if renal function is stable
E. Give IVIg with steroids
Thank You!