Pediatric Myocarditis
Diagnosis, Triage and Treatment

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Disclosure

- I have no relevant financial relationships with any companies related to the content of this course.

Goals:

- Discuss the spectrum of Myocarditis
  - Etiology, pathophysiology and presentation
- Principles of initial Dx
  - Non-Invasive testing (and ??? Invasive)
- How to best safely triage at presentation
  - What’s the data?
- Prediction modeling
- Principles of initial treatment
  - HF treatment
  - “Immuno-modulators”??
- Framework for escalation to MCS?
A Few Definitions from a Dumb Cath Jock

- **Myocarditis:**
  - An injury of the myocardium (usually inflammatory) with cell damage and/or degeneration not caused by ischemia

- **Heart Failure:**
  - The heart isn’t able to do its job well enough
    - Heart failure= imbalance of perfusion/O2 delivery vs. needs
    - Inadequate C.O. to meet demands

**Pathogenesis**

- **Infections (most typical)**
  - **Viral**
    - Adenovirus, Enterovirus (Coxackievirus B, echovirus, poliovirus), Parvovirus, HHV-6
    - Others; influenza, CMV, HSV, EBV, HIV, RSV etc.
  - Probably if we ECHOed everyone with flu all effected……
  - Other infections
    - Rickettsiae, bacteria, protozoa, parasites, fungi, and yeasts

- **Toxin mediated**
  - Drug induced– Anthracyclines other chemo (increasing list)/ radiation
  - Toxins (arsenic)

- **Immune-mediated**
  - Hypersensitivity
  - Autoimmune, or collagen–vascular diseases
    - SLE, connective tissue disease, rheumatic fever, rheumatoid arthritis, and scleroderma, Kawasaki disease, sarcoidosis
  - Idiopathic
    - Most of the time exact etiology is never found

- **Trichinella spiralis**
  - *Yikes!!!!*

- **Pathogen**
  - *Trichinella spiralis*
Pathophysiology

- Viremia with direct viral effect on heart
  - Virus infects cells, replicates and lyases
- Auto-immune effects
  - Immune cell infiltration in response to virus/ viral persistence
    - T-cells, Natural killer cells, Monocytes, Macrophages
    - Initially beneficial, but can get out of control
  - Cytokine release– TNFα, Interferon, interleukins
    - Balance between beneficial and harmful effects
    - May directly damage myocytes and depress inotropy
    - ?? Treatment potential ??
  - Myocyte necrosis/fibrosis final pathway

Presentation- Chronic, Sub-Acute and Acute

- History- may be very subtle
  - Often history of viral disease a few weeks prior (but who doesn’t)
- Symptoms- Very non-specific
  - Lethargy, low-grade fever, poor PO, rash, abdominal cx and malaise
  - CHF symptoms
    - Diaphoresis, palpitations, dyspnea, exercise intolerance,
  - Arrhythmia
    - May present with syncope or sudden death
  - Physical exam findings of congestive heart failure
    - Hepatomegaly, palor, JVD, rales, unexplained tachycardia
      - May be sinus tachycardia or arrhythmia (SVT/VT)

Fulminant myocarditis

- Acute onset of shock
  - Malignant arrhythmias common
- Heart is usually SMALL on ECHO
- Highest risk of needing MCS
  - BUT full recovery may be more likely

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Diagnostics

- HISTORY, HISTORY, HISTORY
- CXR
  - Cardiomegaly, pulmonary congestion
- ECG—usually abnormal
  - Sinus tachycardia, low voltage QRS, ST/T wave changes, arrhythmias
- ECHO
  - Poor cardiac function—does not prove etiology
- Viral studies
  - Can be difficult to get and interpret—worth sending

Biopsy

- Controversial topic in pediatrics
- Biopsy taken from RV side of ventricular septum
- Patchy inflammation with >50% false negatives
  - A mononuclear cell infiltrate is diagnostic of myocarditis
- I do not recommend biopsy routinely
  - Risk/benefit and management decisions do not justify
- 164 pts across 7 centers only 45 (27%) had bx
- In large PHIS DB study use fell from 25% in 2006 to 14% in 2011

Troponins:

- Typically abnormal (but how abnormal not useful)
  - VERY high in peri-myocarditis in teenagers
- Compared troponin levels in myocarditis vs. dilated cardiomyopathy in pediatric patients
  - Total of 43 patients—24 w/myocarditis
  - Median for myocarditis was 0.08 vs 0.01 for DCM
  - Cut off was 0.052 BUT Sensitivity 71%, Specificity 86%

Gross Pathology

- Very patchy process on gross and microscopic level
Biopsy in Myocarditis

• Viral myocarditis
  • There are exceptions to my rules!
    • Giant cell in sarcoidosis
    • Auto-immune (lupus etc)

CMR in Myocarditis

• Useful non-invasive assessment of myocardial edema
• Excellent functional quantification
• Signs of edema (T2), early contrast enhancement (T1 gad) and late GE
• 50/164 patients (30%) in 7ctr study had MRI
• PHIS DB study use rose from 5% in 2006 to 28% in 2011
• BUT again may not impact rx

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Presentation

• 7 large Pediatric Hospitals
• 171 total patients
• Bi-modal age distribution
  • GI symptoms and lower SF associated with death/transplant
  • 13% death/transplant

Presentation

- Predictors of worse outcome:
  - Younger patients
  - Female gender
  - Heart failure/dec. perfusion
  - Worse function
- Worse function at admission predicted worse function at discharge
- BUT – note the range!!!

Presentation of myocarditis

- 76 patients
  - From 1/1/07-1/21/16
  - 45% High Acuity
  - 55% Low Acuity

Pediatric Acute Myocarditis: Predicting Hemodynamic Compromise at Presentation to Healthcare
Wolf, Chaouki, Marino, Adin-Cristian and Gossett Presented at AHA 2016, paper in process

76 Patients with Acute Myocarditis
74 Records Obtained
33 High-Acuity Cohort
41 Low-Acuity Cohort
2 Records Missing

Triaging myocarditis

- 21 Inotropic or Vasoactive Medications only
  - 4 ECMO
  - 1 VAD
  - 4 Transplant
  - 1 Death (no VAD/ECMO)
- 2 VAD to Transplant
  (1 Death post Transplant)
- 1 Transplant from ECMO
- 3 recovery of function

So what to do at presentation??

- Retrospective review of patients with myocarditis
  - Diagnosed by cardiologist (clinical diagnosis)
- We defined 2 cohorts “high acuity” vs “low acuity”
  - High acuity cohort: All patients who required inotropes, CPR, MCS (ECMO or VAD), progressed to transplant or died
  - Low acuity cohort: Everyone else
- Reviewed signs and symptoms at presentation
  - ONLY data collected in first 24 hours
Presentation of myocarditis

- HA—signs, symptoms, physical exam, and findings s/o of heart failure/myocardial dysfunction
- BUT—multiple variables are distinct but overlap:
  - Troponin high in almost all
  - BNP different but abnormal in >40% of LA cohort
  - ECHO of HA cohort suggestive of dysfunction on presentation
- Nothing with good predictive value!

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>High Acuity</th>
<th>Low Acuity</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
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<tr>
<td>Female</td>
<td>74</td>
<td>61%</td>
<td>12%</td>
<td>&lt;0.001</td>
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<tr>
<td>Age (yrs)</td>
<td>74</td>
<td>1.3</td>
<td>15.6</td>
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<tr>
<td>Weight (kg)</td>
<td>74</td>
<td>9.6</td>
<td>59.2</td>
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<tr>
<td>Vital Signs</td>
<td></td>
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<tr>
<td>Tachycardic</td>
<td>71</td>
<td>77%</td>
<td>17%</td>
<td>&lt;0.001</td>
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<tr>
<td>Tachypneic</td>
<td>71</td>
<td>73%</td>
<td>29%</td>
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<tr>
<td>Hypotensive</td>
<td>71</td>
<td>60%</td>
<td>7%</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypoxemic</td>
<td>64</td>
<td>23%</td>
<td>3%</td>
<td>0.01</td>
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<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td>49</td>
<td>54%</td>
<td>94%</td>
<td>&lt;0.001</td>
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<tr>
<td>Shortness of breath</td>
<td>66</td>
<td>74%</td>
<td>36%</td>
<td>0.002</td>
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<tr>
<td>GI Symptoms</td>
<td>70</td>
<td>94%</td>
<td>51%</td>
<td>&lt;0.001</td>
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<tr>
<td>Physical Exam</td>
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<tr>
<td>Wheezing</td>
<td>71</td>
<td>13%</td>
<td>0%</td>
<td>0.016</td>
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<tr>
<td>Gallop</td>
<td>71</td>
<td>40%</td>
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<tr>
<td>Hepatomegaly</td>
<td>70</td>
<td>86%</td>
<td>5%</td>
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<tr>
<td>Abnormal Perfusion</td>
<td>71</td>
<td>50%</td>
<td>0%</td>
<td>&lt;0.001</td>
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<tr>
<td>Abnormal Pulses</td>
<td>71</td>
<td>37%</td>
<td>0%</td>
<td>&lt;0.001</td>
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<tr>
<td>Laboratory</td>
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<td></td>
<td></td>
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<tr>
<td>Troponin (ng/mL)</td>
<td>61</td>
<td>4.3</td>
<td>8.9</td>
<td>0.26</td>
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<tr>
<td>BNP (pg/mL)</td>
<td>52</td>
<td>2842.5</td>
<td>82.9</td>
<td>&lt;0.001</td>
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<tr>
<td>BNP (Abnormal)</td>
<td>56</td>
<td>100%</td>
<td>41%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (Abnormal)</td>
<td>69</td>
<td>43%</td>
<td>13%</td>
<td>0.004</td>
</tr>
<tr>
<td>ALT (Abnormal)</td>
<td>56</td>
<td>65%</td>
<td>37%</td>
<td>0.032</td>
</tr>
<tr>
<td>Bicarbonate (Abnormal)</td>
<td>71</td>
<td>80%</td>
<td>24%</td>
<td>&lt;0.001</td>
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<tr>
<td>Creatinine (Abnormal)</td>
<td>70</td>
<td>41%</td>
<td>7%</td>
<td>&lt;0.001</td>
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<tr>
<td>Radiographic Data</td>
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<td></td>
<td></td>
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<tr>
<td>Cardiomegaly (CXR)</td>
<td>66</td>
<td>64%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary Edema (CXR)</td>
<td>66</td>
<td>50%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bundle Branch Block (ECG)</td>
<td>66</td>
<td>12%</td>
<td>0%</td>
<td>0.023</td>
</tr>
<tr>
<td>Pericardial Effusion (ECHO)</td>
<td>65</td>
<td>58%</td>
<td>7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate or Severe Mitral Regurgitation (ECHO)</td>
<td>64</td>
<td>36%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>59</td>
<td>35%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shortening Fraction (Z-score)</td>
<td>60</td>
<td>-8.3</td>
<td>-1.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Triaging myocarditis

- Symptoms, signs, lab/Xray/echo findings on INITIAL presentation that are associated with hemodynamic compromise
- ~20% of high acuity patients need MCS
- ~25% of high acuity patients need transplant or die
- Highest risk patients are the smaller patients—but NOT ALL
- We suggest initial admission of “High Acuity” patients to units with rapid availability of invasive cardiac support
  - ECMO/MCS/Transplant teams ON SITE

Multivariate modeling

- Model 1:
  - Tachycardia, Tachypnea, Abnormal Creatinine, Cardiomegaly
  - Area under ROC curve: 0.913
- Model 2:
  - Tachycardia, Tachypnea, Abnormal Creatinine, Cardiomegaly, Pericardial Effusion
  - Area under ROC curve: 0.964

Triaging myocarditis

- Here’s where it gets tricky
  - We COULD NOT predict which High Acuity patient would arrest
  - NO ONE ELSE CAN EITHER
  - EITHER ~20% WILL need MCS
  - OR ~80% WON’T need MCS
  - It all depends on perspective and risk tolerance
Why Does it Matter?

- Loss of options/organ function/controlled decision making
- Pre-Transplant condition impacts POST-transplant outcomes
- UNOS based Risk-Prediction in hospital mortality AFTER OHT
  - Used 2707 pediatric patients to generate/validate a model
    - Hemodynamic support (ECMO, vent, VAD, medical only)
    - Cardiac diagnosis (CHD repaired vs. not and CM)
    - Kidney and liver function
  - Pt on ECMO was 5.6x as likely to die post-transplant
  - 3X as likely than if on VAD-how do we get them smoothly


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Myocarditis- Directed Treatments

- Anti-inflammatories/Immune modulators- Controversial topic
  - Steroids- probably don’t help
    - Hypothetically could make things worse
  - IVIG- very limited data, may help…. More in a minute.
  - Immune-suppression (Azathioprine, cyclosporine etc…)
    - Big double-blinded randomized trial in adults had no benefit from treatment with prednisone, and either azathioprine or cyclosporine
    - Postulate a fine balance between positive and negative effects of immune system. Timing may be everything!!
  - Anti-lymphocyte antibody (murmmobab CD3 (OKT3)), Anti TNFa, Anti-cytokines, Interferons, Anti-virals

Treatment

- Starts with supportive care
  - Remember only about half got inotropes
  - Remember the goal is adequate cardiac output
  - However much it takes to provide adequate tissue perfusion
  - Depends on presentation
  - Mild cases may just need nothing or a little afterload reduction
  - Watch out for arrhythmias
IVIG in Pediatric Myocarditis

• Theories:
  - ? Direct binding of virus
  - ? Modulating auto-immune phenomenon
  - ? Indirect effect on modulating inflammation

• Meta-analysis

  - Concluded that inadequate evidence exists
    - Only one RCT 62 adult patients with only 10 proven myocarditis
  - Multiple small reports, but remember most get better anyway….

• Most pediatric centers do it (70% in PHIS study)

  - Theoretically might be better for kids ?Earlier presentation?

• I do it if the kid is sick, but careful of volume load

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Conclusions

• Myocarditis has a very broad spectrum in pediatrics

  - Etiologies are varied, but viral most typical

  - Signs/symptoms/testing at presentation predict a group at risk of poor outcome

  - ~20% of high acuity patients need MCS

  - ~25% of high acuity patients need transplant or die

  - BUT won’t tell you who in that group is going to arrest

  - Supportive care for most

  - Ability to rapidly and smoothly escalate optimizes outcomes

Framing Escalation-- INTERMACS Levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Patient Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Critical cardiogenic shock &lt;br&gt; “Crashing and burning”</td>
</tr>
<tr>
<td>2</td>
<td>Progresive decline &lt;br&gt; “Sliding fast”</td>
</tr>
<tr>
<td>3</td>
<td>Stable but inotrope dependent</td>
</tr>
<tr>
<td>4</td>
<td>Symptome at rest on oral therapy</td>
</tr>
<tr>
<td>5</td>
<td>Exercise intolerance &lt;br&gt; “Bowed-strapped”</td>
</tr>
<tr>
<td>6</td>
<td>Exercise limited &lt;br&gt; “Walking wounded”</td>
</tr>
<tr>
<td>7</td>
<td>Advanced NYHA class 3</td>
</tr>
</tbody>
</table>

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Thank you!

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