Myocarditis
in Infants and Children
Guideline of the German Society of Pediatric Cardiology

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Conflict of Interest – Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship Company
1. Honoraria for lectures – MUSC, Medtronic, St. Jude
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3. Participation in clinical trials – Simon, Neurosis
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Myocarditis
Definition and Etiology

• Process characterized by inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease

• Most cases from common viral infections and post-viral immune-mediated response

• Coxsackievirus A and B, echovirus, poliovirus, PVB 19, HHV6

• Precursor of dilated cardiomyopathy
# Myocarditis

## Etiology

### Table 1  Etiology of Myocarditis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Subgroups Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Bacterial: <em>Chlamydia, Corynebacterium diphtheria, Legionella, Mycobacterium tuberculosis, Mycoplasma, Staphylococcus, Streptococcus A, Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Fungal: <em>Actinomyces, Aspergillus, Candida, Cryptococcus</em></td>
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<td></td>
<td>Helminthic: <em>Echinococcus granulosus, Trichinella spiralis</em></td>
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<td></td>
<td>Protozoai: <em>Toxoplasma gondii, Trypanosoma cruzi</em></td>
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<td></td>
<td>Viral: <em>Adenoviruses, Echoviruses, Enteroviruses (e.g., Coxsackieviruses), Herpes Viruses (Human Cytomegalovirus, Epstein-Barr virus, Human Herpesvirus 6), Hepatitis C Virus, Human Immunodeficiency Virus (HIV), Influenza A virus, Parvovirus B19</em></td>
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<tr>
<td></td>
<td>Rickettsial: <em>Coxiella burnetti, Rickettsia typhi</em></td>
</tr>
<tr>
<td></td>
<td>Spirochetal: <em>Borrelia burgdorferi, Leptospira, Treponema pallidum</em></td>
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<tr>
<td>Autoimmune diseases</td>
<td>Celiac disease, Churg-Strauss syndrome, Crohn’s disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematoses, lymphoproliferative myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis</td>
</tr>
<tr>
<td>Hypersensitivity reactions to drugs</td>
<td>Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamids, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants</td>
</tr>
<tr>
<td>Toxic reactions to drugs</td>
<td>Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab</td>
</tr>
<tr>
<td>Toxic</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Others</td>
<td>Arsenic, copper, iron, radiotherapy, thyreotoxicosis</td>
</tr>
</tbody>
</table>

Kindermann I et al., J Am Coll Cardiol 2012
Time Course of Viral Myocarditis

**Acute Phase**
(Virus replication)

- Days after viral infection: 0, 3, 4, 7, 10
- Infectious virus
- (viral) antibodies
- Cellular infiltration

**Subacute Phase**
(Immune response)

- Days: 14, 18, 30, 90
- Viral genome +/- fibrosis, dilatation, contractile dysfunction

**Chronic Phase**
(Dilated cardiomyopathy)

Kindermann I et al., J Am Coll Cardiol 2012
Pathogenesis of Myocarditis

Cooper LT, N Engl J Med 2009
Myocarditis
Incidence

• ? – often not recognized
• Estimated annual incidence of 1/100,000
• 4 – 5% in young accident victims
• 12% in adolescents and young adults with sudden cardiac death

Levine MC et al., Curr Opin Pediatr 2010
Myocarditis
Clinical Presentation

• Broad spectrum from asymptomatic courses to signs of myocardial infarction to cardiogenic shock and sudden cardiac death

• Symptoms depend on age: infants vs. adolescents

• Acute congestive heart failure, chest pain, cardiac arrhythmias

• Diagnosis based on clinical presentation alone usually not possible
Myocarditis
Laboratory Tests

- Biomarkers (troponins, creatine kinase MB) occasionally elevated in childhood (sensitivity 71%, specificity 86%)
- Normal nonspecific markers of inflammation (CRP, leucocytes) do not exclude acute myocardial inflammatory process
- Utility of virus serology in patients with suspected myocarditis unproven – costly and unreliable
- Detection of viral genome in urine or feces
Myocarditis

ECG

• Abnormalities present in 93-100%, but low sensitivity
• Sinus tachycardia
• Nonspecific T-wave and ST-segment changes
• ST-segment elevation
• AV conduction delays
• Atrial and ventricular arrhythmias
Myocarditis

ECG
Myocarditis
Chest X-ray
Myocarditis
Echocardiography
Myocarditis
MRI/Lake Louis Consensus Criteria

- Noninvasive and valuable clinical tool
- T2-weighted edema imaging for „acute myocardial inflammation“
- ECG-trigged T1-weighted images after Gd-DTPA-infusion
- Late gadolinium enhancement
- Recommended due to high conformity between MRI-based and biopsy-based results in suspected myocarditis
- Lacks data concerning degree of inflammation, presence or type of virus
Myocarditis
MRI

T2-weighted edema images

T1-weighted late gadolineum enhancement

Kindermann I et al., J Am Coll Cardiol 2012
Myocarditis
Endomyocardial Biopsy

Towbin JA 2008
Myocarditis
Endomyocardial Biopsy

• Gold standard for diagnosis

• Invasive, potential complications: pneumothorax, hemothorax, arrhythmias, perforation, death

• Enables identification of lymphocytic invasion and detection of involved virus

• Poor sensitivity and specificity due to patchy myocardial inflammation

• Substantial interobserver variation
Complications of Endomyocardial Biopsy in Children
Pophal et al., J Am Coll Cardiol 1999

1000 Endomyocardial Biopsy Procedures

Cardiomyopathy?

- yes
  - n=154
  - 8/154 perf.
  - 5.2%
  - wt < 10kg?
    - yes
      - n=38
      - 5/38 perf.
      - 12.8%
      - inotropes?
        - yes
          - n=15
          - 5/15 perf.
          - 33.3%
        - no
          - n=23
          - 0/23 perf.
          - 0.0%
    - no
      - n=116
      - 3/116 perf.
      - 2.6%
      - inotropes?
        - yes
          - n=10
          - 1/10 perf.
          - 10.0%
        - no
          - n=106
          - 2/106 perf.
          - 1.9%
  - no
    - n=846
    - 1/846 perf.
    - 0.1%

- no
  - wt < 10kg?
    - yes
      - n=90
      - 0/90 perf.
      - 0.0%
    - no
      - n=756
      - 1/756 perf.
      - 0.1%
Myocarditis
Histology/Dallas Criteria

• Acute myocarditis: lymphocytic infiltrate with myocyte necrosis
• Borderline myocarditis: inflammatory infiltrate without necrosis
• Chronic myocarditis/DCM with inflammation: >14 inflammatory cells/mm² in the myocardium
Myocarditis
Histology and Immunohistochemistry

Kindermann I et al., J Am Coll Cardiol 2012

Acute myocarditis: necrosis and mononuclear cells infiltrates

Chronic myocarditis: fibrosis with inflammatory cells
Myocarditis
In-situ Hybridization

Enterovirus RNA in cardiomyocytes
PVB19 in endothelial cells

Acute Myocarditis
Differential Diagnosis

• Any disease with impairment of LV function
  - DCM
  - ALCAPA
  - Chronic tachycardia
  - Arteriovenous malformation
Acute Myocarditis

Therapy I

• Mainly supportive, no trials for specific heart failure therapy in biopsy-proven myocarditis in adults and children

• Monitoring of vital parameters

• Bed rest initially, no physical activities for 3-6 months

• Heart failure therapy with ACE inhibitors, AT1-antagonists, β-blockers, diuretics and aldosterone antagonists according to current guidelines

• Ventricular assist device <-> HTX

• Therapy of tachyarrhythmias in adults - Life vest and AED
Acute Myocarditis
Therapy II

• In proven viremia: immunoglobulins 2 g/kg for 48 hours (Robinson JL 2005)

• No immunosuppressive therapy – risk of enhanced virus replication and blockade of endogenous interferons

• Steroids only in biopsy-proven virus negative chronic myocarditis (Frustacci A 2009)

• Type-1 interferon (IFN-α, IFN-β) beneficial in animal and human pilot studies (Kühl U 2003, Schmaltz AA 1998)
Acute Myocarditis

Outcome

• ? - significant number of cases undiagnosed
• Complete myocardial recovery
• DCM -> HTX
• Fatal outcome
Acute Congestive Heart Failure/Suspected Acute Myocarditis

Viral Genome (Blood/Feces)

Negative

Heart Failure Therapy

Positive: i.v. Immunoglobulins

Clinical Response:

Insufficient

<2 Weeks

Biopsy

Echo not normalized within 4-6 Weeks

Viral Genome (PCR and in-situ Hybridization)

Pos. + Inflammation

Anti-viral (Interferon, Ganciclovir)

Neg. + Inflammation

Immunosuppressive (Steroids + Azathioprin)

Repeat biopsy depending on clinical course