Cardiology Standards of Care in Duchenne Muscular Dystrophy

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Overview

• Cardiac manifestations in DMD
• Diagnostic tools
  – Screening recommendations
• Current treatment options
  – Limited randomized control trial data
• Advanced heart failure therapies in DMD
  – Small but growing experience
Cardiac involvement in DMD

• Dilated cardiomyopathy is the most common manifestation
• An abnormal ECG and abnormal echo are seen in >90% of DMD patients
• Increasing proportion of cardiac death with improvements in respiratory support
• Early ECG abnormalities (26% by age 6)

AAP Pediatrics 2005
Bushby Neuromuscular Disorders 2003
Cardiac assessment in DMD

- Physical inactivity makes exertional symptoms difficult to elicit
- Diagnostic imaging may be limited by acoustic windows and scoliosis
- Signs of cardiac dysfunction may be subtle and nonspecific:
  - Fatigue, weight loss, decreased ability to tolerate ADLs
  - Cough, orthopnea
  - Nausea, early satiety, vomiting
- Blood pressure may run low at baseline
- “Normal” creatinine may be evidence of renal dysfunction
• After muscular dystrophy is diagnosed, cardiac evaluation by a cardiomyopathy specialist should commence:
  – Clinical visit with history and physical examination
  – Rhythm assessment with an electrocardiogram (ECG)
  – Imaging of the heart with an echocardiogram. Consider MUGA scan or cardiac MRI.

• Cardiac signs and symptoms may be absent or subtle; when present, medications (ACE inhibitors, beta blockers, diuretics) should be considered

• Periodic Holter monitors should be considered in those with cardiac dysfunction; abnormal heart rhythms should be managed carefully

• Ensure good pulmonary care and follow up
Watch out for hypertension and excessive weight gain in patients on corticosteroids.

Evaluate and optimize care before major surgical procedures such as scoliosis surgery; review risks and benefits ahead of time and consider special cardiac monitoring during and after the OR.

Consider anticoagulation if there is severe cardiac dysfunction.

ICU care should include input from a muscular dystrophy specialist.

Nutritional status should be optimized.
• DMD cardiac screening: At diagnosis, biannually until 10 years old, annually at 10 years old or onset of cardiac signs and symptoms

• DMD carriers:
  – Provide education about the risk of cardiomyopathy as well as signs and symptoms of heart failure
  – Screening to start at late adolescence/early adulthood, or onset of cardiac signs and symptoms; continue at least every 5 years starting at 25-30 years old
Rhythm assessment tools

- ECG
- Ambulatory ECG monitoring
  - Holter
  - Event monitor
  - Implantable event recorders
Echocardiographic assessment
Cardiac MRI assessment
Cardiac management in DMD

• What therapies are indicated for all patients with a diagnosis of DCM?
  – Standard American Heart Association recommendations for management of heart failure should be offered to DMD patients
  – These are often based upon HF Staging Criteria

• Are there disease-specific therapies that should be considered in patients with DMD?
ACE inhibitors in DMD

Effect of Perindopril on the Onset and Progression of Left Ventricular Dysfunction in Duchenne Muscular Dystrophy

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Paris, France
Beta Blockers in DMD

Beta-Blocker Therapy for Cardiac Dysfunction in Patients With Muscular Dystrophy

Table 2. Clinical and Echocardiographic Data During Treatment

<table>
<thead>
<tr>
<th></th>
<th>ACEI group (n=15)</th>
<th>C group (n=13)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Pre ACEI</td>
<td>After 3 years</td>
<td>Pre ACEI</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>97±9</td>
<td>92±13</td>
<td>100±10</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>112±10</td>
<td>111±8</td>
<td>115±9</td>
</tr>
<tr>
<td>Cardiac symptoms (+) (n)</td>
<td>2 (13%)</td>
<td>2 (13%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>9±6</td>
<td>26±35</td>
<td>10±7</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>4.8±0.6</td>
<td>5.3±0.8**</td>
<td>5.2±0.7</td>
</tr>
<tr>
<td>LVEDd (Z-value)</td>
<td>0.5±0.8</td>
<td>0.8±0.9**</td>
<td>1.1±0.9</td>
</tr>
<tr>
<td>LVFS</td>
<td>0.20±0.05</td>
<td>0.19±0.06</td>
<td>0.18±0.06</td>
</tr>
<tr>
<td>LVPWTd (mm)</td>
<td>6.5±1.3</td>
<td>6.3±1.6</td>
<td>6.2±1.5</td>
</tr>
<tr>
<td>LVPWTd (Z-value)</td>
<td>-0.0±0.4</td>
<td>-0.0±0.4</td>
<td>-0.1±0.4</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; C, carvedilol; HR, heart rate; BP, blood pressure; (+), symptoms present; BNP, brain natriuretic peptide; LVEDd, left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; LVPWTd, left ventricular posterior wall thickness; Z-value, standard deviation unit.

*Significantly different from the value before C treatment. **Significantly different from the value before ACEI treatment. The mean interval between the start of ACEI and that of C was 13 months in the C group.
Aldosterone antagonists in DMD

Change in LV strain over 12 months was better (less positive) in the eplerenone group ($p=0.020$)

Change in LVEF over 12 months was better (less negative) in the eplerenone group ($p=0.032$)

LV strain stable or improved in 2 year open-label extension study

Raman Lancet Neurol 2015
Raman Orph J Rare Dis 2017
Corticosteroids and DMD CM

Kaplan-Meier Estimate of Freedom from Ventricular Dysfunction

- Steroid treated
- Untreated

Hazard ratio = 0.16 (0.037 - 0.70 95% CI)
Log rank = 0.005

Follow up, days

Markham NMD 2008
Outstanding questions

Contemporary Cardiac Issues in Duchenne Muscular Dystrophy

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• Role of CMR in cardiac surveillance
• When to start ACE inhibition (by 10 years old), beta blockers (when heart rate is high and/or function declines), and mineralocorticoid antagonists (no consensus)
Management of Cardiac Involvement Associated With Neuromuscular Diseases
A Scientific Statement From the American Heart Association

1. The use of glucocorticoids to slow the progression of cardiac disease in patients with DMD may be considered (Class IIb; Level of Evidence B).

2. The use of an aldosterone antagonist in DMD/BMD and with preserved LV systolic function, particularly in those who have evidence of myocardial fibrosis (eg, LGE on CMR), may be considered (Class IIb; Level of Evidence C).

Feingold Circ 2017
2018 Care Guidelines

Diagnosis
Baseline evaluation at diagnosis
- Consultation with cardiologist
- Cardiac medical history
- Family history
- Physical examination
- Electrocardiogram
- Non-invasive imaging:
  - Echocardiogram (<6-7 years old)
  - Cardiovascular MRI (≥6-7 years old)

Assessment of female carriers
Cardiac assessment in early adulthood
- Cardiovascular MRI
- If symptomatic or imaging positive, increase assessment frequency on the basis of cardiologist recommendation
- If negative, repeat evaluation every 3-5 years

Annual assessment
Annual cardiovascular assessment
- Cardiac medical history
- Physical examination
- Electrocardiogram
- Non-invasive imaging

Symptomatic

Ambulatory and early non-ambulatory stage
- Conduct cardiac assessment at least annually
- Initiate angiotensin-converting enzyme inhibitors or angiotensin receptor blockers by age 10

Late non-ambulatory stage
- Monitor closely for signs and symptoms of cardiac dysfunction; symptomatic heart failure can be difficult to diagnose in this stage
- Monitor for rhythm abnormalities
- Treat with known heart failure therapies

Surgery
- Assess with electrocardiogram and non-invasive imaging before major surgery
- Make anaesthetist aware of Duchenne muscular dystrophy diagnosis; patients have increased anaesthesia risks

Figure 2: Cardiac monitoring, diagnosis, and treatment algorithm for patients with Duchenne muscular dystrophy

Birnkrant 2018
Case #1: High risk surgery

- 16 year old with history of DMD presents to clinic for routine follow up; last seen 2 years ago, was asymptomatic with EF 55%
- Diagnosed at age 6 due to awkward gait and falling
- Today he reports significant functional decline, occasional palpitations, diaphoresis, chest pain, and dizziness
- ROS: appetite down, back pain, no shortness of breath, wheelchair bound since age 12
- Meds: Vitamin D
- Exam: WCB, thin, scoliosis, normal cardiac exam
- Echo: Moderate LV systolic dysfunction, EF 40%
- Request for scoliosis surgery planning in the next 6 months
Spinal fusion in DMD

• High risk scoliosis surgery often proposed when cardiac disease has started to manifest
• Blood loss and fluid shifts may cause poorly tolerated alterations in ventricular preload
• Certain anesthetic agents are relatively contraindicated
• Risks include respiratory failure, congestive heart failure, and cardiac arrhythmias
• Pain and narcotic treatment of pain may lead to hypoventilation
Case #1: Outcome

- CMR obtained, confirming moderate LV dysfunction and late gadolinium enhancement
- Enalapril and carvedilol initiated and uptitrated
- Multidisciplinary meetings held for surgical planning:
  - Preadmitted 48 hours in advance for NIPPV initiation on pulmonary service
  - C4 anesthesia team assigned to the OR; CVL placed
  - Baseline TEE performed, and probe left in when pt was placed in prone position so that the echo team could return for follow up imaging as needed
  - PICU recovery with cardiomyopathy team consult following
- Risks/benefits of procedure, code status and limits of care discussed with patient and his mother in advance
- No major complications during 2 week admission; nighttime BIPAP instituted, discussions about possible GT initiated, limited spinal fusion completed
Case #2: Destination VAD?

- 23 year old male with DMD requests new patient visit to establish care for heart failure management, including consideration for VAD therapy
- Has a prior history of VF arrest s/p AICD implantation and severe cardiomyopathy, has been on and off of milrinone therapy
- Wheelchair bound with intermediate degree of neuromuscular involvement; minimal respiratory support; tolerating good cardiomyopathy regimen
“Destination” VAD therapy

• Durable, long-term mechanical circulatory support for pediatric and young adult heart failure patients is increasingly feasible

• Goal: To prolong survival and improve quality of life in those who are not candidates for heart transplantation

• Opting for destination VAD therapy does not preclude future heart transplant candidacy
Continuous flow VAD support

Implantation of the HeartMate II and HeartWare Left Ventricular Assist Devices in Patients With Duchenne Muscular Dystrophy: Lessons Learned From the First Applications

Thomas D. Ryan,* John L. Jefferies,* Hemant Sawnani,† Brenda L. Wong,‡ Aimee Gardner,* Megan Del Corral,* Angela Lorts,* and David L. S. Morales*

Left ventricular assist device in Duchenne Cardiomyopathy: Can we change the natural history of cardiac disease?

Antonio Amodeo *, Rachele Adorisio

Dept. Pediatric Cardiology and Cardiovascular Surgery – Bambino Gesù Pediatric Hospital, Rome, Italy

Brief Report

First use of an intra-pericardial continuous flow ventricular assist device in a child with muscular dystrophy

Ryan R. Davies‡*, Marc Priest‡* and Christian Pizarro‡*

*† Nemours Cardiac Center, Nemours/A.I. duPont Hospital for Children, Wilmington, Delaware, United States of America
Case #2: Outcome

- Patient and appropriate caregiver provided with VAD education
- Team discussion regarding candidacy includes determining whether life expectancy would be severely limited even in the absence of heart failure
- Neurologic, pulmonary, and cardiac regimens optimized in a multidisciplinary fashion
  - Formal input from palliative care, psychosocial, and CT surgery teams would also be required before proceeding with VAD
- Option of advanced heart failure therapies (home milrinone, destination VAD) discussed but not currently indicated
Summary

• Cardiac disease is a common and significant contributor to morbidity and mortality in DMD
• Current diagnostic and treatment recommendations are mostly extrapolated from general heart failure guidelines
• Early initiation of ACE inhibitors may slow echocardiographic evidence of cardiomyopathy; corticosteroids may delay onset of cardiac dysfunction
• Patients and providers are eager for more disease-specific therapies that will slow or prevent the progression of cardiac disease in DMD