

## CLINICAL REPORT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

Section on Cardiology and Cardiac Surgery

## Cardiovascular Health Supervision for Individuals Affected by Duchenne or Becker Muscular Dystrophy

**ABSTRACT.** Duchenne muscular dystrophy is the most common and severe form of the childhood muscular dystrophies. The disease is typically diagnosed between 3 and 7 years of age and follows a predictable clinical course marked by progressive skeletal muscle weakness with loss of ambulation by 12 years of age. Death occurs in early adulthood secondary to respiratory or cardiac failure. Becker muscular dystrophy is less common and has a milder clinical course but also results in respiratory and cardiac failure. The natural history of the cardiomyopathy in these diseases has not been well established. As a result, patients traditionally present for cardiac evaluation only after clinical symptoms become evident. The purpose of this policy statement is to provide recommendations for optimal cardiovascular evaluation to health care specialists caring for individuals in whom the diagnosis of Duchenne or Becker muscular dystrophy has been confirmed. *Pediatrics* 2005;116:1569–1573; *cardiovascular*.

ABBREVIATIONS. DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy.

### INTRODUCTION

Duchenne muscular dystrophy (DMD) is a common genetic disease that affects approximately 1 in 3000 males. Becker muscular dystrophy (BMD) is less common, affecting approximately 1 in 30 000 males.<sup>1</sup> Both diseases result from a mutation in the gene located at Xp21,<sup>2,3</sup> which encodes dystrophin, a sarcolemmal protein abundant in skeletal and cardiac muscle cells.<sup>4</sup> Dystrophin is typically absent in DMD and reduced or abnormal in size in BMD.<sup>5</sup>

DMD typically is diagnosed between the ages of 3 and 7 years and is characterized by progressive skeletal muscle weakness with loss of ambulation between the ages of 7 and 13 years. The BMD phenotype is clinically more heterogeneous with initial presentation in the teenage years. Death secondary to cardiac or respiratory failure typically occurs in the second or third decade in DMD and in the fourth or fifth decade in BMD. Cardiac disease in both DMD and BMD manifests as a dilated cardiomyopathy and/or cardiac arrhythmia.<sup>6,7</sup> End-stage cardiac dis-

ease is characterized by alternating areas of myocyte hypertrophy, atrophy, and fibrosis.<sup>8</sup>

Over the last 20 years, respiratory care of this group of patients has improved as a result of the development of supportive equipment and techniques.<sup>9</sup> Consequently, dilated cardiomyopathy is increasing as the major cause of death.<sup>10–12</sup> The time course for the development of cardiomyopathy has not been well characterized; however, clinical studies demonstrate that the disease process in the heart is underway long before symptoms appear.<sup>13–15</sup> Early manifestations of heart failure often go unrecognized secondary to physical inactivity and a lack of classic signs and symptoms.<sup>16</sup> Signs of cardiac dysfunction may be vague and nonspecific, such as fatigue, weight loss, vomiting, or sleep disturbance. Currently at many medical centers, affected individuals do not come to the attention of the cardiac specialist until late in the disease process when the clinical manifestations of cardiac dysfunction become evident. This reactive, rather than proactive, approach must change if progress is to be made in the treatment of dilated cardiomyopathy in this patient population.<sup>17</sup> Sensitive and specific diagnostic tests to detect early and subtle manifestations of cardiac dysfunction are not available currently and need to be developed. Echocardiography, which remains the standard noninvasive diagnostic modality for cardiomyopathy, is often limited in patients with DMD and BMD by scoliosis and poor echocardiographic acoustic windows.

Cardiac rhythm abnormalities are frequent and play a significant role in morbidity and mortality in both DMD and BMD.<sup>18</sup> Electrocardiographic abnormalities can be seen early in the disease, with an incidence of 26% by 6 years of age.<sup>16</sup> Autonomic dysfunction with increased mean baseline heart rate and decreased rate variability has been well described.<sup>19–21</sup> However, the significance of these findings relative to the course of the cardiomyopathy has not been well established.

Treatment paradigms to date have been individually based and rely on evidence acquired from other patient populations. Cardiac dysfunction is treated by using standard heart-failure strategies that remain suboptimal. Unfortunately, there is minimal evidence-based literature regarding the use and effect of angiotensin-converting enzyme inhibitors or  $\beta$ -blockers

on morbidity and mortality in this patient population.<sup>22-24</sup> Prospective clinical trials are required to evaluate the effectiveness of these treatments in this group of patients. Strategies that target the unique molecular etiology of heart failure in dystrophin-deficient individuals need to be developed if the cardiovascular care of patients with DMD and BMD is to improve.

The cardiovascular system must also be considered when addressing the diverse medical and surgical issues faced by patients with DMD and BMD. The administration of systemic glucocorticoids is becoming standard treatment for the skeletal muscle disease.<sup>25-27</sup> In addition to the potential to improve or stabilize cardiac function, there is the potential to increase long-term cardiovascular risk<sup>28,29</sup> including but not limited to the development of obesity and systemic arterial hypertension. Glucocorticoid treatment also may result in the development of left ventricular hypertrophy, with the potential of altering cardiac function.<sup>30</sup> At present, there is no uniformly accepted or standardized treatment protocol for glucocorticoid use.<sup>31,32</sup> Research is required to determine the cardiovascular effects of long-term glucocorticoid use in patients with DMD.

To manage the musculoskeletal complications in DMD and BMD, orthopedic surgical procedures are frequently recommended.<sup>33,34</sup> The patient with DMD or BMD faces unique risks not only in the operating room but also in the postoperative period.<sup>35,36</sup> Potential complications include respiratory failure, pulmonary aspiration, atelectasis or collapse of major lung segments, postoperative pneumonia, congestive heart failure, and cardiac arrhythmias. The patient with DMD or BMD often has a limited ability to increase cardiac output in response to stress and thus is at risk of inadequate oxygen delivery. Blood loss and fluid shifts during surgical procedures further compromise cardiac output and adequate oxygen delivery.<sup>37</sup> As a result, it is essential that baseline cardiac and pulmonary function be evaluated before any major surgical procedure. Patients with DMD or BMD have additional operative risks. Succinylcholine chloride should be avoided because of its predilection to cause a hyperkalemic response, which is different from malignant hyperthermia but is potentially as life threatening. Prolonged exposure to inhaled anesthetic agents should also be avoided, because they may provoke a life-threatening hypermetabolic state similar to malignant hyperthermia. All patients with DMD or BMD should be monitored during surgery by measuring expired carbon dioxide concentration and body temperature.<sup>38-40</sup>

The patient with DMD or BMD continues to be at risk during the postoperative period. Pain may worsen already compromised pulmonary mechanics, leading to additional increases in oxygen consumption. Treatment with narcotics may result in hypoventilation, which affects airway clearance. In addition, anemia or inadequate volume replacement can impair oxygen delivery. After major surgical procedures such as scoliosis surgery, the patient is likely to experience significant, prolonged fluid shifts, which markedly affect ventricular preload.

Postoperative maintenance of fluid balance and cardiopulmonary monitoring is critical for this patient population.

Nutrition is also critical in the care and management of patients with DMD, because they require regular monitoring to maintain ideal body weight. Obesity and undernutrition are known to occur in this group of patients.<sup>41,42</sup> Both have been shown to be detrimental to cardiac health in other populations,<sup>43</sup> although there is a paucity of literature regarding the effect of nutrition on cardiovascular health in patients with DMD. Glucocorticoid-induced obesity and osteoporosis will further nutritionally affect the patient with DMD.

Patients with DMD and BMD may also be at increased risk of thromboembolic events secondary to the prothrombotic consequences of muscle degeneration.<sup>44-48</sup> This risk is amplified in the presence of cardiac dysfunction. As a result, anticoagulation therapy should be considered in this subgroup of patients. However, there is minimal evidence-based literature regarding the use and effect of anticoagulation therapy in these patients.

Optimal cardiac care cannot be accomplished without maximizing pulmonary function.<sup>49</sup> Hypoventilation and respiratory muscle weakness are known to increase wall stress.<sup>50</sup> Aggressive pulmonary care not only affects morbidity and mortality as a result of reducing respiratory complications but also functions to decrease afterload and left ventricular wall stress, resulting in improved cardiac output. In 2004, the American Thoracic Society released a consensus statement regarding the respiratory care of patients with DMD.<sup>9</sup> These recommendations should be considered carefully.

Female carriers of DMD or BMD are also at risk of developing cardiomyopathy. The age of onset of clinically significant disease is unclear but is thought to be in the adult years.<sup>51</sup> Cardiac involvement in the carrier can be variable, ranging from asymptomatic to severe heart failure necessitating cardiac transplantation.<sup>52,53</sup> Carriers, therefore, require periodic cardiovascular screening.<sup>54,55</sup> In addition, there is a critical need to research the natural history and outcome of therapies in female carriers.

Mutations in dystrophin clearly place affected individuals at risk of developing cardiac disease irrespective of skeletal muscle disease. The dystrophin gene has been shown to be the cause of X-linked dilated cardiomyopathy and some cases of sporadic dilated cardiomyopathy.<sup>56-60</sup>

Ultimately, investigation of cardiomyopathy in patients with DMD and BMD, as well as carriers, will benefit affected individuals, and new knowledge may lead to the elucidation of novel treatment strategies for dilated cardiomyopathy. Given the number of affected children and limited financial resources available for investigation, medical information must be pooled and shared for maximal effectiveness.

#### RECOMMENDATIONS FOR CARDIAC CARE IN PATIENTS WITH DMD OR BMD

1. Cardiac care of the patient with DMD or BMD should begin after confirmation of the diagnosis.

The patient should be referred for evaluation to a cardiac specialist with an interest in the management of cardiac dysfunction and/or neuromuscular disorders.

2. A complete cardiac evaluation should include (but not be limited to) a history and physical examination, electrocardiogram, and transthoracic echocardiogram. Consideration should be given to a multigated acquisition study (MUGA) or cardiac MRI in patients with limited echocardiographic acoustic windows.
3. Clinicians should be aware that the typical signs and symptoms of cardiac dysfunction may not be present secondary to the patient's musculoskeletal limitations. Weight loss, cough, nausea and vomiting, orthopnea, and increased fatigue with a decreased ability to tolerate the daily regimen may represent cardiac impairment and should be investigated. However, the development of dilated cardiomyopathy usually precedes the development of heart-failure symptoms by years and must be identified at its earliest onset.
4. Signs and symptoms of cardiac dysfunction should be treated. Consideration should be given to the use of diuretics, angiotensin-converting enzyme inhibitors, and/or  $\beta$ -blockers.
5. Abnormalities of cardiac rhythm should be promptly investigated and treated. Periodic Holter monitoring should be considered for patients with demonstrated cardiac dysfunction.
6. Respiratory abnormalities contribute to the cardiovascular morbidity and mortality of the disease. Concurrent evaluation and treatment of respiratory abnormalities are recommended.
7. Individuals undergoing treatment with glucocorticoids warrant increased cardiac surveillance with specific monitoring for weight gain and hypertension.
8. Complete cardiac evaluation should be undertaken before scoliosis surgery or other major surgical procedures. Consideration should be given to cardiac stress testing (such as a dobutamine stress echocardiogram) if abnormalities of cardiac function are present during resting evaluation. Medical therapy should be optimized before surgery, and the risks and benefits of the procedure should be discussed in detail with the patient and the family.
9. Intraoperative cardiac monitoring should be undertaken in individuals with DMD or BMD during major surgical procedures. Specific anesthetic techniques and decisions about intraoperative ventilation will depend on the patient and the procedure. Agents known to trigger hyperkalemia (eg, succinylcholine chloride) or a hypermetabolic state (eg, inhaled anesthetic agents) should be avoided. Cardiac monitoring should continue in the postoperative period.
10. Anticoagulation therapy should be considered in patients with severe cardiac dysfunction to prevent systemic thromboembolic events.
11. Clinicians who are experienced in the care of patients with DMD or BMD and are knowledgeable

about the pathogenesis of the disease should be actively involved when patients are treated in an intensive care setting.

12. Nutritional status should be optimized to the special needs of patients with DMD or BMD.

#### RECOMMENDATIONS SPECIFIC FOR CARDIAC CARE IN PATIENTS WITH DMD

1. Patients should be routinely managed in early childhood with a complete cardiac evaluation at least biannually.
2. Yearly complete cardiac evaluations should begin at approximately 10 years of age or at the onset of cardiac signs and symptoms. However, individuals demonstrating these signs and symptoms are relatively late in their course.

#### RECOMMENDATIONS SPECIFIC FOR CARDIAC CARE IN PATIENTS WITH BMD

1. Complete cardiac evaluations should begin at approximately 10 years of age or at the onset of signs and symptoms. Evaluations should continue at least biannually.

#### RECOMMENDATIONS FOR CARDIAC CARE IN CARRIERS OF DMD OR BMD

1. Carriers of DMD or BMD should be made aware of the risk of developing cardiomyopathy and educated about the signs and symptoms of heart failure.
2. Carriers of DMD or BMD should be referred for evaluation by a cardiac specialist with experience in the treatment of heart failure and/or neuromuscular disorders. Patients should undergo initial complete cardiac evaluation in late adolescence or early adulthood or at the onset of cardiac signs and symptoms, if these signs or symptoms appear earlier.
3. Carriers should be screened with a complete cardiac evaluation at a minimum of every 5 years starting at 25 to 30 years of age.
4. Treatment of cardiac disease is similar to that outlined for boys with DMD or BMD.

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