Editorial

# Current Strategies in Management of Duchenne Muscular Dystrophy: Allowing Patients to Live with Hope

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## Introduction

Duchenne muscular dystrophy (DMD) is inherited as an X-linked recessive disorder which affects 1 in 3600 to 6000 live male births and is the most common childhood neuromuscular disorder.[1] Most patients present with delayed motor milestones or proximal muscle weakness and are diagnosed at 5 years of age, when their physical ability diverges markedly from that of their peers. Non-progressive cognitive dysfunction, learning disability and autism are recognised features of the disease.[2] Untreated, these boys have loss of independent ambulation by the age of 9 to 12 years. The mean age at death without intervention is around 19 years, with the leading causes of death being respiratory insufficiency, followed by cardiac complications such as dilated cardiomyopathy.

## Multidisciplinary Management

In the past few decades, significant advances in many areas of management including corticosteroid treatment, rehabilitative interventions, non-invasive ventilatory support, cardiac surveillance and prevention, and scoliosis correction have led to marked improvements in the function, quality of life, health, and longevity of patients with DMD. Boys who are diagnosed today have the possibility of a life expectancy well into their third or fourth decade.[3]

In 2009, the US Center for Disease Control and Prevention selected 84 clinicians to develop care recommendations for patients with DMD. As there are very few large-scale randomised controlled trials (RCTs) done in patients with DMD, the panel used the RAND Corporation-University of California Los Angeles Appropriateness Method (RAM) that combines scientific evidence with the collective judgement of experts to determine the appropriateness and necessity of clinical assessments and interventions.

The DMD Care Considerations Working Group evaluated assessments and interventions for the effective management of diagnostics, gastroenterology and nutrition, rehabilitation, and neuromuscular, psychosocial, cardiovascular, respiratory, orthopaedic, and surgical aspects of DMD. The care recommendations were published in Lancet Neurology in early 2010 and are intended for a wide range of health-care providers who work with individuals who have DMD and their families.[4]

The recommendations provide the essential framework for recognising the primary manifestations and possible complications of DMD at various stages of the disease that will help patients survive into adulthood. The key emphasis of the paper is that a multidisciplinary team and approach coordinated by a primary care physician is crucial in the proper care of patients with DMD (Table 1).

For example, with regard to pharmacological therapy, the panel strongly recommends the use of glucocorticoid therapy for patients with DMD. Glucocorticoids are the only medication currently available that slows the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilises pulmonary function.

Initial RCTs in patients treated with prednisone for up to 6 months showed an improvement in muscle strength, with a daily dose of 0.75 mg/kg having the most favourable profile.[5] Deflazacort, a similar glucocorticoid has been shown to have a similar efficacy at a daily dose of 0.9 mg/kg and has a slightly different chronic risk profile.[6] The recommendations on the timing of initiation of glucocorticoid therapy and the choice of dosing schedule is an individual decision, based on the age and functional state as well as the anticipated side effects for the individual.

## Multi-disciplinary Clinic for DMD Patients in Singapore

A quarterly multidisciplinary neuromuscular clinic has been in existence in the National University Hospital since 1995. In 2010, the University Children's Medical Institute at the National University Hospital adopted the care recommendations and incorporated them into a clinical protocol used for the quarterly multi-disciplinary neuromuscular clinic. The clinic is run by representatives from paediatric neurology, respiratory,

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Table 1. Interdisciplinary management of Duchenne Muscular Dystrophy (DMD), adapted from Bushby K *et al*.[4] The coordination of clinical care is a crucial component of the management of DMD. This care is best provided in a multidisciplinary care setting in which the individual and family can access expertise for the required multisystem management of DMD in a collaborative effort.

| | | | **Neuromuscular and Skeletal Management** | | |
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| | | | **Systems** | **Assessments** | **Interventions** |
| Patient with DMD | Family | Clinical care coordination | Diagnostics | Creatine kinase<br>Genetic testing<br>Muscle biopsy | Genetic counselling<br>Family support |
| | | | Corticosteroids | Clinical evaluation | Several considerations |
| | | | Rehabilitation | ROM<br>Strength<br>Posture/alignment<br>Function<br>Gait | Physiotherapy<br>Orthoses/splints/ devices<br>Submaximum exercise<br>Wheelchairs |
| | | | Orthopaedic management | ROM<br>Spinal assessment<br>Bone age<br>Bone densitometry | Tendon surgery<br>Posterior spinal fusion |
| | | | **Management of Other Complications** | | |
| | | | **Systems** | **Assessments** | **Interventions** |
| | | | Cardiac management | ECG<br>2D-Echo<br>Holter monitoring | ACE inhibitors<br>Beta-blockers<br>Other heart failure medications |
| | | | Pulmonary management | Spirometry<br>Pulse oximetry<br>Capnography<br>ABG | Volume recruitment<br>Ventilators<br>Tracheostomy<br>Mechanical insufflator/ exsufflator |
| | | | Gastrointestinal, speech/swallowing, nutrition management | Upper GI investigations for swallowing dysfunction<br>Anthropometry | Diet control and supplementation<br>Gastrostomy<br>Pharmacological management of reflux and constipation |
| | | | Psychosocial management | Coping<br>Neurocognitive<br>Speech and language<br>Autism<br>Social work | Psychotherapy<br>Pharmacological<br>Social<br>Educational<br>Supportive care |

ROM: range of motion; ACE: angiotensin- converting enzyme; Echo: echocardiogram; ECG: electrocardiogram; ABG: arterial blood gas; GI: gastrointestinal

cardiology, orthopaedics as well as rehabilitative services (physiotherapists, occupational therapists and orthotists). The patient is reviewed by each sub-specialty using the DMD clinical protocol with standardised checklists, investigations and follow-up at various intervals. The protocol also addresses the psychosocial areas of the patient's care as part of the holistic approach in the management of DMD. This form of systematic evaluation has been key in initiating preventive strategies against known complications such as respiratory failure, bone fractures and malnutrition, common occurrences in late disease. The clinic is segregated temporally to separate boys who are still walking with those who are wheelchair bound because of the difference in physical and medical needs.

Starting from 2012, new palliative clinics targeted to older wheelchair bound patients to manage specific difficulties in terminal disease will be set up. These clinics aim to ensure good quality of life in later stages of the disease, introducing sleep support systems, improving nutrition and harnessing external support devices to maintain functionality

e.g. wheelchair joystick adaptation for those with minimal grip strength. Social support services will also be utilised to encourage the socialisation of these increasingly home-bound patients and to provide psychological and emotional support for these patients and their families.

**The Way Forward**

Looking back over the past decades, the standard of care for DMD has advanced significantly and the relentless deterioration in quality of life leading to certain demise has been stemmed to some degree. With the realisation that patients with DMD can now survive into adulthood, it is clear that standardisation of care for patients with DMD in a multi-disciplinary and coordinated care is essential.

The way forward for managing DMD patients must address the following issues:

1. There is a need for the development of further robust protocols for transition of care to the adult medical teams, and in particular, for improvement in rehabilitation, employment, social participation and social services for adults with DMD.[7]

2. While there is success in prolonging the life of DMD patients, there is still little done in the area of their terminal care. Palliative care is necessary to relieve or prevent suffering and to improve quality of life in patients with late stage DMD, as they are often bed-bound with multi-systemic complications. In addition to pain management, palliative care teams can provide emotional support, assist families in clarifying treatment goals and making difficult medical decisions, facilitate communication between families and medical teams, and address issues related to grief, loss, and bereavement.

3. Finally, there remains hope for curative cell and gene therapy. However, this is still at an experimental stage. An example is Ataluren (PTC124), a drug that targets nonsense mutations in DMD but failed to show significant improvements in muscle strength during its phase 2b trials.[8] Another potential exciting gene therapy is the use of antisense oligonucleotides (AONs) to induce potentially therapeutic exon skipping from the DMD pre-mRNA.[9] In 2011, 2 large international randomised placebo controlled studies of AONs had been initiated.[10,11] The outcome of these studies is expected in 2012, bringing hope to many DMD patients for a targeted treatment for their disease.

With the advent of gene-based therapies, there is increasing impetus for optimal management and maintenance of muscle strength in newly diagnosed patients. Comprehensive care at every stage of the disease will not only allow our patients to live with hope but also with confidence for a better quality of life and future.

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