Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management

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Since the publication of the Duchenne muscular dystrophy (DMD) care considerations in 2010, multidisciplinary care of this severe, progressive neuromuscular disease has evolved. In conjunction with improved patient survival, a shift to more anticipatory diagnostic and therapeutic strategies has occurred, with a renewed focus on patient quality of life. In 2014, a steering committee of experts from a wide range of disciplines was established to update the 2010 DMD care considerations, with the goal of improving patient care. The new care considerations aim to address the needs of patients with prolonged survival, to provide guidance on advances in assessments and interventions, and to consider the implications of emerging genetic and molecular therapies for DMD. The committee identified 11 topics to be included in the update, eight of which were addressed in the original care considerations. The three new topics are primary care and emergency management, endocrine management, and transitions of care across the lifespan. In part 1 of this three-part update, we present care considerations for diagnosis of DMD and neuromuscular, rehabilitation, endocrine (growth, puberty, and adrenal insufficiency), and gastrointestinal (including nutrition and dysphagia) management.

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Introduction

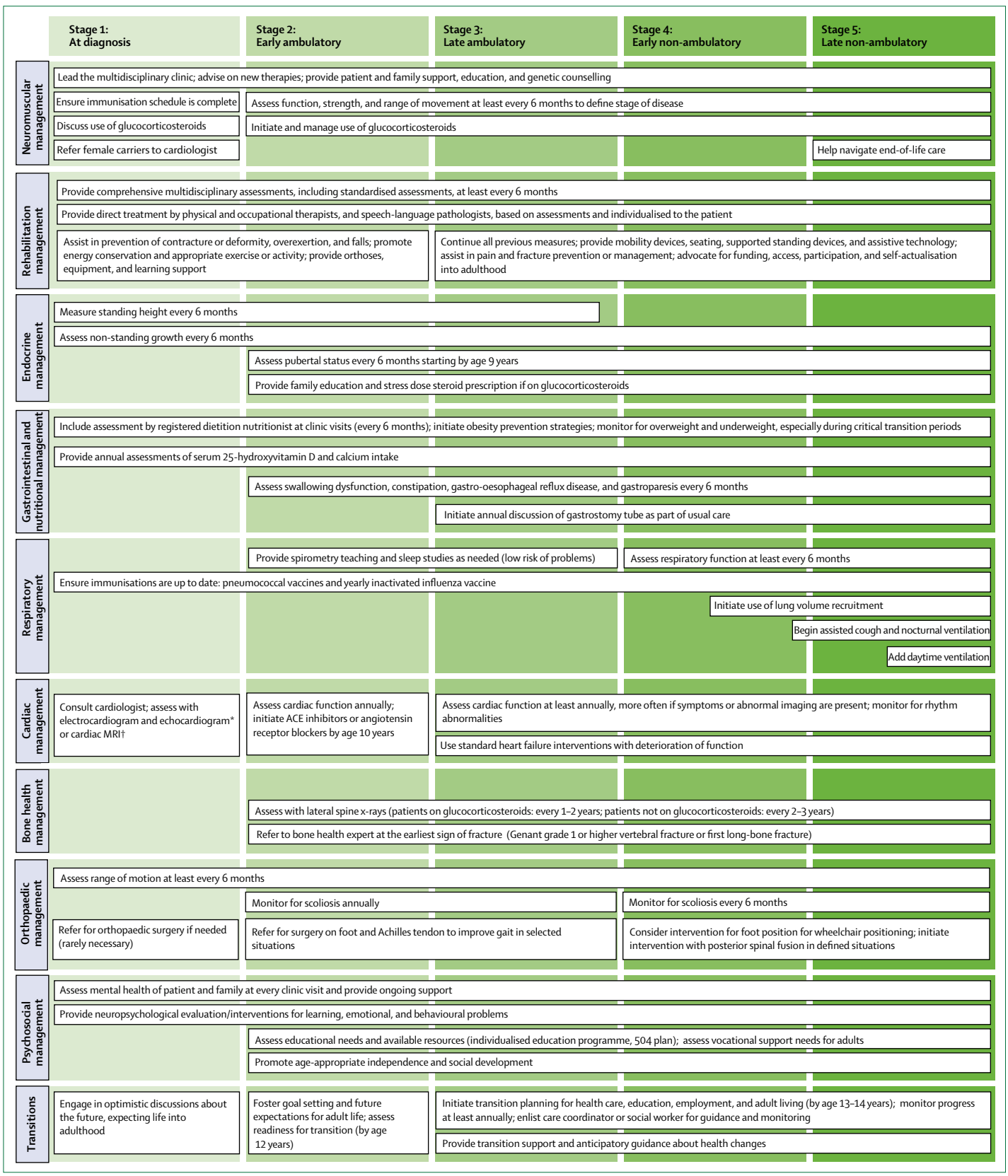
Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive neuromuscular disorder caused by mutations in the dystrophin gene that result in absent or insufficient functional dystrophin, a cytoskeletal protein that enables the strength, stability, and functionality of myofibres. Prevalence of DMD has been reported as 15·9 cases per 100 000 live male births in the USA and 19·5 cases per 100 000 live male births in the UK.[1–3] Progressive muscular damage and degeneration occurs in people with DMD, resulting in muscular weakness, associated motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy. Although the clinical course of skeletal muscle and cardiac involvement can be variable, death usually occurs as a result of cardiac or respiratory compromise.[4,5] This is part 1 of a three-part update of the 2010 DMD care considerations,[6–8] which has been supported by the US Centers for Disease Control and Prevention (CDC) with involvement of the TREAT-NMD network for neuromuscular diseases, the Muscular Dystrophy Association, and Parent Project Muscular Dystrophy.

The decision to update the care considerations was driven by several important developments. First, with multidisciplinary care, the survival of patients with DMD has improved, and the diagnostic and therapeutic approach of the relevant subspecialties is evolving.[9–12] With more widespread realisation of prolonged survival, multiple subspecialties have shifted to more anticipatory diagnostic and therapeutic strategies, to achieve prevention, early identification, and treatment of predictable and potentially modifiable disease complications. Second, accompanying the expectation of longer survival is an increasing emphasis on quality of life and psychosocial management. Moreover, an urgent need now exists to coordinate and improve patient transitions from childhood to adulthood. Third, this update was necessitated by the growing experience with existing therapies and the anticipation of emerging genetic and molecular therapies for DMD.[13] Specifically, new information is available on the efficacy, side-effects, and limitations of glucocorticoids,[14,15] and clinically meaningful and reliable biomarkers and outcome measures need to be identified to assess emerging therapies.

In part 1 of this Review, we cover the following topics: diagnosis, neuromuscular management, rehabilitation management, endocrine management (including growth, puberty, and adrenal insufficiency), and gastrointestinal management (including nutrition and dysphagia). Parts 2 and 3 of this Review describe the care considerations for other topic areas, including an expanded section on psychosocial management and new sections on primary care, emergency management, and transitions of care across the lifespan. Figure 1 provides an overview of assessments and interventions across all topics, organised by stage of disease.

Methods

In 2014, based on their clinical perspectives and expertise, the DMD Care Considerations Working Group (CCWG) steering committee identified 11 topics to be included in this update of the 2010 DMD care considerations.[6]


Stage 1: At diagnosis
Stage 2: Early ambulatory
Stage 3: Late ambulatory
Stage 4: Early non-ambulatory
Stage 5: Late non-ambulatory
Neuromuscular management
Lead the multidisciplinary clinic; advise on new therapies; provide patient and family support, education, and genetic counselling
Ensure immunisation schedule is complete
Assess function, strength, and range of movement at least every 6 months to define stage of disease
Discuss use of glucocorticosteroids
Initiate and manage use of glucocorticosteroids
Refer female carriers to cardiologist
Help navigate end-of-life care
Rehabilitation management
Provide comprehensive multidisciplinary assessments, including standardised assessments, at least every 6 months
Provide direct treatment by physical and occupational therapists, and speech-language pathologists, based on assessments and individualised to the patient
Assist in prevention of contracture or deformity, overexertion, and falls; promote energy conservation and appropriate exercise or activity; provide orthoses, equipment, and learning support
Continue all previous measures; provide mobility devices, seating, supported standing devices, and assistive technology; assist in pain and fracture prevention or management; advocate for funding, access, participation, and self-actualisation into adulthood
Endocrine management
Measure standing height every 6 months
Assess non-standing growth every 6 months
Assess pubertal status every 6 months starting by age 9 years
Provide family education and stress dose steroid prescription if on glucocorticosteroids
Gastrointestinal and nutritional management
Include assessment by registered dietition nutritionist at clinic visits (every 6 months); initiate obesity prevention strategies; monitor for overweight and underweight, especially during critical transition periods
Provide annual assessments of serum 25-hydroxyvitamin D and calcium intake
Assess swallowing dysfunction, constipation, gastro-oesophageal reflux disease, and gastroparesis every 6 months
Initiate annual discussion of gastrostomy tube as part of usual care
Respiratory management
Provide spirometry teaching and sleep studies as needed (low risk of problems)
Assess respiratory function at least every 6 months
Ensure immunisations are up to date: pneumococcal vaccines and yearly inactivated influenza vaccine
Initiate use of lung volume recruitment
Begin assisted cough and nocturnal ventilation
Add daytime ventilation
Cardiac management
Consult cardiologist; assess with electrocardiogram and echocardiogram* or cardiac MRI†
Assess cardiac function annually; initiate ACE inhibitors or angiotensin receptor blockers by age 10 years
Assess cardiac function at least annually, more often if symptoms or abnormal imaging are present; monitor for rhythm abnormalities
Use standard heart failure interventions with deterioration of function
Bone health management
Assess with lateral spine x-rays (patients on glucocorticosteroids: every 1–2 years; patients not on glucocorticosteroids: every 2–3 years)
Refer to bone health expert at the earliest sign of fracture (Genant grade 1 or higher vertebral fracture or first long-bone fracture)
Orthopaedic management
Assess range of motion at least every 6 months
Monitor for scoliosis annually
Monitor for scoliosis every 6 months
Refer for orthopaedic surgery if needed (rarely necessary)
Refer for surgery on foot and Achilles tendon to improve gait in selected situations
Consider intervention for foot position for wheelchair positioning; initiate intervention with posterior spinal fusion in defined situations
Psychosocial management
Assess mental health of patient and family at every clinic visit and provide ongoing support
Provide neuropsychological evaluation/interventions for learning, emotional, and behavioural problems
Assess educational needs and available resources (individualised education programme, 504 plan); assess vocational support needs for adults
Promote age-appropriate independence and social development
Transitions
Engage in optimistic discussions about the future, expecting life into adulthood
Foster goal setting and future expectations for adult life; assess readiness for transition (by age 12 years)
Initiate transition planning for health care, education, employment, and adult living (by age 13–14 years); monitor progress at least annually; enlist care coordinator or social worker for guidance and monitoring
Provide transition support and anticipatory guidance about health changes

Eight of the topics were addressed in the original care considerations: (1) diagnosis, (2) neuromuscular management, (3) rehabilitation management, (4) gastrointestinal and nutritional management, (5) respiratory management, (6) cardiac management, (7) orthopaedic and surgical management, and (8) psychosocial management. Three topics are new: (9) primary care and emergency management, (10) endocrine management (including growth, puberty, adrenal insufficiency, and bone health), and (11) transitions of care across the lifespan.

The guidance in this update is not conventionally evidence based. As is typical for a rare disease, few large-scale randomised controlled trials (RCTs) have been completed for DMD, with the exception of studies of corticosteroids.[16] Therefore, as for the 2010 DMD care considerations,[6,7] guidance was developed using a method that queries a group of experts on the appropriateness and necessity of specific assessments and interventions, using clinical scenarios.[17] This method is intended to objectify expert opinion, and to make the guidance a true reflection of the views and practices of an expert panel, based on their interpretation and application of the existing scientific literature. Using this approach, we were able to produce an essential toolkit for DMD care; only assessments and interventions that have been deemed both appropriate and necessary are recommended.

A comprehensive literature review was done to identify articles relevant to DMD care for each topic area, with the addition of key words for the new topics. A full description of the literature review strategy, table of search terms, and summaries of relevant literature are available in the appendix. From the search results, the steering committee selected articles containing information that might require the 2010 care considerations to be updated. Clinical scenarios were then developed on the basis of the content of those articles. For each of the 11 topic areas, a committee of experts was assembled. Using the RAND Corporation–University of California Los Angeles Appropriateness Method (RAM),[6,17] the committees established which assessments and interventions were both appropriate and necessary for the various clinical scenarios. For the RAM process, the committees had two rounds to establish appropriateness followed by one or two rounds on necessity. For the following sections, not all steps of the two-stage RAM rating process were required, either because of a lack of new literature since the 2010 care considerations were developed, or because immediate unanimous agreement was reached among committee members on the appropriateness and necessity of interventions: diagnosis, neuromuscular management, respiratory management, cardiac management, orthopaedic and surgical management, and psychosocial management. Additionally, the RAM method was not deemed to be applicable for two of the new sections: primary care and emergency management, and transitions of care across the lifespan. The committees for these sections reached consensus during their discussions without first rating clinical scenarios.

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Figure 1: **Comprehensive care of individuals with Duchenne muscular dystrophy**

Care for patients with Duchenne muscular dystrophy is provided by a multidisciplinary team of health-care professionals; the neuromuscular specialist serves as the lead clinician. The figure includes assessments and interventions across all disease stages and topics covered in this three-part Review. *Echocardiogram for patients 6 years or younger. †Cardiac MRI for patients older than 6 years.

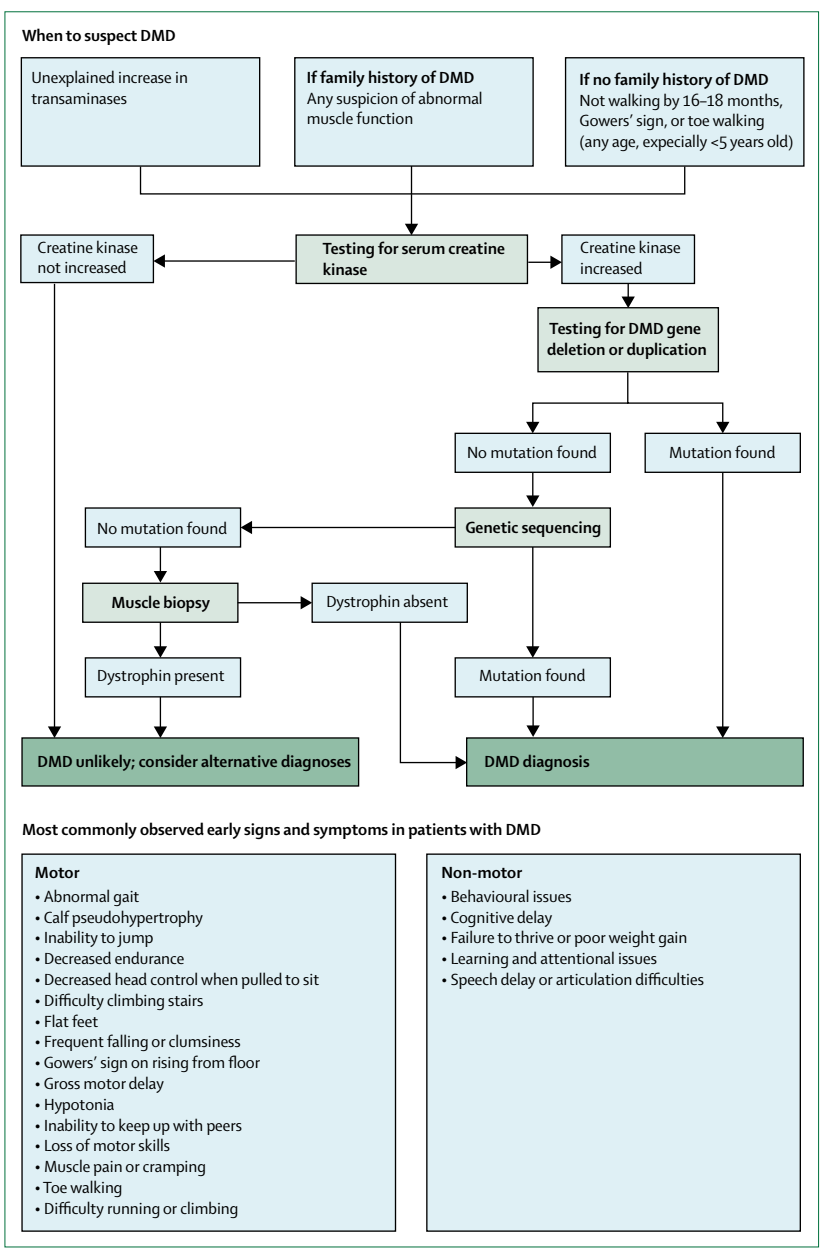

Figure 2: **Diagnosis of Duchenne muscular dystrophy**

Described early signs and symptoms of DMD are based on Ciafaloni and colleagues.[18] DMD=Duchenne muscular dystrophy.

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For more on the **TREAT-NMD network** see http://www.treat-nmd.eu/

For more on the **Muscular Dystrophy Association** see https://www.mda.org/

Diagnosis

Achieving a timely and accurate diagnosis of DMD is a crucial aspect of care. The method for diagnosing DMD has not changed significantly since 2010 (figure 2).[6] The diagnostic process typically begins in early childhood after suggestive signs and symptoms are noticed, such as weakness, clumsiness, a Gowers' sign, difficulty with stair climbing, or toe walking. Prompt referral to a neuromuscular specialist, with input from a geneticist or genetic counsellor, can avoid diagnostic delay.[18] Less commonly, the diagnosis is considered as a result of developmental delay[19] or increased concentrations of serum enzymes such as alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, or creatine kinase. Occasionally, an increased alanine aminotransferase, aspartate aminotransferase, or lactate dehydrogenase concentration prompts an inappropriate focus on hepatic dysfunction, delaying the diagnosis of DMD.

Because approximately 70% of individuals with DMD have a single-exon or multi-exon deletion or duplication in the dystrophin gene, dystrophin gene deletion and duplication testing is usually the first confirmatory test. Testing is best done by multiplex ligation-dependent probe amplification (MLPA)[20] or comparative genomic hybridisation array,[21] since use of multiplex PCR can only identify deletions. Identification of the boundaries of a deletion or duplication mutation by MLPA or comparative genomic hybridisation array might indicate whether the mutation is predicted to preserve or disrupt the reading frame. If deletion or duplication testing is negative, genetic sequencing should be done to screen for the remaining types of mutations that are attributed to DMD (approximately 25–30%).[22] These mutations include point mutations (nonsense or missense), small deletions, and small duplications or insertions, which can be identified using next-generation sequencing.[23–25] Finally, if genetic testing does not confirm a clinical diagnosis of DMD, then a muscle biopsy sample should be tested for the presence of dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract.

Female carriers

Family members of an individual with DMD should receive genetic counselling to establish who is at risk of being a carrier. Carrier testing is recommended for female relatives of a boy or man who has been genetically confirmed to have DMD. If the relative is a child, then the American Medical Association ethical guidelines for genetic testing of children should be followed.[26] Once identified, female carriers have several reproductive choices to consider, including preimplantation genetic diagnosis or prenatal genetic testing through chorionic villus or amniotic fluid sampling. Female carriers also need medical assessment and follow-up, as described in the section on cardiac management in part 2 of this Review.

Newborn screening

The feasibility of newborn screening for DMD was first shown in the mid-1970s[27] through measurement of creatine kinase concentrations from dried blood spots. Recently, a two-tier newborn screening diagnostic system was reported,[2] in which samples that revealed an increased creatine kinase concentration were then tested for dystrophin gene mutations. Newborn screening studies for DMD have been done in several countries, but most have been discontinued,[2,28] and DMD is not currently included on the Recommended Uniform Screening Panel,[29] which is largely restricted to neonatal-onset disorders for which early treatment shows improved outcome. However, renewed interest in newborn screening has been building as a result of support among stakeholders and because emerging DMD therapies might prove to be most effective if they are initiated before symptom onset.[30,31]

Neuromuscular management

After diagnosis, the neuromuscular specialist will serve as the lead clinician, taking overall responsibility for care of the person with DMD and performing multiple roles and responsibilities across the individual's lifetime (panel 1). The neuromuscular specialist is uniquely

Panel 1: **Roles and responsibilities of the neuromuscular specialist in the care of patients with Duchenne muscular dystrophy**

- Assess and characterise each patient's unique disease trajectory over time using validated assessment tools, aiming to establish a patient's expected clinical course and to advise on prognosis and potential complications
- Use assessment information to select therapeutic interventions that define a customised treatment plan designed to meet the particular needs and goals of each patient and family, optimising outcomes and quality of life as defined by the individual patient and family
- Engage specific clinicians who can enact the designated assessments, interventions, and treatment plan, ideally in the context of a dedicated, multidisciplinary DMD clinic that is led, administered, and coordinated by the neuromuscular specialist; assist in the care of female carriers, including cardiac assessment
- Be the first-line medical advisor to patients and their families as they define and revise their individual care goals over time, helping them to personalise their risk-to-benefit analysis of therapeutic interventions, including:
  - Technological interventions for respiratory and cardiac management
  - Surgical and non-surgical interventions, such as spinal fusion, contracture management, and provision of aids and appliances
  - Pharmacological interventions, such as glucocorticoid therapy, emerging therapies, and patient participation in clinical research trials of investigational drugs
- Be an advocate for high-quality DMD care at patients' institutions and in their communities, addressing issues such as transition of care from paediatric to adult clinical providers and provision of hospital care that is designed to address patients' unique medical, physical, and psychosocial needs
- Help patients and families navigate end-of-life care in a way that preserves comfort, dignity, and quality of life as defined by each individual patient and family

qualified to guide patients and their families through the increasingly complex and technological diagnostic and therapeutic landscape of contemporary DMD care.

Assessments

Consistent and reproducible clinical assessments of neuromuscular function done by trained practitioners underpin the management of DMD. Assessments described in the 2010 care considerations remain valid, and clinics should use a set of tests with which they are comfortable and for which they understand the clinical correlates. Multidisciplinary team members must work together to optimise consistency and avoid unnecessary test duplication. Suggested assessments are shown in the appendix and are discussed in the section on rehabilitation management. Newer studies have shown the value of minimum clinically important differences, predictive capabilities of standardised functional assessments, and ranges of optimum responsiveness, confirming the importance of standardised functional assessments across a patient's lifespan.[32–35] Additionally, new assessment tools are helping to guide the management of older, non-ambulatory individuals, illustrating the importance of clinical testing throughout life.

Interventions

Physiotherapy, as described in the section on rehabilitation management, and treatment with glucocorticoids remain the mainstays of DMD treatment and should continue after loss of ambulation. Figure 3 describes glucocorticoid initiation and use.[36] The benefits of long-term glucocorticoid therapy have been shown to include loss of ambulation at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery.[37] Recent studies confirm the benefits of starting glucocorticoids in younger children, before significant physical decline;[38,39] an ongoing trial (ClinicalTrials.gov identifier NCT02167217) of weekend dosing in boys younger than 30 months will soon yield additional insights. Although the benefits of glucocorticoid therapy are well established, uncertainty remains about which glucocorticoids are best and at what doses.[40] These uncertainties increase the risk of undertreatment or overtreatment, which could confound the results of trials of innovative therapies. Large-scale natural history and cohort studies confirm prolongation of ambulation from a mean of 10·0 years in individuals treated with less than 1 year of corticosteroids to a mean of 11·2 years in individuals treated with daily prednisone and 13·9 years in individuals taking daily deflazacort.[41] In a few studies, weekend-only dosing of prednisone has shown efficacy equal to that of daily dosing.[41,42] A phase 3 double-blind RCT compared deflazacort 0·9 mg/kg per day, deflazacort 1·2 mg/kg per day, prednisone 0·75 mg/kg per day, and placebo. All treatment groups had improved muscle strength compared with placebo and deflazacort was associated with less weight gain than prednisone.[14] The benefit-to-risk ratio of deflazacort compared with prednisone is being studied further in an ongoing double-blind trial.[15]

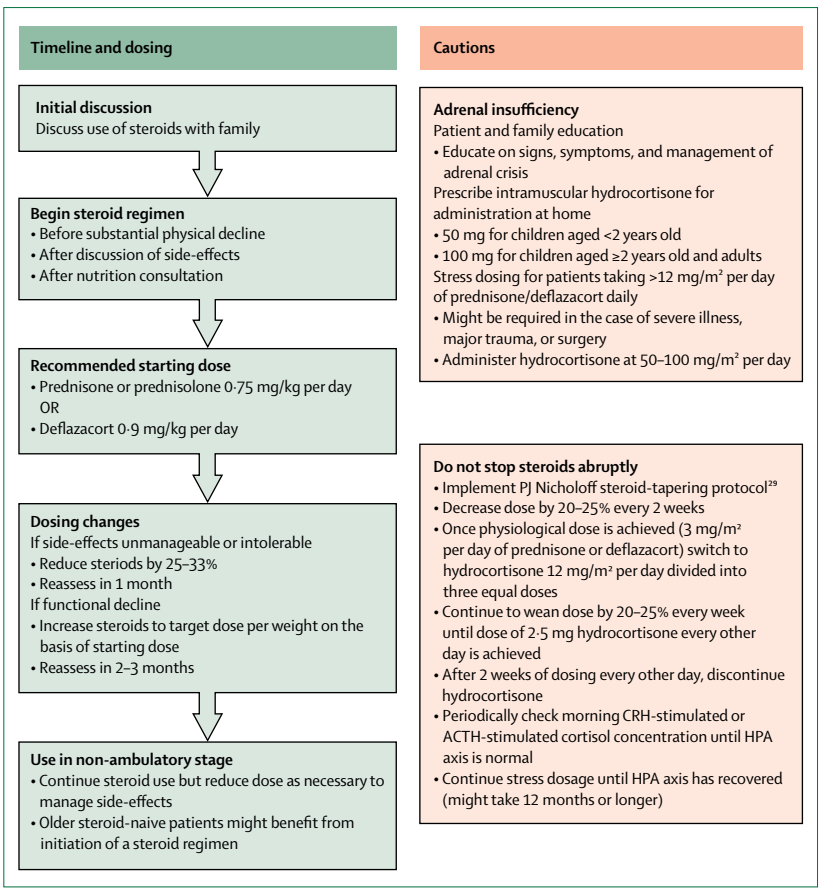

Figure 3: **Care considerations for glucocorticoid (steroid) initiation and use for patients with Duchenne muscular dystrophy**

ACTH=adrenocorticotropic hormone. CRH=corticotropin-releasing hormone. HPA=hypothalamic-pituitary-adrenal.

Emerging treatments

The drug development pipeline for DMD has changed dramatically since the publication of the 2010 care considerations, and the full list of DMD treatment trials changes continually; updated information is available at ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. DMD is a rare disease, and the increasing number of DMD trials is a challenge for clinical trial capacity because of the low numbers of patients who qualify for participation. The need to optimise patient recruitment is expected to promote initiatives supporting trial readiness, such as patient registries, identification of clinically significant outcome measures, and natural history studies.

In August, 2014, ataluren was granted conditional marketing authorisation by the European Commission for use in the European Union, targeting the approximately 11% of boys with DMD caused by a stop codon in the dystrophin gene.[43,44] In September, 2016, the

For more on **Parent Project Muscular Dystrophy** see http://www.parentprojectmd.org/

See **Online** for appendix

For **ClinicalTrials.gov** see https://clinicaltrials.gov/

For the **WHO International Clinical Trials Registry Platform** see http://apps.who.int/trialsearch/

US Food and Drug Administration (FDA) approved use of eteplirsen, which targets the approximately 13% of boys with a mutation in the dystrophin gene that is amenable to exon 51 skipping,[45] via an accelerated approval pathway. Ataluren and eteplirsen are the first of a series of mutation-specific therapies to gain regulatory approval. Other dystrophin restoration therapies are in development and some are near or in regulatory review.[13] The FDA has also granted full approval for deflazacort, making this the first glucocorticoid with a labelled indication specifically for DMD.

Other drug classes in trials for DMD include drugs targeting myostatin, anti-inflammatory and antioxidant molecules, compounds to reduce fibrosis, drugs to improve vasodilatation, drugs to improve mitochondrial function, and drugs to regulate utrophin.[46] However, without completed clinical studies and regulatory approval, none of these drugs can be prescribed for individuals with DMD.

Rehabilitation management

DMD is characterised by well known patterns of progressive muscle degeneration and weakness, postural compensations, risk of progressive contracture and deformity, and functional losses resulting from dystrophin deficiency.[6,7] Improved DMD management has resulted in prolongation of ambulation,[47] decreased prevalence of severe contracture and deformity, including scoliosis,[37] and prolonged function and participation in all areas of life.[47,48] Rehabilitation personnel include physicians, physical therapists, occupational therapists, speech-language pathologists, orthotists, and durable medical equipment providers. Panel 2 and the appendix present an overview of suggested assessments and interventions. Rehabilitation management requires an understanding of DMD pathology, pathokinesiology, natural history, and disease progression; providers should consider each individual's goals and lifestyle to optimise quality of life across the lifespan.[7] Assessment and anticipatory management must be provided across all domains of the International Classification of Functioning, Disability and Health (ICF), from diagnosis onwards, to minimise contractures, deformity, loss of function, compromised skin integrity, pain, and compromised cardiorespiratory status.

For more on the **International Classification of Functioning, Disability and Health** see http://www.who.int/classifications/icf/en/

Assessments

Multidisciplinary rehabilitation assessment includes measures of passive ranges of motion, muscle extensibility, posture and alignment, strength, function, quality of life, and participation in all normal activities of everyday life (panel 2; appendix).[7,32–35,49–59] Specialised functional assessment includes analysis of patterns of movement and standardised assessments specific to DMD and other neuromuscular disorders.[32,33,60] The North Star Ambulatory Assessment (NSAA) and timed function tests are foundational clinical assessments of function during the ambulatory period and should be done every 6 months.[32–35,50,54–56,61] The NSAA and timed function tests have high validity and reliability, as well as correlation between tests across time, minimum clinically important differences, and predictive capabilities regarding functional motor changes that are important in monitoring clinical progression and assessing new and emerging therapies.[32–35,55,56,62] Identification of optimally responsive test ranges improves predictive capabilities, as in the 6-min walk test, in which understanding of interactions between age, baseline distance, and genetics might allow improved research design and inform clinical care.[35,63–66]

Prediction of functional change in clinical settings should be made in the context of a patient's capabilities, with awareness of limitations in effort-based assessments, potential interactions with musculoskeletal impairments such as contracture, and genetics.[66,67] Tests that predict potential upcoming changes can be used to guide proactive care, such as impairment-level interventions and future equipment needs. Specifically, before age 7 years, gains might occur in the 6-min walk test and timed function tests. After 7 years, a 6-min walk test result of less than 325 m, time to stand more than 30 sec, time to climb four stairs more than 8 s, 10-m walk or run time more than 10–12 s, and mean linearised NSAA 34 or less (raw score of nine) have been associated with greater functional decline in ambulation over the subsequent 12 months.[35,68] Functional assessment includes the assessment of activities of daily living and the need for adaptive equipment or assistive technology. Additionally, various tools can be used to assess quality of life.[69–72]

Increasing use of standardised testing in infants and young children with DMD is timely because of new potential for early diagnosis with newborn screening and the emergence of therapies that might work best if used in early childhood (appendix). The Bayley-III scale of infant development and Griffiths Mental Development Scales measure the rate of development in children, and both have the ability to highlight early developmental delays in children with DMD.[49,50,73] The NSAA, with revision, can be used to test children as young as 3 years.[51,74] Hip kinematics during gait are clinically meaningful outcome measures at 4–8 years.[75] Other measures assessing antigravity function, considered exploratory in DMD, include the Alberta Infant Motor Scale, Hammersmith Functional Motor Scale Expanded, and the Gross Motor Function Measure.[49,61,76] Assessment of, and intervention for, learning, attention, and sensory processing should begin at young ages.[77,78] In older individuals who are non-ambulatory, the Brooke Upper Extremity Scale, Egen Klassifikation scale, and elbow flexion and grip strength are responsive to change over 1–2 years,[57,79,80] with testing now including reachable workspace[52,81] and assessment of upper limb function (performance of upper limb test).[51,53,58]

Consistent use of the same functional measures by individual clinics is recommended for tracking change

over time, with inclusion of new assessments as appropriate. Assessment by rehabilitation specialists is recommended at least every 4–6 months throughout life, with more frequent assessment triggered by a clinical concern, a change in status, or specific needs.

Interventions

Direct physical, occupational, and speech and language therapy should be provided in outpatient and school settings and continue throughout adulthood, augmented by therapies provided during hospital admissions and at home (panel 2; appendix).

The goal of muscle extensibility and joint mobility management is to prevent or minimise contracture and deformity (panel 2). The inability to move a joint through its full range of motion, chronic static positioning, muscle imbalance about a joint, and fibrotic changes in muscles cause decreased muscle extensibility and joint contractures.[7] Restricted patterns of breathing and fibrosis of intercostal muscles decrease chest wall mobility. The maintenance of passive ranges of movement, muscle extensibility, chest wall mobility, and symmetry can optimise movement and functional positioning, maintain ambulation, prevent fixed contractures and deformities, optimise respiratory function, and maintain skin integrity.[7] Musculoskeletal management requires a team approach, with input from neuromuscular specialists, physical therapists, occupational therapists, rehabilitation physicians, orthotists, and orthopaedic surgeons.

Panel 2: **Rehabilitation assessments and interventions across all disease stages for patients with Duchenne muscular dystrophy**

Assessment

Multidisciplinary rehabilitation assessment every 6 months or more frequently if concerns, change in status, or specific needs are present (appendix)

Intervention

Direct treatment

Direct treatment implemented by physical therapists, occupational therapists, and speech-language pathologists, tailored to individual needs, stage of disease, response to therapy, and tolerance, provided across the patient's lifespan

Prevention of contracture and deformity

- Daily preventive home stretching 4–6 times per week; regular stretching at ankles, knees, and hips; stretching of wrists, hands, and neck later if indicated by assessment
- Stretching for structures known to be at risk of contracture and deformity* and those identified by assessment
- Orthotic intervention, splinting, casting, positioning, and equipment:
  - AFOs for stretching at night—might be best tolerated if started preventatively at a young age
  - AFOs for stretching or positioning during the day in non-ambulatory phases
  - Wrist or hand splints for stretching of long and wrist finger flexors/extensors —typically in non-ambulatory phases
  - Serial casting—in ambulatory or non-ambulatory phases
  - Passive/motorised supported standing devices—when standing in good alignment becomes difficult, if contractures are not too severe to prevent positioning or tolerance
  - KAFOs with locked knee joints—an option for late ambulatory and non-ambulatory stages
  - Custom seating in manual and motorised wheelchairs (solid seat, solid back, hip guides, lateral trunk supports, adductors, and head rest)
  - Power positioning components on motorised wheelchairs (tilt, recline, elevating leg rests, standing support, and adjustable seat height)

Exercise and activity

Regular submaximal, aerobic activity or exercise (eg, swimming and cycling) with assistance as needed, avoidance of eccentric and high-resistance exercise, monitoring to avoid overexertion, respect for the need for rests and energy conservation, and caution regarding potentially reduced cardiorespiratory exercise capacity as well as risk of muscle damage even when functioning well clinically

Falls and fracture prevention and management

- Minimisation of fall risks in all environments
- Physical therapist support of orthopaedics in rapid team management of long-bone fractures and provision of associated rehabilitation to maintain ambulation and/or supported standing capabilities

Management of learning, attentional, and sensory processing differences

Management in collaboration with team, based on concern and assessment

Assistive technology and adaptive equipment

Planning and education with assessment, prescription, training, and advocacy for funding

Participation

Participation in all areas of life supported at all stages

Pain prevention and management

Pain prevention and comprehensive management, as needed, throughout life

AFOs=ankle-foot orthoses. KAFOs=knee-ankle-foot orthoses. *Areas typically at risk of contracture and deformity include hip flexors, iliotibial bands, hamstrings, plantar flexors, plantar fascia, elbow flexors, forearm pronators, long wrist and finger flexors and extensors, lumbricals, and cervical extensors; isolated joint contracture into hip and knee flexion and plantar flexion, varus at hindfoot and forefoot, elbow flexion, wrist flexion or extension, and finger joints; and deformity of the vertebral column and chest wall including scoliosis, excessive kyphosis or lordosis, and decreased chest wall mobility.

Prevention of contracture and deformity requires daily passive stretching of joints, muscles, and soft tissues at risk of tightness; support of movement by decreasing the effects of gravity and optimising biomechanics to allow more active movement; manual therapy techniques and prolonged elongation of soft tissues; and optimal positioning, including individualised use of splinting, orthotic interventions, standing devices, serial casting, and custom seating and power positioning components in mobility devices.[7,82] A daily preventive home stretching programme[83] should begin before the loss of passive ranges of motion under the guidance of physical and occupational therapists. Stretching is recommended for areas known to be at risk of contracture or deformity (panel 2). Regular stretching of ankle, knee, and hip should begin soon after diagnosis and continue into adulthood. Stretching of the upper extremities is especially important after loss of ambulation.[7]

The appendix provides an overview of care considerations regarding various assistive and mobility devices, including ankle-foot orthoses, knee-ankle-foot orthoses, serial casting, standing devices, and manual and motorised mobility devices.[7] Power stand-and-drive motorised wheelchairs are now frequently used in place of knee-ankle-foot orthoses to support standing mobility. Such orthoses might still be an appropriate choice in some situations, but should be viewed as therapeutic rather than functional tools, supplementing rather than replacing motorised mobility.[84,85] Additionally, technological innovations—from simple devices (eg, elevated lap trays and adaptive straws) to more advanced technologies (eg, robotics, bluetooth capabilities that permit remote activation of devices, infrared environmental controls, smart phones, tablets, computers, and advanced access capabilities such as voice activation in the home)—can optimise function. Possible adaptive equipment and home renovations include patient hoists (lifts) for safe transfers, ramps, stair lifts, bathing and bathroom equipment or renovations, special beds and mattresses, and vehicle modifications. Personal care attendants can help to optimise independence and participation.

Physical therapists prescribe, monitor, and guide exercise, which can prevent an unnecessarily sedentary or immobile lifestyle and the associated problems of social isolation and overweight. However, the effects of exercise on muscle degeneration in dystrophinopathies, although not fully understood, can include damage due to structural fragility of muscles, metabolic abnormalities, nitric oxide abnormalities contributing to ischaemia during exercise, and reduced exercise capacity.[7,86–89] Eccentric muscle activity or exercise and high-resistance exercise or strength training should be avoided.[7,90] Submaximal aerobic exercise or activity has been recommended, especially early in the course of the disease—avoiding overexertion and overwork, and allowing adequate rest.[7] Swimming is highly recommended from the early ambulatory stage and can be frequently continued into adulthood.[7] Cycling has been recommended as a submaximal aerobic form of activity,[91,92] and assisted cycling and robotic-assisted movement can be used into adulthood. Safe physical activity can be supported by appropriate adaptive equipment and assistive technology.

Pain must be assessed and addressed in individuals at all ages.[7,59,93] Interventions require comprehensive team management, including physical therapy, postural correction, orthotic intervention and splinting, wheelchair and bed enhancements that allow independent weight shift, position change and pressure relief, and

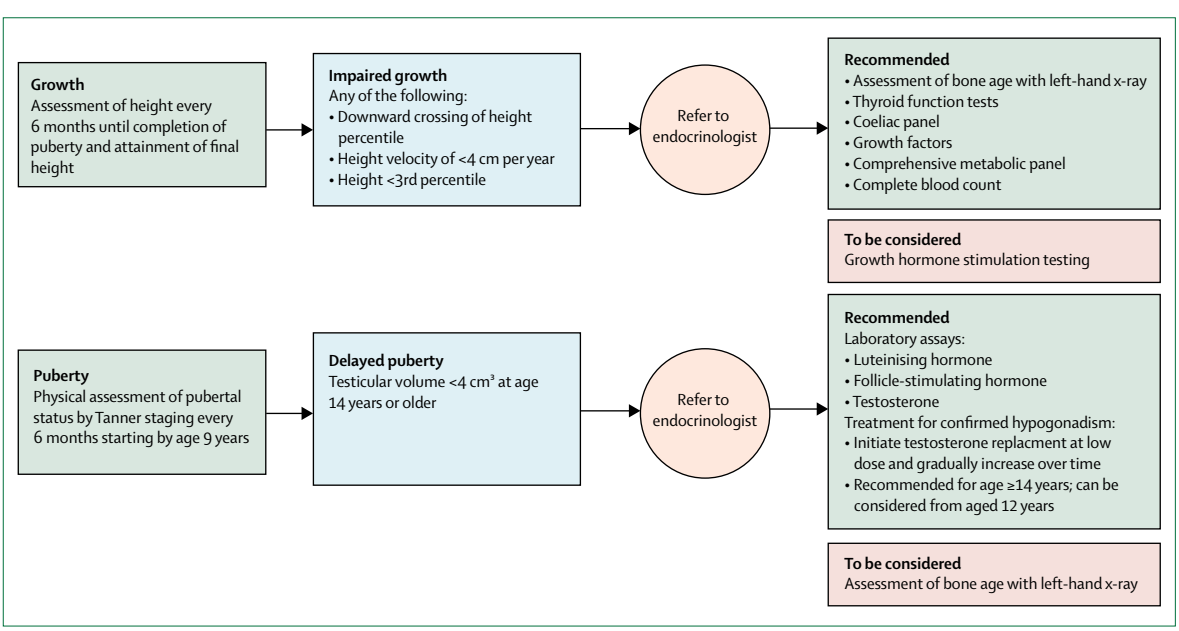

Figure 4: **Assessments and interventions for impaired growth and delayed puberty in patients with Duchenne muscular dystrophy**

pharmacological approaches. Back pain, particularly in the context of glucocorticoid treatment, should prompt assessment for vertebral fractures.[7] A detailed discussion of fracture prevention and management is presented in part 2 of this Review.

Endocrine management

The endocrine complications of DMD and its treatment include impaired growth, delayed puberty, and adrenal insufficiency. The goals of endocrine care are to monitor growth and development, identify and diagnose hormone deficiencies, provide endocrine hormone replacement therapy when indicated, and prevent a life-threatening adrenal crisis. A few relevant expert-opinion papers and reviews have been published,[94–96] but data are scarce on the safety and efficacy of growth hormone and testosterone therapy in individuals with DMD. The care considerations that follow are based on evidence and experience derived from use of these therapies in other diseases, with modifications for use in DMD (figure 4).

Growth

Impaired linear growth is common in individuals with DMD and exacerbated by glucocorticoid treatment.[39,97] Linear growth should be assessed every 6 months until completion of puberty and attainment of final height. Standing height is the most appropriate measure in ambulatory individuals. Height should be plotted and followed on a standardised growth curve. Additionally, regular assessment of growth using a non-standing height measure should begin during the ambulatory stage to allow more accurate assessment after individuals lose ambulation. Arm span, ulnar length, tibia length, knee height, and segmentally measured recumbent length have all been used to assess growth in non-ambulatory children;[98] however, none has been validated in the DMD population, and all require specialised training or specialised equipment. We suggest that each institution select and use the measure that works best in its particular clinical environment.

A decline in growth trajectory, as evidenced by downward crossing of height percentile or an annualised height velocity of less than 4 cm per year, is consistent with impaired linear growth and indicates the need for referral to an endocrinologist. Individuals with a height of less than the third percentile should be referred, irrespective of growth trajectory. Assessment of impaired linear growth should include standard screening tests to assess for endocrine hormone or other abnormalities associated with growth failure. Few data show the safety and efficacy of recombinant human growth hormone in the DMD population. One retrospective study found a short-term benefit on height velocity; however, some boys with DMD had side-effects such as intracranial hypertension, glucose intolerance, and progression of scoliosis.[99] None of the published studies on recombinant human growth hormone has followed patients to their final height, and no studies have been large enough to establish reliably whether recombinant human growth hormone therapy has a negative effect on muscle function or other adverse effects. Additionally, theoretical concerns have been raised that tall stature might be detrimental to muscle function in DMD.[100,101] Until more evidence is available, the routine use of recombinant human growth hormone to treat DMD-related growth failure is not recommended. Instead, the decision to treat with recombinant human growth hormone should be based on a thorough discussion of the potential risks and benefits of the therapy, and preferably reserved for individuals with abnormal growth hormone stimulation test results.

Puberty

Delayed puberty due to hypogonadism is a potential complication of glucocorticoid therapy and can be psychologically distressing, impairing quality of life. The absence of pubertal development by age 14 years requires prompt referral to an endocrinologist. Biochemical testing using appropriate paediatric or ultrasensitive assays should be done to confirm the diagnosis of hypogonadism in individuals with evidence of delayed puberty. A radiograph of the left hand to establish bone age should also be considered.

Testosterone replacement therapy is recommended to treat confirmed hypogonadism in patients older than 14 years and can be considered in boys older than 12 years on glucocorticoids with absent pubertal development. Although no clinical trials have specifically assessed the use of testosterone in boys with DMD, it is considered the standard of care to treat pathological pubertal delay in the paediatric population and is recommended for the treatment of glucocorticoid-induced hypogonadism in adult men.[102] The potential benefits of testosterone on emotional and physical health usually outweigh the potential side-effects, such as behavioural changes, acne, body odour, rapid growth spurt, and epiphyseal closure. A recent retrospective review found that testosterone was generally well tolerated and perceived to be beneficial by individuals with DMD and their families.[103]

In an attempt to mimic normal pubertal development, testosterone replacement should be initiated at a low dose and slowly increased to adult replacement doses over several years. Intramuscular or topical preparations can be used. Testosterone concentrations should be monitored closely in all individuals. Consideration should be given to assessment of lipids, haemoglobin, haematocrit, and blood glucose in treated individuals. A negative effect on an individual's functional status or cardiac function should prompt the clinician to consider discontinuing testosterone therapy or reducing the dose.

Adrenal insufficiency

Adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis is a rare but

life-threatening condition that can develop if glucocorticoids are stopped suddenly because of illness or discontinuation of therapy.[104] All individuals prescribed glucocorticoids should be educated about the signs, symptoms, and management of adrenal crisis and receive prescriptions for intramuscular hydrocortisone for emergency administration at home (50 mg for children <2 years; 100 mg for children or adults ≥2 years). Stress dosing with hydrocortisone at 50–100 mg/m² per day might also be required in the setting of severe illness, major trauma, or surgery in individuals taking more than 12 mg/m² per day of prednisone or deflazacort. Glucocorticoid therapy should not be discontinued abruptly but rather tapered over weeks to months to allow HPA axis recovery.[105] The PJ Nicholoff Steroid Protocol is an appropriate approach to glucocorticoid (steroid) tapering (figure 3).[36]

Gastrointestinal and nutritional management

Individuals with DMD often have gastrointestinal or nutritional complications, including weight gain or loss, dietary or nutrient imbalance, fluid imbalance, low bone density, swallowing dysfunction, and mandibular contracture.[106] Contributing factors include glucocorticoid treatment, decreased energy expenditure, and immobility.[107] These nutritional imbalances can negatively affect the respiratory, skeletal muscle, and cardiac systems.

The aim of nutritional care is to prevent overweight or obesity and undernutrition or malnutrition through regular assessment of growth and weight; it also aims to promote a healthy, balanced diet, with optimum intake of calories, protein, fluid, and micronutrients, especially calcium and vitamin D. Robust evidence-based nutrition research specific to DMD is lacking. Nutrition recommendations applicable to DMD are therefore adapted from those for the general population. The care team should include a registered dietitian nutritionist with appropriate experience, who should see an individual with DMD at every visit, beginning at diagnosis. More frequent monitoring by the dietitian nutritionist will be necessary during periods when weight gain or loss is anticipated. A physical therapist should be consulted to design and enact safe exercise programmes for individuals who are at risk of becoming overweight. A speech-language pathologist should be consulted to assess individuals for suspected dysphagia. A gastroenterologist should be consulted for management of constipation, gastroesophageal reflux, and gastrointestinal motility concerns, and when gastrostomy tube placement is needed. Figure 5 presents an overview of the recommended gastrointestinal and nutritional assessments and interventions.

Nutritional assessment and planning

At each clinic visit, the registered dietitian nutritionist should assess nutritional status, track weight and height, and create a specific nutritional plan. Good nutritional status is defined as weight for length, or body-mass index (BMI) for age, that falls between the tenth and 85th percentiles on standard growth charts. If BMI cannot be calculated because height cannot be measured, weight-for-age percentiles should be used. Individuals with DMD have altered body composition, so the use of standard growth charts is not optimal.

Patients and their family members should practice healthy, balanced eating as recommended in the current Dietary Guidelines for Americans.[108] Adequate fluid

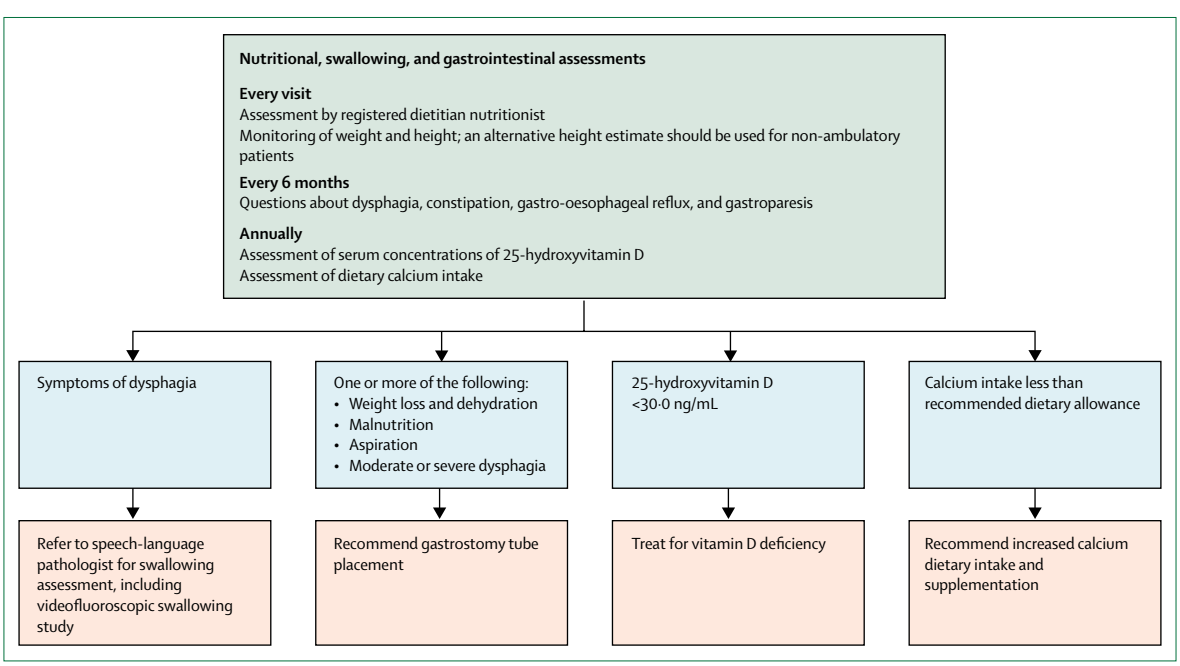

Figure 5: **Assessments and interventions for nutritional, swallowing, and gastrointestinal management in patients with Duchenne muscular dystrophy**

intake should be emphasised, to prevent dehydration, which increases the risk of constipation and renal dysfunction.[109] Panel 3 offers a general nutritional plan for people with DMD.[110]

Monitoring of bone health requires annual assessments of dietary calcium intake and serum 25-hydroxy-vitamin D concentration. If calcium intake is less than the recommended intake for age, or if serum 25-hydroxy-vitamin D decreases to less than 30 ng/mL, appropriate dietary intake and nutrient supplementation should be provided according to Institute of Medicine guidelines.[114] For more details, see the section on bone health and osteoporosis management in part 2 of this Review.

DMD-specific nutritional risks

Individuals with DMD are at risk of overweight or obesity early in life, with an increased risk of undernutrition or malnutrition as they approach adulthood (appendix).[115,116] In early childhood, glucocorticoid therapy increases the risk of overweight or obesity because of increased appetite and caloric intake, and sodium and fluid retention. Loss of ambulation leads to decreased activity, which reduces caloric needs and increases the risk of overweight or obesity. To address these risks, the clinician should create a nutritional plan that includes specific recommendations for calorie, protein, micronutrient, and fluid intake (panel 3). Caloric needs are estimated by calculating resting energy expenditure and adjusting for activity level (panel 3). Healthy eating habits, as suggested by the American Academy of Pediatrics Committee on Nutrition guidelines for the prevention of obesity, should be followed by the entire family (appendix).[117] If weight gain is excessive, an obesity management plan should be created that addresses both diet and physical activity.

For more on the **American Academy of Pediatrics** see https://www.aap.org/

Swallowing dysfunction (dysphagia) is common and frequently progressive in patients with DMD. Anticipatory assessment for dysphagia is important and should be done regularly.[118] Screening questions should focus on perceived difficulty with swallowing of liquids and solids, perception of food sticking in the throat, time necessary to eat an average meal, and interference of eating with quality of life.[119] If a patient responds to screening questions in the affirmative, the speech-language pathologist should be consulted for a comprehensive

Panel 3: General nutritional plan

This general nutritional plan, which is created from recommendations for the general healthy population and is not specific to patients with DMD, provides methods to assess energy, protein, fluid, and micronutrient requirements on the basis of dietary reference intakes. To meet the body's daily nutritional needs while minimising risk of chronic disease, adults should consume 45–65% of their total calories from carbohydrates, 20–35% from fat, and 10–35% from protein. The acceptable ranges for children are similar to those for adults, except that infants and younger children need a somewhat higher proportion of fat in their diets.[110]

Overall caloric needs

Overall caloric needs are based on total energy expenditure, which is equal to resting energy expenditure (REE) multiplied by the physical activity factor.

Indirect calorimetry provides the most accurate measure of REE, but REE can also be estimated in steroid-treated ambulatory boys with DMD (aged 10–17 years) by the Schofield weight equation (REE [kilocalories] = [17·7 × weight in kg + 657] × 4·182/1000).[111] Because of the decline in physical activity that accompanies a loss of ambulation, calorie needs can decrease substantially, and REE might be even lower than the REE before the loss-of-ambulation phase.

Physical activity factors for boys aged 3–18 years are sedentary (1·00), low active (1·13), active (1·26), and very active (1·42).

The calculated energy or caloric intake will need to be decreased if initial energy or caloric prescription does not result in weight maintenance or weight loss. If the goal is weight increase, the calculated energy or caloric intake will need to be increased.

Protein

Recommended dietary allowance for protein differs for boys and men according to age: a dietary allowance of 0·95 g/kg bodyweight per day is recommended for children aged 4–13 years; 0·85 g/kg per day is recommended for those aged 14–18 years; and 0·80 g/kg per day is recommended for men aged 19 years or older.

Fluids

Recommended fluid intake (total beverages, including drinking water) is based on weight or age.

Based on weight, the Holliday–Segar maintenance fluid method[112] recommends 100 mL/kg bodyweight for children who weigh 1–10 kg; 1000 mL + 50 mL for each kg over 10 kg for children who weigh 10–20 kg; and 1500 mL + 20 mL for each kg over 20 kg for children and adults who weigh more than 20 kg.

Based on age, the daily dietary reference intake values for fluids are 1·2 L (approximately 5 cups) for boys and girls aged 4–8 years; 1·8 L (approximately 8 cups) for boys aged 9–13 years; 2·6 L (approximately 11 cups) for boys aged 14–18 years; and 3·0 L (approximately 13 cups) for men aged 19 years or older.

Micronutrients

Recommended dietary allowance for age[113] should be followed, except in the case of vitamin D deficiency, which is defined as 25-hydroxyvitamin D of less than 30.0 ng/mL. A multivitamin or mineral supplement is necessary if calorie intake is low.

Search strategy and selection criteria

We searched Medline, Embase, Web of Science, and the Cochrane Library databases for peer-reviewed English-language articles published from Jan 1, 2006, to Sept 30, 2013, for the eight original topics and from Jan 1, 1990, to Sept 30, 2013, for the three new topics. The literature was searched using the key search terms "Duchenne" or "muscular dystrophy," or both, paired with one of 626 search terms (appendix). The literature search identified 1215 articles after duplicates were removed. Reviews, meta-analyses, case series, case reports, studies of animal models, and articles on unrelated diseases or Becker's muscular dystrophy only were excluded upon further review. Of the 672 remaining articles, the steering committee reviewed 430 articles that were potentially relevant to the update of the care considerations. The steering committee members then classified each one using the following criteria: (1) consistent with the existing care considerations; (2) conflicts with the existing care considerations; (3) requires an update to the care considerations; or (4) presents promising research. Articles that were identified as required for the update were used to create clinical scenarios in accordance with the RAND Corporation–University of California Los Angeles Appropriateness Method. Subject matter experts, with the assistance of RTI International, also continually updated the references during the development of the manuscript. Before publication, an updated literature search was done for articles published between Oct 1, 2013, and July 31, 2017, which identified 880 articles. Committee chairs reviewed 115 articles potentially relevant to care and updated the references and text as necessary.

assessment, including a videofluoroscopic swallowing study.[120]

Individuals often lose weight unintentionally before and during the onset of clinical symptoms of dysphagia. Their BMI or weight percentiles might decrease from the overweight or obese category into the normal range or into the underweight (malnutrition) range as a result of feeding difficulties and disease progression. Care considerations for reducing the risk of underweight or malnutrition during this transition period are provided in the appendix.

Early and ongoing discussion of gastrostomy tube feeding can facilitate timely intervention when clinically indicated. The family and care team should consider gastrostomy tube placement to be a necessary and positive intervention when progressive weakness interferes with self-feeding and swallowing. Indications for gastrostomy tube placement include malnutrition that is unresponsive to interventions to improve oral caloric intake, diagnosis of moderate or severe dysphagia, and inability to maintain adequate hydration. Gastrostomy tube feeding leads to stabilisation or improvement of nutritional status in undernourished individuals with DMD.[121] Assessment of the benefits of gastrostomy tube feeding should be discussed in the context of respiratory, cardiac, and anaesthetic risks of the procedure.

Common gastrointestinal problems

Constipation is a very frequent complication of DMD.[122] Risk factors include decreased colonic transit time, immobility, abdominal muscle weakness, and dehydration (panel 3). Daily treatment with osmotic laxatives such as polyethylene glycol, milk of magnesia, or lactulose might be necessary. Retrograde enemas might be helpful if faecal impaction occurs.

In DMD, risk factors for gastro-oesophageal reflux include oesophageal dysmotility, delayed gastric emptying time, glucocorticoid therapy, and scoliosis.[123] Treatment of gastroesophageal reflux consists of gastric acid suppression using histamine-2 receptor antagonists such as ranitidine, or proton-pump inhibitors such as lansoprazole or omeprazole. The benefits of proton-pump inhibitors must be balanced against potential risks, including a higher incidence of community-acquired pneumonia, chronic kidney disease, and bone fracture.[124,125] Dietary approaches include eating smaller, more frequent meals and decreasing dietary fat intake.

As skeletal muscle weakness progresses in individuals with DMD, a delay in gastric emptying (gastroparesis) can occur,[123] which can lead to postprandial abdominal pain, nausea, vomiting, early satiety, and loss of appetite. Gastric emptying time can be assessed using a scintigraphic gastric emptying scan. Treatment options include dietary modification, pharmacological therapy, and postpyloric feeding via a gastrojejunal feeding tube.

Conclusions and future directions

In part 1 of this three-part update of the DMD care considerations, we have presented guidance on diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal management. Highlights of the new care considerations include guidance on the care of female carriers of DMD; an overview of new molecular and genetic therapies; advances in rehabilitation assessments and the emergence of more advanced, technologically enabled rehabilitation therapies; new guidance on endocrine problems, including growth, puberty, and adrenal insufficiency; and new insights into the anticipation and management of DMD-specific nutritional complications, such as obesity in association with glucocorticoid therapy or loss of ambulation, and malnutrition in the advanced stages of DMD.

The possibility of newborn screening and the anticipated emergence of genetic and molecular disease-modifying treatments for DMD mean that earlier initiation of treatment will become increasingly important in the future. However, the optimum timing for initiation of new therapies will be a key factor in decisions to implement newborn screening for DMD. Non-invasive prenatal testing for DMD is likely to become clinically available, allowing earlier identification of affected fetuses in women without a family history of DMD.[126]

New dystrophin restorative therapies are becoming available, with more expected to follow, and more data are emerging on the best glucocorticoid regimens for patients with DMD.[15] Future care considerations will need to address the role of the new compounds in the overall management of DMD, especially in the context of the

proven benefit of long-term glucocorticoid therapy. When some of these new therapies have been proven safe and effective, treatment for DMD can be personalised, with selection of the best combination of therapies for each individual's particular mutation. In terms of endocrine management, RCTs are needed to better understand the risks and benefits of growth hormone and testosterone therapy and to clarify the best indications, timing, and dosing regimens.

Improved clinical and functional assessments for rehabilitation management continue to be developed, with expansion across the lifespan. With advances in technology, new therapies will probably be assessed increasingly through activity monitoring in combination with measurements of new, clinically meaningful biomarkers.[127] Robotics and other rapid advances in technology will improve independence, participation, and quality of life. Emerging therapies such as dystrophin-restorative therapies might improve exercise or activity capacity and safety. Interventions provided by physical therapists, occupational therapists, speech-language pathologists, and orthotists, alongside new technologies, will optimise musculoskeletal management and function.[128]

Finally, for gastrointestinal and nutritional management, research is needed on resting energy expenditure (measured by indirect calorimetry) and total energy expenditure (measured by the doubly labelled water method) to assess energy expenditure or kilocalorie needs for individuals with DMD. Specific nutritional strategies, such as the potential utility of a protein-enriched or fructose-enriched diet, or branched-chain aminoacid supplementation,[129] and the influence of nutritional status on DMD outcomes (life expectancy, function, and quality of life) need to be better understood. More research is needed to develop DMD-specific growth charts, as well as accurate techniques to establish body composition in patients with DMD. The unique determinants of obesity in boys with DMD should be used to guide more feasible obesity prevention and management strategies, including pharmacological options. The development of safe and effective physical activity prescriptions could positively affect nutritional status, mobility, and social engagement throughout the life of patients with DMD.

Contributors

DJB, KB, CMB, SDA, AB, DB, LEC, PRC, SH, SP, NS, JT, KRW, LMW, and DRW provided intellectual expertise in the study design, generation and interpretation of data, review of the literature, writing of the Review, and the decision to publish. DJB, aided by CMB and NS, drafted and edited the article and approved the final version.

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Declaration of interests

DJB was a paid consultant for Hill-Rom Corporation and has US patents (8651107, 8844530, and 9795752) for respiratory devices, as well as related international patents and patent applications. KB was a consultant for Solid Ventures, Catabasis, LGC Ltd, Bristol-Myers Squibb, PTC therapeutics, GLC Research, Eli Lilly, and Publicis Life Brands Resolute; she has received grant support from PTC Therapeutics. SDA is a principal investigator for multicentre clinical trials sponsored by PTC Therapeutics and Sarepta Pharmaceuticals. LEC has received personal fees for speaking and participating in research supported by Genzyme Corporation of Sanofi; she has participated in research with CINRG (Cooperative International Neuromuscular Research Group), Enobia Pharma Inc/Alexion, Robertson Foundation, GlaxoSmithKline, Eli Lilly, Valerion, Pfizer, Prosensa, BioMarin, Ionis, Ultragenyx, Roivant Sciences, Therapeutic Research in Neuromuscular Disorders Solutions, NS Pharma, and the Marcus Foundation. PRC has received personal fees from Pfizer for serving on a data and safety monitoring board and consulting on study design, and from NS Pharma for FDA preparation; he has received grant support from Amicus, NS Pharma, and Sanofi/Genzyme; and he has received meeting support from Sanofi/Genzyme. KRW is a paid consultant for Myotherix and has received research funding from Sarepta, Pfizer, and Roche. LMW has received grant support and honoraria from Novartis and Amgen. DRW is a paid consultant for Health Research Inc and Marathon Pharmaceuticals. All other authors declare no competing interests.

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