Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care

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Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care

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Optimum management of Duchenne muscular dystrophy (DMD) requires a multidisciplinary approach that focuses on anticipatory and preventive measures as well as active interventions to address the primary and secondary aspects of the disorder. Implementing comprehensive management strategies can favourably alter the natural history of the disease and improve function, quality of life, and longevity. Standardised care can also facilitate planning for multicentre trials and help with the identification of areas in which care can be improved. Here, we present a comprehensive set of DMD care recommendations for management of rehabilitation, orthopaedic, respiratory, cardiovascular, gastroenterology/nutrition, and pain issues, as well as general surgical and emergency-room precautions. Together with part 1 of this Review, which focuses on diagnosis, pharmacological treatment, and psychosocial care, these recommendations allow diagnosis and management to occur in a coordinated multidisciplinary fashion.

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Introduction

In part 1 of this Review, the importance of multidisciplinary care was underscored in the context of diagnosis and pharmacological and psychosocial management of Duchenne muscular dystrophy (DMD), emphasising that no one aspect of the care of this disease can be taken in isolation.[1] This model of care emphasises the value of multidisciplinary involvement to anticipate early changes in many systems and to manage the wide spectrum of complications that can be predicted in DMD. We applied this model of care to the patient and family across the different stages of the disease. The optimum delivery of care by rehabilitation, cardiovascular, gastroenterology/nutrition, orthopaedic/surgical, and respiratory specialties is presented in this second part of the Review. As before, the RAND Corporation–University of California Los Angeles Appropriateness Method was used[2] (full details of the methods are described in part 1 of this Review[1]).

Management of muscle extensibility and joint contractures

Decreased muscle extensibility and joint contractures in DMD occur as a result of various factors, including loss of ability to actively move a joint through its full range of motion, static positioning in a position of flexion, muscle imbalance about a joint, and fibrotic changes in muscle tissue.[3–8] The maintenance of good ranges of movement and bilateral symmetry are important to allow optimum movement and functional positioning, to maintain ambulation, prevent development of fixed deformities, and maintain skin integrity.[9–14]

The management of joint contractures requires input from neuromuscular specialists, physical therapists, rehabilitation physicians, and orthopaedic surgeons.[15,16] Programmes to prevent contractures are usually monitored and implemented by a physical therapist and tailored to individual needs, stage of the disease, response to therapy, and tolerance. Local care needs to be augmented by guidance from a specialist every 4 months.

Physical therapy interventions

Stretching and positioning

Effective stretching of the musculotendinous unit requires a combination of interventions, including active stretching, active-assisted stretching, passive stretching, and prolonged elongation using positioning, splinting, orthoses, and standing devices.[9,10,12,17–20] As standing and walking become more difficult, standing programmes are recommended.

Active, active-assisted, and/or passive stretching to prevent or minimise contractures should be done a minimum of 4–6 days per week for any specific joint or muscle group. Stretching should be done at home and/or school, as well as in the clinic.

During both the ambulatory and non-ambulatory phases, regular stretching at the ankle, knee, and hip is necessary. During the non-ambulatory phase, regular stretching of the upper extremities, including the long finger flexors and wrist, elbow, and shoulder joints, also becomes necessary. Additional areas that require stretching can be identified by individual examination.

Assistive devices for musculoskeletal management

Orthoses

Prevention of contractures also relies on resting orthoses, joint positioning, and standing programmes. Resting ankle–foot orthoses (AFOs) used at night can help to prevent or minimise progressive equinus contractures and are appropriate throughout life.[6,17–19,21,22] AFOs should be custom-moulded and fabricated for comfort and optimum foot and ankle alignment. Knee–ankle–foot orthoses (KAFOs; eg, long leg braces or callipers) for prevention of contracture and deformity can be of value in the late ambulatory and early non-ambulatory stages to allow standing and limited ambulation for therapeutic purposes,[23] but might not be well tolerated at night.[6] Use of AFOs during the daytime can be appropriate for full-time wheelchair users. Resting hand splints for patients with tight long finger flexors are appropriate.

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Standing devices

A passive standing device for patients with either no or mild hip, knee, or ankle contractures is necessary for late ambulatory and early non-ambulatory stages. Many advocate continued use of passive standing devices or a power standing wheelchair into the late non-ambulatory stage if contractures are not too severe to restrict positioning and if devices are tolerable.[24]

Surgical intervention for lower-limb contractures

No unequivocal situations exist in which lower-limb contracture surgery is invariably indicated. If lower-limb contractures are present despite range-of-motion exercises and splinting, there are certain scenarios in which surgery can be considered.[15,25–32] In such cases, the approach must be strictly individualised.

Joints most amenable to surgical correction, and even subsequent bracing, are the ankles, and to a slightly lesser extent, the knees. The hip responds poorly to surgery for fixed flexion contractures and cannot be effectively braced. Surgical release or lengthening of the iliopsoas muscle and other hip flexors might further weaken these muscles and make the patient unable to walk, even with contracture correction. In ambulant patients, hip deformity often corrects itself if knees and ankles are straightened because hip flexion and lumbar lordosis might be compensatory and not fixed.

Various surgical options exist, none of which could be recommended above any other. Options for surgery will depend on individual circumstances, but there can be a role for surgery in the ambulatory and non-ambulatory phases.

Early ambulatory phase

Procedures for early contractures including heel-cord (tendo-Achillis) lengthenings for equinus contractures, hamstring tendon lengthenings for knee-flexion contractures, anterior hip-muscle releases for hip-flexion contractures, and even excision of the iliotibial band for hip-abduction contractures have been performed in patients as young as 4–7 years.[25,26] Some clinics even recommend that the procedures are done before contractures develop.[25,26] However, this approach, developed 20–25 years ago in an attempt to balance musculature when muscle strength is good,[25] is not widely practised today but does still have some proponents.

Middle ambulatory phase

Interventions in this phase are designed to prolong ambulation because a contracted joint can limit walking, even if overall limb musculature has sufficient strength. There is some evidence to suggest that walking can be prolonged by surgical intervention for 1–3 years,[15,25–27,30–32] but consensus on surgical correction of contractures for prolonging ambulation is difficult because it is hard to assess objectively the results reported. Non-operated patients who are not on steroids lose ambulation over a wide range of ages. Consequently, use of mean age as a comparator for a particular intervention is not statistically relevant if small numbers are compared. We found that few studies have addressed the fact that, rather than a sudden loss of ambulation, walking ability gradually decreases over a 1–2-year period. This makes it difficult to assess prolongation of walking with specific interventions. Prolonging ambulation by use of steroids has, for the moment, further increased uncertainty of the value of contracture corrective surgery. Bearing these considerations in mind, certain recommendations can be offered to prolong the period of walking, irrespective of steroid status. Muscle strength and range of motion around individual joints should be considered before deciding on surgery.

Approaches to lower-extremity surgery to maintain walking include bilateral multi-level (hip–knee–ankle or knee–ankle) procedures, bilateral single-level (ankle) procedures, and, rarely, unilateral single-level (ankle) procedures for asymmetric involvement.[15,25–32] The surgeries involve tendon lengthening, tendon transfer, tenotomy (cutting the tendon), along with release of fibrotic joint contractures (ankle) or removal of tight fibrous bands (iliotibial band at lateral thigh from hip to knee). Single-level surgery (eg, correction of ankle equinus deformity >20°) is not indicated if there are knee flexion contractures of 10° or greater and quadriceps strength of grade 3/5 or less. Equinus foot deformity (toe-walking) and varus foot deformities (severe inversion) can be corrected by heel-cord lengthening and tibialis posterior tendon transfer through the interosseous membrane onto the dorsolateral aspect of the foot to change plantar flexion–inversion activity of the tibialis posterior to dorsiflexion–eversion.[15,27–29,32] Hamstring lengthening behind the knee is generally needed if there is a knee-flexion contracture of more than 15°.

After tendon lengthening and tendon transfer, postoperative bracing might be needed, which should be discussed preoperatively. Following tenotomy, bracing is always needed. When surgery is performed to maintain walking, the patient must be mobilised using a walker or crutches on the first or second postoperative day to prevent further disuse atrophy of lower-extremity muscles. Post-surgery walking must continue throughout limb immobilisation and post-cast rehabilitation. An experienced team with close coordination between the orthopaedic surgeon, physical therapist, and orthotist is required.

Late ambulatory phase

Despite promising early results,[30–32] surgery in the late ambulatory phase has generally been ineffective and served to obscure the benefits gained by more timely and earlier interventions.

Early non-ambulatory phase

In the early non-ambulatory phase, some clinics perform extensive lower-extremity surgery and bracing to regain

ambulation within 3–6 months after walking ability is lost. However, this is generally ineffective and not currently considered appropriate.

Late non-ambulatory phase

Severe equinus foot deformities of more than 30° can be corrected with heel-cord lengthening or tenotomy and varus deformities (if present) with tibialis posterior tendon transfer, lengthening, or tenotomy. This is done for specific symptomatic problems, generally to alleviate pain and pressure, to allow the patient to wear shoes, and to correctly place the feet on wheelchair footrests.[27,28] This approach is not recommended as routine.

Assistive/adaptive devices for function

AFOs are not indicated for use during ambulation because they typically limit compensatory movements needed for efficient ambulation, add weight that can compromise ambulation, and make it difficult to rise from the floor. During the late ambulatory stage, a KAFO with locked knee might prolong ambulation but is not essential.

During the early ambulatory stage, a lightweight manual mobility device is appropriate to allow the child to be pushed on occasions when long-distance mobility demands exceed endurance. In the late ambulatory stage, an ultra lightweight manual wheelchair with solid seat and back, seating to support spinal symmetry and neutral lower extremity alignment, and swing-away footrests is necessary. In the early non-ambulatory stage, a manual wheelchair with custom seating and recline features might serve as a necessary back-up to a powered wheelchair.

As functional community ambulation declines, a powered wheelchair is advocated. Increasingly, rehabilitation providers recommend custom seating and power-positioning components for the initial powered wheelchair, to include a headrest, solid seat and back, lateral trunk supports, power tilt and recline, power-adjustable seat height, and power-elevating leg rests (with swing-away or flip-up footrests to facilitate transfers). Some recommend power standing chairs. Additional custom seating modifications could include a pressure-relieving cushion, hip guides, and flip-down knee adductors.

As upper-extremity strength declines, referral to a specialist in rehabilitation assistive technology is necessary for evaluation of alternative computer or environmental control access, such as a tongue-touch control system, switch scanning, infrared pointing, or eye-gaze selection.[33–35]

Other adaptations in the late ambulatory and non-ambulatory stages could include an elevated lap tray, with adaptive straw, hands-free water pouch, and/or turntable (indicated if the hand cannot be brought to the mouth or if biceps strength is grade 2/5), power adjustable bed with pressure relief cushion or mattress, bathing and bathroom equipment, and transfer devices, including a hydraulic patient lift, ceiling lift (hoist), slide sheets, and environmental control options.

Recommendations for exercise

Limited research has been carried out on the type, frequency, and intensity of exercise that is optimum in DMD.[36–48] Many recommendations are made on the basis of the known pathophysiology and animal studies showing contraction-induced muscle injury in dystrophinopathy.[49]

Submaximum, aerobic exercise/activity is recommended by some clinicians, especially early in the course of the disease when residual strength is higher, whereas others emphasise avoidance of overexertion and overwork weakness.[44] High-resistance strength training and eccentric exercise are inappropriate across the lifespan owing to concerns about contraction-induced muscle-fibre injury. To avoid disuse atrophy and other secondary complications of inactivity, it is necessary that all boys who are ambulatory or in the early non-ambulatory stage participate in regular submaximum (gentle) functional strengthening/activity, including a combination of swimming-pool exercises and recreation-based exercises in the community. Swimming, which might have benefits for aerobic conditioning and respiratory exercise, is highly recommended from the early ambulatory to early non-ambulatory phases and could be continued in the non-ambulatory phase as long as it is medically safe. Additional benefits might be provided by low-resistance strength training and optimisation of upper body function. Significant muscle pain or myoglobinuria in the 24-h period after a specific activity is a sign of overexertion and contraction-induced injury, and if this occurs the activity should be modified.[50]

Skeletal management

Spinal management

Patients not treated with glucocorticoids have a 90% chance of developing significant progressive scoliosis[28,51] and a small chance of developing vertebral compression fractures due to osteoporosis. Daily glucocorticoid treatment has been shown to reduce the risk of scoliosis;[52,53] however, risk of vertebral fracture is increased.[54,55] Whether glucocorticoids reduce the risk of scoliosis in the long term or simply delay its onset is, as yet, unclear. Spinal care should involve an experienced spinal surgeon, and comprises scoliosis monitoring, support of spinal/pelvic symmetry and spinal extension by the wheelchair seating system, and (in patients using glucocorticoids, in particular) monitoring for painful vertebral body fractures.

Monitoring for scoliosis should be by clinical observation through the ambulatory phase, with spinal radiography warranted only if scoliosis is observed. In the non-ambulatory phase, clinical assessment for scoliosis is essential at each visit. Spinal radiography is indicated as a baseline assessment for all patients around the time that wheelchair dependency begins with a sitting anteroposterior full-spine radiograph and lateral projection film. An anteroposterior spinal radiograph is warranted annually for curves of less than 15–20° and every 6 months for curves of more than 20°, irrespective

of glucocorticoid treatment, up to skeletal maturity. Gaps of more than a year between radiographs increase the risk of missing a worsening of scoliosis. After skeletal maturity, decisions about radiographs again relate to clinical assessment.

Spinal fusion is done to straighten the spine, prevent further worsening of deformity, eliminate pain due to vertebral fracture with osteoporosis, and slow the rate of respiratory decline.[28,56] Anterior spinal fusion is inappropriate in DMD. Posterior spinal fusion is warranted only in non-ambulatory patients who have spinal curvature of more than 20°, are not on glucocorticoids, and have yet to reach skeletal maturity.[28,57,58] In patients on glucocorticoids, surgery might also be warranted if curve progression continues and is associated with vertebral fractures and pain after optimisation of medical therapy to strengthen the bones, irrespective of skeletal maturation.

When deciding the extent of surgical stabilisation for scoliosis, if there is pelvic obliquity of more than 15°, it is necessary to perform correction and stabilisation with bone fusion from the upper thoracic region to the sacrum.[59,60] If there is no pelvic obliquity, these recommendations can also be used, but fusion to the fifth lumbar vertebra is also effective. Use of a thoraco–lumbar–sacral orthosis is inappropriate if surgery is to be done, but it can be considered for patients unable to undergo spinal fusion.

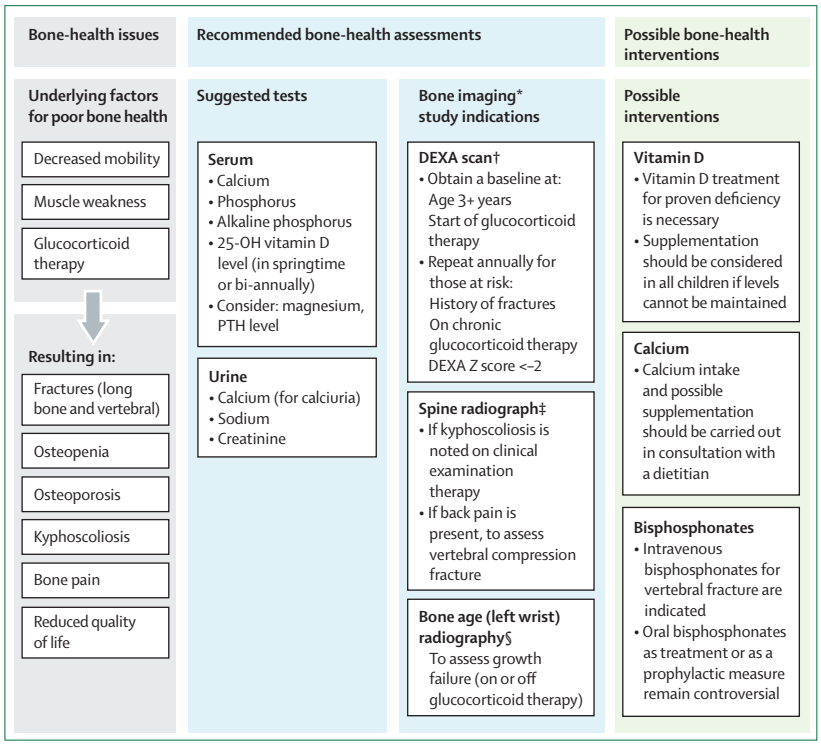

Figure 1: **Bone-health management**
Information provided in this figure was not derived from RAND Corporation–University of California Los Angeles Appropriateness Method data and was produced solely using expert discussion. DEXA=dual-energy x-ray absorptiometry. PTH=parathyroid hormone. *All imaging assessments should be done at a facility capable of performing and interpreting age-appropriate studies. †A DEXA scan is a better measure than plain film radiographs for detection of osteopenia or osteoporosis. DEXA scans, to assess bone mineral content or body composition, need to be interpreted as a *Z* score for children and a *T* score for adults (compared with age-matched and sex-matched controls). ‡Spine radiographs (posterior/anterior and lateral views) are used for the assessment of scoliosis, bone pain, and compression fractures. It is preferable to obtain them in the standing position, especially if bone pain is the presenting symptom. Useful information can still be obtained in the sitting position for the non-weight-bearing patient. §Bone-age measurements should be done in patients with growth failure (height for age <5% percentile or if linear growth is faltering). If abnormal (>2 SD below the mean), a referral needs to be made to a paediatric endocrinologist.

Bone-health management

Bone health is an important part of the lifelong care of patients with DMD. Two previous consensus statements have been published.[61,62] Figure 1 outlines the risk factors, possible assessments, and treatment strategies for patients who have DMD. Awareness of potential problems and means to assess these problems and interventions are important, preferably in conjunction with local specialists in bone health and endocrine assessment. This is an area in which further research is needed to establish parameters for best practice.

Fracture management

Fractures are common in DMD and an increased frequency of fractures has been observed with glucocorticoid treatment.[63] Taking into account the guidelines for safe anaesthesia in DMD, internal fixation is warranted for severe lower-limb fractures in ambulatory patients to allow prompt rehabilitation and the greatest possible chance of maintaining ambulation. In the non-ambulatory patient, the requirement for internal fixation is less acute. Splinting or casting of a fracture is necessary for the non-ambulatory patient, and is appropriate in an ambulatory patient if it is the fastest and safest way to promote healing and does not compromise ambulation during healing.

Respiratory management

The aim of respiratory care is to allow timely prevention and management of complications. A structured, proactive approach to respiratory management that includes use of assisted cough and nocturnal ventilation has been shown to prolong survival.[64–66] Patients with DMD are at risk of respiratory complications as their condition deteriorates due to progressive loss of respiratory muscle strength. These complications include ineffective cough,[67–75] nocturnal hypoventilation, sleep disordered breathing, and ultimately daytime respiratory failure.[76–84]

Guidelines for respiratory management in DMD have already been published.[85] The care team must include a physician and therapist with skill in the initiation and management of non-invasive ventilation and associated interfaces,[36,86–91] lung-volume recruitment techniques,[92–94] and manual and mechanically assisted cough.[95–102] Assessments and interventions will need to be re-evaluated as the condition changes (figures 2 and 3, panel 1). In the ambulatory stage, minimum assessment of pulmonary function (such as measurement of forced vital capacity at least annually) allows familiarity with the equipment and

the team can assess the maximum respiratory function achieved. The main need for pulmonary care is in the period after the loss of independent ambulation. The pulmonary section of figure 2 in part 1 of this Review links these assessments and interventions to the various stages of disease, and comprises a respiratory action plan that should be enacted with increasing disease severity.[1] Although the expert panel recognises that assisted ventilation via tracheostomy can prolong survival, the schema is intended to advocate strongly for the use of non-invasive modes of assisted ventilation. Particular attention to respiratory status is required around the time of planned surgery (see below).

Immunisation with 23-valent pneumococcal polysaccharide vaccine is indicated for patients aged 2 years and older. Annual immunisation with trivalent inactivated influenza vaccine is indicated for patients 6 months of age and older. Neither the pneumococcal vaccine nor the influenza vaccine are live vaccines, so can be administered to patients treated with glucocorticoids, but the immune response to vaccination might be diminished. Up-to-date and detailed information on immunisation indications, contraindications, and schedules can be obtained from various sources, including the American Academy of Pediatrics and the US Centers for Disease Control and Prevention (CDC).

During an established infection, in addition to use of manually and mechanically assisted cough, antibiotics are necessary, irrespective of oxygen saturation if positive evidence of an infection is established on culture, and irrespective of culture results if pulse oximetry remains below 95% in room air. Supplemental oxygen therapy should be used with caution because oxygen therapy can apparently improve hypoxaemia while masking the underlying cause, such as atelectasis or hypoventilation. Oxygen therapy might impair central respiratory drive and exacerbate hypercapnia.[91,95,103] If a patient has hypoxaemia due to hypoventilation, retained respiratory secretions, and/or atelectasis, then manual and mechanically assisted cough and non-invasive ventilatory support are necessary.[66] Substitution of these methods by oxygen therapy is dangerous.[66]

Cardiac management

Cardiac disease in DMD manifests most often as a cardiomyopathy and/or cardiac arrhythmia.[104–106] The myocardium at autopsy displays areas of myocyte hypertrophy, atrophy, and fibrosis.[107] Progressive cardiomyopathy is currently a major source of morbidity and mortality in DMD and Becker muscular dystrophy, particularly since advances have been made in the treatment of the muscle disease and pulmonary function.[65,85,89,108] The natural history of cardiac disease in DMD requires further study, especially to define its onset more precisely with newer imaging technologies; however, there is clearly disease in the myocardium long before the onset of clinical symptoms.[104,109–112]

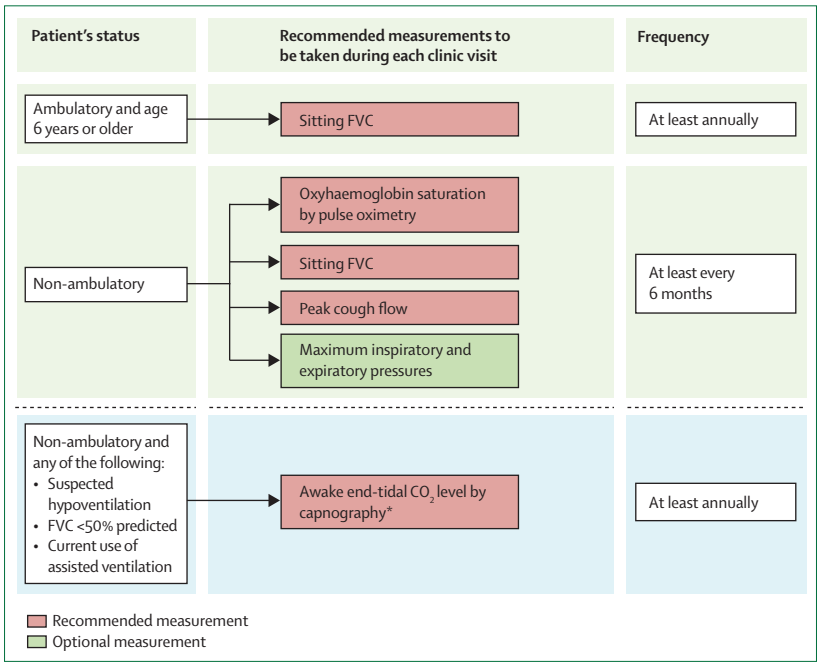

Figure 2: **Respiratory assessment (in the clinic) of patients with Duchenne muscular dystrophy**
FVC=forced vital capacity. *Also measure end-tidal CO_2 any time that a patient with an FVC of <50% predicted has a respiratory infection.

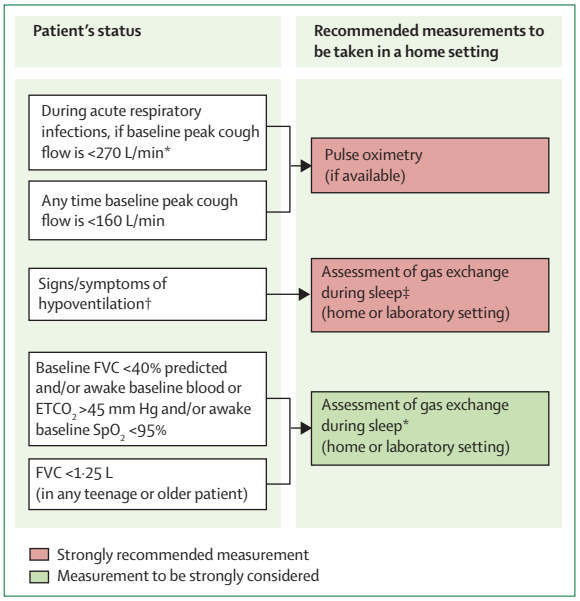

Figure 3: **Respiratory assessment (at home) of patients with Duchenne muscular dystrophy**
$ETCO_2$=end-tidal CO_2. FVC=forced vital capacity. SpO_2=pulse oximetry. *All specified threshold values of peak cough flow and maximum expiratory pressure apply to older teenage and adult patients. †Signs/symptoms of hypoventilation include fatigue, dyspnoea, morning or continuous headaches, sleep dysfunction (frequent nocturnal awakenings [>3], difficult arousal), hypersomnolence, awakenings with dyspnoea and tachycardia, difficulty with concentration, frequent nightmares. ‡Dual-channel oximetry-capnography in the home is strongly recommended, but other recommended methods include home oximetry during sleep and polysomnography, the method of choice being determined by local availability, expertise, and clinician preference.

For the **American Academy of Pediatrics** see http://aapredbook.aappublications.org/

For the **CDC's information on influenza** see http://www.cdc.gov/flu/

Panel 1: **Respiratory interventions indicated in patients with Duchenne muscular dystrophy**

Step 1: volume recruitment/deep lung inflation technique

Volume recruitment/deep lung inflation technique (by self-inflating manual ventilation bag or mechanical insufflation–exsufflation) when FVC <40% predicted

Step 2: manual and mechanically assisted cough techniques

Necessary when:

- Respiratory infection present and baseline peak cough flow <270 L/min*
- Baseline peak cough flow <160 L/min or maximum expiratory pressure <40 cm water
- Baseline FVC <40% predicted or <1·25 L in older teenager/adult

Step 3: nocturnal ventilation

Nocturnal ventilation† is indicated in patients who have any of the following:

- Signs or symptoms of hypoventilation (patients with FVC <30% predicted are at especially high risk)
- A baseline SpO_2 <95% and/or blood or end-tidal CO_2 >45 mm Hg while awake
- An apnoea–hypopnoea index >10 per hour on polysomnography or four or more episodes of SpO_2 <92% or drops in SpO_2 of at least 4% per hour of sleep

Optimally, use of lung volume recruitment and assisted cough techniques should always precede initiation of non-invasive ventilation

Step 4: daytime ventilation

In patients already using nocturnally assisted ventilation, daytime ventilation‡ is indicated for:

- Self extension of nocturnal ventilation into waking hours
- Abnormal deglutition due to dyspnoea, which is relieved by ventilatory assistance
- Inability to speak a full sentence without breathlessness, and/or
- Symptoms of hypoventilation with baseline SpO_2 <95% and/or blood or end-tidal CO_2 >45 mm Hg while awake

Continuous non-invasive assisted ventilation (with mechanically assisted cough) can facilitate endotracheal extubation for patients who were intubated during acute illness or during anaesthesia, followed by weaning to nocturnal non-invasive assisted ventilation, if applicable

Step 5: tracheostomy

Indications for tracheostomy include:

- Patient and clinician preference§
- Patient cannot successfully use non-invasive ventilation
- Inability of the local medical infrastructure to support non-invasive ventilation
- Three failures to achieve extubation during critical illness despite optimum use of non-invasive ventilation and mechanically assisted cough
- The failure of non-invasive methods of cough assistance to prevent aspiration of secretions into the lung and drops in oxygen saturation below 95% or the patient's baseline, necessitating frequent direct tracheal suctioning via tracheostomy

FVC=forced vital capacity. SpO_2=pulse oximetry. *All specified threshold values of peak cough flow and maximum expiratory pressure apply to older teenage and adult patients. †Recommended for nocturnal use: non-invasive ventilation with pressure cycled bi-level devices or volume cycled ventilators or combination volume-pressure ventilators. In bi-level or pressure support modes of ventilation, add a back-up rate of breathing. Recommended interfaces include a nasal mask or a nasal pillow. Other interfaces can be used and each has its own potential benefits. ‡Recommended for day use: non-invasive ventilation with portable volume cycled or volume-pressure ventilators; bi-level devices are an alternative. A mouthpiece interface is strongly recommended during day use of portable volume-cycled or volume-pressure ventilators, but other ventilator-interface combinations can be used depending on clinician preference and patient comfort. §However, the panel advocates the long-term use of non-invasive ventilation up to and including 24 h/day in eligible patients.

In the traditional reactive approach, failure to see a cardiac specialist until late in the disease, after clinical manifestations of cardiac dysfunction are evident, have led to late treatment and poor outcomes.[104] Clinical manifestations of heart failure (fatigue, weight loss, vomiting, abdominal pain, sleep disturbance, and inability to tolerate daily activities) are often unrecognised until very late owing to musculoskeletal limitations.[104]

Two overlapping sets of published guidelines on the cardiac care of patients who have DMD are currently available.[104,113] The care team should include a cardiac specialist who should be involved with the patient and family after confirmation of the diagnosis, not only to manage cardiomyopathy, but also to initiate a relationship to ensure long-term cardiovascular health.

Baseline assessment of cardiac function should be done at diagnosis or by the age of 6 years, especially if this can be done without sedation. Clinical judgment should be used for patients under the age of 6 years who require sedation. The recommendation to initiate echocardiographic screening at the time of diagnosis or by the age of 6 years was judged necessary, even though the incidence of echocardiographic abnormalities is low in children aged less than 8–10 years. However, there are cases in which abnormalities do exist, which can affect clinical decision making, including decisions about the initiation of corticosteroids and planning for any anaesthesia.[114] A baseline echocardiogram obtained at this age also allows for screening for anatomical abnormalities (eg, atrial or ventricular septal defects, patent ductus arteriosus), which might affect long-term cardiovascular function.

Minimum assessment should include, although is not limited to, an electrocardiogram and a non-invasive cardiac imaging study (ie, echocardiogram). Assessment of cardiac function should occur at least once every 2 years until the age of 10 years. Annual complete cardiac assessments should begin at the age of 10 years or at the onset of cardiac signs and symptoms if they occur earlier. Abnormalities of ventricular function on non-invasive cardiac imaging studies warrant increased surveillance (at least every 6 months) and should prompt initiation of pharmacological therapy, irrespective of the age at which they are detected.[104,113]

Consideration should be given to the use of angiotensin-converting-enzyme inhibitors as first-line therapy. β blockers and diuretics are also appropriate, and published guidelines should be followed for the management of heart failure.[104,113,115–118] Recent evidence from clinical trials supports the treatment of cardiomyopathy associated with DMD before signs of abnormal functioning. Further studies are awaited to allow firm recommendations to be made.[108,119–123]

Signs or symptoms of abnormalities of cardiac rhythm should be promptly investigated with Holter or event monitor recording and should be treated.[124–127] Sinus tachycardia is common in DMD, but is also noted in systolic dysfunction. New-onset sinus tachycardia in the absence of a clear cause should prompt assessment, including that of left-ventricular function.

Individuals on glucocorticoids need additional monitoring from the cardiovascular perspective, particularly for

hypertension, which might necessitate adjustment in the glucocorticoid dose (table 2 in part 1 of this Review).[1] Systemic arterial hypertension should be treated.

Prevention of systemic thromboembolic events by anticoagulation therapy can be considered in severe cardiac dysfunction, but is inappropriate in earlier cardiac dysfunction. The usefulness of an internal cardiac defibrillator has not been established and needs further research.

Because of the morbidity and mortality associated with cardiomyopathy, additional research is clearly needed, not only to define the natural history of the disease process, but also to establish treatments specific for the dystrophin-deficient myocardium. Further studies of pharmacological approaches aimed at early intervention are needed to delay the underlying disease process. With generally improved fitness of patients who have DMD, the option of cardiac transplant might need to be addressed in the future.

Nutritional, swallowing, gastrointestinal, and speech and language management

Patients might be at risk of both undernutrition/malnutrition and being overweight/obese at different ages and under different circumstances, in addition to deficiencies in calorie, protein, vitamin, mineral, and fluid intake. In later stages, pharyngeal weakness leads to dysphagia, further accentuating nutritional issues and gradual loss of respiratory muscle strength, combined with poor oral intake, and can result in severe weight loss and the need to consider tube feeding. Constipation might also be seen, typically in older patients and after surgery. With increasing survival, other complications are being reported, including gastric and intestinal dilatation related to air swallowing due to ventilator use, or more rarely to delayed gastric emptying and ileus. As the condition progresses, access to a dietitian or nutritionist, a swallowing/speech and language therapist, and a gastroenterologist is needed for the following reasons: (1) to guide the patient to maintain good nutritional status to prevent both undernutrition/malnutrition and being overweight/obese, and to provide a well-balanced, nutrient-complete diet (adding tube feeding, if necessary); (2) to monitor and treat swallowing problems (dysphagia) to prevent aspiration and weight loss, and to assess and treat delayed speech and language problems; and (3) to treat the common problems of constipation and gastro-oesophageal reflux with both medication and non-medication therapies.

Nutritional management

Maintaining good nutritional status, defined as weight for age or body-mass index for age from the 10th to 85th percentiles on national percentile charts, is essential. Poor nutrition can potentially have a negative effect on almost every organ system. Anticipatory guidance and prevention of undernutrition/malnutrition and being overweight/obese should be goals from diagnosis throughout life. The monitoring and triggers for referral to an expert dietitian/nutritionist in DMD are described in panel 2.[128–132] Diet should be assessed for energy, protein, fluid, calcium, vitamin D, and other nutrients. We recommend that each patient should receive a daily multivitamin supplement with vitamin D and minerals. If this is not general practice, a computer nutrient analysis of the patient's diet can provide evidence for the possible need for specific foods or nutrient supplements. If there is a suspicion of undernutrition/malnutrition and poor intake, serum vitamin concentrations can be obtained and supplements could be recommended. Nutritional recommendations with regard to bone health are shown in figure 1.

Swallowing management

Clinical swallowing examination is indicated if there is unintentional weight loss of 10% or more or a decline in the expected age-related weight gain. Prolonged meal times (>30 min) or meal times accompanied by fatigue, excessive spilling, drooling, pocketing, or any other clinical indicators of dysphagia make referral necessary, as do persistent coughing, choking, gagging, or wet vocal quality during eating or drinking.[133] An episode of aspiration pneumonia, unexplained decline in pulmonary function, or fever of unknown origin might be signs of unsafe swallowing, necessitating assessment. There might be contributory factors for weight loss due to complications in other systems, such as cardiac or respiratory compromise.

A videofluoroscopic study of swallowing (also referred to as a modified barium swallow) is necessary for patients with clinical indicators of possible aspiration and pharyngeal dysmotility.[134] Swallowing interventions and compensatory strategies are appropriate for patients with dysphagia. These should be delivered by a speech and language pathologist, with training and expertise in the treatment of oral-pharyngeal dysphagia, who can assess the likely appropriateness of interventions and deliver an individualised dysphagia treatment plan with the aim of preserving optimum swallowing function.

As the disease progresses, most patients begin to experience increasing difficulty with chewing and subsequently exhibit pharyngeal-phase swallowing deficits in young adulthood.[135–140] The onset of dysphagia symptoms can be gradual and the impact of oral-pharyngeal dysphagia might be under-recognised and under-reported by patients.[140] This leads to risk of complications, such as aspiration and inability to take in enough fluids and food energy to maintain weight.[135–139] Weight problems can also be due to an inability to meet the increased effort of breathing.[135–139]

When it is no longer possible to maintain weight and hydration by oral means, gastric-tube placement should be offered. Discussions between other specialists and the family should involve explanations of the potential risks

For the **US national percentile charts** see http://www.cdc.gov/growthcharts/

Panel 2: **Improving underweight and overweight status**

Monitor regularly for:

- Weight*
- Linear height in ambulatory patients (measured every 6 months)
- Arm span/segmental length in non-ambulatory patients†

Refer for a nutritional/dietetic assessment:

- At diagnosis
- At initiation of glucocorticoids
- If the patient is underweight (<10th age percentile)‡
- If the patient is at risk of becoming overweight (85–95th age percentile)‡
- If the patient is overweight (>95th age percentile)‡
- If there has been unintentional weight loss or gain
- If there has been poor weight gain
- If major surgery is planned
- If the patient is chronically constipated
- If dysphagia is present

National guidelines and recommendations for diets for underweight and overweight individuals can be found in Kleinman,[128] and are often available from charities/associations for cardiac disorders and diabetes. *In non-ambulatory patients, wheelchair weight should be obtained first, then patient and wheelchair weight, or caregiver weight should be obtained first, then the weight of the patient held by the caregiver. †If the patient has scoliosis, the arm span should be measured if possible. ‡Overweight/underweight status should be judged on the basis of local body-mass index percentiles (weight for age is a possible alternative if height is unavailable). Body composition is altered in Duchenne muscular dystrophy (DMD) owing to the relatively low lean body mass seen in DMD with a relatively higher fat body mass.[129]

and benefits of the procedure. A gastrostomy can be placed endoscopically or via open surgery, taking into account anaesthetic and ethical considerations and family and personal preference.[141]

Gastrointestinal management

Constipation and gastro-oesophageal reflux are the two most common gastrointestinal conditions seen in children with DMD in clinical practice.[133,142,143] Stool softeners, laxatives, and stimulants are necessary if the patient has acute constipation or faecal impaction, and use of enemas might be needed occasionally. Daily use of laxatives, such as milk of magnesia, lactulose, or polyethylene glycol, is necessary if symptoms persist. In the case of persistent constipation, adequacy of free fluid intake should be determined and addressed. In cases of faecal impaction, manual/digital disimpaction under sedation or general anaesthesia is of uncertain benefit. Enemas, stimulant laxatives, such as dulcolax and senna, and stool softeners can be tried before considering manual disimpaction. Milk and molasses enemas are not recommended for paediatric patients. Supplementation with dietary fibre for chronic or severe constipation might worsen symptoms, particularly if fluid intake is not increased.

Gastro-oesophageal reflux is typically treated with proton-pump inhibitors or H2 receptor antagonists, with prokinetics, sucralfate, and neutralising antacids as adjunctive therapies. Common practice is to prescribe acid blockers in children on corticosteroid therapy or oral bisphosphonates to avoid complications such as gastritis and to prevent reflux oesophagitis. It is necessary to recommend nutritional interventions for a patient who has symptoms suggestive of reflux.

Speech and language management

Delayed acquisition of early language milestones is common in boys who have DMD, with differences in language acquisition and language-skill deficits persisting throughout childhood.[144] Referral to a speech and language pathologist for assessment and treatment is necessary on suspicion of difficulties with speech acquisition or with continuing deficits in language comprehension or oral expression. Oral motor exercises and articulation therapy are necessary for young boys with DMD with hypotonia and in older patients who have deteriorating oral muscle strength and/or impaired speech intelligibility. For older patients, compensatory strategies, voice exercises, and speech amplifications are appropriate if intelligibility deteriorates due to problems with respiratory support for speech and vocal intensity. Voice output communication aid assessment could be appropriate at all ages if speech output is limited.

Pain management

Pain of varying intensity occurs in DMD.[145,146] Effective pain management requires accurate determination of the cause. Interventions to address pain include physical therapy, postural correction, appropriate and individualised orthoses, wheelchair and bed enhancements, and pharmacological approaches (eg, muscle relaxants and anti-inflammatory medications). Pharmacological interventions must take into account possible interactions with other medications (eg, steroids and non-steroidal anti-inflammatory drugs) and their side-effects, particularly those that might negatively affect cardiac or respiratory function. Rarely, orthopaedic intervention might be indicated for intractable pain that is amenable to surgery. Back pain, particularly in the context of glucocorticoid treatment, is an indication that a careful search for vertebral fractures is needed; such fractures respond well to bisphosphonate treatment and/or calcitonin.[147,148] Research on effective pain interventions across the lifespan of individuals with DMD is warranted.[146,149,150]

Surgical considerations

Various situations, related (muscle biopsy, joint contracture surgery, spinal surgery, and gastrostomy) and unrelated (intercurrent acute surgical events) to DMD, might require the use of general anaesthesia. There are several condition-specific issues that need to be taken into account for the planning of safe surgery. Surgery in a patient who has DMD should be done in a full-service hospital that has experience of patients with DMD. In addition, as with any situation in which

patients are on chronic corticosteroid treatment, consideration needs to be given to steroid cover over the period of surgery.[151]

Anaesthetic agents

The exclusive use of a total intravenous anaesthetic technique is strongly recommended owing to the risk of malignant hyperthermia-like reactions and rhabdomyolysis with exposure to inhalational anaesthetic agents, such as halothane and isoflurane.[152,153] Depolarising muscle relaxants, such as suxamethonium chloride, are absolutely contraindicated owing to the risk of fatal reactions.[152,153]

Blood loss

To minimise blood loss and its effects intraoperatively in major surgeries, such as spinal fusion, it is necessary to use mildly hypotensive anaesthetics, crystalloid bone allograft, and cell-saver technology. Other interventions, such as the use of aminocaproic acid or tranexamic acid to diminish intraoperative bleeding, can be considered.[154] Postoperative anticoagulation with heparin and/or aspirin is inappropriate. Use of compression stockings or sequential compression for prevention of deep-vein thrombosis might be indicated.

Cardiac considerations

An echocardiogram and electrocardiogram should be done before general anaesthesia. They should also be done if the patient is undergoing conscious sedation or regional anaesthesia if the last investigation was more than 1 year previously or if there had been an abnormal echocardiogram in the preceding 7–12 months. For local anaesthesia, an echocardiogram should be done if an abnormal result had been obtained previously.

Respiratory considerations

Respiratory interventions are intended to provide adequate respiratory support during induction of, maintenance of, and recovery from procedural sedation or general anaesthesia. In particular, they are designed to reduce the risk of post-procedure endotracheal extubation failure, postoperative atelectasis, and pneumonia.[153] These goals can be achieved by providing non-invasively assisted ventilation and assisted cough after surgery for patients with significant respiratory-muscle weakness, as indicated by sub-threshold preoperative pulmonary function test results.

Preoperative training in and postoperative use of manual and assisted cough techniques are necessary for patients whose baseline peak cough flow is below 270 L/min or whose baseline maximum expiratory pressure is below 60 cm water (these threshold levels of peak cough flow and maximum expiratory pressure apply to older teenage and adult patients).[155] Preoperative training in and postoperative use of non-invasive ventilation is strongly recommended for patients with a baseline forced vital capacity of below 50% predicted and necessary with a forced vital capacity of below 30% predicted.[155] Incentive spirometry is not indicated owing to potential lack of efficacy in patients with respiratory-muscle weakness and the availability of preferred alternatives, such as mechanical insufflation–exsufflation. After careful consideration of the risks and benefits, patients with significant respiratory-muscle weakness might be eligible for surgery, albeit with increased risk, if these patients are highly skilled preoperatively in the use of non-invasive ventilation and assisted cough.[156,157]

Emergency-care considerations

Because of the involvement of different systems in DMD, many factors must be taken into account on presentation of a patient to an emergency room. From the outset, the diagnosis, current medication, respiratory status, cardiac status, and associated medical disorders should be made clear to the emergency-room staff. Because many health professionals are not aware of the potential management strategies available for DMD, the current life expectancy and expected good quality of life should also be explained to reduce the risk of therapeutic nihilism in acute care. Chronic glucocorticoid use (if relevant) needs to be made clear, with its concomitant risk of reduced stress response, masking of infection, and possible gastric ulceration. Risk of respiratory failure supervening during an intercurrent infection is high in those with borderline respiratory function. Use of opiates and other sedating medication is essential, as is the use of oxygen without ventilation owing to the risk of hypercapnia. If nocturnal ventilation is already being used, then access to the ventilator is essential during any acute event or intervention. For patients who are already using ventilation, the team involved in the respiratory care of the patient should be contacted as soon as possible. Awareness of the risk of arrhythmias and cardiomyopathy is important. Anaesthetic issues, as previously discussed, need to be taken into account at all times if surgery or sedation is needed.

Conclusions

This Review is the result of the first international collaboration of a uniquely broad group of experts in DMD management to develop comprehensive care recommendations. This effort was supported by a rigorous method—the RAND Corporation–University of California Los Angeles Appropriateness Method[2]—which expands the consensus-building process, not only to establish the parameters for optimum care, but also to identify areas of uncertainty in which further work is needed.

A model of care emerged during the process of evaluating assessments and interventions for DMD that emphasises the importance of multidisciplinary care for patients with DMD. For example, the input of physiotherapy, rehabilitation and orthopaedic management of contractures (where necessary) has to be taken as a whole, together with the impact of the use of corticosteroids, which in most boys has a significant effect on muscle

Search strategy and selection criteria

Peer-reviewed literature was searched using the key search terms of "Duchenne" or "muscular dystrophy", or both, paired with one of 410 other search terms related to a comprehensive list of assessment tools and interventions used in DMD management. The full list of search terms is available on request. The databases used included Medline, Embase, Web of Science, and the Cochrane Library. Initial inclusion criteria consisted of available abstracts of human studies published in English between 1986 and 2006. Each working group also incorporated major articles from its discipline published before 1986 and from 2007 to mid-2009 in the process of discussions, final assessments, and write-up of recommendations.

strength and function. In this context, the various specialty reports are presented in this second part of the Review.

Clearly staged assessments and interventions have been described to address the cardiac and respiratory complications that are common in DMD and provide the framework for the safe management of these complications. Respiratory interventions, in particular the institution of nocturnal ventilation, have had a major effect on survival in DMD,[65,66] and early indications are that prompt recognition and treatment of deterioration in cardiac status will also have a significant impact.[119,121] Further trials are awaited to determine the optimum timing to start cardioactive treatment. In the meantime, the recommendations presented here are consistent with previously published guidelines,[113,115] and most importantly reinforce the need for active engagement with a cardiologist at every stage of the condition.

In other areas, including management of complications of the gastrointestinal tract, less work had been done previously, but we conclude that proactive management in this area is important. An increasing awareness of the possibility of gastrointestinal complications in DMD is needed; this area has been relatively poorly studied until now and will merit further investigation in emerging adult populations with DMD to delineate the burden of disease in these patients and its optimum management.

We are in an unprecedented era of hope for therapies for DMD based on the underlying molecular basis of the disease. In the meantime, these care recommendations have been developed with the support of and input from stakeholders in the DMD community to be used as the current and future benchmark for anticipatory planning, appropriate surveillance, and interventions in all areas of this complex disease. It is hoped that they will provide a catalyst to improve care for patients with DMD worldwide.

Contributors

All authors provided intellectual expertise in the study design, generation and interpretation of data, writing of the Review, and the decision to publish. KB, aided by RF, drafted and edited the Review, and approved the final version. DJB, LEC, LC, SP, and CC were involved in the literature search.

Conflicts of interest

KB is a consultant for Acceleron, AVI, Debiopharm, Prosensa, and Santhera. LEC has received honoraria from Genzyme Corporation, has participated in research supported by Genzyme Corporation, PTC Therapeutics, the Leal Foundation, and Families of Spinal Muscular Atrophy, has been awarded grant support from the National Skeletal Muscle Research Center, and is a member of the Pompe Registry Board of Advisors. All other authors have no conflicts of interest.

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