

## Standards of care for Duchenne muscular dystrophy Brief TREAT-NMD recommendations

### Introduction

The present document is a brief TREAT-NMD summary of standards of care (SOC) recommendations for diagnosis and management of Duchenne muscular dystrophy (DMD).

A first draft, based where possible on already available and published guidelines (see Key references), was revised following discussions by expert groups for each of the following areas: Diagnosis, Neurology, GI-Nutrition, Respiratory Care, Cardiac Care, Orthopedics, Psychosocial, Rehabilitation, and Oral Care.

The aim with these brief SOC recommendations for DMD is to achieve the rapid dissemination of existing knowledge in this area while awaiting the more detailed recommendations presently being drawn up by the US Center for Disease Control in collaboration with TREAT-NMD. The present guidelines are to be considered as expert opinion, and are not based on systematic review processes, although an evidence-based approach has guided the work. The feasibility of following these recommendations will vary considerably between different countries and regions. However, in regions where it is not presently possible to follow the guidelines, they may act as goals to be aimed for.

The present document, the CDC recommendations, and key references related to SOC for DMD will be published in the SOC section of the TREAT-NMD website ([www.treat-nmd.eu/soc](http://www.treat-nmd.eu/soc)).

### Diagnosis of DMD

- Clinical examination: must include seeing the child try to run, jump, climb stairs and get up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties in rising from the floor, tip-toe walking, and pseudohypertrophy of calves. Examination may reveal decreased or lost muscle reflexes, and commonly a positive Gower sign, i.e. the need to make use of arms to push to erect position from lying by moving hands up the thighs. Many signs of proximal muscle weakness will be detected much more easily in the corridor than the consulting room.
- Serum creatine kinase (CK): Massive elevation of the serum CK (at least 10–20 x normal and often much more) is nonspecific but always present. The finding of a high CK level should prompt urgent specialist referral for confirmation of the diagnosis. The clinician should be made aware of the association of non-hepatic elevation of AST and ALT in DMD. Unexpected elevation of these enzymes should raise the suspicion of high CK.
- Genetic testing should be performed. A deletion of the dystrophin gene will be found in around 70% of cases, a duplication in around 6% and the remaining cases will have a point mutation. Readily available genetic tests for DMD are not always exhaustive and a negative result on initial testing does not exclude the disease. It is very important to understand the tests offered by a particular laboratory and their limitations—further specialist input may be necessary. A laboratory diagnosis should be possible in > 95% of cases.

- Muscle biopsy: General signs of muscular dystrophy will be seen, including muscle fibre degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis on a muscle biopsy specimen will always be abnormal and offers a route to confirm the diagnosis, complementary to genetic testing. Dystrophin analysis needs to be followed by molecular genetic testing in order to be able to offer genetic counselling to other family members.
- An integral part of the diagnostic process is offering, through professional genetic counselling, determination of the carrier status of the mother by molecular genetic testing. Even if the condition has arisen as a result of a new mutation, there is an average 10% risk of recurrence due to germline mosaicism. Genetic counselling should also be offered to sisters and aunts (mother's side) in reproductive age if the mother carries the mutation.
- Support: around the time of diagnosis it is useful to provide contact with a named member of support staff and imperative to offer details of parent/patient support groups such as the national muscular dystrophy charities and the Parent Project.

## Neurology

The use of corticosteroids in DMD:

- Timing: experience suggests that the best improvement in performance will be seen with the introduction of medication at or before the point at which the physical performance of the child plateaus (as assessed by sequential functional testing); this is most typically seen around the age of 4-6. Less functional gain may be seen if initiation of steroids is delayed until close to the loss of ambulation.
- Regimes: the most common daily dosage regimes are 0.75 mg/kg/day prednisone/prednisolone and 0.9 mg/kg/day deflazacort. They are likely to be equally effective, but have slightly different side-effect profiles. Deflazacort may produce less weight gain but has a higher risk of asymptomatic cataracts. Other regimes suggested to reduce the incidence of steroid-associated side-effects include alternate day dosing, lower dose daily regimes and intermittent regimes (e.g. 10 days on/10 days off; high dose on weekends). It is important to note that none of these regimes have been tested against the daily dosing schedules so that their relative efficacy in the long term is not known.
- Tests before starting steroids: immunity to chicken pox (and in high risk populations, tuberculosis) should be ensured ahead of starting steroids. Boosters of vaccinations should be up to date, and consider giving the 6 year booster early if needed.
- Efficacy: monitoring for efficacy should include tests of muscle function and strength (e.g. timed function tests, Hammersmith motor ability score, MRC muscle strength score), FVC and parent and child perception of the value of the treatment.

- Side effects: monitoring and prophylaxis of the predictable side-effects of steroid use should go hand in hand (<http://enmc.org/workshop/?id=21&mid=88>). Major side effects to consider are behavioural changes, failure to gain height, excessive weight gain, osteoporosis, impaired glucose tolerance, immune/adrenal suppression, dyspepsia/peptic ulceration, cataract, and skin changes. It is for this reason important to monitor weight, height, blood pressure, urinary dipstick (glucose), cushingoid features, mood/behaviour/personality/GI skin changes, red reflex of eyes, bone fractures, and recurrent infections.
- Many side effects can be dealt with without dose reduction or withdrawal of the corticosteroid. Monitoring for weight gain should be accompanied by dietary advice and support prior to starting steroids, behavioural changes should be supported by psychological input and advice on behaviour management, advice on bone health should be provided alongside monitoring of fracture frequency. Concomitant treatment with non-steroidal anti-inflammatory agents should be avoided. Abdominal pain/peptic ulcerations can be treated with antacids.
- Dose reduction: Despite prophylactic measures above certain events may necessitate dose reduction. These include behavioural changes disrupting family/school life, weight gain 25% or 3 centile increase from baseline, failure to gain height or skin changes (e.g. acne, striae, hirsutism) unacceptable to child/family, fasting blood glucose >110 mg/dl (>6.1 mmol/l) or blood glucose 2 hours after meal >140 mg/dl (7.8 mmol/l), unusually high frequency of infections/unusual organism, persistent GI symptoms (abdominal pain, heartburn, GI bleeding) despite treatment with antacids.
- Withdrawal of corticosteroids: Corticosteroids should be stopped if severe and/or unacceptable side effects occur. Events that may necessitate this include severe behaviour changes disrupting family/school life, weight gain/failure to gain height or skin changes unacceptable to the child/family despite dose reduction, diabetes mellitus defined as fasting blood glucose >126 mg/dl (7.0 mmol/l) or blood glucose 2 hours after meal >200 mg/dl (>11.1 mmol/l), or confirmed hypertension (systolic blood pressure increased 15-30 mm Hg over 97th centile or diastolic blood pressure increased 10-30 mm Hg over 97th centile for height), unusually high frequency of infections/unusual organism on lowered dose corticosteroids, or GI symptoms not satisfactorily controlled by antacids and lowered dosage of corticosteroids.
- Tapering: If corticosteroids need to be stopped, they should be tapered/stopped slowly over weeks and not suddenly. Suggested tapering of drug dosage is to take  $\frac{1}{2}$  the regular corticosteroid dose the first week,  $\frac{1}{4}$  the dose during the second week,  $\frac{1}{8}$  the dose during the third week and thereafter stop corticosteroid medication.
- How long to continue steroid treatment: Continuation of steroids beyond the loss of ambulation is common practice in some centres for the possible protective effect on spinal alignment, respiratory and cardiac function. There is, as yet, no evidence for any benefit of starting steroids after a boy has stopped walking. However, some patients may notice an improvement in function and forced vital capacity.
- Patient information resources are available from the European Neuromuscular Centre (ENMC) ([www.enmc.org/workshop/?id=21&mid=88](http://www.enmc.org/workshop/?id=21&mid=88)), as well as via the national muscular dystrophy charities.

## GI-Nutrition

- Adequate dietary advice should be offered from a young age, with focus on healthy eating habits that the whole family could benefit from, with specific focus on weight control, adequate calcium and vitamin D intake and controlled sodium intake. Particular emphasis should be placed on appetite control around time the corticosteroids are started.
- The weight in boys without nutritional problems should be measured 1-2 times a year. If there is active concern about overweight or underweight the weight should be measured more frequently. Situations where changes in weight are to be expected should also initiate weight monitoring (e.g. loss of walking ability, before major surgery).
- A child's ideal weight is determined by his height and is influenced by loss of lean body mass (such as in Duchenne Muscular Dystrophy). Tracking a child's weight and height on a centile chart gives an indication of excessive weight gain. Body Mass Index (BMI) body weight divided by the square of height (kg/m, centile adjusted for age and sex) is a more reliable measure of adiposity and can also be tracked on a chart. Clinical judgment, taking into account all issues such as emotional, psychosocial and familial aspects, will influence the dietary advice.
- To prevent excessive weight gain a dietician should be involved at diagnosis, at initiation of steroids and at loss of ambulation. A dietician should also be involved if there is a tendency to underweight.
- In case of overweight it is preferable to aim for a weight loss of 0.5 kg per month, or stabilization of weight in cases when a long term normalization is preferred.
- Problems with undernutrition are most likely after the boy starts using a wheelchair (approximately 12-13 years of age) and may be multifactorial. The first step is to evaluate intake and to optimize if necessary the existing diet with energy and protein. The next step with more severe malnutrition is enteral nutrition during night time.
- Nutritional status should always be examined before major surgery and in particular undernutrition be addressed before surgery. Particularly overweight patients may have respiratory dysfunction during sleep so may require additional sleep evaluation of oxygen saturation prior to surgery.
- Especially in steroid treated boys, if the diet is not adequate in supply of calcium and vitamin D, these should be added separately to reach a recommended intake of calcium (4-8 years: 800 mg/d; 9-18 years: 1300 mg/d) and vitamin D (400 IU).
- In later stages of the disease there can be difficulty swallowing and where this leads to aspiration and/or undernutrition, discussion of feeding by tube or percutaneous endoscopic gastrostomy (PEG) is indicated.

## Respiratory care

- **Respiratory surveillance:** Serial measurement of forced vital capacity (FVC: absolute values and as predicted for height, arm span, or ulna length) provides an easy way to document the progression of respiratory muscle weakness. Once clinical signs of nocturnal hypoventilation develop or FVC drops to 1.25 l or <40% predicted value, then serial measurement of overnight oximetry allows the recognition of the development of nocturnal respiratory failure. This can be done easily at home through the use of small portable machines. Symptoms should also be sought for at every clinic attendance.
- **Surveillance of cough effectiveness:** Serial measurement of peak cough flow will enable monitoring of cough effectiveness. Methods of augmenting cough such as assisted coughing, volume recruitment techniques, cough assist machine should be considered when the PCF is below 270 l/min in non-ambulant boys and introduced before PCF is less than 160 l/min.
- **Prophylaxis of chest infections:** Once a patient's FVC begins to drop, boys are susceptible to chest infections and should be offered flu, pertussis, and pneumococcal vaccination.
- **Management of chest infections:** When coughing is ineffective, antibiotics should be provided promptly. Chest physiotherapy such as postural drainage and assisted coughing should be taught when coughing is ineffective and may need to be supplemented with cough assist machine or other volume recruitment techniques such as glossopharyngeal breathing.
- **Management of nocturnal hypoventilation:** Ask for symptoms of nocturnal hypoventilation at every visit. Symptomatic nocturnal hypoventilation is an indication for elective non-invasive nocturnal ventilation (NIV). NIV should also be considered if nocturnal oxycapnography / polysomnography shows low SaO<sub>2</sub> or elevated pCO<sub>2</sub>.
- **Extending ventilation to the daytime** should be considered if the patient presents elevated pCO<sub>2</sub> lowered or SaO<sub>2</sub> while awake. Greater patient comfort is achieved with intermittent ventilation with positive pressure, using a mouthpiece.
- **Structured education of the ventilator user and the carers and regular follow-up** should be an integral part of the treatment, and there should be surveillance of NIV complications, e.g. air leaks, gastric distension, mucosal dryness, facial bone deformation.
- **Anaesthetic techniques** must be tailored to minimize intra and post-operative respiratory and cardiovascular depression and may require invasive monitoring and access to intensive care. Depolarizing muscle relaxants should be avoided because of the risk of hyperkalaemia.

## Cardiac care

- Surveillance: Cardiac investigation (echocardiogram and ECG) is indicated at diagnosis, every 2 years thereafter to age 10 and then annually, or more often, if abnormalities are detected. Cardiac investigation should be done prior to general anaesthesia at any age. Cardiac MRI may be useful in patients with limited echocardiographic acoustic window.
- Abnormalities of cardiac rhythm should be promptly investigated and treated. Periodic Holter monitoring should be considered for patients with demonstrated cardiac dysfunction.
- Prophylaxis: ACE-inhibitors should be started at a subclinical deterioration of cardiac function as detected by echocardiography. One long term study suggests that even earlier start of ACE-inhibitor medication prevents later deterioration. Early prophylactic treatment with ACE-inhibitors at a pre-clinical stage is therefore recommended by several centers from 5-10 years of age, although there is still no general consensus on this.
- Treatment: Dependent on type and stage of cardiomyopathy. Dilated cardiomyopathy is the most common form. ACE-inhibition and beta-blocker both at once or ACE inhibitors first followed, when indicated, by beta-blockers should be initiated in the presence of progressive abnormalities, with the addition of diuretics and other with onset of heart failure. Anticoagulation therapy should be considered in patients with severe cardiac dysfunction to prevent systemic thromboembolic events.
- Arrhythmias: Ventricular arrhythmias may occur at any time, but occur more frequently in the late stage of dystrophinopathic cardiomyopathy. Periodic Holter monitoring should therefore be considered for patients with demonstrated cardiac dysfunction. Isolated premature ventricular beats require no treatment, but it is important to monitor the cardiac status carefully. If major ventricular arrhythmias occur, antiarrhythmic treatment should be introduced, bearing in mind the possible negative inotropic effect of agent chosen.
- Carriers should have cardiac investigation (echocardiogram and ECG) every five years, or more frequently if abnormalities are found.

## Orthopedics

- Splinting: In ambulant children night splints should be provided when there is loss of dorsiflexion at the ankle when there is loss of normal grade of dorsiflexion and before the foot can only achieve plantigrade. Daytime AFOs are not recommended before loss of ambulation.
- In non-ambulant children: Sitting AFOs are recommended as painful contractures will develop that also impact negatively on posture. Some children will require tenotomies but AFOs are still needed after surgery.
- KAFOs can be considered to delay contracture development and prolong ambulation. Standing frames or swivel walkers can delay contracture development in non-ambulant children.
- DMD spine deformity presents an onset in the early teens if not long term treated with corticosteroids. A fusion surgery can be recommended as soon as there is clear progression and the Cobb angle passes 25 – 30 degrees.

## Psychosocial

- Every family should be offered a home visit at diagnosis to help come to terms with the emotional and practical problems that the knowledge of the diagnosis bring up. For example, feelings of loss, guilt, anger, talking to affected child and siblings about the disease. Issues about access for home, school, leisure and barriers to independence.
- Social (information, advocacy and advice) and psychological support should be offered at times of changing needs and crises. For example, considering more children, moving/adapting house, loss of ambulation, surgery, cardiac & respiratory problems, starting university/employment, end of life.
- Psychological support should be offered to affected children and their families during times of emotional/behavioral problems.
- Learning difficulties/ autism spectrum disorders should be identified early and recommendations given to parents and educators about managing these difficulties.

## Rehabilitation

- Annual neurological, respiratory and cardiological assessments should ideally be co-ordinated via a centralized DMD rehabilitation unit.
- From the time of diagnosis the boys must be assessed once to twice a year by therapists (physiotherapists and occupational therapists) with special experience in neuromuscular disorders. The interval between the assessments depends on the boy's age, the progression of the disease and his functional ability.
- The aim of the assessments is to set up a plan for interventions for the child to optimize his physical, social and intellectual abilities. The plan should ensure that professionals and parents are ahead of the events and prepared in advance on the next stage of disease. Assessments of physical abilities, that are repeated with fixed intervals, are needed to determine the rate of progression of the disease.
- Major aims of the physiotherapist and occupational therapist are to encourage activity and promote function. This includes interventions to delay or reduce complications due to the deterioration of muscle strength, and to give guidelines regarding activities, possibilities, adaptations and adjustments enabling the boys/men to live a socially active life together with family and friends.
- Annual home visit / assessments performed by an interdisciplinary team from a special DMD rehabilitation unit is recommended to support the family and the local team of physiotherapists, occupational therapists, social worker and teacher.
- Exercise: Resisted exercises should not be prescribed as there is no evidence that they are useful but there are concerns that they may accelerate muscle damage. Moderate levels of active exercise particularly in the hydrotherapy pool is recommended. Children taking steroids may acquire additional motor skills such as riding a bike and this encourages independent play and interaction with peers.

- Wheelchairs: Should be supplied to improve mobility and independence. Tilt-in-space / recline electric wheelchairs with supportive seating should be supplied early to avoid postural contractures and poor sitting posture.
- Annual, centralized courses for young and adults with DMD and their families are recommended, arranged by the NMD-association in co-operation with the centralized rehabilitation unit.

### Oral care

- Boys with DMD should see a dentist with extended experience and detailed knowledge of the disease, preferably at a centralized or specialist clinic. The dentist's mission should be to strive for high-quality treatment, oral health and wellbeing and to function as a resource for the families and the boy's own dentist in his home community. This dentist should be aware of the specific differences in dental and skeletal development in boys with DMD and collaborate with a well-informed and experienced orthodontist.
- Oral and dental care is to be based on prophylactic measures with a view to maintaining good oral and dental hygiene.
- Individually adapted assistive devices and technical aids for oral hygiene are of particular importance when the muscular strength of the patient's hands, arms and neck begins to decrease.

### Key references

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