https://doi.org/10.1590/0004-282X20170112

CONSENSUS

Brazilian consensus on Duchenne muscular dystrophy. Part 1: diagnosis, steroid therapy and perspectives

Consenso brasileiro sobre distrofia muscular de Duchenne - Parte 1 diagnóstico, corticoterapia e perspectivas

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ABSTRACT

Significant advances in the understanding and management of Duchenne muscular dystrophy (DMD) took place since international guidelines were published in 2010. Our objective was to provide an evidence-based national consensus statement for multidisciplinary care of DMD in Brazil. A combination of the Delphi technique with a systematic review of studies from 2010 to 2016 was employed to classify evidence levels and grade of recommendations. Our recommendations were divided in two parts. We present Part 1 here, where we describe the guideline methodology and overall disease concepts, and also provide recommendations on diagnosis, steroid therapy and new drug treatment perspectives for DMD. The main recommendations: 1) genetic testing in diagnostic suspicious cases should be the first line for diagnostic confirmation; 2) patients diagnosed with DMD should have steroids prescribed; 3) lack of published results for phase 3 clinical trials hinders, for now, the recommendation to use exon skipping or read-through agents.

Keywords: muscular dystrophy, Duchenne; practice guideline; consensus; diagnosis; genetic testing; drug therapy; glucocorticoids; utrophin.

RESUMO

Avanços na compreensão e no manejo da distrofia muscular de Duchenne (DMD) ocorreram desde a publicação de diretrizes internacionais em 2010. Nosso objetivo foi elaborar um consenso nacional baseado em evidências de cuidado multidisciplinar dos pacientes com DMD no Brasil. Utilizamos a técnica de Delphi combinada com revisão sistemática da literatura de 2010 a 2016 classificando níveis de evidência e graus de recomendação. Nossas recomendações foram divididas em duas partes. Apresentamos aqui a parte 1, descrevendo a metodologia utilizada e conceitos gerais da doença, e fornecemos recomendações sobre diagnóstico, tratamento com corticosteroides e novas perspectivas de tratamentos medicamentosos. As principais recomendações: 1) testes genéticos deveriam ser a primeira linha para confirmação de casos suspeitos; 2) pacientes com diagnóstico de DMD devem receber corticosteroides; 3) por enquanto, a falta de publicações de resultados dos ensaios clínicos de fase 3, dificulta recomendações de uso medicamentos que "saltam exons" ou "passam" por código de parada prematura.

Palavras-chave: distrofia muscular de Duchenne, guia de prática clínica; consenso; diagnóstico; testes genéticos; tratamento farmacológico; glucocorticoides; utrofina.

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Conflict of interest: There is no conflict of interest to declare.
Support: Genzyme, GSK, PTC, Biomarin, Biogen, Roche. Those do not influence the content of this work.
Received 08 March 2017; Accepted 03 April 2017.

Duchenne muscular dystrophy (DMD), the most common childhood muscular dystrophy, leads to severe disability and early death in the late teenage years if untreated. Duchenne muscular dystrophy is an X-linked degenerative disease and affects approximately one in 3,500 to 5,000 live male births[1]. The condition is characterized by progressive loss of muscle strength with some boys presenting with delayed motor milestones with or without intellectual disability. Diagnosis is generally suspected by the age of five, as physical ability divergent from their peers becomes evident. Females are usually asymptomatic, but some female carriers present with milder forms of the disease, generally associated with chromosomal rearrangements[2]. Duchenne muscular dystrophy occurs as a result of mutations in *DMD* (locus Xp21.2), that codes for the protein dystrophin[3]. Mutations that lead to dystrophin absence result in irreversible degeneration of the muscle tissue, accounting for the DMD phenotype[1,3]. Other mutations that lead to partial dystrophin expression are less severe, leading to milder dystrophinopathy phenotypes, such as Becker muscular dystrophy[4].

International guidelines for DMD care were published in 2010, with recommendations for DMD management, assessment and intervention[4,5]. Those guidelines were generated by an international group of experts, mainly from Europe and the United States of America, based on literature review and expert opinion. They divided their work into the following topics: diagnosis, rehabilitation, orthopedic, psychosocial, cardiac, pulmonary, gastrointestinal/nutritional and steroid management[4,5]. Nevertheless, significant advances in the understanding and management of DMD since then grant paramount importance for an update review of the previous guidelines. Improvements in general care, steroid treatment, noninvasive ventilatory support, cardiomyopathy and scoliosis management may significantly change the course of DMD. Therefore, a review of the previous guidelines is necessary, while some new specific guidelines are underway, or have been recently published[6,7].

Evidence-based practice has been heralded as the most appropriate way of ensuring that patients receive the most effective care possible.

Evidence-based practice involves much more than locating, analyzing, and appraising the best evidence available on the effectiveness of an intervention. Levels of evidence are based on study design and the methodological quality of individual studies. It is also important to make a judgment about the relevance and applicability of the evidence to the targeted patient group for the guideline, the consistency of the evidence, and the likelihood of clinical impact with the intervention. Finally, a link has to be made between the strength of the available evidence and the grade of the recommendation[8].

The need to review the guidelines published in 2010 in the light of the more recent publications, with a methodology that minimizes expert opinion, and with a focus on regional feasibility, was the motivation for the present work. Our objective was to produce an evidence-based consensus statement on the main management issues in DMD that can be used as an excellence guide for health practitioners who follow these patients.

METHODS

A combination of the Delphi technique and evidence-based level recommendations were followed. The Delphi technique is an approach used to gain consensus among a panel of experts[9]. This is normally achieved through a series of rounds where information is fed back to panel members using questionnaires.

This working group started with the invitation of members of the Neuromuscular Disorders Department of the Brazilian Academy of Neurology. Those who accepted were able to nominate other participants; either medical doctors or health professionals who had been involved, in the last two years, in DMD care or research (having followed at least 10 patients). At the end of this process, the working group comprised 25 members, divided into five categories (diagnosis, corticosteroid treatment, rehabilitation, systemic care, future perspectives), with an overall coordinator (APQCA). The group comprised adult neurologists, child neurologists, medical geneticists, physical therapists, pediatricians and cardiologist.

The members could choose one of the following topics: diagnosis, corticosteroid therapy, rehabilitation, systemic care, or future perspectives.

After that, members had to perform a systematic review of the literature of articles published from 2010 through 2016 regarding their chosen topic.

We searched Medline, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Clinical Trials, Web of Science, Database of Abstracts of Reviews of Effects, and Science Citation Index, and references of selected articles and review articles.

The key words used in the search were a combination of "Muscular Dystrophy, Duchenne" with any one of the following alone or in combination: "Practice Guideline", "Diagnosis", "Genetic Testing", "Pathology", "Drug Therapy", "Glucocorticoids", "Therapeutics", "Therapy", "Ataluren", "Utrophin", "Physical Therapy Modalities", "Exercise", "Rehabilitation", "Noninvasive Ventilation", "Cognition", "Quality of Life", "Orthotic Devices", "Muscle Stretching Exercises", "Tracheostomy", "Vital Capacity", "Respiratory Function Tests", "Cardiomyopathies", "Heart Failure", "Nutrition Disorders", and "Nutritional Support".

The eligibility criteria of the publications were defined by each working group member. Most chose not to include narrative reviews, expert opinion or single case reports. The English language was also selected as a filter by most.

A first round of anonymous, independent work began with a general open-ended question to gain a broad

understanding of the experts' views on the specific selected topic: "Based on your literature review and on your expertise following DMD patients, how do you reach the diagnosis, or how and when do you use a corticosteroid, or what are the future therapy perspectives?".

The coordinator then listed all the answers, removing any repeated material and constructed the second-round structured questionnaire.

Again, independent answers were given to each item of this structured questionnaire. Each participant was asked, at this time, to determine for each item the level of evidence, retrieving the reference for this attribution, and its national and regional feasibility.

Table 1. Level of evidence and corresponding recommendation grade.

Study type	Level of evidence	Recommendation
Randomized clinical trials/systematic review	1	A
Cohort studies	2	B
Case control	3	B
Case series	4	C
Expert opinion	5	D

Levels of evidence and recommendation level used in this study are shown in Table 1.

Finally, in a group meeting, all divergent classifications were discussed until a consensus decision was reached. Only when no study specifically addressed a given question, was the expert opinion of the group taken into account.

RESULTS

In Part 1 of this work we focused on diagnosis, steroid therapy and future perspectives. The items listed by the members in each of these working groups, which formed the structured questionnaire, are shown in Table 2.

Diagnosis

Performing an accurate diagnosis is one of the main standards of care related to DMD. Diagnosis confirmation allows the initiation of proper interventions and provision of educational and support information, and adequate genetic counseling for families. Although, ideally, a specialist in neuromuscular diseases who can clinically assess the child and also order and interpret appropriate studies should make the diagnosis, investigation will often start with clinical suspicion

Table 2. List of items retrieved from each working group after rounds of the Delphi Technique.

Topic	List
Diagnosis	Clinical suspicion, male with at least one: Muscle proximal weakness; Developmental delay; Marked elevated CK (liver enzymes); Cognitive impairment; Dilated cardiomyopathy; Calf hypertrophy; Magnetic resonance muscle imaging
	Diagnostic confirmation: MLPA, aCGH, PCR multiplex, Southern Blot for deletions/duplications
	Complete sequencing of the gene in those with a negative result on above tests or single exon deletion (false positive); Muscle biopsy with immunohistochemistry and/or immunoblotting, when the above all are negative and if a nonpathogenic variant is found; For those with only a biopsy confirmation, molecular studies should be done; Carrier detection; Molecular test will depend on the mutation found in the index case; Prenatal diagnosis
Corticosteroid therapy	Start treatment at: age 2, 3, 5?; disease phase 2 or 3?
	Drug: Prednisone; Deflazacort; Prednisolone
	Regimen: Daily; Alternate; Intermittent
	End of treatment
	Wheel chair bound
Perspectives	Exon skipping
	Read-through stop codon
	Utrophin
	AAV gene transfer
	Reducing inflammation
	Reducing fibrosis
	Cardiomyopathy treatment
	Idebenone
	Cell therapy
	Physical therapy (training, cyclo-ergometer, serial casting)
	Nutritional therapy (muscle increase, creatine, metformin)

CK: creatine kinase; MLPA: multiplex ligation-dependent probe amplification; aCGH: array comparative genomic hybridisation; PCR: polymerase chain reaction.

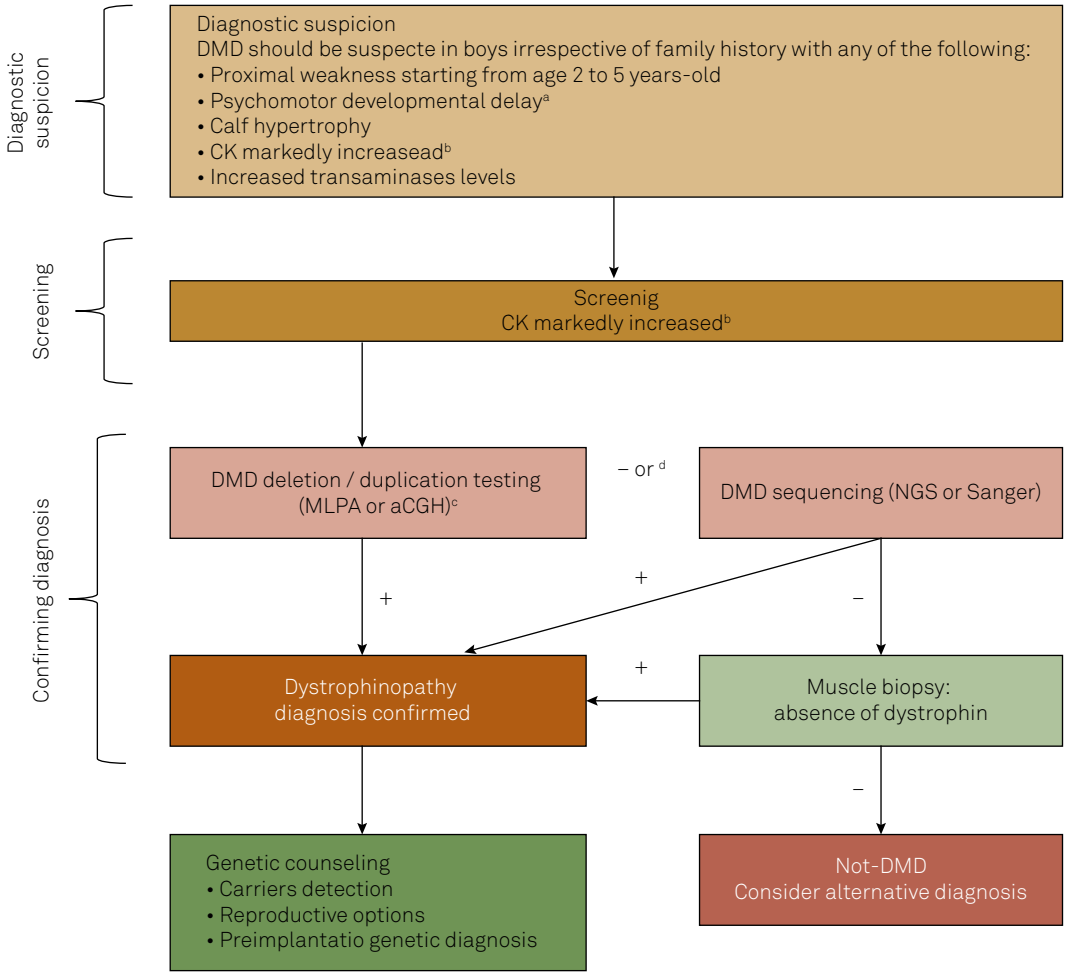
by pediatricians, general practitioners and other health care professionals, who also need to be aware of the condition and its diagnosis. After the DMD diagnosis is confirmed, or during the diagnostic process, support from geneticists who can provide genetic counseling is paramount.

Diagnostic suspicion

Suspicion of a DMD diagnosis (Figure) should be considered in a boy, irrespective of family history with any of the following: 1) proximal weakness starting from age two to five years (Level of evidence: 2B, Class of Recommendation: B)[10]; 2) psychomotor developmental delay including a delay in gait or speech acquisition, intellectual deficiency or autism spectrum disorders (Level of evidence: 4, Class of Recommendation: C)[11-13]; 3) calf hypertrophy (Level of evidence: 4, Class of Recommendation: C)[12]; 4) marked creatine kinase (CK) increase, defined as >2,000U/L (Level of evidence: 2B, Class of Recommendation: B)[14]; or 5) incidental finding of increased transaminases levels (aspartate and alanine aminotransferases, which are also produced by muscle cells) above a normal reference levels for age (Level of evidence: 4, Class of Recommendation: C)[15]. If any of these criteria are present, a screening evaluation of CK levels should be ordered. Ideally, both normal or marked increased CK levels should be confirmed in a second sample assay.

Diagnosis confirmation

If clinical suspicion of DMD is supported by a marked increase in CK levels, then a confirmatory test should be ordered (Figure). The way of confirming the diagnosis may vary according to the local availability of tests. Testing for *DMD* mutation will always be necessary, even if the diagnosis was confirmed by the absence of dystrophin protein expression on muscle biopsy, to provide accurate information for genetic counseling and to allow the detection of mutation carriers. Different types of mutations in *DMD* can be the genetic basis for the disease. The most common mutation types are large deletions and duplications followed by point mutation, small deletions or insertions and splice site mutations[16]. Therefore, first-line genetic testing for *DMD* should be a technique that



[a]: Includes delay of gait or speech acquisition, intellectual deficiency or autism spectrum disorders; [b]: defined as CK levels > 2,000U/L; [c]: southern blot analysis and multiplex PCR of *DMD* are alternatives; [d]: single exon deletion on MLPA should be confirmed by a second method; aCGH: Comparative Genomic Hybridization microarray; CK: Creatine Kinase; DMD: Duchenne muscular dystrophy; MLPA: Multiplex Ligation-dependent Probe Amplification; NGS: next-generation sequencing; +: indicates abnormal results consistent with DMD diagnosis; -: indicates normal results.

Figure. Diagnostic flowchart of DMD.

evaluates copy number variation to detect large deletions of one or more exons and duplications. Multiplex ligation-dependent probe amplification (MLPA) and microarray-based comparative genomic hybridization (aCGH) are superior techniques to multiplex polymerase chain reaction (PCR) for detecting large deletions/duplications in *DMD*. The MLPA and aCGH allow the identification of a greater number of large deletions, and detect large duplications and provide a better estimation of mutation breakpoints than multiplex PCR (Level of evidence: 1B, Class of Recommendation: A)[12,17-20]. Special care should be taken when a single exon deletion is found on MLPA analysis. Apparently a single exon deletion on the MLPA can also occur due to point mutation or polymorphisms in the probe binding site, and therefore a second test, generally Sanger sequencing of the involved exon, should be done to avoid a false positive results[4,18,21]. The accuracy of an aCGH is slightly superior to MLPA of *DMD* due to its ability to detect intronic rearrangements and also because this technique does not have the above-mentioned chance of false positive results related to PCR-based techniques (Level of evidence: 3B, Class of Recommendation: B)[22]. The aCGH for DMD is less available than MLPA and the associated costs are generally higher, therefore both an MLPA or an aCGH of DMD are considered first-line tests for DMD diagnosis (Level of evidence: 1B, Class of Recommendation: A)[12,17-20]. Southern blot analysis and a multiplex PCR of *DMD* may also be performed as first-line tests in centers where these are the only available technologies.

If analysis by one or more of these techniques allows the identification of *DMD* mutation, then no further testing is required. If deletion/duplication testing is negative, then *DMD* sequencing should be done to look for point mutations or small deletions/insertions. The DMD is one of the largest human genes with 79 exons in total[16], which makes conventional Sanger sequencing very difficult, laborious and expensive. Next-generation sequencing, which allows massive and parallel sequencing of DNA fragments can now be considered the test of choice for *DMD* sequencing (Level of evidence: 3B, Class of Recommendation: B)[23,24]. Next-generation sequencing technologies; however, are not widely available and, therefore, there is a need for national or regional-based networks to support the DMD diagnosis in this phase.

If large deletions/duplications and sequencing analysis of *DMD* are negative, then a muscle biopsy should be ordered to confirm DMD or to consider an alternative diagnosis. The key tests done in muscle biopsy for DMD are immunohistochemistry and immunoblotting for dystrophin, which should be interpreted by an experienced neuromuscular pathologist (Level of evidence: 4, Class of Recommendation: C)[25]. Additionally, when variants without defined pathogenicity are found on the next-generation sequencing of *DMD*, confirmation of the DMD diagnosis by muscle biopsy with immunohistochemistry will also be required (Level of evidence: 5, Class of Recommendation: D, Expert opinion).

Electromyography and nerve-conduction studies were not considered by the expert panels to be indicated for specific assessment of DMD, except in exceptional cases (Level of evidence: 5, Class of Recommendation: D, Expert opinion). Muscle magnetic resonance imaging was not included as a confirmatory or screening test for DMD in this guideline. The expert panel considered that, currently, this method only has a clinical research role (Level of evidence: 5, Class of Recommendation: D, Expert opinion).

Carriers' detection

Detection of adult female carriers of DMD should be performed with molecular testing. The method of choice will depend on the identified mutation in the index case, generally MLPA or aCGH for large deletions/duplications and Sanger sequencing for point mutations, small deletions or insertions and splice site mutations (Level of evidence: 2B, Class of Recommendation: B)[18,19,20]. It is important to emphasize that multiplex PCR cannot detect heterozygous carriers for large deletions or duplications and, therefore, it is not recommended for carrier detection[12]. When the DMD diagnosis has only been confirmed by muscle biopsy with immunohistochemistry (no mutation found in the index case), serial CK measures (generally three different samples) may be used to estimate the probability of the individual being a carrier (Level of evidence: 2B, Class of Recommendation: B)[26,27]. Of note, more recent studies have shown that up to 47% of carriers of DMD and up to 70% of carriers of the Becker muscular dystrophy mutation have normal CK levels[28], indicating that counselors should be very cautious in assessing a carrier status based only on CK levels.

Prenatal and preimplantation diagnosis

A prenatal diagnosis of DMD can be performed with molecular analysis of the mutation identified in the family after amniocentesis or chorionic villus sampling[18]. However, considering that the current Brazilian criminal code prohibits pregnancy interruption due to DMD or other degenerative disorders, and that there is no prenatal or early neonatal intervention for DMD, a prenatal diagnosis of DMD is not currently justified in Brazil (Level of evidence: 5, Class of Recommendation: D, Expert opinion). Recommendations regarding prenatal diagnoses of DMD will vary according to each country's abortion legislation. Preimplantation diagnoses with embryo selection can be offered to women carriers of the *DMD* mutation (Level of evidence: 4, Class of Recommendation: C)[29,30]. A preimplantation diagnosis is an expensive procedure that is not available in the Unified Health System (Sistema Único de Saude, SUS) of Brazil. Of note, genetic counseling and discussion with couples of the many reproductive options (adoption, embryo sexing, egg donation, etc.) should be the first step in the reproductive care of families, before following any of the abovementioned strategies (Level of evidence: 5, Class of Recommendation: D, Expert opinion).

Steroid Therapy

Since the early 1970s, several studies have been published pointing to the benefits of glucocorticoids on the motor function of patients with DMD[31]. However, some practical issues regarding the best therapeutic schemes remain controversial. In order to clarify some hallmarks of glucocorticoid therapy for DMD patients, this working group proposed some pivotal topics of recommendation.

Are glucocorticoids recommended for DMD patients?

All patients diagnosed with DMD should have glucocorticoids prescribed (Level of evidence: 1A, Class of Recommendation: A)[32]. Comparisons between the natural history studies in the pre-glucocorticoid era and those after glucocorticoid therapy have demonstrated benefits in the motor function, giving longer independent gait, better core stabilization and upper limb function, prevention of spine deformities, and delaying the settlement of lower limb deformities[32-39]. The use of glucocorticoids is also responsible for nonmotor benefits, particularly in preserving respiratory function, preventing cardiomyopathy, improving quality of life parameters and prolonging life itself[38,40,41].

When to start glucocorticoids for DMD patients?

Glucocorticoid therapy is recommended for those boys with DMD in the two- to five-year-old age group, preferably in the plateau phase of motor deficits (also known as phase 2) or even in the decline phase of motor function (known as phase 3), and for all boys over the age of five no matter what the functional status is (Level of evidence: 4C, Class of Recommendation: C)[4,42,43].

The wide availability of genetic testing for high diagnostic suspicion patients has made the earlier diagnosis of DMD possible. Some examples are cases with familial history and/or early postnatal serum CK testing. However, due to immunological immaturity and the possibility of a precocious closure of the epiphyseal plate, a glucocorticoid prescription should not be offered to boys under the age of two years old, and should be carefully discussed with the family for those in the two- to three-year age group, taking into account the installation of a significant functional impairment involving the acquisition of motor skills (Level of evidence: 5, Class of Recommendation: D, Expert opinion).

Which glucocorticoid should be prescribed and what dose is recommended?

The first studies focusing on glucocorticoid therapy for DMD boys have demonstrated that prednisone, in a dose of 0.75/mg/Kg/daily, can achieve substantial effects on motor function in a six-month period[4,6,43]. Later studies have demonstrated that different drugs with an equivalent dose show similar effects: prednisone or prednisolone 0.75mg/Kg daily (Level of evidence: 1A, Class of Recommendation: A)[35] or deflazacort 0.9 to 1mg/Kg daily (Level of evidence: 3C, Class of Recommendation: C)[44,45].

Several different drug regimens have been evaluated, but not as extensively as the above daily schemes[44,45,46,47,48]. These different regimens aim to minimize side effects and/or improve the treatment adherence. Similar results to the standard glucocorticoid doses have been reached with intermittent doses of prednisolone 0.75mg "10 days on and 10 days off" regimen and prednisone 5mg/Kg on each weekend day (Level of evidence: 2B, Class of Recommendation: B)[33]. A slightly reduced effect on motor function was also observed with the regimen of prednisone 0.3mg/Kg daily, but with fewer side effects[49].

Therefore, the recommended first-line plan would be prednisone 0.75mg/kg or prednisolone 0.75mg/Kg on a daily basis, followed by prednisone or prednisolone in intermittent doses (10 days on and 10 days off), with the alternative being the use of deflazacort 0.9–1 mg/Kg daily.

Which parameters, and how often, should they be monitored while a DMD patient is on glucocorticoids?

Since DMD patients have, in general, a lifelong prospect of glucocorticoid usage, an optimal follow-up schedule is necessary for monitoring possible side effects[6]. An ideal outline of routine consultations takes into account three relevant factors: the patient's age, the type of glucocorticoid prescribed and the drug regimen adopted. As a general rule, we recommend a reevaluation in periods no longer than six months. Boys under the age of five and/or using an intermittent regimen (10 days on and 10 days off) should be seen three or four times a year, and those boys who are older, or on the other regimens, twice a year.

Several clinical parameters should routinely be monitored no matter which glucocorticoid therapy was chosen. Blood pressure, heart rate, oxygen saturation levels, height, wingspan, weight, Cushingoid features and ophthalmological evaluations are strongly recommended. Radiological assessment for bone age evaluation is important at the very first visit for proper follow-up[6]. (Level of evidence: 5D, Class of Recommendation: D, Expert opinion)

When should corticosteroid therapy be ended?

All patients with DMD should remain on glucocorticoid therapy as long as there are no side effects severe enough to justify its interruption. Although this is one question that remains unanswered[6], indirect evidence suggests it should be continued throughout life (Level of evidence: 5D, Class of Recommendation: D, Expert opinion). Significant side effects should be properly managed during regular clinical reassessments and a regimen shift is recommended in those patients with significant side effects[6].

There are some special situations that require a dose adjustment considering the metabolic modifications during chronic glucocorticoid therapy. Stressful situations usually require a dose increment, as in the case of infectious diseases that require a three-day dose doubling. The same holds true for surgical procedures, which demand a dose doubling on the day of the procedure.

Should corticosteroids be prescribed to nonambulant DMD patients?

There are few studies that specifically address the usefulness of glucocorticoids for nonambulant DMD boys. Three studies recommend the continuation of glucocorticoid therapy for the wheelchair-bound stage of the disease (Level of evidence: 3B, Class of Recommendation: B)[40,50,51]. For these patients, the aim of glucocorticoid therapy is to preserve heart, lung and upper limb function as much as possible[40,50,51].

The above recommendations are summarized in the Table 3.

Future drug therapy perspectives

A number of promising molecular targeted therapies have been developed and some of them have gone from preclinical to clinical trials in the present century. For this topic, clinicaltrials.gov, new drugs online, and the regulatory agencies sites were also reviewed. By December 2016, there were 12 interventional studies listed as completed, and 33 phase 3 studies (clinicaltrials.gov); however, not all those listed are indeed phase 3 studies.

Therapies directed toward cardiac protection, supplementation, corticosteroids or physical therapy interventions were not included, although initially listed by this working group, as they will be topics in the Part 2 article. The recommendations in this section are made based on phase 3 clinical study publications. However, as DMD is a rare and incapacitating disease, phase 2 studies with relevant results between treated and placebo groups have also been considered.

International regulatory agencies have been handling some new DMD drug submissions and a quick overview of their statements follow.

Exon skipping agents

Drisapersen is an oligonucleotide (given by subcutaneous route) that alters the splicing of the dystrophin mRNA transcript, eliminating exon 51 and restoring the reading frame of *DMD* for some specific exon deletions and allowing the production of shorter, but functional, dystrophin. The phase 3 trial was completed, but results were not published at our last search. Results of a phase 2 study were published with positive results[52]. The submitted data of phase 2 and 3 studies were not approved by the Food and Drug Administration (FDA), which considered that substantial evidence of effectiveness had not been met[53]. In May 2016, the marketing authorization application to the European Medicines Agency for drisapersen was withdrawn by the sponsoring pharmaceutical company [54]

Eteplirsen is a morpholino antisense oligomer, with a similar mechanism of action to drisapersen, but administered intravenously. The FDA gave accelerated approval of eteplirsen in September 2016, based on a phase 2 trial and its extended study comparing matched historical controls[55,56]. This has raised discussion and concern[57]. At the time of our last search, there had been no European Medicines Agency approval for eteplirsen[58]

Read-through agent

Ataluren is an oral drug that acts at the ribosome level inducing reading-through premature stop codons due to nonsense mutations. A phase 3 trial of ataluren has been completed, but the results were not published at the time of our search. Results of a phase 2 have been published[59]. Ataluren received conditional marketing authorization from the European Commission to treat ambulatory DMD patients, aged five years and older with *DMD* nonsense mutation, considering its risk-benefit ratio[60]. A management plan with detailed activities and interventions has been developed to ensure that ataluren is used as safely as possible. Every year, the European Medicines Agency will review any new information that becomes available and an update will follow. At our last search, there was no FDA approval for ataluren[61].

Antioxidants

Idebenone is a potent antioxidant agent with a similar structure to coenzyme Q10 that has been tested for a variety of neurologic disorders (e.g. Alzheimer's disease, Friedreich's ataxia, mitochondrial disorders, etc.) and, most recently, for DMD. Although nonspecific for DMD, the working group

Table 3. Steroid therapy drugs and regimens.

Drug (dose- regimen)	Favorable features	Disadvantages	Follow up schedule*
Deflazacort (0.9mg/Kg - daily)	Fewer mineralocorticoid effects; less weight gain	Cataracts; high-priced; unavailable in Brazilian public health care system	2/year
Prednisone (0.75mg/Kg - daily)	Reasonable cost; available in Brazilian public health care system	Higher bone decalcification risk; more weight gain	2/year
Prednisone (5mg/Kg – weekend days)	Low cost; available in Brazilian public health care system	Higher bone decalcification risk; more weight gain	2/year
Prednisolone (0.75mg/Kg - daily)	Low cost;	Unavailable in Brazilian public health care system; higher bone decalcification risk; more weight gain	2/year
Prednisolone (0.75mg/Kg – 10 days on and 10 days off)	Low cost; fewer side effects	Unavailable in Brazilian public health care system; higher bone decalcification risk; more weight gain	3/year

*Periods no longer than six months for clinical reassessment are desirable for side effect monitoring. Children under the age of five should have four routine visits per year.

considered it to be worthy of mention. A phase 3 trial was completed, and results were published. The studies aimed at patients who were not taking steroids, and the authors used pulmonary function tests as the primary endpoints[52]. The drug is not approved by the FDA[63] (but is authorized for use in the European community for Leber's hereditary optic neuropathy[64].

A summary of the exon skipping and read-through studies can be found in Table 4.

The working group considered that the strength of evidence of prospective drugs was not sufficient for a formal recommendation at this point. However, this statement should be reviewed in the near future after publication of known completed phase 3 clinical trials.

Table 4. Main findings of clinical trials for the new agents directed at specific *DMD* mutations.

Molecule	Action	Target population	Sample size – study phase – duration	Primary / Secondary endpoint	Conclusion
Drisapersen[52]	2'-*O*-methyl–Phosphorothioate RNA oligonucleotide that facilitates exon 51 skipping in dystrophin pre-mRNA	DMD ≥ 5 years; time to rise from floor ≤ 7 s; mutation correctable by skipping exon 51	53 patients (18 continuous once a week; 17 intermittent with 9 doses in 10 weeks; 18 placebo) – phase 2 – 48 weeks	Change in 6MWD at week 25	At week 25, 6MWD was higher for continuous treatment (p = 0.014).
				Change in 6MWD at week 49; muscle strength, timed tests, NSAA, dystrophin levels at muscle biopsy	At week 49 no significant difference was observed between groups. Other secondary endpoints were not statistically different in treated and control groups.
Eteplirsen[55]	Phosphorodiamidate morpholino oligomer (PMO); facilitates skipping of exon 51 during pre-mRNA splicing	DMD with mutations correctable by skipping exon 51	12 treated and 13 historical controls – phase 2 – 3 years	Change in 6MWD Rate of loss of independent ambulation; relative stability of pulmonary function	Slower rate of decline in ambulation (p < 0.01)
Ataluren[59]	Small molecule that promotes translational read-through of premature stop codons	DMD patients ≥ 5 years with nonsense point mutation	174 patients (57 on 40 mg/kg/day; 60 on 80 mg/kg/day; 57 on placebo) – phase 2 – 48 weeks	Change in 6MWD at week 48	Mean decline in 6MWD at week 48: difference of 29.7 m between 40mg/kg/day and placebo (p = 0.149). Difference between 80 mg/kg/day and placebo was negligible. Patients with 6MWD < 350m treated with 40mg/kg/day: 6MWD mean at week 48 was 68.2m better than placebo (p = 0.0053)
				Timed function tests, functional test method grading, at home activity, myometry, patient/caregiver-reported accidental falls, PedsQL physical functioning and psychological domains	Timed function tests: group 40mg/kg/day trended toward less decline in muscle function compared with placebo. However they met the threshold for clinically meaningful differences.

mRNA: messenger RNA; 6MWD: 6-minute walking distance; NSAA: North Star Ambulatory Assessment; DMD: Duchenne muscular dystrophy.

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