

**Adverse events:** Not described.

**Study ID:** Resende 2001

(Published as abstract only)

**Design:** Open

**No of patients:** 36

**Age (years):** Not described

**Regimen:** Deflazacort

1 mg/kg/day

**Treatment period:** 15 treated for 12 - 43 months

**Outcome:** 11 of the 15 boys ambulant beyond 10 years.

**Adverse events:** Gastrointestinal disturbances and depression needing discontinuation of treatment in 1 patient. Cataracts in 2 patients.

**Study ID:** de Groot 2002

(Published as abstract only)

**Design:** Open

**No of patients:** 18

**Age (years):** 4.5 - 9 years

**Regimen:** Prednisolone 0.75mg/kg/day, given 10 days on and 10 days

**Treatment period:** Not described

**Outcome:** "Functional ability improved".

**Adverse events:** "Osteoporosis 2 -3 SD at the start, but did not change under treatment".

**Study ID:** Ahlander 2003 (Published as abstract only)

**Design:** Retrospective review

**No of patients:** 43 (15 not treated)

**Age (years):**

**Regimen:** Prednisone 0.35mg/kg/day

**Treatment period:** Up to 7.5 years

**Outcome:** Authors perceived a prolongation of walking by 0.9 years, but the patient groups compared are from different eras and there may be confounding factors.

**Adverse events:** Behavioural problems, weight gain, dyspepsia, growth retardation.

### Table 03 Excluded (randomised studies)

**Study ID:** Fenichel 1991a

**Design:** Double-blind

**No. of patients:** 103

**Age (years):** 5 to 15 years

**Regimen:** Prednisone 1.25mg/kg/alternate day

Prednisone 2.5mg/kg alternate day

**Treatment period:** 6 months

**Outcome:** Improved at 3 months

**Adverse events:** Similar side effects on daily and alternate day regimens

**Study ID:** Griggs 1993

**Design:** Randomised

**No. of patients:** 107

**Age (years):** 5 to 15 years

**Regimen:** Prednisone 0.75mg/kg/day

Azathiaoprine 2.5mg/kg/day

**Treatment period:** 18 months

12 months

**Outcome:** Strength and function improved

**Adverse events:** No additional benefit of

Azathiaoprine

**Study ID:** Bonifati 2000

**Design:** Randomised

**No. of patients:** 18

**Age (years):** 5 to 14 years

**Regimen:** Prednisolone 0.75mg/kg/day

Deflazacort 0.9mg/kg/day

**Treatment period:** 1 year

**Outcome:** Prednisolone and deflazacort equally effective

**Adverse events:** Weight gain more significant in prednisolone group

**Study ID:** Brooke 1996

(published as abstract only)

**Design:** Randomised

**No. of patients:** 34

**Age (years):** 5 to 17 years

**Regimen:** Phase 1

Placebo

Prednisone 0.75mg/kg/? (day/

Deflazacort 0.9mg/kg/?/day

Deflazacort 1.2mg/kg/?/day

Phase 2

Prednisone 0.75mg/kg/?/day

Deflazacort 0.9mg/kg/?/day

Deflazacort 1.2mg/kg/?/day

**Treatment period:** Phase 1

3 months

Phase 2

9 months

**Outcome:** Increased strength in treatment groups at 3 months

Not reported

**Adverse events:** Weight gain in prednisone group

Weight gain more significant in prednisone group

**Study ID:** Todorovic 1998

(published as abstract only)

**Design:** Randomised

**No. of patients:** 34

**Age (years):** 5 to 17 years

**Regimen:** Prednisone 2mg/kg alternate days

**Treatment period:** Mean follow-up 20 months

**Outcome:** "Strength improved over 8 months and plateaued for 8 months.

"Ambulation prolonged for 1 year 2 months".

**Adverse events:** "Few side effects" - with "maximum efforts" including strict deprivation of salt and reduced sugar

**Study ID:** Reitter 1995

(Data reported in Dubowitz 2000b)

**Design:** Double-blind

**No. of patients:** 100

**Age (years):** 5 to until ambulant

**Regimen:** Prednisone 0.75mg/kg/day

Deflazacort 0.9mg/kg/day

**Treatment period:** 2 years

**Outcome:** Muscle function stabilised

**Adverse events:** Excessive weight gain in prednisolone group

Cataracts in 27% of deflazacort.

**Study ID:** Vasanth 1996

(published as abstract only)

**Design:** Randomised controlled trial of prednisolone, ayurvedic drug and placebo

**No. of patients:** 28

**Age (years):** not reported

**Regimen:** Prednisone

1 mg/kg/day

**Treatment period:** 7 months

**Outcome:** Stability in prednisolone group, Deterioration in the other two groups

**Adverse events:** "mild weight gain" in Prednisolone group

**Study ID:** Vasanth 1996

(Unpublished Data provided by Dr A B Taly at the National Institute of Mental Health & NeuroSciences, Bangalore)

**Design:** Randomised, non-blinded trial, comparing prednisolone with a combination of ayurvedic drugs. (participants who had been given placebo in the initial part of the study, were put on ayurvedic drug treatment)

**No. of patients:** 128

(32 on prednisolone treatment, and 96 on ayurvedic drug treatment)

**Age (years):** not reported

**Regimen:** Prednisone

1 mg/kg/day

**Treatment period:** 2 years

(2 year follow up data available only for 18/32 participants in the prednisone group and 29/96 in the ayurvedic treatment group.)

**Outcome:** Strength and function not statistically different in the two groups at 2 years.

Of the boys who lost walking ability, Mean age of loss of ambulation in 13 boys in the prednisone group was 11.88 (SD 2.7) years. and 10.97 (SD 2.2) years in the ayurvedic treatment group.

**Adverse events:** "Most children had weight gain and developed striae"

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# Practice Parameter: Corticosteroid treatment of Duchenne dystrophy

## Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society

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**Abstract—Background:** The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society develop practice parameters as strategies for patient management based on analysis of evidence. **Objective:** To review available evidence on corticosteroid treatment of boys with Duchenne dystrophy. **Methods:** Relevant literature was reviewed, abstracted, and classified. Recommendations were based on a four-tiered scheme of evidence classification, and areas for future research are defined. **Results:** Seven class I studies and numerous less rigorous trials all demonstrated that corticosteroid treatment for 6 months with prednisone (0.75 or 1.5 mg/kg/day) increased muscle strength, performance, and pulmonary function and significantly slowed the progression of weakness. Two class I trials examined the effect of lower dosage of prednisone (0.30 and 0.35 mg/kg/day), demonstrated lesser but similar benefits, and showed a lower frequency of side effects (e.g., weight gain). The only significant side effects in all class I trials were weight gain and development of a cushingoid facial appearance. One longer-term trial of daily prednisone (0.3 to 0.7 mg/kg/day), a class III study, showed prolongation of functional ability and slower progression of weakness in patients during 3 years of treatment. One class IV, open trial of alternate-day prednisone (2 mg/kg for 2 months, then two-thirds dose every other day) extended ambulation by approximately 2 years in treated compared with untreated patients. Deflazacort, a corticosteroid similar in structure to prednisone, produced similar improvement in muscle strength and function with a similar side effect profile. **Conclusions:** Prednisone has been demonstrated to have a beneficial effect on muscle strength and function in boys with Duchenne dystrophy and should be offered (at a dose of 0.75 mg/kg/day) as treatment. If side effects require a decrease in prednisone, tapering to dosages as low as 0.3 mg/kg/day gives less robust but significant improvement. Deflazacort (0.9 mg/kg/day) can also be used for the treatment of Duchenne dystrophy in countries in which it is available. Benefits and side effects of corticosteroid therapy need to be monitored. The offer of treatment with corticosteroids should include a balanced discussion of potential risks.

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Duchenne dystrophy (DD), an X-linked, recessive disorder, with onset before age 5 years, is the most common and severe form of childhood muscular

dystrophy.<sup>1–3</sup> The specific molecular defect is an absence or marked deficiency of dystrophin, a large membrane-associated protein that is part of the dystrophin–glycoprotein complex.<sup>1</sup> Affected boys develop neck flexor, anterior abdominal, hip, and shoulder girdle muscle weakness in early childhood, with loss of ambulation between ages 7 and 12.<sup>4,5</sup>

Additional material related to this article can be found on the *Neurology* Web site. Go to [www.neurology.org](http://www.neurology.org) and scroll down the Table of Contents for the January 11 issue to find the title link for this article.

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Death usually occurs in the 20s, with the chance of surviving to age 25 being determined mainly by the use of ventilatory support.<sup>6</sup> Until treatment of the basic genetic defect becomes available, management depends on medical, surgical, and rehabilitative approaches that optimize and maintain patient function and comfort.<sup>7</sup> Of the different medications that have been tried as potential treatments for DD, only the corticosteroids prednisone and deflazacort have shown potential for providing temporary improvement. This improvement results mainly from slowing the rate of progression or stabilizing muscle strength and function. Corticosteroid therapy also leads to side effects; as yet, there is no consensus regarding its use as standard treatment for DD.<sup>8</sup>

The specific cellular events responsible for the beneficial effects of corticosteroid therapy in DD are not known. Investigators have proposed various possibilities based mainly on observations in mouse models of muscular dystrophy and on a limited number of studies in patients.<sup>9</sup> These possibilities include 1) altering the mRNA levels of structural, signaling, and immune response genes<sup>9</sup>; 2) reducing cytotoxic T lymphocytes<sup>10,11</sup>; 3) lowering calcium influx and concentration<sup>12,13</sup>; 4) increasing laminin expression and myogenic repair<sup>14</sup>; 5) retarding muscle apoptosis and cellular infiltration<sup>15</sup>; 6) enhancing dystrophin expression<sup>16</sup>; 7) affecting neuromuscular transmission<sup>17</sup>; 8) protecting against mechanically induced fiber damage<sup>18</sup>; 9) attenuating muscle fiber necrosis<sup>19</sup>; 10) slowing the rate of skeletal muscle breakdown<sup>20-22</sup>; and 11) increasing muscle levels of taurine and creatine.<sup>23</sup> More studies are necessary to establish the precise cellular mechanism(s) by which corticosteroids produce their beneficial effects in DD. Studies using azathioprine as an alternative immunosuppressive treatment to prednisone showed no beneficial effect and suggested that the effects of prednisone observed in clinical studies are unlikely to result from its immunosuppressive actions.<sup>24</sup>

This practice parameter examines previously published data on the use of different corticosteroids in the treatment of DD to determine whether there are sufficient benefits with limited risks to recommend their use in this condition.

**Description of process.** Computer-assisted literature searches were conducted with the assistance of the University of Minnesota Biomedical Information Services Research Librarian for relevant articles published from 1966 to 2004. Databases searched included Medline (1966 to 2004) and Current Contents using the search terms Duchenne dystrophy, corticosteroids, steroids, prednisone, deflazacort, and treatment. All search titles and abstracts were analyzed for content. The search included all languages. Articles on therapy, prognosis, and side effects were selected, including original and review articles. There were 25 peer-reviewed articles chosen for detailed review. Individual committee members reviewed, abstracted, and classified these articles to

assess the quality of data related to study design and treatment effect. Abstracted data included the number of patients, age range, design of study, duration, dosage, outcome measures, response to treatment, and side effects.

A four-tiered classification scheme for therapeutic evidence recently approved by the Quality Standards Subcommittee was utilized as part of this assessment (see appendix 1). Depending on the strength of this evidence, it was decided whether specific recommendations could be made and, if so, the strength of these recommendations (see appendix 2). Evidence pertinent to each treatment together with the committee's evidence-based recommendations is presented.

**Prednisone/prednisolone: What are the benefits and side effects of prednisone/prednisolone in boys with DD? Evidence.** Class I studies: therapeutic effects. Seven class I studies (n = 276) have demonstrated that prednisone is beneficial in DD and that 0.75 mg/kg/day is optimal as an initial dosage for boys between 5 and 15 years old (see table E-1 on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)). Six of the seven studies involved the vast majority of patients (n = 221) and ranged in duration from 6 to 18 months.<sup>24-29</sup> The relatively short duration of treatment in these six studies made the use of endpoints, such as cessation of ambulation or decline in forced vital capacity (FVC), impractical as measures of efficacy. These potential endpoints to evaluate treatment require a few years or longer to reach. The seven class I studies have relied on standardized measurements of muscle strength and function as described below to assess efficacy.

Four of the class I trials evaluated the dose-response relation, onset of action, and duration of response to daily treatment with prednisone and were performed by the Collaborative Investigations in Duchenne Dystrophy Study Group.<sup>24-27</sup> Prednisone (1.5, 0.75, or 0.3 mg/kg/day) was given daily for 6 months, and at each dose, it led to improvements in muscle strength, in the 24-hour urinary excretion of creatinine (a surrogate measure of muscle mass), and in muscle and pulmonary function.

**Muscle strength.** Strength was assessed using a standardized scoring system that evaluated 34 muscle groups (using a scale of 0 to 10 for each muscle, in which 10 equaled normal strength). Scores were combined to calculate an average muscle strength score for the 34 muscle groups. In these studies, strength reached a maximum by 3 months and was maintained at 6 months<sup>25,27</sup> and at 18 months.<sup>24</sup> Comparison of the average muscle strength scores before and after 6 months of treatment showed a 4.8% decrease in the placebo group compared with a 6.7% increase in the 0.75 mg/kg/day prednisone group ( $p < 0.0001$ ) and a 5.0% increase in the 1.5 mg/kg/day prednisone group ( $p < 0.0001$ ). This response to treatment gives a net percentage increase in average strength score of 11% for boys receiving

0.75 mg/kg/day of prednisone and 9.8% for boys receiving 1.5 mg/kg/day compared with placebo.<sup>25</sup> These improvements were accompanied by an increase in muscle mass and by an improvement in function.

*Twenty-four-hour urinary excretion of creatinine.* After 6 months, boys receiving placebo showed a decline in 24-hour excretion of creatinine (baseline = 203 mg/24 hours; after 6 months = 190 mg/24 hours), consistent with a mild loss of muscle bulk.<sup>25</sup> In contrast, urinary creatinine excretion increased after 6 months by 30.5% in boys taking 0.75 mg/kg/day of prednisone and by 28.6% in those taking 1.5 mg/kg/day ( $p < 0.0001$ ), consistent with an increase in muscle mass for both doses of prednisone. These findings demonstrate an anabolic action of prednisone in DD in contrast to its stated catabolic effects on skeletal muscle in normal unaffected individuals.

*Muscle function.* Each patient had standardized timed function testing (e.g., time to climb four stairs, travel 9 m, or arise from supine to standing), and comparisons were carried out between the mean times for each group. Results after 6 months of treatment showed that the average time to climb four stairs was 7.05 seconds in the placebo group and approximately 4.0 seconds in the 0.75 and 1.5 mg/kg/day prednisone groups ( $p < 0.0001$ ), an average of 3.0 seconds faster (i.e., 43% faster) with prednisone treatment.<sup>25</sup> The average time to travel 9 m was 9.68 seconds in the placebo group and approximately 2 seconds faster (i.e., 28% faster) in the two treatment groups ( $p < 0.005$ ). The average time to arise from supine to standing was 6.17 seconds in the placebo group and was 2.0 (32%) and 2.7 (44%) seconds faster in the 0.75 and 1.5 mg/kg/day prednisone groups ( $p < 0.0002$ ).<sup>25</sup>

*Pulmonary function.* Standardized measurements of FVC were higher after 6 months of daily prednisone. In the placebo group, FVC averaged 1.52 L, whereas FVC was 10.5% ( $p < 0.0004$ ) and 8.3% ( $p < 0.002$ ) higher in the 0.75 and 1.5 mg/kg/day prednisone groups.<sup>25</sup>

*Every-other-day treatment with prednisone.* At the completion of one of the 6-month trials of daily prednisone (placebo vs 0.75 and 1.5 mg/kg/day dosages of prednisone),<sup>25</sup> patients were kept blind to their treatment; each group underwent a switch to alternate-day therapy (every other day) with prednisone (placebo group to 2.5 mg/kg every other day, 0.75 mg/kg/day group to 1.25 mg/kg every other day, and 1.5 mg/kg/day group to 2.5 mg/kg every other day).<sup>26</sup> During the initial 3 months of alternate-day therapy, there was no significant difference in average muscle strength score comparing alternate-day with daily prednisone between the groups (see table E-1 on the *Neurology* Web site). However, during months 4 to 6 of alternate-day therapy, patients taking prednisone 1.25 or 2.5 mg/kg every other day lost the major benefits on strength and muscle function<sup>26</sup> that had occurred previously with daily prednisone

and showed a decline in average muscle strength that paralleled the previously established rates typical for the natural history of DD.<sup>4,5</sup> These findings indicate that alternate-day prednisone at dosages of 1.25 and 2.5 mg/kg every other day is not sufficient to achieve the sustained beneficial effects that occur with daily prednisone in dosages ranging from 0.3 to 1.5 mg/kg/day.

An earlier class I study<sup>30</sup> evaluated the efficacy of 5.0 mg/kg every other day of prednisolone. Investigators gave prednisolone 5.0 mg/kg every other day or placebo every other day for 3 years. All seven boys in the placebo group became nonambulatory, whereas six of the seven boys receiving prednisolone remained ambulatory after 36 months of treatment. At the time of publication, the authors felt that prednisolone had no ultimate value in the treatment of DD. In recent years, they have changed their interpretation (personal communication at MDA Clinic Directors Meeting, 2002). Their observations suggest that a dosage of prednisolone higher than 2.5 mg/kg every other day is necessary to produce sustained improvement comparable with the improvement that occurs with daily prednisone (see tables E-1 and E-2 on the *Neurology* Web site). The observations that 5.0 mg/kg of prednisolone every other day is effective but 2.5 mg/kg of prednisone does not produce a sustained benefit provides a rationale for future research to investigate the efficacy of high-dosage alternate-day or intermittent corticosteroid treatments.

*Lower portion of dose response for prednisone in DD.* Three class I studies in which prednisone was given daily have examined the lower end of the dose-response curve (see table E-1 on the *Neurology* Web site).<sup>24,27,29</sup> In two of these studies, there was a comparison of the efficacy of 0.3 and 0.75 mg/kg/day of prednisone.<sup>24,27</sup> Average muscle strength increased significantly by 10 days with 0.3 and 0.75 mg/kg/day dosages of prednisone, indicating that there is an early beneficial effect prior to the time that one would expect an increase in muscle mass. The increase is significantly greater for 0.75 compared with 0.3 mg/kg/day. There is continued improvement in strength up to 3 months, at which point improvement in strength and function reached a maximum. This maximum benefit was sustained for at least 18 months.<sup>24,27</sup>

The beneficial effects most apparent to patients and their care providers were improvements in their timed function tests. Each timed function test showed a parallel and highly significant improvement after 6 months of treatment with 0.3 and 0.75 mg/kg/day doses of prednisone.<sup>27</sup> The time to climb four stairs averaged 8.44 seconds in the placebo group and was 2.7 (32%) seconds faster in the 0.3 mg/kg/day prednisone group and 4.2 (50%) seconds faster in the 0.75 mg/kg/day group ( $p < 0.0001$ ). The time to travel 9 m averaged 8.51 seconds in the placebo group and was 1.2 (14%) and 2.1 (25%) seconds faster in the 0.3 and 0.75 mg/kg/day prednisone

groups ( $p < 0.003$ ). The time to arise from supine to standing averaged 8.23 seconds in the placebo group and was 1.6 (19%) and 3.7 (45%) seconds faster in the 0.3 and 0.75 mg/kg/day prednisone groups ( $p < 0.0003$ ). The FVC also increased after 6 months of prednisone. It averaged 1.48 L in the placebo group and increased by 10% in the 0.3 mg/kg/day prednisone group and 11.6% in the 0.75 mg/kg/day group ( $p < 0.001$ ).<sup>27</sup>

Optimal time to begin treatment with prednisone. There have been no class I studies that examined the optimal age to begin treatment or the optimal duration of treatment with corticosteroids.

Class I studies: side effects. The class I studies that evaluated daily prednisone treatment (0.3, 0.75, or 1.5 mg/kg/day) found that the most common side effects were weight gain and development of a cushingoid facial appearance 6 to 18 months after treatment.<sup>24,25,27</sup> There was no significant increase in the number of patients with hypertension, diabetes mellitus, gastrointestinal bleeding, psychosis, compression fractures, or cataracts (see table E-1 on the *Neurology* Web site). Frequency and severity of side effects were similar in patients receiving high-dose daily prednisone (0.75 or 1.5 mg/kg/day) and comparable alternate-day treatment (1.25 or 2.5 mg/kg every other day).<sup>26</sup> Behavioral changes, gastrointestinal symptoms, and acne occurred equally in boys receiving placebo or prednisone for 6 to 18 months.<sup>24,25,27</sup>

Weight gain. Weight gain was the most common side effect and occurred over a range of prednisone dosages (0.3 to 1.5 mg/kg/day). Table E-2 (see the *Neurology* Web site) presents data on the weight gained over baseline weight for two of the class I studies of 6 months' duration<sup>25,27</sup> and for one class I study of 18 months' duration. In patients treated for 6 months, 20 to 24% of those receiving placebo developed an increase in weight of  $\geq 10\%$  in contrast to 48% of patients receiving 0.3 mg of prednisone and to 75 to 80% of patients receiving 0.75 mg/kg/day.<sup>24,27</sup> Likewise, 43% of patients receiving placebo gained  $>20\%$  of their baseline weight after 18 months in contrast to 66% of patients receiving 0.3 mg/kg/day and 75% of patients receiving 0.75 mg/kg/day.<sup>24</sup> Despite gain in weight, patients showed clinical improvement as described above.

The distribution of the weight gained (fat vs muscle) differed between patients receiving prednisone compared with placebo. Analysis of the 24-hour urinary creatinine excretion at the completion of the 18-month prednisone trial demonstrated a 36% increase in muscle mass in the 0.75 mg/kg/day prednisone group compared with placebo-treated patients.<sup>24</sup> This observation points out that the weight gained with prednisone is not solely an undesirable side effect, and it also poses a challenge to us as care providers to determine an appropriate definition of "excessive weight gain" in DD patients receiving corticosteroids.

Table E-2 (see the *Neurology* Web site) provides additional data describing the weight gain observed

in patients receiving 0.3 and 0.75 mg/kg/day of prednisone. Patients receiving these dosages of prednisone had similar increases in appetite and irritability, whereas patients receiving 0.75 mg/kg/day had a greater frequency of hirsutism and cushingoid appearance.<sup>24</sup>

It is interesting to note that in one study, the investigators found no difference in weight gain in ambulatory prednisone-treated patients compared with those receiving placebo,<sup>29</sup> but in the nonambulatory patients receiving prednisone, those patients had a greater weight gain than the placebo group. A similar observation, that weight gain is not a significant side effect in ambulatory patients receiving the corticosteroid deflazacort, has been made in other studies.<sup>32</sup> The beneficial effects of ambulation and physical activity in preventing weight gain during treatment with prednisone and deflazacort suggest that weight bearing and exercise ameliorate weight gain during corticosteroid therapy in patients with DD. Further studies are necessary to clarify the role of exercise in DD in patients receiving or not receiving prednisone or other corticosteroids. For the present, it seems prudent for patients to follow an individualized preventive nutrition and exercise program to avoid weight gain associated with corticosteroid therapy.

Class IV studies and treatment regimens. Results of 11 class IV studies ( $n = 237$ ) of prednisone (see table E-3 on the *Neurology* Web site) are all consistent with the results of the class I studies summarized in table E-1. Five studies involved participation of  $\geq 14$  patients whose ages ranged from 3 to 15 years.<sup>33-36,40</sup> The duration of treatment varied from 6 months to 11 years.

Long-term daily prednisone. One long-term study of daily prednisone showed significant sustained improvements in arm and leg function, timed function tests, and FVC after 3 years of treatment.<sup>31</sup> In this study, the most common side effect was weight gain. The annual percentage weight gain was 24% for boys receiving prednisone in a dosage of  $>0.65$  mg/kg/day and 28% in the group receiving a dose of  $<0.65$  mg/kg/day. Of the total population of 92 boys receiving daily prednisone, 10 developed asymptomatic cataracts and 10 had transient glucosuria. Glucosuria resolved after dosage reduction.

Combinations of dosage regimens for prednisone. Four studies have examined various combinations of daily, alternate-day, or cyclical prednisone treatment (see table E-3 on the *Neurology* Web site).<sup>33,34,36,40</sup> Two class IV studies ( $n = 30$ ; 2 mg/kg/day for 2 months followed by alternate-day prednisone at two-thirds the original daily dose) have demonstrated that alternate-day prednisone prolongs ambulation.<sup>33,34</sup> In the 12 patients who received long-term treatment, ambulation was prolonged for  $>2$  years.<sup>34</sup> A study of 32 patients, age 6 to 14 years, found that intermittent cyclical daily prednisone (0.75 mg/kg/day for 10 days each month) had no long-term benefit.<sup>36</sup> In contrast, another class IV study of 20

patients, age 5 to 11, found that high-dose, intermittent, weekly oral prednisone (5 mg/kg given each Friday and Saturday) significantly improved strength over a 6-month period but did not improve timed function tests.<sup>40</sup>

**Studies of prednisone in patients under age 5.** Limited publications are available to guide clinicians as to the desirability of initiating corticosteroids in patients before age 5 years.<sup>37-39,41</sup> Two previous reports describe initiating treatment in two very young patients: one age 3 years and the other age 3 years 6 months.<sup>33,34</sup> Only a few more recent studies are available to guide clinicians in determining if starting prednisone in preschool-age patients is safe and appropriate.

Four reports, encompassing a total of 12 patients, have described encouraging results when corticosteroid therapy was begun before 5 years of age. In these studies, the treatment regimens have employed either pulsed therapy, giving corticosteroid four to six times per year,<sup>37</sup> intermittent corticosteroid treatment, given in cycles of 10 days on and 10 days off,<sup>38,39</sup> or alternate-day prednisone.<sup>41</sup> It is important to note that these class IV studies are not randomized controlled investigations. They are observational studies and need confirmation with appropriately designed double-blind, randomized, controlled studies.

**Deflazacort: What are the benefits and side effects of treatment with deflazacort in boys with DD?** Deflazacort is an oxazoline analogue of prednisone and has an estimated dosage equivalency of 1:1.3 compared with prednisone. That is, 1.3 mg of deflazacort is approximately equivalent to 1.0 mg of prednisone, and in the trials of daily treatment, 0.9 mg/kg/day of deflazacort is almost equivalent to 0.75 mg/kg/day of prednisone.<sup>42</sup> It is important to emphasize that biologic equivalence between deflazacort and prednisone also depends on the specific actions under examination. Deflazacort was evaluated in the hope that it would have fewer side effects than prednisone. It is not available in the United States.

**Evidence. Class I studies: therapeutic effects.** Evidence from two class I studies of deflazacort (see table E-4 on the *Neurology* Web site) demonstrated that daily treatment for 9 months with 1.0 mg/kg/day<sup>43</sup> and alternate-day treatment for 2 years with 2.0 mg/kg every other day<sup>44</sup> increase muscle strength and function. In contrast to the results of alternate-day therapy with prednisone (1.25 and 2.5 mg/kg every other day),<sup>30</sup> one study used a dosage of deflazacort of 2.0 mg/kg every other day and showed sustained improvement over 2 years, including improvement in average muscle strength and in timed function testing (gait, stair climb, arising from the floor).<sup>44</sup> Eleven patients lost their ability to ambulate during the trial of deflazacort: seven in the placebo group and four in the deflazacort groups. The mean prolongation of ambulation was 13 months.

**Class I studies: side effects.** Side effects are summarized in table E-4 (see the *Neurology* Web site). The findings in both class I trials of deflazacort indicate that deflazacort, like prednisone, produces beneficial effects on muscle strength and function and that side effects were similar to prednisone.

**Class II to IV studies. Therapeutic effects.** Table E-4 (see the *Neurology* Web site) includes and summarizes two relatively long-term class IV (3.2 and 5.4 years) open trials of daily treatment with deflazacort.<sup>32,45</sup> In one study, all 24 untreated patients stopped walking at an average age of  $9.8 \pm 1.8$  years.<sup>32</sup> Of the 30 boys receiving deflazacort, only 7 stopped walking (at  $12.3 \pm 2.7$  years). Of the 23 boys who continued to walk, 21 are older than 10. Treatment with deflazacort maintained their FVC, and spine stabilization surgery was not needed in any of the deflazacort-treated patients.<sup>32</sup> The second trial of treatment with deflazacort also showed a significant and sustained increase in muscle strength and FVC compared with untreated patients.<sup>45</sup>

**Side effects.** Mean weight in deflazacort-treated patients in one of the above-mentioned studies remained between the 25th and 50th percentiles, whereas the untreated group mean weight rose to the 75th to 90th percentiles at age 13.<sup>32</sup> As noted previously, the beneficial effects of greater increased muscular activity may have lessened the potential side effect of weight gain. Ten of the 30 deflazacort-treated patients in this study had asymptomatic cataracts. There were no cataracts in the untreated group.

Side effects were more frequent in a longer-term study that lasted for >5 years.<sup>46</sup> Two of 13 children were obese, 6 had asymptomatic cataracts, and 11 had decreased linear growth. There was no difference in the occurrence of fractures or degree of osteoporosis in the group receiving deflazacort compared with untreated patients. Three of the studies with deflazacort provide specific data comparing weight gain in deflazacort-treated patients and control subjects.<sup>44,45,32</sup> One class I study found that 8 of 13 patients (only 13 of 17 treated boys completed 2 years of therapy) receiving alternate-day deflazacort (2 mg/kg) gained weight (>20% over baseline) compared with 3 of 6 placebo-treated patients (only 6 of 11 boys receiving placebo completed 2 years of treatment).<sup>44</sup> Data from two class IV studies in which lower-dose daily deflazacort (0.9 mg/kg/day) was used showed few side effects.<sup>45,32</sup> For example, in one of the studies, there was a range in body mass index (i.e., weight in kg/m<sup>2</sup> surface area) of 13.3 to 27.0 kg/m<sup>2</sup> for the 13 boys receiving deflazacort and 10.3 to 26.4 kg/m<sup>2</sup> for the 13 untreated boys after 65 months.<sup>45</sup> In the other study, the mean height for the 12 boys who received deflazacort for >3 years was at the 3rd percentile, while their weights ranged between the 25th and 50th percentiles.<sup>32</sup> Of the 24 untreated boys, their mean heights and weights both ranged between the 25th and 50th percentiles, indicating a greater mean weight for age for height after 3 years of treat-

ment.<sup>32</sup> Despite this relative weight gain, the treated boys had greater function (ability to walk, climb stairs, arise from the floor) than untreated boys with normal weight for height.

*Studies comparing deflazacort with prednisone.* There are three additional open trials in which deflazacort (0.9 mg/kg/day) was compared with prednisone (0.75 mg/kg/day)<sup>45-47</sup> (see table E-4 on the *Neurology* Web site). These trials ranged in duration from 12 to 24 months and found that daily prednisone and daily deflazacort produced similar sustained improvement in muscle strength and function. One study provided the most comparative details about side effects, although the number of patients enrolled was small (n = 9 for deflazacort, n = 9 for prednisone, n = 7 for ambulant control subjects, total n = 25).<sup>47</sup> The mean increase in body weight in patients receiving deflazacort was 2.17 kg (9%) compared with 5.08 kg (21.3%) in patients receiving prednisone after the first 12 months of treatment. No specific data were given about differences in lean body mass between groups. Both deflazacort- and prednisone-treated boys showed comparable improvement in function as well as strength testing.

**Conclusions.** Seven class I studies and a larger number of class IV trials have all demonstrated that prednisone is beneficial in the treatment of DD. There is a significant increase in strength, timed muscle function, and pulmonary function. Daily treatment with prednisone at a starting dosage of 0.75 mg/kg/day or deflazacort at a starting dosage of 0.9 mg/kg/day offers an optimal and effective initial treatment. The most frequent side effects are weight gain and development of a cushingoid facial appearance. Very recently, there was a Cochrane review of glucocorticoid corticosteroid therapy in DD, and the conclusions were in full agreement with those cited above.<sup>49</sup> Two class I studies and several class II to IV studies have also demonstrated similar efficacy and side effect profiles with deflazacort. There are insufficient data that directly compare prednisone and deflazacort to determine if deflazacort has fewer side effects.

### Recommendations

1. Prednisone has been demonstrated to have a beneficial effect on muscle strength and function in boys with DD and should be offered (at a dose of 0.75 mg/kg/day) as treatment (Level A). Maintaining a dosage of 0.75 mg/kg/day is optimal, but if side effects require a decrease in prednisone, a gradual tapering of prednisone (as indicated below) to dosages as low as 0.3 mg/kg/day will give less robust but significant improvement.
2. Benefits and side effects of corticosteroid therapy need to be monitored. Timed function tests, pulmonary function tests, and age at loss of independent ambulation are useful to assess ben-

efits. An offer of treatment with corticosteroids should include a balanced discussion of potential risks. Potential side effects of corticosteroid therapy (weight gain, cushingoid appearance, cataracts, short stature [i.e., a decrease in linear growth], acne, excessive hair growth, gastrointestinal symptoms, and behavioral changes) also need to be assessed. If excessive weight gain occurs (>20% over estimated normal weight for height over a 12-month period), based on available data, it is recommended that the dosage of prednisone be decreased (to 0.5 mg/kg/day with a further decrease after 3 to 4 months to 0.3 mg/kg/day if excessive weight gain continues) (Level A).

3. Deflazacort (0.9 mg/kg/day) can also be used for the treatment of DD in countries in which it is available (Level A). Patients should be monitored for asymptomatic cataracts as well as weight gain during treatment with deflazacort.

### Future research

1. Double-blind, randomized, controlled studies are needed to compare daily treatment with prednisone (0.75 mg/kg/day) with other treatment regimens such as 1) higher-dose alternate-day treatment (5 mg/kg every other day), 2) intermittent treatment (0.75 mg/kg/day for 10 days—stop for 10 days—repeat cycle), 3) high-dose pulses on weekends (5 mg/kg on Friday and Saturday), and 4) deflazacort (0.9 mg/kg/day). The goal of these studies is to establish more clearly the optimal dose, optimal age to initiate treatment, and optimal dose schedule to improve function with the least possible side effects.
2. Studies are needed to determine if daily prednisone has a beneficial effect on cardiac, respiratory, gastrointestinal, and cognitive function in patients with DD.
3. Natural history studies of DD from birth to age 6 years and dose-response studies of corticosteroid treatment with prednisone and deflazacort beginning at an early age (2 to 4 years) are needed to determine if corticosteroid therapy is beneficial if it is started in very young patients.
4. In vitro and animal model studies are needed to identify the mechanism(s) responsible for the beneficial effects of corticosteroids in DD.
5. Better methods need to be developed and studies performed to assess the quality of life in patients with DD from infancy to adulthood. Those methods need to be used to examine the influence of long-term corticosteroid therapy on the quality of life in DD.
6. Long-term studies evaluating corticosteroid treatment given over many years are needed to assess its effect on the natural history of all

manifestations of DD, including the effect on ambulation, respiratory and cardiac function, as well as quality of life.

7. Studies to define the natural history of changes in bone mass and density as well as scoliosis and the incidence of fractures are needed in children with DD and other muscle-wasting diseases in childhood. Trials of treatment with calcium supplements and bisphosphates in these patients deserve consideration.
8. Evaluation is needed of short- and long-term effects of corticosteroid treatment on the spine and the role of calcium supplements and bisphosphonates as adjuvant therapies in DD.
9. Studies to document the natural history of the late stages of DD and investigations to determine the efficacy of corticosteroid therapy when initiated late in the course of DD (e.g., after 15 years of age) are needed.
10. Studies of dietary modification and exercise are needed to evaluate their efficacy in ameliorating the weight gain associated with corticosteroid therapy in DD.

**Disclaimer.** This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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#### Appendix 1

##### AAN evidence classification scheme for a therapeutic article

**Class I:** Evidence provided by a prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.

The following are required:

- a) primary outcome(s) is/are clearly defined
- b) exclusion/inclusion criteria are clearly defined
- c) adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias
- d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

**Class II:** Evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a randomized control trial in a representative population that lacks one criteria a–d

**Class III:** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

**Class IV:** Evidence from uncontrolled studies, case series, case reports, or expert opinion

#### Appendix 2

##### AAN system for translation of evidence to recommendations

Translation of evidence to recommendations	Rating of recommendation
Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies	A = Established as effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population
Level B rating requires at least one convincing class II study or at least three consistent class III studies	B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population
Level C rating requires at least two convincing and consistent class III studies	C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population
	U = Data inadequate or conflicting; given current knowledge, treatment is unproven

#### Appendix 3

**Quality Standards Subcommittee Members:** Gary Franklin, MD, MPH (co-chair); Gary Gronseth, MD (co-chair); Charles E. Argoff, MD; Stephen A. Ashwal, MD (ex-officio); Christopher Bever, Jr., MD; Jody Corey-Bloom, MD, PhD; John D. England, MD; Jacqueline French, MD (ex-officio); Gary H. Friday, MD; Michael J. Glantz, MD; Deborah Hirtz, MD; Donald J. Iverson, MD; David J. Thurman, MD; Samuel Wiebe, MD; William J. Weiner, MD, and Catherine Zahn, MD (ex-officio).

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