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## ***Growth Hormone Therapy in Duchenne Muscular Dystrophy***

### **Clinical Question**

- P (population/problem) In children with Duchenne Muscular Dystrophy  
I (intervention) do growth hormone injections  
C (comparison) compared to placebo  
O (outcome) improve muscle function and strength?

### **Target Population**

Children with Duchenne Muscular Dystrophy (DMD)

### **Recommendations** (See Table of Recommendation Strength following references)

1. It is recommended, because of insufficient evidence on the benefits and risks of growth hormone (GH) therapy in children with Duchenne Muscular Dystrophy, that GH **not** be prescribed **for the primary purpose of improving muscle function and strength** (Myers 2007 [2b], Hansen 2005 [2b], Cittadini 2003 [2b], Liu 2003 [2b], Schibler 2003 [2b], Carrel 2002 [2b], Vahl 2000 [2b], Carrel 1999 [2b], Myers 1999 [2b], Osterziel 1998 [2b], Cuneo 1991 [2b], Schweizer 2007 [3a], Carroll 2004 [3b], Merlini 1988 [5], Local Consensus [5]). See Appendix.  
**Note:** Several small randomized controlled trials of GH therapy have been conducted in diverse study populations to evaluate lean body mass and muscle strength and function. Administration of GH for as long as four years, appears to result in increased lean body mass, but associated improvements in muscle strength or function are not consistently observed. These study populations have included children with DMD, adults with Becker muscular dystrophy, children and adults with GH deficiency (GHD), pre-pubertal children born small for gestational age, children with Prader-Willi syndrome, children with cystic fibrosis, healthy young males and adults with cardiomyopathy (Liu 2008 [1a], de Lind van Wijngaarden 2009 [2b], Myers 2007 [2b], Chihara 2006 [2b], Hansen 2005 [2b], Cittadini 2003 [2b], Liu 2003 [2b], Schibler 2003 [2b], Carrel 2002 [2b], Vahl 2000 [2b], Carrel 1999 [2b], Myers 1999 [2b], Osterziel 1998 [2b], Cuneo 1991 [2b], Eiholzer 2009 [4b]). See Appendix.
2. It is recommended, for children with DMD who exhibit severe short stature and/or severe slowing of growth rate<sup>1</sup> (such as those receiving long-term glucocorticoid treatment), that GH **for treatment of short stature** be discussed with the patient and family as a treatment option, and include in this discussion the potential for a positive impact on lean muscle mass (Bryant 2002 [1a], Rider 2008 [2b], Simon 2007 [2b], Rutter 2008 Conference abstract [4b], Allen 1998 [4b], Local Consensus [5]).  
**Note 1:** Use of GH is FDA-approved for children who exhibit growth failure or short stature due to growth hormone deficiency or idiopathic short stature. The evidence for these indications has been summarized elsewhere (Bryant 2002 [1a]).  
**Note 2:** Use of GH therapy has shown beneficial effects for growth in patients receiving long-term glucocorticoid treatment for juvenile idiopathic arthritis (JIA) with adverse effects limited to glucose intolerance not requiring insulin therapy in some patients (Bechtold 2007 [2b], Simon 2007 [2b], Saha 2004 [3b], Allen 1998 [4b]).  
**Note 3:** A cohort at Cincinnati Children's Hospital of eight boys with DMD and severe steroid-induced growth failure were treated with GH and showed an improvement in growth velocity within the first year from 0.5 cm/year (range 0 to 1.8 cm/year) to 5.4 cm/year (range 3.2 to 8.4 cm/year). There was improvement in neuromuscular and lung function among some younger boys (ages 9 to 13), and lack of deterioration in these functions in some older boys (ages 14 to 17). Improvements in neuromuscular and pulmonary function are in

<sup>1</sup> Severe short stature is defined as height < 3 standard deviations below the norm. Severe growth deceleration is defined as height velocity < 2 standard deviations below the norm over 12 months (Rosenfeld 2008 [5]).

contrast to the natural history of children with DMD above nine years of age who show progressive decline in motor and pulmonary function. Mild progression of scoliosis was observed in two patients (*Rutter 2008 Conference abstract [4b]*).

**Note 4:** A key consideration in the shared decision-making process is the cost of GH therapy which is in the range of \$20,000 to \$30,000 per year, or about \$42 per mg (*Bryant 2002 [1a]*, *Cuttler 2005 [4a]*).

**Note 5:** Lack of sufficient studies of the safety of GH therapy in DMD warrants close monitoring for changes of neuromuscular function, development or progression of scoliosis, abnormalities in glucose metabolism, benign intracranial hypertension, and abnormalities in cardiopulmonary function (*Myers 2007 [2b]*, *Simon 2007 [2b]*, *Osterziel 1998 [2b]*, *Fideleff 2008 [3b]*, *Rutter 2008 Conference abstract [4b]*, *Allen 1998 [4b]*).

**Note 6:** GH improves bone mineral density in adults with GHD (*Bex 2002 [2a]*, *Baum 1996 [2b]*, *O'Halloran 1993 [2b]*). Studies in children evaluating the protective effects of GH on bone mineral density (BMD), as well as on bone mineral content (BMC), strength-strain index (SSI), markers of bone formation and bone resorption, and bone cross-sectional area demonstrate inconsistent results (*Grote 2006 [2b]*, *Schweizer 2007 [3a]*, *Fideleff 2008 [3b]*, *Saha 2004 [3b]*, *Simon 2003 [3b]*, *Rooney 2000 [3b]*, *Touati 2000 [3b]*, *Bechtold 2005 [4b]*).

## References (evidence grade in [ ]; see Table of Evidence Levels following references)

**Note:** When using the electronic version of this document,  indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the CCHMC network.

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Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

**Table of Evidence Levels** (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

**Table of Recommendation Strength** (see note above)

<b>Strength</b>	<b>Definition</b>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

**Dimensions:** In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (*direct benefit*)
4. Burden to patient of adherence to recommendation (*cost, hassle, discomfort, pain, motivation, ability to adhere, time*)
5. Cost-effectiveness to healthcare system (*balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis*)
6. Directness (*the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]*)
7. Impact on morbidity/mortality or quality of life

**Appendix: Effect of Growth Hormone on Lean Body Mass and Neuromuscular Function**

Study Citation	Age Range	N	Condition	GH Dose*	Length of Study	Findings for LBM and Neuromuscular Function	P Value	Adverse Effects
<i>(Cittadini 2003 [2b])</i>	9 to 19 years 24 to 55 years	6 10	DMD BMD	0.23 mg/kg/wk 0.07 mg/kg/wk	3 months	<ul style="list-style-type: none"> <li>GH activates myocardial growth</li> <li>slight improvement in systolic function</li> <li>no change in skeletal muscle function</li> </ul>	NS	none
<i>(Rutter 2008 Conference abstract [4b])</i>	9.4 to 17.5 years	8	DMD	0.23 – 0.43 mg/kg/wk (median 0.29 mg/kg/wk)	6 to 20 months	<ul style="list-style-type: none"> <li>stabilized neuromuscular function</li> <li>improved pulmonary function (forced vital capacity)</li> </ul>	not available	mild progression of scoliosis (2 patients)
<i>(Merlini 1988 [5])</i>	2 to 10 years	10	DMD	none	cross-section	no correlation between blood level of GH, somatomedin C and functional ability of DMD patients	not applicable	none
<i>(Schweizer 2007 [3a])</i>	4 to 10 years	203	GHD SGA	0.21 mg/kg/wk 0.385 mg/kg/wk	12 months and 24 months	<p>increases during 0 to 12 months</p> <ul style="list-style-type: none"> <li>muscle area</li> </ul> <p>24 month continues to improve:</p> <ul style="list-style-type: none"> <li>muscle area</li> <li>muscle mass</li> </ul>	< 0.01  < 0.001	none reported
<i>(Chihara 2006 [2b])</i>	18 to 65 years	73	Adult GHD CO or AO	0.021 mg/kg/wk wk 1 thru wk 4 0.042 mg/kg/wk wks 5 thru wk 8 then 0.084 mg/kg/wk the remaining 16 wks	24 weeks	<ul style="list-style-type: none"> <li>LBM was significantly increased for those treated with GH compared to placebo</li> </ul>	= 0.0003	<ul style="list-style-type: none"> <li>upper respiratory tract infection</li> <li>muscle weakness</li> <li>oedema</li> </ul>
<i>(Liu 2003 [2b])</i>	39 to 55 years	12	Adult GHD	0.035 mg/kg/wk	18 months	<ul style="list-style-type: none"> <li>increase in LBM</li> <li>improved muscle function</li> <li>improved aerobic performance</li> </ul>	< 0.01 = 0.016 = 0.09	persistent joint arthralgias (relieved with reduced dose)
<i>(Vahl 2000 [2b])</i>	16 to 26 years	19	Adult GHD	1.2 mg/day  0.67 mg/m <sup>2</sup> /day	1 <sup>st</sup> 12 months randomized to GH or placebo  2 <sup>nd</sup> 12 months all got GH	<ul style="list-style-type: none"> <li>significant increase LBM in those who resumed GH after 1 year interruption</li> <li>no changes in LBM in those who continued GH</li> <li>no significant change in muscle strength either group</li> </ul>	< 0.006	<ul style="list-style-type: none"> <li>1 patient experienced extreme tiredness</li> <li>2 patients peripheral edema</li> </ul>
<i>(Cuneo 1991 [2b])</i>	18 to 55 years	24	Adult GHD	0.16 mg/kg/wk	3 and 6 months	<ul style="list-style-type: none"> <li>GH increases LBM</li> <li>muscle mass and hip flexion force</li> </ul>	< 0.001 = 0.004	none

Study Citation	Age Range	N	Condition	GH Dose*	Length of Study	Findings for LBM and Neuromuscular Function	P Value	Adverse Effects
(Gotherstrom 2009 [3a])	22 to 74 years	109	Adult GHD	0.88 mg/day	10 years (reviewed at baseline, 1 yr, 3 yr, 5 yr, 7 yr & 10 yr)	<ul style="list-style-type: none"> <li>• knee isometric 60° flexion increased from 88.5% to 110.2% of predicted</li> <li>• knee isometric 60° extension 90.8% to 92.9% of predicted</li> <li>• grip strength right hand 83.3% to 93.3% of predicted</li> <li>• increase in LBM – males</li> <li>• increase in LBM– females</li> </ul>	<p>&lt; 0.001</p> <p>NS</p> <p>&lt; 0.001</p> <p>&lt; 0.001</p> <p>NS</p>	mild intensity of fluid retention
(Carroll 2004 [3b])	14 to 20 years	24	GHD	0.12 mg/kg/wk	12 months	LBM increased in those continuing GH, and unchanged in those discontinuing GH	< 0.05	none
(de Lind van Wijngaarden 2009 [2b])	Infants 6 months to 3.5 years Pre-pubertal 3.5 to 16 years	38 44	PWS	Infants & Pre-pubertal 1 mg/m <sup>2</sup> /day	Infants – 12 months  Pre-pubertal 12 & 24 months	Improvement in trunk LBM <ul style="list-style-type: none"> <li>• Infants at 12 months</li> <li>• Pre-pubertal <ul style="list-style-type: none"> <li>- at 12 months</li> <li>- at 24 months</li> </ul> </li> </ul>	<p>&lt; 0.0001</p> <p>&lt; 0.0001</p> <p>&lt; 0.0001</p>	none
(Myers 2007 [2b])	4 to 37 months	25	PWS	1 mg/m <sup>2</sup> /day for 24 months or no treatment for 12 months	12 months and 24 months	<ul style="list-style-type: none"> <li>• increase in LBM at 12 months in treated patients</li> <li>• no increase in LBM in untreated patients</li> </ul>	<p>&lt; 0.005</p> <p>NS</p>	1 treated patient experienced progression of scoliosis from 28 to 57 degrees
(Carrel 2002 [2b])	6 to 17 years	46	PWS	3 dosing groups: 0.3 mg/m <sup>2</sup> /day or 1 mg/m <sup>2</sup> /day or 1.5 mg/m <sup>2</sup> /day	24 months	<ul style="list-style-type: none"> <li>• findings dose dependent</li> <li>• LBM: <ul style="list-style-type: none"> <li>- unchanged with 2.1 mg dose</li> <li>- increased with 7 and 10.5 mg doses</li> </ul> </li> <li>• muscle strength and agility neither improved nor regressed during 24 to 48 months of GH therapy</li> </ul>	<p>NS</p> <p>&lt; 0.001</p> <p>NS</p>	headache reported by 2 patients (Carrel 1999 [2b])  no significant progression of scoliosis
(Carrel 1999 [2b])	4 to 16 years	54	PWS	1 mg/m <sup>2</sup> /day	12 months	increase in: <ul style="list-style-type: none"> <li>• LBM</li> <li>• timed run</li> <li>• broad jump</li> <li>• sit-ups (abdominal strength)</li> <li>• weight lifting (upper extremity)</li> <li>• respiratory muscle forces <ul style="list-style-type: none"> <li>- inspiratory</li> <li>- expiratory</li> </ul> </li> </ul>	<p>&lt; 0.01</p>	headache reported by 2 patients
(Eiholzer 2009 [4b])	4.0 ± 3.9 years divided into 2 groups Grp 1 > 2.5 years Grp 2 < 2.5 years	37	PWS	Aprox. 6 mg/m <sup>2</sup> /day	24 months	LBM (corrected for sex and height) increased significantly during the first 24 months of GH therapy	<p>Grp 1 p = 0.05</p> <p>Grp 2 p &lt; 0.02</p>	none reported

Study Citation	Age Range	N	Condition	GH Dose*	Length of Study	Findings for LBM and Neuromuscular Function	P Value	Adverse Effects
(Schibler 2003 [2b])	10 to 23 years	20	CF	0.33 mg/kg/wk	12 months	increase in exercise capacity	< 0.05	long-term may increase blood glucose
(Osterziel 1998 [2b])	25 to 70 years	50	chronic heart failure and dilated cardiomyopathy	0.66 mg/day	12 weeks	<ul style="list-style-type: none"> <li>increase in septal thickness and left ventricular mass</li> <li>left ventricular end-diastolic volumes unchanged</li> <li>no relation between changes and ejection fraction</li> </ul>	< 0.001  not clinically significant	1 patient progression of left ventricle failure (therapy stopped)  several patients experienced an array of non-threatening symptoms treated without ill effects.
(Liu 2008 [1a])	Mean age 27 years SD 3 years	44 articles 27 (study population) N = 303	Healthy physically fit young adults	Mean daily dose 0.036 mg/kg/day	Varied 1 day up to 3 months	• LBM increased significantly in GH treated group compared to group not treated with GH	none reported	<ul style="list-style-type: none"> <li>soft tissue edema</li> <li>arthralgia</li> <li>fatigue</li> </ul>
(Hansen 2005 [2b])	23 to 26 years	16	young healthy men	2 mg/day	2 weeks	<ul style="list-style-type: none"> <li>increase in LBM</li> <li>increase in energy expenditure</li> </ul>	< 0.005 < 0.05	none reported

BMD =Becker's muscular dystrophy; CF = cystic fibrosis; DMD = Duchenne muscular dystrophy; GH = growth hormone; GHD = growth hormone deficiency; LBM = lean body mass; N = number of patients; PWS = Prader-Willi syndrome; SGA = small for gestational age; CO = Childhood onset; AO = adult onset; wk = week; wks = weeks; Aprox. = approximately; NS = not significant

\*For purposes of standardization within this table, doses as reported in a study may have been converted: a) weight-based doses have been converted to weekly doses, b)  $\mu\text{g}$  have been converted to mg, and c) units (U), also called international units (IU), have been converted to mg (3 IU = 1 mg).

## Supporting information

### Background

Interest in GH in children with DMD began with a case study of a child who had both DMD and GHD. He had a benign course of DMD, compared to his siblings and cousins at the same age (Zatz 1986a [5], Zatz 1981a [5], Zatz 1981b [5]). Based on this observation, it was suggested that a GH inhibitor might be a possible treatment for DMD, and thus mazindol therapy was studied in several children. These case studies reported inconsistent results and adverse effects were documented (Collipp 1984 [3b], Coakley 1988 [4b], Zatz 1986b [5], Zatz 1981b [5]). A randomized double-blind placebo-controlled trial of mazindol was conducted in 86 children with DMD for 12 months (Griggs 1990 [2b]). Mazindol did not provide any beneficial effect for children with DMD, and no further studies of mazindol in children with DMD have been published.

Interest in GH itself as a therapy for DMD, similarly began with a case study in another child who had both DMD and GHD. Two years of treatment with GH apparently resulted in improved growth velocity and motor development with few if any adverse experiences (Frank 2001 [5]). A small study in which 16 children with X-linked muscular dystrophy, 6 of whom had DMD, were randomized to a three-month trial of GH or placebo, suggested cardiovascular benefits such as left ventricular hypertrophy, and improvement of systolic function with few or no clinical side effects (Cittadini 2003 [2b]). However, there is a lack of good data regarding the use and safety of GH in patients with DMD (Ghafoor 2003 [5]).

Current research on therapies indirectly related to growth hormone may have future application in improving muscle function and strength in patients with DMD. These include insulin-like growth factor 1 (IGF-1) therapy or over-expression currently being studied in the DMD-mouse model (Tidball 2004 [5], Lynch 2001 [5]), and oral MK-677, a ghrelin mimetic currently being studied in the elderly (Nass 2008 [2b]).

## Group/team members

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## Search strategy

### 1. Original Search

#### ▪ OVID DATABASES

MedLine, CINAHL, Cochrane Database for Systematic Reviews (CDSR)

#### ▪ OVID FILTERS

Publication Date 1996 to present  
 Limits English language and (humans or animals)

#### ▪ SEARCH TERMS & MeSH TERMS (MedLine & CINAHL)

Patients/Population exp Muscular Dystrophy, Duchenne/exp terms/  
 limit to (“all child (0 to 18 years)” or all child <0 to 18 years>)(pediatr\$ or child\$).mp.  
 Intervention/Exposure exp Growth Hormone/ or exp Injections, Subcutaneous/ exp terms/  
 Outcomes exp Muscle Contraction/ or exp Muscle, Skeletal/ or muscle.mp. exp terms/

### 2. Additional searches

#### ▪ For protective effect of GH on bone density

▪ OVID – All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED

**Search terms:** growth hormone, in title AND bone density, keyword

**Limits:** humans, English, no age limits

#### ▪ For effect of GH on growth in patients on glucocorticoids

▪ OVID – MedLine

**Search terms:** growth hormone, focus of study AND (juvenile idiopathic arthritis OR juvenile rheumatoid arthritis), focus of study

**Limits:** humans, English, 0 to 18 yrs

#### ▪ For cost and cost-effectiveness of GH therapy

▪ OVID – MedLine

**Search terms:** (Cost-Benefit Analysis/ OR Health Care Costs/ or Drug Therapy/) AND growth hormone

**Limits:** humans, English, 0 to 18 yrs

### 3. Additional articles – identified from reference lists and clinicians

## Applicability issues

Measures have been developed to evaluate improvement in patient outcomes:

- Age of Loss of Ambulation: Mean age of loss of ambulation for patients with Duchenne Muscular Dystrophy
- Independent Ambulation: Percent of patients less than 13 years old with independent ambulation (functional mobility score equal to or less than 3)
- Lumbar Spine: Percent of patients with Z-score of the lumbar spine within the normal range (-2 to +2)
- Functional Mobility: Percent of patients equal to or greater than 10 years old but less than 13 years old with improved or stable functional mobility scores during the past 6 months (*Larson 2000 [2b], Swinyard 1957 [5]*)
  - Functional Mobility Classification Scale
    1. Mild abnormalities in gait. Able to climb stairs without assistance.
    2. More apparent gait abnormalities. Requires a railing or other support for stairs.
    3. Walks and arises from a chair independently, but cannot negotiate stairs without help.
    4. Independent walking is the primary means of mobility, but a walker, braces or other support is necessary. Unable to arise from a chair independently.
    5. Primary means of mobility is a wheelchair. May stand with support for transfers. Good trunk control in the chair and able to perform all activities of daily living from the chair.
    6. Wheelchair dependent and unable to stand. Needs some help propelling a manual wheelchair and with activities of daily living.

7. Unable to propel manual wheelchair. Some difficulty feeding self
8. Unable to sit without considerable support. Requires maximal assistance for activities of daily living  
(Larson 2000 [2b])

- Timed Gower's Maneuvers: Percent of patients less than 12 years old with improved or stable Timed Gower's maneuvers during the past 6 months

The details of these measures for reporting purposes (operational definitions) are on file.

Consideration and re-evaluation at frequent intervals for the cost-effectiveness of initiation, continuation and discontinuation of growth hormone therapy is prudent. Cost has been reported as \$42 per mg for GH in 2005, which would result in an annual cost in the range of \$20,000 to \$30,000 (Bryant 2002 [1a], Cuttler 2005 [4a]).

## Copyright Statement

Copies of this Best Evidence Statement (BESt) are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm>.

Examples of approved uses of the BESt include the following:

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- hyperlinks to the CCHMC website may be placed on the organization's website;
- the BESt may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

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## Note

**This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.**

**Reviewed by** the Division of Health Policy & Clinical Effectiveness