CADTH Reference List

Somatropin for Short Stature Secondary to Small for Gestational Age

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Summary of Abstracts

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Key Message

We identified 1 evidence-based guideline about the use of growth hormone therapy for children with short stature secondary to small for gestational age.

Research Question

What are the evidence-based guidelines regarding the use of growth hormone therapy for children with short stature secondary to small for gestational age?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concept was human growth hormone. CADTH-developed search filters were applied to limit retrieval to guidelines. The search was completed on June 6, 2023, and limited to English-language documents published since January 1, 2013.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications. Open access full-text versions of evidence-based guidelines were reviewed when available, and relevant recommendations were summarized.

Table 1: Selection Criteria

Criteria	Description
Population	Children (age < 18 years) with short stature secondary to small for gestational age
Intervention	All somatropin products
Comparator	NA
Outcomes	Recommendations regarding best practices (e.g., dose and timing of treatment, duration of treatment, laboratory cut-offs for eligibility, monitoring treatment response)
Study designs	Evidence-based guidelines

NA = not applicable.

Results

One evidence-based guideline was identified regarding the use of growth hormone (GH) therapy for children with short stature secondary to small for gestational age (SGA).[1]

Guidelines and recommendations that did not meet the inclusion criteria due to alternative or unclear methodology are summarized in Appendix 1. Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 2.

Overall Summary of Findings

The guideline identified has relevant recommendations about the indication and recommended dosage for GH therapy for children with short stature secondary to SGA (recommendations 18 to 20).[1] The guideline also has recommendations related to the clinical management of children with short stature secondary to SGA on GH therapy (recommendations 20 to 25).[1] Additionally, the guideline provides a consideration for the addition of gonadotropin-releasing hormone agonist treatment with GH therapy (recommendation 26).[1] Refer to Table 2 for a detailed summary of relevant recommendations.

Table 2: Summary of Recommendations in Included Guideline

Study citation	Summary of recommendations	Strength of recommendations
Hokken-Koelega et al. (2023)[1]	"Recommendation 18: GH treatment is recommended in children born SGA with persistent short stature at an age after which catch-up growth is unlikely to occur (which is in most children at the age of 3 years to 4 years) provided other common causes for short stature have been ruled out."	A +++
	"Recommendation 19: GH treatment is not recommended in several genetic disorders with a high predisposition to develop cancer, such as chromosomal breakage syndromes and DNA repair disorders."	A +++
	"Recommendation 20: The recommended GH dose should cover the range 0.033 to 0.067 mg/kg/day, with a starting dose of 0.033 mg/kg/day. The GH dose can be increased within the dose range when the growth response is unsatisfactory (delta height gain < 0.5 SDS) during the first year of treatment, and a higher starting dose within the dose range could be considered in those with the most marked growth retardation."	A ++
	"Recommendation 21: GH dosing based on IGF-I titration alone is not recommended."	A +++
	"Recommendation 22: It is recommended to determine serum IGF-I at 3 to 6 months after the start of GH treatment to evaluate adherence to the treatment and whether the GH dose requires adjustment for safety reasons. Thereafter, it is advised to determine the serum IGF-I concentrations at least annually."	A +++
	"Recommendation 23: Bone maturation is a poor predictor of pubertal timing and height attainment in SGA children. Therefore, during GH treatment, yearly bone age assessment is not recommended in prepubertal children."	A ++

Study citation	Summary of recommendations	Strength of recommendations
	"Recommendation 24: During GH treatment, annual assessment of serum concentrations of thyroid hormone (free T4, TSH) is recommended. Routine evaluation of metabolic parameters such as fasting serum lipid and glucose/insulin/ hemoglobin A1C concentrations is only recommended for children born SGA treated with GH with risk factors, such as overweight, obesity, and family history."	A +++
	"Recommendation 25: GH treatment is discontinued in case of (near-) adult height attainment defined as growth rate less than 1 cm in 6 months in combination with closed epiphyses or when there are repeated and clear signs of nonadherence or no response to GH treatment."	A +++
	"Recommendation 26: In short children born SGA, addition of GnRHa treatment to GH treatment could be considered if the expected adult height is below −2.5 SDS at the onset of puberty; further longitudinal studies should validate the benefits of GnRHa treatment."	A++

GH = growth hormone; GnRHa = gonadotropin-releasing hormone agonist; IGF-1 = insulin-like growth factor 1; SDS = standard deviation score; SGA = small for gestational age; TSH = thyroid-stimulating hormone; T4 = thyroxine.

References

Guidelines and Recommendations

1. Hokken-Koelega ACS, van der Steen M, Boguszewski MCS, et al. International Consensus Guideline on Small for Gestational Age: Etiology and Management From Infancy to Early Adulthood. *Endocr Rev.* 2023; 44(3):539-565. PubMed
   Refer to Recommendations #18-26

Appendix 1: Summary of Identified Guidelines

The following publications did not meet the methodological criteria to be considered an evidence-based guideline, and therefore were not eligible for inclusion in the main body of this report. However, these 2 publications provide relevant guidance or recommendations related to GH therapy for children with short stature secondary to SGA.

The standard treatment guidelines by Indian Academy of Pediatrics (2022) outline the indications and criteria for GH therapy. Infants born SGA are eligible for GH therapy if they meet the following conditions:

- Birth weight/length: > 2 standard deviations (SD) below the mean
- Height: < −2.5 SD of mean at the start of therapy
- Current height: > 1 SD below mid parental height
- Failure to catch up by 4 years

The guideline by Collett-Solberg et al. (2019) recommends older children born SGA start recombinant human GH therapy at a dose that is at the higher end of the approved range. Additionally, the same guideline also suggests considering adding gonadotropin-releasing hormone analogue therapy to recombinant human GH therapy in cases where the child's height SD score is low at the onset of puberty.

Guidelines and Recommendations

Unclear Methodology

Standard treatment guidelines 2022: Approach to short stature. Mumbai (India): Indian Academy of Pediatrics. 2022. https://iapindia.org/pdf/Ch-097-Approach-to-Short-Stature.pdf Accessed 2023 Jun 8.
Refer to GH: Indications and Criteria – SGA infants

Alternative Methodology

Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. *Horm Res Paediatr*. 2019; 92(1):1-14. PubMed
Refer to rhGH Starting Doses on page 8; Alternative Treatments for Children with Suboptimal Response to rhGH on page 9

Appendix 2: References of Potential Interest

Guidelines and Recommendations

Not Specific to Short Stature Secondary to SGA

Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. *Horm Res Paediatr*. 2016; 86(6):361-397. PubMed

Additional References

Position Paper Allen DB, Backeljauw P, Bidlingmaier M, et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. *Eur J Endocrinol*. 2016; 174(2):P1-9. PubMed
Refer to Risk reduction: pediatric patients

Article – Roundtable Discussion

Navarro R, Dunn JD, Lee PA, Owens GM, Rapaport R. Translating clinical guidelines into practice: the effective and appropriate use of human growth hormone. *Am J Manag Care*. 2013; 19(15 Suppl):s281-9. PubMed