Growth Hormone Guidelines Roundtable

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Panelists:
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Disclosure
• Dr. Miller is a consultant for Abbvie, Ferring, Genentech, Novo Nordisk, Pfizer, Sandoz and Versartis and has received research support from Alexion, Ascendis, Endo Pharmaceuticals, Genentech, Novo Nordisk, Sandoz, Shire, Tolmar, Ultragenyx and Versartis.
• We will not be discussing off-label use of medications.

Objectives:
• Review new Pediatric Endocrine Society (PES) guidelines for GH and IGF1 treatment for children and adolescents.
• Identify implications for clinical management of patients related to new PES guidelines.
• Discuss challenges related to implementation of patients related to new PES guidelines.
• Share ideas and suggestions to facilitate successful implementation of new PES guidelines.
Pediatric Growth Hormone Clinical Treatment Guidelines: Impact on Patients, Current Practice, and Access to Treatment

Adapted from: Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Rossi WC, Feudtner C, and Murado MH on behalf of the Drug and Therapeutics and Ethics Committees of the Pediatric Endocrine Society


1. Efficacy of GH Treatment for GHD

- 1.1. We recommend use of GH to normalize adult height (AH) and avoid extreme shortness in children and adolescents with GHD. (Strong recommendation, ⚫⚫⚫⚫)


2. Consideration and Diagnosis of GHD

- 2.2.1. We recommend against reliance on GH provocative test results as sole diagnostic criterion of GHD. (Strong recommendation, ⚫⚫⚫⚫)

- Technical Remark: Very low peak [GH]'s on provocative testing are consistent with severe GHD, and patients with such results are expected to benefit greatly from GH treatment.

- However, threshold test result that distinguishes normal from partial GHD that responds to treatment has not been well-established.

2. Consideration and Diagnosis of GHD

• Technical Remark: Given substantial number of healthy, normally growing children who test below accepted limits, inadequate response to 2 different stimuli is required for diagnosis of GHD.
  – While it is possible that combining tests might yield different results from tests performed on separate days, there is no evidence against performing both tests sequentially on same day.


2. Consideration and Diagnosis of GHD

• 2.2.2. Given large discrepancies between GH assays, we recommend that institutions require laboratories to provide harmonized GH assays using the somatropin standard, IRP IS 98/574, 22K rhGH isoform, as recommended by 2006 and 2011 consensus statements. (Strong recommendation, ⚫⚫⚫⚫)


2. Consideration and Diagnosis of GHD

• 2.2.3. We suggest sex-steroid priming prior to provocative GH testing in prepubertal boys > 11 and in prepubertal girls > 10 yr with AH prognosis within –2 SD of reference population mean in order to prevent unnecessary GH treatment of children with CDGP. (Conditional recommendation, ●●○○)

3. Dosing of GH Treatment for Patients with GHD

- **3.1.** We recommend use of weight-based or BSA-based GH dosing in children with GHD. (Strong recommendation, ⚫⚫⚫⚪)
  - Technical Remark: We cannot make recommendation regarding IGF-I-based dosing because there are no published AH data using this method. Rationale is logical, but target IGF-I level has not been established to optimize balance between AH gain, potential risks, and cost.

- **3.2.** We recommend initial GH dose of 0.16-0.24 mg/kg/wk (22-35 µg/kg/day) with individualization of subsequent dosing. (Strong recommendation, ⚫⚫⚪⚪)
  - Technical Remark: Some patients may require higher doses.

- **3.4.** During puberty, we recommend **against** routine increase in GH dose to 0.7 mg/kg/wk in every child with GHD. (Strong recommendation, ⚫⚫⚪⚪)
4. Safety Issues of GH Treatment for Patients with GHD

4.3. We recommend re-assessment of both adrenal and thyroid axes after initiation of GH therapy in patients whose cause of GHD is associated with possible multiple pituitary hormone deficiencies (MPHD). (Strong recommendation, ●●○○

- GH reduces hepatic 11β-HSD1-mediated conversion of inactive cortisol to active cortisol and increasing CYP3A4-mediated cortisol catabolism
- GH lowers serum free [T4], often used to diagnose central hypothyroidism, by increasing peripheral de-iodination of T4 to T3


4.4. Counseling prospective recipients of GH treatment regarding risk of neoplasia

4.5.1. We recommend informing at-risk patients about available data and encourage long-term follow-up with their oncologist. (Ungraded good practice statement)

4.5.1.1. For children with acquired GHD due to effects of a primary malignancy

- 4.5.1.1.1. We recommend shared decision-making that involves patient, family, oncologist, and treating endocrinologist. Before initiation of GH treatment, we recommend sharing with families most recent data about risks, including potential effect of GH treatment on timing of second-neoplasm occurrence. (Ungraded good practice statement)


4.5.1.1.2. For GH initiation after completion of tumor therapy with no evidence of ongoing tumor, standard waiting period of 12 mo to establish “successful therapy” of primary lesion is reasonable, but can also be altered depending on individual patient circumstances. (Ungraded good practice statement)

Technical Remark: Although many intracranial tumors are not “malignant” (i.e., craniopharyngioma), they have potential to recur. There are no data to suggest treating them differently than malignant tumors with regard to observation periods before initiating GH treatment.
4. Safety Issues of GH Treatment for Patients with GHD

• 4.5.1.2. In rare situation where child with GHD has accompanying condition with intrinsic increased risk for malignancy (e.g., NF-1, Down syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome, and Diamond-Blackfan anemia), we recommend providing counseling regarding lack of evidence concerning GH effect on malignancy risk in these groups. (Ungraded good practice statement)


4. Safety Issues of GH Treatment for Patients with GHD

• 4.5.2. For children considered not to be at risk, we recommend that counseling includes information about unknown long-term (i.e., post-treatment) risks of neoplasia. (Ungraded good practice statement)


5. Transitional Care after Childhood GH Treatment

• 5.1. We recommend that patients with multiple (≥3) pituitary hormone deficiencies regardless of etiology, or GHD with documented causal genetic mutation or specific pituitary/hypothalamic structural defect, except ectopic posterior pituitary, be diagnosed with persistent GHD. (Strong recommendation, ●●●O)

• 5.2. We recommend re-evaluation of somatotropic axis for persistent GHD in persons with GHD and deficiency of only one additional pituitary hormone, idiopathic isolated GHD (IGHD), IGHD with or without a small pituitary/ectopic posterior pituitary, and in patients after irradiation. (Strong recommendation, ●●●O)

5. Transitional Care after Childhood GH Treatment

- **Technical Remark:** Testing can be performed after trial of at least 1 mo off GH.

- **5.2.1.** We suggest that measurement of serum [IGF-I] be initial test of somatotropic axis if re-evaluation of axis is clinically indicated. (Conditional recommendation, ● ○ ○ ○)

- **5.2.2.** We recommend GH provocative testing to evaluate function of somatotropic axis in transition period if indicated by low [IGF-I]. (Strong recommendation, ● ● ● ○)


6. GH Treatment of Patients with ISS

- **6.1.** In US, for children who meet FDA criteria, we suggest shared decision-making approach to pursuing GH treatment for child with ISS. The decision can be made on case-by-case basis after assessment of physical and psychological burdens, and discussion of risks and benefits. We recommend against routine use of GH in every child with height SDS (Ht SDS) ≤-2.25. (Conditional recommendation, ● ● ● ○)

- **Technical Remark:** While studies have shown GH treatment increases mean height of treated cohorts, there is marked inter-individual variability in responses, including some individuals who do not respond to treatment.


6. GH Treatment of Patients with ISS

- **6.2.** We suggest follow-up assessment of benefit in Ht SDS and psychosocial impact 12 mo after GH initiation and dose optimization. (Conditional recommendation, ● ● ○ ○)
6. GH Treatment of Patients with ISS

• 6.3. Because there is overlap in response between dosing groups, we suggest initiating GH at dose of 0.24 mg/kg/wk, with some patients requiring up to 0.47 mg/kg/wk. (Conditional recommendation, ⚫⚫⚪⚪)


GH Treatment: Balance of Benefit, Risk, and Cost

• Further studies are needed to clarify benefits and long-term risks of GH treatment in ISS population
  – Potentially, degree of physical and/or psychosocial disability that individual child suffers due to short stature could be used to determine which children should receive GH therapy
  – Those ISS patients with extremely short AH prediction could be considered physically disabled as it may be difficult for them to navigate a world built to accommodate much taller adults
  – For these children, even small increase in AH may be considerable benefit


GH Treatment: Balance of Benefit, Risk, and Cost

• Further studies are needed to clarify benefits and long-term risks of GH treatment in ISS population
  – For children whose height will be closer to adult normal range, benefit of GH therapy vs risk and high cost of treatment may be less acceptable
  – Additionally, high cost of GH therapy (USD 35,000-50,000 per inch of height gained) is difficult to justify for those in whom it is unclear if there are benefits of treatment

GH Treatment: Balance of Benefit, Risk, and Cost

- In light of these considerations, treating patients with ISS requires careful evaluation and monitoring, with consideration of alternative treatments such as psychological counseling.