Complete Summary

GUIDELINE TITLE

American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children--2003 update.

BIBLIOGRAPHIC SOURCE(S)

American Association of Clinical Endocrinologists (AACE). American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children--2003 update. Endocr Pract 2003 Jan-Feb;9(1):64-76. [30 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE). AACE clinical practice guidelines for growth hormone use in adults and children. Endocr Pract 1998 May-Jun;4(3):165-73.

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SCOPE

DISEASE/CONDITION(S)

- Growth hormone deficiency (GHD)
- Short stature associated with chronic renal insufficiency, Turner syndrome or Prader-Willi syndrome
- Small for gestational age or intrauterine growth retardation
- Human immunodeficiency virus (HIV)-associated wasting

GUIDELINE CATEGORY

Diagnosis
Treatment

CLINICAL SPECIALTY

Endocrinology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide a systematic review of recent data and a summary of guidelines for growth hormone use

TARGET POPULATION

- Children and adults with growth hormone deficiency (GHD) with a history of hypothalamic pituitary disease
- Children with short stature associated with chronic renal insufficiency before renal transplantation, Turner syndrome or Prader-Willi syndrome
- Infants born small for gestational age who have not caught up in height
- Adults with human immunodeficiency virus (HIV)-associated wasting

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Physical Examination
    - Growth charts/curves
2. Laboratory Studies
    - Insulin tolerance test
    - Growth hormone provocation tests
    - Serum insulin-like growth factor-I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3) concentrations
    - Testing for genetic mutations (available only in research laboratories)
    - Peripheral blood karyotyping
    - Fibroblast studies
    - Metabolic studies
3. Radiologic Studies
    - Radiograph of left wrist and hand to estimate bone age
    - Magnetic resonance imaging or computed tomography

Treatment

1. Growth hormone replacement (somatropin [Nutropin, Humatrope, Norditropin, Genotropin, Saizen, Serostim], somatrem [Protropin])

2. Concomitant anabolic steroid (e.g., oxandrolone) treatment or estrogen replacement with diagnosis of Turner syndrome
3. Monitoring/Surveillance
    - Growth, weight, body mass measurements
    - Serum IGF-I concentrations, lipid levels, blood glucose

MAJOR OUTCOMES CONSIDERED

Safety and efficacy of growth hormone therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The guideline document states the developers searched for, selected, and synthesized the known information about the safety and efficacy of growth hormone use in clinical practice.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines were reviewed by 10 board certified endocrinologists, identified by name in the guideline document, and approved by the Board of Directors of the American Association of Clinical Endocrinologists.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Review of Specific Guidelines for Use of Growth Hormone Therapy

Adults With Growth Hormone Deficiency (GHD)

Growth hormone (GH) treatment of adults with GHD should be considered and has been associated with improved body composition, reduced body fat, and increased lean body mass. Patients with documented idiopathic GHD in childhood should be restudied in adulthood. For the average 70-kg man, the recommended dosage at the start of therapy is not more than 0.3 mg, given as a daily subcutaneous injection. Maximal doses are variable, with younger patients (<25 years) sometimes requiring up to 2 mg/day and older patients much less (sometimes only 0.1 or 0.2 mg/day). The clinician must exercise good clinical judgment by assessing side effects, serum insulin-like growth factor I (IGF-I) levels, and changes in body composition to determine the appropriate maintenance dose. In older or overweight patients, lower doses may be needed to minimize the occurrence of adverse events. During therapy, the dosage should be decreased if side effects occur or IGF-I levels are excessive. The maintenance dose depends on the clinical and biochemical response. These doses should be altered to maintain circulating levels of IGF-I in the normal range for the patient´s age and sex. Serum free thyroxine and lipid levels should be assessed initially and at 6 to 12 months thereafter. Plasma glucose concentration is analyzed initially and every 3 months. Long-term treatment is being evaluated at this time.

Children With GHD

GH treatment is indicated in children with documented GHD for correction of hypoglycemia and for induction of normal statural growth. If such patients are known to have had malignant tumors, remission should be substantiated for 6 to 12 months before initiation of GH treatment. A weekly dosage of up to 0.3 mg/kg

of body weight divided into daily or 6-times-per-week subcutaneous injections is recommended. Periodic monitoring of thyroid function is indicated at approximately 6-month intervals. The appropriate time to discontinue GH treatment is controversial. Treatment for growth promotion should be continued at least until the handicap of short stature is ameliorated or until the patient is no longer responding to such treatment.

Turner Syndrome

GH treatment is indicated for girls with Turner syndrome. Patients may be treated with GH in starting dosages of 0.05 mg/kg per day. Anabolic steroids, such as oxandrolone, may be used concomitantly in dosages of less than 0.05 mg/kg per day, with careful monitoring of bone maturation and of serum glucose levels. Estrogen replacement therapy should be discussed with each patient. If adolescent patients strongly believe that estrogen replacement is desirable, very low doses should be given (such as ethinyl estradiol, 50 ng/kg per day) until adequate growth has been achieved.

Chronic Renal Insufficiency

In patients with end-stage renal disease and growth retardation, GH treatment may be considered after growth-inhibiting metabolic derangements (such as acidosis, secondary hyperparathyroidism, and undernutrition) are minimized. Treatment may be initiated with GH in a dosage of 0.35 mg/kg per week.

Small for Gestational Age (SGA) or Intrauterine Growth Retardation

The recommended dosage of GH is 0.48 mg/kg per week, with continuous treatment until final height is achieved. The GH dose in SGA is higher because data suggest that these children may have partial GH resistance.

Prader-Willi Syndrome

GH treatment is indicated for patients with Prader-Willi syndrome. Their short stature should be treated with GH at a dosage of 0.24 mg/kg per week.

Clinical Practice of GH Therapy

GH therapy is best accomplished under the direct supervision of a clinical endocrinologist. Short-term GH treatment is safe in both children and adults. Continued monitoring of side effects and long-term treatment results is needed.

Optimal replacement dosages in adults have not been well defined; studies have suggested 0.1 to 1.0 mg/day. Considerable variability exists, however, in the appropriate GH dose for different patients and the various conditions being treated. A single subcutaneous self-injection of GH into the abdomen, preferably in the evening, is best. The injection site should be rotated to minimize lipoatrophy. Daily administration is more effective in stimulating growth than injections 3 times per week. Although twice-daily GH schedules produce higher GH levels and may be superior to once-daily injections, the inconvenience may compromise compliance.

Physiologic GH replacement must be distinguished from pharmacologic therapy. Replacement therapy of daily GH injections does not simulate the normal, physiologic pulsatile pattern of GH secretion. Starting replacement therapy dosages for GH range from 0.02 to 0.05 mg/kg per day in children and from 0.001 to 0.008 mg/kg per day in adults. For a 70-kg man, the usual starting dosage is 0.1 to 0.3 mg/day, with a maintenance dosage of 0.3 to 0.6 mg/day, or approximately 2 to 4 mg of GH weekly. The dosage should be increased slowly (probably best at monthly intervals), on the basis of clinical and biochemical responses.

GH replacement may be given throughout most of the lifetime of some affected patients. Physicians caring for these patients should be aware that dose requirements may decrease with time. Replacement therapy should be monitored carefully as the patient ages, and special emphasis should be placed on perceived and objectively measured benefits and side effects. If the patient receives no benefit, a withdrawal period should be considered. Because the diagnosis of GHD in adult patients, initiation of therapy, maintenance treatment, and monitoring of side effects are complex, these patients should remain under long-term surveillance by an endocrinologist experienced in treating pituitary-related disorders. Such a program of surveillance, which is the cornerstone of successful therapy, can be undertaken in partnership with an internist or family practitioner. Initial follow-up should be at monthly intervals. Thereafter, visits may be less frequent but should never be less than twice yearly. Because reimbursement for testing and treatment is often complex and time-consuming, patient advocacy involves a considerable commitment. The practicing endocrinologist can help the patient achieve appropriate and lasting reimbursement for optimal medical care.

The GH products approved for use in the United States in 2002 are summarized in Table 6 in the original guideline document.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is not specifically stated for each recommendation. The recommendations were based primarily on a comprehensive review of published reports and recent clinical data.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- In adults, correction of the abnormalities associated with growth hormone deficiency (GHD) (i.e., improved body composition, reduced body fat, and increased lean body mass) and prevention of the development of abnormalities consequent to long-term deficiency.

- In children with GHD, Turner syndrome and chronic renal insufficiency: induction of growth acceleration and correction of growth delay resulting in optimal statural growth.

POTENTIAL HARMS

Side Effects of Growth Hormone (GH)

- In the initial clinical trials, which were composed predominantly of adults with adult-onset growth hormone deficiency (GHD), starting doses of GH were higher than those now recommended. The most common side effects during initiation of GH replacement therapy were fluid retention in conjunction with edema of the extremities, carpal tunnel syndrome, arthralgia, and myalgia. In a study of 115 adult patients with GHD who were given GH replacement therapy for 6 months, edema developed in 37.4%, arthralgia in 19.1%, myalgia in 15.7%, paresthesias in 7.8%, and carpal tunnel syndrome in 1.7%. Of note, these symptoms most commonly occurred at the outset of therapy, and most symptoms resolved within 1 to 2 months while therapy was continued.
- Arthralgia, myalgia, and carpal tunnel syndrome are more frequent in adults but occur occasionally in GH-treated children. Peripheral edema is also more frequent in adults than in younger patients receiving GH therapy. Pseudotumor cerebri or benign intracranial hypertension, however, may occur more frequently in children. The US Food and Drug Administration (FDA) has received reports of 23 cases of benign intracranial hypertension associated with GH replacement; only 1 of these cases has been in an adult. In all cases, papilledema and symptoms of intracranial hypertension (for example, headaches) resolved after GH replacement therapy was discontinued. Only a few of the patients who resumed GH therapy experienced recurrent headaches and papilledema.
- Slipped capital femoral epiphysis may occur more frequently in children with GHD than in others. Investigators are uncertain whether GH has this effect or whether this problem is the result of a diathesis induced by the condition of GHD, exacerbated by rapid growth. GH treatment has been suggested to increase the incidence of this problem. If treated with GH, children with knee or hip pain or with a limp should be carefully examined for slipped capital femoral epiphysis.
- Occasionally, lipoatrophy may occur in GH injection sites, but this finding is relatively uncommon. Some reports suggest that GH may increase creatinine levels in patients with end-stage renal disease. This phenomenon is more frequent in renal transplant recipients and may reflect increased risk of graft rejection.
- GH induces transient resistance to the actions of insulin. In most patients, this action of GH increases circulating levels of insulin but not of glucose. In patients with limited insulin reserve, however, glucose intolerance may result. The GH effect on glycemia also should be monitored periodically by measurement of glycated hemoglobin levels. Several cases of pancreatitis associated with GH therapy have been reported. The precise cause for this complication in GH treatment is uncertain.
- Reports from Japan initially suggested an increased incidence of leukemia in GH-treated patients; however, subsequent studies have not confirmed such an increase. Careful studies in the United States have not confirmed an

increased frequency of leukemia attributable to GH therapy. A major unanswered question is whether GH treatment further increases the incidence of leukemia in patients with other risk factors for leukemia (such as patients who previously have received radiation therapy).

- The development of colonic neoplasms in patients with acromegaly has raised the question of whether GH therapy is associated with tumorigenesis. The Growth Hormone Research Society recently reviewed this subject extensively; they concluded that GH therapy is not associated with the promotion of pituitary tumor recurrence or the development of any other neoplasm. Benign pituitary tumors have long been known to be associated with a 10% recurrence rate during the 10-year period after surgical removal. GH therapy does not affect the risk of recurrence. Although no available evidence indicates that GH stimulates tumor recurrence, a baseline pituitary scan before initiation of therapy is warranted. No additional monitoring for other malignant tumors (such as tumors of the prostate, breast, or colon) is currently suggested beyond the accepted standard of care for the patient´s age and sex.
- Transient gynecomastia has been described in children and adults during GH replacement therapy.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Overall, growth hormone (GH) is contraindicated in patients with active malignant disease*, benign intracranial hypertension, and proliferative or preproliferative diabetic retinopathy. Potential for childbearing is not a contraindication, but GH therapy should be discontinued when pregnancy is confirmed.

  *Note: GH therapy can be initiated in an adult in whom malignant disease has been absent for at least 5 years.

- At this time, GH is not recommended for treatment of patients with acute catabolism, including preoperative and postoperative patients, critically ill patients, and burn patients. This recommendation does not apply to US Federal Drug Administration-approved conditions.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This document consists of recommendations for the clinical use of growth hormone (GH). These guidelines should be used by physicians in conjunction with their best clinical judgment. Periodically, these guidelines will be revised to reflect the latest developments in the use of GH in patients with non-GH-deficient conditions such as Turner syndrome, a clinical condition that is not associated with GH deficiency (GHD) but is improved by use of GH. As expanded indications and new indications (approved by the US Food and Drug Administration [FDA]) for the use of GH arise, the guideline will be updated.

- Considerable interest exists in using GH therapy in various other patients, including those with chronic fatigue syndrome, fibromyalgia, battered-wife syndrome, or obesity. Moreover, GH has been of interest as a means to enhance athletic performance or as an antiaging treatment. These applications have not been approved by the FDA, and further studies are needed to evaluate the use of GH in other disorders. Indeed, the prescribing of GH for off-label indications is a matter of major concern. Because third-party payers (sometimes reluctant to cover patients with documented pituitary disease) may be asked to provide coverage, misuse of GH might ultimately endanger patients who genuinely require GH therapy.
- Because most of the early studies of GH treatment for GHD in adults were done in Europe, publications cited dosing in IU or mU (international units), and early recommendations were often on a weight-adjusted (IU/kg) or square meter-adjusted (IU/m^2) basis. More recently, studies have recommended beginning with single low doses in IU/day. The conversion of IU or mU to mg is 3:1. For example, a mean starting dose of 0.6 IU is equivalent to 0.2 mg/day. Mean maintenance dosages of 0.15 to 0.25 mU/kg per week are equivalent to 0.05 to 0.08 mg/kg per week, which, for a 70-kg man, would be 0.35 to 0.56 mg/day.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Association of Clinical Endocrinologists (AACE). American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children--2003 update. Endocr Pract 2003 Jan-Feb;9(1):64-76. [30 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 (revised 2003)

GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society
American College of Endocrinology - Medical Specialty Society

SOURCE(S) OF FUNDING

Genentech, Inc. provided an unrestricted educational grant to support the publication and distribution of this guideline.

GUIDELINE COMMITTEE

American Association of Clinical Endocrinologists (AACE) Growth Hormone Task Force

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE). AACE clinical practice guidelines for growth hormone use in adults and children. Endocr Pract 1998 May-Jun;4(3):165-73.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 245 Riverside Avenue, Suite 200, Jacksonville, FL 32202.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines. Endocrine Pract 2004 Jul/Aug; 10(4):353-61.

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 245 Riverside Avenue, Suite 200, Jacksonville, FL 32202.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on October 1, 1998. The information was verified by the guideline developer on December 15, 1998. This summary was updated by ECRI on May 21, 2003. The updated information was verified by the guideline developer on June 27, 2003.

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Date Modified: 11/3/2008