SUPPLEMENT TO
MANAGED Care

Growth Hormone Treatment: Evidence, Practice, And Emerging Issues

An Educational Initiative for Managed Care Plans

HIGHLIGHTS

- Clinical Management of GH Therapy for Children
- Clinical Management of GH Therapy for Adults
- Plan and Pharmacy Perspectives

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A Continuing Education Activity

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SELF-STUDY CONTINUING EDUCATION ACTIVITY

Growth Hormone Treatment: Evidence, Practice, and Emerging Issues

Overview and needs assessment

The effects of growth hormone deficiency (GHD) on the stature and maturation of children are well established. Limitations and safety concerns related to extracting growth hormone (GH) from pituitary tissue have been obviated by the advent of recombinant DNA technology, which now permits the production and use of recombinant growth hormone to correct the effects of GHD. More recently, GH therapy has gained acceptance for treating idiopathic short stature (ISS) in children whose growth rate is considered subnormal but for whom no deficiency of GH or other endocrine abnormality has been identified.

The normal aging process also is accompanied by a substantial decline in GH. In cases where severe GH deficiency results from pituitary gland dysfunction due to disease or surgery, the indication for GH therapy for adults is clear. However, recent research has established evidence of the damaging effects of GHD in adults associated with vascular changes and atherosclerosis and with osteoporosis. Furthermore, just as the indications for GH therapy in children have recently been extended, clinical trials are underway to examine the potential of GH therapy in adults to ameliorate the bone fragility and muscle wasting associated with AIDS and the consequences of severe burns and chronic fibromyalgia. Resistance to expanded indications for GH therapy in both children and adults can be anticipated due to concerns over its potential long-term effects as well as cost.

This continuing education program provides information on the current status of GH therapy in the United States for children, including those with ISS, and for adults, so that managed care professionals can gain a broader understanding of the diagnostic and treatment algorithms for GH therapy and the scientific rationale for the expanded use of GH therapy.

Target audience

This program is intended for the education of managed care medical directors and pharmacy directors, clinical pharmacists, nurses, and case managers.

Educational objectives

After reading this publication, participants should be able to:

1. Outline the practical challenges and safety considerations of clinical testing for GH deficiency.
2. Identify the conditions and syndromes that are clear indications for GH therapy.
3. Interpret accurately the diagnostic significance of direct and indirect laboratory measures of GH deficiency.
4. Explain evidence-based principles that will be used to guide decisions for the approval of GH therapy for adults in whom there is no severe GH deficiency.
5. List the principal elements of recent consensus statements of pediatrician and endocrinologist groups regarding GH therapy and explain how they will affect the approval process.

Method of instruction

Participants should read the learning objectives and the articles in this supplement and review the activity in its entirety. Participants should then complete the post-test and submit the assessment/evaluation form with the test answers. Upon achieving a passing score of 70 percent or better on the post-test, a statement of credit will be awarded.

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INTRODUCTION

Growth Hormone Treatment: Evidence, Practice, and Emerging Issues

PINCHAS COHEN, MD, *Guest Editor*
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Short stature is defined as height significantly below the norm, generally more than 2 standard deviations below the mean on an age- and gender-specific growth chart (Hardin 2007). Although short stature often is predetermined by genes, a substantial number of cases are due to idiopathic growth inhibition — i.e., idiopathic short stature (ISS) children who are born small for their gestation age (SGA) and fail to catch up to age-matched peers — or physiologic failure of the pituitary/hypothalamic system and a resultant deficiency in the production of growth hormone (GH) and its effector protein insulin-like growth factor 1 (IGF-1). The secretion of GH by the pituitary is a key regulator of growth and development in children, and any defect in this pathway is likely to inhibit linear growth (Hardin 2007).

PINCHAS COHEN, MD

The importance of GH in overall health extends beyond its impact on height. GH contributes to optimal bone mineralization, normal accrual of lean mass, and the regulation of adipose tissue accumulation (Boguszewski 2005, Hardin 2007, Saggese 1996, Underwood 2003). Without normal GH secretion, children experience reduced bone mineral density (BMD) and lean body mass with a concomitant increase in visceral body fat (Boot 1997, Saggese 1996). In addition, due to the numerous metabolic effects of GH, including the stimulation of lipolysis and protein synthesis, promotion of anabolic activity, insulin antagonism, and regulation of body water, underproduction of GH can lead to insulin resistance and diabetes, increased cardiovascular risk, and poor immune system function — complications that can and do continue to challenge the health of children into adulthood (AACE 2003, Boguszewski 2005, Boot 1997, Hardin 2007, Saggese 1996, Underwood 2003). Short stature, furthermore, can lead to psychosocial impairment and symptoms of depression. Thus, correction of this physiologic deficiency has the potential for substantial benefit to a patient's overall health and well being.

The availability of human GH, particularly in its recombinant form (rhGH), has greatly helped to correct the physiologic, metabolic, functional, and psychological challenges associated with GH deficiency (GHD) and short stature. Supplementation with rhGH has been approved and shown to be effective and safe when used to increase GH levels, and to improve adult height and metabolism in patients with GHD as well as those with genetic syndromes associated with short stature such as the Turner, Prader-Willi, and Noonan syndromes (Hardin 2007). Patients with ISS and children who are born SGA also have been shown to achieve normalization of adult height with GH supplementation, and children with growth retardation secondary to chronic renal insufficiency experience an increase in linear growth, BMD, body weight, and lean mass (Hardin 2007).

In this continuing education publication, I review the guidelines for diagnosing disorders of growth inhibition in children and recommendations for the use of GH in their treatment. Roberto Salvatori, MD, reviews the guidelines and recommendations for GH therapy for adults. Albert Tzeel, MD, and Michael J. Fine, MD, consider the indications, duration, and cost of GH replacement to help pharmacy staff and formulary decision

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makers make informed decisions about the optimal role of rhGH use in patients with GHD and other disorders of short stature. rhGH has a long history of clinical use and has proven to be both safe and effective in improving short stature.

Despite the debate over the impact of morbidities associated with short stature, we must not forget the potential improvement in patient function, metabolism, and psychological well being associated with GH therapy so that those patients who will benefit most from rhGH therapy are sure to receive it.

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Clinical Management of Growth Hormone Therapy for Children

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An estimated 10,000 to 15,000 children, or about 3 to 5 percent of children in the United States, exhibit short stature, defined by some guidelines as height more than 2 standard deviations below the mean for age and gender on a growth chart (Krysiak 2007). Many of these cases are due to human growth hormone deficiency (GHD) (Regal 2001) that may result from such genetic defects as the Turner, Prader-Willi, and Noonan syndromes, or expression of the SHOX homeobox gene, or from physiologic problems, such as chronic renal insufficiency. Small for gestation age (SGA) children who never catch up to their peers, called idiopathic short stature (ISS), also results from GHD and is estimated to occur in as many as 120 of every 10,000 children (Cassidy 2000, Hardin 2007, Jamieson 1994, Lee 2003, Rao 2001 Saenger 1996).

Treatment with GH replacement therapy has proven effective in achieving adult height within a normal range in these children (Drake 2001). For many years, due to concerns about the transmission of Creutzfeld-Jakob disease or other viral infections associated with human pituitary extracts, the use of GH replacement was limited to the treatment of extreme GHD in children (Root 2002, Shimon 2003). Development of a recombinant human formulation of GH (rhGH), however, has improved the safety of treatment and expanded the range of indications (Regal 2001, Shimon 2003).

Today, a variety of rhGH products are available with indications in one or more of the genetic, metabolic, and developmental abnormalities previously mentioned, and ongoing research is investigating benefits in wasting disorders from acquired immune deficiency syndrome (AIDS) and short bowel syndrome (Natelson 1975, Powers 2005, Regal 2001, Takahashi 1968). Furthermore, some adults will continue to require GH therapy for GHD treated during childhood, or will need treatment for an acquired adult GHD secondary to brain tumors or trauma. As a result, the use of GH therapy has increased substantially in the past 2 decades and is first-line therapy for many growth failure syndromes.

Physiology: growth and growth hormone deficiency

Normal human body growth is under the control of the polypeptide GH, produced by the somatotrophic cells of the anterior pituitary gland (Baumann 1991, Lewis 1994). GH activity is modulated directly by GH-releasing hormone (GHRH), which stimulates its production, and somatostatin, which has a strong inhibitory effect on GH secretion from the pituitary. Both of these key modulators are discharged into the portal circulation from the hypothalamus and regulate the characteristic pulsatile surges of GH release, which generally occur in 3- to 5-hour intervals. The largest secretory pulses occur during rapid eye movement sleep, and the greatest frequency and amplitude of pulses are evident during the adolescent growth spurt after which levels of GH begin to decline (Regal 2001). In addition, acute stress, hypoglycemia, exercise, and fasting may stimulate GH release, while hyperglycemia, glucocorticoids, and estradiol can inhibit secretion.

Upon release into the circulation, GH binds to a binding protein, and this complex stimulates the production of insulin-like growth factor-1 (IGF-1), a polypeptide protein hormone produced in the liver that is a major effector of childhood growth. IGF-1 also is produced at the growth plate, where it promotes proliferation of prechondrocytes (Collett-Solberg 2008, Regal 2001). IGF-1, like GH secretion, peaks in adolescence and then declines into adulthood (Brabant 2003, Vance 1999). Deficiency or abnormality in either factor can negatively influence growth velocity and height achieved. IGF-1 also functions in promoting growth in muscle, cartilage, and bone and inducing cellular DNA synthesis. IFG-1 and GH have similar effects in some tissue, such as promotion of bone metabolism and growth, but opposing effects on glucose and insulin homeostasis, where GH inhibits insulin's effects and IGF-1 mimics insulin, and on fatty tissue, where GH is lipolytic and IGF-1 is lipogenic (Gharib 2003, Rosenfeld 2002). IGF-1 works in a negative feedback fashion to inhibit the secretion of GH,

thereby maintaining a physiologic balance between levels and activity of the two factors. The GH/IGF-1 axis is a key mediator of linear growth and also modulates normal metabolism and body composition.

GH stimulation also is influenced by ghrelin, a peptide secreted primarily from the stomach (with smaller amounts arising from the intestines, lungs, and kidneys) that, it is believed, stimulates GH secretion via both hypothalamic and pituitary influences (Lengyel 2006). Ghrelin appears to act in synergy with GHRH to induce GH release, as evidenced by peak circulating levels that correlate with the pulses of GH secretion. Whether this indicates a causal effect or a parallel regulation has not yet been determined.

Underproduction of GH may be part of a genetic condition or due to a congenital defect in the hypothalamic/pituitary/IGF-1 axis. In some cases, GHD is observed secondary to trauma, infection, radiation, or tumors. The result of absent or diminished hormone levels is growth failure and short stature with normal body proportions, often accompanied by delayed bone maturation, late puberty, slowed muscle development, and altered body composition; i.e., the relative concentration of bone, muscle, and fat. Some patients also may suffer psychological symptoms, such as poor memory or depression.

It also is important to recognize that GH deficiency often is accompanied by reductions in other pituitary hormones, particularly in subjects with tumors or genetic diseases. All pituitary hormone deficiencies must be corrected in these subjects or adult height will not be improved.

Diagnosis

The diagnosis of GHD is complicated by sometimes unreliable monitoring, failure to recognize underlying diseases, and challenges in diagnostic testing. Yet, accurate assessment of GH levels is important for the purpose of detecting underlying causes of GHD and making treatment decisions. Standard procedure requires that children with suspected GHD undergo auxologic evaluation; a complete physical examination, including personal and family medical histories; genetic and laboratory testing, particularly looking at specific endocrine profiles such as bone age and thyroid disease; and possible magnetic resonance imaging (MRI) assessment of the pituitary-hypothalamic region (Rosenfeld 2008, Hardin 2007, Wit 2008a, Wit 2008b).

When growth failure is suspected, specific tests of GH levels or activity are indicated. Although a number of assays are available to assess for serum GH concentration, many of them have limitations. Physicians at one time relied on GHRH testing, which today is contraindicated in children. Direct serum testing for GH levels is unreliable, because hormone levels fluctuate considerably throughout the day. As an alternative, there are many stimulation tests used to evaluate GH response, but safety or reliability concerns associated with many of the provocative agents, such as insulin, clonidine/arginine, glucagon, and levodopa (L-dopa), limit their use (Gandrud 2004). For instance, both short- and long-term reproducibility has been shown to be inconsistent with arginine, clonidine, and L-dopa stimulation tests (Cacciari 1994, Carel 1997, Gandrud 2004, Loche 2002, Tassoni 1990, Wit 2008b), and insulin stimulation testing may lead to hypoglycemic seizure and the potential for long-term sequelae (Gandrud 2004, Northam 2001, Rovet 1999). Clonidine and arginine stimulation tests, which require careful dosing by weight and height, are generally used in children today (Table).

TABLE

Pediatric GHD diagnostic: GH stimulation testing

GH stimulation testing[a]; peak GH concentration <10 µg/L supports diagnosis of GHD[b]; GHRH currently unavailable.

Stimulus	Dosage	Side effects
Levodopa (PO)	<15 kg: 125 mg 15–30 kg: 250 mg >30 kg: 500 mg	Nausea
Clonidine (PO)	0.15 mg/m[b]	Tiredness, postural hypotension
Arginine HCl (IV)*	0.5 g/kg (max 30 g) 10% arginine HCl in 0.9% NaCl over 30 min	
Insulin (IV)	0.05-0.1 U/kg	Hypoglycemia; use with caution in children
Glucagon (IM)	0.03 mg/kg IM (max 1 mg)	Nausea; use with caution in children

- **IGF-1 and IGFBP-3 assays are supportive for diagnosis of GHD**
- **Low levels suggestive of GHD[a]**

Tests should be performed after overnight fast. Patients should be euthyroid.
*GHRH is often used in combination with arginine.
GH=growth hormone, GHD=growth hormone deficiency, GHRH=growth hormone releasing hormone, IM= intramuscular, IV=intravenous, PO=by mouth.

[a]Adapted from Rosenfeld 2002. [b]Gharib 2003.

Measuring IGF-1 serum concentration is an accepted and safe alternative to GH stimulation assays. A simple blood measurement determines the level of IGF-1 in the serum, which, because GH mediates its production, correlates closely with GH secretion. In addition, there are six IGF-binding proteins (IGFBPs) that bond with IGF to assist with transport through the bloodstream. In neonates and prepubescent children, bound IGFBP-3 levels, in particular, have been shown to correlate with GH activity (Diamandi 1998, Gandrud 2004, Loche 2002).

A number of genetic tests to determine the underlying causes of GHD and hypopituitarism are gaining ground as reliable diagnostic tools (Gandrud 2004). As the DNA profiles for the Turner, Noonan, and Prader-Willi syndromes and SHOX mutation are defined and rapid tests for the genetic defects are developed, those tests will fast become useful substitutes for GH measures or stimulation tests.

Treatment

Treatment indications

A normal growth distribution in children is considered to fall between the 5th and 95th percentiles specific to age and gender. The decision to treat for GHD is generally based on low measures on GH tests and/or growth patterns outside this norm. Children who fall in the –1.5 to –2 standard deviation (SD) range on a standard growth distribution chart , corresponding with about the 3rd to 5th percentile, should be evaluated for GHD; however, the U.S. Food and Drug Administration has approved GH therapy only for patients at the –2.5 SD level (~1.2 percentile).

The use of GH assays and SD scale cut points to guide indications for GH treatment has been shown to be effective in distinguishing children who are likely to exhibit extreme short stature with potential medical and psychological complications. There are some situations, however, where these guidelines may be deferred. For instance, children with severe IGF-1 deficiency, defined as a height –3 SD on the growth chart coupled with a very low IGF-1 level (–3 SD score [SDS]), would qualify according to recent FDA approval for therapy with recombinant IGF-1. In addition, some children who pass a GH stimulation test may have problems with GH sensitivity rather than limitations in serum concentrations. Many, although not all, of these children may respond to GH supplementation therapy regardless of the results of GH assays.

As a result, the guidelines of the Lawson Wilkins Pediatric Endocrinology Society reflect these alternative patient types (Wilson 2003). In the published guidelines, the society supports the use of GH therapy in some children and adolescents who do not exhibit GH deficiency on standard testing assays, but who have classic GH deficiency phenotype, including short stature and height >2.25 SDs below the mean for age or >2 SDs below the midparental height percentile; a growth velocity <25th percentile for bone age; bone age >2 SDs below the mean for age; low serum IGF-1 and/or IGFBP-3; and/or other clinical features of GHD. This profile is termed atypical GH deficiency.

Treatment options

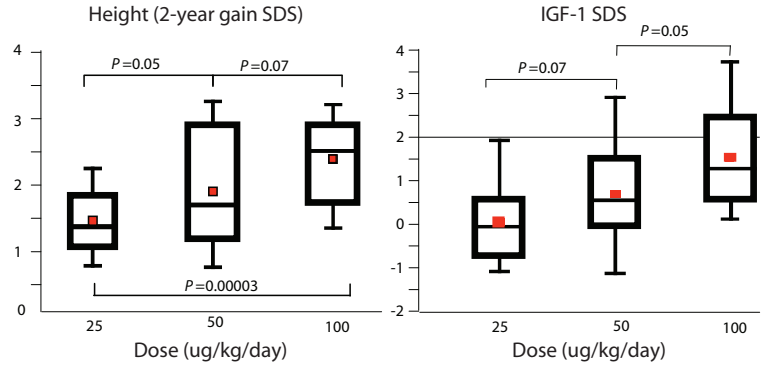
The FDA has approved for use a variety of rhGH formulations to treat childhood GHD. GH replacement therapy has been shown to be effective in increasing adult height in children with GHD, ISS, Turner syndrome, Prader-Willi syndrome, SHOX mutation, chronic renal insufficiency, and SGA (Carrel 1999, Clayton 2007, Fine 1994, Lee 2003, Sas 1999). In one study (Sas 1999) of girls with Turner syndrome who typically exhibit height well below the normal range, 85 percent receiving 7 years of treatment with GH achieved height within the normal range for their healthy peers. In another study (Carrel 1999), 12 months of treatment with GH replacement significantly increased height velocity, decreased percent body fat, and improved respiratory muscle function, physical strength and agility ($P<.001$) in 54 children, ages 4 to 16 years, with Prader-Willi syndrome. Similar benefit has been reported in the other conditions as well (Clayton 2007, Hokken-Koelega 2003, Sas 1999).

Several trials have shown that, in both prepubertal and pubertal children, the activity of GH is dependent on the dose used. Cohen (2002) showed that doses of GH increasing from 25 to 50 to 100 ug/kg/day yielded successively greater effects on both 2-year height gain, measured as the increase in SDS and serum IGF-1 SDS, particularly among boys. Figure 1 illustrates these improved outcomes as measured in 71 GH-deficient prepubertal boys. Girls (n=33, data not shown) exhibited a somewhat different dose response curve, suggesting a gender effect on GH action.

In addition, based on the understanding that IGF-1 is the central mediator of GH activity, a 2-year randomized, open-label study attempted to determine if guiding GH therapy by IGF-1 levels achieved could improve height compared with standard weight-based dosing in children with GHD. Among 147 prepubertal short boys and girls with low IGF-1 levels (mean SDS, -3.56) who completed 2 years of GH treatment to either a mean IGF-1 level or to IGF-1 levels at the upper limit of normal range, or with conventional dosing at 40 ug/kg/day, achieving higher IGF-1 serum levels through targeted dosing significantly increased the linear growth response (Figure 2). There was no significant difference in safety among the three groups.

FIGURE 1

Dose-dependent efficacy of GH supplementation therapy on height and IGF-1 levels, as measured in GH-deficient boys

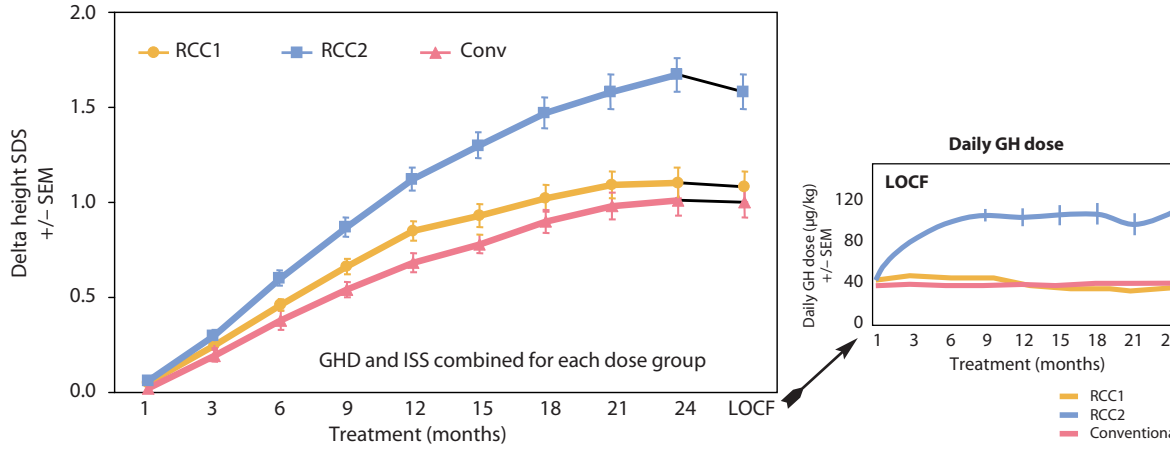


GH=growth hormone, IGF-1=insulin-like growth factor 1, SDS=standard deviation scores.
Source: Cohen 2002

Children born SGA represent a unique group of patients. Most of these children do not test as deficient in GH, and the cause of growth retardation remains unknown, although about 90 percent will experience "catch-up" growth by 2 years of age. Nonetheless, about 10 percent will continue to exhibit short stature throughout childhood and into their adult lives. The majority of these children can be treated successfully with GH replacement therapy to attain adult height at or near the normal range. However, Argente (2007) showed that initiation of GH therapy at a younger age (<4 years) in SGA children ages 2 to 5 who had not achieved catch-up growth significantly improved height gain over 2 years of treatment compared with delayed start of therapy ($P<.001$). Higher doses, furthermore, achieved greater benefit. In addition, GH therapy has been shown to increase bone maturation and improve bone mineral density in children born SGA, with the potential to protect against osteoporosis later in life (Arends 2003). Thus, early GH therapy may offer substantial long-term benefit in this group of children.

FIGURE 2

Dosing of GH targeted to achieve IGF-1 levels in the upper limit of normal range improves height outcomes compared with conventional dosing (40 ug/kd/d) or dosing to mean IGF-1 levels



Conventional dosing according to BW; 40 ug/kg/day (n=34). RCC1: Target IGF-1 Z-score to the mean (n=70); RCC2: Target IGF-1 Z-score +2 SDS (n=68).

BW=body weight, GH=growth hormone, GHD=growth hormone deficiency, ISS=idiopathic short stature, LOCF=last observation carried forward, SEM=standard error of the mean.
Source: Cohen 2007

Similarly, children with ISS, who represent a large population with short stature of unknown etiology, generally respond to GH treatment. Leschek (2004) showed that boys and girls ages 9 to 16 years with ISS (height <2.5 SDS) achieved significantly greater adult height with three times weekly GH therapy than without such therapy ($P<.02$). Mean height velocity was significantly greater in the first 2 years in active treatment patients compared with the placebo group ($P<.01$) In addition, some of the potential adverse psychological consequences of severe growth retardation in ISS, such as poor self-image, poor psychological adaptation, problem behavior, and inferior performance, have all been shown to improve with the greater linear growth in children treated with GH (Ross 2004, Tanaka 2009). Thus, corrections in growth velocity and attained height may positively influence some of the psychological complications of GHD and improve quality of life.

Safety

GH treatment is, by and large, a safe and tolerable therapy. The most common adverse events are injection-site reactions, such as early edema, joint pain, and local bruising, which usually do not necessitate discontinuation. Rare side effects of GH treatment include slipped capital femoral epiphysis (SCFE), gynecomastia in boys, increased intracranial pressure, growth of existing benign nevi (not new growths), increase in fasting insulin, and worsening of scoliosis. Many of these side effects are reversible on discontinuation of the drug, although with pinning of the joint hip in SCFE, treatment may continue.

Monitoring for second cancers is required in children who have had brain tumors, and active malignancy is a contraindication to GH use. Apnea is a concern in children with Prader-Willi syndrome, who must be carefully evaluated and watched during treatment. Annual fasting blood sugar evaluation is recommended for children with SGA who may have underlying insulin resistance, and use in severely ill children should be done only with caution in extreme cases.

Conclusion

GHD and related disorders marked by growth inhibition affect a large portion of U.S. children. The growth retardation can be small, falling just outside the normative values for age- and gender-matched children, or severe, in which case there may be concomitant medical and psychological complications. Treatment guidelines offer well-described parameters for using GH supplementation to increase growth velocity and improve adult height attained in these children, but because of the diversity of causes and outcomes in this condition, diagnostic and management decisions must be individualized to offer safe testing, recognize underlying causes of short stature, and treat patients according to their expectations for growth and medical and psychological outcomes.

The rhGH therapies available today are effective and safe. Thus, their use has expanded to include patients with diagnoses ranging from GH or IGF-1 deficiencies or genetic syndromes marked by growth failure, such as the Turner, Prader-Willi, and Noonan syndromes, to idiopathic causes of short stature, both ISS and SGA. Future investigations may refine dosing strategies, disease- and gender-specific responses to GH, and targeted treatments to reduce toxicity. But the growth benefits and improved health associated with GH therapy are well established and should be the goal of GH treatment in this population.

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Clinical Management of Growth Hormone Therapy in Adults

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The impact of growth hormone (GH) on linear growth disappears after puberty, but its influence on metabolism, body composition, bone density, psychological health, and overall well being continues into adulthood (Cummings 1999, Cummings 2003). In adults, lower-than-normal GH levels can lead to altered body composition, impaired physical and psychologic function, and biochemical pattern of increased cardiovascular risk, although an effect on cardiovascular morbidity and mortality has not been proven. GH therapy is indicated to treat GH deficiency (GHD) in adults with hypothalamic-pituitary disease (AACE 2003, Ho 2007, Molitch 2006). Debate exists, however, about the proper use of GH replacement, the safety of long-term GH therapy, and the means to monitor its effects in adults without the benefit of following growth as with children. Thus, although patients with severe GHD may benefit from hormone replacement therapy, we must consider the implications of GH use for mildly deficient or asymptomatic patients, clarify the cost efficacy of GH replacement, and justify or dismiss its potential role in other disorders for which it is being used off label.

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This article provides a comprehensive overview of current knowledge and the standard of practice in the care of the adult patient with GHD.

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Evidence for use of GH therapy in adults

The use of GH to treat adults is a relatively new concept, originating in large part with the work of Thord Rosén and colleagues from Goteborg, Sweden. After reporting higher-than-expected vascular mortality in hypopituitary patients with presumed GHD (Rosén 1990), in a later study, Rosén (1993) reported a loss of bone mineral density (BMD) among the same group of patients. Following up on this finding, Rosén (1997) compared the rates of fracture in 107 men and women with hypopituitarism who were treated to replace all hormones (cortisone acetate, L-thyroxine, and testosterone or estradiol) except GH with those noted among 323 healthy controls. The investigators observed a threefold increase in fracture frequency among GHD patients (24.1 percent) compared with control subjects (8.7 percent, $P<.001$). The trend was particularly strong among men, with an odds ratio (OR) for fracture frequency of 3.97 compared with controls; the OR was 2.64 for women. These findings led to speculation that GH replacement therapy might help correct bone defects in patients with GHD, although another possible explanation is that it is well known that the suboptimal (or excessive) replacement of other hormones (glucocorticoid, thyroid, and sex hormones) influences bone apposition and several metabolic parameters. Furthermore, many of the patients included in the Rosén studies had undergone pituitary surgery and/or radiation, which may also have had a direct influence on some of the outcomes studied; in particular, cranial radiation may predispose to cerebrovascular disease (Ayuk 2009).

Subsequent research has established evidence of the effects of GHD in adults. Sen (2008) reported a 20 percent increase in carotid intima thickness among adult subjects with GHD compared with body mass index (BMI)-, age-, and sex-matched healthy controls ($P<.01$), with concomitant increases in total and low-density lipoprotein (LDL) cholesterol levels and percent fat mass. In a cross-sectional observational study of adults

with GHD, Leonsson (2003) noted significant increases in the inflammatory markers interleukin-6 (208 percent, $P<.01$, and 248 percent, $P<.001$, vs. BMI-matched and nonobese controls, respectively) and C-reactive protein (CRP) (237 percent vs. nonobese controls, $P<.01$). The results from these two trials suggest that adult GHD is associated with an atherosclerotic environment and vascular changes that may lead to early cardiovascular disease. However, a higher prevalence of myocardial infarction or stroke in GHD adults has yet to be demonstrated. Surprisingly, however, there was no evidence of premature atherosclerosis in a large kindred of adult subjects with congenital, lifetime, and untreated isolated GHD who reside in a rural area of northeast Brazil (Menezes Oliveira 2006).

Altered body composition, such as increased abdominal adiposity and reduced muscle mass, are well-known consequences of GHD (AACE 2003, Sartorio 2008). This is supported further by the fact that GH replacement therapy improves muscle mass and, as shown in selected studies (Abrahamsen 2004, Rodriguez-Arnao 1999, Sartorio 2008), muscle function over the long term in GHD patients of all ages.

Several reports (Blum 2003, Bjork 1989, Burman 1995, Rosén 1994) have found a psychological impact associated with GHD with symptoms of emotional lability, social isolation, and reduced mental energy, which translates into impaired quality of life (QoL), compared with the general population. Correcting the GH defect has been shown in several studies (Burman 1995, Moock 2009, Mukherjee 2005) to improve QoL measures. Again, such effect on QoL was not observed in the same Brazilian kindred (Barbosa 2009), questioning whether GHD by itself has such effects or whether a lifetime lack of GH leads to adaptation phenomena.

These medical morbidities stated a strong case for treating GHD in adults. As a result, the use of GH replacement therapy is approved by the U.S. Food and Drug Administration for adults with GHD due to established etiologies, such as pituitary tumor, pituitary damage during surgery, hypothalamic disease, irradiation, trauma, and reconfirmed childhood GHD. Treatment should be reserved for those adults with documented GHD in the appropriate clinical setting based on recognizable clinical features and supportive laboratory findings. On the other hand, a number of additional indications, such as chronic fatigue syndrome, fibromyalgia, performance enhancement in sports, and antiaging therapy, are unsupported and potentially dangerous.

Diagnosis

Several organizations, including the American Association of Clinical Endocrinologists (AACE), Endocrine Society, and Growth Hormone Research Society (GRS), have published guidelines defining the population eligible for GH therapy and recommendations for appropriate tests and cut points (AACE 2003, GRS 1998, Ho 2007, Molitch 2006). They define patients with suspected GHD as those who have a history of childhood onset GHD, or who have a pituitary tumor or have undergone radiation or surgery for pituitary disease, or who have experienced a traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH). To confirm the diagnosis, GH testing may be considered, but detection of this hormone in the bloodstream is unreliable due to the episodic release and short serum half-life (<20 minutes) (AACE 2003). Use of GH stimulation tests is necessary, although many of these tests are faulted by limited sensitivity and specificity. For this reason, these tests must be performed in the appropriate clinical setting. Adults with childhood-onset isolated GHD must be retested, as up to 50 percent are no longer deficient when they reach adult age, particularly if pituitary magnetic resonance imaging (MRI) is normal.

The insulin tolerance test (ITT), which evaluates the body's ability to respond to insulin-induced hypoglycemia, is the preferred test for GHD. The ITT, however, requires experienced staff to perform it and can be unpleasant for the patient, causing such symptoms as sweatiness, drowsiness, and difficulty in concentrating. In addition, some patients, particularly those older than age 65 and those with past history of seizures or coronary artery disease, may be at risk for seizures or stroke during ITT. Thus, safer and easier alternative procedures have been explored but with mixed results. Biller (2002) compared the sensitivity and specificity of ITT with that of stimulation tests using arginine plus GH-releasing hormone (GHRH), arginine plus L-dopa, arginine alone, and L-dopa alone to assess the reliability of each as a measure of GHD. Biller found widely disparate cut-points, with mean values ranging from 1 to >5 ug/L (Table 1, page 12). The ITT and arginine plus GHRH tests, with cut-points of 5.1 and 4.1 ug/L, were similarly reliable with high sensitivity and specificity. Due to the absence of unpleasant symptoms, most patients preferred the latter test. The authors concluded, therefore, that arginine plus GHRH represents a good alternative to ITT for testing adults with suspected GHD. However, GHRH has been commercially unavailable in the United States since Oct. 30, 2008. An alternative option — the glucagon stimulation test — is gaining popularity due to its safety and easy access to glucagon. More data are needed, however, to establish its validity in assessing adult GHD. Presently, a cutoff point of 3 ug/L is recommended to interpret this test conservatively (Gomez 2002).

TABLE
Comparison of GH stimulation agents as a measure of GHD

Test	95% sensitivity cut point	95% specificity cut point	Minimize misclassification cut point ("CART")
ITT	5.0	3.3	5.1
Arg/GHRH	4.6	1.5	4.1
Arg/L-dopa	1.5	0.25	1.7
Arginine	1.4	0.21	0.4
L-dopa	0.64	NA	1.1

- ***The glucagon GH test is a reliable alternative to ITT***[a]
- Arg/GHRH is the best alternative to ITT for making the diagnosis of GHD, except in patients with recent radiation or hypothalamic disease[b]
- GHRH is not available in the United States
- Arginine and Arg/L-dopa are less stringent tests and should not be used
- Very low IGF-1 in patients with multiple pituitary hormone deficiencies provides the diagnosis.[c] Over 83% of patients with 2 or more additional pituitary deficits have peak stimulated GH of less than 2.5 µg/L.

Arg=arginine; GHRH=growth hormone releasing hormone; ITT=insulin tolerance test.
[a]Gomez 2002; [b]Biller 2002; [c]Hartman 2002.

In some patients, stimulation testing may not be necessary at all. Due to the causal relationship between GH secretion and insulin-like growth factor-1 (IGF-1) production, low serum IGF-1 levels often are considered suggestive of GH deficiency; however, an IGF-1 measure alone is not a very sensitive marker. Among subjects with frankly low serum IGF-1 in the setting of hypopituarism, i.e., deficits in multiple pituitary hormones, the likelihood of GHD increases with each additional hormonal deficit. In one study, 41 percent of patients with a pituitary tumor and with serum levels of IGF-1 <84 ug/L exhibited GH deficiency, rising to 67 percent in the presence of one hormone deficiency, 83 percent with two hormone deficits, and at least 96 percent in those with low levels of three or more hormones (Hartman 2002).

It is important to recognize that obese individuals may have a low GH response on stimulation testing unrelated to pituitary disease. A substantial potential exists for false positive results on GH stimulation testing among individuals with a BMI >30; therefore, unique GHD cut points may be necessary when evaluating GH activity in this population (Qu 2005). Until new criteria are developed for this purpose, obese individuals who do not exhibit medical features consistent with GHD probably should not undergo testing.

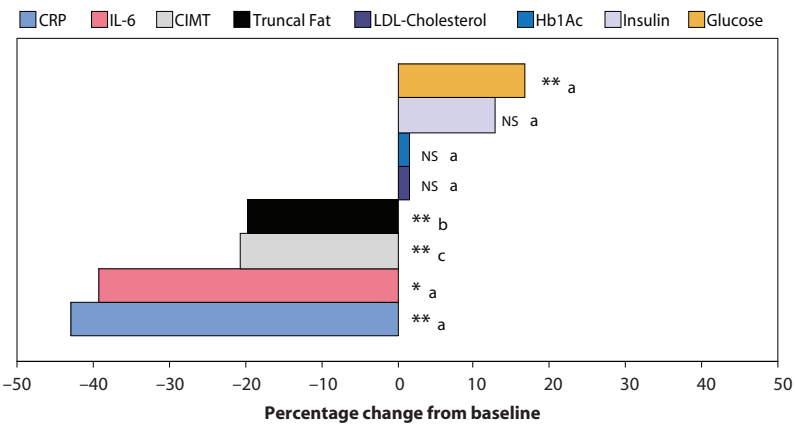
GHD treatment: Guidelines and outcomes

Experience with GH in adults. Doses of GH for adult replacement therapy generally range from 2 ug/kg/day subcutaneously (SC) to 8 ug/kg day SC. Due to a greater likelihood of GH side effects in adults compared with children, treatment should be initiated with a low dose (no more than 0.2 mg/day in men and 0.3 mg/day in women) and titrated upward monthly in increments of 0.1 to 0.2 mg/day (AACE 2003). Women generally require higher doses than men, and women receiving oral estrogen may require doses much higher than women using transdermal estrogen or those with endogenous estrogen (AACE 2003, Cook 1999). For this reason, I propose to all my female patients on estrogen replacement that they switch to transdermal estrogen therapy before starting rhGH therapy. Careful monitoring of serum IGF-1 should be performed monthly during dose titration and biannually thereafter with the goal of maintaining age-appropriate values. GH therapy has been shown to positively alter a number of markers of GHD in adults. As shown in Figure 1, treatment with 4 ug/kg/day reduced levels of the inflammatory markers IL-6 and CRP, but did not cause a persistent reduction in total and LDL cholesterol (Sesmilo 2000). Treatment with a significantly higher dose of 12.5 ug/kg/day was shown to decrease total and LDL cholesterol (Hoffman 2004). More importantly, at 5.9 ug/kg, rhGH significantly decreased carotid intima medial thickness (IMT) by about 20 percent compared with baseline within 3 months, an effect that persisted for the duration of the study (18 months) (Pfeifer 1999). Surprisingly, an increase in IMT after 6 months of submaximal GH replacement therapy in adults with lifetime congenital and very severe isolated GHD has been noted (Oliveira 2007).

Sesmilo (2000) showed that glycosylated hemoglobin (HbA_{1c}) concentrations generally stayed the same on 4 ug/kg/day rhGH therapy, and insulin levels generally remained stable. Fasting glucose levels, however, increased mildly, which is a known side effect of GH therapy. Accordingly, at the higher doses, Hoffman (2004) reported moderate increases in mean fasting and postchallenge glucose and insulin and HbA_{1c} levels of unclear clinical significance.

GH therapy also has been shown to improve BMD in adults with GHD. Johannsson (1996) showed that 2 years of treatment significantly improved BMD in the lumbar spine L2-L4 (3.8 percent), femoral neck (4.1 percent), and femoral trochanter (5.6 percent) in 24 men and 20 women with adult-acquired GHD. The greatest benefit

FIGURE 1
Efficacy of GH therapy



Mean percentage changes from baseline values of GHD patients at the end of 6 to 18 months of GH treatment.

CIMT=carotid artery intima-media thickness; CRP=C-reactive protein; GH=growth hormone; GHD=growth hormone deficiency; IL-6=interleukin 6; LDL=low-density lipoprotein; NS=not significant.

a. Sesmilo 2000: GH dosage of 4 ug/kg/day
b. Hoffman 2004: GH dosage of 12.5 µg /kg/day
c. Pfeifer 1999: GH dosage of 5.9 ug/kg/day

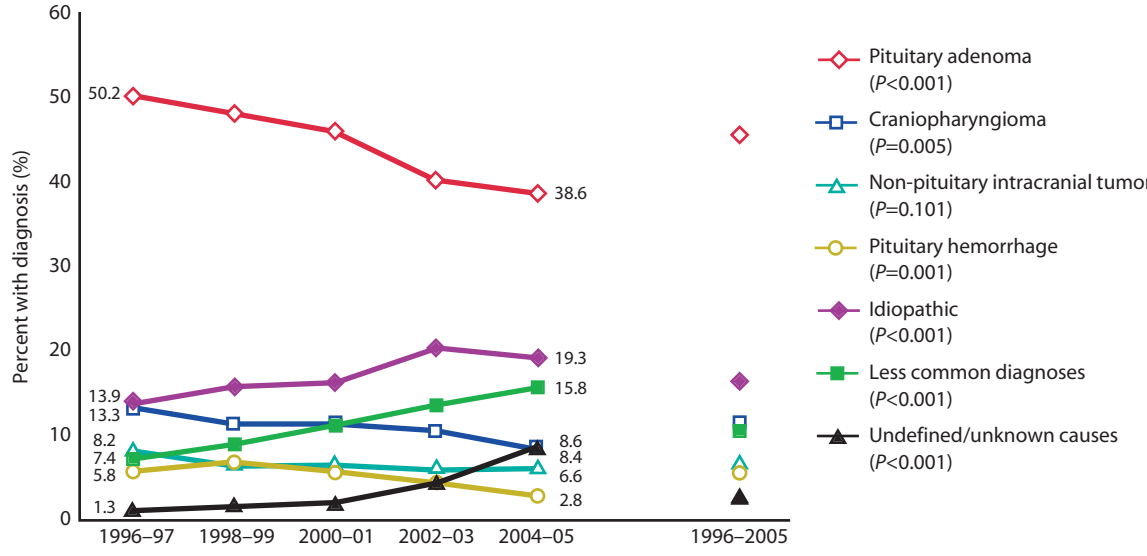
was observed in patients with the lowest z-scores (z-score <−1), and led to a 40 percent to 50 percent reduction in the number of patients at greatest risk for fracture. These findings in a population with adult-onset GHD complemented earlier data supporting the bone remodeling benefits of GH replacement in adults with childhood-onset GHD. In general, the beneficial effect of GH requires treatment longer than 1 year.

Several studies (Gibney 1999, Verhelst 1997) also have established a benefit in QoL associated with GH treatment for adult GHD. In a 10-year follow-up of 21 adult GHD patients (Gibney 1999), scores on the Nottingham Health Profile indicated significant improvement in overall score, energy levels, and emotional reaction among GH-treated subjects compared with 11 age- and sex-matched normal controls. This study, however, was not blinded or placebo controlled. In addition, postmarketing data obtained from 148 adult patients treated with GH replacement therapy for 2 years indicated that GH treatment improved overall well being, as indicated on the Nottingham Health Profile and a social self-reporting questionnaire (Verhelst 1997). Furthermore, the authors noted a significant reduction in the number of sick days among treated subjects, decreasing from 12.17±3.90 days at baseline to 7.15±3.50 at 6 months (P=.009), 2.93±1.55 at 12 months (P=.01), and 0.39±.07 at 18 months (P<.001). If these findings are substantiated by placebo-controlled studies, the socioeconomic implications are compelling in support of GH therapy in adults.

Expanding use. Since the approval of GH replacement for adult GHD, the range of indications has continually expanded. GH supplementation was originally prescribed only for patients with such organic pituitary disease as tumor, bleeding, or reconfirmed childhood GHD (AACE 2003). Today, the use of GH therapy has grown to include a number of less common diagnoses and idiopathic forms of GHD (Webb 2009, Gasco 2008, Toogood 2007). The Hypopituitary Control and Complications Study (HypoCCS) (Webb 2009), a 10-year observational trial analyzing patterns of the use of GH replacement in adults, revealed a decline in the percentage of patients receiving GH therapy for traditional indications, such as pituitary adenoma (from 50.2 percent to 38.6 percent, P<.001), craniopharyngioma (13.3 percent to 8.4 percent, P<.005), or pituitary hemorrhage (5.8 percent to 2.8 percent, P<.001); it also has led to a rise in cases of "idiopathic" GHD (13.9 percent to 19.3 percent, P<.001) and less-common diagnoses such as sarcoidosis, empty sella, pituitary infection, (7.4 percent to 15.8 percent, P<.001), and undefined/unknown diagnoses (1.3 percent to 8.6 percent, P<.001) (Figure 2, page 14). Given the recent awareness of false-positive GH stimulation tests in obese patients, one is left to wonder if a percentage of "idiopathic" cases are indeed just overweight patients.

The association of TBI and SAH with hypopituitarism and GHD are examples of newer diagnoses (Aimaretti 2004, Ceballos 1996, Kelly 2000, Lieberman 2001). Based on previous reports of neuroendocrine dysfunction after TBI or SAH, Aimaretti (2004) performed an epidemiologic analysis of pituitary function among 140 patients 3 months post-TBI (n=100) or SAH (n=40) and noted some evidence of hypopituitarism in 35 percent and 37.5 percent, respectively, of these patients. The most frequent defect was severe GHD, occurring in 21 percent of TBI and 25 percent of SAH patients in each group using a GHRH plus arginine test with the cutoff of 9 ug/L. Using a more conservative cutoff of 5 ug/L, the percentage of GHD was 12 percent in TBI and 10 percent in SAH (Biller 2002). Thus, although the underlying pathophysiology of brain injury-induced hypopituitarism re-

FIGURE 2
Significant shifts in patterns of use for GH therapy indicate a trend to less severe forms of GHD



Source: Webb 2009 with permission.

mains to be elucidated, the potential to correct the sequelae of post-traumatic GHD in these patients (e.g., fatigue, poor endurance, and reduced sense of well-being) suggests a role for GH replacement. Therefore, a neuroendocrine evaluation should be considered for all adult patients after TBI or SAH to determine the need for GH or other pituitary hormone replacement.

Although some of the increase in the use of rhGH is well intentioned, such use for antiaging regimens, bodybuilding, or athletic enhancement should be discouraged. Studies have consistently failed to show an increase in muscle strength or aerobic exercise capacity associated with GH therapy in otherwise healthy individuals, yet rhGH continues to be abused by professional athletes (Olshansky 2008, Liu 2008). In addition, although GH therapy to slow the aging process has not been demonstrated, the off-label use of GH as an antiaging therapy continues to grow (Olshansky 2008).

Safety. GH treatment is generally safe when dosed according to recommended procedures (Krysiak 2007). In clinical trials, the most common side effects are edema, arthralgia, and muscle pain. Most of the side effects can be minimized during titration by treating to maximum efficacy with minimal side effects. Local injection site reactions generally do not warrant discontinuation and can be minimized by changing the injection site regularly. A proposed risk for tumor recurrence or *de novo* malignancies has been discounted (AACE 2003). Nevertheless, a history of malignancy within 5 years is commonly considered a contraindication to rhGH therapy. Other relative contraindications are proliferative diabetic retinopathy and increased intracranial pressure.

GH therapy may increase the requirement for L-thyroxine and glucocorticoid in hypopituitary patients; therefore, the dose of these replacement therapies should be adjusted as necessary during GH therapy (Molitch 2006).

Summary

GH replacement is an effective and rational therapy for adult men and women with known pituitary disease or risk factors for hypopituitarism; for example, severe head trauma or pituitary irradiation, provided that GHD is proven. Only at-risk adults should be tested, and adults with childhood GHD should be retested before prescribing GH for adult needs. A neuroendocrine review should be considered in all cases of TBI and SAH.

The AACE, Endocrine Society, and GRS have issued detailed GHD treatment guidelines. Diagnostic evaluations should follow these guidelines, and physicians should stay abreast of changing information about testing cut-points and the use of IGF-1 as a marker for GHD. The pros and cons of GH treatment must be discussed with each patient, after which GH doses should be individualized and titrated to maximum efficacy with minimal side effects. Off-label use of GH therapy as an antiaging treatment or sports enhancement is clearly at odds with current guidelines and should not be prescribed under any circumstances.

GH replacement therapy has been shown to improve

the clinical features of GHD in adults, although there yet have been no studies on endpoints such as cardiovascular events, fractures, and death. When used in an approved and ethical fashion for the defined population, this treatment can enhance the health and well-being of the many patients who suffer from the complications of GHD.

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Plan and Pharmacy Perspectives: Growth Hormone Therapy, Formulary, And Benefit Authorization

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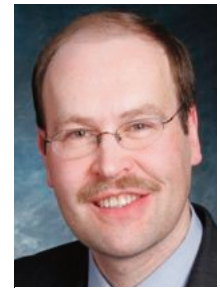
Growth hormone (GH) therapy has been shown to be an effective and safe means to increase linear growth to achieve adult height within the normal range for children with GH deficiency (GHD). GH supplementation also is currently indicated to correct the physiologic and metabolic defects associated with GHD in children, which can continue to plague these children into adulthood (AACE 2003, Ho 2007, Krysiak 2007). With the development of recombinant human growth hormone (rhGH), however, a rapid rise in the use of GH therapy and an expansion of indications has led to several ethical and economic questions: What degree of short stature warrants diagnostic testing for GHD? How valuable are the nongrowth, or metabolic, effects of GH treatment? What are the outcomes of long-term rhGH therapy? Which diagnoses warrant treatment and at what cost? These questions can have a substantial impact on payer and pharmacy decisions about which products to include on a formulary and which indications should be covered.



ALBERT TZEEL, MD, MHSA, CPE, FACPE, FAAP

In this article, we review some of the concerns about GH therapy and discuss from both a payer and a pharmacy perspective the issue of balancing limited resources while providing appropriate rhGH supplementation to patients who need it.

Extent of the problem

The National Cooperative Growth Study (Wyatt 2004) is the only longitudinal observational study of the safety and efficacy of rhGH therapy and of the number of pediatric patients in North America receiving therapy for growth disorders. The data obtained by the NCGS provide a valuable source of information not only on the clinical use of rhGH, but also on the changing patterns of diagnosis and the prevalence of different diagnoses currently considered for rhGH prescription. The 2004 report of the NCGS indicated an increase in nongrowth hormone-deficient U.S. Food and Drug Administration-approved diagnoses of short stature such as idiopathic short stature (ISS) and small for gestation age (SGA). This was the last NCGS update, and more recent data on the observed trends are much needed.

Although the prevalence of a GHD etiology plays a role in the development of a pharmacy formulary or a payer's decision on how to provide plan coverage, it must be remembered that the growing number of FDA-approved indications will inflate the number of children eligible for rhGH therapy and will challenge the economics of health plans. With non-GHD diagnoses comprising a substantial portion of the newly eligible population — e.g., up to 120/10,000 children have ISS versus 5-10/10,000 with GHD — payers will continue to thor-

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oughly investigate the efficacy, safety, and long-term implications of rhGH therapy in these populations.

Diagnostic testing

A range of tests have been developed to detect GHD, including the insulin tolerance test (ITT). The risk of hypoglycemia and the limited reproducibility associated with ITT, as well as its expense, suggest that this test should be used sparingly. Although the growth hormone-releasing hormone (GHRH) plus arginine stimulation test is a safer and well-standardized alternative in adults suspected of having GHD, GHRH currently and temporarily is not available in this country. For children and adults, other options, including the arginine-clinidine stimulation test, are commonly employed. Insulin-like growth factor-1 (IGF-1) levels linked with GH secretion do not correlate perfectly with GH concentration in children and require other clinical features for validation of the diagnosis, although IGF-1 is a reasonable surrogate for GHD in adults. Given that research has shown that patients with panhypopituitarism marked by deficits in more than three pituitary hormones will nearly universally also have GHD, it is not cost-efficient to use the ITT in this population (Hartman 2002).

Similarly, the use of stimulation testing in obese individuals presently is not reliable. Increased body mass index (BMI) is linked with reduced GH secretion not indicative of pituitary disease, leading to many instances of false-positive GHD diagnoses (Qu 2005). Thus, health plans discourage testing this population. The cut points specific to overweight and obese BMI measures have been shown to be lower than in lean individuals; thus, this group of patients should not undergo stimulation testing unless there are clear clinical signs of GHD.

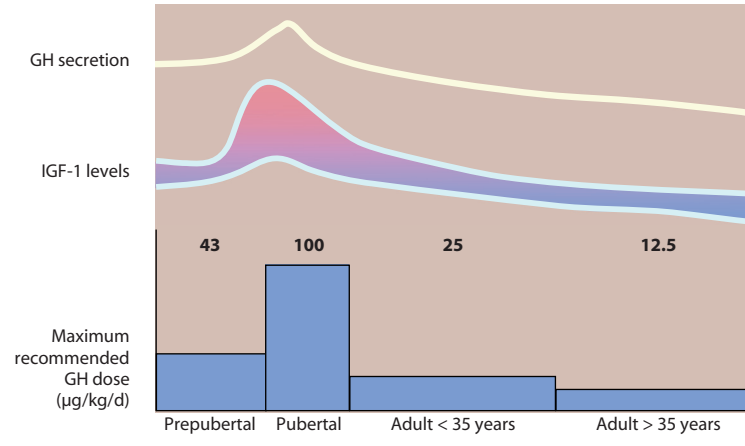
Authorized uses of GH therapy

Historically, GH supplementation has been indicated for the treatment of growth failure in children with measurable deficiency of endogenous GH secretion on stimulation testing. Also, there is no question that GH therapy is appropriate to increase linear height in those children with genetic diseases marked by short stature, such as Turner syndrome and Prader-Willi syndrome. In other situations, however, the use of GH supplementation is less clear; for example, to "normalize" stature in children, a term about which there is ongoing debate. What is *normal,* and does defining normal by auxological criteria determine a true disease that warrants treatment? In adults, rhGH therapy should be used only if it can be shown that treatment will result in improvement to health and well being.

SGA and ISS are considered by many payers to be controversial indications for rhGH therapy. It is unclear whether there are any complications of small stature. For example, in SGA, at what point in time does the "catch-up" period become pathologic; that is, when will children lose their potential for stature growth forever? The fact that only 10 percent of these children do not catch up in height to their peers within 2 to 4 years, however, is encouraging, because this narrows the diagnosis and the potential population likely to be considered for treatment. The two indications, however, are still under intense scrutiny and debate among payers.

As a rule, health plans will accept a physician's recommendation for GH therapy based on whatever diagnostic procedures have been used to rule out other disease possibilities for growth failure. For those health plans that do not cover ISS or SGA, the only criteria acceptable for the prescription of hormone supplementation therapy is proof of low GH secretion on a stimulation test. Most insurers will accept a diagnosis of Turner, Prader-Willi, or Noonan syndrome in the presence of clearly below-normal growth as a reason to prescribe rhGH without further testing. Payers may not be aware of the evidence that body fat decreases among patients receiving rhGH in Prader-Willi syndrome, but the rationale for treatment is so strong for this condition, that this finding will not alter practice (Carrel 1999).

FIGURE
rhGH dosing is based on patterns of GH secretion throughout life



Source: Brabant 2003

GH supplementation also is indicated for children with renal insufficiency up to the time of kidney transplantation. However, it is not known if their growth pattern will return to normal after transplant — that is, will they achieve normal height after having received GH during dialysis, or will they be short despite therapy due to continued growth delay after transplant?

The evidence highlighting the permanent loss of height gain due to delayed initiation of GH therapy in children with GHD is not strong but should be considered by health plans. Some studies have shown that the loss of bone mineralization due to GHD, while not necessarily impacting children to a great extent, can substantially increase the risk for osteoporosis in adults, posing a strong argument for pediatric GHD therapy.

Dosing

Dosing of rhGH is based on patterns of GH secretion throughout life (Figure). Thus, the recommended doses are higher in the prepubertal period and during puberty than for adult patients (Brabant 2003, Vance 1999).

IGF-1–based dose titration is becoming a widely accepted means to maximize the benefit of GH therapy. Although IGF-1 levels have not been shown to correlate necessarily with response, payers accept this newer dosing approach as a means to ensure best outcomes. Furthermore, payers must acknowledge the dose-dependent improvement in outcome measures that Cohen (2002) showed, reporting a significant increase in height gain and IGF-1 level among GHD children with doubling of GH doses from 25 to 50 to 100 mg/kg/day. On the other hand, in children with SGA, lower doses of rhGH appear to yield benefit similar to higher doses and, therefore, should suffice (Hokken-Koelega 2003).

Summary

Overall, third-party payers accept many of the indications for GH therapy. The evidence of pathology in GHD and other causes of short stature are compelling, and the support for improvement in height and metabolic outcomes with GH therapy in most of these disorders is well accepted. To provide well-intentioned coverage and safe and effective treatments to clients who most need it, health plans must do due diligence and ensure that the indications for which they cover rhGH are compelling, beneficial, and safe. Ensuring that those patients who will most benefit from GH therapy do receive treatment may require that unsupported diagnoses are excluded from coverage.

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Michael Fine, MD, serves on the advisory boards of Abbott Laboratories, Allergan, AstraZeneca, Bayer, Eli Lilly and Company, Genentech, Genomic Health, Johnson & Johnson, sanofi-aventis U.S. LLC, and Wyeth.

CONTINUING EDUCATION ASSESSMENT/EVALUATION/CERTIFICATE REQUEST

Growth Hormone Treatment: Evidence, Practice, and Emerging Issues

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EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on page 21. There is only ONE correct answer per question. Place all answers on this form.

	A.	B.	C.	D.	E.	F.	G.
1.	☐	☐	☐	☐	☐	☐	
2.	☐	☐	☐	☐			
3.	☐	☐	☐	☐	☐	☐	
4.	☐	☐	☐	☐	☐	☐	
5.	☐	☐					
6.	☐	☐	☐	☐	☐	☐	☐
7.	☐	☐	☐	☐	☐		
8.	☐	☐	☐				
9.	☐	☐					
10.	☐	☐	☐	☐	☐		

PROGRAM EVALUATION: So that we may assess the value of this self-study program, we ask that you please fill out this form.

Have the objectives for the activity been met?

1. Outline the practical challenges and safety considerations of clinical testing for GH deficiency. ☐ Yes ☐ No
2. Identify the conditions and syndromes that are clear indications for GH therapy. ☐ Yes ☐ No
3. Interpret accurately the diagnostic significance of direct and indirect laboratory measures of GH deficiency. ☐ Yes ☐ No
4. Explain evidence-based principles to guide decisions for the approval of GH therapy for adults in whom there is no severe GH deficiency. ☐ Yes ☐ No
5. List the principal elements of recent consensus statements of pediatrician/endocrinologist groups regarding GH therapy and explain how they will affect the approval process. ☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias? ☐ Yes ☐ No. If no, please explain: _____

What other topics would you like to see addressed? _____

Comments: _____

PERFORMANCE SELF-REFLECTION: Please take a moment to reflect on your current and planned use of the practice strategies discussed in this monograph. You will not be graded on these responses.

In the table below, on the left, please check your **current** frequency of use of each of the listed strategies for optimizing GH therapy. Then, on the right, check your **planned** frequency of use of the same strategies, based on your participation in this CE activity.

CURRENT **FREQUENCY OF USE**						***PLANNED*** **FREQUENCY OF USE**				
0 Not applicable	1 Never	2 Annually	3 Semi-annually	4 Regularly	**Diagnosis/Treatment Strategy**	0 Not applicable	1 Never	2 Annually	3 Semi-annually	4 Regularly
					a. Review current FDA and clinical society guidelines on the diagnosis and treatment of conditions for which GH therapy may be considered					
					b. Re-evaluate appropriateness and interpretation of laboratory tests and procedures bearing on medical need for GH therapy, based on current evidence					
					c. Reconsider endpoints used for decisions on GH dosage, efficacy, and discontinuation					
					d. Appraise current clinical safety and efficacy data on GH therapy					

CONTINUING EDUCATION POST-TEST

Growth Hormone Treatment: Evidence, Practice, and Emerging Issues

Please tear out the assessment/evaluation form on page 20. On the answer sheet, place an X through the box of the letter corresponding to the correct response for each question. There is only ONE correct answer to each question.

1. **Two primary causes for short stature in children are:**
   a. Genetic defects.
   b. Growth hormone deficiency (GHD) due to a defect in the pituitary/hypothalamic system.
   c. Preterm birth.
   d. Metabolic disorders in the mother.
   e. a and b.
   f. b and c.

2. **The recommended diagnostic procedure for a child suspected of GHD includes all of the following EXCEPT:**
   a. An auxologic evaluation combined with a complete physical examination, genetic testing, and possibly an MRI assessment of the pituitary/hypothalamic axis.
   b. GH-releasing hormone testing.
   c. Serum testing for IGF-1 levels.
   d. Clonidine and arginine GH stimulation test.

3. **According to the Lawson Wilkins Pediatric Endocrinology Society guidelines, a trial of GH therapy is warranted in children and adolescents who may have atypical GHD with unexplained short stature and which of the following clinical findings:**
   a. Short stature and height >2.25 SD below the mean for age and gender on a standard growth chart.
   b. A growth velocity <25th percentile for bone age.
   c. Bone age >2 SD below the mean for age.
   d. Low serum IGF-1 and/or IGFBP-3.
   e. a and c.
   f. All of the above.

4. **Which of the following diagnoses qualify a child for GH therapy?**
   a. Diagnosis of Turner, Noonan, or Prader-Willi syndrome.
   b. Chronic renal insufficiency.
   c. Small for gestational age (SGA) that fails to catch up to the normal range (–2 SDS).
   d. Height <2 SD below the mean for age and gender on a standard growth chart.
   e. a, b, and c.
   f. a, b, and d.

5. **The majority of children with ISS can attain adult height at or near the normal range with GH replacement therapy.**
   a. True.
   b. False.

6. **The FDA has approved the use of GH replacement therapy in adults for which of the following etiologies:**
   a. Surgery for a pituitary tumor or disease.
   b. Head trauma.
   c. Fibromyalgia.
   d. History of childhood-onset GHD.
   e. Hypothalamic disease.
   f. a, b, and c.
   g. a, b, d, and e.

7. **Adult patients with lower than normal GH levels have an increased risk of which of the following:**
   a. Impaired physical and psychologic function.
   b. Altered body composition.
   c. Colon cancer.
   d. a and b.
   e. a and c.

8. **Which of the following stimulation tests is the gold standard to properly assess adult GHD?**
   a. Arginine stimulation test.
   b. Insulin tolerance test.
   c. Levodopa stimulation test.

9. **According to Tzeel and Fine, most payers will accept a diagnosis of Turner, Prader-Willi, or Noonan syndrome in the presence of clearly below-normal growth in children as a reason to prescribe GH therapy without further testing.**
   a. True.
   b. False.

10. **According to Tzeel and Fine, which of the following treatment regimens is acceptable for the treatment of children with GHD?**
    a. Consistent low doses of rhGH throughout the course of therapy.
    b. Consistent high doses of rhGH throughout the course of therapy
    c. Dose titration based on IGF-1 levels throughout the course of therapy.
    d. a or b.
    e. a or c.