



Disclosure

The speaker does not have conflicts with the information to be presented.



"It's cheaper than <u>human</u> growth hormone, but you'll have to trim your tail once a week."



Objectives

- Review importance of a seamless transition care for pts w/ persistent COGHD going into adulthood.
- Determine how and when individuals w/ CO GHD should be re-tested.
- How should GHD pts be monitored during and after the transition period.



- CC: Blood glucose of 0 mg/dl & microphallus.
- HPI: Term infant born after uneventful pregnancy. At birth noticed w/ small genitalia & at 24 hours of age developed generalized seizure with a central blood glucose level of 24 mg/dl.



 HPI: Transferred to the University Pediatric Hospital for further evaluation and care. Examination on arrival was small phallus of 1.5 cm x 0.4 cm (nl \geq 2.5 cm) w/ descended testes. He was unable to control body temperature & demonstrated poor sucking without evidence of sepsis.



F/U: At 8 days old, developed an episode of profound hypoglycemia w/ a central glucose level of **0** mg/dl. Laboratories during spell demonstrated fail in counter regulation: GH < 1.0 ng/ml & cortisol 0.27 ug/dl.



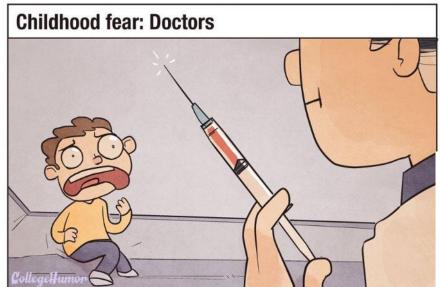
F/U: Insulin serum levels were appropriately diminished (2.3 uIU/ml). Also presented hyponatremia (122 meq/L), and hypothyroxinemia with low thyrotropin serum levels (total T₄ 1.42 ug/dl, T₃U 29.7%, FTI 0.48, TSH 0.42 uIU/ml).



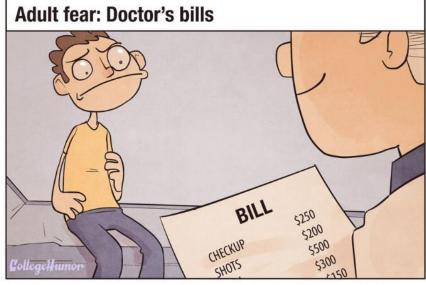
F/U (cont.): He required up to
 12 mg/Kg/min (nl 5-6) of IV glucose
 continuous infusion to prevent hypoglycemia
 before starting hormonal replacement.



• F/U (cont.): Results were felt to be most compatible w/ hypopituitarism. Normalization of metabolic derangements followed after started on replacement w/ GH, cortisol, & levothyroxine. A head CT scan showed normal size of the sella turcica without evidence of hemorrhage.









- Seamless
 - "smooth & without seams or obvious joins"
 - Smooth & continuous, with no apparent gaps or spaces between one part and the next.

- Anxiety
- Fear
- Avoid cross-talk for success

- The effects of GH deficiency (GHD) differ markedly depending on the life phase.
- During childhood, the most important effects of GH are on linear growth, & high doses of GH are required.
- During adulthood, GHD is associated with altered body composition & \uparture quality of life, & much lower GH doses are needed to counteract these effects.



- Only a <u>minority</u> of children with GHD will remain deficient as adults & require ongoing GH therapy.
- The "transition period" between these phases is loosely defined as occurring from mid-to-late teens until 6-7 yrs after reaching near-adult ht.



- The transition period raises the following clinical questions:
 - Which individuals with childhood GHD will remain deficient as adults?
 - When and how should testing be performed to determine whether an individual has persistent GHD?
 - How should patients be monitored during and after the transition period to determine appropriate dosing for GH therapy?

- Planning for management of GHD during the transition period should start at the <u>initial diagnosis</u> of GHD.
- In the past, most ped endos only planned to treat the child w/ GHD until near -adult ht (ie, GV < $2.5_{\rm cm/yr}$).
- Individuals w/ persistent GHD benefit from continuing GH treatment into adulthood.
- This because GH is required to achieve full adult body composition, regional distribution of body fat, & accrual of normal bone mineral content.



Issues to be discussed w/ family before GH treatment is begun:

- The child may require ongoing GH treatment during the transition period.
- The child should be retested for GH deficiency during late adolescence (usually when they reach near-adult height).
- The exception is the child with one of the genetic, organic, or structural disorders that predictably leads to permanent GHD.



Issues to be discussed w/ family before GH treatment is begun:

- If the child remains GH-deficient when retested, he or she will be *referred* to an endocrinologist who evaluates and treats adults with GHD.
- For individuals who remain GH-deficient during adulthood, lower doses of GH are required for treatment as compared with childhood.



- This discussion prepares the patient and his/her parents for the <u>retesting</u> and possible <u>referral</u> to another endocrinologist, when the appropriate time arrives.
- Thus, the pediatric endocrinologist typically should initiate the process for retesting.





- Among children diagnosed with isolated GHD (IGHD) during childhood, > 2/3 will have normal results when retested for GHD during late adolescence or adulthood.
- These discrepancies are probably in part because of the inherent <u>imprecision</u> in diagnosing GHD, because of the <u>low reproducibility</u> of the stimulation tests.

Tauber M, Moulin P, Pienkowski C, et al. Growth hormone (GH) retesting and auxological data in 1 31 GH-deficient patients after completion of treatment. J Clin Endocrinol Metab 1997; 82:352.



A mild GHD may <u>not</u> have clinically important effects during adulthood because the metabolic effects of GH are seen at <u>low</u> doses, whereas the same individual may have clinically important effects during childhood because high concentrations of GH are required to stimulate growth.

Tauber M, Moulin P, Pienkowski C, et al. Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment. J Clin Endocrinol Metab 1997; 82:352.

Transition Period

- It is important to repeat the GH stimulation test during this time because the majority of pts w/ IGHD will become sufficient by late adolescence.
- Retesting is also appropriate for pts w/ deficiency of:
 - only one additional pituitary hormone,
 - ectopic posterior pituitary
 - those who have received irradiation, a number of these pts may not have permanent GHD.



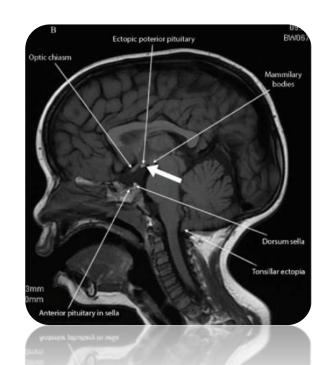
Genetic, organic, or structural causes of GHD

- GHD is <u>permanent</u> in virtually all pts w/ the following causes of GHD.
 - Genetic GHD usually recognized by the presence of affected relatives & confirmed by molecular testing for the causative genes, i.e., *POU1F1* (*Pit-1*), *PROP-1*, & *GH-1*.
 - Pts w/ GH-1 mutations tend to develop neutralizing antibodies shortly after initiation of GH treatment.

Genetic, organic, or structural causes of GHD



- GHD is highly likely to be permanent in pts w/ congenital anomalies, eg, agenesis of the hypothalamic-pituitary stalk (infundibulum), in the sellar or suprasellar region.
- An exception is the finding of an ectopic posterior pituitary, which is <u>not</u> consistently associated with permanent GHD.



Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96:1587.

Organic causes of GHD



- GHD following brain surgery & radiation therapy for craniopharyngioma or other brain tumors.
- GHD following irradiation therapy to the brain for hematologic malignancies (common with doses >40 Gy).
- Infants or young children are particularly vulnerable to developing permanent GHD after brain radiation.
- Multiple pituitary hormone deficiencies (**MPHD**). Ex. those w/ deficiencies of 3+ pituitary hormones, the likelihood of persistent GHD is > 95%.

Genetic, organic, or structural causes of GHD



- Because pts w/ these characteristics are very likely to have permanent GHD, extensive testing for GHD during the transition period is <u>not</u> needed.
- Instead, the ongoing deficiency can be confirmed by discontinuing GH therapy for ~1 month and then measuring the serum [IGF-1].
- If the [IGF-1] is < -2 SD, ongoing GHD is confirmed.



- In the past, some insurance companies required more extensive GH stimulation testing.
- Clinical practice guidelines specifically state that stimulation testing is <u>NOT</u> necessary to confirm permanent GHD in pts w/ these characteristics.
- Other predictors Pts who have very low GH peaks during stimulation tests done as children (GH <3 ng/mL) are more likely to have permanent GHD.

Secco A, di Iorgi N, Napoli F, et al. Reassessment of the growth hormone status in young adul ts with childhood-onset growth hormone deficiency: reappraisal of insulin tolerance testing. J Clin Endocrinol Metab 2009; 94:4195.



- The optimal timing for testing for continuing GHD during the transition period has <u>not</u> been proved.
- Retesting as near-adult height is reached
 (ie, when GV ↓ to < 2.0-2.5 _{cm/year}), ~ <u>late</u> puberty.
- Retesting in <u>mid</u>-puberty: This is based on the hypothesis that entry in to puberty stimulates the GH-secreting apparatus in those children who would eventually become GH sufficient.

Loche S, Bizzarri C, Maghnie M, et al. Results of early reevaluation of growth hormone secretion in short children with apparent growth hormone deficiency. J Pediatr 2002; 140:4



- Retesting in mid-puberty (cont.):
 - Pros: If the pt is no longer GH deficient, then testing at this time would \(\psi\$ the length of GH treatment by 3 years or more.
 - Cons: This approach is not optimal for patients with a high likelihood of having permanent GHD (eg, pts w/ MPHD).

Q

- Retesting at the <u>end</u> of the transition phase (age in mid-20s):
 - Disadvantages pts w/out ongoing GHD would have <u>several</u> years of unnecessary treatment, & those with ongoing GHD would be treated for several years with the higher doses required for growth stimulation, rather than the lower dose required for metabolic effects in an adult.
 - Therefore, this approach is not optimal for pts w/ IGHD, among whom the <u>majority</u> will <u>not</u> need ongoing GH tx.

- Pts who have a history of <u>cranial radiation</u>, the results of retesting should not be considered <u>definitive</u> because radiation tends to cause <u>gradual damage</u> to the hypothalamus/pituitary.
- hypothalamus/pituitary.
 Even if GH testing is normal several years after completion of radiation therapy, the pt may still become increasingly GH deficient.
- Therefore, pts should be retested for GHD for 5-10 years after completion of radiation therapy.

- Tests to evaluate for continuing GHD
- Pts w/ isolated GHD, or those w/ GHD + one additional hypothalamic-pit hormonal axis, should be evaluated to verify if their GHD is permanent.



- 1st step -> measure IGF-1 during a trial off GH.
- Those w/ a low level should be further evaluated with a GH stimulation test.

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



Tests to evaluate for continuing GHD

- Testing is <u>not</u> necessary for:
 - pts w/ multiple (3 or 3+) pituitary hormone deficiencies,
 - or an established genetic or structural cause other than ectopic posterior pituitary –GHD can be presumed to be permanent, and GH therapy continued–

Caveat -> some experts still prefer to establish the diagnosis of permanent GHD by at least confirming that IGF-1 levels are low.



When/who should have GH tested

- GH therapy should be stopped for ~1 mo @ IGF-1 testing.
- Pts w/ isolated GHD, or GHD + 1 additional pituitary hormone, + low IGF-1 result (< -2 SD for age and gender).
- Caveat -> A nl IGF-1 (>0 SD) suggests that permanent GHD is <u>unlikely</u>, & GH therapy can be stopped.

GH stimulation test

- One stimulation test is generally considered sufficient (although 2 different stimulants are recommended for the initial diagnosis of GHD in children).
- Several different stimuli have been used for this purpose: Insulin Tolerance Test —"Gold standard"—, Glucagon



GH stimulation test



- Insulin tolerance test:
 - "Gold standard" test for the diagnosis of adult GHD.
 - Induces hypoglycemia
 - Cx in pts w/ coronary & cerebrovascular disease, those at risk for seizures, pts who had transcranial surgery for craniopharyngioma.
 - In adult pts w/ MPHD tested with ITT, a peak GH response of <5.1 mcg/L has ~95% specificity & sensitivity for detecting GHD, better than glucagon.



GH stimulation test

Glucagon:

- Common approach is to use glucagon (1 mg) for a stimulation test.
- Sampling is continued for 3-4 hours because there are some late responders to this stimulus.
- Sensitivity ~97 to 100% & a specificity of 88 to 100%
- Caveat: GH response to glucagon depends on BMI as well as glycemic dynamics –obese have blunted response.



GH stimulation test

- The cutoff values for adolescents may be slightly higher than those in adults:
 - Infancy <10 ng/ml</p>
 - Transition <5 ng/ml
 - Adult <3 ng/ml</p>

Maghnie M, Aimaretti G, Bellone S, et al. Diagnosis of GH deficiency in the transition period: accuracy of insulin tolerance test and insulin-like growth factor-I measurement.

Eur J Endocrinol 2005; 152:589.



- GH during childhood is higher compared w/ doses required to treat GHD during adulthood.
- The relatively high doses of GH are continued until linear growth is nearly complete (GV < 2.0-2.5 cm/year).

Stage	Dose	IGF-I Target (SDS)
Infant, Child, Early Adolescent	25-50 μg/kg/d	0 to +1
Transition (without hiatus)	12.5-50 μg/kg/d	0 to +1
Transition (with hiatus) / Adult	300-1,000 μg/d	0 to +1

- After linear growth is complete the pt is transitioned to "adult dosing" if ongoing GH treatment is indicated.
- Starting dose for an adult is ~200 to 300 ug/day (total dose).
- Q will often require a larger dose
 (~600 to 900 ug/day & more if they are receiving oral estrogens).



- Begin w/ the adult dose & then titrate to a serum [IGF-1] in the upper portion of the nl range for age & gender.
- Measure serum [IGF-1] 1-2 months after beginning the adult dose of GH & titrate the GH dose until the IGF-1 level is within the appropriate range without side effects such as those related to fluid retention.



- When the appropriate dose is attained without side effects,
 the frequency of visits can ↓ to 1-2/year.
- At each visit review possible treatment-emergent adverse events, IGF-1 level, FBS, Hgb A_{1c}, & lipids.
- Consider obtaining DEXA scan for body composition & bone mineral density at the onset of therapy.
- Repeat at least 18 months later if abnormal to objectively define the response to therapy.



- A quality of life (QoL) inventory may be helpful in pts w/ somatic & psychological complaints because

 QoL can be an indication for GH therapy in GHD adults.
- QoL is usually assessed via self-administered questionnaires that reflect a variety of health-related, economic, & social factors.
- QoL measures may be broadly correlated w/, but are different from, assessments of affect or cognition.
- Disease-specific QoL exist.

Adverse events GH therapy adult



- GH therapy of adults w/ GHD has generally been regarded as being quite <u>safe</u>.
- Concerns remain regarding the potential for cancer risk and tumor regrowth.
- Therefore, GH therapy is <u>not</u> recommended for pts w/ active malignancy.
- Although GH treatment \(\psi \) insulin sensitivity, abnormal fasting glucose levels rarely occur.
- Periodically check free T₄ (& not TSH) & an early
 AM [cortisol] –mainly those tx'ed w/ radiation–

$$T_4$$
 + GH -> \uparrow T_3
Cortisone + GH -> \downarrow
11 $\&$ HSD & \downarrow cortisol

Available Tools for transition care





https://www.endocrine.org/improving-practice/patient-resources/transitions/ghd

Available Tools for transition care



Clinical Summary for New Health Care Team

BY THE ENDOCRINE SOCIETY Form to be completed, signed, and dated on last page by referring provider and patient. Patient and family to review and give completed form to new adult health care provider. Please consider printing a copy for the patient. Patient Name Date of Birth Date of Diagnosis Age of Diagnosis PRESENTING SYMPTOMS ETIOLOGY OF GH DEFICIENCY: Isolated □ Organic Congenital Chiari Malformation ■ Mulitiple Pituitary Hormone Abnormalities ■ Thyroid Genetic Testing Deficiency ■ Mutation Excess ■ No Genetic Testing Adrenal Optic Nerve Hypoplasia/ ■ Hypercortsolism Septo-Optic Dysplasia Deficiency Holoprosencephaly ■ Gonadotropins Other Midline Syndrome Deficiency Acquired: Precocious Puberty ■ Mass Lesions ■ ADH □ Craniopharyngioma Diabetes Insipidus Rathke's Cleft Cyst □ SIADH Other Brain Tumor: □ Cerebral Salt-Wasting Prolection Post-Surgical Excess ☐ Post-Radiation Deficiency □ Traumatic Post-Hydrocephalus ■ Vascular Lesion □ Pituitary Adenoma

Other:

Self-Assessment of Worries, Concerns, and Burdens Related to Pituitary Hormone Deficiencies and Preparation for Transitioning

BY THE ENDOCRINE SOCIETY

Consider the following statements and note how important it would be to discuss the item with your healthcare team as you are moving on from pediatric to adult endocrinology care.

Patient Name Date			
GENERAL CONCERNS	YES	MAYBE	NO
 I feel confused about managing my hormone deficiencies on my current treatment plan. 			
My medical condition keeps me from doing many things that I want to do in life now.			
3. I feel "burned out" from daily growth hormone injections.			
4. I feel "burned out" from having to take multiple medications daily.			
SOCIAL/EMOTIONAL/COGNITIVE ISSUES			
5. I have trouble paying attention in class or at work.			
6. I seem to forget things more than most of my friends.			
7. I struggle to keep up with my class work or job responsibilities.			
8. Organizing my life every day is a challenge for me.			
9. I do not get along well with classmates and/or co-workers.			
10. I am not able to do things that others my age can do.			
11. I often feel sad or 'blue'.			
12. I worry about my future.			
13. My health conditions make it hard to find a significant other.			
14. I am worried about how my health conditions will affect my future fertilit	у. 🗆		
TRANSITION PREPARATION AND READINESS TO TRANSFER FROM PEDIATRIC TO ADULT CARE			
 I know how each of my medications work and what to do if things don't seem to be going right. 			
16. I know what to do with my medications if I get sick.			
17. I have a MedicAlert ™ bracelet or other identifier.			

Available Tools for transition care



Physician and Care Team Assessment of Patient Skill Set

BY THE ENDOCRINE SOCIETY

This form can be used to help assess the teen/emerging young adult's knowledge and skills regarding pituitary hormone deficiencies and their management. The tool is intended as an aide to help assess the readiness of older teens/emerging young adults in the transition from pediatric to adult endocrinology care providers. Note that some questions may not apply to all patients. At the end of this document, please write your name along with discipline and initials, and then provide the date along with your initials when each item is assessed.

BASIC KNOWLEDGE OF YOUR MEDICAL HISTORY AND DIAGNOSES:	DATE AND INITIAL
Recount what hormone deficiencies you have	
☐ Recount your medical history (ages and dates of any surgeries, radiation treatments, and/or other medical treatments) related to your pituitary condition	
Recount the names and doses of the medications you are taking	
Describe the symptoms of inadequate hormone replacement	
☐ Describe the need for periodic lab work to assess adequacy of hormone replacement	
Describe the need for and recommended frequency of routine check-ups	
FOR PERSONS WITH GROWTH HORMONE DEFICIENCY:	
Describe storage conditions required for your medication	
Accurately measure and give yourself hormone injections	
Describe the reasons for changing/rotating injection sites	
 Describe the benefits of growth hormone treatment for bone health, cholesterol, and general well-being 	
Describe what to do if doses are missed	
FOR PERSONS WITH ADRENAL INSUFFICIENCY:	
☐ Describe when to take 'stress' doses of your cortisol ("steroid") replacement	
Recount the 'stress' doses of your cortisol replacement	
 Describe when the emergency injection of cortisol replacement would be necessary 	
 Describe the consequences of not taking 'stress' doses of cortisol replacement when needed 	
☐ Identify a person that can provide the emergency cortisol injection when needed	
Identify when emergency health systems should be activated and persons who could activate the systems for you	
■ Wear a MedicAlert™ identification	

Dosing of GH in GH-Deficient Emerging Adults

BY THE ENDOCRINE SOCIETY

The first goal is to determine whether the adolescent with GH-deficiency remains GH-deficient as an adult. This will often require measurement of IGF-1 levels at least one month off treatment and a GH stimulation test. At present the other indications for therapy with GH as a child/adolescent do not carry over to the emerging adult. The attainment of adult body composition, including maximal bone mineral content, occurs 5 or more years following achievement of (near) adult height, so the goal of growth hormone therapy for persistent GHD in the transition period is generally different than in older adults, in whom it is to maintain body composition or to prevent bone loss. With this goal in mind, studies examining the efficacy of GH in the transition period have generally tested a dose of 12.5-25 ug/kg/day. higher than the usual adult dose range of 300 to 1,000 µg/d (~4-14 ug/kg/day for 70 a kg individual). At these higher doses, IGF-1 levels are generally within +2 standard deviations for age. In general, side effects are reported less often in this age group, but

at a higher rate if GH therapy had been discontinued for a number of years prior to restarting.

Studies evaluating GH efficacy after more than two years of treatment have not been done, so it is unknown when to decrease from the higher transition dose to the lower adult dose [1]. In the absence of these data, one strategy is to re-start at a dose of 12.5 to 25 µg/kg/d (~1/2 the adolescent dose) and down-titrate it at 6-12 month intervals while monitoring the IGF-I levels to keep them between 0 to +1 SDS, given the changing normal range at the end of adolescence for the emerging adult [1-3]. If the patient has not received rhGH for at least 6-12 months, it may be prudent to begin at the low end of the adult dose of 300 µg per day and titrate (usually upward) as one would do for an adult just starting GH therapy. The adverse events of edema and joint discomfort are usually mild and the subject continues to be on the trajectory to attain full adult body composition [2-3].

Stage	Dose	IGF-I Target (SDS)
Infant, Child, Early Adolescent	25-50 µg/kg/d	0 to +1
Transition (without hiatus)	12.5-50 µg/kg/d	0 to +1
Transition (with histus) / Adult	300-1,000 μg/d	0 to +1

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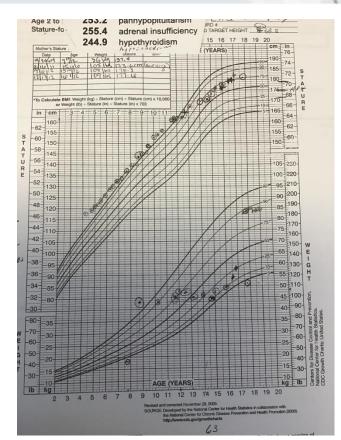








- F/U: At age 17 years rGH was stopped w/ an IGF-1 of 285 ng/ml (nl 113 – 566; LabCorp) & growth rate ~1.7 cm/yr.
- Six months later he returned with an IGF-1 level at 22. He underwent re-testing with glucagon and GH peaked at 0.3 ng/ml w/ a repeated IGF-1 of 21 ng/ml.
- rGH was restarted at 0.4 mg SC daily. IGF-1 levels couple months after rGH restarted went up to 107.



Summary

- No single model for transition is going to be universally successful & tailored care is required for pts who require continued GH
- Most of isolated GHD children become sufficient as they approach adulthood.
- Optimal timing for GH retesting should be individualized.

treatment from childhood to adulthood.

- Pts w/ MPHD are likely to need to continue rGH as adults.
- Empowered the emerging adult but be flexible, open mind, and aim for seamless transition.



- Pt is now 22 yrs. He currently works as a barber and is followed by Adult Endocrinology.
- Currently on rGH 0.3 mg SC daily, Testosterone Cypionate 200 mg IM q15 days; Synthroid 0.200 mg a day, Cortef 10 mg in AM & 5 mg PM.



References:

- 1. Cook DM, Yuen KCJ, Biller BMK, Kemp SF, Vance ML. ACEE medical guidelines for clinical practice for GH use in GH-deficient adults and transition patients – 2009 update. Endocrine Practice. 15(suppl 2) Sept/Oct 2009
- 2. Alvarez-Escola C, Fernández-Rodríguez E, Recio-Cordovac JM, Bernabéu-Morónb I, Fajardo-Montañana C. Documento de co nsenso del área de conocimiento de neuroendocrinología de la Sociedad Española de Endocrinología y Nutrición para el aborddaj e del hipopituitarismo durante la transición. Endocrinol Nutr. 2014;61(2):68.e1---68.e11.
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- 8. Hartman ML, Crowe BJ, Biller BM, et al. Which patients do not require a GH stimulation test for the diagnosis of adult GH defici ency? J Clin Endocrinol Metab 2002; 87:477.
- 9. Secco A, di lorgi N, Napoli F, et al. Reassessment of the growth hormone status in young adults with childhood-onset growth ho rmone deficiency: reappraisal of insulin tolerance testing. J Clin Endocrinol Metab 2009; 94:4195.
- 10. Loche S, Bizzarri C, Maghnie M, et al. Results of early reevaluation of growth hormone secretion in short children with apparen t growth hormone deficiency. J Pediatr 2002; 140:445.

QUESTIONS?



