THE USE OF

GROWTH HORMONE IN CHILDREN AND ADULTS

QUICK REFERENCE FOR HEALTHCARE PROVIDERS

Ministry of Health Malaysia

MEMS Established 1981
Malaysian Endocrine and Metabolic Society

Academy of Medicine of Malaysia

KEY MESSAGES

1. All growth hormone deficient (GHD) children should be treated using the recommended dose of recombinant human growth hormone (rhGH).

2. rhGH therapy can also be used in non-GHD children such as in Turner syndrome and small for gestational age (SGA).

3. Early recognition and early referral is important for optimal outcome.

4. rhGH therapy should not be taken lightly in view of its high cost, the need of prolonged therapy with close follow up by practicing clinicians familiar with rhGH therapy, potential adverse effects and the negative psychological impact from unsuccessful therapy.

5. All rhGH-treated patients should be re-evaluated during transition period.

6. In adults, rhGH should only be given to patients with GHD symptoms with proven adverse quality of life (QoL) and confirmed growth hormone (GH) deficiency.

7. Adults with normal GH status (burns, critically ill patients, ageing, sports, infertility and obesity) should not be offered rhGH.

I. USE OF GH IN CHILDREN

WHO SHOULD BE INVESTIGATED FOR GH DEFICIENCY IN CHILDREN?

In neonates/ infants	Evaluation for GH deficiency should be conducted if they manifest **persistent, intractable hypoglycaemia ± convulsions** associated with any of these:	• Micropenis in a male infant • Prolonged neonatal jaundice • Midline craniofacial defects (such as cleft palate, cleft lip, nasal or frontal encephalocoele, single central incisor, visual impairment and optic nerve hypoplasia) • Traumatic delivery (breech) or perinatal asphyxia • Post-natal failure to thrive (affecting both length and weight)
In order children	Evaluation for GH deficiency should be conducted if **history is positive** for any of these:	• Surgery to the hypothalamic pituitary region • Cranial irradiation • Intracranial tumour such as craniopharyngioma • Traumatic brain injury (accidental or non-accidental) • Central nervous system infection • Signs and symptoms of multiple pituitary hormones deficiency (MPHD) • Signs indicative of intracranial lesion • Parental consanguinity ± an affected family member (genetic cause) • Failure to show normal growth spurt by breast stage 3 in girls and genital stage 3 in boys

DIAGNOSIS OF GH DEFICIENCY IN CHILDREN

All of the following criteria must be fulfilled to confirm the diagnosis of GH deficiency:	
Clinical and auxological criteria	• Short stature as defined by: ➢ Height <3rd centile on the NCHS chart **AND/OR** ➢ Height below target height (TH) range i.e. mid parental height (MPH) minus 10 cm **AND** • Slow growth as defined by : ➢ Downward deviation of height ≥1 centile band over at least 12 months *Children with acquired hypothalamic-pituitary disease are considered to have fulfilled the above criteria if they have slow growth even in the absence of short stature.*
Biochemical criteria	A minimum of **TWO** growth hormone stimulation tests using either ITT, GST or AST are needed. • Peak GH level of <10 mcg/L is diagnostic *Sex steroid priming is useful for peripubertal children. Children with MPHD should have received adequate adrenal and thyroid hormone replacement before biochemical evaluation.*
Radiological criteria	• Delayed bone age
After confirmation of GH deficiency, subsequent investigations should include MRI of hypothalamic-pituitary region and genetic study (if facilities are available).	

CRITERIA FOR REFERRAL

- Neonates/infants with features of GH deficiency
- Children at risk of GH deficiency showing slow growth and/or short stature
- Children who fulfill clinical and auxological criteria for GH deficiency

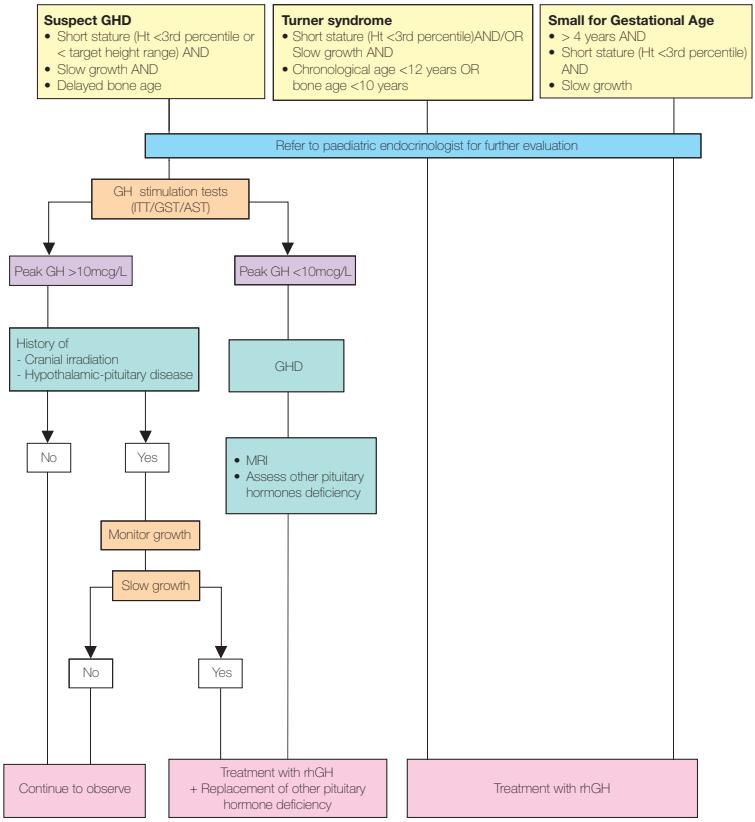
TREATMENT OF GROWTH HORMONE DEFICIENCY IN CHILDREN

Aim	• Normalisation of height during childhood and attainment of normal adult height
Dose	• Starting dose 0.025 mg/kg/day and adjusted within the range of 0.025 to 0.05 mg/kg/day based on the growth response and IGF-1 level • rhGH should be given as a daily SC injection 7 days a week • rhGH should be given uninterrupted for at least 4 years prior to closure of the epiphyses
Monitoring	• Height: 3 - 6-monthly • Serum IGF-1: 3-monthly in the first year, then yearly • Free T4, TSH: yearly • Fasting plasma glucose, HbA1c and insulin: before starting rhGH • HbA1c: yearly or more frequently in patients at risk for type 2 diabetes mellitus • Bone age: prior to starting rhGH and yearly thereafter

USE OF GROWTH HORMONE IN NON-GHD CHILDREN

Turner Syndrome	• GH should be started early for optimisation of final height (FH). • Oestrogen replacement therapy should not be initiated before the age of 12 years.
Small for Gestational Age (SGA)	SGA children who remained short (<3rd percentile) after 4 years of age should be referred to a paediatric endocrinologist for evaluation and consideration of rhGH therapy.
rhGH should not be used in familial/genetic short stature, idiopathic short stature, chronic renal insufficiency, Prader-Willi syndrome, Noonan syndrome, Russell-Silver syndrome and skeletal dysplasia.	

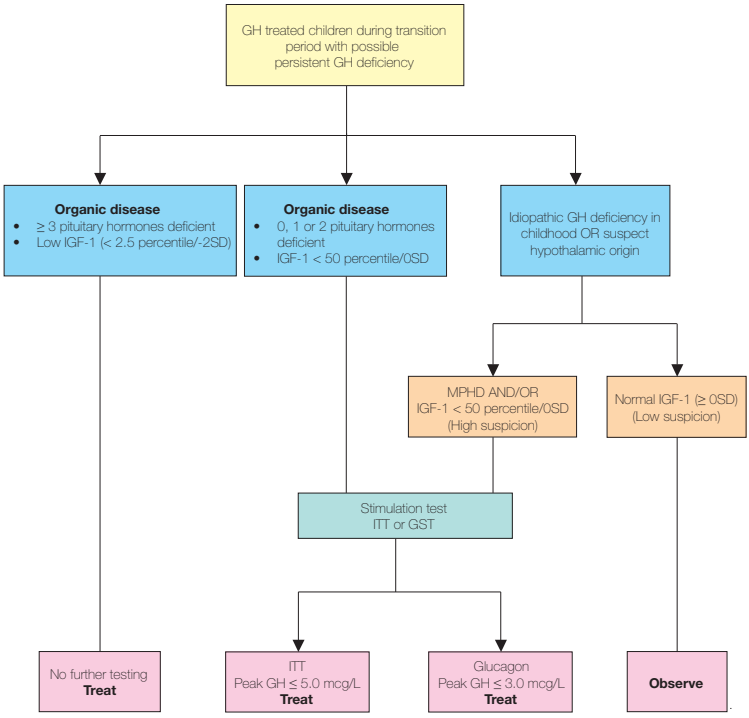
ALGORITHM FOR GROWTH HORMONE THERAPY IN CHILDREN



II. USE OF GH IN TRANSITION PERIOD

Definition of transition period	Period of adolescence/young adulthood after attainment of final height (FH) in GH-treated childhood onset GHD (COGHD) patients until 6 to 7 years later (approximately from 17 to 25 years old)
Who to be re-evaluated	All COGHD patients who have reached FH
Who should continue GH therapy	Those with: • ≥3 pituitary hormone deficiencies and serum IGF-1 below –2 SD or • Peak GH after ITT <5 mcg/L or after GST <3 mcg/L
Dose	Starting dose 0.0125 – 0.0250 mg/kg/day and the dose of rhGH should be adjusted to maintain normal serum IGF-1 level

ALGORITHM FOR MANAGEMENT OF GROWTH HORMONE-TREATED CHILDREN DURING TRANSITION PERIOD



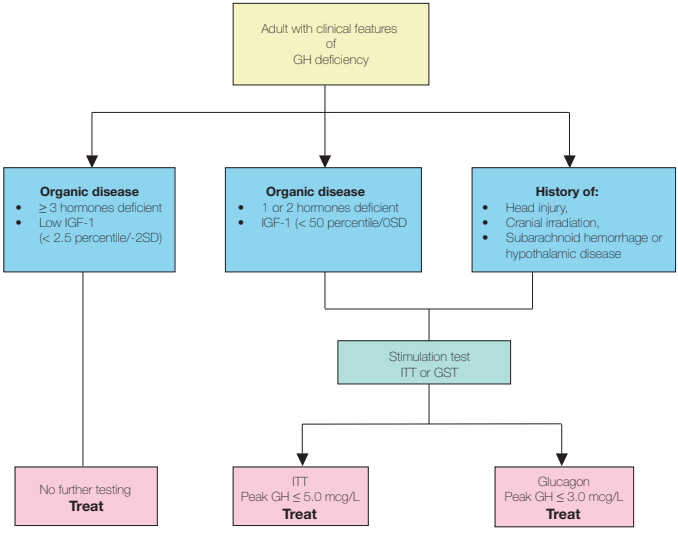
III. USE OF GH IN GH DEFICIENT ADULTS

Whom to screen? In adults with the following symptoms and signs and suspected to have hypothalamic-pituitary disease:

Symptoms	Signs
• Increased body fat • Reduced muscle bulk • Reduce strength and physical fitness • Reduced sweating • Impaired psychological well-being • Depressed mood • Anxiety • Reduced physical stamina • Reduced vitality and energy • Increased social isolation	• Overweight • Increased adiposity especially abdominal • Poor muscular development • Reduced exercise performance • Thin, dry skin • Depressed affect

GH deficiency should be excluded in adult patients with any of the following:
- Hypothalamic-pituitary disease
- Previous cranial irradiation
- Traumatic brain injury

ALGORITHM FOR SCREENING AND DIAGNOSIS FOR ADULT WITH POSSIBLE GROWTH HORMONE DEFICIENCY



DIAGNOSTIC TOOLS AND CRITERIA TO TREAT

Gold standard	Insulin Tolerance Test (ITT) is the gold standard for diagnosing adult GH deficiency, but should be avoided in patients with one or more of the following: • History of seizures • History of strokes • Presence of coronary artery disease • >55 years of age
Alternative test	Glucagon stimulation test (GST) is an alternative in patients who are unsuitable for ITT
Patients with irreversible hypothalamic-pituitary lesions and with evidence of at least 3 pituitary hormone deficiencies and serum IGF-1 levels below the age and sex-appropriate reference range are deemed GHD and **do not require GH stimulation test**.	
Quality of life (QoL)	A QoL questionnaire should be administered before beginning GH replacement as psychological well-being is the most compelling indication for GH replacement in adults with GH deficiency.
	Adults with GH deficiency on GH replacement should be evaluated using the QoL questionnaire at 6 - 12-monthly intervals to document the effects of GH on their psychological well being.

All of the following criteria must be fulfilled to confirm the diagnosis of adult GH deficiency:	
Clinical criteria	Adults with symptoms and signs of GH deficiency
Biochemical criteria	Peak GH after ITT ≤5 mcg/L or after GST ≤ 3 mcg/L
Investigation after confirmation of GHdeficiency	• MRI of hypothalamic-pituitary region • Evaluation of QoL using suitable QoL questionnaire

TREATMENT OF GROWTH HORMONE DEFICIENCY IN ADULTS

rhGH should only be prescribed to patients with clinical features suggestive of adult GH deficiency, biochemically proven GH deficiency and have adverse quality of life.	
Aim	• Normalisation of IGF-1 level and improvement in QoL
Dose	• The starting dose of rhGH is 0.1 mg daily for men and 0.2 mg daily for women. • The dose is increased by 0.1 mg or 0.2 mg to achieve a maintenance dose based on clinical response and IGF-1 levels • rhGH dose should be individualised independent of body weight
Monitoring	• Serum IGF-1: 3-monthly in the first year and then yearly • Fasting plasma glucose, HbA1c and insulin: before starting rhGH

- HbA1c: yearly or more frequently in patients at risk for type 2 diabetes mellitus
- QoL questionnaire at 6 - 12-monthly intervals
- Adverse effects such as arthralgia, myalgia, peripheral oedema and occurrence of new tumours or recurrence of hypothalamic-pituitary tumours
- DEXA scan should be performed prior to starting GH replacement and at 1 - 3 years intervals

USE OF GH IN NON-GHD ADULTS

rhGH therapy **should not be used** for routine treatment of fibromyalgia. However, it may be considered as an adjuvant in low IGF-1 patients. rhGH therapy **should not be used** in adults with burns, critically ill patients, elderly as an anti-ageing therapy, sports to enhance athletic performance, treatment of infertility and simple adult obesity.

This Quick Reference provides key messages and a summary of the main recommendations in the Clinical Practice Guidelines (CPG) The Use of Growth Hormone in Children and Adults (November 2010).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:

Ministry of Health Malaysia : http://www.moh.gov.my
Academy of Medicine Malaysia : http://www.acadmed.org.my
Malaysian Endocrine and Metabolic Society : http://www.endocrine.my/index.php

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