Clinical Standards for GH Treatment of GH Deficiency (GHD) in Childhood and Adolescence

The Clinical Standards for GH treatment were produced by the BSPED Clinical Committee in November 2017. They were evidence based where possible or developed by a Delphi consensus of Paediatric Endocrinologists and other professionals with relevant expertise and input from stakeholders. The standards are reviewed regularly to include any new evidence. These standards were updated by **BSPED Growth Disorders Special Interest Group (SIG)** in September 2021.

The BSPED National Growth Hormone audit was initiated at the start of January 2013 at 79 hospitals across the UK. Each participating site was invited to submit quarterly data on patients aged from 0.1-16.0 years who started GH at their hospital or in their care. Summary reports from this audit provided national and regional benchmarks for the participating sites.

Aim of Standards for GH Treatment:

- Improve patient experience
- Improve equity of access to specialist services
- Identify optimal service requirements
- Improve clinical outcomes

Original Working Group: Dr E Crowne (Chair), Dr H Mitchell, Dr N Shaw, Dr Leena Patel, Linda Willingham, Dr Dani Eddy.

BSPED Growth Disorders SIG: Helen Storr (Chair), Justin Davies (Deputy), Gary Butler, Jenny Child, Peter Clayton, Renuka Dias, Phillip Murray, Pooja Sachdev, Senthil Senniappan, Jarod Wong.

Introduction

Somatropin (recombinant human growth hormone; rhGH) is recommended and approved by NICE (1) as a treatment option for children with growth failure associated with the [1-6] conditions listed below. In 2019, Noonan syndrome was added to the approved UK licenced indications (but not yet NICE approved) for the somatropin preparation Norditropin.

1. Growth hormone deficiency
2. Turner syndrome
3. Prader–Willi syndrome
4. Chronic renal insufficiency
5. Born small for gestational age with subsequent growth failure at 4 years of age or later
6. Short stature homeobox-containing gene (SHOX) deficiency.
7. Noonan syndrome

GROWTH HORMONE DEFICIENCY

A. Clinical Standards for rhGH Treatment in children and adolescents with GH deficiency.

No	Standard	Adapted from Source
1 Specialist/Network centre accreditation		
	All centres should have a database of children/young people treated with rhGH and the indication for therapy	Consensus / Peer Review
2 Equity of service		
	a. All children and adolescents with GH deficiency will be offered treatment with recombinant human growth hormone (rhGH)	(1)
	b. Off label treatment with somatotropin should only be initiated by a tertiary paediatric endocrinologist and the growth response reviewed after 4-6 months	(1)
3 Professional Expertise		
	Diagnosis & treatment with somatropin should always be initiated and monitored by a paediatrician with specialist expertise in managing growth hormone disorders	(1-3)
4.Diagnostics		
	a. UK centres undertaking provocation tests for GH status should only use test protocols approved by the BSPED Clinical Committee	DELPHI CONSENSUS 91%
	b. GH stimulation testing should only be undertaken in centres with designated nursing personnel trained and experienced in performing these tests who each perform sufficient tests/year to maintain competency (BSPED recommends at least 10 tests per year), and designated medical personnel experienced in their supervision and interpretation	DELPHI CONSENSUS 78%

	c. In view of safety concerns, insulin tolerance tests (ITT) should only be performed in children over 5years in tertiary endocrine centres with designated trained staff	(2,4) DELPHI CONSENSUS 95%
	d. All UK centres undertaking provocation tests for GH status should use a priming protocol approved by the BSPED Clinical Committee. The use of oestrogen or testosterone to 'prime' the GH axis prior to pharmacological stimulation tests has been demonstrated to increase peak GH concentrations and reduce false positive rates in healthy peri-pubertal subjects from 39% to 5%	(5) DELPHI CONSENSUS 94%
	e. A peak GH concentration after stimulation of <6.7 mcg/L (or equivalent assay specific level identified for each centre) in pharmacological stimulation tests undertaken in a child with clinical features/history of GH deficiency supports the diagnosis of GH deficiency (see f below)	DELPHI CONSENSUS 90%
	f. Unless there is a confirmed genetic cause of GHD the diagnosis of GHD requires evidence of one of the following in addition to one	DELPHI CONSENSUS 87%
	abnormal growth hormone provocation test: • Evidence of multiple pituitary hormone deficiency • Abnormality on hypothalamic-pituitary MRI explaining GHD • Known predisposing cause of GHD (cranial irradiation, hypothalamic-pituitary damage) • A second abnormal GH provocation test	
	g. In the neonatal period where there are clinical and/or radiological features of hypopituitarism, a random GH measurement of <6.7 mcg/L (or equivalent assay specific cut- off) can be used to support the diagnosis of growth hormone	DELPHI CONSENSUS 70%

	deficiency without the use of a provocation test	
	h. Children / young people with a diagnosis of GHD should have a pituitary MRI within 3 months of endocrine testing which is reviewed by a paediatric neuroradiologist	(6) DELPHI CONSENSUS 96%
	i. Young people diagnosed with childhood onset isolated GHD* should have a repeat serum IGF-I level and GH provocation test to confirm GHD at the end of growth (puberty mature and height velocity < 2cm/yr for 6 months). RhGH should be discontinued for at least 6 weeks prior to re-testing The appropriate GH cut-off level should be agreed with the adult endocrinology team: 5 mcg/l (transition period in accordance with ESPE guidance) or 3 mcg/l (adult cut-off) to identify GHD in young adulthood ***Addendum** Recently published data suggest patients with isolated GHD without a hypothalamic-pituitary abnormality on MR scanning (including small anterior pituitary) can also be considered for early retesting of the GH axis once they are established in puberty (Tanner stages B2/3 in girls & 6-12ml testes in boys). Those retesting with a normal GH peak level (peak GH ≥6.7µg/L) could be offered the opportunity to discontinue GH therapy.	(7) DELPHI CONSENSUS 98% (8)
	j. Young people diagnosed with childhood onset GHD and high likelihood of persistent GHD (genetic, structural pituitary abnormality and/or MPHD) should have serum IGF-I measured: If IGF-I ≤ -2SDS, rhGH should be restarted. If IGF-I > -2SDS, GH provocation testing should be undertaken as above after discontinuing rhGH for at least 6 weeks (i)	(6,7)
	k. If GH and IGF-I are both normal on retesting discharge unless risk of evolving endocrinopathy (e.g. abnormal MRI, cranial irradiation)	(7)

	l. For safety and quality assurance, all centres undertaking GH provocation tests should audit the performance of their GH tests 3-5 yearly either via a national audit or the BSPED Peer Review process	(2) DELPHI CONSENSUS 92%
5 Patient Experience		
	a. The start of GH treatment should be within 18 weeks of the time when specific investigation of a licensed indication for GH treatment began (i.e. after the period of growth monitoring)	NHSE targets for elective treatment.
	b. The expectation of the growth response should be discussed with the patient and parent(s)/carer(s) prior to commencing rhGH therapy	Consensus
	c. The choice of rhGH delivery device should be decided following an informed discussion between the patient and/or their carer with the responsible clinician. This decision should be made on an individual basis taking into consideration therapeutic need and the likelihood of adherence to treatment.	(1,9,10)
	d. Education of the parents / carers and patient (if old enough) by a designated appropriately trained health care professional should precede the start of rhGH treatment. This should encompass information concerning GHD and rhGH treatment and its administration	(1-3,11,12)
6 Clinical Outcomes		
	a. Follow-up by a paediatrician with specialist expertise in managing growth disorders should be a minimum of every 6 months in an OP clinic with accurate growth measurements	(1,2)

	b. Follow-up should monitor and document the response to rhGH treatment and monitor for evidence of evolving endocrinopathies	(1-3,7)
	c. If growth response is inadequate, the clinician should review the indication to treat, adherence to treatment and exclude additional pathology. In the absence of an adequate response to rhGH treatment after 12 months of therapy, the responsible paediatrician should consider stopping rhGH treatment	(1)
7 Transition		
	End of growth rhGH therapy assessment should always be initiated and monitored by a paediatrician with specialist expertise inmanaging growth disorders	(1,13)
	Young people diagnosed with persistent GHD following re-investigation at completion of linear growth (4i-k) should be managed in adult endocrine centres with expertise in rhGH replacement treatment in young adults	(1,13)

References

1. https://www.nice.org.uk/guidance/ta188.
2. https://www.bsped.org.uk/media/1580/uk-standards-for-paediatric-endocrinology-2019.pdf.
3. https://www.england.nhs.uk/wp-content/uploads/2013/06/e03-paedi-medi-endo-diabet.pdf.
4. https://www.rcn.org.uk/professional-development/publications/pub-007-287.
5. https://www.bsped.org.uk/media/1875/bsped-priming-guidelines-v3-16521.pdf.
6. Society GR. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab. 2000;85:3990-3993
7. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M, European Society of Paediatric E. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol. 2005;152:165-170
8. Laurer E, Sirovina A, Blaschitz A, Tischlinger K, Montero-Lopez R, Hörtenhuber T, Wimleitner M and Högler W. The landscape of retesting in childhood-onset idiopathic growth hormone deficiency and its reversibility: a systematic review and meta-analysis. Eur J Endocrinol. 2022;187(2):265-278.
9. Gau M, Takasawa K. Initial patient choice of a growth hormone device improves child and adolescent adherence to and therapeutic effects of growth hormone replacement therapy. J Pediatr Endocrinol Metab. 2017;30:989-993

10. BSPED Position Statement on Choice of Delivery Device for Growth Hormone Prescribing (2020). https://wwwbspedorguk/clinical-resources/position-statements/.
11. https://www.eurospe.org/media/2076/growth-hormone-deficiency-average-read.pdf.
12. https://www.eurospe.org/media/2086/growth-hormone-deficiency-easy-read.pdf.
13. https://www.nice.org.uk/guidance/ng43/chapter/Recommendations.