In this issue of *Hormone Research in Paediatrics*, Grimberg et al. [1], on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society, present a very comprehensive and well-structured paper containing updated and expanded guidelines for growth hormone (GH) and insulin-like growth factor-I (IGF-I) treatment in children and adolescents with growth hormone deficiency (GHD), idiopathic short stature (ISS), and primary insulin-like growth factor-I deficiency (PIGFD). It is the result of a very labor-intensive endeavor to evaluate a great deal of the relevant literature using a structured analytical method of grading evidence (GRADE), focusing on adult height as the primary efficacy outcome.

This is an important and timely paper, as the previous guidelines on the use of GH by a PES Committee were published in 2003, and did not include the use of IGF-I. We believe that the paper may well contribute to an improvement of the quality of treatment with these drugs, and to a more cautious use of GH and IGF-I in short children.

In this commentary, we discuss three issues related to the guidelines. First, we shall discuss the definitions and diagnosis of the three conditions that are the subject of the new guidelines, but have not been exhaustively dealt with. Second, we discuss several issues related to GH treatment. Third, we comment on the present status of IGF-I treatment in a somewhat broader context.

**Definitions and Diagnosis**

In the first place, the focus on treatment with GH and IGF-I in the guidelines may be interpreted as reinforcement of the traditional idea that every growth disorder has something to do with the GH-IGF-I axis. Instead, Baron et al. [2] convincingly argued that disorders of this axis represent only a small part of the spectrum of growth disorders. In fact, the majority of growth disorders are associated with one of the many other regulatory pathways of the epiphyseal growth plate.

With regard to the definitions of the three diagnostic groups, the PES Committee decided to stick to the texts given in the FDA indications, and provide no further explanation of the delimitations and uncertainties of these relatively poorly defined conditions, nor of the diagnostic process to arrive at these diagnoses. While they appropriately refer to the International Classification of Pediatric Endocrine Diagnoses (ICPED) that recently became available (www.icped.org) [3], even these definitions of-
fer only limited information on the advised diagnostic procedures and the uncertainties surrounding the diagnosis.

With regard to GHD, the cornerstone of the diagnosis is that an inadequate secretion of endogenous GH must be proven or at least be made likely. GHD may be idiopathic or organic (e.g., congenital abnormalities of the pituitary region or acquired damage [surgery, X-ray, trauma, etc.]) and may be isolated or combined with other hormonal deficits. In children diagnosed with GHD before the age of 4 years, brain magnetic resonance imaging (MRI) shows abnormalities in most cases, so that MRI may represent the first-line investigation for diagnosis of GHD in infancy and early childhood [4]. In addition, after radiotherapy there is a dynamic element to the development of pituitary/hypothalamic inadequacies, which require different methods to be detected.

In children in whom GHD is part of multiple pituitary deficiencies or associated with anatomical abnormalities of the hypothalamic-pituitary region, or associated with known genetic causes, there is no or very little doubt about the diagnosis. However, there is general consensus among pediatric endocrinologists that in most cases of idiopathic isolated GHD (which based on the literature after 1985 represent the majority of cases), even after a full diagnostic workup (clinical features, linear growth, bone age delay, serum IGF-I, GH peak after two provocation tests, brain MRI), the clinician usually ends up with some degree of uncertainty about the diagnosis. Thus, rather than with a black-and-white yes-or-no statement, one often ends up with only an estimate of a certain likelihood of GHD. Even if the new guidelines would be carefully followed, including GH testing after sex hormone priming, the many reports about normal GH peaks in adolescence or young adulthood if children diagnosed as ISSGHD in childhood are retested later, often after many years of GH treatment [e.g., 5], serve to show that GH provocation tests can lead to a false-positive diagnosis of GHD in a substantial percentage.

The definition of ISS is even more difficult, because it is not a real diagnosis, but rather a descriptive term of a short height in comparison to national reference charts in the absence of further obvious abnormalities. It is therefore a ‘diagnosis of exclusion’, so that it is vital to carefully define which clinical abnormalities and diagnoses have to be excluded before the ‘diagnosis’ may be made [6]. In this context, we wish to emphasize that in every short child body proportions should be measured and compared with age references, and that the term ISS should not be used for children with abnormal body proportions. Since the number of genetic causes of growth disorders is expanding rapidly [7], the list of conditions that should be excluded (if financially feasible) will expand accordingly. For example, it can be argued that the prevalence of abnormalities of SHOX (and its enhancer) and NPR2 in children with normal body proportions is sufficiently high to consider testing for these genes in children with a tentative diagnosis of ISS [8–10]. Given the fast expansion of the use of exome-based genetic panels, one may foresee that in the future a negative result on a panel of known genetic causes may be mandatory before reimbursement of GH treatment for ISS is accepted (in countries where ISS is a registered indication for GH treatment).

PIGFD is a term created out of the idea that the GH-IGF system, analogous to other endocrine regulatory systems, is involving a regulating central hormone (GH) and a peripheral regulated hormone (IGF-I). It is usually defined as the combination of growth failure, low serum IGF-I and normal or elevated GH secretion [11, 12]. GH insensitivity syndrome (GHIS) is a term often used synonymous to PIGFD, although strictly speaking GHIS refers to the inability to achieve an intended therapeutic effect with GH treatment in patients with low serum IGF-I and IGFBP-3 in contrast to a normal or elevated GH secretion. Over recent decades, our understanding of PIGFD has developed from purely descriptive GHIS disorders (growth-attenuating antibodies, Laron syndrome) to a multitude of defined defects at the level of the GH receptor (GHR mutations), intracellular signal transduction (e.g., STAT5B mutations), gene defects resulting in an impairment of components of the IGF system (e.g., mutations of IGF1 and IGFBP3) [13], and several other conditions [7, 14]. However, it is noteworthy that at least two conditions which are expected to respond well to GH treatment may clinically present as PIGHD: Kowarski syndrome (caused by specific GHIH mutations encoding a bioinactive GH) and GHSR mutations [for review, see 7]. We believe that there is a need for a more detailed separate guideline on etiology, nomenclature, pathogenesis, diagnostic procedures, treatment and outcomes in PIGHD, potentially after calling an expert meeting on the subject.

**GH Treatment**

An issue that receives relatively little attention in the new guidelines is the value of concomitant medication in children with GHD. This is probably associated with the
strict rules of the GRADE system that the authors used, although statements on several topics were still made in the absence of sufficient evidence. We believe that the evidence is quite convincing that in GHD children in whom height standard deviation score is low at the onset of puberty, the addition of a GnRH analogue for a number of years can increase adult height [15, 16]. The addition of an aromatase inhibitor may have a similar effect [17], but unfortunately, there are no published adult height data available for that approach.

Another topic that was not fully covered is a description of the clinical, biochemical, and radiological parameters that are useful to measure during follow-up of GH-treated children, for example, serum IGF-I (as an indicator of the appropriateness of the GH dose and adherence, as well as a safety parameter), other biochemical parameters (e.g., FT4), and bone age assessments.

A third topic that could have deserved more attention is the concept of individualizing the GH dose, which has been studied over about two decades. It has become clear that there is not only a wide range of GH secretion among individuals, but a similarly wide range of sensitivity to GH, so that one standard dose (per body size) of GH would not seem rational (although still generally practiced) [18]. Essentially, there are two approaches to individualize (personalize) the GH dose: using prediction models based on clinical parameters, either in a retrospective fashion (adapt the dose according to the attained 1-year response) [19] or prospectively (calculate the dose to obtain the desired growth response) [20], or using IGF-I titration [18] [for review, see 21].

There are several issues with respect to the indication for GH treatment in children with ISS. First, there is the heterogeneity within the diagnosis (familial and nonfamilial ISS, with or without pubertal delay). Second, it is difficult to predict for the individual child what the exact untreated spontaneous adult height will be. The approval of GH for ISS in the US, in contrast to Europe and most other geographical regions, is based on studies with only a slim numerical basis. Furthermore, the approved doses are based on the doses used in these studies and may not be optimal, neither for the diagnosis in general nor for individual children.

Given the limits of our knowledge about the effects of GH in ISS, we believe that the recommendation about up-titrating the GH dose is merely a guess. If one accepts that the first year gives most of the response, which in ISS is dose driven, it could be argued that the highest allowed dose should be used initially and in the case of acceptable responsiveness be followed by a titration downward. The results of the European dose-response study on GH treatment in ISS are consistent with the idea that a relatively high starting dose is more effective than a lower dose up-titrated after 1 year [22].

**IGF-I Treatment**

All defects that fall under the umbrella of PIGFD vary quantitatively in their biochemical expression, and are associated with a broad spectrum of clinical phenotype. GH receptor deficiency (including several variants of GHR defects) is the most frequent of these disorders and forms the basis of our current experience in terms of the diagnosis of PIGFD and its treatment with IGF-I. The variability and complexity of the GH-IGF system and rarity of PIGFD, together with its heterogeneous phenotype, are probably the main reasons for the limited empirically derived evidence for the long-term efficacy and safety of treatment with IGF-I, particularly if compared to GH deficiency (“secondary IGFD”). One needs to be aware of the fact that this evidence is basically gained from cohorts with severe PIGFD recruited in Israel, Ecuador, Europe, and USA collected in the 1990ies [23–26] and from heterogeneous groups with mostly less severe PIGFD collected more recently [27–29]. While in the former, the diagnostic criteria were quite well defined [30], this is less so in the latter. In addition to the increase in known diagnostic PIGFD entities, there is a greater demand for methods for the determination of peptides like IGFs, IGFBPs, ALS, and GHBPs, as well as for molecular genetic investigations of which many have not reached a uniform level of standardization.

Present recommendations for replacement therapy with IGF-I are derived from studies which were conceived in a time when the understanding of the IGF system and its regulation was still limited. Treatment with IGF-I given once or twice daily as is still suggested today, does neither mimic the natural situation of continuous IGF-1 levels in blood (and at cellular targets) nor does it (in most instances) restore the normal balance of the IGFBP system, which appears to be required for its optimally directed biological action and the avoidance of adverse effects. It is therefore welcome that in these guidelines, the PES Committee has given very thoughtful and cautious advice as to how to diagnose and treat PIGFD. However, given the fact that by the currently recommended mode of IGF-I treatment, the long-term results in terms of growth are at best very modest and that the therapy poses severe risks, we believe that the commu-
nity of experts should jointly reevaluate all aspects of PIGFD and should try to define the areas of research required to find better ways of treatment. This should probably also include the call for an international database of all patients treated for PIGFD and the development of new therapeutic approaches and drugs (e.g., long-acting IGF-I, IGFBPs, specific proteinase inhibitors/promotors) in collaboration with research-oriented industry and facilitated by orphan drug programs.

**Conclusion**

We wish to reiterate that we applaud the publication of the guidelines, and we expect that these will have an important positive impact on the pediatric endocrine community worldwide. While we appreciate that it was already a complicated endeavor to prepare this on behalf of one large regional pediatric endocrine society, we regret that the PES Committee did not seek collaboration with Drug and Therapeutic Committees in sister societies for pediatric endocrinology outside North America, in order to give an even more general view. We believe that this would have strengthened the impact of the guidelines, since we speculate that the “ungraded good practice statements” may well be globally heterogeneous. The recent publication of an International Classification of Pediatric Endocrine Diagnoses (www.icped.org) shows that such global collaboration is possible for rare but important tasks.

**Disclosure Statement**

The authors have no conflicts of interest to disclose.

---

**References**


