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CONFERENCE REPORT

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Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement

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Abstract Growth failure is a clinically important issue in children with chronic kidney disease (CKD) and is associated with significant morbidity and mortality. Many factors contribute to impaired growth in these children, including abnormalities in the growth hormone (GH)–insulin-like growth factor-I (IGF-I) axis, malnutrition, acidosis, and renal bone disease. The management of growth failure in children with CKD is complicated by the presence of other disease-related complications requiring medical intervention. Despite evidence of GH efficacy and safety in this population, some practitioners and families have been reluctant to institute GH therapy, citing an unwillingness to comply with daily injections, reimbursement difficulties, or impending renal transplantation. Suboptimal attention to growth failure management may be further compounded by a lack of clinical guidelines for the appropriate assessment and treatment of growth failure in these children. This review of growth failure in children with CKD concludes with an algorithm developed by members of the consensus committee, outlining their recommendations for appropriate steps to improve growth and overall health outcomes in children with CKD.

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Introduction

Growth failure is a common and significant clinical problem in children with chronic renal insufficiency (CRI). Affected children exhibit a range of potentially serious medical and psychological complications, as well as increased mortality [1–8]. The etiology of growth failure in this population is multifactorial, reflecting both abnormalities in the growth hormone (GH)–insulin-like growth factor (IGF)-I axis and a variety of nutritional and metabolic problems, each requiring management to improve growth potential. Although the safety and efficacy of recombinant human GH therapy in promoting growth in children with CRI are proven, the frequency of GH administration in pediatric nephrology patients remains low. One potential barrier to the use of GH therapy is the lack of clear guidelines regarding the initiation and monitoring of GH therapy in children with CRI. This article provides an overview of our current understanding of growth failure in children with CRI and proposes an algorithm for the rational evaluation and treatment of growth failure in this population. This overview is derived from information presented by the authors at a consensus conference on growth failure in children with chronic kidney disease (CKD) in December 2003.

Defining chronic renal insufficiency and chronic kidney disease

Historically, the term *chronic renal insufficiency* has been used to describe patients with a glomerular filtration rate (GFR) <75 ml/min per 1.73 m^2 body surface area. More recently, clinical practice guidelines developed by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) have introduced the term *chronic kidney disease* and a classification schema to

promote early disease detection, delay disease progression, and prevent related complications [9]. This classification identifies five stages of CKD, based on the presence of kidney damage and the degree of functional impairment observed, irrespective of the underlying diagnosis (Table 1). Kidney damage relates to the presence of any pathologic abnormality or renal disease marker, such as proteinuria. Functional impairment is determined by estimating the GFR; values between 30 ml/min per 1.73 m^2 and 59 ml/min per 1.73 m^2 for at least 3 months signify stage 3 CKD [9]. At this value the GFR is reduced by at least 50%, and clinical complications become more prevalent. At stage 5 CKD, kidney failure is present, as characterized by a GFR <15 ml/min per 1.73 m^2 or the need for renal replacement therapy (dialysis or transplantation). The GFR cutoff values for CKD staging shown in Table 1 apply only to children aged 2 years and older, because younger children normally have a lower GFR [9].

Growth failure in children with CKD: the North American Pediatric Renal Transplant Cooperative Study experience

The annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) provides a comprehensive profile of growth in pediatric patients with CRI undergoing dialysis or after renal transplantation [10]. This report provides evidence that growth failure is a significant problem in this population and is not being adequately managed. Of the 5,927 enrolled children with CRI included in the 2005 annual report, more than one-third exhibited significant growth failure at the time of registry entry, defined by a standardized height measurement below the third percentile for age [height standard deviation score (SDS) ≤−1.88]. Patients who entered the NAPRTCS CRI registry at a younger age tended to exhibit substantial height deficits more frequently, with significant growth failure reported in 58%, 43%, 33%, and 23% of patients aged 0 to 1 years, 2 to 5 years, 6 to 12 years, and more than 12 years, respectively. Although a correlation was found between renal function and growth impairment, significant short stature was seen at all levels of renal function. Specifically, among those with a relatively good estimated GFR (50–75 ml/min per 1.73 m^2), nearly 20% exhibited significant short stature. Overall, minimal changes in standardized height occurred in patients followed up over a 2-year period, except for the youngest children (<1 year), who demonstrated an initial 6-month period of catch-up growth as reflected by a change in height SDS of 0.5 [10].

Children enrolled in NAPRTCS remain short at the initiation of dialysis, suggesting that prevention and treatment strategies during the period of CRI before dialysis may be suboptimal. After 1 month of dialysis (equivalent to baseline), the mean height SDS in 3,910 evaluable patients was −1.66. Similarly to the subset of children enrolled in the CRI registry, younger age at the initiation of dialysis was associated with more severe growth failure, with mean height SDS values after 1 month of dialysis of −2.54, −1.98, −1.69, and −1.30 in patients aged 0 to 1 years, 2 to 5 years, 6 to 12 years, and older than 12 years, respectively. Subsequent evaluations following 6 and 12 months of dialysis demonstrated little-to-no improvement in height SDS during dialysis [10]. Growth impairment was similarly evident at the time of renal transplantation, again with greater height deficits in younger patients. Among evaluable transplant recipients (n=8,141) who underwent renal transplantation between 1987 and 2004, the mean baseline height SDS was −1.85; mean values of −1.98, −2.34, −2.07, and −1.49 were observed in patients aged 0 to 1 years, 2 to 5 years, 6 to 12 years, and older than 12 years, respectively. Younger patients (aged 0–5 years) showed some improvement in growth after transplantation, whereas older patients (>12 years) showed no increase in mean height SDS score after renal transplantation.

An encouraging finding of the NAPRTCS is that the standardized height of children at the time of initial renal transplantation has improved from a mean of –2.40 SDS in 1987 to −1.4 SDS in the most recent cohort [10]. This improvement may reflect, at least in part, the increased use of GH therapy before primary transplantation.

Table 1 National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of the stages of chronic kidney disease [28]

Stage	GFR (ml/min per 1.73 m^2)[a]	Description
1	⩾90	Kidney damage and co-morbid conditions
2	60−89	Kidney damage with mild reduction of GFR
3	30−59	Moderate reduction of GFR
4	15−29	Severe reduction of GFR
5	<15 (or dialysis)	Kidney failure

[a]GFR ranges apply to children aged 2 years and older

Impact of growth failure in children with CKD

Two important long-term registry studies by Furth and colleagues showed that growth impairment in children requiring dialysis may be associated with an increased risk of mortality. In the first study based on data from the United States Renal Data System (USRDS) Pediatric Growth and Development Study involving 1,112 dialysis patients followed up from 1990 to 1995, 5-year death rates were higher in children with severe growth failure (height velocity SDS <−3.0) or moderate growth failure (height velocity SDS <−2.0 and > −3.0) during the first year of the study compared with patients with normal growth (height velocity SDS >−2.0) (16.2%, 11.5%, and 5.6%, respectively) [2]. This translated into an almost threefold increase in mortality in the patients with severe growth impairment. Growth failure was also associated with an increased incidence of hospitalization, primarily for the treatment of infection. These investigators

suggested that, although short stature was unlikely to have been the direct cause of mortality, it might reflect other factors, such as poor nutritional status, which is known to be associated with increased infectious complications and adverse outcomes. In addition, GH insensitivity due to diminished hepatic GH receptor expression may contribute to the catabolic state observed in patients with CKD [11].

In a second study investigating 2,306 patients from the NAPRTCS who began dialysis between 1992 and 2001, death rates were higher in shorter patients (height SDS < −2.5) compared with rates in their taller counterparts (90.5 vs 39.6 deaths per 1,000 patient-years, respectively) based on their height at dialysis initiation [1]. Younger patient age was independently associated with higher mortality, but poor growth was a risk factor for death in both very young children (<1 year) and older children. Patients with short stature spent significantly more days per month in the hospital, although the reason for hospital admission was not reported. Although the causes for increased mortality in these two studies were not clear, the results suggest that short stature may be associated with a more complex clinical course and less favorable outcomes in children with end-stage renal disease (ESRD) [1].

Although limited data are available on the subject from children with CRI, clinical experience in patients with growth hormone deficiency (GHD) has shown that growth failure can have important effects on a child's psychosocial development, psychological development, and quality of life (QOL) [12, 13]. Short children are often perceived by adults to be younger than their true age, leading to "juvenilization" or lowered expectations, whereby children are not given age-appropriate authority, responsibility, or respect and may be overprotected and given excessive attention. As a result, they may become dependent, remain immature, and achieve "secondary gain," a perceived special status that allows children to manipulate family members. Children may also adopt "mascot" or "clown-like" behaviors to gain temporary acceptance by their peers; however, these behaviors may become dysfunctional, reinforcing the child's perceived immaturity and impairing self-esteem and QOL. Furthermore, patients with growth failure may develop co-morbidities that affect psychological development and QOL, such as attention deficit hyperactivity disorder, learning disability, and mood disorders. On occasion, the magnitude of the psychological disturbance has been correlated with the degree of GHD [12]. In turn, a clinical trial by Stabler and colleagues showed that 3 years of GH therapy in 196 children with GHD or idiopathic short stature (ISS) not only improved standardized height measurements, but also produced a significant and sustained reduction in problem behavior as measured by the Child Behavior Checklist [14].

Finally, children with a history of poor growth associated with CKD often become very short adults. Hokken-Koelega and colleagues retrospectively evaluated the growth of 52 patients who underwent renal transplantation before the age of 15 years [15]. Their results showed that the median height SDS was below the third percentile for age at the time of first dialysis (reflective of CRI management), decreased significantly during dialysis, and did not improve following renal transplantation. Final height remained below the third percentile for age for 77% of male patients and 71% of female patients [15]. Other, more recent, clinical trials continue to support the observation that final height remains decreased following renal transplantation in children with pre-existing height deficits related to CKD [16, 17].

Some researchers believe that short stature during childhood may be associated with academic underachievement and social impairment with possible implications in later life [13], although others have argued that the psychosocial burden of adult short stature is either less dramatic or nonexistent [18].

A study by Busschbach and colleagues evaluated QOL in five groups of short adults, including 17 male patients with childhood-onset renal failure [19]. QOL in the renal failure group was close to average as measured by the Nottingham Health Profile. In all groups the patients perceived their chance of having a partner as low, except those patients with idiopathic short stature who had been selected from the general population. Only 40% of renal failure patients had a partner; however, this was attributed primarily to the constant risk of transplant rejection rather than to short stature. Nevertheless, 60% of renal failure patients reported they would like to be taller, and 33% were prepared to sacrifice an average of 4% of expected life-years to be taller. Time trade-offs for all symptoms associated with renal transplantation or dialysis (respectively, 15% and 47% of expected life-years) were considerably larger than for height alone [19].

Using a questionnaire to determine long-term social outcomes among 244 adults who had received a kidney transplant in childhood, Broyer and colleagues have shown that final height is significantly associated with marital status ($P<0.0001$) and level of education ($P<0.001$), and inversely related to level of employment ($P=0.02$) [20]. Most recently, a survey conducted by Rosenkranz et al. found that, among 39 young adults with CKD requiring dialysis, or after transplantation, 36% were dissatisfied with their adult height. This dissatisfaction correlated significantly with subjective patient perceptions regarding overall quality of life at the time the survey was conducted ($r=0.41$, $P=0.008$) [21].

Causes of growth failure in children with CRI

Growth failure in children with CRI may have multiple causes. The GH–IGF-I axis is an important regulator of growth and metabolism, and substantial abnormalities in this axis have been identified in children with CRI [22]. As shown in Fig. 1a, normal GH production and release by the anterior pituitary is regulated by hypothalamic GH-releasing hormone (GHRH) and somatostatin (SRIF), with circulating GH and IGF-I levels providing negative feedback to the hypothalamus. Release of GH is also stimulated by the GH-releasing peptide ghrelin, which is expressed by the stomach and hypothalamus and is possibly involved in nutritional regulation of the GH–IGF-I axis. Circulating GH stimulates the production and release of IGF-I, primarily from the liver. Most circulating IGF-I is bound as a complex with IGF-binding protein (IGFBP)-3 and acid-labile subunit (ALS),

and a smaller amount is associated with other IGFBPs; less than 1% occurs in the free or bioactive form. Circulating free IGF-I mediates many of the biological effects of GH, including stimulation of longitudinal bone growth and regulation of renal hemodynamics. GH also has a direct effect on several tissues, including bone [22].

Children with CRI demonstrate increased circulating levels of GH as a result of increased pulsatile release and reduced renal GH clearance; however, they show reduced responsiveness to endogenous GH and IGF-I [22]. This resistance is thought to play an important role in the reduction of linear bone growth observed in CRI and, therefore, in growth impairment. An important mechanism for GH resistance in uremia involves a defect in the post-receptor GH-activated Janus kinase 2 (JAK2) signal transducer and activator of the transcription (STAT) pathway [23]. This signaling pathway must be intact in order for GH-stimulated IGF-I gene expression to occur. A decrease in the density of GH receptors in target organs also likely plays a role in GH insensitivity in patients with uremia. The receptor density is reflected by the circulating level of GHBP, a product of proteolytic cleavage of the GH receptor [24], and GHBP serum levels are inversely related to the severity of renal dysfunction.

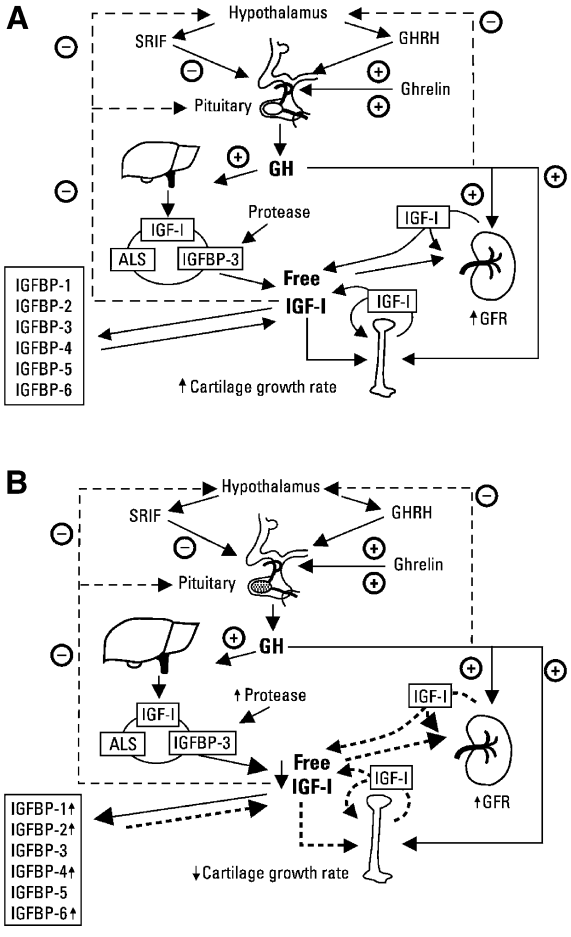

Fig. 1 The GH–IGF-I axis. **a** Normal GH–IGF-I physiology. **b** In patients with CRI, several abnormalities in the GH–IGF-I axis exist. IGF-I resistance likely reflects an increase in circulating IGFBPs-1, -2, -4, and -6, which leads to a reduction in bioavailable IGF-I. In addition, increased proteolysis of IGFBP-3 leads to a reduction in IGF-I circulating in the IGF-I–ALS–IGFBP-3 complex. The reduced bioavailability of IGF-I and increased concentrations of IGFBPs-1 and -2 in patients with CRI are thought to contribute to the lack of responsiveness to GH. In addition, the direct effects of GH on bone are inhibited in patients with CRI [19]

The presence of IGF-I resistance reflects an increase in levels of circulating IGFBPs-1, -2, -4, and -6, leading to a reduction in the concentration of bioavailable IGF-I (Fig. 1b). In addition, increased proteolysis of IGFBP-3 leads to a decrease in IGF-I available for the formation of IGF-I–ALS–IGFBP-3 complexes. Taken together, these events impair both the direct and indirect effects of GH on the growth of children with CRI [22].

In addition to the abnormalities associated with the GH–IGF-I axis, disturbances in the gonadotropic hormone axis have also been described in children with CRI. While gonadotropin levels may be elevated due to decreased renal clearance in patients with CRI, pituitary secretion of bioactive luteinizing hormone (LH) is substantially reduced in these patients compared with normal adolescents [25]. Subsequently, plasma testosterone concentrations are reduced in CRI, and free testosterone levels are further decreased due to a rise in sex hormone-binding globulins; these physiological abnormalities may contribute to suboptimal pubertal growth and development in affected children [26].

Several other factors can contribute to growth impairment in children with CRI, including age at onset of renal disease; etiology of renal disease; and the presence of calorie–protein malnutrition, metabolic acidosis, and renal osteodystrophy (ROD) [5, 8, 27]. Because children attain one-third of their final adult height during the first 2 years of life, growth impairment during infancy has a greater impact on adult stature than has later-onset disease [8, 27]. Nevertheless, renal insufficiency limits growth throughout childhood and, as mentioned above, is associated with a delayed pubertal growth spurt and reduced pubertal height gain.

The influence of disease origin is reflected by the fact that children with renal dysplasia tend to exhibit the most severe height deficits, whereas those with focal segmental glomerulosclerosis display less severe height deficits [28]. This may be a manifestation of the age at onset of renal disease, or alternatively, the degree of tubular abnormality inherent in the condition and the resultant loss of renal substances important for growth [5].

Caloric deficiency and abnormal protein metabolism may also play an important role in growth impairment, particularly in younger children [5, 8, 29]. In their classic study, Betts and Magrath demonstrated that energy intake significantly correlated with growth velocity in children whose CRI developed during infancy such that normal growth could continue if energy intake exceeded 80% of recommended values, but it would be expected to cease if intake fell below 40% [29]. In a separate study utilizing the infancy–childhood–puberty model, the European Study Group reported significant growth failure (height SDS –3) in children with CKD during infancy, a period of growth strongly impacted on by nutritional factors [30]. Reduced caloric intake in these patients may be a result of anorexia,

emotional distress, altered taste sensation, or nausea and vomiting. Optimization of protein intake is important as well, since excessive intake can lead to hyperfiltration and accelerated progression to ESRD (although pediatric data to substantiate this claim are limited), whereas inadequate protein intake can lead to malnutrition and insufficient growth [31]. Importantly, studies have shown that nutritional supplementation in malnourished children with CRI can improve growth [4, 32, 33].

Metabolic acidosis is well recognized as a cause of impaired growth, as previously demonstrated in children with untreated renal tubular acidosis [34]. Metabolic acidosis may contribute to derangements in the GH–IGF-I axis by reducing GH secretion and serum IGF-I levels [5]. Research has shown that metabolic acidosis can also cause resistance to the anabolic actions of GH [35], suppress albumin synthesis, promote calcium efflux from bone [36], and promote protein degradation [37, 38]. In a study of children with renal insufficiency, Boirie and colleagues observed a significant inverse correlation between plasma bicarbonate and the leucine rate of appearance, a measure of protein breakdown, suggesting that growth in children with CRI may be impaired as a result of protein breakdown induced by metabolic acidosis [38].

Growth may be further impaired by the development of ROD, one of the most severe clinical problems complicating CRI. ROD represents a range of disorders, from high-turnover bone disease as a result of secondary hyperparathyroidism to low-turnover osteomalacia and adynamic bone [5]. Secondary hyperparathyroidism may cause growth failure by modulating genes involved in endochondral bone formation and altering the architecture of the growth plate [5]. The consequences of long-standing ROD can include reduced bone mineral density, increased numbers of bone fractures, and bone deformities, in addition to growth impairment [5, 8]. Noteworthy is the finding by Kuizon et al. that growth failure can occur in children with adynamic bone disease undergoing peritoneal dialysis in association with high-dose pulse calcitriol therapy [39].

Other causes of growth failure in children with CRI must also be considered. Children with salt-wasting disease may experience growth failure if salt and water losses are not corrected [31]. Additionally, long-term steroid therapy may affect growth by several mechanisms, such as depressing pulsatile GH secretion, inhibiting hepatic production of IGF-I, and by peripherally interfering with cartilage metabolism, bone formation, nitrogen retention, and calcium metabolism [40].

Treatment of growth failure

The current NKF K/DOQI pediatric nutrition guidelines recommend correction of existing nutritional deficiencies and metabolic abnormalities prior to consideration of GH therapy for growth failure [41]. The guidelines state that dietary adjustment or supplemental nutritional support may be necessary in patients with insufficient intake of energy, protein, or other nutrients. It is further recommended that patients with metabolic acidosis (serum bicarbonate <22 mmol/l) receive orally administered alkali therapy or are dialyzed against a higher bicarbonate concentration during maintenance dialysis, if the latter option is available. It is necessary to maximize control of serum phosphorus before starting GH therapy as well; serum phosphorus levels should be less than 1.5-times the upper limit for age. Serum phosphorus and serum parathyroid hormone (PTH) must be controlled to avoid exacerbation of secondary hyperparathyroidism subsequent to the initiation of GH and to avoid the associated risk of development of bone deformities [42]. Although a recommendation regarding the target PTH level during GH therapy in children on dialysis is currently published in the nutritional guidelines (goal: intact PTH <500 pg/ml prior to starting GH), updated recommendations on this issue are forthcoming from the NKF K/DOQI pediatric bone work group.

Efficacy of GH therapy in children with CKD

Clinical trials have demonstrated the safety and efficacy of GH therapy in promoting linear growth in children with CRI, on dialysis, or following renal transplantation (Tables 2 and 3). A multicenter, randomized, double-blind, placebo-controlled trial by Fine and colleagues showed that GH therapy may significantly improve the height of growth-impaired children with CRI [43]. In total, 125 pre-pubertal children with irreversible renal insufficiency and growth failure were randomly allocated to receive GH 0.05 mg/kg per day (n=82) or placebo (n=43) for 2 years. GH-treated patients achieved a significant improvement in mean height SDS from baseline to year 2 of treatment (−2.9 to −1.6, P<0.00005) and as compared with placebo (P<0.00005) [43]. Mean growth rates were significantly higher in the GH-treated group at both the first year (10.7±3.1 vs 6.5±2.6 cm/year, respectively) and the second year (7.8±2.1 vs 5.5±1.9 cm/year, respectively) of treatment (P<0.00005, both comparisons).

Long-term GH therapy in children with CRI has been shown to result in catch-up growth, and many patients achieve a final height within the normal range. Hokken-Koelega and associates evaluated growth in 45 pre-pubertal children with CRI and severe growth deficiency who had received GH therapy for up to 8 years [3, 44]. Although most patients (34 of 45) received treatment for fewer than 6 years, long-term GH therapy resulted in catch-up growth and a significant improvement in height relative to baseline (P<0.001). Mean standardized height reached the lower limit of normal [height (ht) SDS −2] after 3 years of therapy and approached target height after 6 years. In addition, recombinant human growth hormone (rhGH) treatment during puberty was associated with a sustained improvement in height SDS without deleterious effects on GFR and bone maturation. Similar growth outcomes were reported by Kari and Rees, who demonstrated a significant increase in the height SDS of 21 conservatively managed children (−2.5±−1.4 to −1.6±0.6, P=0.001) who were treated with GH for a mean of 3.7±2.5 years) [45].

Table 2 Efficacy of GH therapy in patients with renal disease and short stature: height SDS

Study	Design	Duration (years)	No. of patients examined	Study drug[b] (no. of patients)	Height SDS[a]		
					Baseline	Year 1	Year 2
Fine et al. 1994 [43]	R, DB, PC	2	82 CRI, pre-pubertal	GH (55)	−2.94 (±0.86)	−1.93 (±1.01)	−1.55 (±1.16)[c]
				P (27)	−2.82 (±0.97)	−2.90 (±0.95)	−2.91 (±1.04)
Hokken-Koelega et al. 2000 [44]	Mixed[d]	≤8	45 CRI, pre-pubertal	GH (45)	−2.96 (±1.00)	NR	−2.20 (±1.50)[d,e]
Haffner et al. 2000 [46]	OL, HC	Long-term[f]	38 CRI, pre-pubertal	GH (38)	−3.1 (±1.2)	NR	−1.6 (±1.2)[e,h]
			50 Matched controls	Nil (50)	approx. −1.5		−2.1 (±1.2)[e,h]
Kari and Rees, 2005 [45]	Retrospective	>1	21 CRI	GH	−2.5 ±1.4	−2.1 ±0.7[e]	−2.0 ±0.7[e]
			11 Dialysis	GH	−2.7±0.5	−2.3 ± 0.5[g]	−2.2±0.6[g]
Powell et al. 1997 [54]	R, OL	1	44 CRI, pre-pubertal	GH (30)	−2.7 (±0.7)	Δ0.8 (±0.5)[a]	–
				Nil (14)	−2.7 (±0.8)	Δ0.0 (±0.3)[a]	–
Van Dyck et al. 2001 [59]	OL	1	10 CRI, pre-pubertal	GH (10)	−2.24[a] (−1.07 to −3.56)	−1.21[a,e] (0.44 to −2.75)	–
Berard et al. 1998 [48]	OL	1−5	42 Dialysis, pre-pubertal and early pubertal	GH (42)	−4.2 (±1.0)	−3.7 (±1.0)[j]	–
Postlethwaite et al. 1998 [6]	Obs	≤2	30 Renal failure[k], pubertal status unknown	GH (30)	−3.1 (±1.0)	−2.6 (±1.2)	NR
Guest et al. 1998 [50]	R, OL	≥1	85 Transplant, pre-pubertal and early pubertal	GH (41)	−3.3 (±1.0)	−3.0 (±1.2)[l]	NR
				Nil (44)	−3.7 (±1.3)	−3.7 (±1.3)	
Fine et al. 2002 [49]	R, C	1	68 Transplant, pre-pubertal and pubertal	GH (39)	−2.95 (±0.16)	−2.58 ±0.19)[j]	–
				Nil (29)	−2.96 (±0.18)	−2.99 (±0.17)	–
Maxwell and Rees 1998 [53]	R, OL	2	15 Transplant, pre-pubertal	GH (9)	−3.6 (±1.0)	−3.0 (±1.0)[m]	−2.6 (±1.3)[n]
				Nil (6)	−3.0 (±0.8)	−3.3 (±1.0)	−2.8 (±1.0)[o]
			7 Transplant, pubertal	GH (4)	−2.4 (±1.4)	−1.9 (±1.3)[n]	−0.9 (±0.4)
				Nil (3)	−2.6 (±0.2)	−2.7 (±0.5)	−2.3 (±0.8)
	R, PC	1	63 Transplant, pre-pubertal and pubertal	GH (36)[p]	−2.95 (±0.16)[a]	−2.58 (±0.19)[a,p,q]	–
				Nil (27)[p]	−2.96 (±0.18)[a]	−2.99 (±0.17)[a,p]	–

(*DB* double-blind, *HC* historical control, *NR* not reported, *Obs* observational, *OL* open-label, *P* placebo, *PC* placebo-controlled, *R* randomized)
[a]Results presented as mean (± SD) height SDS, except for Powell et al. 1997 [54] [mean (± SD) change in height SDS], Van Dyck et al. 2001 [59] (median [range]) height SDS
[b]GH dosage was generally equivalent to 0.05 mg/kg per day
[c]$P<0.00005$ vs control group for change from baseline to year 2
[d]Pooled results, including a randomized, double-blind, placebo-controlled, 6-month, crossover study followed by long-term GH therapy ($n=16$) and randomized and open-label studies of long-term treatment with various GH dosages ($n=29$). The condition of 26 patients was evaluable at year 2
[e]$P<0.001$ vs baseline
[f]Mean duration of GH therapy 5.3 years (range 2.8–8.8 years)
[g]$P=0.02$ vs baseline
[h]Final height SDS
[i]$P<0.0001$ vs control group
[j]$P<0.0001$ vs baseline
[k]Patients with severe chronic renal failure, on dialysis, or with a functioning renal transplant
[l]$P=0.005$ vs control group
[m]$P=0.001$ vs baseline
[n]$P=0.02$ vs baseline
[o]$P=0.02$ vs previous year
[p]30 GH-treated patients and 22 untreated patients were evaluable at Year 1
[q]$P<0.0001$ vs placebo for change in heights SDS from baseline

Table 3 Efficacy of GH therapy in patients with renal disease and short stature: height velocity

Study	Design	Duration (years)	No. of patients examined	Study drug[b] (no. of patients)	Height velocity (cm/year)[a]			
					Pre-study	Month 6	Year 1	Year 2
Fine et al. 1994 [43]	R, DB, PC	2	82 CRI, pre-pubertal	GH (55)	NR	–	10.7 (±3.1)[c]	7.8 (±2.1)[c]
				P (27)	NR	–	6.5 (±2.6)	5.5 (±1.9)
Hokken-Koelega et al. 1991 [71]	R, DB, PC, X	1	16 CRI, pre-pubertal	GH/P (8)	1.5 (±0.7)	5.2 (±1.2)[a,d,e]	1.5 (±0.4)[a,g,h]	–
				P/GH (8)	1.5 (±0.5)	2.4 (±1.0)[a,f]	4.4 (±1.6)[a,g,h]	–
Haffner et al. 2000 [46]	OL, HC	Long-term[i]	38 CRI, pre-pubertal	GH (32 boys)	3.3	–	8.4[k,l]	8.8[m]
				GH (6 girls)	3.7	–	9.7[k,l]	7.8[m]
			50 Matched controls[j]	Nil (31 boys)	NR	–	NR	7.6[j]
				Nil (19 girls)	NR	–	NR	6.7[j]
Van Dyck et al. 2001 [59]	OL	1	10 CRI, pre-pubertal	GH (10)	5.1[a] (3.0–8.8)	–	10.6 [a,k] (8.2–12.7)	–
Berard et al. 1998 [48]	OL	1–5	42 Dialysis, pre-pubertal and early pubertal	GH (42)	3.5 (±2.2)	–	7.0 (±2.3)[d]	–
Postlethwaite et al. 1998 [6]	Obs	≤2	30 Renal failure[n], pubertal status unknown	GH (30)	4.9 (±2.6)	–	7.4 (±2.7)[k]	5.2 (2.6)
Guest et al. 1998 [50]	R, OL	≥1	85 Transplant, pre-pubertal and early pubertal	GH (41)	4.1 (±2.0)	–	7.7 (±2.5)[o]	–
				Nil (44)	4.2 (±2.1)	–	4.6 (±2.7)	–
Maxwell and Rees 1998 [53]	R, OL	2	15 Transplant, pre-pubertal	GH (9)	3.9 (±1.7)	–	8.1 (±2.7)[p]	5.7 (±2.9)[q]
				Nil (6)	4.9 (±1.8)	–	3.7 (±1.5)	8.5 (±1.6)[q]
			7 Transplant, pubertal	GH (4)	4.5 (±2.5)	–	10.1 (±1.2)[p]	6.4 (±2.1)
				Nil (3)	2.7 (±1.6)	–	3.9 (±2.3)	6.1 (±4.7)
Hokken-Koelega et al. 1996 [73]	R, DB, PC, X	1	11 Transplant, pre-pubertal	GH/P (6)	1.5 (±0.7)	5.3 (±1.0)[a,d]	1.5 (±0.9)[a,g,h]	–
				P/GH (5)	1.0 (±0.5)	1.9 (±0.7)[a]	3.9 (±1.3)[a,g]	–

(*DB* double-blind, *HC* historical control, *NR* not reported, *Obs* observational, *OL* open-label, *P* placebo, *PC* placebo-controlled, *R* randomized, *X* crossover)

[a]Results presented as mean (± SD) height velocity (cm/year), except for Hokken-Koelega et al. 1991 [71] [mean (± SD) height velocity (cm/6 months)] and Van Dyck et al. 2001 [59] [median (range) height velocity (cm/year)]

[b]GH dosage was generally equivalent to 0.05 mg/kg per day

[c]$P<0.00005$ vs control group

[d]$P<0.0001$ vs pre-study period

[e]$P<0.001$ vs control group

[f]$P<0.04$ vs pre-study period

[g]Results for the second 6-month period following crossover

[h]Overall mean effect of GH minus placebo, +2.9 cm/6 months, $P<0.0001$

[i]Mean duration of GH therapy 5.3 years (range 2.8–8.8 years)

[j]Patients in the matched control group had little or no growth impairment at baseline, declined participation in the trial, or were ineligible for GH therapy because of advanced puberty

[k]$P<0.001$ vs pre-study period

[l]Peak results for the pre-pubertal period; $P<0.001$ vs control group

[m]Peak results for the pubertal period; not significantly different from control group ($P=0.26$, boys; $P=0.18$, girls)

[n]Patients with severe chronic renal failure, on dialysis, or with a functioning renal transplant

[o]$P=0.0001$ vs control group

[p]$P=0.005$ vs control group

[q]$P=0.005$ vs pre-study period

In a study of 38 children with CKD (47% with CRI), Haffner and colleagues demonstrated that the administration of GH over a mean of 5 years resulted in significantly greater pre-pubertal height gain than in children who did not receive GH (boys 18.6±9.3 cm vs 9.9±4.8, $P<0.001$; girls 16.6±8.7 cm vs 9.1±9.8, $P=0.014$) [46]. Although the pubertal height gain achieved and the duration of the pubertal growth spurt of the former group was similar to that experienced by untreated children and inferior to that of healthy children, two-thirds of treated patients achieved a normal final adult height (ht SDS >−1.88) [46]. Similar benefits have been demonstrated in rhGH-treated adolescents following renal transplantation [47].

Additional clinical studies support the efficacy of GH therapy in patients requiring renal replacement therapy. Berard and co-workers retrospectively evaluated the effects of GH treatment (1 IU/kg per week by daily subcutaneous injection for 1 to ≥5 years) in 42 pre-pubertal and early pubertal growth-impaired children undergoing hemodialysis [48]. During the first year of GH therapy, the mean growth velocity increased from 3.5 cm/year to 7.0 cm/year ($P<0.0001$). Growth rates declined in subsequent years but remained significantly higher than baseline in year 2 (6.2 cm/year, $P<0.0001$), year 3 (5.5 cm/year, $P<0.0002$), and year 4 (5.3 cm/year, $P<0.002$). In contrast, while Kari and Rees described an initial improvement in the growth velocity of 11 patients on dialysis (height SDS from −2.7± 0.5 to −2.3±0.5, after 1 year, $P=0.002$), no subsequent improvement in the ht SDS was observed with continued GH treatment [45].

Poor growth outcomes observed in the post-transplantation population are associated with a number of factors, including corticosteroid administration, decreased GFR, and an abnormal GH–IGF-I axis [49]. Nevertheless, Guest and colleagues have shown that GH therapy can significantly enhance height velocity in renal transplant recipients [50]. Ninety pre-pubertal or early pubertal growth-impaired patients who were at least 12 months past transplantation and with stable renal function were randomly chosen to receive GH, 30 U/m^2 per week, either immediately ($n=46$) or 1 year later (control group, $n=44$). GH-treated patients achieved a significant increase from baseline in height velocity after 1 year (from 4.1 cm/year to 7.7 cm/year) vs no change in the control group ($P<0.0001$). First-year growth velocities in GH-treated children after renal transplantation did not, however, increase to the level observed in patients with CRI (~10 cm/year). In patients followed up for up to 4 years of GH treatment, growth velocities declined following the first year of treatment but remained higher than baseline values.

Similarly, data from 68 growth-retarded pediatric renal allograft recipients enrolled in NAPRTCS demonstrated a significant increase in the height SDS of patients who received 1 year of GH therapy compared with untreated controls (+0.49±0.1 vs −0.10±0.08, $P<0.001$) [51]. In a more recent study from the NAPRTCS database, Fine and Stablein have shown that final adult height SDS scores were significantly better in transplant recipients who received GH therapy ($n=513$) than in those who did not ($n=2,263$) (−1.83±0.14 vs −2.60±0.05, $P<0.001$) [16]. Comparison of the two groups also revealed no difference in the incidence of either graft rejection or graft loss.

A recent meta-analysis identified four randomized, controlled trials (including two already mentioned) that examined the effect of GH versus placebo or no treatment on height SDS in children with CKD either before dialysis or after transplantation [52]. After 1 year, GH treatment produced a significant increase in height SDS as measured by a weighted mean difference (WMD) of 0.77 (95% CI

Table 4 Incidence of adverse events associated with growth hormone therapy [65]

Parameter	CRI		Dialysis		Transplant	
	GH	No GH	GH	No GH	GH	No GH
Number of patients	1,376	4,550	478	2,030	479	1,953
Mean (± SD) duration of therapy (years)	3.2±5.9	NA	2.1±2.9	NA	7.7±8.5	NA
Mean (± SD) GH dose (mg/kg per week)	0.33±0.20	NA	0.35±0.13	NA	NA	NA
Incidence of adverse events: slipped capital femoral epiphysis						
Number of events	1	1	2	4	1	2
Events per 1,000 patients	0.726	0.220	4.184	1.970	2.088	1.024
Avascular necrosis						
Number of events	1	2	0	0	4	12
Events per 1,000 patients	0.726	0.440	0	0	8.351	6.144
Benign intracranial hypertension						
Number of events	3	0	0	2	0	5
Events per 1,000 patients	2.180	0	0	0.985	0	2.560
Other serious adverse events						
Number of events	34	106	68	183	86	247
Events per 1,000 patients	13.081	14.066	50.206	45.320	102.296	76.805

GH dosage was not collected for patients in the transplant component of the North American Pediatric Renal Transplant Cooperative Study.
NA not applicable

0.51 to 1.04). In a child aged 10 years, this WMD translates into a height gain of 4.7 cm in 1 year [43, 50, 53, 54].

It should be re-emphasized that, although dialysis patients and transplant recipients show improved growth with GH therapy, children with CRI respond better to treatment with GH than do children with ESRD [8, 55]. As mentioned previously, this may be partially related to differences in the severity of alterations in IGF-binding protein concentrations and GH receptor density. Therefore, it is recommended that GH therapy be considered and initiated at a young age and/or early in the evolution of CKD in order to make possible the greatest achievement of growth potential.

Recommendations for long-term GH therapy in patients with CRI have been made with recognition that discontinuation of GH once the target height has been achieved may result in a substantial reduction in growth velocity [56]. In one study, 16 of 22 (73%) children experienced catch down growth to 2.7±1.7 cm/year after a mean (± SD) of 9±4.6 months off GH. Restarting GH in these patients increased the growth velocity to 7.2 ± 1.7 cm/year. In contrast, stopping GH prior to transplantation in a separate study of 29 children did not result in significant catch down growth after transplantation [45].

Finally, in addition to promoting growth, GH therapy may provide other benefits to children with CRI that deserve mention. Early trials by Fine and colleagues demonstrated significant GH-related anabolic effects, as evidenced by improvements in body weight, midarm circumference, and midarm muscle circumference [57]. Although data from patients with CRI are limited, research has shown that GH therapy may also improve QOL and parameters of bone metabolism [14, 58]. A study of ten pre-pubertal patients with CRI showed that GH therapy for 1 year produced a significant increase in lumbar spine and total body bone mineral content and bone mineral density [59]. Whereas GH therapy may be associated with neurodevelopmental and cardiovascular improvements, more research is needed to elucidate these benefits in the CRI population [60, 61]. Several studies have already documented the important role of GH in maintaining cardiovascular health in children and adolescents with GHD [62–64].

Safety of GH therapy

Several clinical studies support the safety of GH therapy in children with CRI. Over a 6.5-year period, Fine and colleagues compared the frequency of GH-related adverse events in patients in the CRI, dialysis, and renal transplant registries of the NAPRTCS to untreated children with CKD (Table 4) [65]. Compared with untreated children, GH-treated patients showed no significant increase in the incidence of malignancy, slipped capital femoral epiphysis, avascular necrosis (AVN), glucose intolerance, pancreatitis, progressive deterioration of renal function, acute allograft rejection, or fluid retention. There was no significant increase in the incidence of benign intracranial hypertension (ICH) observed among GH recipients, and three of 1,376 GH-treated patients showed signs and symptoms related to ICH at 2, 50, and 1,131 days, respectively, after discontinuing GH treatment. Interestingly, ICH occurred in two and five children who did not receive GH in the dialysis and transplant registries, respectively.

Several studies have reported a significant elevation of insulin levels during the first year of treatment, which is consistent with the known activity of GH [66]; however, a return toward baseline was generally observed with long-term treatment [43, 53, 67, 68]. One long-term study involving 152 children with short stature of various etiologies, including 16 patients with CRI, showed that mean insulin levels increased but remained within normal limits during 5 years of GH treatment [68]. Thus, while irreversible diabetes mellitus has not been observed in patients with CKD [43, 50, 53, 67–69], careful monitoring of glucose metabolism is advised.

Of particular interest to the CKD population is a radiographic evaluation of 205 children with CKD by Boechat et al., which revealed no association between the incidence of AVN and the type or duration of renal disease or GH therapy [70]. In other studies, no apparent acceleration in deterioration of renal function has been observed in GH-treated patients with CRI or following renal transplantation [47, 50, 51, 66, 71, 72]. Furthermore, and as already stated, GH therapy has not been associated with a significant increase in acute rejection episodes in renal transplant recipients compared with rejection rates prior to GH treatment or in untreated controls [50, 73]. Although some authors have suggested that patients with a history of more than one prior acute rejection episode are at an increased risk of acute rejection following initiation of GH therapy, no definitive evidence of a causal relationship has been found in this regard [50, 51].

Dosing recommendations

Currently, somatropin (recombinant human growth hormone for injection) is approved for the treatment of growth failure in children with CRI in the United States of America (Nutropin AQ, Genentech), Europe (Nutropin AQ, Ipsen; Genotonorm, Pharmacia & Upjohn; Norditropin, Novo Nordisk), Japan (Genotropin, Pfizer Japan; Norditropin, Novo Nordisk), and Australia (Genotropin, Pfizer Australia). In children with GHD, the recommended dosage in pre-pubertal children is up to 0.30 mg/kg per week (24 IU/m^2 per week) administered as a daily subcutaneous injection [74]. In contrast, patients with CRI require higher GH doses, and in accordance with results from the numerous clinical trials reviewed, it is recommended that these patients receive 0.35 mg/kg per week (28 IU/m^2 per week) to achieve the desired growth response [74].

Although the recommended GH dosage for patients with CRI has been extensively evaluated in clinical trials, future research may allow further optimization of the therapeutic regimen in this population. Two dosing considerations of interest to clinicians include a pubertal dosing regimen and

dose modifications based on IGF-I levels. Studies in patients with GHD suggest that higher doses of GH may be required during puberty for some patients, such as those with severe growth failure or a delayed diagnosis of growth impairment [75, 76]. A study in adolescents with GHD showed that "pubertal doses" of GH (0.7 mg/kg per wk) resulted in greater near-adult height (defined as height attained at a bone age of >16 years for boys and >14 years for girls) than conventional doses, did not produce undue advancement of bone age, and were well tolerated [75]. Research is required to determine the optimal pubertal GH dosing regimen in patients with CRI.

Because administration of GH should increase plasma IGF-I levels, and many of the growth-promoting effects of GH are mediated by IGF-I, it has been suggested that a relationship might exist between plasma IGF-I concentrations and catch-up growth in children with GHD receiving GH therapy [77]. Thus, IGF-I may be a useful measure of therapeutic efficacy and adherence to prescribed therapy. On the other hand, there are no data on this subject as it relates to patients with CRI. Accordingly, what, if any, relationship exists between the concentration of IGF-I, the growth rate of children with CRI, and the value of IGF-I in predicting growth and modifying the GH dosage, remains to be determined.

Current GH utilization in children with CRI

Currently, a large proportion of growth-impaired children with CRI are not receiving GH therapy. The NAPRTCS 2005 annual report showed that GH utilization in patients with CRI and growth failure (height SDS <−1.88 and Tanner stages I–III) was low, reaching a maximum of 22.1% at 12 months after entry into the registry (Fig. 2) [28]. This low level of use is an area of concern, given that GH is an approved therapy for patients with growth failure associated with CRI. Accordingly, it is important for clinicians to identify and address the possible reasons for such low GH usage.

In our clinical experience, the most significant barriers to GH use in children with CKD include the patient's and family's unwillingness to begin and comply with treatment,

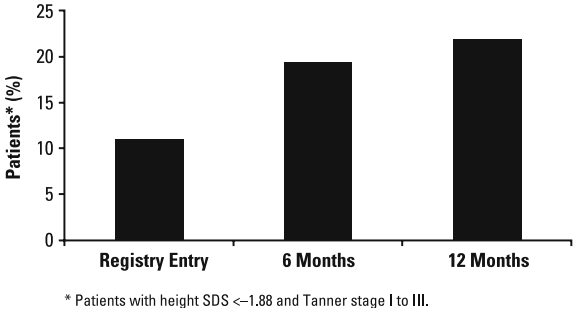

Fig. 2 GH utilization in children with CRI and growth failure (n=1,727). GH utilization in patients with CRI and growth failure (ht SDS <−1.88 and Tanner stages I–III) is low, with fewer than 25% of children receiving GH therapy at 12 months after entry into the NAPRTCS registry [10]

difficulties with reimbursement, and an expected short time until transplantation. We believe that additional barriers reflect the clinician's perception of the impact of short stature and a lack of urgency to treat children with CRI-related short stature because it may be deemed a cosmetic issue by clinicians and families that does not warrant immediate and aggressive intervention. The perception that growth is primarily an endocrine problem, perceived complexity associated with the initiation of GH therapy, and lack of familiarity or guidelines related to the evaluation and implementation process for GH therapy in CKD may also hinder GH use.

As mentioned previously, the cost of GH and the belief that treatment might not be reimbursed likely contribute to the reluctance to initiate therapy in patients with CKD in some centers [78]. In addition to the direct costs of GH therapy (e.g., drug and training expenses), indirect costs also may be incurred, such as those related to the development of adverse events and their management and the psychological and family burden associated with therapy. These costs are less easily measured and may vary considerably among patients. On the other hand, a dollar "value" defining the clinical benefits of GH therapy may be nearly impossible to determine. Both the social and psychological benefits and the positive effects on morbidity and mortality are difficult to quantify. Nevertheless, the cost-effectiveness of GH therapy is an area that requires continued exploration.

Proposed algorithm for the evaluation and treatment of growth failure in children with CRI

To address the need for clear clinical guidelines, an algorithm for the evaluation and treatment of growth failure in children with CRI was developed (Fig. 3). These recommendations are based on the results of clinical studies demonstrating the safety and efficacy of GH therapy in this population [6, 42–44, 51, 52, 59], appraisal of the relevant GH and CRI guidelines [41, 74, 79, 80], and the expert opinion of the consensus conference participants. At this time, limited data are available regarding the non-growth-related benefits of GH therapy in children with CRI, such as the psychosocial and QOL benefits, bone development, neurodevelopment, and cardiovascular benefits, and thus they are not addressed by this algorithm.

We propose that the target population include children with clinically defined CRI (GFR <75 ml/min per 1.73 m^2 body surface area) and significant growth impairment (height SDS <–1.88 or height velocity SDS <−2.00) [28]. As described, complicating factors for poor growth—such as metabolic acidosis, malnutrition, salt-wasting, ROD, and hypothyroidism—must be adequately addressed before GH therapy is initiated [41, 66, 79]. Correction of these abnormalities is not likely to fully correct growth abnormalities in these children, but it is necessary to ensure an optimal growth response in those patients who ultimately receive GH therapy. GH treatment is contraindicated in patients with active malignancies and should

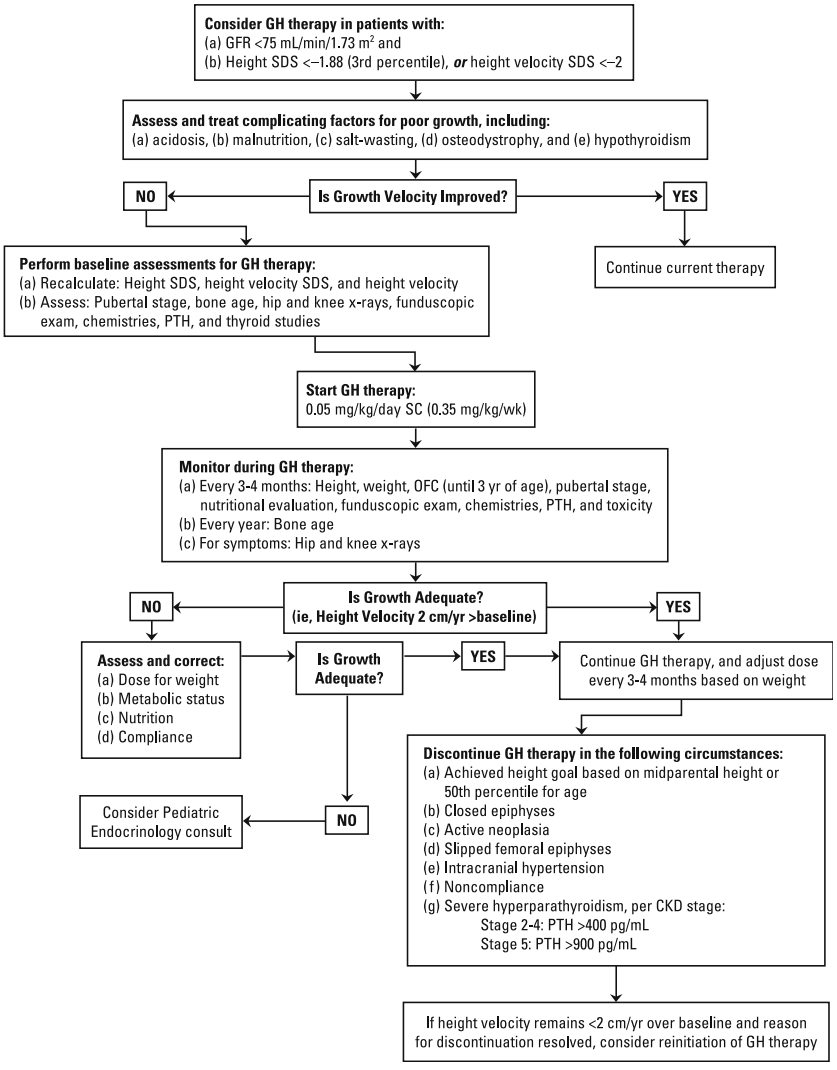

Fig. 3 Proposed algorithm for evaluation and treatment of growth failure in children with CRI

be used with caution in disorders associated with an increased risk of malignancy.

Once metabolic and nutritional factors affecting growth have been addressed (e.g., over a 3–6-month period), patients may be evaluated for GH therapy. Height SDS, height velocity SDS, absolute height velocity, pubertal stage, and bone age should be reassessed before treatment to confirm the patient's eligibility for GH and to allow accurate monitoring of growth while receiving treatment. Baseline hip and knee X-rays, funduscopic examination, blood chemistries, PTH levels, and thyroid studies should also be performed to assist in monitoring for more rare events such as slipped capital femoral epiphysis, glucose intolerance, and benign ICH.

Following a comprehensive pretreatment workup, patients may be initiated on GH therapy at 0.05 mg/kg per day (0.35 mg/kg per week or 28 IU/m^2 per week) administered by subcutaneous injection. Throughout GH therapy, patients must be monitored regularly for dose modification based on weight gain, response to therapy, adverse events, and complicating factors that may result in poor growth. Clinic visits every 3 to 4 months are recommended for the assessment of height, weight (and GH dose modification), occipitofrontal circumference (until 3 years of age), pubertal maturation, nutritional status, funduscopic examination, serum chemistries, and PTH. Yearly monitoring of bone age should be accompanied by hip and knee X-rays only if persistent hip or leg pain is present.

Patients demonstrating an inadequate growth response may require correction of their weight-based GH dose or complicating nutritional or metabolic factors for poor growth and should be assessed for treatment compliance. Patients with persistent poor growth despite correction of these issues may require referral to a pediatric endocrinologist for further evaluation of other possible causes for inadequate growth.

Finally, we recommend that GH therapy should be discontinued when the epiphyses close or if the patient's height goal has been achieved (based on midparental height or 50th percentile for age). It should be at least temporarily discontinued in the presence of active neoplasia, slipped capital femoral epiphyses, benign intracranial hypertension, severe hyperparathyroidism (PTH >900 pg/ml for stage 5 CKD and lower values for early CKD), non-

compliance with treatment, or at the time of renal transplantation. We recommend continued monitoring of growth after the patient discontinues GH therapy, since re-initiation of GH may be appropriate if the height velocity decreases and the reasons for the discontinuation of GH are resolved.

Summary

In summary, growth failure remains a significant clinical problem in children with CRI, and growth assessment should be a routine component of nephrology care. Growth failure in this population is often multifactorial; it may reflect substantial derangements of the GH–IGF-I axis and may be compounded by nutritional and metabolic abnormalities, each of which must be adequately addressed to improve growth. Although the safety and efficacy of GH therapy in growth-impaired children with CRI have been demonstrated in numerous clinical trials, current use of GH therapy in this population remains surprisingly low. Several barriers to GH use exist, including the lack of clear guidelines for clinicians regarding the initiation and monitoring of GH therapy and the target height for treated patients. Our proposed algorithm for the evaluation and treatment of growth failure in children with CRI is designed to address this important need.

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