Growth and Growth Hormone Therapy in Children with CKD: Four Cases and a Plea

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Nationwide Children’s Hospital
The Ohio State University College of Medicine
Overview

Why is \textit{Growth in CKD} so important?

Why do so many children with CKD demonstrate poor growth?

How can we best promote growth in this special population?

\textbf{Growth: A Paramount Concern!}
Overview

Why is growth in CKD so important?
Why do so many children with CKD demonstrate poor growth?
How can we best promote growth in this special population?

Growth: A Paramount Concern!
4 Questions

Q1: Why is Growth in Children with CKD so Important?
Q2: What is the Most Common Cause of Growth Failure in Children with CKD?
Q3: Why Does GH Work to Improve Growth in CKD?
Q4: How is GH Used in Children with CKD?
Q1: Why is Growth in Children with CKD so Important?

**Patient MH**
Identical twin with Prune Belly Syndrome
Twin unaffected
LRD (father) transplant 1 week prior to 6th birthday with bilateral nephrectomy and orchidopexy
## Patient MH

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Wt SDS</th>
<th>Ht (cm)</th>
<th>Ht SDS</th>
<th>Wt/Ht SDS</th>
<th>Cr (mg)</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>25.5</td>
<td>1.96</td>
<td>115.9</td>
<td>-0.04</td>
<td>2.16</td>
<td>0.6</td>
<td>106</td>
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<td>9.6</td>
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<td>1.1</td>
<td>66</td>
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<tr>
<td>11.2</td>
<td>31</td>
<td>-0.87</td>
<td>135.6</td>
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<td>0.23</td>
<td>1.8</td>
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<tr>
<td>12.9</td>
<td>37.6</td>
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<td>-1.89</td>
<td>1.07</td>
<td>1.5</td>
<td>46</td>
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</tbody>
</table>

On CSA/Imm/Pred post transplant; rejection x 1, Rx solumedrol
Better Growth in Childhood CKD is Associated with Better

- Survival [Furth 2002; Ku 2016; Li 2019]
- Morbidity (hospitalizations, infections, etc) [Furth 2002]
- Adult height [Hoekken-Kolega 2001; Haffner 2000]
- Satisfaction with adult life [Boyer 2004; Rosenkrantz 2005]
- Childhood physical and social functioning [Al-Uzri 2013]
- Patient/Parent regard [Reynolds 1995]
- Bone mineralization [Nawrot-Wawrzyniak 2013]
Growth Failure in Children with CKD is Associated with Poorer Survival


Furth S, Pediatrics 2002
Children with Short Stature at Initiation of RRT Have Increased Mortality

USRDS, retrospective
13,218 children (2-19 yo)
First RRT 1995-2011
1721 deaths

Short children = higher risk of cardiac & infection deaths
Tall children = higher risk of cancer deaths

Ku E. CJASN 2016
Short Stature at Time of Renal Transplant is Associated with Faster Time to Reduced Kidney Function

CKiD, 138 children
Renal Tx mean age 13 yo
Median time to eGFR <45 = 6.6 yrs
20% (28) short stature before Tx

Children with short stature = lower SES, nephrotic proteinuria, higher BP, lower mid-parental height before transplant
Children with growth failure = 40% shorter time to eGFR < 45 ml/min/1.73 m² than those with normal stature
Long-Term Intervention (GH Therapy) Continues to Improve Growth in Children with CKD

Hokken-Koelega A. J Ped Endocrinol Metab 2001
Hokken-Koelega A. Ped Neph 2000
Final Adult Height is Better in Children with CKD Treated with GH Therapy

Social Outcome Following Renal Transplantation is Greatly Influenced by Adult Height

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P value</th>
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<tr>
<td>Year of transplantation</td>
<td>.04</td>
</tr>
<tr>
<td>Higher educational level achieved</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Higher rate of paid employment</td>
<td>.02</td>
</tr>
<tr>
<td>Greater likelihood of marriage</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Greater likelihood of independent living</td>
<td>.0003</td>
</tr>
</tbody>
</table>

N = 244; mean age = 31.7; mean age Tx = 11.9
Height Dissatisfaction Impacts Quality of Life

Mean adult height SDS score: $-1.56 \pm 1.55$

Height satisfaction correlated with height SDS score ($r = 0.42; P = .006$)

Quality of life correlated significantly with height satisfaction ($r = 0.41; P = .008$)

N = 39; mean age = 26.7

Rosenkranz J. Ped Neph 2005
Impact of Growth in CKD on QoI

Participants split into Normal Height or Short Stature groups

**Multivariate modeling:** significant association between both

- catch-up growth
- growth hormone use

child physical functioning
social functioning
[based on parent reports]

CKiD, 483 children &/or parents
Peds QL (4.0) on 2 visits

Al-Uzri A. J Peds 2013
What Concerns Children and Parents About Living with CKD*?

<table>
<thead>
<tr>
<th>Concern</th>
<th>Percent (Children)</th>
<th>Percent (Parents)</th>
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<tbody>
<tr>
<td>General</td>
<td>10 – 15</td>
<td>15</td>
</tr>
<tr>
<td>CRF/dialysis</td>
<td>20 – 25</td>
<td>20</td>
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<tr>
<td>Other</td>
<td>10 – 15</td>
<td>15</td>
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<tr>
<td>Growth</td>
<td>30 – 35</td>
<td>30</td>
</tr>
<tr>
<td>Appearance</td>
<td>15 – 20</td>
<td>20</td>
</tr>
<tr>
<td>Coming to...</td>
<td>10 – 15</td>
<td>15</td>
</tr>
<tr>
<td>School and...</td>
<td>15 – 20</td>
<td>20</td>
</tr>
<tr>
<td>Effect on...</td>
<td>40 – 50</td>
<td>50</td>
</tr>
<tr>
<td>Future health</td>
<td>40 – 50</td>
<td>50</td>
</tr>
<tr>
<td>Future</td>
<td>20 – 25</td>
<td>25</td>
</tr>
<tr>
<td>Future</td>
<td>15 – 20</td>
<td>20</td>
</tr>
</tbody>
</table>

*CKD: Chronic Kidney Disease

Reynolds JM
Arch Dis Child 1995
Growth Hormone (and Growth) Improves Bone

18 short children on dialysis
Iliac bx pre and post 1 yr GH Rx

Nawrot-Wawrzyniak K. Am J Kid Dis 2013
<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Wt SDS</th>
<th>Ht (cm)</th>
<th>Ht SDS</th>
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<td>46</td>
</tr>
<tr>
<td>13.2</td>
<td>37.2</td>
<td>-0.87</td>
<td>143</td>
<td>-1.33</td>
<td>0.23</td>
<td>1.4</td>
<td>56</td>
</tr>
<tr>
<td>15.4</td>
<td>49.2</td>
<td>-0.75</td>
<td>160.5</td>
<td>-1.84</td>
<td>1.07</td>
<td>1.7</td>
<td>52</td>
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<tr>
<td>17.6</td>
<td>61.3</td>
<td>-0.79</td>
<td>175.5</td>
<td>-0.21</td>
<td>0.2</td>
<td>2.6</td>
<td>37</td>
</tr>
</tbody>
</table>

On CSA/Imm/Pred post transplant; rejection x 1, Rx solumedrol
Q2: What are the Modifiable Causes of Growth Failure in Children with CKD?
Variables That Can Contribute to Growth Failure in CKD*

**Non-Modifiable**
- Age of onset of CKD
- Abnormal birth history
- Primary renal disease
- Degree of renal dysfunction
- Genetic factors (parental ht)
- Delayed puberty?
- Steroid and other therapies

**Modifiable**
- Protein and Calorie deficiency
- Abnormal protein metabolism
- Metabolic acidosis
- CKD-MBD
- Salt-wasting/concentration defect

Growth Failure May Occur at Any Level of CKD (GFR)
Growth Does Not Typically Improve with Dialysis
Growth Failure is Related to Multiple Factors

Mahan JD. Ped Neph 2006
Factors that Contribute to Growth Failure in Children with CKD

Drube J. Nat Rev Neph 2018
Abnormal Birth History: Impact on Growth

<table>
<thead>
<tr>
<th></th>
<th>Poor Growth</th>
<th>Good Growth</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term (%)</td>
<td>43.2</td>
<td>25.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGA (%)</td>
<td>36.8</td>
<td>18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBW (%)</td>
<td>30.8</td>
<td>15.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CKiD, 426 children
Detailed birth history

Greenbaum L. CJASN 2011
Malnutrition-Inflammation Cachexia Syndrome: Protein-Energy Wasting in KD

‘Cachexia in Slow Motion’ – Protein-energy malnutrition + inflammation

<table>
<thead>
<tr>
<th>Malnutrition</th>
<th>Protein Energy Wasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate intake of nutrients</td>
<td>Inadequate intake of nutrients only partially responsible</td>
</tr>
<tr>
<td>Body fat is lost</td>
<td>Normal or even increase fat mass</td>
</tr>
<tr>
<td>Lean body mass initially preserved, later loss of muscle mass and protein stores</td>
<td>Loss of lean body mass</td>
</tr>
<tr>
<td>Low resting energy expenditure</td>
<td>High resting energy expenditure</td>
</tr>
<tr>
<td>Can be reversed by dietary supplements</td>
<td>Inadequate response to dietary supplements</td>
</tr>
</tbody>
</table>
Protein Energy Wasting in CKD

Carrero JJ. J Ren Nutr 2013
### Metabolic Acidosis

- Associated with resistance to anabolic actions of GH
- Suppresses albumin synthesis
- Promotes Ca efflux from bone
- Promotes protein degradation

<table>
<thead>
<tr>
<th>Carbon Dioxide</th>
<th>N (%)</th>
<th>Avg Effect on Age Specific Ht SDS</th>
<th>Avg Effect on Age Specific Wt SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18 mEq/L</td>
<td>40 (5%)</td>
<td>-0.67 (-1.03, -0.31)</td>
<td>-0.40 (-0.81, 0.02)</td>
</tr>
<tr>
<td>18 - &lt;22 mEq/L</td>
<td>158 (21%)</td>
<td>-0.14 (-0.34, 0.05)</td>
<td>-0.08 (-0.31, 0.15)</td>
</tr>
<tr>
<td>≥ 22 mEq/L</td>
<td>551 (74%)</td>
<td>0 (reference)</td>
<td>0 (reference)</td>
</tr>
</tbody>
</table>

CKiD, 799 children
Median age = 11.0 yrs
Median GFR = 49.9
Growth in Childhood CKD

Barriers to Achieving Pro-Growth State

- Insufficient calories/protein
- Metabolic acidosis
- CKD-Metabolic Bone Disease
- Insufficient Na/H2O
- Uremic milieu
- Inflammation
- Abnormal GH/IGF-1 Axis
- Sex Hormone Dysregulation

Outcomes of Pro-Growth State

- Normal height
- Normal weight for height
- Normal muscle mass/function
- Normal neurodevelopment

Parent/Family Engagement

Interdisciplinary Care Team
Pro-Growth Agenda in Childhood CKD - Complicated

- Easy to ignore
  - Hard to overcome anorexia, dysgeusia, fatigue
  - ? Nutritional supplements/NG Tube-G Tubes – complicated!
- Control of metabolic acidosis and CKD-MBD requires multiple meds, multiple times/day
- Lab monitoring complicated
Pro-Growth Agenda in Childhood CKD - Complicated

- **Inflammation** often insidious, challenging
- **Uremia control** – *complicated!*
- GH Rx to overcome GH/IGF-1 resistance state – *complicated!*

- Never too soon to start additional efforts to promote – do not wait for significant growth failure!
- Best way to achieve normal adult height and good quality of life/satisfaction = *good growth!*
<table>
<thead>
<tr>
<th>Barrier</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Insufficient calories/protein</td>
<td>100% RDA calories/protein for ideal weight</td>
</tr>
<tr>
<td>2. Metabolic acidosis</td>
<td>Alkali as needed to maintain HCO3 &gt;22</td>
</tr>
<tr>
<td>3. CKD-Mineral Bone Disease</td>
<td>P restriction; maintain normal 25D, Ca and P; maintain PTH in CKD appropriate range</td>
</tr>
<tr>
<td>4. Insufficient Na/H2O</td>
<td>Na/H2O supplements as needed</td>
</tr>
<tr>
<td>5. Uremic milieu</td>
<td>CKD5 – dialysis for adequacy + more</td>
</tr>
<tr>
<td>6. Inflammation</td>
<td>Prevent/treat infections</td>
</tr>
<tr>
<td>7. Abnormal GH/IGF-1 Axis</td>
<td>GH in pharmacologic doses if needed</td>
</tr>
<tr>
<td>8. Sex Hormone Dysregulation</td>
<td>Typically not treated; evaluate significant delays</td>
</tr>
</tbody>
</table>
Aggressive Nutrition in CKD: Evidence for Good Outcomes

Prevention of growth disturbances as major goal nutrition Rx

- Initiation of enteral feedings (NG/GT) before important height deficits provides superior height outcomes [Parekh]
- Infants show significant increases in growth velocity after provision of adequate calories NG/GT [Parekh, Kari, Ledermann]
- Childhood CKD data not as rich – growth benefits not clear – often BMI gains but not Ht gains – however improved albumin may be critical marker [Rees]
- GT associated with better growth than NG [Rees] – may have less oral aversion with GT; neither associated with more obesity
Q3: Why Does GH Work to Improve Growth in CKD?

**Uremia is State of GH/IGF-1 Resistance [Altered GH/IGF-1 Axis]**

**GH Resistance**
- GH receptor density diminished in target organs
- GH signal transduction impaired (JAK/STAT)
- Diminished IGF-1 release

**Increased IGFBPs**
- Decreased bioactive IGF-1

**Altered GH Signalling**
- Inflammatory cytokines activate *Suppressor of Cytokine Signaling 2 (SOCS2)* pathway that suppresses GH release
Uremia as a GH/IGF-1 Resistance State
[Altered GH/IGF-1 Axis]

Normal

CKD
Improved Growth After rhGH Treatment in Children with CKD

Children with CKD who receive rhGH therapy have better growth rates than placebo-treated children.

Fine R. J Pediatr 1994

**P<0.00005 compared to placebo.
Children with Poor Growth Treated with GH Experience Significant Height Prepubertal Gains

Children with CKD who receive GH therapy show a significant improvement in prepubertal height gain.

GH Treatment Provides Significant Height Gains in Children with CKD During Puberty

It is important to initiate GH therapy early in children with CKD

Adapted from Haffner *NEJM*. 2004;343:923-930.
Children with CKD After RTx & GH Treatment Have Better Final Adult Height Than Those Without GH Rx

rhGH effectively improves FH in CKD RTx patients, without affecting kidney function

Gil S. Ped Nephrol 2012
Effect of rhGH Rx on Height SDS in Children with CKD: A Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n</th>
<th>Control n</th>
<th>WMD (95% CI Random)</th>
<th>Weight %</th>
<th>WMD (95% CI Random)</th>
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<tbody>
<tr>
<td>Maxwell 1998</td>
<td>4</td>
<td>3</td>
<td></td>
<td>3.4</td>
<td>0.60 (-0.81, 2.01)</td>
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<tr>
<td>Pubertal</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Maxwell 1998</td>
<td>9</td>
<td>6</td>
<td></td>
<td>6.7</td>
<td>0.90 (-0.08, 1.88)</td>
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<tr>
<td>Prepubertal</td>
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<td></td>
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<tr>
<td>Guest 1998</td>
<td>41</td>
<td>44</td>
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<td>19.7</td>
<td>0.30 (-0.21, 0.81)</td>
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<tr>
<td>Fine 1994</td>
<td>55</td>
<td>27</td>
<td></td>
<td>24.4</td>
<td>1.10 (0.66, 1.54)</td>
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<tr>
<td>Powell 1997</td>
<td>30</td>
<td>14</td>
<td></td>
<td>45.8</td>
<td>0.80 (0.56, 1.04)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>139</td>
<td>94</td>
<td></td>
<td>100</td>
<td>0.77 (0.51, 1.04)</td>
</tr>
</tbody>
</table>

Vimalachandra DV. J Pediatr 2001
Success!!

[Image of a baby]

[Graph showing length-for-age and weight-for-age percentiles]


CDC/NCDS: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/nchs/ncds00.htm

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

THE OHIO STATE UNIVERSITY
## Patient AC: Growth and Renal Status

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Wt SDS</th>
<th>Ht (cm)</th>
<th>Ht SDS</th>
<th>Wt/Ht %tile</th>
<th>Cr (mg)</th>
<th>GFR (mL/min/1.73 m²)</th>
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<tr>
<td>Birth</td>
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<td>-1.11</td>
<td>74</td>
<td>1.9</td>
<td>11.1</td>
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<tr>
<td>0.5</td>
<td>5.4</td>
<td>-3.57</td>
<td>58.5</td>
<td>-4.26</td>
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<td>1.5</td>
<td>17.5</td>
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<tr>
<td>0.9</td>
<td>8.84</td>
<td>-1.27</td>
<td>71</td>
<td>-1.42</td>
<td>53</td>
<td>1.0</td>
<td>31.9</td>
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<tr>
<td>1.9</td>
<td>11.2</td>
<td>-0.99</td>
<td>82</td>
<td>-1.16</td>
<td>43</td>
<td>1.0</td>
<td>45</td>
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<td>GH Started</td>
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<td>12.9</td>
<td>-0.92</td>
<td>-2.06</td>
<td>60</td>
<td>1.1</td>
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<td>73</td>
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<td>16.9</td>
<td>-0.13</td>
<td>-1.09</td>
<td>79</td>
<td>1.4</td>
<td>39.5</td>
</tr>
</tbody>
</table>
Patient AC: Growth Chart 2-9 yrs

Midparental height
Q4: How is GH Used in Children with CKD?

**Not Often Enough**

**Growth Hormone Therapy**

![Graphs showing growth hormone therapy usage over time for children on dialysis.](image)
**Growth Hormone Treatment in Childhood**

**GH Evaluation**
- Determine pubertal stage
- Analyze bone age; Hip & knee X-Rays
- Hip and knee X-rays
- Baseline funduscopic exam
- Labs: Baseline chemistries; PTH; T4/TSH

**Treatment**
- Evaluation
- Insurance approval
- GH Dose: 0.35 mg/kg/wk; divided into daily SC injections
- Patient education

**GH Considerations**
- Typically administered in evening
- HD patients receive injections at bedtime or 3-4 hrs post HD
- CCPD receive injections AM after dialysis
- CAPD receive injections in evening, at overnight exchange

Adapted from Mahan JD. Ped Neph 2006
Growth Hormone Therapy in CRD:

Ongoing

Monitor growth response/safety - every 3-4 months
- Height, weight, height velocity; OFC* (until 3 years of age)
- Pubertal stage
- Nutritional intake
- Funduscopic exam
- Labs (chemistries, PTH)
- Bone age, hip and knee X-rays (every year)

Adjust GH doses as needed

Encourage compliance/measure IGF-1 levels

Consider pubertal dosing if growth response lagging during puberty
- 125-200 % of standard dose
- If limited time until epiphyseal closure
- If IGF-1 response is not large (large = > 3-4 times normal)

Adapted from Mahan JD. Ped Neph 2006
Obstacles to Growth Hormone Therapy in Children with CKD

Lack of urgency
- rhGH treatment can be delayed
- Short stature as a cosmetic issue

Evaluation and documentation
- Uncertainty - evaluation, rhGH dosing, monitoring
- Reimbursement worries – lack of appropriate support for reimbursement

Patient compliance

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of patients (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reason identified</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Family refusal</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>Severe hyperparathyroidism</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Too young</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Poor nutrition</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Neurologically impaired</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Maintaining growth curve(^a)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Overwhelmed family</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Transplantation scheduled</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Concurrent or recent malignancy</td>
<td>2 (3%)</td>
</tr>
</tbody>
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\(^a\) SD score was below −1.88, but growth velocity was normal
Algorithm for Evaluation and Treatment of Growth Retardation in Children with CKD: Overview

Short stature or declining height velocity in CKD 2-5 → Assess and treat poor growth

- **Yes**: Continue therapy
- **No**: IS GROWTH VELOCITY IMPROVED?
  - **Yes**: Start GH therapy
  - **No**: Monitor GH therapy

**GH therapy assessment**

- **No**: IS GROWTH ADEQUATE?
  - **No**: Assess and correct: Dose, metabolic status, nutrition, compliance
    - **No**: Consider consult
    - **Yes**: Continue GH therapy
  - **Yes**: IS GROWTH ADEQUATE?
    - **Yes**: Continue GH therapy
    - **No**: Discontinue GH therapy if necessary*

Adapted from Mahan JD. *Ped Neph* 2006
Patient RP: Growth Chart 2-20 yrs

DOB: 3/9/03

Mother's Stature: 160 cm
Father's Stature: 175 cm

Midparental height: 167.5 cm

3 Years/4 Months
5 Years/7 Months

5 Years/11 Months

On GH Rx
Plea: Growth is a Beautiful Thing......

And You Should Regard Your Patient’s Growth as Your Paramount Responsibility!
Q1: Why is Growth in Children with CKD so Important?
Q2: What is the Most Common Cause of Growth Failure in Children with CKD?
Q3: Why Does GH Work to Improve Growth in CKD?
Q4: How is GH Used in Children with CKD?
Take Home Points

1. Growth is one of the MOST important medical issues for children with CKD!
2. Growth is important to patients and families.
3. We are doing better in promoting growth in children with CKD – but have a long way to go to see 100% of children with CKD growing well and in normal range for height and weight.
4. The barriers to promoting growth in children with CKD are surmountable with vigilance and attention to detail.
5. Promoting growth leads to better outcomes – survival, quality of life, development and adult life satisfaction.
6. Successfully optimizing growth in children with CKD really demonstrates your value as a pediatric nephrologist!