Growth in Infants and Young Children with CKD: Are We Making Progress?

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Overview

Why is **Growth in CKD** so Important?

How are we doing in promoting growth in children with CKD?

What are the barriers to doing better promoting growth?

How can we best promote growth in this special population?

**Growth: A Paramount Concern!**
Question 1

The fact that a child with CKD4 has a weight SDS score at -1.0 and height SDS score at -3.2 indicates that the child is

A. A candidate for initiation of dialysis
B. Getting sufficient calories for height
C. In need of better treatment of metabolic acidosis
D. Likely to do better with paricalcitol than calcitriol
Question 2

In Reynolds study addressing CKD patient and parent concerns, the next most important concern for parents after future prospects for the child was

A. Appearance
B. Effect on the family
C. Growth
D. School activities
Question 3

In the U.S. more children are coming to dialysis (hemo- and peritoneal) on Growth Hormone in the recent past than more than 10 years ago

A. Yes

B. No, less

C. No, the prevalence is unchanged
Question 4

In the U.S. final adult height in children who receive a transplant in childhood is getting closer to the SDS normal value of 0.0.

A. True
B. False
C. Uncertain, since there is not good data
1. Why is Growth in CKD so Important?
Better Growth in Childhood CKD is Associated with

- Better survival [Furth 2002]
- Less morbidity (hospitalizations, infections, etc) [Furth 2002]
- Better adult height [Hoekken-Kolega, Haffner]
- Greater satisfaction with adult life [Boyer, Rosenkrantz]
- Higher physical and social functioning for the child [Al-Uzri]
- Less patient angst [Reynolds]
- Less parent worry [Reynolds]
Poor Growth in Children on Dialysis is Associated with Poorer Survival

1,112 patients < 18 yo ESRD – USRDS
Tanner Stage I to IV, ht data Jan-Dec 1990

Survival (%) vs Days

- Normal growth
- Moderate growth failure
- Severe growth failure

Furth S. Pediatr Nephrol 2002
Growth Failure in Children with CKD is Associated with Poorer Survival

- Age > 1, Z > -2.5
- Age > 1, Z < -2.5
- Age 0-1, Z > -2.5
- Age 0-1, Z < -2.5


Furth S, Pediatrics 2002
Long-Term GH Therapy Continues to Improve Growth in Children with CRI

Hokken-Koelega A. J Pediatr Endocrinol Metab 2001
Hokken-Koelega A. Pediatr Nephrol 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>
</tr>
</thead>
<tbody>
<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>

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

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

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

Impact of Growth in CKD on QOL

483 children and/or parents enrolled in multicenter CKiD study completed Pediatric Quality of Life Inventory (PedsQL, V4.0) on at least two CKiD study visits.

Participants were dichotomized into NH or SS groups.

Multivariate modeling = significant association between both catch-up growth and growth hormone use on parent reports of child physical functioning (p<.05) and social functioning (p<.05).

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

- General health
- CRF/dialysis/transplant
- Other Treatment
- Growth
- Appearance
- Coming to hospital
- School and friends
- Effect on family
- Future health
- Future prospects
- Future (general)

Percent (%)

Estimated prevalence of CKD (top) and ESRD (bottom) in children worldwide
2. How are we doing in promoting growth in children with CKD?
Growth Hormone Therapy in Children with CKD 5

**Growth Hormone Therapy**

Dialysis initiation 2006-2016

Dialysis initiation 2011-2016

- Human Growth Hormone
- PD
- HD

<table>
<thead>
<tr>
<th></th>
<th>1 Month</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2016</td>
<td>13</td>
<td>18</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>2011-2016</td>
<td>12</td>
<td>25</td>
<td>22</td>
<td>19</td>
</tr>
</tbody>
</table>

**NAPRTCS**

**Nationwide Children’s**

*When your child needs a hospital, everything matters.*
Growth Deficits Over Time

Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry

Donald J. Weaver Jr¹ · Michael J. G. Somers²³ · Karen Martz⁴ · Mark M. Mitsnepes⁵

Children with CKD

<table>
<thead>
<tr>
<th>Time Periods (years)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-2001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>2002-2011</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

Ht > -2 SD
Ht < -2 SD

= p < 0.001 vrs 1992-2001
Transplant Children – Final Adult Height

<table>
<thead>
<tr>
<th>Cohort Group</th>
<th>N</th>
<th>Median</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
<th>Median</th>
<th>Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987-1991</td>
<td>597</td>
<td>-1.81</td>
<td>-1.93</td>
<td>0.07</td>
<td>241</td>
<td>-0.51</td>
<td>-0.88</td>
<td>0.15</td>
</tr>
<tr>
<td>1992-1996</td>
<td>757</td>
<td>-1.33</td>
<td>-1.51</td>
<td>0.06</td>
<td>294</td>
<td>-0.19</td>
<td>-0.29</td>
<td>0.09</td>
</tr>
<tr>
<td>1997-2001</td>
<td>572</td>
<td>-0.96</td>
<td>-1.06</td>
<td>0.06</td>
<td>231</td>
<td>-0.22</td>
<td>-0.23</td>
<td>0.11</td>
</tr>
<tr>
<td>2002-2006</td>
<td>453</td>
<td>-0.82</td>
<td>-0.98</td>
<td>0.07</td>
<td>186</td>
<td>0.37</td>
<td>-0.35</td>
<td>0.52</td>
</tr>
<tr>
<td>2007-2013</td>
<td>190</td>
<td>-0.87</td>
<td>-0.89</td>
<td>0.10</td>
<td>87</td>
<td>0.22</td>
<td>-0.02</td>
<td>0.21</td>
</tr>
<tr>
<td>Total</td>
<td>2569</td>
<td>-1.23</td>
<td>-1.37</td>
<td>0.03</td>
<td>1039</td>
<td>-0.10</td>
<td>-0.40</td>
<td>0.11</td>
</tr>
</tbody>
</table>

NAPRTCS 2014 Annual Report
Growth in Children Post Renal Transplant Over Time

NAPRTCS 2014 Annual Report

Nationwide Children's
When your child needs a hospital, everything matters.
THE OHIO STATE UNIVERSITY
Trends in Growth in Children with CKD Over Time

Franke D. Ped Neph 2013
3. What are the barriers to doing better promoting growth?
Pro-Growth Agenda in Childhood CKD - Complicated

- Never too soon to start additional efforts to promote – do not wait for significant growth failure!
  - 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
- GH Rx to overcome GH/IGF-1 resistance state – complicated!
- Monitor, intervene for inflammation
- Uremia control – complicated!
- Anchor – Best way to achieve normal adult height and good quality of life/satisfaction = good growth!
Obstacles to Growth Hormone Therapy in Children with CKD - 2008

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 curvea</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>
</table>

^aSD score was below −1.88, but growth velocity was normal
Obstacles to Growth Hormone Therapy in Children with CKD - 2017

- Family refusal
- Medical contraindications
- Difficulties with insurance
- High likelihood of transplant
- Non-adherence
- Risks outweigh benefit

Percent of responses (%)
4. How can we best promote growth in this CKD population?
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 + growth velocity
- Normal weight for height
- Normal muscle mass/function
- Normal neuro-development

Parent/Family Engagement
Interdisciplinary Care Team
## CKD Management to Promote Growth

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient calories/protein</td>
<td>100% RDA calories/protein for ideal weight</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Alkali as needed to maintain HCO3 &gt;22</td>
</tr>
<tr>
<td>CKD-Mineral Bone Disease</td>
<td>P restriction; maintain normal 25D, Ca and P; maintain PTH in CKD appropriate range</td>
</tr>
<tr>
<td>Insufficient Na/H2O</td>
<td>Na/H2O supplements as needed</td>
</tr>
<tr>
<td>Uremic milieu</td>
<td>CKD5 – dialysis for adequacy + more</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Prevent/treat infections</td>
</tr>
<tr>
<td>Abnormal GH/IGF-1 Axis</td>
<td>GH in pharmacologic doses if needed</td>
</tr>
<tr>
<td>Sex Hormone Dysregulation</td>
<td>Typically not treated; evaluate significant delays</td>
</tr>
</tbody>
</table>
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>Maxwell 1998 Pubertal</td>
<td>4</td>
<td>3</td>
<td></td>
<td>3.4</td>
<td>0.60 (-0.81, 2.01)</td>
</tr>
<tr>
<td>Maxwell 1998 Prepubertal</td>
<td>9</td>
<td>6</td>
<td></td>
<td>6.7</td>
<td>0.90 (-0.08, 1.88)</td>
</tr>
<tr>
<td>Guest 1998</td>
<td>41</td>
<td>44</td>
<td></td>
<td>19.7</td>
<td>0.30 (-0.21, 0.81)</td>
</tr>
<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>
</tr>
<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>

Improved Growth After rhGH Treatment in Children with CKD

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

**P<0.00005 compared to placebo.

Growth is a Beautiful Thing!!!
Conclusions

1. Growth is one of the MOST important medical issues that children with CKD confront!
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 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 results in better outcomes – survival, quality of life, neuro-development and adult life satisfaction.
6. Successfully optimizing growth in children with CKD really demonstrates your value as pediatric nephrologist!