“This is Too Much Pressure!” The Use of ACE Inhibitors for Hypertension Post-Renal Transplant in the Pediatric Population

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Learning Objectives:
1. Discuss the significance, pathophysiology, and management of hypertension (HTN) post-kidney transplant in the pediatric population.
2. Review the pharmacokinetic properties of angiotensin converting enzyme (ACE) inhibitors and their potentially beneficial effects in pediatric kidney transplant recipients (KTRs).
3. Discuss potential barriers for the use of ACE-Inhibitors post-kidney transplant.
4. Review available literature regarding the use of ACE-Inhibitors for post-renal hypertensive management in pediatric patients.
I. Renal Transplant in Pediatrics

A. End Stage Renal Disease (ESRD)
   1. ESRD is defined as chronic kidney disease (CKD) stage 5 defined as a glomerular filtration rate (GFR) < 15 mL/min per 1.73 m²
   2. The estimated incidence varies throughout the world
      a. United States: 14.8 cases per million children
   3. Renal diseases responsible for CKD in children are different from those observed in adult patients.
      a. Renal disease and failure can have a negative impact on a child’s growth, bone strength and neurologic function
   4. Renal transplantation is accepted as the treatment of choice for children with ESRD, as it:
      a. Provides better quality of life
      b. Improves long-term survival than in comparison to other types of renal replacement therapies

B. Renal Transplantation
   1. Epidemiology
      a. In the United States, approximately 800 renal transplants are performed in children below 18 years of age annually.²
         i. 2018: 755 transplants were performed in patients 1-17 years of age³
   2. Etiology
      a. Congenital malformations of the kidney and urinary tract (CAKUT), including obstructive uropathy and renal aplasia, hypoplasia, or dysplasia
      b. Hereditary renal disease including polycystic kidney disease, nephrolithiasis, congenital nephrotic syndrome, and Drash syndrome
      c. Focal segmental glomerulosclerosis (FSGS)
      d. Other causes of glomerulonephritis
      e. Hemolytic uremic syndrome (HUS)
   3. Complications post-kidney transplant
      a. HTN (50-90%)
      b. Anemia (60-80%)
      c. Infection (20-30%)
      d. Malignancy (3-6%)
      e. Diabetes mellitus (1-7%)
      f. Mineral bone disorders

II. Pediatric Hypertension

A. Background⁴⁻⁵
   1. In 2017, the American Academy of Pediatrics (AAP) released the “Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents”
   2. Prevalence in the general pediatric population
      a. National Health and Nutrition Examination Survey (NHANES)⁶⁻⁷
         i. More than one in seven U.S. youth aged 12–19 years had HTN or elevated blood pressure (BP) in 2013–2016
3. BP should be:
   a. Assessed in all children/adolescents (≥ three years of age) at every health care visit, especially if they are obese, are taking medications known to increase BP, have renal disease, a history of aortic arch obstruction, congenital heart disease, or diabetes

4. Approach to BP Measurement
   a. Three modalities to measure BP:
      i. Casual BP monitoring: includes a seated patient who has rested for ≥ 5 minutes, duplicate manual readings in an upper extremity, and the appropriate cuff size
      ii. 24-hour ambulatory monitoring (ABPM): includes a device that is programmed to record BP every 20-30 minutes during waking hours and every 30-60 minutes during sleep hours
      iii. Home BP monitoring: more accurate and predictive of target-organ damage than casual BP in children and adolescents

b. The initial BP measurement may be
   i. Oscillometric: performed using an automated BP device that analyzes pulse waves collected from the cuff during constricted blood flow
   ii. Auscultatory: performed manually and allows for the audible detection of Korotkoff sounds that occur during constricted blood flow

c. The 2017 Updated AAP Guidelines include a new simplified table for initial BP screening based on the 90th percentile BP for age and sex for children at the 5th percentile of height (see Appendix A)
   i. Designed as a screening tool for the identification of children and adolescents who need further evaluation of their BP

d. If the initial BP is elevated using the simplified table, providers should perform two additional BP measurements at the same visit and average them to classify BP (See Appendix B)

e. Classification of BP can be performed once a confirmation of HTN has been determined

<table>
<thead>
<tr>
<th>Table 1. Classification of Blood Pressure in children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children Aged 1 to less than 13 years</strong></td>
</tr>
<tr>
<td>Normal BP: &lt; 90th percentile</td>
</tr>
<tr>
<td>Elevated BP: ≥ 90th percentile to &lt; 95th percentile or 120/80 mmHg to &lt;95th percentile (whichever is lower)</td>
</tr>
<tr>
<td>Stage I HTN: ≥95th percentile to &lt; 95th percentile + 12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower)</td>
</tr>
<tr>
<td>Stage II HTN: ≥95th percentile + 12 mmHg, or ≥ 140/90 mmHg (whichever is lower)</td>
</tr>
</tbody>
</table>

II. Post-Transplant Hypertension in Pediatrics

A. Background
   1. Poorly controlled blood pressure is common among kidney transplant recipients (KTRs); only 20-50% of treated children reach normal BP
   2. Prevalence of HTN in children after renal transplant ranges from 50-90% during the first month following transplantation; incidence decreases over time
Table 2. Prevalence of HTN in children after renal transplant

<table>
<thead>
<tr>
<th>Prevalence of HTN</th>
<th>Study size</th>
<th>BP Method</th>
<th>Definition of HTN</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>59%</td>
<td>277</td>
<td>Casual BP</td>
<td>Use of antihypertensive drugs regardless of BP</td>
<td>Baluarte et al. 17</td>
</tr>
<tr>
<td>58%</td>
<td>2774</td>
<td>Casual BP</td>
<td>Use of antihypertensive drugs regardless of BP</td>
<td>Sorof et al. 18</td>
</tr>
<tr>
<td>70%</td>
<td>27</td>
<td>ABPM</td>
<td>BP &gt;95th centile for clinic BP or use of drugs</td>
<td>Lingens et al. 19</td>
</tr>
<tr>
<td>62%</td>
<td>37</td>
<td>ABPM</td>
<td>BP &gt;95th centile</td>
<td>Giordano et al. 20</td>
</tr>
<tr>
<td>83%</td>
<td>42</td>
<td>ABPM</td>
<td>BP load &gt; 25% (95th centile for clinic BP)</td>
<td>Sorof et al. 21</td>
</tr>
<tr>
<td>62%</td>
<td>45</td>
<td>ABPM</td>
<td>BP &gt; 95th centile for BP load &gt;30%</td>
<td>Morgan et al. 22</td>
</tr>
<tr>
<td>73%</td>
<td>26</td>
<td>ABPM</td>
<td>BP &gt;95th centile for ABPM and BP load &gt; 30%</td>
<td>Serdarogl et al. 23</td>
</tr>
<tr>
<td>89%</td>
<td>36</td>
<td>ABPM</td>
<td>BP &gt;95th centile for ABPM or use of drugs</td>
<td>Seeman et al. 24</td>
</tr>
</tbody>
</table>

B. Etiology
1. Pre-transplant factors
   a. Pre-existing HTN and left ventricular hypertrophy (LVH)
   b. Body mass index
2. Donor related
   a. Living or deceased donor
   b. Hypertensive donor
3. Transplantation related
   a. Prolonged ischemia time
   b. Delayed graft function
4. Presence of native kidneys causes unregulated renin release through the activation of the renin-angiotensin system (RAS) 25
   a. ↑ Salt and water retention
   b. ↑ Extracellular volume and cardiac output
   c. ↑ Peripheral vascular resistance
5. Renal-graft artery stenosis
6. Renal transplant dysfunction
   a. Chronic allograft nephropathy (CAN)
7. Immunosuppressive medications

C. Hypertensive Effects of Immunosuppressive medications:

<table>
<thead>
<tr>
<th>Immunosuppressive Agent</th>
<th>Pathogenic Mechanism</th>
<th>Special Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>↑ Sodium retention&lt;br&gt;↑ Fluid retention&lt;br&gt;↑ Responsiveness to vasoconstriction</td>
<td>Dose-dependent effect</td>
</tr>
<tr>
<td>Cyclosporine (CsA)</td>
<td>↓ Inducible nitric oxide levels and prostacyclin&lt;br&gt;↑ Systemic vascular resistance&lt;br&gt;↑ Endothelin and prostaglandins</td>
<td>CsA &gt; TAC</td>
</tr>
<tr>
<td>Tacrolimus (TAC)</td>
<td>↓ Inducible nitric oxide levels and prostacyclin&lt;br&gt;↑ Systemic vascular resistance&lt;br&gt;↑ Endothelin and prostaglandins</td>
<td>CsA &gt; TAC</td>
</tr>
</tbody>
</table>
1. Calcineurin Inhibitors (CNIs)
   a. Evidence of hypertensive effects of TAC and CsA after renal transplantation with greater effects seen with cyclosporine \(^{26,27}\)
   b. Proposed mechanism of HTN
      i. Impaired vasodilation, systemic and renal vasoconstriction, and sodium and fluid retention
2. Steroids
   a. Steroid minimization can reduce the risk of post-transplant HTN
   b. Cause sodium retention resulting in dose-related fluid retention

D. Complications of HTN Post-Renal Transplant
1. Allograft Failure
   a. Defined as an acute deterioration in allograft function associated with specific pathologic changes in the graft
   b. Opetz, et al.: retrospective cohort of 1,666 kidney transplant recipients
      a. For every 10 mmHg increase of systolic blood pressure (SBP), there was ~5% increased risk of graft failure and death \(^{28}\)
      b. Figure 1 shows the association of SBP at one year with subsequent graft survival in recipients of deceased donor kidney transplants

![Figure 1. Association of HTN at 1 year with transplant survival \(^{28}\)](image)

2. Left Ventricular Hypertrophy (LVH)
   a. Defined as the enlargement and thickening of the walls of the heart’s left ventricle – An adaptive response to volume and pressure overload
   b. Pediatric KTRs have a 10-to 15-fold increased risk of cardiovascular death compared with the general population due to LVH \(^{29}\)

3. Morbidity and Mortality
   a. Each 10-mmHg increment of SBP>140 mmHg is associated with a hazard ratio of death of 1.18 (95% CI, 1.12 to 1.23 \(^{30}\))
E. Pathophysiology
1. A complex interplay exists resulting from decreased GFR, vasoconstriction, and sodium retention that are then adversely affected by immunosuppressive agents

![Figure 2. Mechanisms by which HTN after kidney transplant is mediated](image)

F. Management
1. The management of HTN in the pediatric transplant patient can be challenging
   a. Rates of control of HTN in renal transplant patients generally range from 33-55%\(^\text{10}\)
   b. Children who achieve normotension have increased and prolonged graft function
2. Goals of therapy
   a. Prolong graft survival and minimize cardiovascular risk
3. Non-pharmacologic management
   a. Lifestyle modifications should be considered as the first line approach\(^\text{10}\)
      i. Dietary Approaches to Stop Hypertension (DASH) diet
      ii. Mild to moderate physical activity 3-5 days per week
4. Pharmacologic management
      i. Section 11.3 HTN and the Posttransplant Patient\(^4\)
      ii. Limited evidence that ACE inhibitors and ARBs may be superior to other agents in achieving BP control
      iii. Do not recommend the use of ACE inhibitors or angiotensin receptor blockers (ARBs) as first line in renal transplant
      iv. No step-wise treatment approach for HTN medication management in pediatrics
   b. 2012 Kidney Disease Improving Global Outcomes (KDIGO) “Clinical Practice Guideline for the Care of Kidney Transplant Recipients”\(^31\)
      i. No antihypertensive agent is contraindicated in kidney transplant recipients
      ii. Choose a BP-lowering agent after taking into account the time after transplantation, use of CNIs, presence or absence of persistent albuminuria, and other co-morbid conditions
      iii. No step-wise treatment approach for HTN medication management in pediatrics
c. Dihydropyridine calcium channel blockers (DHP-CCBs)\textsuperscript{32,33}
   i. Most studied and routinely recommended as first line therapy
   ii. Most effective antihypertensive class post-transplant
   iii. Mitigate nephrotoxicity by counteracting the afferent arteriolar
        vasoconstriction caused by CNIs ultimately reducing nephrotoxicity
   iv. Side effect profile is not as significant as other anti-hypertensive agents

<table>
<thead>
<tr>
<th>Table 4. Classes of Antihypertensive medications used after transplant in pediatrics \textsuperscript{31,31}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Interactions with Immunotherapy</strong></td>
</tr>
<tr>
<td>Dihydropyridine CCBs</td>
</tr>
<tr>
<td>Non-dihydropyridine CCB</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>ARBs</td>
</tr>
<tr>
<td>Beta-blockers</td>
</tr>
</tbody>
</table>

* CCB: calcium channel blocker, ARB: angiotensin II receptor blockers, MI: myocardial infarction

III. ACE Inhibitors in Pediatric Kidney Transplant Recipients

A. Use of ACE inhibitors/ARBS for treatment of HTN and for slowing the progression of chronic kidney disease has been well defined in the non-transplant pediatric population

1. The role of ACE inhibitors in the pediatric transplant patient is incompletely defined

<table>
<thead>
<tr>
<th>Table 5. Agents and Pediatric Doses</th>
</tr>
</thead>
</table>
| **Benazepril** (Lotensin\textsuperscript{a}) | **Children \(\geq 6\) years and adolescents:**
   Initial: 0.2 mg/kg/dose once daily (max dose: 10 mg/day)
   Maintenance: 0.1-0.6 mg/kg/dose once daily (max: 40 mg/day) |
| **Captopril** (Capoten\textsuperscript{a}) | **Infants:** 0.05 mg/kg/dose Q6-24 hours (max: 6 mg/kg/day)
   **Children and adolescents:** 0.3-0.5 mg/kg/dose Q8 hours (max: 6 mg/kg/day) |
| **Enalapril** (Epaned\textsuperscript{a}) | **Infants, children, and adolescents:** 0.08 mg/kg/dose (max: 5 mg) |
| **Fosinopril** (Monopril\textsuperscript{a}) | **Children \(\geq 6\) years and adolescents:**
   \(\leq 50\) kg: Initial: 0.1 mg/kg/ dose once daily (max: 0.6 mg/kg/day)
   \(> 50\) kg: Initial: 5 mg once daily (max: 40 mg/day) |
| **Lisinopril** (Prinivil\textsuperscript{a}, Zestril\textsuperscript{a}) | **Children < 6 years:** Limited data available; Initial: 0.07 mg/kg/dose once daily (max: 0.6 mg/kg/day or 40 mg/day)
   **Children \(\geq 6\) years and adolescents:**
   Initial: 0.07 mg/kg/dose once daily (max: 0.6 mg/kg/day or 40 mg/day) |
| **Quinapril** (Accupril\textsuperscript{a}) | **Children and adolescents:** Limited data available; Initial: 5 mg once daily (max: 80 mg/daily) |
| **Ramipril** (Altace\textsuperscript{a}) | Not specified in the pediatric population |
B. Proposed mechanism for benefit post-transplant:
   1. Vasodilation: dilate arteries and veins by blocking angiotensin II formation and inhibiting bradykinin metabolism
   2. Regulation: down regulate sympathetic adrenergic activity and reuptake of norepinephrine
   3. Promote renal excretion of sodium and water
   4. Inhibition of cardiac and vascular remodeling

C. Assessment of potential risks:
   1. GFR
      a. May cause or exacerbate a decrease in GFR which may mask or mimic early signs of acute transplant rejection
   2. Hyperkalemia
      a. May exacerbate the frequency and severity of this electrolyte abnormality especially when given concomitantly with CNIs; can be life-threatening
      b. CNIs tend to raise the plasma potassium concentration, primarily by decreasing urinary potassium excretion
   3. Anemia
      a. Causes the inhibition of erythropoiesis
      b. Can decrease the hematocrit by as much as 5-10%

D. There are some populations who may benefit from an ACE inhibitor post-transplant:
   1. Evidence of proteinuria
   2. Presence of chronic kidney disease (CKD)
   3. Presence of congestive heart failure (CHF)
   4. High risk for coronary artery disease (CAD)

IV. Clinical Question and Overview of Literature

Clinical Question: Can ACE inhibitors be used as first line pharmacologic therapy, in pediatrics, for the treatment of HTN post-renal transplant?


Figure 3. Overview of Literature
V. Literature Review


<table>
<thead>
<tr>
<th>Objective</th>
<th>To evaluate the pharmacokinetics (PK), safety/tolerability profile, and impact on BP of lisinopril in children and adolescents with HTN after kidney transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
</tbody>
</table>
### Results

#### Baseline Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LD: 0.1 mg/kg (n=12)</th>
<th>MD: 0.2 mg/kg (n=8)</th>
<th>HD: 0.4 mg/kg (n=2)</th>
<th>All (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs.)</strong></td>
<td>14.9 ± 2.3</td>
<td>13 ± 3</td>
<td>9.5 ± 3.5</td>
<td>13.8 ± 3.0</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>56.8 ± 19.4</td>
<td>50.2 ± 28.7</td>
<td>23.1 ± 3</td>
<td>51.3 ± 23.8</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>4 (42%)</td>
<td>2 (25%)</td>
<td>1 (50%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7 (58%)</td>
<td>2 (25%)</td>
<td>2 (100%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (25%)</td>
<td>4 (50%)</td>
<td>0</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>Am. Indian or Alaska Native</td>
<td>0</td>
<td>1 (13%)</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>2 (17%)</td>
<td>2 (25%)</td>
<td>0</td>
<td>4 (18%)</td>
</tr>
<tr>
<td><strong>eGFR -baseline (ml/min/1.73m²)</strong></td>
<td>72.5 ± 25.7 (29.6, 111.2)</td>
<td>62 ± 16.7 (29.2, 79.8)</td>
<td>89.3 ± 44.4 (57.8, 120.6)</td>
<td>70.2 ± 24.4</td>
</tr>
<tr>
<td><strong>eGFR at PK visit (ml/min/1.73m²)</strong></td>
<td>73.1 ± 30.7 (36.7, 139.0)</td>
<td>63.2 ± 18.4 (30.3, 86.0)</td>
<td>100.2 ± 56.6 (60, 140.2)</td>
<td>72 ± 29.4</td>
</tr>
</tbody>
</table>

*LD: low dose, MD: middle dose, HD: high dose

- There was a trend to a shorter time since transplant in the lisinopril-naïve vs. lisinopril SoC patients (3.1 ± 3 years vs. 6.1 ± 4.7 years; p=0.08)
- Concomitant antihypertensive medications: amlodipine (n=15), atenolol (n=2), clonidine (n=2), isradipine (n=2), and carvedilol (n=1)
- Concomitant immunosuppressive medications: mycophenolate (n=19), prednisone (n=18), tacrolimus (n=16), sirolimus (n=7), and azathioprine (n=1)

#### Outcomes

**Pharmacokinetics:**
- Lisinopril PK exhibited dose proportionality with AUC₂₄ 2-fold higher in the 0.2 mg/kg dose group compared with the 0.1 mg/kg dose group (p < 0.001)
- Oral clearance:
  - Similar between the 0.1 mg/kg and 0.2 mg/kg dose groups (p= 0.84)
  - Clearance was affected by renal function: 11.9 (95% CI 8.4, 7.0) L/h/70 kg in the low GFR group vs 24 (95% CI 19.4, 29.5) L/h/70 kg in the high GFR group (p< 0.001)

**BP:**

- **Systolic**
  - 0.1 mg/kg (n=6): 121.2 ± 3.9, 115.3 ± 7.6, -5.8 (-13.9, 2.2)
  - 0.2 mg/kg (n=5): 129.6 ± 6.7, 117.6 ± 6.5, -12 (-19.6, -4.4)
  - 0.4 mg/kg (n=2): 124.5 ± 9.2, 113.5 ± 6.4, -11 N/A

- **Diastolic**
  - 0.1 mg/kg (n=6): 75.7 ± 12.8, 69.2 ± 6.6, -6.5 (-21, 8)
  - 0.2 mg/kg (n=5): 73.8 ± 7.5, 68.2 ± 11.8, -5.6 (-15, 3.8)
  - 0.4 mg/kg (n=2): 76.5 ± 16.3, 69.5 ± 14.8, -7 N/A

*Data are mean ± SD. BP: blood pressure; CI: confidence interval

- 5/9 (56%) achieved a systolic BP < 90th percentile and 3/5 (60%) also achieved a diastolic BP < 90th percentile at the lisinopril Cmin time point

**Safety:**

- Adverse event (AE) rates by dose group: 2/6 in 0.1 mg/kg/day, 2/6 in 0.2 mg/kg/day, and 2/3 in 0.4 mg/kg/day (AE reported: dizziness, nausea, stomach ache, and eGFR decline)
- The median change from baseline in eGFR and serum potassium was -2 ml/min per 1.73m² and 0.1 mEq/L in lisinopril-naïve patients

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*Chambers 10*
Discussion

Authors' Conclusions
• The PK of lisinopril in patients with a kidney transplant was comparable to children who did not have a kidney transplant and who were given the drug for HTN management
• GFR was the major determinant of drug clearance and concomitant administration of immunosuppressive agents did not appear to affect lisinopril clearance
• More than 75% of patients had a reduction of ≥ 6 mmHg in systolic and/or diastolic pressure on lisinopril after kidney transplant, which proves its benefit in reduction of BP in this population

Reviewer's Interpretation

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Comprehensive PK evaluation</td>
<td>• Only evaluated one drug in the ACE inhibitor class</td>
</tr>
<tr>
<td>• Assessment of kidney function</td>
<td>• Concomitant anti-hypertensive medication use</td>
</tr>
<tr>
<td>• Corrected for the impact of potential covariates</td>
<td>• Short study duration</td>
</tr>
</tbody>
</table>

• Promising pharmacokinetic and safety data but small population limits the utility of this data
• Lisinopril may be effective at reducing HTN post-renal transplant and exhibits similar clearance when compared to the non-transplant population

Table 7. Antihypertensive Pharmacotherapy and Long-Term Outcomes in Pediatric Kidney Transplantation (Suszynski, et al, 2013) 35

Objective
To assess the impact of HTN and antihypertensive pharmacotherapy on patient survival (PS), graft survival (GS), and death censored graft survival (DCGS) in pediatric kidney transplant recipients with graft function

Methods

Trial Design
Retrospective, single-center chart review at the University of Minnesota

Participants and Settings
• Inclusion criteria: pediatric (≤ 18 years old) transplant recipients with GS for ≥ 5 years
• Of these recipients: deceased donor (DD) → 51; living donor (LD) → 242
• No recipients with ≥ 5 years GS were excluded

Intervention
• All donor and recipient data were retrospectively reviewed (February 1984 to August 2005) using an Institutional Review Board-approved database at the University of Minnesota
• HTN was defined as use of antihypertensive(s) at the 5-year post kidney transplant point
• Antihypertensives were prescribed by the attending nephrologist based on standard pediatric definitions of HTN
• Mediations were stratified by class and included the following classes: alpha-1 antagonists, alpha-2 agonists, ACEIs, ARBs, beta-blockers, CCBs, and direct vasodilators
• GFR was calculated using the modified Schwartz formula
• Immunosuppressive protocol: each KTR received quadruple therapy, which included: ATGAM 15 mg/kg x 14 doses or thymoglobin 1.5 mg/kg x 6-4 doses, prednisone, azathioprine or mycophenolate mofetil, and cyclosporine
• Rejection protocol: recipients with ≥ 25% increase in serum creatinine level from baseline underwent percutaneous allograft biopsy

Outcomes
• PS, GS, or DCGS
• Improved GS with angiotensin blockade with use of ACEIs

Statistical Methods
• Categorical variables: Chi-square test and Fisher’s exact test
• Continuous variables: two-sided student’s t-test
• PS, GS, and DCGS rates were calculated using Kaplan-Meier analyses
• Statistical significance corresponded to p-values < 0.05 using a 95% confidence interval
• Logistic regression analysis: pre- and post- kidney transplant factors for possible associations with antihypertensive medication use at 5 years post-transplant
• Cox proportional hazards modeling: pre- and post-kidney transplant factors for possible associations with GS at 5 years post-kidney transplant
### Results

#### Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>Without HTN (N=160)</th>
<th>With HTN (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>86 (53.8%)</td>
<td>39 (29.3%)</td>
</tr>
<tr>
<td>5-11 years</td>
<td>36 (22.5%)</td>
<td>39 (29.3%)</td>
</tr>
<tr>
<td>11-18 years</td>
<td>38 (23.7%)</td>
<td>55 (41.4%)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54 (33.7%)</td>
<td>42 (31.6%)</td>
</tr>
<tr>
<td>Male</td>
<td>106 (66.3%)</td>
<td>91 (68.4%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>153 (95.6%)</td>
<td>126 (94.7%)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>7 (4.4%)</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td><strong>Pre-transplant HTN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>138 (86.3%)</td>
<td>72 (54.1%)</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (13.7%)</td>
<td>61 (45.9%)</td>
</tr>
<tr>
<td><strong>Donor type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>28 (17.5%)</td>
<td>23 (17.3%)</td>
</tr>
<tr>
<td>Living</td>
<td>132 (82.5%)</td>
<td>110 (82.7%)</td>
</tr>
</tbody>
</table>

#### Outcomes

**Patient survival:**
- Did not differ between cohorts \(p=0.8\)

**Graft survival:**
- Without HTN: 10, 15, and 20-year was 86%, 68%, and 53%
- With HTN: 10, 15, and 20-year was 78%, 53%, and 33%
- LD: graft survival was higher in those without HTN \(p=0.002\)
- DD: no difference in graft survival between the cohorts \(p=0.9\)
- There was a difference between those treated with 0 versus 1 antihypertensive agent \(p=0.003\) and 1 versus ≥ 2 antihypertensive agents \(p=0.002\)

**ACEI use:**
- LD:
  - GS was significantly higher for recipients using an ACEI versus those using another antihypertensive \(p=0.04\)
  - HTN treated with no ACEI was also a significant risk factor for graft failure at > 5 years post kidney transplant \(p=0.02\) but HTN treated with an ACEI was not \(p=0.7\)
  - ACEI/ARB use did not significantly impact PS \(p=0.7\)
- ACEI/ARB use significantly impacted GS \(p=0.03\)
- No difference in PS or GS when comparing the use of a CCB versus another antihypertensive agent \(p=0.7; p=0.7\)
- DD: Numbers were too low to assess for effects of any particular drug class

### Discussion

**Author’s Conclusion**
- There is an association between antihypertensive medication use at 5 years post-kidney transplant and increased long term GS
- Pediatric recipients are more likely to require antihypertensive pharmacotherapy at 5 years post-kidney transplant if they were older, had an older donor, had an acquired cause of end-stage renal disease, had pre-transplant HTN, and were transplanted in a more recent era
- The use of an ACEI exhibited a positive association with post-kidney transplant GS and DCGS which may be due to renoprotection via angiotensin blockade
### Reviewer’s Interpretation

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Long pediatric recipient follow-up (&gt;20 years)</td>
<td>• Analysis was not based on actual BP measurements and only on use of antihypertensive medications at a single point in time</td>
</tr>
<tr>
<td>• Adjusted for multiple confounders normally related to complications after kidney transplant</td>
<td>• Absence of racial diversity</td>
</tr>
<tr>
<td></td>
<td>• Presence of proteinuria undetermined</td>
</tr>
</tbody>
</table>

• Future studies are needed to prospectively examine the impact of BP control and the use of ACE inhibitors on GS in children after kidney transplant
• ACE inhibitors provide some type of benefit for long term GS and can be considered in certain populations


<table>
<thead>
<tr>
<th>Objective</th>
<th>To report on the efficacy and safety of ACE-I in children with refractory HTN and/or chronic graft dysfunction after renal transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Trial Design</td>
<td>Retrospective, single-center chart review at the Vienna General Hospital, University of Vienna</td>
</tr>
<tr>
<td>Participants and Settings</td>
<td>• Inclusion and exclusion criteria not reported</td>
</tr>
<tr>
<td></td>
<td>• The records of all children undergoing renal transplantation between January 1989 and December 1998 were reported</td>
</tr>
<tr>
<td>Intervention</td>
<td>• Data of patients in whom ACE-I were started within the first 6 months after transplantation (ACE-I group) were compared to data of children who were not treated with ACE-I during the observation period (non-ACE-I group)</td>
</tr>
<tr>
<td></td>
<td>• Data were collected in both groups immediately before or at the time of discharge from hospital and at months 6, 12 and 24 after transplantation.</td>
</tr>
<tr>
<td></td>
<td>• To analyze a renoprotective effect of ACE-I: a subgroup of chronic allograft dysfunction (CAD) was clinically defined according to the following criteria:</td>
</tr>
<tr>
<td></td>
<td>▪ Abnormal graft function: measured using the Schwartz formula</td>
</tr>
<tr>
<td></td>
<td>▪ Consistently decreasing graft function (negative slope of &gt;3 estimations of CrCl by the Schwartz formula for at least three months before the start of an ACE-I</td>
</tr>
<tr>
<td></td>
<td>• Antihypertensive treatment:</td>
</tr>
<tr>
<td></td>
<td>▪ Standard protocol was to start with a CCB (nifedipine or nitrendipine). If BP was not adequately controlled, a beta-blocker (propranolol, metoprolol) or furosemide was added. ACE-I were added when BP was refractory to this medication</td>
</tr>
<tr>
<td></td>
<td>▪ Captopril was started at 0.15 mg/kg/day on the day before the next clinic visit</td>
</tr>
<tr>
<td></td>
<td>▪ If the creatinine remained stable, the dose was slowly elevated until BP was controlled or a dose of 2 mg/kg/day was reached.</td>
</tr>
<tr>
<td></td>
<td>▪ In stable children, captopril was frequently switched to enalapril at an equivalent dose</td>
</tr>
<tr>
<td>Outcomes</td>
<td>• Changes in BP</td>
</tr>
<tr>
<td></td>
<td>• Number of antihypertensive drugs</td>
</tr>
<tr>
<td></td>
<td>• Serum creatinine derived clearance (Schwartz formula)</td>
</tr>
<tr>
<td></td>
<td>• Proteinuria</td>
</tr>
<tr>
<td>Statistical Methods</td>
<td>• Non-parametric tests were performed for statistical comparison between the groups and influence of treatment on the time course of continuous variables</td>
</tr>
<tr>
<td></td>
<td>• Qualitative variables: Fisher’s exact test</td>
</tr>
</tbody>
</table>
Results

Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>ACEI (n=19)</th>
<th>Non-ACEI (n=26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12 (3.5-19)</td>
<td>10 (1.5-15.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/11</td>
<td>11/15</td>
<td>n.s.</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired renal disease</td>
<td>4</td>
<td>4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Congenital renal disease</td>
<td>6</td>
<td>11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Congenital urologic disease</td>
<td>9</td>
<td>11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/HD/PD</td>
<td>5/7/7</td>
<td>5/9/12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>8.3 (3.5-37)</td>
<td>5 (0.5-23)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Re-transplants (2/&gt;2)</td>
<td>5/1</td>
<td>3/1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Type of transplant (LD/DD)</td>
<td>3/16</td>
<td>4/22</td>
<td>n.s.</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual/triple/quadruple</td>
<td>0/17/2</td>
<td>3/19/4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Acute rejection episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>14</td>
<td>8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Number of patients</td>
<td>8</td>
<td>7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number per patient</td>
<td>1.75</td>
<td>1.14</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Outcomes

- No significant differences between the two groups
- ACE-I treatment (captopril dose: median 0.6, range 0.2–4.9 mg/kg; enalapril dose: median 0.15, range 0.04–0.6 mg/kg): BP rapidly decreased to normal values in 94% within 6 months and in 100% within 12 months after initiation (p<0.05)
- After 24 months, BP control was no longer statistically different between the two groups (ACEI group versus No-ACEI group)
- CrCl and proteinuria: differences between and within groups never reached statistical significance
- No difference in the use of any other antihypertensive or immunosuppressive drugs than ACE inhibitors
- Renoprotective effects of ACE-I: in the subgroup of eight children with clinical CAD, graft function stabilized in all children and four of them experienced an improved creatinine clearance after start of ACE-I (p<0.01)
- Side effects:
  - Serum potassium: no significant changes before the start of ACE-I (median 4.6 mmol/l) and the control 2–4 weeks later (median 4.52 mmol/l)
  - Proteinuria: data inconclusive
  - No patient developed hyperkalemia
  - Hemoglobin remained stable at a median of 11.3 g/dl
  - Cough or angioedema: not reported

Discussion

Author's Conclusions

- ACE-I should be considered as an effective and safe therapy in children after renal transplantation with refractory HTN and/or accelerated decline of graft function
- Allograft function and proteinuria demonstrated a similar course in children treated with or without ACE-I during a 2-year observation period after renal transplantation

Reviewer's Interpretation

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong patient follow-up period</td>
<td>No report on the definition of HTN and the criteria for starting antihypertensives</td>
</tr>
<tr>
<td>Adjusted for multiple confounders normally related to complications after kidney transplant</td>
<td>Assessment of kidney function</td>
</tr>
<tr>
<td>ACE inhibitors provide some type of benefit for long term GS and can be considered in certain populations</td>
<td></td>
</tr>
</tbody>
</table>
VI. Conclusions and Recommendations

A. Summary
a. Potential effects of HTN post-transplant include allograft failure, LVH, and mortality.
b. Lifestyle modifications are the first line treatment approach but are often not enough to adequately control BP.
c. There is no consensus between transplant and pediatric guidelines for how to properly manage HTN post-transplant.
d. There are several solid organ transplant factors that must be taken into consideration when choosing an antihypertensive agent.

B. Recommendations
a. ACE inhibitors should be considered as first line if the patient has concomitant proteinuria, an underlying cardiac condition, or higher baseline kidney function
b. First line: DHP CCBs
   i. Well tolerated and most evidence
   ii. Proven to reduce mean arterial pressure and total renal vascular resistance
   iii. Proven to reduce CsA toxicity and combat the vasoconstrictive effect of CNIs

c. Data evaluating ACE inhibitor use for HTN after transplant is lacking, but practitioners must create a consensus on how to address pharmacologic treatment options
   i. More data is needed to determine which ACE inhibitor is most effective
   ii. Medication formulations (suspensions, tablet/capsule size) must be taken into consideration for children

C. Future Directions
a. Randomized controlled clinical trials are needed to determine the effects of ACE inhibitors on patient survival and graft survival
b. More antihypertensive medication class comparator studies in pediatrics need to be performed to help standardize HTN treatment after kidney transplant

VII. References

VII. Appendices

Appendix A 4-5

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
</tr>
<tr>
<td></td>
<td>Systolic</td>
</tr>
<tr>
<td>1</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
</tr>
<tr>
<td>4</td>
<td>102</td>
</tr>
<tr>
<td>5</td>
<td>103</td>
</tr>
<tr>
<td>6</td>
<td>105</td>
</tr>
<tr>
<td>7</td>
<td>106</td>
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<tr>
<td>8</td>
<td>107</td>
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<tr>
<td>10</td>
<td>108</td>
</tr>
<tr>
<td>11</td>
<td>110</td>
</tr>
<tr>
<td>12</td>
<td>113</td>
</tr>
<tr>
<td>≥ 13</td>
<td>120</td>
</tr>
</tbody>
</table>

Appendix B 4

1. Creatinine-based Modified “Bedside Schwartz” Equation:
   a. \[ \text{eGFR (mL/min/1.73 m}^2 = 0.413 \times (\text{height/SCr}) \]
   b. The formula was updated in 2009 and is currently considered the best method for estimating GFR in children

2. Original Schwartz Equation:
   a. \[ \text{eGFR (mL/min/1.73 m}^2 = k + \text{L/Scr} \]
   b. L: height in centimeters; k: 0.45 (0 mos.-1 year of age), 0.55 (children and adolescent girls), 0.7 (adolescent boys)
Appendix C

Seat child correctly and measure BP by auscultation or by using oscillometric device

Is percentile ≥ 90th?

Remeasure BP twice and then average these two

Is average ≥ 90th percentile?

Yes

Was repeat ausculatory?

No

Remeasure BP by using ausculatory technique; average these two

Is average ≥ 90th percentile?

Yes

Classify BP

No

Normal BP

Figure 4. Modified BP Measurement Algorithm