Blood pressure control in children following kidney transplantation in the UK

Manish Sinha
Evelina Children’s Hospital
London

UKRR and NHS Kidney Care Audit meeting
9th October 2012
Background (1)

- Hypertension in renal transplant (TX) recipients is associated with transplant dysfunction, accelerated graft failure, left ventricular hypertrophy and increased future cardiovascular morbidity and mortality
  - Data in children is limited
Hypertension following kidney transplantation is multifactorial and related to

i. Donor status

ii. Pre-transplant recipient status – previous hypertension, pre-TX dialysis status and modality, genetics, primary hypertension

iii. Factors that develop following TX – IFTA, transplant renal artery stenosis, adverse effects of immunosuppressants, BMI, pyelonephritis
Paediatric RR report in 2003

- UK paediatric TX population in 2003
- Observed that the management of hypertension in children appeared to be ‘sub-optimal’
BAPN blood pressure audit: objectives

• To describe the distribution of systolic and diastolic BP and the prevalence of systolic and/or diastolic hypertension in children over first 5-years following TX
  – Nationally and at individual centres in the UK

• To evaluate risk factors associated with systolic and/or diastolic hypertension in this cohort

• To assess if there are ‘centre-specific’ factors leading to any differences between centres
Methods (1)

• Development of audit proposal, objectives, data collection and analysis procedures

• Travel to individual units and hand searching of case-notes (13 in total: 10 in England, 1 each in Scotland, Wales and Northern Ireland)

• Centre-specific audit committee approval and authorizations
Methods (2) – inclusion and exclusion criteria

• Included (i) all aged <18 years receiving a kidney-only TX and (ii) receiving follow-up in a paediatric nephrology centre at the time of collecting data

• Excluded: (i) <6m post-TX (ii) if no clinic BP measurements were available

• Blood pressure measured using different devices at centres
  – 9 oscillometric; 2 doppler detection (systolic only) and one aneroid
Methods (3)

- Pre-defined time points at pre-TX, 6-monthly until 5y
- In addition to baseline demographics, allograft source, dialysis duration and type and past hypertension
- At each point data collected and analysed as
  - Systolic and diastolic blood pressure \( \rightarrow \) z-scores
  - Height, weight and BMI \( \rightarrow \) z-scores
  - Haemoglobin and eGFR
  - Treatment with anti-hypertensive medications (yes/no)
  - Immunosuppressive drug therapy
Problem with regard to “normal” range

A fixed normal range cannot apply across all body sizes
Methods (4)

• Hypertension defined as systolic and/or diastolic BP greater than the 95\textsuperscript{th} percentile i.e. >1.645 z-score as per the ‘Fourth Report’

• Non-hypertensive:
  – Pre-hypertension: 90\textsuperscript{th}-95\textsuperscript{th} percentile (1.28-1.645 z-score)
  – Normal with BP <90\textsuperscript{th} percentile (<1.28 z-score)

• If systolic and diastolic BP levels belonged to different categories, the higher of the two level were used for categorization
Methods (5) – analysis of prevalence of hypertension

• Prevalence of systolic and/or diastolic hypertension

1. Defined as the proportion of patients with systolic and/or diastolic BP >95\textsuperscript{th} percentile +/- anti-hypertensive use

2. Defined by use of anti-hypertensive medication alone

3. Centre-specific prevalence
Systemic arterial hypertension in children following renal transplantation: prevalence and risk factors

Manish D. Sinha\textsuperscript{1}, Larissa Kerecuk\textsuperscript{2}, Julie Gilg\textsuperscript{3}, Christopher J.D. Reid\textsuperscript{1} and on behalf of the British Association for Paediatric Nephrology

\textsuperscript{1}Department of Paediatric Nephrology, Evelina Children’s Hospital, Guys & St Thomas NHS Foundation Trust, London, UK, \textsuperscript{2}Department of Paediatric Nephrology, Birmingham Children’s Hospital, Birmingham, UK and \textsuperscript{3}UK Renal Registry, Southmead Hospital, Bristol, UK.

Correspondence and offprint requests to: Manish D. Sinha; E-mail: manish.sinha@gstt.nhs.uk
Results (1)

- We reviewed case notes from 12 UK centres including 524, 505, 430 and 231 TX patients at 6m, 1, 2 and 5-years post-TX
- 484 (92%) with first TX, 7.2% with second TX
- 73% transplanted since year 2000
- Caucasian: Asian: Black 83.3%: 14.7%: 2%
### Table 1.
Demographics of patients with and without hypertension at 6 months following transplantation

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Hypertensive (n = 117)</th>
<th>Non-hypertensive (n = 311)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years [median (IQR)]</td>
<td>9.0 (4.5–12.0)</td>
<td>9.6 (5.4–12.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Male (%)</td>
<td>66.7</td>
<td>66.6</td>
<td>0.98</td>
</tr>
<tr>
<td>White Caucasian (%)</td>
<td>82.1</td>
<td>84.2</td>
<td>0.59</td>
</tr>
<tr>
<td>Structural disease (%)</td>
<td>55.5</td>
<td>58.1</td>
<td>0.64</td>
</tr>
<tr>
<td>Dialysis pre-transplantation (%)</td>
<td>80.3</td>
<td>68.8</td>
<td>0.02</td>
</tr>
<tr>
<td>LRD transplant (%)</td>
<td>13.7</td>
<td>36.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>eGFR in mL/min/1.73m²</td>
<td>64.2 ± 16.2</td>
<td>64.8 ± 17.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Height z-score</td>
<td>−1.95 ± 1.33</td>
<td>−1.62 ± 1.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight z-score [median (IQR)]</td>
<td>−0.35 (−1.37 to 0.84)</td>
<td>−0.23 (−1.10 to 0.79)</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>1.27 ± 1.29</td>
<td>1.02 ± 1.29</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI z-score group (%)</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Obese (≥ 98th percentile)</td>
<td>25.4</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Overweight (≥ 91st and &lt; 98th percentile)</td>
<td>16.7</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>Normal (&lt; 91st percentile)</td>
<td>57.9</td>
<td>58.8</td>
<td></td>
</tr>
<tr>
<td>Dialysis vintage (%)</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>1990–2000</td>
<td>36.7</td>
<td>26.7</td>
<td></td>
</tr>
<tr>
<td>2001–07</td>
<td>63.3</td>
<td>73.3</td>
<td></td>
</tr>
<tr>
<td>Anti-hypertensive medications (%)</td>
<td>69.9</td>
<td>54.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Immunosuppressant medicationsb</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Tacrolimus (%)</td>
<td>54.0</td>
<td>53.6</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A (%)</td>
<td>29.2</td>
<td>27.2</td>
<td></td>
</tr>
<tr>
<td>Otherc (%)</td>
<td>16.8</td>
<td>19.2</td>
<td></td>
</tr>
</tbody>
</table>

---

aSubjects were categorized as being hypertensive if systolic and/or diastolic BP > 95th > 6 months following transplantation and non-hypertensive otherwise. Data shown as mean ± SD unless stated otherwise. LRD, living-related donor.

bNearly all patients were on alternate-day prednisolone in addition to other agents.

c‘Other group’ comprises patients on combination therapy tacrolimus + mycophenolate mofetil (MMF) or cyclosporine A + MMF or on MMF, sirolimus or azathioprine.
Distribution of systolic and diastolic BP z-scores at four time points in the three subgroups


© The Author 2012. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com
Results (2): prevalence of hypertension

• Blood pressure characteristics of those with hypertension
  – Isolated systolic hypertension predominantly (approx 60-65%)
  – Systolic and diastolic hypertension (22-26%)
  – Diastolic hypertension alone (<10%)

• Similar findings at different time-points
Results (3): those with persistent hypertension

- 117 children hypertensive at 6m post-TX
  - f/u: 113 (1-year); 101 (2-years) and 56 (5-years)
- In total, 51% (1-year); 48% (2-years) and 29% (5-years) remained hypertensive
- No significant differences in graft function observed between hypertensive and non-hypertensive patients
The distribution of systolic BP z-scores by individual centre at four time points following transplantation
Funnel plots illustrating the prevalence and variability of children with systolic hypertension at individual centres following transplantation.
Results (4): risk factors associated with hypertension

- **Univariate analysis**
  - Younger age, short stature, received dialysis pre-TX, DD transplant and be currently on anti-hypertensive medication
    - No difference in BMI or eGFR
  - Patients transplanted pre-2000 more likely to be hypertensive

- **Multivariate analysis**: strongest relationship with hypertension
  - Donor source OR 4.16 (DD vs LD)
  - Height z-score OR 2.65 (lowest vs highest height quartile)
    - More likely to have had haemodialysis pre-TX and be obese post-TX
    - No difference in donor source or duration
  - Anti-hypertensive use OR 2.05 (yes vs no)
Discussion

• Our findings provide key data relating to the level of blood pressure control in this cohort in both treated and untreated patients
  - Compare with report of the NAPRTCS database
• Role of diastolic blood pressure
• Effects of events during transplantation on subsequent hypertension rates
• Short stature – surrogate marker for ? more severe ERF course
• Limitations particularly relating to different techniques and clinic BP only
Conclusion

- Just over 25% children remained hypertensive following transplantation with little improvement several years after TX despite active treatment
- There is wide variation in prevalence of hypertension between centres
  - no patient specific cohort characteristics at each centre that would account for this effect
- Management of hypertension in the UK post-TX is sub-optimal with 30% patients with hypertension on no treatment
Judgment remains important !!!!
Acknowledgements

• Chris Reid and Larissa Kerecuk
• Julie Gilg, Biostatistician
• Renal Registry
• BAPN and colleagues at all other units
• Roche pharmaceuticals
THANK YOU
<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>P</th>
<th></th>
<th>Multivariate</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( &lt; 12 years versus ≥12 years)</td>
<td>2.11 (1.11-3.99)</td>
<td>0.02</td>
<td></td>
<td></td>
<td>2.03 (1.00-4.12)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Gender (female versus male)</td>
<td>0.81 (0.48-1.39)</td>
<td>0.45</td>
<td></td>
<td></td>
<td>0.61 (0.33-1.13)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Ethnic group (Caucasian versus non-Caucasian)</td>
<td>0.79 (0.42-1.51)</td>
<td>0.47</td>
<td></td>
<td></td>
<td>1.01 (0.50-2.04)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>BMI z-score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese versus normal</td>
<td>1.47 (0.81-2.65)</td>
<td>0.20</td>
<td></td>
<td></td>
<td>1.50 (0.79-2.83)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Overweight versus normal</td>
<td>0.70 (0.34-1.44)</td>
<td>0.34</td>
<td></td>
<td></td>
<td>0.72 (0.38-1.58)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Height z-score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest quartile versus highest quartile</td>
<td>2.26 (1.15-4.46)</td>
<td>0.02</td>
<td></td>
<td></td>
<td>2.65 (1.25-5.61)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Second quartile versus highest quartile</td>
<td>1.10 (0.53-2.29)</td>
<td>0.80</td>
<td></td>
<td></td>
<td>1.09 (0.50-2.38)</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Third quartile versus highest quartile</td>
<td>0.88 (0.41-1.90)</td>
<td>0.74</td>
<td></td>
<td></td>
<td>0.85 (0.36-1.93)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Donor source (deceased versus living donor)</td>
<td>5.03 (2.30-11.02)</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
<td>4.16 (1.82-9.51)</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>Dialysis pre-transplantation (any versus none)</td>
<td>1.79 (0.97-3.29)</td>
<td>0.06</td>
<td></td>
<td></td>
<td>1.78 (0.88-3.60)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Anti-hypertensive use (yes versus no)</td>
<td>1.97 (1.15-3.35)</td>
<td>0.01</td>
<td></td>
<td></td>
<td>2.07 (1.13-3.76)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Primary disease (structural versus non-structural)</td>
<td>1.04 (0.63-1.72)</td>
<td>0.86</td>
<td></td>
<td></td>
<td>1.36 (0.76-2.42)</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Transplant vintage year (2001 or after versus 2000 and before)</td>
<td>0.65 (0.37-1.14)</td>
<td>0.13</td>
<td></td>
<td></td>
<td>1.31 (0.69-2.49)</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>
Systemic arterial hypertension in children following renal transplantation: prevalence and risk factors

Table 2.
Level of systolic and diastolic BP in ‘millimetres of mercury’ and z-scores for all patients by three subgroups: hypertension (> 95th >), pre-hypertension BP (90th–95th >) and normal BP (< 90th >) at 6 months, 1 year, 2 years and 5 years post-transplantation

<table>
<thead>
<tr>
<th>BP level</th>
<th>6 Months (n = 428)</th>
<th>1 Year (n = 428)</th>
<th>2 Years (n = 365)</th>
<th>5 Years (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, n (%)</td>
<td>117 (27.3%)</td>
<td>118 (27.6%)</td>
<td>95 (26.0%)</td>
<td>50 (25.6%)</td>
</tr>
<tr>
<td>BP in mmHg</td>
<td>121 ± 11</td>
<td>121 ± 11</td>
<td>124 ± 9</td>
<td>128 ± 11</td>
</tr>
<tr>
<td>SBP z-score</td>
<td>2.35 ± 0.78</td>
<td>2.22 ± 0.85</td>
<td>2.33 ± 0.75</td>
<td>2.32 ± 0.88</td>
</tr>
<tr>
<td>DBP in mmHg</td>
<td>73 ± 10 (n = 97)</td>
<td>73 ± 10 (n = 101)</td>
<td>72 ± 11 (n = 83)</td>
<td>74 ± 12 (n = 40)</td>
</tr>
<tr>
<td>DBP z-score</td>
<td>1.39 ± 0.82</td>
<td>1.48 ± 0.87</td>
<td>1.24 ± 0.96</td>
<td>1.16 ± 0.99</td>
</tr>
<tr>
<td>Pre-hypertension, n (%)</td>
<td>61 (14.3%)</td>
<td>52 (12.1%)</td>
<td>42 (11.5%)</td>
<td>29 (14.9%)</td>
</tr>
<tr>
<td>BP in mmHg</td>
<td>112 ± 9</td>
<td>111 ± 10</td>
<td>113 ± 9</td>
<td>115 ± 8</td>
</tr>
<tr>
<td>SBP z-score</td>
<td>1.24 ± 0.44</td>
<td>1.19 ± 0.52</td>
<td>1.25 ± 0.42</td>
<td>1.27 ± 0.52</td>
</tr>
<tr>
<td>DBP in mmHg</td>
<td>67 ± 10 (n = 44)</td>
<td>69 ± 8 (n = 39)</td>
<td>67 ± 8 (n = 39)</td>
<td>69 ± 8 (n = 22)</td>
</tr>
<tr>
<td>DBP z-score</td>
<td>0.79 ± 0.72</td>
<td>0.96 ± 0.64</td>
<td>0.85 ± 0.69</td>
<td>0.87 ± 0.68</td>
</tr>
<tr>
<td>Normal BP, n (%)</td>
<td>250 (58.4%)</td>
<td>258 (60.3%)</td>
<td>228 (62.5%)</td>
<td>116 (59.5%)</td>
</tr>
<tr>
<td>BP in mmHg</td>
<td>99 ± 12</td>
<td>101 ± 11</td>
<td>101 ± 12</td>
<td>103 ± 10</td>
</tr>
<tr>
<td>SBP z-score</td>
<td>0.16 ± 0.84</td>
<td>0.15 ± 0.78</td>
<td>0.10 ± 0.79</td>
<td>0.12 ± 0.77</td>
</tr>
<tr>
<td>DBP in mmHg</td>
<td>58 ± 10 (n = 152)</td>
<td>58 ± 9 (n = 152)</td>
<td>59 ± 8 (n = 141)</td>
<td>62 ± 8 (n = 81)</td>
</tr>
<tr>
<td>DBP z-score</td>
<td>0.09 ± 0.71</td>
<td>0.02 ± 0.73</td>
<td>0.08 ± 0.66</td>
<td>0.16 ± 0.66</td>
</tr>
</tbody>
</table>

*The classification into subgroups uses whichever is higher of SBP and DBP z-score. Data shown as mean ± SD. SBP, systolic BP; DBP, diastolic BP.*
Z-scores

Normally distributed population
Example

- Child with systolic BP at 130 mm, the mean for age and height is 110 mm and the standard deviation is 10.

\[
Z = \frac{130 \text{ (measured value)} - 110 \text{ (mean value)}}{10} \text{ standard deviation (10)}
\]

\[
Z = \frac{130 - 110}{10} = +2
\]

This allows sequential comparison in a single individual and between individuals.
Tall v short : fat v thin
Indexation for body size

- Why not just index the value for body size?

- The indexed value may change across body size

Foster 2008

The indexed value may change across body size
What indicator of body size should we use to plot z-scores against?

Z-score

Body size  ? Weight ? Height ? BSA
Indicator of body size

- Care necessary about what function of body size is used in the calculation of z-scores
- Should not assume BSA will be best
- Height or other variable may be better
- Depends on parameter being measured
- Be careful about z-scores of sizes plotted
Background (1)

- Modern management of chronic kidney disease (CKD) and advances in dialysis therapy during childhood have resulted in an improvement of their life expectancy.
- Increasing numbers survive to adulthood but as young adults have an increased risk of cardiovascular disease.
- Restoration of renal function by transplantation reduces though does not eliminate this increased risk.
Background (1)

• Cardiovascular disease is one of the commonest cause of morbidity and mortality in young adults with childhood-onset ERF

• Young adults with dialysis dependent renal failure have an almost 700 fold increase in risk of cardiac mortality

• Children and adults with *childhood onset* ERF have a 30 times increase in mortality
  - 40-45% of these are cardiovascular deaths