Impact of symptomatic UTI on long term transplant function

Rhana Hassan Zakri, Theo Kasimatis, Pinkie Kotecha, Rohit Srinivasan, Katie Wong, Sandeep Sasuke, Elham Asgari, Jonathon Olsburgh
Guy’s & St Thomas’ NHS Trust, London
‘Urinary tract infection (UTI) is the commonest infection post renal transplant’ (RTx)
Unanswered questions

• Long term effect of symptomatic UTI on RTx function?
  • The role of ABU. Should all ABUs be treated?

• Is the effect of cystitis and pyelonephritis the same on graft function?

• Is one post RTx UTI one too many?
Urinary Tract Infections in Kidney Transplant Recipients Hospitalized at a Transplantation and Nephrology Ward: 1-Year Follow-up

J. Gozdowska, M. Czerwińska, Ł. Chabros, G. Młynarczyk, A. Kwiatkowski, A. Chmura, and M. Durlik

Late Urinary Tract Infection After Renal Transplantation in the United States

Kevin C. Abbott, MD, S. John Swanson, MD, Erich R. Richter, MD, Erin M. Bohen, MD, Lawrence Y. Agodoa, MD, Thomas G. Peters, MD, Galen Barbour, MD, Robert Lipnick, ScD, and David F. Cruess, PhD


Urinary Tract Infections in Renal Transplant Recipients

J. Gołębiewska, A. Dębska-Ślisień, J. Komarnicka, A. Samet, and B. Rutkowski

Transplantation Proceedings, 43, 2985–2990 (2011)
Hypothesis

‘Long-term graft dysfunction occurs in patients with upper tract UTI (pyelonephritis) as a result of renal scarring’
Material & Methods

• Population:
  • Renal transplant recipients 2010 -2012
• Retrospective analysis from EPR
• Inclusion:
  • Adult patients
  • Transplant follow-up at Guy’s
• Exclusion:
  • Primary non function/graft nephrectomy <1 month post transplant

• Follow-up:
  • 5 year: Number of UTIs eGFR
• Primary outcome:
  • Δ Graft function eGFR ml/min
• Secondary outcome:
  • Graft Survival
Definitions

Asymptomatic Bacteriuria (ABU)
Urine culture proven bacteriuria. Absent clinical symptoms, RTx dysfunction or biochemical inflammatory response.

Lower UTI (Cystitis)
Absent systematic upset. Localised cystitis symptoms and CRP <50

Upper UTI (RTx or native kidney pyelonephritis)
CRP >50, pyrexia >38°C, RTx dysfunction, systemic symptoms, RTx/native pain
Results

• Adult renal transplants 2010 – 2012 n = 610

• Total patients followed up at Guy’s n = 213

• Total patients in analysis after exclusions n = 206

(1° non-function =6, Graft nephrectomy <1 month =1)
Results

Mean recipient age: **47.3 Yrs**

Male : Female **129:77 (62.6% : 37.3%)**

Cause of End Stage Renal Disease
Bacterial Incidence: 1st year post RTx

- E-coli
- Klebsiella
- Enterococcus
- Morganella
- Proteus
- Enterobacter
- Pseudomonas
- Candida
- Staph epidermidis
- Streptococcus
- Mixed
- VRE
UTIs

• Positive urine cultures  206 pts over 5 years  n = 447
Unanswered questions

• Long term effect of symptomatic UTI on RTx function?

• Is the effect of cystitis and pyelonephritis the same on graft function?
Type of UTI

<table>
<thead>
<tr>
<th>Worst clinical episode</th>
<th>UTI</th>
<th>Symptomatic UTI</th>
<th>Cystitis</th>
<th>Pyelonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No UTI</td>
<td>ABU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 206</td>
<td>118</td>
<td>29</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>Overall</td>
<td>57%</td>
<td>14%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Recurrent n = 14</td>
<td></td>
<td></td>
<td>Recurrent n = 11</td>
<td></td>
</tr>
<tr>
<td>Mean age/yrs</td>
<td>47.5</td>
<td>47.0</td>
<td>49.9</td>
<td>44.9</td>
</tr>
<tr>
<td>Ratio Male:Female</td>
<td>2:1</td>
<td>1:1.8</td>
<td>1:2.5</td>
<td>1:2.7</td>
</tr>
</tbody>
</table>
## ΔGraft function over 5 years

<table>
<thead>
<tr>
<th></th>
<th>No UTI n=118</th>
<th>UTI n= 88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline eGFR mL/min</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Mean eGFR 5 yr post RTx mL/min</td>
<td>50.9</td>
<td>39.3</td>
</tr>
<tr>
<td>Mean ΔeGFR mL/min</td>
<td>8.1</td>
<td>18.7</td>
</tr>
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</table>

Mann Whitney U Test
P <0.001
**ΔGraft function over 5 years**

|                      | No UTI  
n=118 | ABU  
n=29 | SYMPTOMATIC UTI  
n= 59 |
|----------------------|-----------|---------|--------------------------|
| **Mean baseline eGFR**  
mL/min | 59        | 58      | 59.2                     |
| **Mean eGFR**  
5 yr post RTx  
mL/min | 50.9      | 43.6    | 37.4                     | 37.1   |
| **Mean ΔeGFR**  
mL/min | **8.1**   | **14.4**| **20.9**                 |

Kruskal-Wallis Test  
P <0.001  
Pair wise analysis  
P = 0.353  
P = 0.001
# Graft function over 5 years

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**Kruskal-Wallis Test**

*P* < 0.004

**Pair wise analysis**

*P* = 0.033

*P* = 0.029
### ΔGraft function over 5 years

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**Kruskal-Wallis Test**

- P < 0.004

**Pair wise analysis**

- P = 0.033
- P = 0.029
Graft survival – UTI

Survival Functions

Overall worst clinical 0 = No UTI, 1 = ABU, cystitis = 2, Pyelonephritis = 3

Cum Survival

Survival in months

Overall Comparisons

<table>
<thead>
<tr>
<th>Test Statistic</th>
<th>Chi-Square</th>
<th>df</th>
<th>Sig</th>
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<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>1.029</td>
<td>3</td>
<td>.794</td>
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Test of equality of survival distributions for the different levels of
Overall worst clinical 0 = No UTI, 1 = ABU, cystitis = 2, Pyelonephritis = 3.
Asymptomatic Bacteriurias

- The role of ABU. Should all ABUs be treated?
ABUs

Treated Vs non-treated ABU:
Further episodes in next 5Yrs

- Total number of ABU episodes: n = 172
- Patients treated with antibiotics: n = 88 (51%)
- Patients not treated: n = 84 (49%)

Bar chart showing the comparison between treated and non-treated ABUs, with categories for No UTI, ABU, Cystitis, and Pyelonephritis.
Unanswered questions

• Is one post RTx UTI one too many?
Frequency of UTI episodes 2010-2017

- Mean: 3.7 episodes
- Median: 2 episodes
- 13pts > 10 UTIs
- 35pts > 5 UTIs

△ in eGFR and Number of UTIs

Kruskal Wallis – Pair wise analysis

447 episodes in 88 pts
### Summary

#### UTI Incidence
- 29% symptomatic UTI in the first 5 years post RTx
- 17% pyelonephritis
- 1:20 (5%) recurrent pyelonephritis

#### Number of UTI "hits"
- Detrimental effect on ∆ graft function

#### Importance of identifying risk groups

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**Kruskal-Wallis Test**
- Pair wise analysis
- P = 0.033
- P = 0.029
Hypothesis

‘Long-term graft dysfunction occurs in patients with upper tract UTI (pyelonephritis) as a result of renal scarring’

....but have we underestimated the effect of ‘cystitis’ and ‘number of hits’ on graft dysfunction?
The Future

• **Tx UTI clinic:** MDT / ‘One stop model’
  • Transplant UTI ‘Care bundle’
  • Streamline, early management
  • Prospective 10-15yrs follow-up data

• **Consider Post RTx RCT:** Aim to prevent Tx UTI
  • Standard practice Vs prophylactic abx Vs Probiotic
  • Necker technique v Lich-Gregoir (Campos Freire)
Thank-you!
Antibiotic stewardship  *E-Coli* resistance patterns

2010 - 2012

- Cefuroxime
- Trimethoprim
- Ciprofloxacin
- Amoxicillin
- Nitrofurantoin
- Cephalexin
- Co-amoxiclav
- Gentamicin
UTIs and Rejection

- Total patients with rejection: \( n = 50 \)
- Patients with rejection on first Bx: \( n = 44 \)
- Patients with rejection but no UTI excluded: \( n = 32 \)
- Total patients in analysis after exclusions: \( n = 18 \)
Graft survival – Rejection

Survival Functions

Overall Comparisons

| Test of equality of survival distributions for the different levels of BPAR. |
|-------------------------|-----------------|-------|
| Log Rank (Mantel-Cox)   | Chi-Square      | df    | Sig.  |
|                         | 7.862           | 1     | .005  |
Graft survival – DGF

Survival Functions

Cum Survival

Survival in months

Overall Comparisons

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<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
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<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>3.658</td>
<td>1</td>
<td>.056</td>
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Test of equality of survival distributions for the different levels of DGF: 0 = no, 1 = yes.
Limitations

- Retrospective observational study
- Confounders
  - E.g. changes in immune-suppression over 5yrs
- Assumptions
  - Cystitis – (CRP 0-10 v 10-50)
    - “Statistically significant” is “clinically significant”
- Need for further multivariate analysis / mixed repeated measure model
ΔGraft function over 5 years

- No UTI
- ABU
- Cystitis
- Pyelonephritis
Unresolved issues

• **Literature:**
  - Inconsistent, small series, short follow-up

• **Guidelines:**
  - No national guidelines
  - Need for streamlined services

• **Is statistically significant the same as clinically significant?**
Definitions

• **ABU**
  Urine culture proven bacteriuria. Absent clinical symptoms, RTx dysfunction or biochemical inflammatory response.

• **Lower UTI (Cystitis)**
  Absent systematic upset. Localised cystitis symptoms and CRP <50

• **Upper UTI (RTx or native kidney pyelonephritis)**
  CRP >50, pyrexia >38°C, RTx dysfunction, systemic symptoms, RTx/native pain

• **Positive urine culture**
  >10^5 but consider >10^2 with pyuria

• **Patient with UTI**
  Includes ABU (either Rx or unRx), cystitis and pyelonephritis

• **Symptomatic UTI**
  Includes cystitis + pyelonephritis

• **Worst episode recorded**
  eg ABU v cystitis v Pyelonephritis
Rejection (n=45)

| Rejection on 1st renal bx | No UTI  
n=118 | ABU  
n=29 | Cystitis  
n=25 | Pyelonephritis  
n=34 |
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<tr>
<td></td>
<td>22</td>
<td>8</td>
<td>5</td>
<td>10</td>
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| Type of rejection  
n  | Tubulo-interstitial 1A | Tubulo-interstitial 1B | Vascular 2A | Vascular 2B | TMR/AMR | Type 3 |
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