Infectious complications following transrectal ultrasound (TRUS) - guided prostate biopsy:
New challenges in the era of antimicrobial resistance

ASID Gram-negative ‘Superbugs’ meeting, 2013

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Outline

• Nature and incidence of post-TRUS biopsy infectious complications
• Potential risk factors for post-TRUS biopsy infections
• Pathophysiology and causative organisms
• Antimicrobial prophylaxis
• Pre-biopsy screening
Transrectal ultrasound guided prostate biopsy

- Standard technique to obtain tissue for histological diagnosis of prostate carcinoma
- Approximately one million biopsies performed annually in the United States
- Increasing rates of hospitalisation due to infectious complications post-biopsy \(^1, 2\)

\(^1\) Loeb S, et al. *J Urol* 2011; 186:1830–4

The national burden of infections after prostate biopsy in England and Wales: a wake-up call for better prevention

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Infectious Complications Following Transrectal Ultrasound–Guided Prostate Biopsy: New Challenges in the Era of Multidrug-Resistant Escherichia coli

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Nature and incidence of infectious complications

• Clinical spectrum of infectious complications, ranging from urinary tract infection through to severe sepsis

• Wide variability in reported rates due to differences in biopsy technique; antimicrobial prophylaxis, and patient follow-up

• Reported incidence: UTI is 2-6%; severe sepsis 0.2-2% ¹

• True incidence likely to be underestimated as majority of infections managed in community ²

² Loeb et al. Eur Urol 2012; 61: 1110-4
Causative pathogens and antimicrobial resistance profiles

- Commonest pathogen in post-TRUS biopsy infection is *Escherichia coli* ¹
- Antimicrobial resistant *E. coli* an increasing problem:
  - Fluoroquinolone resistant *E. coli* (11-22% men pre-biopsy) ²
  - ESBL-producing *E. coli*
- Why are resistant *E. coli* infections increasing in the setting of TRUS biopsy??
  - Increasing community reservoir
  - Increasing global spread of clones associated with resistance, most notably ST131 *E. coli*

¹ Williamson DA et al. *Clin Infect Dis* 2013; 57: 267-74
² Duplessis CA et al. *Urology* 2012; 79: 556-563
Predicting risk factors for post-biopsy infections

- No consistent data regarding:
  - Patient-specific risk factors \(^1\)
  - Pre-existing urological pathology \(^2\)
  - Procedural risk factors

- Risk factors for resistant *E. coli* infection post-biopsy:
  - Receipt of fluoroquinolone antibiotic \(^3\)
  - International travel \(^3, 4\)

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\(^2\) Simsir et al. *Urol Int* 2010; 84: 395-9
\(^3\) Patel et al. *BJU Int* 2012; 109: 1781-5
Five patients (5/47; 11%) had an ESBL-producing *E. coli* bacteraemia isolated post-TRUS biopsy between 2007 - 2010.

Four of five had travelled to either India or South-East Asia in preceding month.

- Areas of high endemicity for resistant organisms

- All CTX-M-15 ESBLs (most globally prevalent ESBL type)

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**TABLE 1** Clinical and microbiological characteristics of four patients with extended-spectrum β-lactamase-producing *Escherichia coli* bacteraemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ethnicity</th>
<th>Geographic region of travel</th>
<th>ESBL-type</th>
<th>Antimicrobial resistance profile of <em>E. coli</em> isolate</th>
<th>Empiric treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NZE</td>
<td>South-East Asia</td>
<td>CTX-M-15</td>
<td>AMO; AUG; CTO; COT; GEN; CIP AMK; ERT; MER</td>
<td>AUG; GEN</td>
</tr>
<tr>
<td>2</td>
<td>NZE</td>
<td>South-East Asia</td>
<td>CTX-M-15</td>
<td>AMO; AUG; CTO; COT; GEN; CIP AMK; ERT; MER</td>
<td>AUG; GEN</td>
</tr>
<tr>
<td>3</td>
<td>NZE</td>
<td>Indian subcontinent</td>
<td>CTX-M-15</td>
<td>AMO; AUG; CTO; COT; GEN; CIP GEN; AMK; ERT; MER</td>
<td>AUG; GEN</td>
</tr>
<tr>
<td>4</td>
<td>NZE</td>
<td>Indian subcontinent</td>
<td>CTX-M-15</td>
<td>AMO; AUG; CTO; COT; GEN; CIP AMK; ERT; MER</td>
<td>AMO; GEN</td>
</tr>
</tbody>
</table>

NZE, New Zealand European; AMO, amoxycillin; AUG, amoxycillin clavulanate; CTO, ceftriaxone; COT, trimethoprim/sulphamethoxazole; GEN, gentamicin; CIP, ciprofloxacine; AMK, amikacin; ERT, ertapenem; MER, meropenem.

Role of antibiotic prophylaxis pre-TRUS biopsy

Antibiotic prophylaxis for transrectal prostate biopsy (Review)

Zani EL, Clark OAC, Rodrigues Netto Jr N

Authors’ conclusions

Antibiotic prophylaxis is effective in preventing infectious complications following TRPB. There is no definitive data to confirm that antibiotics for long-course (3 days) are superior to short-course treatments (1 day), or that multiple-dose treatment is superior to single-dose.

Zani EL et al. Cochrane Database Syst Rev. 2011
Escherichia coli Bloodstream Infection After Transrectal Ultrasound–Guided Prostate Biopsy: Implications of Fluoroquinolone-Resistant Sequence Type 131 as a Major Causative Pathogen

Deborah A. Williamson,¹ Sally A. Roberts,¹ David L. Paterson,³ Hanna Sidjabat,³ Anna Silvey,³ Jonathan Masters,² Michael Rice,² and Joshua T. Freeman¹

¹Department of Microbiology, and ²Department of Urology, Auckland District Health Board, New Zealand; and ³University of Queensland Centre for Clinical Research, Brisbane, Australia
## TRUS biopsy and ST131 *E. coli*

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No. (%) (n = 258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>96 (37.2)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>83 (32.2)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>58 (22.5)</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Perforated appendix</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td>Perianal abscess</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td><strong>Post TRUS biopsy</strong></td>
<td><strong>47 (18.2)</strong></td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>19 (7.4)</td>
</tr>
<tr>
<td>Skin and soft-tissue infection</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (3.8)</td>
</tr>
</tbody>
</table>

Abbreviation: TRUS, transrectal ultrasound-guided.
In 35/47 patients (74.5%) the isolate was resistant to one (18/47; 38.3%) or both (17/47; 36.2%) agents used for empiric therapy

Table 3. Comparison of Antimicrobial Resistance in *Escherichia coli* Isolates From Men After Transrectal Ultrasound–Guided Biopsy or Men Admitted With *E. coli* Bacteremia Secondary to Other Causes

<table>
<thead>
<tr>
<th>Antimicrobial Resistance</th>
<th>Isolates, No. (%)</th>
<th>TRUS Biopsy (n = 47)</th>
<th>No TRUS Biopsy (n = 211)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin</td>
<td></td>
<td>44 (94)</td>
<td>111 (53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Amoxycillin-clavulanate</td>
<td></td>
<td>16 (34)</td>
<td>41 (19)</td>
<td>.03</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td></td>
<td>19 (40)</td>
<td>54 (26)</td>
<td>.049</td>
</tr>
<tr>
<td>Cephalothin</td>
<td></td>
<td>28 (60)</td>
<td>86 (41)</td>
<td>.02</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td></td>
<td>7 (15)</td>
<td>16 (8)</td>
<td>.15</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>5 (11)</td>
<td>11 (5)</td>
<td>.18</td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td>0</td>
<td>0</td>
<td>&gt;1</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td></td>
<td>29 (62)</td>
<td>30 (14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td>20 (43)</td>
<td>14 (7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td>0</td>
<td>0</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Trimethoprim-sulphamethoxazole</td>
<td></td>
<td>28 (60)</td>
<td>55 (26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Ciprofloxacin and gentamicin</strong></td>
<td></td>
<td>17 (36)</td>
<td>11 (5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Ciprofloxacin and trimethoprim-sulphamethoxazole</strong></td>
<td></td>
<td>17 (36)</td>
<td>22 (10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Ciprofloxacin, gentamicin, trimethoprim-sulphamethoxazole</strong></td>
<td></td>
<td>9 (19)</td>
<td>8 (3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: TRUS, transrectal ultrasound–guided.

TRUS biopsy and ST131 *E. coli*

- Post-TRUS *E. coli* bacteraemia accounted for 20% of all cases of CO-EC bacteraemia in males in our locale.
- High rates of resistance in post-biopsy isolates has practical implications for empiric therapy.
- The ST131 clone accounted for 40% of all *E. coli* isolates post-biopsy.

Clinical and molecular correlates of virulence in post-TRUS biopsy *E. coli* bacteremia

• Are post-TRUS *E. coli* isolates more virulent than “classic” urosepsis *E. coli* isolates from males?

• Why is ST131 *E. coli* particularly prevalent in the post-TRUS biopsy population?

• Are there any differences in clinical outcomes between patients with ST131 and non-ST131 post-TRUS bacteremia?
Clinical and molecular correlates of virulence in *Escherichia coli* causing bloodstream infection following transrectal ultrasound-guided (TRUS) prostate biopsy

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Molecular profiling of post-TRUS biopsy *E. coli* bloodstream isolates

- Multiplex PCR was used to detect 50 virulence associated genes in post-TRUS biopsy and spontaneous urosepsis isolates
- Virulence score assigned based on number of virulence genes detected (adjusting for multiple detection of certain operons)
- Phylogenetetic group and ST131 status determined
- Aggregate antimicrobial resistance score determined for each isolate
Phylogeny of post-TRUS biopsy vs. non-TRUS biopsy isolates

<table>
<thead>
<tr>
<th>Phylogenetic group or sequence type</th>
<th>Post-TRUS biopsy (n = 47)</th>
<th>Non-TRUS biopsy (n = 54)</th>
<th>P (^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>A / B1 (^{b})</td>
<td>6 (13)</td>
<td>0</td>
<td>0.009</td>
</tr>
<tr>
<td>B2</td>
<td>25 (53)</td>
<td>48 (89)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D</td>
<td>16 (34)</td>
<td>6 (11)</td>
<td>0.007</td>
</tr>
<tr>
<td>ST131 (^{c})</td>
<td>18 (38)</td>
<td>9 (17)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: TRUS, transrectal ultrasound-guided; ST131, sequence type 131

\(^{a}\) Fisher’s exact test

\(^{b}\) 5 isolates from group A and 1 from group B1

\(^{c}\) Proportion of post-TRUS biopsy vs. non-TRUS biopsy ST131 from group B2 isolates only: 18/25 (72%), vs. 9/49 (18%) (P < 0.001).
Virulence profile and antimicrobial resistance of TRUS vs. non-TRUS isolates

Differences in functional gene categories

Gene frequency per category

- Adhesins
- Toxins
- Protectins and invasins
- Siderophores
- Capsule-associated
- Miscellaneous

TRUS biopsy isolates
Non-TRUS biopsy isolates

$P < 0.001$

Functional virulence gene category

Clinical outcomes between ST131 and non-ST131 post-TRUS biopsy bacteremia

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>ST131</th>
<th>Non-ST131</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years ± SD</td>
<td>61.3 ± 8.5</td>
<td>61.4 ± 7.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Charlson score, mean ± SD</td>
<td>0.50</td>
<td>0.52</td>
<td>0.92</td>
</tr>
<tr>
<td>Hospitalized in preceding year, no. (%)</td>
<td>0</td>
<td>3 (10)</td>
<td>0.27</td>
</tr>
<tr>
<td>Median time from biopsy to first positive blood culture, days</td>
<td>1.5</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>Median length of hospital stay, days</td>
<td>4.5</td>
<td>5.0</td>
<td>0.88</td>
</tr>
<tr>
<td>ICU admission, no. (%)</td>
<td>3 (17)</td>
<td>9 (31)</td>
<td>0.32</td>
</tr>
<tr>
<td>30-day mortality, no. (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Data are number of patients (%) unless otherwise stated. Abbreviations: TRUS, transrectal ultrasound-guided prostate; ICU, intensive care unit.
Insights into pathogenesis of post-TRUS sepsis

- Post-TRUS biopsy *E. coli* isolates were less virulent and more phylogenetically diverse than spontaneous urosepsis *E. coli* isolates
  - Likely reflects differential pathophysiology between two syndromes
- Post-TRUS biopsy isolates were more resistant than spontaneous urosepsis isolates and were more likely to be ST131
  - Probably reflects widespread use of FQ prophylaxis
- No difference in clinical outcomes between ST131 and non-ST131 post-TRUS biopsy bacteraemia
  - ST131 status alone is unlikely to be the primary determinant of the severity of post-TRUS biopsy *E. coli* bacteraemia
Pre-biopsy screening for resistant *E. coli*

- May allow tailored prophylaxis in patients who harbour resistant *E. coli* pre-biopsy
- Initial studies suggest that pre-biopsy screening may:
  - Reduce incidence of infectious complications \(^1,^2\)
  - Reduce overall cost of care \(^1\)
- Prior use of FQs strongly associated with pre-biopsy carriage of FQ-resistant isolate \(^2\)
  - 15/178 (8.4%) with FQ-susceptible *E. coli* vs. 20/52 (38.5%) with FQ-resistant *E. coli*

\(^1\) Taylor K et al. *J Urol* 2012; 187: 1275-79
\(^2\) Steensels D et al. *Clin Microbiol Infect* 2012; 575-81
Elderly NZ male with known low-grade prostatic carcinoma

‘Surveillance’ TRUS biopsy booked for early 2013

Returned from India (no healthcare contact)

Pre-biopsy screen demonstrated NDM-producing *Escherichia coli*

Should he have a biopsy??

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Unanswered questions

• Clinical utility and cost-effectiveness of pre-biopsy screening
• FQ’s as adjunct vs. alternative prophylaxis
• Role of older agents e.g. fosfomycin; mecillinam
• Role of pre-biopsy antiseptics / enemas
• Utility of transperineal approach
• Overall risk vs. benefit of biopsy
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• Dr Joshua Freeman
• Dr Jonathan Masters
• Department of Clinical Microbiology
• Department of Urology

Institute of Environmental Science and Research, Wellington, New Zealand
• Helen Heffernan
• Dr Kristin Dyet
• Antimicrobial Reference Laboratory

University of Auckland, New Zealand
• Dr Siouxsie Wiles
• Grant Mills (MSc student)
• Maurice Wilkins Centre for Biodiscovery

University of Queensland Centre for Clinical Research, Queensland, Australia
• Professor David Paterson
• Dr Hanna Sidjabat
• Dr Ben Rogers

University of Minnesota, United States
• Professor James Johnson
• Stephen Porter

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