Recurrent UTI in Adult Women: Contemporary Management & Future Prospects

Chris Harding
What is the definition of recurrent UTI (rUTI)?

• No universally accepted definition
• Most commonly used is “2 in 6 months or 3 in a year”

Schoof and Hill 2005
Hooton and Stamm 2006

• Estimated 20-50% of young women with UTI will have another within a year


• Finnish study showed older (>55yrs) more likely to have recurrence in first year (53% vs 36%)

Ikaheimo Clin Infect Dis 1996
Common Problem

50% of all women will have a UTI in their lifetime

Nearly 20% of women who have one UTI will have another

30% of those will have yet another UTI (recurrent)

80% of those, 2.4% of all women, will have very frequent UTI

All women

Antibiotic Resistance in Cystitis

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>N.-Europe, Canada</td>
<td>USA, Canada</td>
<td>Europe, Brazil</td>
</tr>
<tr>
<td>SRGA standard</td>
<td>CLSI standard</td>
<td>CLSI standard</td>
</tr>
<tr>
<td>Ampicillin – 26/28%</td>
<td>Ampicillin – 38%</td>
<td>Ampicillin – 51%</td>
</tr>
<tr>
<td>TMP/SMX – 13/17%</td>
<td>TMP/SMX – 21%</td>
<td>TMP/SMX – 29%</td>
</tr>
<tr>
<td>Nalidixic acid – 4/10%</td>
<td>Nalidixic acid – n.d.</td>
<td>Nalidixic acid – 18%</td>
</tr>
<tr>
<td>Ciprofloxacin – 1/4%</td>
<td>Ciprofloxacin – 5%</td>
<td>Ciprofloxacin – 8%</td>
</tr>
<tr>
<td>Nitrofurantoin – 1/0.3%</td>
<td>Nitrofurantoin – 1%</td>
<td>Nitrofurantoin – 5%</td>
</tr>
<tr>
<td>Mecillinam – 2/1%</td>
<td>Mecillinam – n.d.</td>
<td>Mecillinam – 3%</td>
</tr>
<tr>
<td>Fosfomycin – 0.4/1%</td>
<td>Fosfomycin – n.d.</td>
<td>Fosfomycin – 1%</td>
</tr>
</tbody>
</table>

Contemporary Management
Contemporary Management

• Non-antibiotic (and non-invasive)
  – Cranberry Products
  – Topical Oestrogens
  – Methenamine Hippurate
  – Vaccines

• Antibiotics
  – Prophylactic Antibiotics
  – Self Start Therapy

• Intravesical agents
Non-antibiotic prophylaxis

Outcome = Clinical UTI during prophylaxis

Beerepoot et al


Methenamine hippurate 424
Total events: 50 (Treatment), 121 (Control)

0.53 (0.24-1.17)
Cranberry Products

• Postulated to acidify urine and reduce bacterial adhesion/prevent fimbrial expression
• Some evidence that rUTIs reduced but optimum dose /duration unclear.
• Original Cochrane review (2008) identified some benefit

BUT

Meta-analyses in updated review (2012) showed that compared with placebo, water or non-treatment,
“cranberry products did not significantly reduce the occurrence of symptomatic UTI overall” (RR 0.86, 95% CI 0.71 to 1.04)
Topical Oestrogens

• Falling oestrogen levels lead to a change in vaginal flora and pH
• Local oestrogen can reverse this without SE of systemic oestrogen
  Esposito et al. Gynaecological Endocrinology 1991
• Oestrogen may also enhance innate immune mechanisms against urinary tract infection
  Lüthje et al. Science Translational Medicine 2013
• Systematic review found no reduction in UTIs with oral oestrogen but showed vaginal preparations superior to placebo
  (RR 0.25/0.64)
  Perrotta et al. Cochrane Database 2008
Methenamine Hippurate

- Methenamine has antibacterial properties - hydrolysed to formaldehyde in acid urine
- Systematic review highlighted heterogeneity of data but some studies report reduction in symptomatic UTIs (RR 0.24)
- Ineffective in pts with neuropathic bladder / abnormal renal tract.
- “There is a need for further large well-conducted RCTs to clarify...”
Vaccines

- **Uro Vaxom® (OM-89)** is only one recommended by EAU guidelines: EAU Guidelines Urological Infections 2015

- Oral administration of immunologically active bacterial lysates of 18 *E. coli* strains. Better than placebo in several RCTs.

- The vaginal vaccine Urovac® slightly reduced UTI recurrence and increased time to re-infection.

- New agent, **UROMUNE®** (under the tongue spray) currently undergoing multi-centre trials in Spain.
Prophylactic Antibiotics

• Long term prophylaxis can range from 4 mths to 5 yrs!!

• 95% will remain UTI free but 50% relapse following cessation

• Cochrane review of RCT’s - RR 0.21 for single recurrence (NNT 1.85) but RR after prophylaxis 0.82
  Albert et al. Cochrane Database 2004

• Single randomised study found prophylactic nitrofurantoin superior to oestrogen
Antibiotic prophylaxis

### Microbiological UTI during prophylaxis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>195</td>
<td>177</td>
<td>0.21 [0.13, 0.34]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.17$, $\chi^2 = 13.90$, df = 10 ($P = 0.18$); $I^2 = 28\%$

Test for overall effect: $Z = 6.36$ ($P < 0.00001$)

Favours Antibiotic 0.005 0.1 1 10 200

Favours Placebo

### Microbiological UTI after completion of prophylaxis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>44</td>
<td>26</td>
<td>0.82 [0.44, 1.53]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.16$, $\chi^2 = 4.38$, df = 2 ($P = 0.11$); $I^2 = 54\%$

Test for overall effect: $Z = 0.62$ ($P = 0.53$)

Favours Antibiotic 0.2 0.5 1 2 5

Favours Placebo

Self Start Antibiotics

- 85-95% of women with previous UTI can self diagnose successfully  
  Gupta *et al.* Ann Intern Med 2001
- Clinical and Microbiological cure rates > 90%
- Best used in motivated women with previous culture confirmed cystitis  
  Hooton NEJM 2012
- Advantages are less antimicrobial exposure and high patient satisfaction rates
- Post coital antibiotics reserved for group where it has been identified as the dominant risk factor.
Intravesical Treatments

- Glycosaminoglycan hyaluronic acid (HA) and chondroitin sulphate (CS) used to enhance protective function of urothelium. GAG layer damage / deficiency may be aetiological in rUTI.
- Agents available: Cystistat® (HA), Hyacyst® (HA), Gepan® (CS), iAluril® (HA & CS)
- Systematic review demonstrates ↓cystitis recurrence, UTI recurrence, and Pelvic Pain & Urgency/Frequency (PUF) total score.
- Study limitations include the small no. of pts and possible bias. “Further studies needed to validate this promising treatment...”

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HA/HA-CS Mean</th>
<th>HA/HA-CS SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constantinides 2004</td>
<td>0.3</td>
<td>0.55</td>
<td>4.3</td>
<td>1.55</td>
<td>40</td>
<td>26.1%</td>
<td>-4.00 [-4.51, -3.49]</td>
<td>2004</td>
</tr>
<tr>
<td>Lipovac 2007</td>
<td>0.56</td>
<td>0.82</td>
<td>4.99</td>
<td>0.9</td>
<td>20</td>
<td>25.9%</td>
<td>-4.43 [-4.96, -3.90]</td>
<td>2007</td>
</tr>
<tr>
<td>Damiano 2011</td>
<td>0.67</td>
<td>0.68</td>
<td>4.19</td>
<td>0.98</td>
<td>28</td>
<td>26.7%</td>
<td>-3.52 [-3.96, -3.08]</td>
<td>2011</td>
</tr>
<tr>
<td>De Vita 2012</td>
<td>1</td>
<td>1.2</td>
<td>2.3</td>
<td>1.4</td>
<td>12</td>
<td>21.3%</td>
<td>-1.30 [-2.30, -0.30]</td>
<td>2012</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100</td>
<td>103</td>
<td>100.0%</td>
<td>-3.41 [-4.33, -2.49]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.77; Chi² = 31.29, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 7.27 (P < 0.00001)

Significantly decreased urinary tract infection (UTI) rate per patient-year
Future Prospects
New Antibiotics?

1920: Penicillins
1930: Sulfonamides
1940: Tetracyclines
1943: Aminoglycosides, Bacitracin (topical)
1948: Cephalosporins
1947: Polymyxins, Phenicol
1946: Nitrofurans
1950: Pleuromutilins
1952: Macrolides
1953: Glycopeptides, Nitroimidazoles, Streptogramins
1955: Cycloserine, Novobiocin
1957: Rifamycins
1961: Trimethoprim
1962: Quinolones, Lincosamides, Fusidic acid
1969: Fostomycin
1971: Mupirocin
1976: Carbapenems
1978: Oxazolidinones
1979: Monobactams
1987: Lipopeptides

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Unlikely....
Future Prospects

• Vaccination
  – Mucosal multivalent bacterial vaccine
  – Virulence factor vaccines

• Bacterial Adhesion Inhibitors

• Immune Modulation
  – Boosting bacterial expulsion
  – Exogenous enhancement of innate immunity

• Natural flora modulation
  – Probiotics
  – Gastrointestinal decolonisation

• Acupuncture
Importance of Innate Immunity

The immune system
Infection of the human body by pathogenic microorganisms such as bacteria, viruses, parasites or fungi triggers the immune response. It occurs in a two-step process: innate immunity halts the infection, and adaptive immunity subsequently clears it.
Mucosal Immunisation

300 m²

- Respiratory
- Digestive
- Genitourinary
Table 1. Comparative anatomic dissemination of the mucosal SlgA antibody response after different routes of immunization

<table>
<thead>
<tr>
<th></th>
<th>Sublingual</th>
<th>Nasal</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>+++</td>
<td>+ to +++</td>
<td>-</td>
</tr>
<tr>
<td>Stomach</td>
<td>/+++/</td>
<td>-</td>
<td>++/++</td>
</tr>
<tr>
<td>Small intestine</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Colon</td>
<td>?</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Rectum</td>
<td>?</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Genital tract</td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Blood</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Çuburu et al. Vaccine, 2007
Czerkinsky et al. Human Vaccines, 2011
Uromune®
Multivalent Bacterial vaccine

A suspension of selected strains of $10^9$ inactivated bacteria/mL, for mucosal oral/sublingual administration (spray).

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus vulgaris*
- *Enterococcus faecalis*
Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics

M. F. Lorenzo-Gómez · B. Padilla-Fernández · F. J. García-Criado · J. A. Mirón-Canelo · A. Gil-Vicente · A. Nieto-Huertos · J. M. Silva-Abuin

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Uromune® - 15month Trial

• Observational retrospective study
• 319 patients with prophylactic treatment:
  • Uromune: 159 patients treated during 3 months (group A)
  • SMX/TMP: 160 patients treated during 6 months (group B)
• Evaluation variables:
  – Number of UTIs before the treatment.
  – Number of episodes of UTI after the initiation of treatment.
  – Number of positives urocultures (UC+).
• Data collection:
  – Before the treatment’s beginning.
  – After 3, 9 and 15 months of treatment’s initiation.
### Uromune® - Patients’ Epidemiological Data (before treatment)

<table>
<thead>
<tr>
<th></th>
<th>A (Uromune)</th>
<th>B (SMX/TMP)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.7</td>
<td>48.1</td>
<td>0.8536</td>
</tr>
<tr>
<td>Range of age</td>
<td>16-85</td>
<td>16-87</td>
<td></td>
</tr>
<tr>
<td>Months of evolution</td>
<td>56.7</td>
<td>59.2</td>
<td>0.7641</td>
</tr>
<tr>
<td>Average of UTI in 6M</td>
<td>3.2</td>
<td>3.1</td>
<td>0.2789</td>
</tr>
<tr>
<td>Average of UC+ in 6M</td>
<td>2.4</td>
<td>2.2</td>
<td>0.6392</td>
</tr>
<tr>
<td>Average of UTI/month</td>
<td>0.53</td>
<td>0.51</td>
<td>0.6408</td>
</tr>
<tr>
<td>Average of UC+/month</td>
<td>0.41</td>
<td>0.36</td>
<td>0.2788</td>
</tr>
</tbody>
</table>
Uromune® - Trial Results

- Average number of episodes of UTI/month.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Uromune</th>
<th>SMX/TMP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>0.53</td>
<td>0.51</td>
<td>0.6408</td>
</tr>
<tr>
<td>0 to 3M</td>
<td>0.12</td>
<td>0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0 to 9M</td>
<td>0.08</td>
<td>0.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0 to 15M</td>
<td>0.09</td>
<td>0.38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 to 9M</td>
<td>0.06</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 to 15M</td>
<td>0.08</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>9 to 15M</td>
<td>0.10</td>
<td>0.34</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Vaccination Against Virulence Factors
Fimbriae

- **Fimbriae or Pili** are filamentous organelles expressed on the surface of gram-negative bacteria and mediate attachment to host tissues.

- First described by Duguid et al. in 1955

- Found on a variety of gram-negative bacteria including saprophytes, commensals and pathogens.

- Adhesin (FimH) binds to mannose oligosaccharides attached to uroplakin on surface of urinary bladder epithelium
FimH Vaccine

- Fimbrial adhesin FimH has been used as an effective vaccine antigen in mouse models.
- Less immunogenicity and lack of safe & effective adjuvant has prevented use in humans.
- Several new safe and efficacious adjuvants for human use, which will facilitate use of FimH vaccines in clinical trials.

Source: Solomon Langermann et al. Science 276:607-611
FimH-mediated cellular adhesion to mannosylated proteins is critical for uropathogenic E. coli (UPEC) to invade bladder epithelium.

Small-molecule FimH bacterial adhesion antagonists, mannosides, have been developed and awaiting trials.
Immune Modulation: Boosting Bacterial Expulsion

• Expulsion of intracellular *E. coli* in urothelial cells can be greatly accelerated by increasing intracellular cAMP levels.

• Forskolin originates from the Asiatic herb Coleus forskohlii, used for centuries as an Ayurvedic medication to treat a various ailments, including 'painful micturition’

• In *E. coli* infected mice treated systemically or intravesically with forskolin after infection, up to 90% of the bacterial burden was reduced compared to controls.
Like Forskolin, Phosphodiesterase inhibitors can also increase intracellular cAMP levels....
PDEs & c-AMP and c-GMP

- Could we use Sildenafil or another PDE inhibitor in UTI?
Immune Modulation: Exogenous Enhancement of Innate Immunity

- Innate immunity provides the immediate defences against infection and is the most important part of the body’s response to UTI.

- Over the past 5-years, greater realisation that Estrogen enhances innate immunity. In particular, Estrogen enhances secretion of antimicrobial peptides (AMPs) in bladder and vaginal cells.

- **Antimicrobial peptides are:**
  - Gene encoded ‘natural antibiotics’ secreted at epithelial surfaces.
  - Small, +ve charged (cationic) molecules
  - Broad spectrum (kill gram +ve & –ve bacteria, fungi & some viruses)
  - Target & disrupt microbial membranes

Membrane disruption in bacteria incubated with antimicrobial peptide
Exogenous Enhancement of Innate Immunity

In Newcastle University, Hyaluronic acid has been used to induce innate immune defences.
Probiotics

- Probiotic therapy and faecal transplant used successfully in treating severe *C. difficile* and pseudomembranous colitis.
- UTIs often preceded by presence of pathogenic microbiota in the vagina and urethra.
- Possible prevention strategy could be to normalise vaginal and urethral microflora by direct administration of probiotics
- Possibilities:
  - Innoculate asymptomatic bacteruria (ABU) strains of *E. coli* into bladder
  - Use commensal Lactobacilli in vagina to ‘out-colonise’ *E. coli*
  - Oral probiotics to displace pathogenic *E. coli* in gut
Probiotics

• Randomised study of 100 women with a history of recurrent UTI
  – All received antimicrobials for acute UTI.
  – Randomised to receive either Lactin-V or placebo daily for 5 days then once weekly for 10 wks.
  – Participants were followed up at 1 and 10 wks after intervention and for UTIs
  – Urine samples for culture and vaginal swabs for real-time quantitative 16S ribosomal RNA gene polymerase chain reaction for Lactobacillus
Probiotics

Results

– Recurrent UTI occurred in 7/48 15% of women receiving Lactin-V vs 13/48 27% of women receiving placebo (relative risk [RR], .5; 95% confidence interval, .2–1.2).

– High-level vaginal colonisation with Lactobacilllus was associated with significant reduction in rUTI (RR for Lactin-V, .07; RR for placebo, 1.1; P < .01).

Conclusion

– Authors concluded that “Lactin-V after treatment for cystitis is associated with a reduction in recurrent UTI.”

– EAU guidelines suggest that Lactobacillus may be used in rUTI where suitable preparations available
If all else fails, you could try....
• In trial of acupuncture in female recurrent UTI, 67 pts received real acupuncture, sham acupuncture, or no treatment twice weekly for 4 weeks.
  – Real acupuncture - needles inserted to correct depth at known acupuncture points
  – Sham acupuncture - needles inserted superficially, outside known acupuncture points and without manipulation.

• **Real acupuncture significantly reduced UTI vs no treatment** (RR 0.48, 95% CI 0.29–0.79).

• Sham acupuncture comparable to no treatment.

• **Mechanism of action remains unclear** and larger well-designed double-blind randomized trials needed.

Conclusions

• rUTI is prevalent in adult women.
• Non-antibiotic treatments preferable for recurrent UTI *where possible*...
• Several treatment options exist for rUTI with varying levels of supporting evidence.
• Further RCTs are needed to evaluate these treatments.
• New non-antibiotics treatments on the horizon