Non-antibiotic prophylaxis for recurrent urinary tract infections

Suzanne Geerlings
Infectious disease physician
“I don’t have sex when I have an important appointment coming up, ‘cause I am afraid I’ll get one.”

“I cancel appointments because I don’t want to be a burden to my company.”

“It’s a painful disorder that often makes it impossible for me to leave the house.”

“I drink lots of water, I don’t go swimming anymore, I take vitamin C, I shower before I have sex, I go to the toilet afterwards... Whatever I do, it keeps coming back.”

“There are times that I stay at home crying on the couch.”
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 118)</th>
<th>Premenopausal n = 55 (47%)</th>
<th>Postmenopausal n=63 (53%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical status UTI:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- complicated</td>
<td>14 (25%)</td>
<td></td>
<td>29 (46%)</td>
</tr>
<tr>
<td>- uncomplicated</td>
<td>41 (75%)</td>
<td></td>
<td>34 (54%)</td>
</tr>
<tr>
<td><strong>Amount of UTIs:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>25 (45%)</td>
<td></td>
<td>30 (48%)</td>
</tr>
<tr>
<td>&gt;= 6</td>
<td>30 (55%)</td>
<td></td>
<td>33 (52%)</td>
</tr>
<tr>
<td><strong>Sexual activity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>50 (91%)</td>
<td></td>
<td>29 (46%)</td>
</tr>
<tr>
<td>no</td>
<td>5 (9%)</td>
<td></td>
<td>34 (54%)</td>
</tr>
<tr>
<td><strong>Hospital inclusion:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>university hospital</td>
<td>38 (69%)</td>
<td></td>
<td>42 (67%)</td>
</tr>
<tr>
<td>non-university hospital</td>
<td>17 (31%)</td>
<td></td>
<td>21 (33%)</td>
</tr>
<tr>
<td>Randstad</td>
<td>44 (80%)</td>
<td></td>
<td>44 (70%)</td>
</tr>
<tr>
<td>non-Randstad</td>
<td>1 (20%)</td>
<td></td>
<td>19 (30%)</td>
</tr>
<tr>
<td>Statement</td>
<td>AGREE</td>
<td>NO AGREE/ NO DISAGREE</td>
<td>DISAGREE</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-------</td>
<td>-----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>1. I cancel appointments as a consequence of UTIs</td>
<td>40(33.9%)</td>
<td>24(20.3%)</td>
<td>54(45.8%)</td>
</tr>
<tr>
<td>2. My holiday/ weekend away has been spoiled once by a UTI</td>
<td>75(63.6%)</td>
<td>16(13.6%)</td>
<td>27(22.9%)</td>
</tr>
<tr>
<td>3. Suffering from UTIs does not influence my social life (n=117)</td>
<td>44(37.6%)</td>
<td>25(21.4%)</td>
<td>48(41.0%)</td>
</tr>
<tr>
<td>4. I do not let a UTI spoil a party</td>
<td>55(46.6%)</td>
<td>37(31.4%)</td>
<td>26(22.0%)</td>
</tr>
<tr>
<td>5. I am well able to work when I suffer from a UTI</td>
<td>32(27.1%)</td>
<td>44(37.3%)</td>
<td>42(35.6%)</td>
</tr>
<tr>
<td>6. My work/ study is not affected by having a UTI</td>
<td>45(38.1%)</td>
<td>25(21.2%)</td>
<td>48(40.7%)</td>
</tr>
<tr>
<td>7. A UTI does not bother me during sports</td>
<td>23(19.5%)</td>
<td>54(45.8%)</td>
<td>41(34.7%)</td>
</tr>
<tr>
<td>8. I do not practice any intensive sports when I suffer from a UTI</td>
<td>55(46.6%)</td>
<td>30(25.4%)</td>
<td>33(28.0%)</td>
</tr>
<tr>
<td>9. I am not afraid of getting another UTI because of sexual contact</td>
<td>39(33.1%)</td>
<td>29(24.6%)</td>
<td>50(42.4%)</td>
</tr>
<tr>
<td>10. I have less sexual contact because of a UTI</td>
<td>50(42.4%)</td>
<td>42(35.6%)</td>
<td>26(22.0%)</td>
</tr>
<tr>
<td>11. I suffer mainly from a UTI whenever I am in an unfamiliar surrounding</td>
<td>12(10.2%)</td>
<td>13(11%)</td>
<td>93(78.8%)</td>
</tr>
<tr>
<td>12. I always make sure that I am close to a toilet (n=116)</td>
<td>36(31.0%)</td>
<td>31(26.7%)</td>
<td>49(42.2%)</td>
</tr>
<tr>
<td>13. I change my underwear or bed sheets more often</td>
<td>61(51.7%)</td>
<td>18(15.3%)</td>
<td>39(33.1%)</td>
</tr>
</tbody>
</table>
Recurrent urinary tract infections

• Definition: 3 UTIs/year or 2 UTIs/last 6 months
• 50-70% all women will have UTI during their lifetimes
• 20-30% of these women will have recurrent UTI
• Differentiation between relapse and reinfection
UTI DIAGNOSIS

Voided midstream urine cultures are generally obtained to determine the etiology of UTI.

Potential contamination by periurethral flora complicates interpretation of results in women.

Not possible to distinguish whether bacteriuria originates from the bladder or periurethra.

As a result, colony count thresholds have been established.
Early studies showed the value of quantitative urine culture in discriminating between UTI and contaminated urine

≥10^5 CFU/mL in MSU predictive of bladder bacteriuria in asx women and women with pyelo

Lower counts more likely to be associated with contamination

However, later studies showed that women with sx of cystitis often had lower colony counts
In young women with cystitis, voided MSU often grow enterococci or Group B streptococci with or without coliforms in similar or higher counts.

We were interested in gaining a better understanding of voided MSU culture results and how often enterococci and Group B streptococci represented contamination rather than bladder bacteriuria.
Voided Midstream Urine Culture and Acute Cystitis in Premenopausal Women

Thomas M. Hooton, M.D., Pacita L. Roberts, M.S., Marsha E. Cox, B.S., and Ann E. Stapleton, M.D.

METHODS

Women from 18 to 49 years of age with symptoms of cystitis provided specimens of midstream urine, after which we collected urine by means of a urethral catheter for culture (catheter urine). We compared microbial species and colony counts in the paired specimens. The primary outcome was a comparison of positive predictive values and negative predictive values of organisms grown in midstream urine, with the presence or absence of the organism in catheter urine used as the reference.
N= 200 women With Cystitis
Conclusions
Voided MSU cultures in AUC accurately reflect evidence of *E. coli* in the bladder, but not that of enterococci or GBS, which are usually co-isolated with *E. coli* and appear to rarely cause AUC themselves
Polymicrobial AUC is rare
The etiology of a quarter of AUC is unknown

Hooton et al. NEJM 2013
Are you experienced? Understanding bladder innate immunity in the context of recurrent urinary tract infection

Valerie P. O’Brien, Thomas J. Hannan, Anthony J. Schaeffer, and Scott J. Hultgren

Recent findings—Chronic bladder inflammation during prolonged bacterial cystitis in mice causes bladder mucosal remodelling that sensitizes the host to rUTI. Although constitutive defenses help prevent bacterial colonization of the urinary bladder, once infection occurs, induced cytokine and myeloid cell responses predominate and the balance of immune cell defense and bladder immunopathology is critical for determining disease outcome, in both naïve and experienced mice. In particular, the maintenance of the epithelial barrier appears to be essential for preventing severe infection.
Disease outcome 4 wpi

Persistent bacteriuria
Chronic Cystitis

Self-resolve bacteriuria
Q1Rs

Acute bacterial virulence
Adhesins
Toxins
Biofilm

Acute UPEC infection

Mucosal innate immunity
PRR signaling

Adaptive immunity
Tissue remodeling

Sensitization to recurrent, chronic cystitis

Severe inflammation: biomarkers of chronic cystitis

Weak to moderate host response

Weak or absent host response (immunodeficiency)

Acute Host-pathogen checkpoint
0–24 hpi
Pathogenesis (1)
Colonization microorganism

Colonization

• Postmenopausal women: estrogen ↓
• → vaginal lactobacilli ↓
• → competition with uropathogens ↓
  → number uropathogens ↑
• → chance UTI ↑
Pathogenesis (1) Colonization microorganism

• Double-blind RCT: 93 postmenopausal women rUTI
• Topically applied intravaginal estriol cream vs placebo

• Reappearance lactobacilli in 22 of 36 estriol-treated women
• Vaginal colonization with Enterobacteriaceae 67% → 31% → prevention of colonization

• UTI 0.5 vs. 5.9 episodes per patient-year

• No change in 3 endpoints in 24 placebo recipients

Non-antibiotic versus Antibiotic Prophylaxis for Recurrent Urinary Tract Infections (NAPRUTI)-study

Multi-center trial in postmenopausal women

- Randomized and “double dummy” and double-blind

- 12 months intervention: 480 mg TMP/SMX (n=127) vs capsules (oral) with
  *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (n=125)

- 3 months wash-out period

- Women fill in questionnaires and collect material for culture (urine, faeces) monthly

Arch Intern Med. 2012;172(9):704-12
Antibiotic resistance faecal *E. coli* isolates

Arch Intern Med. 2012;172(9):704-12
Pathogenesis (2)
Adherence microorganism-cell

- Increased adherence *E. coli* to uroepithelial cell receptor in women with rUTI

- 70.9% women with recurrent cystitis 42.4% controls have a UTI history in 1 or more female relatives with rUTIs
  Urol. 2010 Aug;184(2):564-9
STUDY AIM

To assess the efficacy of increased daily water intake on the frequency of recurrent acute uncomplicated cystitis in premenopausal women

METHODS

Randomized, open-label, controlled trial
METHODS: PARTICIPANTS

140 healthy premenopausal women

• At least 3 episodes AUC in the past 12 months
• Self reported fluid intake < 1.5L/d
• Measured 24h urine volume < 1.2L
• Measured 24h urine osmolality ≥500 mOsm/Kg
METHODS: INTERVENTION

Water Group
Usual fluid intake + 1.5 L/d

vs.

Control Group
Usual fluid intake
CUMULATIVE UTI EPISODES BY STUDY GROUP

Cumulative number of UTI over time, by group

Control Group

Water Group
CONCLUSIONS

In women at high risk for recurrent cystitis, additional water intake resulted in:

✓ 48% reduction in rate of rAUC

✓ 70% increase in time interval between rAUC episodes

✓ 47% reduction in no. of antimicrobial treatment regimens

JAMA Intern Med. 2018 Nov 1;178(11):1509-1515
Cranberries

• 13 studies (2380 participants) cranberry juice/concentrate; 9 studies (1032 participants) cranberry tablets or caps; 1 study cranberry juice and tablets; 1 study cranberry caps and tablets.
• Some evidence cranberries may lower number of symptomatic UTIs (RR 0.86, 95% CI 0.71 to 1.04)
• Large number dropouts/withdrawals (acceptability problems of consuming cranberry products particularly juice over long periods), and benefit is small
• Cranberry juice cannot currently be recommended for the prevention of UTIs.
• Other preparations (such as powders) need to be quantified using standardised methods to ensure the potency, and contain enough of the 'active' ingredient, before being evaluated in clinical studies or recommended for use.

Non-antibiotic versus Antibiotic Prophylaxis for Recurrent Urinary Tract Infections (NAPRUTI)-study

Multi-center trial in pre-menopausal women

• randomized and “double dummy” double-blind

• 12 months intervention: 480 mg TMP/SMX (n=110) vs cranberry capsules 2x500 mg (n=111)

• 3 months wash-out

• women fill in questionnaires and collect material for culture (urine, faeces) monthly

Arch Intern Med. 2011 Jul 25;171(14):1270-8
Mean number UTIs after 12 months

- Cranberry's, IPW: 4.0
- Cranberry's, unadjusted: 2.6
- TMP/SMX, IPW: 1.8
- TMP/SMX, unadjusted: 1.6
Antibiotic resistance faecal E. coli isolates

Cranberries

%R

baseline
1 months
12 months
1 month after stop
3 months after stop

Antibiotic

TMP/SMX

AMOX Aug TMP SXT GEN NOR CIP NIT

ZonMw
Correlation between asymptomatic and symptomatic *E. coli*

- Lane 1 = ASB
- Lane 2 (and 3) = UTI
- Interval: 1 month
- Same patient (n=50), 70% *E. coli* similar:
- Result of intracellular invasion *E. coli*?
- Intracellular bacterial communities?
- Or bacterial interference?

Clin Microbiol Infect. 2012 Apr;18(4): E84-90
• Vaccination?

• No treatment?

• Faeces transplantation in special patient groups
Oral immunostimulant OM-89

- Extract 5 serotypes heat-killed uropathogenic *E. coli*
- “Stimulates immune system”
- 4 studies: 891 participants (79-89% women)
- Reduced UTI recurrence RR=0.61, 95%CI 0.48-0.78; during 6-12 months follow-up
- Good safety profile

REVIEW ARTICLE

Oral vaccine (OM-89) in the recurrent urinary tract infection prophylaxis: A realistic systematic review with meta-analysis

K.A. Taha Neto\textsuperscript{a}, L. Nogueira Castilho\textsuperscript{b}, L.O. Reis\textsuperscript{a,\*}

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Uro-Vaxom Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer 2005</td>
<td>99</td>
<td>171</td>
<td>125</td>
<td>179</td>
<td>45.5%</td>
<td>0.59 [0.38, 0.92]</td>
</tr>
<tr>
<td>Frey 1986</td>
<td>4</td>
<td>32</td>
<td>16</td>
<td>32</td>
<td>12.4%</td>
<td>0.14 [0.04, 0.50]</td>
</tr>
<tr>
<td>Magasi 1994</td>
<td>19</td>
<td>58</td>
<td>42</td>
<td>54</td>
<td>25.9%</td>
<td>0.14 [0.06, 0.32]</td>
</tr>
<tr>
<td>Tammen 1990</td>
<td>23</td>
<td>61</td>
<td>29</td>
<td>59</td>
<td>16.2%</td>
<td>0.63 [0.30, 1.30]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>322</td>
<td>324</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.43 [0.31, 0.59]</td>
</tr>
<tr>
<td>Total events</td>
<td>145</td>
<td></td>
<td>212</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi\textsuperscript{2}=12.92, df=3 (P=0.005); I\textsuperscript{2}=77%
Test for overall effect: Z=5.17 (P<0.00001)

**Figure 5** Urinary tract infection at 6 months.
A Randomized, Double-Blind, Parallel-Group, Multicenter Clinical Study of *Escherichia coli*-Lyophilized Lysate for the Prophylaxis of Recurrent Uncomplicated Urinary Tract Infections

Florian M.E. Wagenlehner\(^a\)  Stefania Ballarini\(^c\)  Adrian Pilatz\(^a\)
Wolfgang Weidner\(^a\)  Lorenz Lehr\(^c\)  Kurt G. Naber\(^b\)
## Products and Key Intermediates

<table>
<thead>
<tr>
<th>Production step</th>
<th>OM-89</th>
<th>OM-89S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomass for alkaline lysis</td>
<td>Same vegetal culture medium grown in industrial fermenter Harvested and frozen -20°C</td>
<td>Same vegetal culture medium grown in industrial fermenter Harvested and frozen -20°C</td>
</tr>
<tr>
<td>Alkaline lysis</td>
<td>strong alkaline lysis 9 NCTC strains strong alkaline lysis 9 IP strains</td>
<td>strong alkaline lysis (18 strains) weak alkaline lysis (18 strains)</td>
</tr>
<tr>
<td>Minimal lysis</td>
<td><strong>Large amount of culture medium containing little biomass</strong></td>
<td><strong>None</strong></td>
</tr>
<tr>
<td>Purification → Concentrate</td>
<td>Same MF / TFF</td>
<td>Same MF / TFF</td>
</tr>
<tr>
<td>Lyophilizate</td>
<td>Mannitol, glutamate, gallate, anti-foam</td>
<td>Mannitol only</td>
</tr>
<tr>
<td>Capsules 6 mg (60 mg lyophilizate)</td>
<td>Same excipients</td>
<td>Same excipients</td>
</tr>
</tbody>
</table>
NSAIDs as treatment of UTIs?

Double-blind, randomized controlled pilot trial in 29 German general practices. Healthy women with uncomplicated UTI ibuprofen 3 × 400 mg oral or ciprofloxacin 2 × 250 mg (+1 placebo), 3 days.

Symptom resolution Day 4/Day 7

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen n = 36</th>
<th>Ciprofloxacin n = 33</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td>21/36 (58.3%)</td>
<td>17/33 (51.5%)</td>
<td>0.744</td>
</tr>
<tr>
<td>Day 7</td>
<td>27/36 (75%)</td>
<td>20/33 (60.6%)</td>
<td>0.306</td>
</tr>
</tbody>
</table>
Our results suggest that more than a third of women with UTI symptoms are willing to delay antibiotic treatment when asked by their GP.

More than half of these women (28/51) will not have used antibiotics after one week, of whom more than 70% (20/28) will have improvement of their symptoms.
Women with symptoms of uncomplicated urinary tract infection are often willing to delay antibiotic treatment: a prospective cohort study

NHG-standaard Urineweginfecties.

Bespreek de mogelijkheid van een afwachtend beleid (ruim drinken en zonodig pijnstilling) en het meegeven van een ‘uitgesteld antibioticumrecept’.
Donor feces infusion for eradication of Extended Spectrum beta-Lactamase producing *Escherichia coli* in a patient with end stage renal disease

R. Singh¹, E. van Nood², M. Nieuwdorp³, B. van Dam⁴, I. J. M. ten Berge¹, S. E. Geerlings² and F. J. Bemelman¹

Within the first 2 days after donor feces infusion the patient experienced mild diarrhoea and abdominal cramps, but no other adverse events occurred. Follow-up ESBL swab cultures of the rectum, perineum and throat were taken at week one, two, four, and twelve after the donor feces infusion. During these four follow-up time points the ESBL cultures of the throat and perineum remained negative.