Recurrent Urinary Tract Infection

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Local symptoms
- Dysuria, frequency, urgency, pain or bladder tenderness

General symptoms
- Fever, Flank pain
- Nausea, vomiting

Systemic response SIRS
- Fever, shivering
- Circulatory failure

Organ failure
- Single-, multiple-
- Organ failure

No symptoms

Gradient of severity

Clinical diagnosis
- ABU
- CY-1
- PN-2
- PN-3
- US-4
- US-5
- US-6

Febrile UTI

Investigations

Risk factors

Medical and Surgical

* Two exceptions: pregnancy and prior to urological procedure
Recurrent UTI – different populations

Women
- rUTI in women in fertile age
- rUTI in post-menopausal women
- rUTI in institutionalised women
- rUTI in women with diabetes mellitus
- rUTI in other situations (e.g.)
  - Dysfunction of the lower UT
  - Indwelling catheter
  - Abnormalities of the UT
  - Stone disease

Men
- rUTI in men < 60-65
- rUTI in BPH
- rUTI in institutionalised men
- rUTI in men with indwelling catheter
- rUTI in abnormalities of the UT
Setting the scene

Uncomplicated UTI\(^1\): (Young) non-pregnant woman with no known urologic abnormality

Complicated UTI: Anyone else

Young: Premenopausal

Older: Postmenopausal

<table>
<thead>
<tr>
<th>Culture</th>
<th>Urinalysis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASB(^2)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cystitis</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

Lifetime prevalence of UTI: 50%

\(^1\)IDSA, EAU, \(^2\)Asymptomatic bacteriuria, \(^3\)Frequency, urgency, dysuria, etc.
General rule – don’t treat ASB...*but*

- **NO** 3B.5.1 Patients without identified risk factors
- **NO** 3B.5.2 Patients with ABU and recurrent UTI, otherwise healthy
- **NO** 3B.5.3 Pregnant women
- **NO** 3B.5.4 Patients with identified risk-factors
  - **NO** 3B.5.4.1 ABU in postmenopausal women
  - **NO** 3B.5.4.2 Diabetes mellitus
  - **NO** 3B.5.4.3 Elderly institutionalised patients
  - **NO** 3B.5.4.4 Patients with dysfunctional and/or reconstructed lower urinary tracts
  - **NO** 3B.5.4.5 Patients with catheters in the urinary tract
  - **NO** 3B.5.4.6 Patients with ABU subjected to catheter placements/exchanges
  - **NO** 3B.5.4.7 Patients with renal transplants
  - **NO** 3B.5.4.8 Immuno-compromised and severely diseased patients, patients with candiduria
- **!!!** 3B.5.5 Prior to surgery

rUTI AMU Apr 2016/MG
Recurrent UTI (rUTI)

A UTI may be recurrent when it follows the complete clinical resolution of a previous UTI

- Prevalence: ~3%
- Twice as common in postmenopausal women

Pathogenesis of rUTI involves:
  - Bacteriologic persistence, bacteriologic relapse, reinfection

rUTI: 3 episodes of a UTI in the preceding 12 month or 2 episodes in the preceding 6 month
## Risk factors

<table>
<thead>
<tr>
<th>Premenopausal women</th>
<th>Postmenopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual activity*</td>
<td>Estrogen deficiency</td>
</tr>
<tr>
<td>Use of spermicide</td>
<td>Atrophic vaginitis</td>
</tr>
<tr>
<td>Life time history of UTI</td>
<td>Increased post-void urine volume</td>
</tr>
<tr>
<td></td>
<td>- Detrusor contractility</td>
</tr>
<tr>
<td></td>
<td>- Cystocele</td>
</tr>
<tr>
<td>History of UTI during childhood</td>
<td>Urinary or faecal incontinence</td>
</tr>
<tr>
<td>A mother with a history of UTI</td>
<td>Catheterisation</td>
</tr>
</tbody>
</table>

*Older women (might) still have sex. Ask them!
Pathogenesis of rUTI

• Similar to that of sporadic infection
• Most common causative agent: uropathogenic *Escherichia coli* (UPEC)

Two hypothesis:
1. Old: Rectal reservoir, colonisation of the periurethral area, ascending into the bladder
2. More recent: Bacteria invade and persist within the bladder epithelium and cause recurrence by re-emerging into the bladder

The same *Escherichia coli* strain can cause recurrence one to three years after initial UTI

Diagnosis and management of recurrent urinary tract infections in non-pregnant women (2013). K. Gupta, BMJ
Uro-epithelial cells get infected

The host cells start signals through the "Toll" receptors

The host cells kills bacteria

Blood vessels

By courtesy C Svanborg, Lund

PMN+IL-8 receptor

IL-8

GSL

Tlr4

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**E. coli**

With virulence factors such as fimbriae on the surface, toxin-production and iron-binding capacity

**Asymptomatic E. coli**

Rarely fimbriae
Lost of all or part of the genes expressing virulence

By courtesy C Svanborg, Lund
Figure 1

Activation of innate immunity

Inhibition of innate immunity

PMNs

Dendritic cells

Mucosal mast cells

Lymphocytes

Monocytes

Cytokines

Capsule Metabolic genes Metal-binding proteins

TcpC

No/weak innate immunity

Symptomatic infection

Asymptomatic carriage

Svanborg, 2012
Pathogenesis of rUTI

1. IBC

2. QIR

3. Exfoliation

Diagnostic evaluation

Clinical presentation of rUTI:
Similar to acute cystitis

Urine culture is useful:
1. Confirmation of the diagnosis
   - Distinction between OAB or interstitial cystitis
2. Direction of antimicrobial therapy

Women with uncomplicated rUTI have a high accuracy of correct self diagnosis

In premenopausal women the diagnostic yield of an extensive routine workup is low.
Diagnostic evaluation Premenopausal women

Atypical cases:

- Gross hematuria
- Obstructive symptoms, low uroflowmetry or high PVR
- Neurogenic bladder
- Recent genitourinary surgery
- Bacterial persistence after sensitivity based therapy
- Unusual organisms (e.g. *M. tuberculosis*, Candida spp.)
- Diabetes or otherwise immunocompromised

Further investigation is important and should be performed in atypical cases

Guidelines for the diagnosis and management of recurrent urinary tract infection in women (2011), S. Dason et al., CUAJ
Diagnostic evaluation: Postmenopausal women

Postmenopausal women:

- Evaluation of medication
- Urologic evaluation to exclude host factors that classify the urinary tract infection as complicated:
  - Anatomic abnormalities (e.g. cystocele, fistula)
  - Voiding dysfunction (e.g. neurologic disease)
  - Urinary tract obstruction (e.g. bladder outlet obstruction)
  - Other (e.g. urolithiasis, diabetes, etc.)

Postmenopausal women should be screened (cystoscopy, imaging*) for complicating factors

*MRI, CT urogram ± abdominopelvic ultrasound
Treatment Acute phase

Antimicrobial regimes:

- Fosfomycin trometamol 3g, SD\textsuperscript{1}
- Nitrofurantoin 100 mg bid\textsuperscript{2}, 5 days
- Pivmecillinamin 400mg bid\textsuperscript{2}, 3 days
- TMP, 200 mg bid\textsuperscript{2}, 5 days
- TMP-SMX, 160/800 mg bid\textsuperscript{2}, 3 days

Recurrent UTIs can be treated with the same antimicrobial regimes as used for sporadic UTI

\textsuperscript{1}SD: Single dose, \textsuperscript{2}bid: two times a day, EAU Guidelines on Urological Infections, 2015
The presence of ASB in patients affected by rUTI has a protective role in development of subsequent symptomatic UTI!!

1. ASB treatment is associated with a higher probability to develop symptomatic recurrence

2. ASB treatment is associated with a modification of the isolated bacterial strains

Do not treat asymptomatic bacteriuria (ASB) in women affected by rUTI

The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: To treat or not to treat? (2012), T. Cai et al., Clin Infect Dis
### Prophylaxis – Evidence?

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioural modifications</strong></td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td><strong>Non-antimicrobial prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vaginal estrogens</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>• Immunoactive prophylaxis</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>• Probiotics&lt;sup&gt;1&lt;/sup&gt;</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>• Cranberry</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>• D-mannose</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>• Endovesical instillation</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td><strong>Antimicrobial prophylaxis</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<sup>1</sup> Vaginal application of *Lactobacillus crispatus*
Hormonal replacement Background

1. Vulvovaginal atrophy
   - Symptoms: vaginal dryness, itching, urinary frequency↑, urinary incontinence↑

2. Vaginal pH ↑(pH 7, distilled water)
   - Glycogen↓, Lactobacillus spp. ↓

3. Flow↓, residual volume↑, mechanical clearance of bacteria↓
   - Volume of smooth muscle cells↓, vascularization↓, collagen↑ (contractility↓)

4. Antimicrobial peptides↓, strengthening intercellular junctions↓
Hormonal replacement  Vaginal estrogens

- The use of vaginal estrogen was evaluated in 5 trials involving 596 patients
- Three studies used estradiol (cream, silicone ring and pessaries), 2 estriol (ovules)
  - All preparations of vaginal estrogen decreased the number of UTIs
  - Patients treated with vaginal estradiol reported in up to 36% about local side effects, no side effects were reported in estriol treated patients

Estriol might be the estrogen of choice due to less side effects compared to estradiol
Antimicrobial prophylaxis

1. Continuous (daily or every-other-day) antimicrobial prophylaxis
   - Initial duration of 6 month
     • 50% of women experience recurrence after discontinuation

2. Postcoital antimicrobial prophylaxis
   - One RCT compared postcoital vs continuous daily ciprofloxacin
     • No difference in rate of UTIs
     • Postcoital prophylaxis might be offered

3. Self-diagnosis and self-treatment

Low-dose daily or postcoital antimicrobial prophylaxis is effective in the prevention of recurrent UTIs

Antibiotics for preventing recurrent urinary tract infection in non-pregnant women (2004), X. Albert et al., Cochrane Database Sys Rev
Antimicrobial prophylaxis

Continuous or postcoital antimicrobial drug regimes:
1. Nitrofurantoin 50 mg or 100 mg daily
   – Caution: Pulmonary toxicity, hepatic side effects
2. Fosfomycin trometamol 3g every 10 days
   – Caution: Every 10 days, not daily!!!

Issues to be considered:
• Collateral damage (no fluoroquinolones and cephalosporins)
• E. coli resistance against trimethoprim

The use of long-term antimicrobial prophylaxis in recurrent UTI has to be reconsidered
Breach of the last line of defense

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

CID (online), 2 weeks ago
- 88-years old man
- History of rUTI
Urinary Tract Infections in elderly population
Take home message

- Recurrent UTIs are a major healthcare problem
- In premenopausal women an extensive routine workup is not necessary
- Postmenopausal women with rUTI should be screened (cystoscopy, imaging) for complicating factors
- Vaginal estrogens are helpful to reduce the rate of rUTIs in postmenopausal women
- Antimicrobial prophylaxis reduces the rate of rUTIs in pre- and postmenopausal women, but it has to be well-considered due to the worldwide emergence of antimicrobial resistance