Recurrent urinary tract infections in neurological patients: A urologist's perspective

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Affiliations to disclose:

Astellas: consultant, speaker, investigator
Boston scientific: consultant
Allergan: consultant, speaker
Medtronic: speaker
Pierre Fabre: consultant
Ipsen: investigator

Funding for speaker to attend:

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Problems of definition of a UTI

Symptomatic UTI ≠ Asymptomatic bacteriuria

Asymptomatic bacteriuria: presence of bacteria in urine without clinical symptoms
70% of patients with a neurogenic bladder

No benefits of antibiotics: incidence of febrile UTIs, severity, duration of bacteriuria

*Van der Wall E. Lancet 1992
*SPILF 2014
Definition

UTI = Clinical symptoms + positive urine culture*

Concerns:
- Heterogeneous literature
- Wide variability of diagnostic criteria according to mode of voiding

Recurrent UTIs
- ≥3/year, ≥4/year
- ≥2/6 months

Threshold values
- Significant bacteriuria $10^5$ UFC/mL
- ISC= $10^2$ UFC/mL
- Condom catheter $10^4$ UFC/mL
- Indwelling catheter: no threshold
- Suprapubic aspiration: no threshold

*EAU Guidelines on neuro-urology, 2016
*SPILF 2014
Clinical symptoms

Urological symptoms
- Frequency
- Dysuria
- Leaks
- Urgency
- Pelvic or lumbar pain
- Malodorous dirty urine
- Hematuria

Non-urological symptoms
- Temperature
- Spasticity
- Headache
- Autonomic dysreflexia
- Fatigue

Patients can help with the diagnosis
However, 39% of them will be wrong*
Prediction of the absence of UTI > presence**

Urine culture

- Identification of bacteria
- In case of favourable outcomes, no need to be controlled after treatment
- Infections with multiple bacteria *:
- Bacteria difficult to treat
  - Pseudomonas aeruginosa, Enterobactéria (enterobacter, serratia)
- Multiresistant bacteria
  - Risk factors: frequent hospitalizations, iterative antibiotic treatments, invasive urological procedures, indwelling catheters

*Biering-Sorensen F, Drugs 2001
Disptick test

Rapid method of screening for UTIs

Limitations

- Leucocytes + in patients with catheters or already treated by antibiotics
- Nitrites – if non-nitrate reducing bacteria (enterococcus)

In women:
- Dipstick serves to exclude UTIs (NPV 95% leucocytes and/or nitrites -)
- But NPV≠100% so always confirm with a urine culture
- PPV<76%, so always confirm with a urine culture

In men
- Positive dipsticks (leucocytes + and/or nitrites +) PPV>90%, confirm with a urine culture
- Negative dipsticks cannot exclude a UTI

*Dévillé et al. BMC Urol 2000*
Diagnosis of a UTI

Suspicion of a UTI in a neurological patient based on symptoms

Catheters+

- Urine culture

Catheters -

Dipstick

- Leucocytes And/or nitrites (+)
- Leucocytes And nitrites (-)

In women: stop
In men: diagnosis cannot be excluded

High clinical suspicion of a UTIs
Risk factors for recurrent UTIs

Factors resulting in compromise of normal host defences to bacterial colonization are an important step in the pathogenesis of UTIs.

**Risk factors**

**Iatrogenic/drugs**
- Indwelling catheter
- Antibiotic use
- Spermicides

**Behavioural**
- Voiding dysfunction
  - Frequent or recent sexual intercourse

**Anatomic/physiologic**
- Vesicoureteral reflux
- Female sex
- Pregnancy

**Genetic**
- Familial tendency
- Susceptible uroepithelial cells
- Vaginal mucus properties

**Indwelling Foley catheters** provide an ascending route for perineal bacteria to enter the bladder. Recent antibiotic use disrupts the normal bacterial flora at the vaginal introitus, allowing uropathogens (e.g., *E. coli*) to colonize. Spermicides cause irritation and attachment sites for *E. coli*.

**Voiding dysfunction** causes increased post-void residual urine volumes, which allows more time for bacterial proliferation. Frequent or recent sexual intercourse may introduce bacteria into the urinary tract.

**Vesicoureteral reflux** causes urinary retention and allows more time for bacterial growth. The retrograde flow also allows bacteria to ascend to the kidneys. **Females** have a shorter urethra (4 cm vs 25 cm in males). Pregnancy results in progesterone-mediated smooth muscle relaxation to the bladder and ureters, and compression of the ureters by the uterus. Both result in urinary retention for increased bacterial growth.

**UTI occurrence tends to cluster in families. Susceptible uroepithelial cells secrete less IgA, which is the main humoral defence mechanism at the physiologic mucosa. Properties of vaginal mucus may allow *E. coli* binding more readily.**

*In neurological patients:
Bladder dysfunction, Immunosuppression, Chronic Disease, Immobility, Catheter*

## Risk factors for recurrent UTIs

### Risks factors for recurrent urinary tract infections in patients with multiple sclerosis

**Véronique Phé, Carmel Curtis, Neha Sihra, Bernadette Porter, Jeremy Chataway, Jalesh Panicker, Mahreen Pakzad**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 MS with recurrent UTIs, n=50</th>
<th>Group 2 MS without recurrent UTIs, n=50</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.5 (43.5-60)</td>
<td>48 (41-51.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Gender</td>
<td>39 females/11 males</td>
<td>29 females/21 males</td>
<td>0.03*</td>
</tr>
<tr>
<td>Type of multiple sclerosis</td>
<td></td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>• Relapsing remitting</td>
<td>28 (56%)</td>
<td>27 (54%)</td>
<td></td>
</tr>
<tr>
<td>• Secondary progressive</td>
<td>13 (26%)</td>
<td>17 (34%)</td>
<td></td>
</tr>
<tr>
<td>• Primary progressive</td>
<td>9 (18%)</td>
<td>6 (12%)</td>
<td></td>
</tr>
<tr>
<td>Duration of multiple sclerosis, years</td>
<td>14.5 (8.7-21.7)</td>
<td>14 (8-20)</td>
<td>0.21</td>
</tr>
<tr>
<td>EDSS score</td>
<td>6.5 (6-7)</td>
<td>6 (3.4-6.5)</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

Female gender and worse EDSS score were significant predictive factors for recurrent UTIs
Management of recurrent UTIs

- No recommendations
- Treatment of risk factors
- Urological investigations
  - Upper urinary tract: kidney function, kidney ultrasound/CT scan
  - Urodynamics
  - Cystoscopy
- Treatment of bladder dysfunction (antimuscarinics, botulinum toxin A, sacral neuromodulation, PTNS, surgery etc)
- Mode of bladder emptying+++
Catheterization

- **Intermittent self-catheterization** = method of choice to empty the bladder
- **Suprapubic catheter**
  - Preservation of the urethra
  - But risk of infection in 60% patients
- **Indwelling catheter**
  - Complications: Kidney, infections, stones, urethral lesions

⇒ To avoid as much as possible
Antibiotic prophylaxis

- The use of oral antimicrobial prophylaxis for preventing UTIs
  - is not supported in meta-analysis
  - is currently not recommended as a routine by NICE

- Problem: emerging problem of antimicrobial resistance (two-fold increase in resistant bacteria was reported with this approach)

- In a observational prospective pilot study suggests that a weekly oral cyclic antibiotic (WOCA) regimen to prevent UTIs is both safe and efficacious in adult spinal cord–injured patients with LUT dysfunction performing ISC.
  - alternate administration of two antibiotics once a week over a period of at least 2 years.
Prevention of urinary tract infection in spinal cord-injured patients: safety and efficacy of a weekly oral cyclic antibiotic (WOCA) programme with a 2 year follow-up—an observational prospective study

Jérôme Salomon¹, Pierre Denys², Corinne Merle¹, Emmanuel Chartier-Kastler², Christian Perronne¹, Jean-Louis Gaillard³ and Louis Bernard¹

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before WOCA</th>
<th>Under WOCA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic UTI/patient-year</td>
<td>9.4</td>
<td>1.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>including:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>febrile UTI/patient-year</td>
<td>0.74</td>
<td>0.31</td>
<td>0.04</td>
</tr>
<tr>
<td>orchitis</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>pyelonephritis</td>
<td>150</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>prostatitis</td>
<td>40</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hospitalization and antibiotic consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalizations/patient-year</td>
<td>0.23</td>
<td>0.09</td>
<td>0.0012</td>
</tr>
<tr>
<td>total hospital days/patient-year</td>
<td>3.97</td>
<td>1.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>total days of curative antibiotic/patient-year</td>
<td>111</td>
<td>14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>total duration of antibiotic</td>
<td>111</td>
<td>68</td>
<td>0.04</td>
</tr>
<tr>
<td>(including preventive and curative therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>broad-spectrum antibiotic</td>
<td>77.7%</td>
<td>12.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bacterial evolution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>percentage of positive urine sample cultures</td>
<td>98.4%</td>
<td>31.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDR colonized patients</td>
<td>6/38</td>
<td>2/38</td>
<td>NS</td>
</tr>
</tbody>
</table>

No severe adverse events reported (15% grade I)

aUrine sample culture reflects urinary colonization before and under WOCA.
bPatients colonized with MDR bacteria.
Cranberry extracts


171 adult MS patients

Primary endpoint : Time to first symptomatic infection

Outcome: No difference in groups
D-Mannose

Open label feasibility study evaluating D-Mannose combined with home-based monitoring of suspected urinary tract infections in patients with multiple sclerosis

Véronique Phé, Mahreen Pakzad, Collette Haslam, Gwen Gonzalez, Carmel Curtis, Bernadette Porter, Jeremy Chataway, Jalesh Panicker

- D-mannose- natural food supplement shown to be safe and effective in preventing UTIs
- Competitively inhibits urothelial bacterial

**Aim:** To assess the feasibility of using D-Mannose, a natural food supplement, in patients with multiple sclerosis (MS) reporting recurrent urinary tract infections (UTIs) as a preventative.
Material and methods

- A single-centre, open-label, feasibility study

- Patients with MS, using and not using urinary catheters, experiencing recurrent UTIs (≥3/year or ≥2/6 months)

- D-mannose powder 1.5 grams twice daily for 16-weeks and were instructed to monitor suspected UTIs at home using urine dipsticks

- Diaries were used to record compliance, number of prescriptions of antibiotics received for UTIs, results of urine dipsticks and cultures

ClinicalTrials.gov (identifier NCT02490046)
D-Mannose

Results

• 22 patients with MS, median age 50 years (46-59)
  - 10 were not using catheters
  - 12 were using catheters

• The compliance rates for using D-Mannose and dipsticks for testing suspected UTIs were 100% and 90.2% respectively

• 61 episodes of suspected UTIs were recorded
  - 19/61 (31.1%) were confirmed UTIs
  - 29/61 (47.5%) prescriptions of antibiotics were made

• The number of monthly proven UTIs decreased both in catheter users and non-users (p<0.01)

• No adverse effects were reported
Take home messages

• Patients with neurogenic bladder have important risk factors for recurrent UTIs

• The diagnosis is based on the association of symptoms and positive culture

• DO NOT prescribe a urinalysis in the absence of symptoms of planned invasive urological procedure

• DO NOT prescribe a urinalysis for the monitoring

• Treat all risk factors of recurrent UTIs but mode of voiding is the key element

• Need for a long-term multidisciplinary follow-up