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

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Population: Spinal cord injury (SCI) patients with neurogenic bladder have an increased risk for symptomatic urinary tract infection (UTI). Recurrent UTI requires multiple courses of antibiotic therapy, markedly increasing the incidence of multidrug-resistant (MDR) bacteria.

Methods: During an observational prospective study, we determined the safety and efficacy of a weekly oral cyclic antibiotic (WOCA) regimen to prevent UTI in SCI adult patients with neurogenic bladder undergoing clean intermittent catheterization. The WOCA regimen consisted of the alternate administration of an antibiotic once per week over a period of at least 2 years. The antibiotics chosen were efficient for UTI, well tolerated and with low selection pressure.

Results: There was a significant decrease in antimicrobial consumption linked to the dramatic decrease in the incidence of UTI. Before intervention, there were 9.4 symptomatic UTIs per patient-year, including 197 episodes of febrile UTI responsible for 45 hospitalizations. Under the WOCA regimen there were 1.8 symptomatic UTIs per patient-year, including 19 episodes of febrile UTI. No severe adverse events and no new cases of colonization with MDR bacteria were reported.

Conclusions: In this prospective, observational pilot study a novel approach to the prevention and treatment of UTI in SCI was investigated. Our study shows the benefit of WOCA in preventing UTI in SCI patients.

Keywords: UTIs, antibiotic therapy, antibiotic prescription, antimicrobial susceptibility, healthcare-associated infections, infection control

Introduction

The annual worldwide incidence of spinal cord injury (SCI) is approximately 40 per million persons. Asymptomatic bacteriuria is common (70%) in SCI patients under self-catheterization,¹ with urinary tract infection (UTI) the most frequent complication.² The symptoms of UTI are non-specific. Factors increasing the risk of infection include over-distention of the bladder, vesico-ureteric reflux, high pressure voiding, large post-void residuals and stones in the urinary tract.³ Although these can be minimized by improved patient education as regards clean intermittent catheterization, correct voiding (a minimum of 1000 mL per day) and maintaining sufficient control of neurogenic detrusor overactivity (with anticholinergic treatment), UTI is still one of the leading causes of morbidity.⁴,⁵ Antiseptics and acidification or alkalinization of the urine have not demonstrated efficacy in preventing UTI in this population.⁶ While curative antibiotic therapy is effective, recurrences are frequent and bladder colonization is inevitable because the inability to empty the bladder requires catheterization. Daily antibiotic prophylaxis has yielded discordant results and is not recommended because of the risk of the emergence of multidrug-resistant (MDR) bacteria and a decreasing effect over the long-term.⁷–¹⁵ This study describes the impact of a weekly oral cyclic antibiotic (WOCA) programme to prevent symptomatic UTIs.
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UTI in adult SCI patients undergoing intermittent clean self-catheterization.

Methods

Study design

This was an observational prospective study.

Patients

We included adult SCI patients undergoing intermittent clean catheterization and under efficient treatment to control neurogenic bladder overactivity. All patients were followed for more than 2 years in our University hospital and had recurrent UTI (>3 per year). Exclusion criteria included patients without informed consent; those with vesicoureteric reflux, uncontrolled neurogenic bladder over-activity, urinary stones, bladder diverticula or renal dysfunction; and those patients who were voiding <1000 mL per day or underwent less than four bladder catheterizations per day. A complete medical history was obtained including the level of SCI and date of injury, co-existing medical conditions, allergies, the number of bladder catheterizations per day, the mean daily void, history of UTI, number of related hospitalizations and number and types of courses of antibiotic therapy. In our institution each patient with neurogenic bladder was followed regularly with a voiding calendar, creatinine clearance (minimum one per year), urological consultation, urodynamic examination and echography. Apart from reinforcing basic standards and principles of managing the urinary tract no specific teaching programme was provided to either the general practitioners or patients during the study period. The WOCA regimen was prescribed according to specific inclusion criteria and results of urine cultures (Figure 1).

Bacteriological analysis

The survey included a weekly culture of a urine specimen for 6 weeks, and detection of possible MDR in anal and urinary samples. The protocol was explained to each patient and informed consent was obtained. Susceptibility testing was done using both the disc diffusion method and an automated broth microdilution method. The breakpoints were those defined by the National Committee for Clinical Laboratory Standards. MDR bacteria included Enterobacteriaceae species producing extended-spectrum β-lactamase (ESBL), MDR Acinetobacter baumannii, MDR Pseudomonas aeruginosa or MDR Klebsiella pneumoniae.

Figure 1. WOCA regimen.
**Treatment**

The WOCA regimen consisted of the alternate administration of an antibiotic once per week over a period of at least 2 years. The antibiotics that were chosen (efficient for UTI, well tolerated, low selection pressure) included: amoxicillin 3000 mg, cefixime 400 mg, fosfomycin trometamol 6000 mg, nitrofurantoin 300 mg, and trimethoprim/sulfamethoxazole 320–1600 mg. During week A, the patient received a single antibiotic (A), and the following week (B) the patient was given another antibiotic (B). For each patient, antibiotics were specifically chosen according to the results of urine cultures. Quinolones were not recommended as the first choice for curative treatment. Adverse events were recorded using the international common terminology criteria.17

**Follow-up**

At each monthly visit we evaluated patient compliance, fever, UTI (orchitis, prostatitis, pyelonephritis) with or without fever and hospitalization (event and length). The definition of infection was established according to specific guidelines.2 During the study period all patients had a weekly urine culture and their general practitioners were requested to provide clinical information by telephone or fax. The patients were asked to provide a regular sample of urine. Follow-up was a minimum of 2 years for all patients thereafter if the culture was sterile. Renal function was monitored weekly during the first 3 months following inclusion and monthly thereafter if the culture was sterile. Renal function was monitored on a regular basis. Follow-up was a minimum of 2 years for all patients (median, 29 months; range, 24–50).

**Statistical analysis**

Statistical analysis was performed with the SAS system. Data was analysed with ANOVA procedure and Bartlett’s test for homogeneity for repeated measures, non-parametric test of Kruskal–Wallis and exact Fisher’s test.

**Ethical approval**

The study has been approved by the Research Committee of the Hospital Infection Committee. All patients received written information. All the patients gave informed consent.

**Results**

**Patients**

Thirty-eight patients (22 men, 58%; 16 women, 42%, sex ratio: 0.6) with neurogenic bladder were included. The mean age was 45.9 ± 13.9 years (mean ± SD). Six patients were tetraplegic and 32 were paraplegic, all stable more than 2 years after injury. Each patient was performing an average of 6 ± 1.4 intermittent catheterizations daily.

**UTI**

Before the WOCA programme, the patients had an average of 9.4 ± 5.34 UTI per year and a history of 197 febrile UTI (0.75 per patient-year) consisting of orchitis (7), prostatitis (40) and acute pyelonephritis (150) responsible for 50 hospitalizations (4 days per patient).

Under the WOCA programme, at a 2 year follow-up (Table 1), there were 1.84 ± 2.81 UTI per patient-year (P < 0.01) and 19 febrile UTI observed in seven patients or 0.31 per patient-year (P = 0.04). This included 6 prostatitis in two patients and 13 acute pyelonephritis in six patients. There was no patient with orchitis. These events were responsible for seven hospitalizations (P < 0.01) in four patients, 45 days per year for all patients and 1.2 days per patient (P < 0.01). Thirty-one patients (81%) did not experience a severe UTI after introduction of WOCA.

**Table 1. Evolution of UTI, antibiotic consumption and bacteriological results under the WOCA programme**

<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>
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<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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>98.4%</td>
<td>31.8%</td>
<td>&lt;0.0001</td>
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<tr>
<td>sample cultures †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR colonized patients ‡</td>
<td>6/38</td>
<td>2/38</td>
<td>NS</td>
</tr>
</tbody>
</table>

†Urine sample culture reflects urinary colonization before and under WOCA.

‡Patients colonized with MDR bacteria.

**Bacteriological results**

Infection was monomicrobial in 65% of patients and mixed in 35%. The principal microorganisms isolated in urine cultures before WOCA regimen included Enterobacteriaceae spp. in 60% (E. coli 25%, Proteus 15%, other 20%) and Gram-positive cocci in 40% (Enterococcus spp. 25%, other Streptococcus spp. 10%, other 5%). No case of vancomycin-resistant Enterococcus was observed before or under WOCA. Under WOCA the number of positive urine cultures decreased from 98% to 31% (P < 0.01). A significant evolution of bacterial colonization was noted. The bacteria isolated from urine samples at the end of the follow-up period were Enterobacteriaceae spp. in 80% (E. coli 55%, Proteus 15%, other 10%) and Gram-positive cocci in 20% (Enterococcus spp. 10%, Streptococcus spp. 10%). At inclusion six patients (15.8%) were colonized with MDR bacteria. Only two of them (5.2%) were still colonized with MDR bacteria at the last follow-up visit. No new case of colonization was reported.

**Antibiotic consumption**

There was a significant decrease in antimicrobial consumption linked to the dramatic decrease in the incidence of UTI. At the
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In this prospective, observational pilot study a novel approach to the prevention and treatment of UTI in SCI patients was investigated. Our study shows the benefit of WOCA in preventing UTI in SCI patients. We observed a significant reduction in (i) the number of UTI, (ii) the level of antibiotic consumption and (iii) the number and length of hospitalizations, without severe side effects or emergence of MDR bacteria. SCI usually occurs in young male adults. The prevention and management of UTI in such individuals is difficult, and urinary complications are responsible for a large proportion of hospitalization-related episodes. There is growing bacterial resistance and simultaneously a decreasing rate of introduction of new antibacterial agents. There are no useful methods to prevent UTI in patients with SCI. The use of topical antiseptics, medicated soap or antiperspirants prior to catheterization has proved disappointing in preventing bacteriuria.4–6 There is no consensus on the use of oral antiseptics, acidifying or alkalinizing agents, or the effectiveness of cranberry juice.18,19 Continuous antimicrobial use reduces the incidence of bacteriuria initially, but the long-term efficacy of this method has not demonstrated any benefit.10–13 A recent meta-analysis14 concluded that continuous antibiotic prophylaxis is significantly associated with a reduced amount of bacteriuria among patients in the acute phase of illness but has no efficiency for non-acute patients.

In our study, we observed a significant reduction in the number of positive urine cultures and UTI. This is probably due to the heavy dose of antibiotic administered once weekly, which inhibits bacterial multiplication. A similar method using a combination of trimethoprim/sulfamethoxazole has also been shown to be effective.13–15 While the efficacy of continuous long-term antimicrobial prophylaxis is uncertain, one must be aware of the possibility of adverse reactions. We obtained different results from those reported by Reid et al.,20 perhaps due to the fact that these authors used trimethoprim/sulfamethoxazole alone and more frequently each week. During WOCA therapy, such treatment is given one day and then again 15 days later, alternating with another antibiotic.

During the WOCA regimen no severe adverse event was observed. There is evidence that the use of continuous oral antibiotic prophylaxis results in a twofold increase in the proportion of MDR bacteria.10–15 Several studies confirmed a greater increase in the proportion of antibiotic-resistant organisms in the treated groups. This doubling of the rate of resistant organisms represents a potential serious harm against which any potential benefit needs to be measured. Many authors have suggested that antimicrobial cycling may slow the evolution and spread of resistance.9–15 A significant evolution of the antibiotic sensitivity was noticed under WOCA. No new case of colonization with MDR bacteria was detected, and the number of patients colonized with MDR bacteria decreased as well. In this specific population with numerous ethical problems, we conducted an observational prospective study for longer than 2 years. Even if we were aware of a potential investigator’s bias, to date no long-term solution has been found. Our data suggest that a WOCA regimen could be a real alternative, and it is essential to design a prospective, randomized, placebo-controlled double blind study.

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Transparency declarations

No declarations were made by the authors of this paper.

References


