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REVIEW ARTICLE

Chronic urinary tract infections in patients with spinal cord lesions – biofilm infection with need for long-term antibiotic treatment

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Patients suffering from spinal cord injuries resulting in complete or incomplete paraplegia or tetraplegia are highly disposed to frequent, recurrent or even chronic urinary tract infections (UTIs). The reason for the increased risk of acquiring UTIs is multifactorial, including reduced sensation of classical UTI symptoms, incomplete bladder emptying, frequent catheterizations or chronic urinary tract catheters. Biofilms in relation to UTIs have been shown both on catheters, on concrements or as intracellular bacterial communities (IBCs). Due to the increased risk of acquiring recurrent or chronic UTIs and frequent antibiotic treatments, patients experience an increased risk of being infected with antibiotic-resistant bacteria like extended-spectrum β-lactamase–producing *Escherichia coli* or *Klebsiella* spp., but also bacteria like *Pseudomonas aeruginosa* inherently resistant to several antibiotics. Diagnosing the UTI can also be challenging, especially distinguishing harmless colonization from pathogenic infection. Based on a previous study showing activation of humoral immune response toward UTI pathogens in patients with spinal cord lesions (SCL), the present mini review is an evaluation of using antibody response as an indicator of chronic biofilm UTI. In addition, we evaluated the effect of long-term treatment with antibiotics in patients with SCLs and chronic UTI, defined by culturing of a uropathogen in the urine and elevated specific precipitating antibodies against the same uropathogen in a blood sample. Elimination of chronic UTI, decrease in specific precipitating antibody values and avoiding selection of new multidrug-resistant (MDR) uropathogens were the primary markers for effect of treatment. The results of this evaluation suggest that the long-term treatment strategy in SCL patients with chronic UTI may be effective; however, randomized prospective results are needed to confirm this.

Key words: Spinal cord lesion; chronic urinary tract infection; antibiotic treatment; specific precipitating antibodies; multidrug-resistant uropathogens.

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Urinary tract infection (UTI) is the most frequent medical complication in patients with spinal cord lesions (SCLs) (1). In the past, renal failure and other urinary tract complications were the primary cause of death in this group of patients. During the past 30 years, the causes of death have become more similar to those of the general population (2, 3). However, UTIs are the most frequent cause of hospitalization in this population (4, 5) and recurrent or chronic UTIs might in part be responsible for reduced renal function (6). In addition, the pathogens cultured from the SCL patients become increasingly resistant and thereby increasingly difficult to treat, in some cases due to the development

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of hypermutating isolates (7, 8). Moreover, the risk of acquiring an UTI with a resistant isolate is significantly increased if previous UTI(s) had been caused by resistant isolates (9). However, if time between positive cultures increased, reduced risk repeated identification of the resistant phenotype was observed (9).

Both the spinal cord lesion and the bladder drainage methods increase the risk of UTI and often lead to a lack of classical UTI symptoms. The frequency of UTI depends on the drainage method, indwelling catheters being responsible for most cases of UTIs (2, 10, 11). The uropathogen might form a biofilm either on the surface of a catheter, in concrements or in the bladder epithelia (4, 12, 13) and can then survive significantly higher concentrations of, and standard length of treatments with, antibacterial agents than usual and thereby cause chronic infections. There is no general consensus on how these chronic biofilm infections should be treated. The use of long-term treatment with antibacterial agents in biofilm infections is well known and accepted in patients with cystic fibrosis (CF) (14, 15). In this study, we apply this knowledge to another group of patients, the SCL patients, and analyze the effects of long-term treatment with antibacterial therapy in the management of chronic UTIs. Also, the use of measuring specific precipitating antibodies as a diagnostic and monitoring tool was applied (6). Elimination of chronic UTI, decrease in precipitating antibody values and avoiding selection of new multidrug-resistant (MDR) uropathogens were the primary markers for effect of treatment.

EVALUATION OF TREATMENT STRATEGY

We evaluated the incidence of chronic UTIs and the effect of long-term treatment with antibiotics in patients at the Clinic for Spinal Cord Injuries, Rigshospitalet, Copenhagen University Hospital. All patients who had a chronic UTI between May 2005 and April 2008 underwent evaluation. Information of these patients was sent to the Department of Microbiology for counseling concerning antibiotic therapy. Each patient was only included once with his or her latest chronic UTI (in the study period), but in cases where patients were chronically infected with more than one microorganism, both isolates were included.

Elimination of the chronic UTI, decrease in precipitating antibody values and avoiding selection of new MDR uropathogens were the primary markers for effect of treatment, comparing patients treated in accordance with the recommendations from the Department of Microbiology and patients not treated in accordance with this. No ethical approval was required for this evaluation.

DEFINITIONS

For the novel treatment strategy and to be able to evaluate the effect, we had defined a chronic UTI. UTI was defined as chronic when uropathogens were found in the urine culture and there were increased levels of precipitating antibodies specific to this uropathogen in at least one blood sample detected by crossed immunoelectrophoresis using water-soluble antigens obtained by sonication and counting the number of immunoprecipitates (= number of precipitating antibodies) as detailed previously (6, 16, 17). The diagnosis was supported by findings of the same uropathogen several times, reduction in renal function and recurrent UTI symptoms. The physician taking the clinical history assessed the symptoms. The patients were all asked if they had already been treated with antibiotics, if so this was taken into account in the counseling. No patients received antibiotic treatment when the urine sample was taken. The clinical routine concerning bladder stones was to screen the patients with stone-CT-scan and isotope renography every 2 years and if clinical suspicion of stones the CT-scan may have been repeated before the 2-year mark. Nearly all the patients have had urodynamic investigations performed, the bladder emptying method was described according to the International SCI Lower Urinary Tract Basic Data Set (18).

The present evaluation was performed before the International SCI Urinary Tract Infection Basic Data Set had been developed (19).

Reduction in renal function is noted as a decline in corrected chrome EDTA glomerular filtration rate. All patients in the clinic has this value measured every second year.

The normal value of precipitating antibodies to *Escherichia coli* and *Klebsiella* sp. is 0–2 precipitins, for *Pseudomonas aeruginosa* the normal value is 0–1 precipitins as reported previously (6). The normal values reflect what can be seen in the background population. Precipitating antibodies are only formed during chronic infections and vanish very slowly over the course of months to years. A value exceeding the normal values therefore indicates previous or present chronic infections with the pathogens to which they are directed (6).

Significant bacteriuria was defined as 10^3 CFU/mL [lower in case of classic UTI symptoms (dysuria, frequency and urgency) and increased levels

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of specific precipitating antibodies]. MDR was defined as acquired non-susceptibility to two or more groups of antibacterial agents (penicillins, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, sulfonamides and polymyxins) that the uropathogen is normally susceptible to. The present evaluation was performed before the international expert proposal for interim standard definitions for antibiotic acquired resistance was published (20).

TREATMENT REGIMES

The recommendations from the Department of Microbiology concerning UTIs in patients with SCLs were the following: non-chronic UTIs were treated with relevant antibacterial therapy for 10–14 days. Chronic UTIs with uropathogens with normal susceptibility were treated initially with one type of antibacterial therapy (often beta-lactam antibiotics) for 5–7 days followed by 3–4 weeks of treatment with another type of antibacterial therapy (preferably fluoroquinolones if the microorganism was susceptible to this). Some patients might have been treated for non-chronic UTI before they developed chronic UTI.

Chronic UTIs with MDR bacteria or any of the following uropathogens (*Proteus* sp., *Pseudomonas* sp., *Serratia* sp. or *Acinetobacter* sp.) were treated similarly. Initially, they were treated with a combination of two types of antibiotics with different antibacterial killing mechanism (e.g., beta-lactam antibiotics inhibit cell wall biosynthesis whereas fluoroquinolones inhibit the DNA synthesis) and to which the pathogen was susceptible for 5–7 days, if necessary including hospitalization. This was followed by treatment with another group of antibiotic for 4 weeks (often fluoroquinolones if the microorganism was susceptible to this). If the pathogen was only susceptible to the two groups of antibiotics used in the initial treatment, the treatment was continued with one of these, most often beta-lactam antibiotics.

A detailed drug history could not be obtained for all patients and it is possible that some patients have received antibiotic treatment other than that recommended; however, in this analysis, we only included patients who were followed up regularly at the Clinic for Spinal Injuries. All these patients were asked whether they had received any other antibiotic treatment.

All indwelling catheters were recommended to be replaced 2 days after treatment was initiated. If urinary tract stones were present, long-term antibiotic treatment was not recommended. The primary treatment was removal of the stones, sometimes in combination with antibiotic treatment.

STATISTICS

The data were analyzed using Microsoft Excel and Prism6. The Mann–Whitney test was used for the analysis of inter-group comparisons of continuous data. For the analysis of inter-group comparisons of categorical data, the chi-square test or Fisher's exact test was used. For analysis of intra-group data, the paired t-test was used. A p-value of < 0.05 was considered as statistically significant.

RESULTS

In total, 129 patients were defined as chronically infected; of these, nine patients had two microorganisms significant for chronic urine infection and

Table 1. Demographic data

	Entire cohort (n = 129)	Treated (n = 81)	Non-treated (n = 27)	Probably treated (n = 7)	Probably non-treated (n = 6)	No data (n = 12)
Patients, gender, male/female						
	94/35	59/22	19/8	6/	1	9
Age, median (min–max)						
	53 (16–94)	53 (18–94)	50 (16–71)	58 (20–66)	55.5 (47–64)	47 (26–82)
Duration of spinal cord lesion, years, median (min–max)						
	21 (1–73)	21 (2–73)	21 (1–48)	28 (19–41)	16 (6–26)	27 (7–41)
Cause of spinal cord injury, n (%)						
Traumatic	42	27	7	3	1	4
Innate	26	17	6	1	0	2
Other	37	22	9	2	1	3

The patients are divided into five groups, treated and non-treated, according to the recommendations from the Department of Microbiology. Probably treated and probably non-treated when some data were missing and the last group (no data) when data were too inadequate to establish if the patient was treated or if the patient died shortly after counseling was given. Causes of spinal cord injuries were many primary traumatic, innate and birth injuries and others. The large group of "other" consists of a wide variety of acquired causes including benign tumors, vascular malformations or thrombosis, degenerative and immune-mediated causes and postsurgical sequelae.

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therefore 138 isolates were included. Table 1 shows the demographic data for the entire cohort. Complete data were available for patients in the treated and non-treated groups. Two patients from the treated group and three patients from the non-treated group, with urinary diversion by intestinal segments, were excluded from the outcome analysis because of missing data. In the last group of patients (n = 9), the data are not adequate to establish whether treatment recommendations were followed at all. Three patients died shortly after counseling; the causes of death were lung edema following sepsis, lung edema following heart failure and in the last case unknown. In the analysis of outcome, only the treated and non-treated groups of patients are included.

Concerning the type of bladder drainage, 50% (n = 64) of the patients used intermittent catheterization, 30% (n = 39) had indwelling catheters, and 10% (n = 13) had near-normal bladder emptying whereas 10% (n = 13) used other methods [suprapubic tapping, urosheath, Koch pouch and uretero ilio cutaneostomia (a.m. Bricker)]. The proportion of patients using intermittent and indwelling catheters in the treated group was 52% (n = 42) and 27% (n = 22), respectively. In the non-treated group, 41% (n = 11) used intermittent catheterization whereas 37% (n = 10) used indwelling catheters. Of the 138 isolates, the three most frequently found microorganisms were *E. coli* (n = 75), *Klebsiella* sp. (n = 28) and *P. aeruginosa* (n = 25). Other bacteria were found in the rest of the isolates [*Citrobacter* sp. (n = 3), *Proteus* sp. (n = 3), *Enterobacter cloacae* (n = 3) and *Enterococcus faecalis* (n = 1)]. In an analysis of the type of uropathogen found in relation to the type of bladder drainage method, it was seen that of the 25 patients that had an infection with *P. aeruginosa*, 68% (n = 17) had indwelling catheters. This was only the case in 22% (n = 25) of the patients with other uropathogens ($p < 0.0001$).

Table 2 shows the treated group (n = 79) and non-treated group of patients (n = 24) in relation to the number of chronic UTIs with specific uropathogens.

Figure 1 shows the specific precipitating antibodies before and after treatment in the treated group and the non-treated group of patients. For the two groups, we only had measured paired specific precipitating antibodies for 46 treated and nine non-treated patients. This was especially due to lack of measurement of follow-up specific precipitating antibodies. In the treated group, there was a statistically significant decrease in the number of precipitating antibodies after treatment ($p < 0.02$), whereas this was not the case in the non-treated patients. The follow-up was 3–12 months; the mean time of follow-up was 6 months.

Figure 2 shows the change in the number of specific precipitating antibodies in the treated and non-treated groups. No difference in change in specific precipitating antibodies was observed between the two groups.

Table 3 shows the number of positive urine cultures with the specific uropathogens that the patients are chronically infected with, in relation to the bladder emptying method. In the treated group, there was a statistically significant decrease in the number of positive urine cultures after treatment; in the non-treated group, the number of patients is not enough for statistical analysis.

Ten patients had MDR isolates; eight of these were *E. coli* and two were *Klebsiella* sp. Of the eight patients with *E. coli*, six received recommended long-term antibiotic treatment and three of these MDR *E. coli* were not found again after treatment was given. In the two patients with *E. coli* that were in the non-treated group, one did not have MDR *E. coli* again later. The two patients with *Klebsiella* sp. were also in the non-treated group; one patient did not have MDR *Klebsiella*

Table 2. Number of chronic infections and specific uropathogens

	Entire cohort	*Escherichia coli*	*Klebsiella* sp.	*Pseudomonas aeruginosa*	Others[1]	Two uropathogens[2]
Treated	79	49	14	7	4	5
Indwelling catheter	22	12	3	5	0	2
Intermittent catheterization	42	28	9	2	1	2
Other methods	15	9	2	0	3	1
Non-treated	24	8	4	8	2	2
Indwelling catheter	10	1	3	3	1	2
Intermittent catheterization	11	6	1	4	1	0
Other methods	3	1	0	1	0	0

Number of chronic infections and the responsible uropathogen in the treated (n = 79) and non-treated (n = 24) groups of patients in relation to the bladder emptying methods.
[1]Others include *Enterobacter cloacae*, *Citrobacter* sp., *Enterococcus faecalis* and *Proteus* sp.
[2]*Escherichia coli* and *Klebsiella* sp. (n = 3), *P. aeruginosa* and *E. coli* (n = 4).

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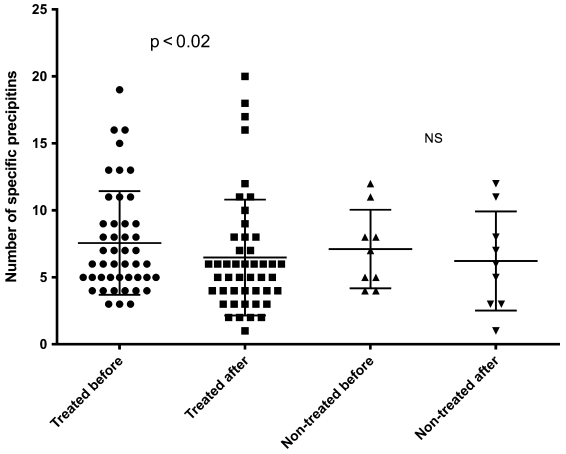

Fig. 1. Number of specific precipitating antibodies in the treated and non-treated groups 6 months before treatment and 3–12 months after counseling concerning treatment. Patients chronically infected with more than one uropathogen were not included. Data on paired specific precipitating antibodies were obtained from 46 treated patients and nine non-treated patients. We found a significant ($p < 0.02$) decline in the number of specific precipitating antibodies in the treated group ($n = 46$). There was no significant change in the number of specific precipitating antibodies in the group of non-treated patients ($n = 9$). Line represents means and standard deviations.

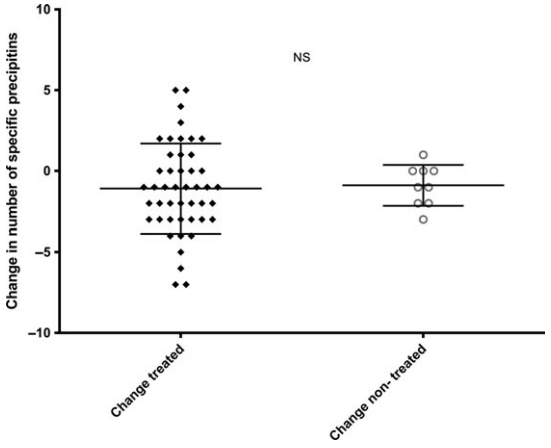

Fig. 2. Change in the number of specific precipitating antibodies in the treated and non-treated groups. Comparison of change in specific precipitating antibodies against uropathogens from before treatment or recommended treatment until 3–12 months after end of treatment or recommended treatment in the treated ($n = 46$) and non-treated ($n = 9$) groups. Line represents means and standard deviations. There was no statistical significance between the changes in the two groups.

sp. in the following urine samples. There were no urine cultures from the other patient after the time of counseling. There does not seem to be a difference between treated and non-treated patients concerning elimination of MDR bacteria but the data are too limited to make conclusions. It is possible that some patients in the non-treated group have received antibiotic treatment other than that recommended. Interestingly, no new MDR uropathogens appeared in either group of patients.

DISCUSSION

UTI is a frequently seen medical condition in patients with SCLs and especially chronic UTIs are a great challenge in relation to treatment. There is only one prospective study concerning chronic UTIs in this patient population. Clayton et al. suggest that antibiotic therapy appropriate to all members of the complex microbial community in the urine of SCL patients should be used to achieve successful treatment (21). Studies of other groups of patients with long-term catheterization do not focus on the aspect of treatment (22–24). There is no consensus on the treatment approach. In respect to prevention of UTI with antibacterial agents, previous studies have shown a significant decrease in the incidence of UTI in SCL patients given weekly oral cyclic antibiotics (alternate administration of an antibiotic once a week, week A one type of antibiotic and week B another type of antibiotic); however, these studies only included patients using intermittent catheterization (5, 25). Another study has shown remarkable efficacy of long-term low-dose ciprofloxacin in the prevention of UTIs in SCL patients, but only patients without indwelling catheters were included (26). No studies concerning prevention of UTI have been performed in chronically infected SCL patients with indwelling catheters.

The aim of the present evaluation in connection to a mini review on biofilms and UTIS was to analyze the effect of long-term treatment with antibiotics in patients with SCL and chronic UTI. One hundred twenty-nine patients over a 3-year period were evaluated. UTI was defined as chronic when there was a positive urine culture and elevated levels of specific precipitins (6), supported by repeated positive urine cultures, recurrent UTI symptoms and reduction in renal function.

The number of specific precipitating antibodies decreased significantly in the group of patients that received the recommended treatment and there was a trend toward a decrease in the number of positive urine samples. The recommended antibiotic treatment seemed effective in the elimination of chronic UTIs in SCL patients. The long-term treatment did not seem to enhance the elimination of MDR

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Table 3. Positive urine cultures before and after counseling

	Treated	p-value		p-value	Non-treated*	
	Intermittent		Indwelling		Intermittent	Indwelling
Escherichia coli – before	21/21 (100%)		7/7 (100%)		3/3 (100%)	1/1 (100%)
E. coli – after	9/21 (43%)	$p < 0.005$	4/7 (57%)	n.s. (few patients)	2/3 (67%)	1/1 (100%)
Klebsiella sp. – before	6/6 (100%)		2/2 (100%)		0/0	1/1 (100%)
Klebsiella sp. – after	0/6	$p < 0.005$	1/2 (50%)	*	0/0	1/1 (100%)
Pseudomonas aeruginosa – before	1/1 (100%)		4/4 (100%)		2/2 (100%)	2/2 (100%)
P. aeruginosa – after	1/1 (100%)	*	1/4 (25%)	$p < 0.005$ (few patients)	1/2 (50%)	1/2 (50%)
Total – before	28/28 (100%)		13/13 (100%)		5/5 (100%)	4/4 (100%)
Total – after	10/28 (36%)	$p < 0.005$	6/13 (46%)	$p < 0.005$	3/5 (60%)	3/4 (75%)

Number of positive urine culture with the specific uropathogens in the treated and non-treated patients. Only patients with indwelling or intermittent catheterization are included in this table. Six months before treatment and 3–12 months after counseling concerning treatment.
*Not enough patients for statistical analysis.

uropathogens; however, with the limited number, it is difficult to show a trend. More importantly, the aggressive treatment strategy did not select new MDR uropathogens.

An evaluation of outcome of novel treatment and diagnostic strategies confers important limitations. The single-center approach limits the number of patients available; however, all SCL patients in Eastern Denmark were followed up at this center and thereby all other treatments they received were according to the same guidelines. A detailed drug history could not be obtained for all patients and it is possible that some patients received antibiotic treatment other than that recommended; however, in the analysis, we only included patients who were followed up regularly at the Clinic for Spinal Injuries. Even though the patients were asked about the antibiotic treatment, there may be information bias. Furthermore, in many cases, there were limited data from after counseling in relation to urine cultures and precipitin values. It was possible to obtain paired precipitating antibodies for 58% of the patients in the treated group ($n = 46$) in contrast to only 38% of the patients in the non-treated group ($n = 9$). This also influences the interpretation of the results on possible changes in specific precipitating antibodies. There may be selection bias in this analysis, as it is possible that patients in the non-treated group were not followed up after counseling due to compliance problems or that the patients who no longer had UTI symptoms were no longer motivated to have new blood and urine samples taken.

One could speculate that the group reluctant to follow the treatment recommendations was also the group less compliant. This can only be further clarified through a follow-up controlled study. In addition, the non-treated group could actually have received a short antibiotic course by a private practitioner, which potentially could influence our results. With reference to the strategy used in CF where chronically infected patients are treated four times a year, our patients only received one antibiotic course (or no antibiotic course) with up to 12 months to experience a new UTI, which again could induce production of precipitating antibodies.

The present results suggest that the long-term treatment strategy is effective, and measurement of specific antibody response could be included as a diagnostic marker of chronic biofilm-related UTI. However, randomized trials, with the possibility of closer follow-up of the patients and more markers of effect and detailed and complete drug history, are needed to confirm this.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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