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Eradication of urinary tract infection following spinal cord injury

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A prospective study to evaluate the microbiological efficacy of antimicrobial treatment for urinary tract infection (UTI) was performed in 64 catheter-free spinal cord injured (SCI) patients who were visited monthly by a public health nurse who collected urine for culture and urinalysis. Patients also mailed urine dip slides for weekly bacterial counts. UTI was defined as a culture yielding $\geq 100{,}000$ colonies/ml. Treatment was given to asymptomatic patients only if pyuria (≥ 10 urinary leukocytes/high powered microscopic field) was present. Initial treatment was for 7–14 days (group 1). When it became apparent during the study that eradication was difficult and relapse or reinfection frequently occurred within a short time after cessation of antibiotic, a second treatment course of ≥ 28 days (group 2) was given. By the end of the study, in which all patients were followed for a minimum of 30 days post treatment, 39/42 (93%) cases in group 1 and 11/13 (85%) in group 2 who had initial eradication, had relapsed or become reinfected. The median number of days and standard error for group 1 to relapse or become reinfected was 16 ± 2.5, and for group 2 it was 27 ± 6. Development of drug resistance was documented when bacteria isolated prior to any treatment were compared with strains isolated after ≥ 28 days of antibiotics. In this study, urine sterility was achieved in a minority of treated UTIs and was relatively short lived. Advisability of treating asymptomatic UTI following SCI is questionable from both a medical-economic and microbiologic standpoint, particularly in view of the likelihood of inducing multidrug resistance with prolonged antibiotic exposure.

Keywords: urinary tract infection; spinal cord injury; antibiotics.

Introduction

Chronic or recurring urinary tract infections (UTI) are a major problem throughout the lives of many spinal cord injured (SCI) persons with neurogenic bladder dysfunction. Acute UTIs or their secondary complications are responsible for much of the medical care costs incurred by these individuals. The nature of the neurological lesion and pathophysiology of the genitourinary tract following SCI results in many infections occurring without overt symptoms. Treatment for patients with a positive urine culture in the absence of symptoms in this population is controversial in view of the lack of data regarding microbiological efficacy and its unproven value in preventing short term recurrences and/or secondary complications. Overall, there appear to be few benefits and treatment is often excessive. However, the uncertainty of the risk at which bacteriuria may affect the remainder of the urinary tract, coupled with patient attitudes, leads many clinicians to elect to treat asymptomatic bacteriuria in catheter-free SCI patients. In addition to lack of consensus on when treatment should be offered, there is also no universal agreement as to what constitutes the most appropriate duration of therapy, even for symptomatic patients. We performed a prospective study in a group of catheter-free SCI outpatients to quantify the microbiological efficacy of oral antibiotics used to treat UTI and to evaluate the effect of antibiotic exposure on

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susceptibility patterns of subsequent urinary bacterial isolates. This study was performed with the approval of the Institutional Review Board for Human Use, and informed consent was obtained from all participants.

Patients and methods

Patient population

Sixty-four SCI patients who were part of an ongoing prospective study of UTI epidemiology were included in the treatment program. For the detection and follow up of UTI, patients underwent monthly surveillance urinalysis, urine cultures and antibiotic susceptibility testing for up to 12 months, mean 44 weeks. Urine specimens were collected monthly by a public health nurse in the patients' homes. Either clean-catch or clean in and out catheterization was employed, depending on the patient's usual method of bladder management, whether it be an external urine collection device (condom catheter) or intermittent catheterization, respectively. In addition, urine dip slides (Starplex, Mississauga, ONT) were inoculated weekly by patients themselves by immersing the slide into a sterile container of freshly voided urine collected in the same manner as that of the public health nurse. The dip slide was then reinserted into its plastic cylinder and mailed to the microbiology laboratory for bacterial counts. Entrance requirements included neurological lesions classified as Frankel grades (A) neurologically complete; (B) neurologically incomplete-preserved sensation only; or (C) neurologically incomplete-preserved motor (nonfunctional), with a neuropathic bladder. Only patients meeting these criteria and who were free from indwelling or suprapubic catheters were enrolled in the study. Factors for exclusion included previously documented intrarenal or vesicoureteral reflux, urinary calculi, or severely diminished renal function as measured by scintigraphic scanning.[1] A summary of the demographic features of the population is given in Table I.

Table 1 Characteristics of patient population

Demographic variable	No. of patients
Total enrolled	64
Sex	
Males	59
Females	5
Race	
Whites	32
Blacks	32
Injury level	
Paraplegic	42
Quadriplegic	22
Frankel grade	
Complete (A)	51
Sensory preserved (B)	7
Motor nonfuctional (C)	6
Bladder management	
Intermittent catheterization	18
External (condom) catheter	46

Laboratory methods

Urine collected by the public health nurse was maintained on ice until its delivery to the microbiology laboratory at the end of each day. Urine was inoculated onto MacConkey and 5% sheep blood agar (BBL, Cockeysville, MD) using a quantitative calibrated loop technique. Agar plates were incubated at 35 °C for 48 hours before being designated negative. Bacterial isolates were identified and antibiotic susceptibility testing was performed according to standard procedures using the API System and Uniscept Microbroth Dilution (Analytab Products, Plainview, NY). Upon receipt, inoculated dip slides, containing MacConkey and cysteine-lactose-electrolyte-deficient agar, were incubated at 35 °C for 48 hours before being designated negative. Colony counts on dip slides were determined by visual examination according to the manufacturer's instructions. Dip slide isolates were identified and susceptibilities determined when necessary to initiate or evaluate antimicrobial chemotherapy. The use of agar dip slides to monitor the urinary tracts of SCI patients has been previously described.[2] Quantitation of urinary leukocytes from monthly specimens was performed microscopically by direct manual counts in a hemocytometer following centrifugation of 10 ml of urine and resuspension of sediment in 1 ml. Results were enumerated as leukocytes per high powered field (hpf) and per mm^3.

Definition of urinary tract infection

UTI was defined as a culture or dip slide containing ⩾ 100,000 colonies/ml. Although this criterion was initially established in neurologically normal women, it has withstood the test of time and is still widely accepted by physicians caring for SCI patients to define significant bacteriuria, particularly in asymptomatic cases. Gribble *et al*[3] concluded that bacterial counts of ⩾ 100 colonies/ml may be indicative of true bacteriuria based on a comparison of paired urine samples obtained by suprapubic aspiration and catheterization. However, they also pointed out that the predictive value utilizing the lower threshold of significance would be lessened in patients managed with condom catheters if such devices promote heavy urethral colonization.

Antimicrobial treatment and bacteriological outcomes

Monthly urine cultures and weekly bacterial counts from dip slides along with urinalysis were used to identify UTI and determine when antimicrobial chemotherapy was to be administered. In addition to the monthly nurse visits which included physical examination and questioning regarding the status of the urinary tract, patients were called by telephone weekly. They were questioned specifically on a number of topics including the presence of fever, chills, abdominal or flank pain and hematuria. Patients were considered to have symptomatic UTI if any of the above complaints were voiced in conjunction with a positive culture ⩾ 100,000 colonies/ml. UTI was considered asymptomatic if these conditions were absent. Treatment was reserved for patients whose urine colony counts met the 100,000 colonies/ml threshold and who had accompanying pyuria of ⩾ 10 leukocytes/hpf, if asymptomatic. Pyuria was used as a means to identify asymptomatic patients who might be more likely to benefit from antimicrobial therapy since this variable has been suggested as a marker for urinary tract inflamation which may distinguish true invasive infection from colonization.[4,5] Symptomatic UTIs meeting the colony count threshold were treated regardless of urinalysis results. A UTI was considered totally eradicated only if the urine culture or dip slide showed 0 colonies/ml when tested 1 week post treatment.

The choice of antimicrobial agent was made according to *in vitro* susceptibility tests, except in cases of symptomatic UTIs which necessitated empiric treatment until laboratory data were available. Antibiotics were limited to a small number of commonly used, orally administered drugs which were the most cost effective. Since this study was not aimed at evaluating a particular drug or group of drugs, no attempt was made to limit use to a single agent. The initial treatment for the first documented UTI was for 7–14 days (group 1). After initiation of treatment, patients continued in the surveillance program with weekly dip slides and monthly urine cultures, allowing for at least one mid-treatment specimen and another approximately 1 week following completion of antibiotic. Compliance with medication was monitored by telephone calls to the patient during therapy. Patients whose infections were designated eradicated based on a negative culture 1 week post treatment, were carefully followed with weekly dip slides and monthly cultures for subsequent relapse with the original infecting organism(s) or reinfection with new bacterial species. Subsequent positive cultures warranted repeated courses of antibiotics according to the above inclusion criteria. Therefore, some patients were entered into the treatment trial on multiple occasions. When it became apparent (data described in results section) that eradication was difficult to achieve in many patients, and relapse and/or reinfection tended to occur soon after cessation of antibiotic, it was decided to offer a longer course of treatment to those who relapsed or became reinfected and otherwise met the defining criteria for UTI. Group 2 consisted of patients from group 1 who had already received one or more courses of the 7–14 day treatment regimen and had a new or relapsed UTI. The duration of treatment for group 2 was ⩾ 28 days, the choice of drug again based on *in vitro* susceptibility tests. During and following the longer course of treatment,

patients continued to be monitored as described above.

Statistical analysis

Chi square analysis[6] was used to evaluate differences between microbiological outcomes in the two treatment groups. It was also used to compare antibiotic resistance among bacteria isolated from group 1 prior to any antibiotic treatment and following ⩾28 days of treatment in those same patients from group 1 who were subsequently evaluated as group 2. Because a few patients remained free of UTI following treatment until the end of the surveillance period, the duration of infection-free urine following initial eradication for each group was assessed using Kaplan-Meier analyses.[7]

Results

Microbiological efficacy of antimicrobial treatment

A total of 89 UTIs were treated for 7–14 days, mean 12 days, in 51 patients. An additional 32 UTIs were treated for ⩾28 days, range 28–48 days, mean 32 days, in 30 patients. The antibiotics used and the number of UTIs treated with each drug for both groups are shown in Table II. The distribution of antibiotics between the two treatment groups was similar. Microbiological outcomes for treated UTIs in groups 1 and 2 are shown in Table III. The sterility rates for mid-treatment urine specimens were 54% and 72%. Although there was an 18 percentage point difference between the two regimens in favor of the longer period, it was not statistically significant. Total eradication of infection as measured in a urine specimen collected 1 week after completion of antibiotic showed similar percentages of 47% and 41% for groups 1 and 2 respectively, which were also not significantly different. Symptomatic UTI was not a prerequisite for inclusion in the study and no attempt was made to evaluate any sort of clinical response of symptomatic infections to treatment.

Duration of infection-free urine following initial eradication

The duration of urine sterility in UTIs which were completely eradicated when assessed 1 week after completion of treatment is shown in Figure 1. Three cases from group 1 and two cases from group 2 remained free of infection until the end of the surveillance

Table II Antibiotics used to treat urinary tract infections

Antibiotic	Group 1 (7–14 days) (n = 89)	Group 2 (⩾28 days) (n = 32)
Norfloxacin	29	7
Trimethoprim/sulfamethoxazole	25	11
Ciprofloxacin	15	8
Ampicillin	6	0
Cephalothin	3	0
Other (includes combinations)	11	6

Table III Microbiological outcomes for urinary tract infections

Treatment group	No. treated	No. sterile mid-treatment (%)	No. sterile 1 week post-treatment (%)
1 (7–14 days)	89	44/82 (54)[a]	42/89 (47)
2 (⩾28 days)	32	23/32 (72)[b]	13/32 (41)[b]

[a]Cultures were available during treatment from 82 of the 89 total patients treated for 7–14 days.
[b]Not significantly different ($p > 0.05$).

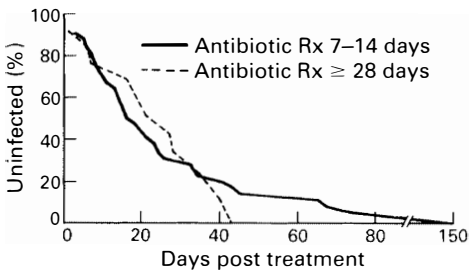

Figure 1 Duration of urine sterility following antimicrobial treatment for group 1 (7–14 days) and group 2 (≥ 28 days). Range of days for group 1 until the first positive culture was 3–146, median and standard error 16 ± 2.5. For group 2, the range was 3–43 days, median and standard error 27 ± 6.

period. All cases were followed for a minimum of 30 days post treatment. Calculations of days elapsed before a subsequent positive urine culture were approximations based on weekly intervals between samples, assuming a positive culture had been present for 3 days on average. A precise measurement would require daily cultures which was not feasible for outpatients in this study. By the end of the study, 39/42 (93%) of UTIs in group 1 and 11/13 (85%) in group 2 which had been eradicated at the first post-treatment culture had relapsed or become reinfected with ≥ 100,000 colonies/ml.

Microbial characteristics of infections and effect of antibiotic exposure on susceptibilities

Bacterial species isolated prior to any antibiotic treatment and those recovered from urine from patients in group 2 who relapsed or became reinfected were similar overall. Sixty-two percent of 121 isolates from group 1 identified prior to any treatment and 52% of 54 isolates from group 2 recovered following the ≥ 28 day treatment belonged to only four genera: *Enterococcus* species, *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. Remaining isolates consisted of a variety of predominantly Gram negative bacteria, with each individual species accounting for less than 6% of the total. The single exception was *Acinetobacter calcoaceticus*, occurring in 4% in group 1 and 13% in group 2. Further analysis of bacteria isolated from the subgroup of patients from group 1 who subsequently participated as group 2 showed that 63% of 41 isolates consisted of the same four genera described above with each remaining species constituting less than 5% of the total. Even though the bacteria comprising the two groups were similar, there were changes in the antibiotic susceptibility patterns. Resistance patterns to four major antibiotics for bacteria isolated from patients in group 1 in comparison to those isolated from the same patients from group 1 who also participated in group 2 are shown in Figure 2, illustrating greater resistances among the latter. Although the trend towards greater resistance after prolonged antibiotic exposure was apparent for each of the four drugs evaluated, statistical significance in this small sample was achieved only with ciprofloxacin ($p < 0.05$). Numbers of individual species were not large enough for separate analysis.

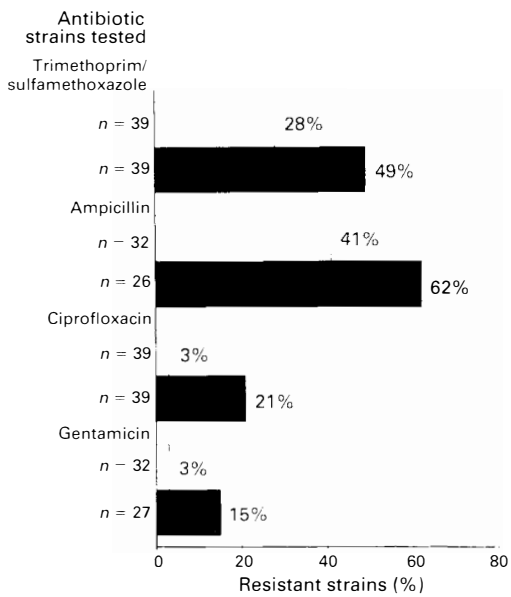

Figure 2 Comparative resistance rates among urine bacterial isolates to four antibiotics prior to any treatment and following ≥ 28 days of treatment. A statistically significant increase in resistance was shown only for ciprofloxacin ($p < 0.05$).

Discussion

Complicated UTIs in persons with SCI represent perhaps the most complex and difficult type of urological infection from a management standpoint. UTIs in this population are frequently asymptomatic, polymicrobial, caused by bacteria which are resistant to multiple antibiotic therapy, and are very likely to recur or relapse.[8] The occurrence of serious urological complications is usually related to ascending or hematogenous spread of uncontrolled infection from a focus in the lower urinary tract to the upper tract, or even to remote organs.[8] The unavoidability of UTI, its potential seriousness and high costs of management, have made it the subject of many studies in the SCI population that have attempted to determine the optimal means for prevention, diagnosis and treatment.

Sticker and Chawla,[5] in a recent review of published literature on UTI following SCI, summarized the therapeutic advice from experts in the field regarding usage of antibiotics under a variety of circumstances. A number of different viewpoints on treatment were discussed, but the authors correctly pointed out that an objective assessment of the relative merits of the various policies is severely lacking because little or no comparative work on their efficacy has been reported. Most studies published to date have been aimed at comparing the merits of various antimicrobial prophylactics, *in vivo* evaluation of a particular drug, or have dealt exclusively with recently injured hospitalized patients and have not included longitudinal follow up of persons after 1 month post treatment. Very little quantitative information exists on the subject of the microbiological efficacy of antimicrobial treatment of UTI in SCI patients and the ability to maintain a urinary tract free of infection for any considerable length of time.

There are a few recent studies involving SCI patients treated for UTI for which mid-treatment and short term post-treatment measures of microbiological efficacy are available for comparison. Mid-treatment urine sterility rates in the two patient groups in the present study of 54% and 72% were somewhat lower than values reported by others. Stannard *et al*,[9] in a study of 38 hospitalized SCI patients treated with ciprofloxacin for 5 days found 97% of patients had negative cultures on day 3 of therapy. Pedersen *et al*[10] reported that urine sterilization was achieved on day 3 of a 6 day course of ciprofloxacin treatment in nine of 11 (83%) SCI outpatients. Previous studies performed at our institution in SCI inpatients undergoing intermittent catheterization[11] and catheter-free SCI outpatients[12] treated with a 10–14 days course of norfloxacin for UTI, showed mid-treatment eradication in 21 of 23 (91%) and 58 of 79 (73%) cases, respectively. Eradication rates measured 1 week post treatment, of 41% and 47% for the two treatment groups in the present study, were generally consistent with reports of others. In Pedersen's study,[10] microbial eradication was achieved in 9/11 (83%) patients cultured immediately after treatment, but only four of 10 (40%) evaluable patients remained free of infection when cultured 1 week later, which declined to two of 10 (20%) after 4 weeks. Stannard[9] did not reculture until 14 days post treatment, but at that time only six (20%) of 30 specimens were negative, four (13%) had insignificant growth, and 20 (67%) had $\geqslant 100{,}000$ cfu/ml. Their evaluation after 35 days showed that only two of 25 (8%) remained sterile. Urine cultures collected 1 week post treatment in the studies of Waites *et al*[11,12] showed eradication in seven of 23 (30%) and 42 of 79 (53%) cases, respectively. In the study of Waites *et al*[12] post-treatment cultures obtained after 8–12 weeks in 32 of 42 cases with initial eradication showed relapse or reinfection in 27 (84%) cases, a finding consistent with the present study. Since the majority of persons with a previous UTI relapsed or became reinfected before completion of the present study, it seems likely that those who were treated late and followed for only 30 days would eventually develop a positive culture. Though multiple antibiotics were administered, the follow up of patients with documented eradication 1 week post treatment until the first positive culture is valid since each was essentially starting from the same measured level.

One explanation for the generous range of mid-treatment urine sterility rates between the present study and those described above could be potential differences in the efficacy of the antibiotics used or variations in microbial characteristics and virulence factors of the infecting organisms. Differences might also be related to the fact that many of the mid-treatment and follow up urine specimens in the studies of Waites *et al*[12] and the present investigation were cultured by patients themselves with dip slide technique rather than having a quantitative urine culture performed in a clinical setting. However, good correlation between dip slides and conventional streaked plates for quantitating low-density bacteria as well as $\geqslant$ 100,000 cfu/ml in urine cultures from SCI patients has been previously reported.[2] Finally, it should be noted that in the two studies cited above,[11,12] eradication rates do not refer to total eradication with 0 colony count, but to a colony count of $<$ 100,000 colonies/ml.

The idea of continuing antibiotic treatment for UTI longer than the commonly used regimens which typically are limited to 14 days or less duration has a legitimate basis. Electron micrographs of the bladder epithelium from patients suffering from chronic UTI have shown gross disturbance of the urothelium with extensive exfoliation of underlying cells, suggesting that prolonged therapy may be required for a chronically infected bladder to allow regeneration of the urothelium, a process which could take up to 6 weeks.[13] For these reasons, some investigators have suggested a course of antimicrobial therapy for 6 weeks or more for symptomatic UTI in order to thoroughly eradicate any bacteria which may reside within deep-seated, protected renal or prostatic foci. Such organisms are very likely to relapse after transient suppression or reenter the urinary tract from the perineal–fecal reservoir.[10,14–17] Boerema and Van Saene[14] reported surprisingly encouraging results in their long term treatment trial with norfloxacin which support the longer treatment alternative. They studied 24 patients with complicated UTI, including seven with spinal cord lesions who were given one of two dosage regimens of norfloxacin for a total of 3 months. They achieved bacteriological cure rates of 75% and 92%, respectively, during therapy. One month after discontinuation of therapy, cure rates for the two groups were 75% and 83%. They concluded that the effectiveness of their regimen was due to the superior effects of norfloxacin against the endogenous reservoir of urinary pathogens and its high concentrations in feces and urine without seriously disrupting the anaerobic bowel flora.

The manner in which the present study was performed, ie that patients in group 2 consisted of those from group 1 who had relapsed or become reinfected, and might therefore harbor more virulent or resistant organisms, favors not finding a significant difference in duration of urine sterility in the latter group, even though the treatment course was longer. If all patients had been given the longer treatment course initially, the eradication rates and duration of urine sterility might have been somewhat improved. Nonetheless, the measured difference, a matter of days, in duration of urine sterility between the two groups was probably not clinically meaningful.

It is hardly surprising that increases in antibiotic resistance were detected among bacteria isolated following the second treatment course in the present study. SCI patients are colonized soon after injury and hospitalization with a diverse, multidrug resistant Gram negative enteric.[17] Development of drug resistance by bacteria during or after treatment as well as reinfection with new and resistant organism(s) commonly occurs in complicated UTIs.[12] The increase in quinolone and aminoglycoside resistance among isolates from the patients in group 2 following treatment is of particular concern and provides further rationale for careful consideration prior to using antibiotics in this population and risking further selection of multiply resistant strains.

In conclusion, the findings of this study prove that complete urine sterility measured within 1 week following antimicrobial therapy for UTI in a group of SCI patients was achieved in a minority of cases. Sterility, when it did occur was relatively short lived, even in the patients who had received

the longer treatment. This raises further doubts on the rationale for treatment in the absence of significant symptomatology from both a medical-economic and microbiological standpoint. Whether a still longer treatment course of 6 weeks or more would have made a significant difference in microbial eradication or prolonged the duration of urine sterility is not known. Unless such beneficial effects are eventually proven, caregivers should limit judiciously use of antibiotics in this population when no physical evidence or symptoms of urinary tract disease are present. The threat of emerging resistant organisms, risk of unwanted side effects of antibiotics, unnecessary and ever increasing expense associated with drug administration, and potential risk to other patients from cross infection with resistant organisms widely dispersed in both the hospital setting and the community at large would seem adequate justification for adoption of such policies.

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