Spinal Cord (2008) 46, 622–626

www.nature.com/sc

ORIGINAL ARTICLE

Evaluation of cranberry tablets for the prevention of urinary tract infections in spinal cord injured patients with neurogenic bladder

MJ Hess[1], PE Hess[2], MR Sullivan[3], M Nee[2] and SV Yalla[3]

[1]Department of Spinal Cord Injury, VA Boston Health Care System, West Roxbury, MA, USA; [2]Department of Anesthesiology, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA and [3]Department of Urology, VA Boston Health Care System, West Roxbury, MA, USA

Study Design: Randomized, double blind, placebo-controlled trial with a crossover design.
Objective: To evaluate cranberry tablets for the prevention of urinary tract infection (UTI) in spinal cord injured (SCI) patients.
Setting: Spinal Cord Injury Unit of a Veterans Administration Hospital, MA, USA.
Methods: Subjects with spinal cord injury and documentation of neurogenic bladder were randomized to receive 6 months of cranberry extract tablet or placebo, followed by the alternate preparation for an additional 6 months. The primary outcome was the incidence of UTI.
Results: Forty-seven subjects completed the trial. We found a reduction in the likelihood of UTI and symptoms for any month while receiving the cranberry tablet ($P<0.05$ for all). During the cranberry period, 6 subjects had 7 UTI, compared with 16 subjects and 21 UTI in the placebo period ($P<0.05$ for both number of subjects and incidence). The frequency of UTI was reduced to 0.3 UTI per year vs 1.0 UTI per year while receiving placebo. Subjects with a glomerular filtration rate (GFR) greater than 75 ml min^{-1} received the most benefit.
Conclusion: Cranberry extract tablets should be considered for the prevention of UTI in SCI patients with neurogenic bladder. Patients with a high GFR may receive the most benefit.
Sponsorship: Spinal Cord Research Foundation, sponsored by the Paralyzed Veterans of America
Spinal Cord (2008) **46,** 622–626; doi:10.1038/sc.2008.25; published online 8 April 2008

Keywords: cranberry; spinal cord injury; neurogenic bladder; urinary tract infection

Introduction

Cranberries have been widely used by the public for the prevention and treatment of urinary tract infection (UTI). Anecdotal evidence of the beneficial effects of a diet including cranberries dates back almost a century. Recently, several randomized studies evaluating cranberries for the prevention of UTI in high-risk populations found conflicting results. Adult women with recurrent UTI appeared to receive a significant benefit, but children with neurogenic bladder did not.[1–5] The adult spinal cord injured (SCI) population are at high-risk for UTI, with estimates as high as 1.8 episodes per year.[6] Infections are often polymicrobial and antibiotic resistant, and long-term antibiotic prophylaxis has not shown significant benefit.[7,8] Despite advances in the management of neurogenic bladder, UTI represents a leading cause of morbidity and hospitalization.[9] This trial was designed to evaluate the effects of cranberry tablets as a prevention of UTI in the adult spinal cord injury population with neurogenic bladder.

Correspondence: Dr MJ Hess, Department of Spinal Cord Injury, VA Boston Health Care System, Building 2, 1400 VFW Parkway, West Roxbury, MA 02132, USA.
E-mail: Marika.hess@med.va.gov
Received 11 March 2007; revised 3 December 2007; accepted 15 December 2007; published online 8 April 2008

Methods

This randomized, double blind, placebo-controlled crossover trial was approved by the hospital Institutional Review Board. Written informed consent was obtained prior to enrollment and randomization. All subjects were recruited from the spinal cord injury service in the Veteran's Administration Boston Health Care System, where they received all of their medical care. All subjects had a clinically documented spinal cord injury determined by a staff physician with documentation of neurogenic bladder. Subjects were of ASIA A, B or C. Exclusion criteria included SCI of less than 1-year duration, a glomerular filtration rate (GFR) of less than 30 ml min^{-1}, immunosuppressive medications or current malignancy.

Baseline examination

Patients received baseline history and physical examination, including age, gender, level of injury, ASIA exam, method of

bladder drainage, surgical history, allergies, medications and the number of UTI in the past 12 months. Hospital records were reviewed to ensure accuracy of UTI history. Evaluation also included the most recent measure of GFR, either by renal scan or 24-h creatinine clearance. Baseline urine sample was examined for urinary pH, leukocytes and Gram stain and culture.

Randomization and measurements

Patients were randomly assigned to receive either cranberry extract tablet or placebo tablet for 6 months, followed by the alternate preparation for an additional 6 months. All tablets were dispensed through the pharmacy. There was no washout time between periods. Both the investigators and the patient were blinded to the group assignment. The cranberry extract tablet contained concentrated cranberry fruit extract with 500 mg of *Vaccinium macrocarpon* (CranMax, Swiss Herbal, Canada). The placebo tablet was identical in all ways, and consisted of rice flour. Tablets were taken twice per day during the study periods.

Patients were followed in the SCI clinic every month for the signs or symptoms of UTI. UTI was defined as:

(1) The presence of $>10^4$ organisms per milliliter of urine
(2) The presence of one or more new symptoms and
(3) Evidence of tissue invasion such as hematuria ($\geqslant$4 RBC/HPF) or pyuria ($\geqslant$10WBC/HPF).

Symptoms considered consistent with a UTI were: sweats, malaise, increased bladder spasm, autonomic dysreflexia, abdominal discomfort, fevers and chills. A urinalysis and culture was performed at each monthly exam. If the subject had an unscheduled admission between visits, the records were reviewed and any occurrence of a UTI was included if the criteria were met. Requirements for antibiotic treatment of UTI were assessed on a monthly basis. Patients who were identified as having a UTI were given a 10-day antibiotic course based on culture sensitivities. Elimination of the UTI was assessed after treatment. The study medications were continued throughout the period of antibiotics. Finally, to assess patient compliance with the study, the pills remaining in the pillbox were counted at each monthly visit.

Statistical analysis

Comparison of rates of UTI (per person-year) was performed using the Wilcoxon signed rank test. The 6-month cumulative incidence of UTI between periods was performed using χ^2 test with Yates correction. The monthly incidence of UTI was compared using random effects logistic regression with correction of standard errors for repeated measures. Analysis of additional factors, including all demographic and medical characteristics that may have proved beneficial was performed using Pearson χ^2, or Mann–Whitney test, as appropriate. Multivariate random effects logistic regression analysis was performed to identify those factors that contributed to the development of an UTI during the year of study. *A priori* power analysis for a 35% reduction in the incidence of significant bacteriuria (baseline rate of 18.4 events per year)[6] and of UTI (baseline rate of 1.8 UTI per year) suggested that we would need 75 and 48 subjects, respectively, with a power of 0.8 and a significance of 0.05. Our goal was to enroll 75 subjects during the trial. Presentation of differences between groups are reported with 95% Confidence Intervals (CI), where appropriate. Significance was determined at a *P*-value of $\leqslant$0.05. Analysis performed using Stata 8.0.

Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Results

Fifty-seven subjects were enrolled between August 2002 and August 2004, and were followed with monthly evaluations at the Veteran's Administration hospital for a period of 1 year. Subjects received all of their care at the hospital for at least 1 year prior to enrollment. One subject died during the year, six subjects were non-compliant with either monthly visits or pill counts, two subjects developed urinary stones and one subject completed only the first 6 months of the trial. Thus, 47 subjects successfully completed the study. All subjects were men, the median age was 53 years (range: 28–79) and the ASIA class distribution was A = 27, B = 10 and C = 10. Twenty-three subjects were quadraplegic, and the remainder paraplegic. Bladder management was by condom catheter ($n=35$), intermittent catheterization ($n=8$) and four subjects had indwelling catheters (two foley and two suprapubic). The baseline GFR was 73 ml min^{-1} (range: 35–147). The baseline urine pH median was 6.65 (range: 5.0–8.5). No subject met the criteria for UTI at the start of the trial. The mean rate of UTI in the year prior to enrollment was 1.3 UTI per person-year (s.e.m. = 0.2), with differences by method of drainage of: condom catheters: 1.0 UTI per person-year; intermittent catheterization: 1.3 UTI per person-year and indwelling: 2 UTI per person-year. During the study, 28 episodes of UTI were diagnosed in 22 subjects. The median number of new symptoms was 3 (range 1–5). The most common symptom was sweating ($n=21$), followed by spasm ($n=14$), autonomic dysreflexia ($n=11$), fever ($n=9$), malaise ($n=9$) and abdominal discomfort ($n=1$).

We found no difference in the incidence of significant bacteriuria between groups; there were 31 episodes in the cranberry period and 37 in the placebo period ($P=0.52$). However, we found fewer UTI during the cranberry period than the placebo period (7 UTI per 6months vs 21 UTI per 6months, $P=0.01$). Fewer subjects experienced at least one UTI during the 6-month period of cranberry tablet consumption than during the placebo period (6/47 subjects (13%) compared with 16/47 subjects (34%), $P=0.03$; 21% difference 95% CI = 5–38%). The incidence rate of UTI (prorated to 12 months) during the placebo 6 months was similar to the rate reported during the 12 months prior to the study (0.9 vs 1.3 UTI per person-year, $P=0.07$). The rate of UTI was significantly lower during the cranberry period

(0.3 vs 0.9 UTI per person-year, $P=0.01$). By logistic regression analysis, we found a favorable reduction in the month-by-month likelihood of UTI during the cranberry period compared with the placebo period ($P=0.01$, odds ratio = 0.3, 95% CI = 0.1–0.7, Figure 1). Furthermore, there was a reduction in the likelihood of monthly symptoms except bladder spasms ($P<0.05$ for all, $P=0.07$ for spasm). The organisms identified during each of the periods are listed in Table 1. We found no difference in urinary pH between treatment and placebo periods (cranberry pH = 6.3 ± 0.7 vs placebo pH = 6.3 ± 0.6, $P=0.91$; Figure 2). Because we were unable to meet our enrollment target, we conducted a *post hoc* power analysis, which determined our power = 0.73.

We found two univariate predictors of developing a UTI: a history of UTI, and the method of bladder management ($P<0.05$ for both). Subjects with a GFR greater than 75 ml min^{-1} had an improved outcome ($P<0.01$); that is, among the 22 subjects with a high GFR, 9 had 11 UTIs during the placebo period, and none during the cranberry period ($P<0.01$). On the other hand, among the 25 subjects with a low GFR, 7 subjects had 10 UTIs during the placebo period, which was reduced to 6 subjects with 7 UTIs with cranberry tablets (P = NS for both subjects and infections). By multivariate analysis, only cranberry administration and a history of UTI were found to be significant (Table 2). We also conducted analysis using a nested model (GFR within cranberry/placebo) and found that a GFR >75 ml min^{-1} was associated with a lower rate of UTI during the cranberry period.

Discussion

We found a significant reduction in UTI during the period of cranberry tablet consumption. We found a 60% reduction both in the number of UTI and of subjects who experienced any UTI. On subgroup analysis we found that a subject's GFR appeared to influence the success of cranberry tablets; that is, UTI was virtually eliminated while taking cranberry supplements among subjects with a GFR above 75 ml min^{-1}. We hypothesize that the combination of bacterial adherence inhibition and a high urinary filtration rate functioned together to prevent bacterial biofilm formation and to eliminate the pathogens. To our knowledge, we are the first to identify this effect.

We found no effect of cranberry extract on the pH of the subjects' urine. The historical hypothesis was that benzoic acid, which is excreted as hippuric acid in the urine, prevented bacterial growth. Most recent studies, including our own, have found no change in urine pH.[1,10] Thus, whatever impact cranberries have on bacterial colonization might be due to an effect on cell wall adherence. Cranberries have been shown to inhibit bacterial adherence to the uroepithelial cell wall. This property has been best studied with *Escherichia coli*,[11–13] but has been shown to affect all Gram-negative rods.[14] Furthermore, cranberry juice has been shown to reduce the biofilm load of both Gram-negative and Gram-positive bacteria on the uroepithelial cells of SCI patients.[15] It is believed that the active component found in cranberries leading to this effect is a proanthocyanidin molecule. Only about 5% of the cranberry juice proanthocyanidin ingested by humans is excreted in the urine;[16] however, this appears to be sufficient to prevent bacterial adherence.[11]

Two studies have evaluated the use of cranberries in the adult SCI population. Linsenmeyer *et al*.[17] assessed cranberry tablets for prevention of bacteriuria and pyuria in 21 patients. Their crossover study compared cranberry extract to placebo each over 4 weeks. They found no favorable benefit to cranberry extract in reducing bacterial or leukocyte counts, or the combination of the two. It is not clear whether that study examined the incidence of UTI in each group. The short period of study may have caused the negative results, as the positive effect of cranberries on bacteriuria with pyuria takes up to 1 month to manifest and may persist for a period of 4 weeks.[1] Thus, any potential impact would not have manifested by the end of the study period. In a randomized study by Waites *et al*.,[18] two groups of patients with significant bacteriuria received either cranberry (26 patients) or placebo (22 patients) over 6 months for treatment of bacteriuria. There was no difference

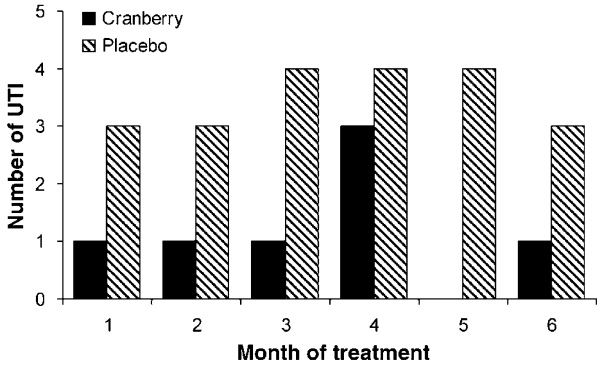

Figure 1 The number of urinary tract infections (UTI) in the subjects during each month of either cranberry or placebo treatment. The odds ratio on logistic regression was 0.3, suggesting a 70% reduction in the monthly likelihood of having a UTI during the cranberry period ($P=0.01$).

Table 1 Identification of urinary tract infection bacterial species during placebo and cranberry periods

Placebo period		*Cranberry period*	
Organism	*Number of patients*	*Organism*	*Number of patients*
Escherichia coli	5	Mixed[b]	2
Mixed[a]	4	*E. coli*	1
Staphylococcus	4	*Serratia*	1
Klebsiella	2	*Proteus*	1
Enterococcus	1	*Pseudomonas*	1
Proteus	1	*Staphylococcus*	1
Serratia	1		
Pseudomonas	1		
Morganella	1		
E. faecalis	1		

[a]Mixed consisted of: *E. coli* and *Staphylococcus* ($n=2$); *E. faecalis* and *Staphylococcus*; *Serratia* and Enterococcus.
[b]Mixed consisted of: *Staphylococcus* and *Klebsiella*; *Pseudomonas* and *Klebsiella*.

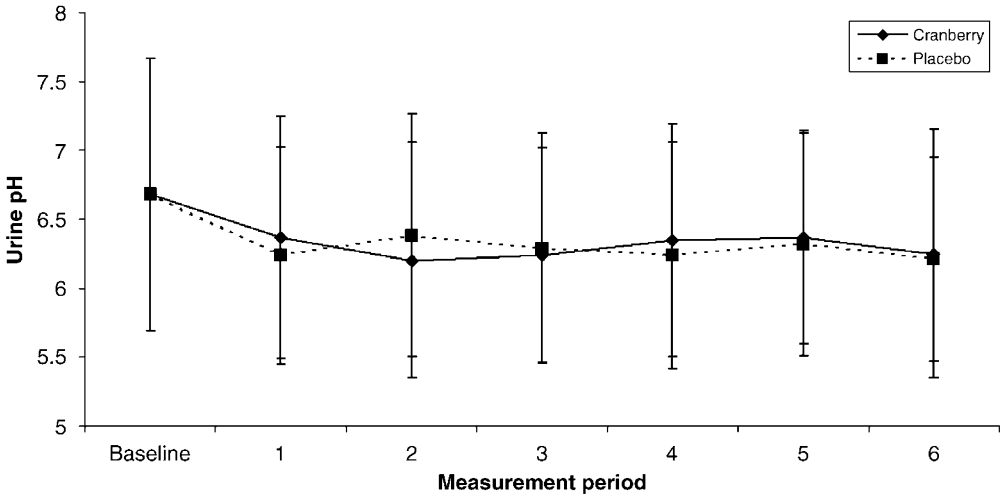

Figure 2 The measured urinary pH from subjects during each month of the study periods. Baseline measurement was taken at enrollment; other measures were taken at each monthly follow-up exam for 6 months while on cranberry or placebo. There were no significant differences between periods.

Table 2 Results of multivariate logistic regression

Factor	P-*value*	*Odds ratio*	*95% confidence interval*
Full factorial model			
Treatment group			
Placebo	—	Ref.	
Cranberry	0.02	0.28	0.1–0.8
History of UTI			
None	—	Ref.	
One or more	>0.01	2.2	1.5–3.2
Age (per year)	0.23	0.97	0.93–1.02
ASIA exam	0.7	0.78	0.21–2.9
Bladder drainage	0.3	0.49	0.13–1.9
Nested relationship			
Placebo			
GFR > 75 ml min^{-1}	—	Ref.	
Cranberry			
GFR > 75 ml min^{-1}	>0.01	0.03	0.003–0.25
GFR < 75 ml min^{-1}	0.24	0.56	0.22–1.5

Abbreviations: GFR, glomerular filtration rate; UTI, urinary tract infection.
Multivariate analysis of the factors associated with the development of a UTI during the year of study involvement. A significant association was noted between UTI and the cranberry period and the number of UTI in the year prior to enrollment. No independent relationship was found with age, ASIA exam or method of bladder drainage. We found that a high GFR (>75 ml min^{-1}) was associated with lower odds of developing a UTI when nested within the cranberry period compared to the placebo period, but not as an independent predictor.

in bacterial or urinary leukocyte counts, or in the rates of symptomatic UTI. There are some differences between that study and ours. First, in that study, patients were mailed their supply of tablets and compliance was performed by telephone interview. Because of the nature of our population, we were able to personally assess each patient and ensure compliance through pill counts. Second, our primary outcome was the incidence of UTI, which included both symptoms and evidence of tissue invasion. It is not clear whether the incidence of symptomatic UTI in their study included similar criteria. Finally, there was an imbalance in the characteristics of the randomized groups; namely, the cranberry group was more likely to use intermittent catheterization and the placebo group tended to external catheterization. Because the method of bladder drainage influences the rate of UTI in the SCI population,[19] this difference may be important, as this would bias toward a higher rate of UTI in the cranberry group. Although the authors used multivariate statistical methods to limit this effect, there may be residual influence due to the small sample size.

Cranberries have been found to be beneficial for the prevention of recurrent UTI in adult women. In a randomized, placebo-controlled trial, Avorn *et al*.[1] demonstrated a 42% reduction in the odds of having bacteriuria with pyuria, and a significant reduction in the requirement for antibiotic therapy in elderly women, a high-risk group for UTI. A similar finding was noted in two other randomized studies.[2,5] Two crossover studies in children with neurogenic bladder found no difference in either UTI or in bacteriuria with the use of cranberry juice, for either 3 or 6 months.[3,4] The natural history of UTI in congenital neurogenic bladder may not be the same as that of adult onset, or cranberry extract may not be effective for preventing bacterial colonization in that population. It is also conceivable that the dosage was inadequate for children.

We can identify several limitations to our study. Because the onset of activity and the duration of effect of cranberry extract may be delayed for 1 month, it would have been ideal to include a washout period. However, lack of a washout period would tend to underestimate the effect. Second, the influence of GFR on the effectiveness of cranberry tablets was not a primary outcome; further evaluation is necessary to confirm this finding. To our knowledge, we are the first to evaluate this. Third, we included subjects with heterogenous methods of bladder management. We believe that our study population is characteristic of a SCI population, thus the

results are clinically relevant. Fourth, we were unable to enroll the full number of subjects that were initially targeted. Our *post hoc* power analysis showed that our results are meaningful. Finally, the diagnosis of UTI in this population is complex. Asymptomatic bacteriuria is the norm and should not be treated, and the identification of significant bacteriuria vs infection is challenging.[20] Our diagnosis of a UTI was based on significant bacteriuria with symptoms and with evidence of tissue invasion. We believed that the best outcome for this study was the incidence of UTI, and not surrogates such as bacteriuria.

Conclusion

During the 6 months of cranberry tablets, we found a significant reduction in both the incidence of UTI and the number of subjects with a UTI. Patients with a high GFR received the most benefit. Cranberry extract tablets should be considered for the prevention of UTI in SCI patients with neurogenic bladder.

References

1 Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994; **271**: 751–754.
2 Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol* 2002; **9**: 1558–1562.
3 Foda MM, Middlebrook PF, Gatfield CT, Potvin G, Wells G, Schillinger JF. Efficacy of cranberry in prevention of urinary tract infection in a susceptible pediatric population. *Can J Urol* 1995; **2**: 98–102.
4 Schlager TA, Anderson S, Trudell J, Hendley JO. Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. *J Pediatr* 1999; **135**: 698–702.
5 Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ* 2001; **322**: 1571.
6 Waites KB, Canupp KC, DeVivo MJ. Epidemiology and risk factors for urinary tract infection following spinal cord injury. *Arch Phys Med Rehabil* 1993; **74**: 691–695.
7 Cardenas DD, Hooton TM. Urinary tract infection in persons with spinal cord injury. *Arch Phys Med Rehabil* 1995; **76**: 272–280.
8 Jayawardena V, Midha M. Significance of bacteriuria in neurogenic bladder. *J Spinal Cord Med* 2004; **27**: 102–105.
9 Cardenas DD, Hoffman JM, Kirshblum S, McKinley W. Etiology and incidence of rehospitalization after traumatic spinal cord injury: a multicenter analysis. *Arch Phys Med Rehabil* 2004; **85**: 1757–1763.
10 Linsenmeyer MA, Linsenmeyer TA. Accuracy of bladder stone detection using abdominal x-ray after spinal cord injury. *J Spinal Cord Med* 2004; **27**: 438–442.
11 Sobota AE. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. *J Urol* 1984; **131**: 1013–1016.
12 Ahuja S, Kaack B, Roberts J. Loss of fimbrial adhesion with the addition of *Vaccinum macrocarpon* to the growth medium of P-fimbriated *Escherichia coli*. *J Urol* 1998; **159**: 559–562.
13 Zafriri D, Ofek I, Adar R, Pocino M, Sharon N. Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated *Escherichia coli* to eucaryotic cells. *Antimicrob Agents Chemother* 1989; **33**: 92–98.
14 Schmidt DR, Sobota AE. An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates. *Microbios* 1988; **55**: 173–181.
15 Reid G, Hsiehl J, Potter P, Mighton J, Lam D, Warren D *et al*. Cranberry juice consumption may reduce biofilms on uroepithelial cells: pilot study in spinal cord injured patients. *Spinal Cord* 2001; **39**: 26–30.
16 Ohnishi R, Ito H, Kasajima N, Kaneda M, Kariyama R, Kumon H *et al*. Urinary excretion of anthocyanins in humans after cranberry juice ingestion. *Biosci Biotechnol Biochem* 2006; **70**: 1681–1687.
17 Linsenmeyer TA, Harrison B, Oakley A, Kirshblum S, Stock JA, Millis SR. Evaluation of cranberry supplement for reduction of urinary tract infections in individuals with neurogenic bladders secondary to spinal cord injury. A prospective, double-blinded, placebo-controlled, crossover study. *J Spinal Cord Med* 2004; **27**: 29–34.
18 Waites KB, Canupp KC, Armstrong S, DeVivo MJ. Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. *J Spinal Cord Med* 2004; **27**: 35–40.
19 Esclarin DR, Garcia LE, Herruzo CR. Epidemiology and risk factors for urinary tract infection in patients with spinal cord injury. *J Urol* 2000; **164**: 1285–1289.
20 Biering-Sorensen F, Bagi P, Hoiby N. Urinary tract infections in patients with spinal cord lesions: treatment and prevention. *Drugs* 2001; **61**: 1275–1287.