



# The Brazilian Journal of INFECTIOUS DISEASES

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## Brief communication

# Comparison of different antibiotic protocols for asymptomatic bacteriuria in patients with neurogenic bladder treated with botulinum toxin A

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## ARTICLE INFO

### Article history:

Received 21 March 2016

Accepted 2 August 2016

Available online 18 October 2016

### Keywords:

Botulinum toxin, type A

Urinary tract infections

Bacteriuria

Antibiotic prophylaxis

## ABSTRACT

Intravesical botulinum toxin A (BoNTA) injection has been widely used for the treatment of detrusor overactivity in patients with neurogenic bladder due to spinal cord injury who do not respond to conventional treatment. There is no consensus about antibiotic prophylaxis for this procedure. We conducted a retrospective analysis of medical records of adult patients with spinal cord injury who underwent detrusor BoNTA injection between January of 2007 and December of 2013 in a rehabilitation hospital. Occurrence of symptomatic urinary tract infection (UTI) was assessed in 3 groups in accordance with their use of antibiotics (prophylactic dosage, 3 days, more than 3 days) for the treatment of asymptomatic bacteriuria. All patients were performing self or assisted clean intermittent bladder catheterization and underwent a rigid cystoscopy, under general or regional anesthesia with sedation, and the drug used was Botox<sup>®</sup>. A total of 616 procedures were performed during the study period. There were 11 identified cases of UTI (1.8%) with a trend to a higher rate in the group that used antibiotics for longer time. This report shows that a single dose of antibiotics before the detrusor BoNTA injection is enough to prevent UTI. Randomized clinical trial should be conducted for definitive conclusions.

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Antimicrobial prophylaxis is the systemic administration of antibiotics before or during surgery with the intent of reducing the risk of local or systemic infection after the procedure. The potential benefit of antimicrobial prophylaxis is determined by factors inherent to the patient, to the procedure, and the potential morbidity of infection. Antimicrobial prophylaxis is recommended only when the benefits outweigh

the risks and anticipated costs (including cost of the antibiotic and its administration, risk of allergic reactions or other adverse events, and induction of bacterial resistance).<sup>1</sup> With the growing problem of bacterial resistance, the discussion of antimicrobial prophylaxis and its duration are extremely important to prevent bacterial resistance induced by unnecessary use of antibiotics.

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<http://dx.doi.org/10.1016/j.bjid.2016.08.012>

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Antimicrobial prophylaxis in urologic endoscopic procedures is a controversial topic.<sup>2,3</sup> A study published in 2013 evaluating the use of antibiotic prophylaxis in urological procedures in Europe observed a significant discrepancy between practices in different countries, regions, and hospital profiles, as well as poor adherence to the published recommended guidelines.<sup>4</sup>

Detrusor botulinum toxin A injection is an endourologic procedure which has been widely used for the treatment of overactivity in patients with neurogenic bladder due to spinal cord injury who do not respond to conventional treatment.<sup>5</sup> The procedure involves injections that penetrate the mucosal barrier.<sup>6</sup>

The guidelines of the American and European urological associations refer to endourologic and transurethral procedures, but do not mention injection of botulinum toxin into the detrusor.<sup>1,7</sup> For these kind of procedures, the main complications are bacteriuria, urinary infection and, more rarely, bacteremia and sepsis. Asymptomatic bacteriuria following endourologic procedures generally has no clinical significance and may spontaneously disappear.<sup>5,7,8</sup> A systematic review that assessed the effectiveness of antimicrobial prophylaxis in reducing the risk of urinary tract infection in transurethral urologic procedures evaluated 42 studies, all of which used the presence of negative urine cultures prior to the procedure as inclusion criteria. Patients with neurogenic bladder were excluded.<sup>9</sup> The only study we found assessing the need for antibiotic prophylaxis in patients with neurogenic bladder for detrusor BoNTA injection included patients with negative urine cultures before the procedure.<sup>10</sup>

In the guidelines published by the Infectious Diseases Society of America, it is clear that there is no evidence of benefit in treating asymptomatic bacteriuria. Asymptomatic bacteriuria (AB) is present in approximately 70% of patients with spinal cord injury and neurogenic bladder who perform intermittent bladder catheterization<sup>11</sup> due to functional abnormalities, urinary stasis, and the bladder emptying technique. There is an indication to treat AB only if the patient exhibits clinical symptoms of infection.

To assess the benefit of treating asymptomatic bacteriuria in the prevention of UTI, a retrospective study was conducted in a rehabilitation hospital, with evaluation of medical records of patients admitted for detrusor BoNTA injection from January 2007 to December 2013. Patients aged 18 years or older with traumatic and nontraumatic spinal cord injury, performing self or assisted clean intermittent bladder catheterization with a single-use catheter lubricated with 2% xylocaine gel were included. Urine culture with antibiotic susceptibility test was performed for all patients in the first day of hospitalization using midstream urine sample collected by aseptic bladder catheterization. The exclusion criteria were the application of BoNTA into the sphincter or other concomitant surgical procedure.

Patients were divided into three groups for comparative analysis, according to the recommendations of the institutional protocol, which guided the management of AB. From January 2007 to February 2008, the protocol recommended the use of antibiotics for seven days based on the results of urine culture, and the urological procedure was performed on the fifth day of treatment (group 1); from March 2008 to

March 2009, the recommendation has changed to the use of antibiotics for three days with the procedure performed on the second day of treatment (group 2); from April 2009 to December 2013, the recommendation was to use a single dose of antibiotic during anesthetic induction (cefazolin as first option, ciprofloxacin as second option) without taking into account the urine culture (group 3). All patients with negative urine specimens had a single antibiotic dose, regardless of the treatment group.

According to the National Institute on Disability and Rehabilitation Research quantitative urine-culture criteria for the diagnosis of asymptomatic bacteriuria included catheter specimens from individuals on intermittent catheterization in an amount equal to or greater than 102 CFU/mL.<sup>11,12</sup> The criteria for symptomatic urinary tract infection were the presence of bacteria in catheter specimens from individuals in an amount equal to or greater than 105 CFU/mL, associated with at least one of the following clinical symptoms, occurring within 7seven days of the detrusor BoNTA injection<sup>13</sup>: fever (temperature greater than or equal to 37.8 °C); worsening of neuropathic pain and/or spasticity; autonomic dysreflexia of unknown cause; increased urine loss between bladder catheterization; gastric symptoms (nausea, vomiting, loss of appetite); lower back or suprapubic pain; dysuria; antibiotic use for treatment of UTI within seven days of the procedure. Data following discharge were collected through active searching (phone call). Patients were submitted to urine culture 45 days after the procedure, when returning for outpatient evaluation.

All patients underwent a rigid cystoscopy under general or regional anesthesia with sedation and remained hospitalized for at least 48 h. The drug used was Botox® (Allergan Inc., Irvine, CA, USA), 30 applications of 1 mL (10 international units reconstituted with saline), distributed throughout the bladder excluding the trigone (total dose of 300 IU). All procedures were performed by the same surgeon.

Demographic data included gender, age and type of injury (traumatic or nontraumatic). Risk factors investigated were hematuria and insertion of an indwelling urinary catheter (IUC) following the procedure, previous diagnosis of *Diabetes mellitus*, chronic use of corticosteroids, and smoking. The information was recorded in a database developed in ACCESS 2003 and analyzed using the statistical package SPSS. Absolute and relative frequencies were used for categorical variables and measures of central tendency and dispersion were used for others. Mann-Whitney or Kruskal-Wallis tests were used for variables with no normal distribution. Categorical variables were analyzed using the chi-square test with Yates' correction, Fisher's exact test and the binomial test. *p*-Values less than 5% were considered statistically significant.

A total of 616 procedures performed during the study period on 487 patients (1.3 procedures/patient) were evaluated: 332 (68%) were male; the mean age was 37 ( $\pm 11.6$ ) years; 321 (66%) patients had a traumatic spinal cord injury, and 168 (34%) had a nontraumatic spinal cord injury (Table 1). Among patients with a traumatic spinal cord injury, 26% had tetraplegia and 74% had paraplegia and in the group with a nontraumatic spinal cord injury, the most common conditions were myelitis (38%), followed by HTLV myelopathy (25%), and myelomeningocele (10%).

**Table 1 – Demographics, risk factors, and UTI distribution within the patient groups.**

Risk factors	Groups			p-Value
	Single dosage n = 342	3 days n = 170	>3 days n = 104	
Male, n (%)	227 (66.4)	103 (60.6)	61 (58.7)	0.23 <sup>a</sup>
Mean age (SD)	36.6 (11.1)	37 (11.4)	35.4 (10.7)	0.41 <sup>b</sup>
Traumatic, n (%)	238 (69.6)	106 (62.4)	64 (61.5)	0.14 <sup>a</sup>
Hematuria, n (%)	100 (29.2)	55 (32.4)	38 (36.5)	0.35 <sup>a</sup>
IUC, n (%)	73 (21.3)	49 (28.8)	67 (64.4)	<0.05 <sup>a</sup>
Diabetes, n (%)	6 (1.8)	4 (2.4)	4 (3.8)	0.45 <sup>a</sup>
Corticosteroids, n (%)	2 (0.6)	1 (0.6)	1 (1.0)	0.08 <sup>c</sup>
Smoking, n (%)	1 (0.3)	3 (1.8)	0 (0)	0.52 <sup>c</sup>
UTI	5 (1.5)	1 (0.6)	5 (4.8)	0.06 <sup>d</sup>

IUC, indwelling urinary catheter; UTI, urinary tract infection.

<sup>a</sup> Chi-square test without continuity correction.

<sup>c</sup> Chi-square test with continuity correction.

<sup>b</sup> Kruskal-Wallis test.

<sup>d</sup> Likelihood ratio chi-square test.

Most patients (92%) had asymptomatic bacteriuria before the procedure, while 8% had negative urine cultures. The most common bacteria grown from urine specimens taken before and after the procedure were *Escherichia coli*, followed by *Klebsiella pneumoniae*. The prevalence of multidrug resistant bacteria in the urine culture taken before the procedure was 7.3%; in the postprocedure exam it was 9.3%.

We observed a difference with respect to the use of indwelling urethral catheter (IUC) between the groups, which was more common in the group that used antibiotics for more than three days ( $p < 0.05$ ). No patient was on corticosteroids or declared to smoke in the three study groups (Table 1).

During the study period, 11 cases of symptomatic UTI were identified: five in the group that treated bacteriuria for more than three days (4.8%), one in the group that treated for three days (0.6%), and five (1.5%) in the group that received a single dose. We detected a trend to higher UTI rates in the group that used antibiotics for longer time ( $\geq 3$  days), in comparison with those that used antibiotics for three or less days ( $p = 0.05$ ). No patient had more than one symptomatic UTI event. The symptoms observed in the patients that developed a symptomatic UTI were fever and/or chills (81.8%), suprapubic pain/discomfort (36.4%), urinary incontinence (27.3%) and dysuria (9%). No patient had pyelonephritis, sepsis, or required intensive care. We observed no difference between frequency of symptoms for patients with clinical signs of infection, regardless of duration of antibiotic use.

In conclusion, the majority of patients in this study had asymptomatic bacteriuria. The study reported 11 cases of symptomatic UTI (1.8%) with no difference between the groups, but with a tendency for a higher rate in the group that used more than three days of antibiotics ( $p = 0.05$ ). Most reported clinical symptoms were fever and/or chills. According to the risk factors, only the insertion of IUCs in patients that used antibiotics for more than three days showed statistical difference ( $p < 0.05$ ).

The findings of this study are in accordance with previous reports, confirming that patients with spinal cord injury who perform intermittent bladder catheterization have high rates of asymptomatic bacteriuria.<sup>11,14</sup> These patients need

to undergo urologic procedures frequently and preventing the emergence of multidrug-resistant bacteria through rational use of antibiotics is a priority.<sup>15</sup> According to some experts, the presence of asymptomatic bacteriuria is not a contraindication for the detrusor BoNTA injection and the use of antibiotic prophylaxis should follow the normal routine of each hospital site.<sup>16</sup> There are studies that show that a single dose of antimicrobial has been effective and feasible for the prevention of postoperative infection in urological surgery.<sup>17</sup> A study published in 2010,<sup>10</sup> with neurological patients with sterile urine showed a UTI rate of 7.1% in patients who did not receive prophylactic antibiotic for detrusor botulinum toxin injection. Randomized clinical trials suggest higher rates, but some studies do not distinguish between symptomatic UTI and asymptomatic bacteriuria. This study describes a low urinary tract infection rate in all treatment groups, suggesting that a single-dose of antibiotic prevents infection complications even in patients with asymptomatic bacteriuria.

Risk factors for UTI include advanced age, smoking, anatomical and functional abnormalities, the use of corticosteroids, immunosuppression, and urethral catheters. The large majority of the patients evaluated in this study had asymptomatic bacteriuria and the risk factors for UTI were similar between the groups. The fact that the group that received antibiotics for more than three days in this study kept an IUC in 64.4% after the procedure, may have been related to the team experience, since we found that this rate decreased over the years without relation to complications. The only difference found between the groups was related to the use of antimicrobials for longer periods in patients that used an IUC. In these cases, we found a tendency for statistical difference in the rates of UTI in comparison to the groups that used antibiotics for shorter periods of time ( $p = 0.05$ ), suggesting that excessive exposure to antibiotics favors the occurrence of infection. No differences were observed between groups for the other assessed risk factors.

In current practice updates protocols in institutions aimed at preventing microbial resistance induction generated by unnecessary use of antibiotics, as well as reducing adverse reactions, hospitalization time and costs. Because it was a

non-randomized, retrospective study, the external validity of these data are limited. Another issue is that the 487 patients were submitted to 616 interventions, i.e. 20% of patients approximately participated in more than one group. The similarity in the percentage of symptomatic UTI after the procedure in the three groups may have been due to a population under similar risk further aggravated by the low incidence of the outcome (11 in total).

Our results confirm that the use of a single dose of antibiotics before the detrusor BoNTA injection in patients with asymptomatic bacteriuria is enough to prevent symptomatic UTI. It is necessary to conduct a randomized clinical trial to assess the effect of different interventions for the management of asymptomatic bacteriuria in patients with neurogenic bladder before detrusor botulinum toxin type A injection.

### Conflicts of interest

The authors declare no conflicts of interest.

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