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REVIEW

# Antibiotic prophylaxis and its appropriate timing for urological surgical procedures in patients with asymptomatic bacteriuria: A systematic review

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**KEYWORDS**

Antibiotic prophylaxis;
Asymptomatic bacteriuria;
Surgical site infection;
Urological surgery;
Urological surgical procedures

**ABBREVIATIONS**

AB, asymptomatic bacteriuria

**Abstract** ***Objective:*** To review the existing literature on when and how to treat patients with asymptomatic bacteriuria (AB) who undergo urological surgery, as uncertainty about this issue persists.

***Methods:*** A systematic review was conducted to compare the different timing of administration of antibiotic prophylaxis in patients with AB undergoing urological surgery. We used predefined inclusion and exclusion criteria, and we also developed a specific quality scale to assess the quality of the papers included.

***Results:*** Nine studies met the inclusion criteria. Of the nine studies included, eight evaluated antibiotic prophylaxis regardless of the presence of AB, as their purpose was to evaluate the effectiveness of antibiotic prophylaxis for urological procedures. Of these, four studies showed a significant reduction in the rate of infections in the intervention group compared with placebo, or with the same antibiotic therapy but using different durations of therapy. Four studies found no significant differences in infectious complications between the intervention and comparison arms. Only one study assessed the duration of antibiotic prophylaxis in patients with AB.

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***Conclusions:*** With the available evidence, antibiotic therapy should be considered only for procedures in which studies have shown a clinical benefit in the prevention of infection. It is important to establish the duration and type of treatment for antimicrobial therapy for surgical prophylaxis in patients with AB who are going to receive urological invasive procedures.

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## Introduction

Asymptomatic bacteriuria (AB) or urinary tract colonisation is defined as the isolation of bacteria in a urine sample collected properly from a person who has no signs or symptoms of a UTI [1]. This colonisation of the urinary tract is common in diabetic women, with a prevalence of 8–14% [2], in pregnant women (2–7%) [3], in men aged >60 years (6–15%) [4], and in patients with spinal cord injury, with a prevalence rate of >50% [5].

There is clinical evidence that AB should be treated in pregnant women because it decreases the risk of pyelonephritis by between 4% and 20% [6], and reduces the risk of premature birth [7]. Antibiotic therapy should be used for patients with AB who are going to undergo urological surgery due to a 60% risk of presenting with infectious complications such as bacteraemia and a 10% risk of sepsis [1].

For this condition, some clinical trials have shown that antibiotic prophylaxis in patients with AB decreases the risk of bacteraemia and sepsis in the postoperative period [1]; but there is no consensus on the treatment type or when to start antibiotic therapy. Studies have started prophylaxis from 1 to 7 days before the procedure [8], without determining the differences in the results for each intervention.

For this reason it is important establish the appropriate therapy and the ideal starting time of antibiotic prophylaxis to prevent surgical infections in urological procedures in patients with AB, with the aim of reducing the potential morbidity for these patients and also to reduce costs. To answer this question we performed a systematic review of the scientific literature.

## Methods

### *Study design*

We systematically reviewed the scientific literature following the Patient, Intervention, Comparison, and Outcome (PICO) scheme. The patients were individuals with AB with urological surgery scheduled. The intervention was antibiotic prophylaxis, single-dose antibiotic therapy or starting 3–5 days before the surgical procedure. The main outcome was postoperative infection. The main objective was to determine if there were differences in the results depending on the different timing of administration of antibiotic prophylaxis.

The search was conducted in PubMed, the Literatura Latino-Americana e do Caribe em Ciências da Saúde database (LILACS), EBSCO, and Cochrane databases using the Medical Subject Heading (MeSH) terms 'antibiotic prophylaxis' AND 'urologic surgical procedures' AND 'asymptomatic bacteriuria'. The search was limited to humans and there were no restrictions on language or sample size. Studies published up to August 2015 were included with no date restriction.

### *Inclusion criteria*

Randomised clinical trials and observational studies (cohort studies, case-control studies) that compared the start and treatment regimens of antibiotic prophylaxis in patients with AB scheduled for a urological surgical procedure were included. An additional inclusion criterion was that patients had to be followed for a minimum of 7 days.

Titles and abstracts of the retrieved studies were reviewed to determine if they met the inclusion criteria. The full text was consulted to determine definitive inclusion or not if there were doubts.

The most frequent reasons for rejecting investigations were: (i) patients had had a previous transplantation; (ii) patients with active UTIs; (iii) the primary outcome was not infection of the surgical site; (iv) the follow-up was <7 days after surgery, and (v) information was incomplete.

The main outcome variable was post-surgical infectious complications and secondary outcomes were readmissions and hospital stay. To consider a surgical site infection we used the definition of the Center for Disease Control of the USA: infection has to occur within 30 days after the surgical procedure, and it affects the skin, subcutaneous tissue, muscle or the manipulated organ during surgery.

### *Study quality assessment*

Two experts independently assessed the quality of all papers included. The methodological quality and the

external validity of the included studies were evaluated using a specifically developed scale where five items were evaluated with a score range between 0 and 10 points. The items considered were: type of study, sample size, follow-up period, comparable groups at baseline, and control covariates. Each item was rated between 0 and 2 points, and a study was considered as being of good quality if it had $\geqslant 7$ points. Studies rated at 5–6 points were considered as being of moderate quality and those of $\leqslant 4$ points as low quality. The scale used with its items is shown in Table 1.

Additionally, the quality of the studies was assessed using the method recommended by the Cochrane Collaboration for measurement biases (domain-based assessment) [9]. The possibility of presenting selection bias (randomisation), detection and control of bias (masking), bias for losses, and reporting biases was scored as low, medium or high.

## Results

The literature search retrieved 14 investigations, with nine fulfilling the inclusion criteria. Five studies analysed antibiotic prophylaxis for transrectal prostate biopsy [10–14], only one study evaluated antibiotic prophylaxis for urological procedures at a general level [15], and the remaining studies analysed antibiotic therapy for cystoscopy, transurethral prostatic resection and urethral lithotripsy [16]. The studies were published between 1998 and 2013, and were carried out in Chile, Colombia, Taiwan, India, France, Turkey, and China. Most of them were written in English (77.8%). The characteristics of the included studies are shown in Table 2.

**Table 1** Quality scale used to score the included studies.

| Item assessed | Characteristic | Weight |
|---|---|---|
| Study design | Other designs | 0 |
| | Cohort study | 1 |
| | Controlled clinical trial | 2 |
| Total sample size, *n* | $\leqslant 100$ | 0 |
| | 101–200 | 1 |
| | $>200$ | 2 |
| Co-variables adjustment (number) | $\leqslant 2$* | 0 |
| | $>2$ | 2 |
| Comparable groups | Heterogeneous | 0 |
| | Homogeneous | 2 |
| Follow-up period, days | 7–9 | 0 |
| | 10–20 | 1 |
| | $>20$ | 2 |
| Total | | 10 |

* Age and sex.

Of the nine studies included, eight evaluated antibiotic prophylaxis regardless of the time of treatment initiation or the presence of AB (Table 2); only one of them assessed the duration of antibiotic prophylaxis in patients with AB (Table 2).

Four studies showed a significant reduction in the rate of surgical infection in the intervention group; of these, two were conducted in patients scheduled for transrectal prostate biopsy and their comparison group received placebo [10,14]. They also had two intervention groups each having the same antibiotics but with different durations of treatment, without significant differences between the intervention groups.

The first study conducted in China, between 1998 and 2001, included 192 patients. It concluded that an oral single dose of prophylactic antibiotics (ciprofloxacin 500 mg and metronidazole 400 mg) is effective and safe to prevent infectious complications in patients undergoing transrectal prostate biopsy [14]; the second, performed in India between 1996 and 1998 also concluded that an oral single dose (ciprofloxacin 500 mg and tinidazole 600 mg) was adequate as prophylaxis for transrectal prostate biopsy [10]. Both studies used placebo for comparison and its intervention groups were different in antibiotic and duration (Table 2).

Another study conducted in Chile, between 2001 and 2002, in patients scheduled for transurethral resection found a lower infection rate in the intervention group (cefazolin 1 g i.v. every 8 h in 1 day and ciprofloxacin every 12 h until removal of the bladder catheter) compared with the comparison group (cefazolin 1 g i.v. every 8 h by two doses followed by nitrofurantoin 100 mg orally until removal of the urinary catheter); however, the presence of AB before the procedure was not determined [17]. The fourth study conducted in Italy included 138 patients and showed a lower rate of infection in the intervention group (piperacillin tazobactam 2250 mg i.m. every 12 h for 2 days) compared with the comparison group (ciprofloxacin 500 mg orally ever 12 h for 7 days); however, again the presence of AB before the procedure was not determined [11].

The remaining four studies found no significant differences in reducing infectious complications. One was conducted in Colombia in 138 patients with negative urine cultures with an indication for cystoscopy, where they compared single-dose levofloxacin 500 mg as a prophylactic antibiotic with placebo and found no difference in infectious complications [18]. Another study in France with 288 men scheduled for transrectal prostate biopsy, found no difference between the duration of antibiotic therapy (single dose vs 3 days) with ciprofloxacin 500 mg orally, without checking for the presence of AB [12]. The third study, conducted in Taiwan between 2009 and 2012 in 206 patients with negative urine cultures scheduled for ureterorenoscopic lithotripsy found no differences in infectious complications in the three

**Table 2** Description of the nine included studies.

| Refs. | Study location | Participants, *n* | Intervention | Comparison | Main results | Score |
|---|---|---|---|---|---|---|
| Garcia-Perdomo et al. [18] | Colombia | Group I: 138<br>Group C: 138 | Levofloxacin 500 mg single dose | Placebo 500 mg single dose | The incidence of UTI was 0.7% Group I) and 3% (Group C)<br>$P = 0.17$ | 7 |
| Valdevenito Sepúlveda [17] | Chile | Group I: 45<br>Group C: 45 | Cefazolin 1 g i.v. preoperatively and every 8 h during the first day (3 doses). Followed by ciprofloxacin 250 mg orally every 12 h until removal of the bladder catheter | Cefazolin 1 g i.v. preoperatively and 8 h later (2 doses). Nitrofurantoin followed by 1000 mg orally daily until removal of the bladder catheter | Post-surgical UTI occurred in 2% of Group I and 16% of Group C<br>$P = 0.026$ | 6 |
| Cormio et al. [11] | Italy | Group I: 72<br>Group C: 66 | Piperacilin tazobactam 2250 mg i.m. every 12 h for 2 days | Ciprofloxacin 500 mg orally every 12 h for 7 days | Post-surgical UTI occurred in 0% in Group I and in 3.03% in Group C<br>$P = 0.026$ | 6 |
| Briffaux et al. [12] | France | Group I: 139<br>Group C: 149 | Ciprofloxacina 500 mg orally 2 h before the procedure | Ciprofloxacin for 3 days | One patient in each group presented with prostatitis | 8 |
| Hsieh et al. [19] | Taiwan | Group I1: 53<br>Group I2: 52<br>Group I3: 50<br>Group C: 51 | 1. Cefazolin 1 g 60 min before the procedure<br>2. Ceftriazone 1 g 60 min before the procedure<br>3. Levofloxacin 500 mg 2 h before the procedure | No antibiotics | The rate of infection after the procedure was 1.3% in Group I and 5.9% in Group C<br>$P = 0.09$ | 3 |
| Agbugui et al. [13] | Benin | Group I: 42<br>Group C: 45 | Ciprofloxacin 500 mg orally and metronidazole 400 mg every 8 h for 1 day | Ciprofloxacin 500 mg orally and metronidazole 400 mg every 8 h for 5 days | The rate of infection after the procedure was 19% in Group I and 15.6% in Group C | 4 |
| Yang et al. [14] | China | Group I1: 64<br>Group I2: 66<br>Group C: 62 | 1. Ciprofloxacin 500 mg and metronidazole 400 mg<br>2. Ciprofloxacin 500 mg and metronidazole 400 mg for 3 days | Placebo (no antibiotics) | The incidence of infectious complications in the Group C was higher than in Group I<br>$P < 0.01$)<br>There were no significant differences in infectious complications between the Group I groups<br>$P > 0.05$ | 5 |
| Aron et al. [10] | India | Group I1: 79<br>Group I2: 77<br>Group C: 75 | 1. Single dose of ciprofloxacin 500 mg and 600 mg tinidazole<br>2. Single dose of ciprofloxacin 500 mg and tinidazole 600 mg every 12 h for 3 days | Placebo tablet twice a day for 3 days (no antibiotics) | The incidence of infectious complications in Group C was higher (19%) than in the Group I groups (6% and 8%)<br>$P < 0.01$ | 5 |
| Sayin Kutlu et al. [15] | Turkey | Group I: 31<br>Group C: 28 | Single dose of an appropriate antibiotic, determined by antimicrobial sensitivity testing, 30–60 min before surgery | Antibiotic treatment before surgery until negative culture | None of the patients presented infectious complications<br>Differences in length of stay and costs for antibiotic therapy were found | 4 |

Group I, intervention group; Group C, comparison group.

intervention groups compared with the control group that received no antibiotic [19]. Finally, a study conducted in Benin in 87 patients undergoing transrectal prostate biopsy found no significant differences comparing both groups, with no monitoring for the presence of AB [13].

Only the study by Sayin Kutlu et al. [15] conducted in Turkey between 2005 and 2008 in 59 patients scheduled

for a urological procedure assessed the duration of antibiotic prophylaxis in patients with AB, indicating that there were no significant differences between single-dose therapy (30–60 min before the procedure) with an antibiotic treatment lasting 3–15 days until the urine was sterile before surgery. That study also found significant differences in the reduction of hospital stay and costs of antimicrobials in the single-dose group ($P < 0.001$).

*Quality of the included studies*

The quality of the included studies was not high. Only two had >7 points in the ad hoc scale and four had a score of 5–6 points. The average score was 5.3 points.

## Discussion

This is the first systematic review to analyse the type of antibiotic prophylaxis and its adequate duration for patients with AB scheduled for invasive urological procedures. The use of antibiotic prophylaxis for urological surgical procedures has sufficient clinical evidence for reducing post-surgical urinary infections and it is recommended in the 2015 Canadian Urological Association antibiotic prophylaxis guideline for urological procedures [8].

From the studies reviewed, no one was carried out in patients with AB, as the variable was not controlled for or because they were carried out in patients with negative urine cultures. The purpose of the studies evaluated was to identify the effectiveness of antibiotic prophylaxis for urological procedures, without evaluating the adequate scheduling of this therapy. A further limitation of the studies was the small sample size, which made it difficult to have statistically significant results due to the low infection rate both in the intervention and in the control/placebo groups.

*Schemes of antibiotic prophylaxis*

The included studies had multiple schemes of antibiotic prophylaxis, with variations in the antibiotics used, dosage, and duration of treatment. For example, the most used antibiotic was ciprofloxacin in the studies of Aaron et al. [10], Yang et al. [14], Agbugui et al. [13], Briffaux et al. [12], Valdevenito and Cormio [17], as single or combined therapy. The study schemes were all different and the most utilised duration of therapy was 1 day or single-doses, without significant differences in the intervention groups. The difference observed in the included studies was a decrease in the risk of post-surgical infections in patients undergoing antibiotic prophylaxis compared with those of the placebo group. The above reflects the guideline recommendations, where antibiotic prophylaxis for AB is recommended, although there is no specific recommendation on the duration of therapy [1,5,8].

All studies employed wide-spectrum antibiotics, with ciprofloxacin and levofloxacin the most common, so may generate multi-resistant bacteria by selective pressure [20]. Regarding the follow-up to assess post-surgical infectious complications, the maximum length was 5 weeks in the Chilean study [17] with an average of 10 days after the urological intervention.

It is noteworthy that in two studies by Garcia-Perdomo et al. [18] and Hsieh et al. [19], the intervention group was compared with the placebo group and they did not find significant differences, which suggests that antibiotic prophylaxis does not reduce the risk of infectious complications. However, these studies had a low statistical power due to their small sample size, which makes it difficult to identify significant differences.

*Methodological aspects*

The sample size of the included studies was very heterogeneous, from 59 patients to >200. This sample size is insufficient to show an effect of antibiotic treatment and therefore cannot either ascertain if it is more or less effective for specific subgroups (i.e. age, gender or different urological procedures).

One of the most key problems of the studies included is that most of the studies (89%) did not control for the variable of AB before the intervention, whilst in others it was done in patients with negative urine cultures. Only the study of Sayin Kutlu et al. [15] controlled for AB, but this study had a low sample size (31 patients in the intervention group and 28 in the comparison group) and did not control for confounding variables such as permanent vesicle catheter or immunosuppression. In addition, most of the urological procedures were insertion or change of JJ catheters.

*Limitations and advantages*

The main limitation of the present review is that it does not provide evidence about the research question (therapy and starting time of antibiotic prophylaxis to prevent infection in urological procedures in patients with AB). Another limitation is the impossibility of applying meta-analytic techniques due to the high heterogeneity of the included studies (different sample sizes, different groups of comparison, including placebo, different surgical indications, etc.) that does not make them comparable. Another important limitation is that most of the studies did not control for variables such as AB, surgical procedures, and prophylaxis duration. A last limitation is that only two studies had a quality score of >7 points in the ad hoc quality scale.

The main advantage of the study is the use of a systematic review, as this methodology analyses the avail-

able evidence using a consistent and coherent procedure. In this same way, the quality scale developed for this review helps to grade the quality of studies included using a homogeneous approach.

The guide diagnosis and treatment of AB in adults recommended clinical trials to determine the duration of therapy for the treatment of AB in patients scheduled for urological surgery.

To conclude, it is important to establish the duration and type of treatment for antimicrobial therapy for surgical prophylaxis in patients with AB that are going to receive urological invasive procedures. If we can show that a short duration of antibiotic therapy is equally effective and safe this would decrease hospital stay, the delay in time of surgery, the costs in providing services, and most importantly, the risk would be controlled infection selection of multi-resistant bacteria, which could lead to generating a health policy impact in this group of patients.

## Conflicts of interest

The authors declare not to have any conflicts of interest.

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None.

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