


# Appropriateness of Empirical Antibiotic Therapy for Cervicitis and Urethritis Prescribed in the Emergency Department

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## Abstract

**Objectives:** Sexually transmitted infections are a prevalent global health care problem. Treatment guidelines have recently been updated as a result of antimicrobial resistance and public health trends. The aim of the study was to assess the appropriateness of empirical antibiotic therapy prescribed for cervicitis and urethritis in the emergency department. **Methods:** We designed a retrospective observational cohort study. We included adult patients with suspected cervicitis or urethritis who attended the emergency department of a tertiary hospital in 2020. We excluded patients with suspected pelvic inflammatory disease, pregnancy or prostatitis and those requiring admission to hospital. Appropriateness of empirical antibiotic therapy was evaluated taking into account 4 aspects: indication, dosing, duration of therapy, and route of administration. Data were obtained from the electronic medical record, the electronic prescription program, and the discharge summary. **Results:** The study population comprised 176 patients; mean age was 28.9 years (SD = 7.7), and 90.9% were men. The most prescribed treatment was the combination of ceftriaxone and azithromycin (83.0%). Treatment was inappropriate in 71.6% of patients. A total of 159 drug errors were recorded. The most frequent cause was undertreatment (36.4%) related to underdosing (46.5%), particularly with regard to ceftriaxone. The percentage of errors was 11.9% for indication, 84.9% for dosing, 3.1% for duration, and 0% for route of administration. **Conclusions:** A high percentage of patients who attended the emergency department for suspected cervicitis or urethritis received an inappropriate empirical antibiotic regimen. The main reason was undertreatment due to underdosing.

## Keywords

anti-infectives, infectious diseases, medication errors

## Introduction

Sexually transmitted infections (STIs) are a major global public health concern because of their prevalence and incidence and because of related complications if the infection is not properly diagnosed and treated.<sup>1</sup> STIs are the most frequent cause of urethritis and cervicitis, with the most prevalent causes being *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.<sup>2</sup>

The goals of antimicrobial therapy are to eradicate infection and prevent complications and transmission. The guideline published in 2010 by the Centers for Disease Control and Prevention (CDC) for the empirical treatment of gonorrhea recommended a single intramuscular dose of ceftriaxone 250 mg and a single oral dose of azithromycin 1 g for uncomplicated gonococcal infections of the cervix, urethra, and rectum as a strategy for preventing resistance to ceftriaxone and treating possible coinfection with *Chlamydia trachomatis*.<sup>3</sup> In

recent years, the increased incidence of azithromycin resistance has led to a re-evaluation of the recommendations.<sup>4</sup> In 2020, the CDC guideline report, which updates previous guidelines, recommends a single intramuscular dose of ceftriaxone 500 mg for treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea. If chlamydial infection has not been excluded, concurrent treatment with doxycycline is recommended.<sup>5</sup>

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Given the increasing resistance to cephalosporins reported for gonorrhea in recent years in Europe (in Spain almost 5% of isolates were resistant to cefixime in 2018),<sup>6</sup> the European guidelines maintained the recommendation of dual therapy.<sup>6</sup> The recommended treatment for non-gonococcal urethritis and cervicitis is doxycycline 100mg orally twice daily for 7 days.<sup>7,8</sup>

Despite not being a disease that puts the patient at immediate risk, it is often managed by Emergency physicians who play an important role in diagnosing and managing STIs.

## Aim

To assess the appropriateness of empirical antibiotic therapy for cervicitis and urethritis prescribed in the emergency department.

## Methods

We designed a retrospective observational cohort study. We included adult patients ( $\geq 18$  years) who attended the emergency department of a tertiary hospital with suspected infectious cervicitis or urethritis in 2020. Patients with suspected pelvic inflammatory disease or prostatitis, pregnant women and those requiring admission to hospital were excluded. The diagnosis was based on history and physical examination. Urine tests were collected for most patients as well as endocervical or urethral swabs.

Since the research objective was to assess the appropriateness of empirical antibiotic therapy, only patients who received antimicrobial treatment during their stay in the emergency department were selected. We considered appropriate therapy to be dual therapy with a single 500-mg intramuscular dose of ceftriaxone and a single 1-g oral dose of azithromycin or dual therapy with a single 500-mg intramuscular dose of ceftriaxone and oral doxycycline 100mg twice daily for 7 days. During the study period Emergency physicians did not receive any formative session regarding this topic.

The appropriateness of the treatment prescribed was evaluated taking into account 4 aspects:

- Indication: prescribing the drug without indication (eg, triple drug regimen of ceftriaxone, azithromycin, and doxycycline) and omission of treatment (eg, prescribing azithromycin without ceftriaxone).
- Dosage: prescribing higher or lower than recommended doses.
- Length of treatment: longer or shorter than recommended duration.
- Route of administration: right or wrong.

Thus, patients were classified in 2 groups according to whether their treatment was appropriate or inappropriate. Patients whose treatment was inappropriate were further

cataloged as undertreated (omission of treatment, lower dose or shorter duration than recommended), overtreated (treatment without indication, higher dose or longer duration than recommended), or mixed (both over- and undertreatment in the same patient).

Data were obtained from the electronic medical record (HCIS<sup>®</sup>, DXC), and antibiotic therapy was reviewed in the electronic prescription program (Farhos<sup>®</sup>, Visual Limes) and the emergency department discharge summary. Other variables collected were: allergies to antibiotics, any previous STIs, as well as urogenital abnormalities (defined as any condition described by the physician that could have altered the urogenital functionality). Patient's weight could not be obtained because it is not systematically recorded at the emergency department. In addition, to ensure continuity of treatment, we reviewed dispensing by pharmacies via the electronic prescription module used in the Community of Madrid.

A statistical analysis was performed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Qualitative variables were expressed as frequency distributions. Normally distributed continuous variables were presented as mean  $\pm$  standard deviation (SD). The normality of the distribution of continuous variables was tested using the 1-sample Kolmogorov-Smirnov test.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Clinical Research Ethics Committee of Hospital General Universitario Gregorio Marañón, Madrid, Spain (date of approval: 13.9.21). Since this was a quality improvement study, the ethics committee waived the need to obtain informed consent.

## Results

The study population comprised 176 patients; mean age was 28.9 years (SD=7.7), and 90.9% were men (Table 1). The most commonly prescribed treatment was the combination of ceftriaxone and azithromycin (83.0%) (Table 1).

Inappropriate treatment was prescribed in 71.6% of cases. There were 159 drug errors, meaning that most patients with inappropriate prescriptions presented only 1 error (Table 2). The percentage of errors was 11.9% for indication, 84.9% for dosing, 3.1% for duration, and 0% for route of administration.

The most frequent cause was undertreatment (36.4%) related to underdosing (46.5%), particularly with regard to ceftriaxone (Tables 1 and 2). Patients treated with azithromycin received their treatment in the emergency department, and most of them received the appropriate dosage, namely, a single 1-g oral dose (75.6%) (Table 1).

All patients treated with doxycycline received 100mg orally twice daily. However, the principal cause of inappropriateness in this group was longer duration of therapy than recommended (27.8%) (Table 1). Unlike ceftriaxone and azithromycin, doxycycline is not administered as a single dose. Therefore, 33.3%

**Table 1.** Baseline Characteristics of the Patients and of the Antibiotics Prescribed in the Emergency Department.

	Total N= 176
Sex, n (%)	
Male	160 (90.9)
Female	16 (9.1)
Age, y, mean $\pm$ SD	28.9 $\pm$ 7.7
Allergy to antibiotics	9 (5.1)
Fluoroquinolone	3 (1.7)
Lincosamide	1 (0.6)
Penicilline	5 (2.8)
History of STIs, n (%)	30 (17.0)
Urogenital abnormalities, n (%)	8 (4.5)
Men who have sex with men, n (%)	18 (10.2)
Antibiotic regimen, n (%)	
Ceftriaxone	12 (6.8)
Ceftriaxone + azithromycin	146 (83.0)
Ceftriaxone + doxycycline	11 (6.2)
Ceftriaxone + doxycycline + azithromycin	7 (4.0)
Treatment dosage, n (%)	
Ceftriaxone 125 mg im single dose	1 (0.5)
Ceftriaxone 250 mg im single dose	63 (35.8)
Ceftriaxone 400 mg im single dose	1 (0.5)
Ceftriaxone 500 mg im single dose	61 (34.7)
Ceftriaxone 750 mg im single dose	1 (0.5)
Ceftriaxone 1000 mg im single dose	43 (24.4)
Ceftriaxone 2000 mg im single dose	6 (3.4)
Azithromycin 250 mg oral single dose	1 (0.5)
Azithromycin 500 mg oral single dose	8 (4.5)
Azithromycin 1000 mg oral single dose	133 (75.6)
Azithromycin 1500 mg oral single dose	1 (0.5)
Azithromycin 2000 mg oral single dose	10 (5.7)
Doxycycline 100 mg/12 h orally for 7 days	13 (7.4)
Doxycycline 100 mg/12 h orally for 10 days	3 (1.7)
Doxycycline 100 mg/12 h orally for 14 days	1 (0.5)
Doxycycline 100 mg/12 h orally for 21 days	1 (0.5)

Note. im = intramuscular.

of patients did not collect their medication from the pharmacy, because the doctor from the emergency department did not include the prescription in the electronic prescription program (2 cases) or the patient was prescribed the drug but did not withdraw it of his/her own accord (4 cases).

## Discussion

Despite the availability of multiple guidelines that standardize empirical antibiotic therapy for infectious cervicitis and urethritis,<sup>5-8</sup> our study revealed that a high percentage of patients who attended the emergency department received an inappropriate empirical antibiotic regimen (72.7%).

While the motives are unclear, they are most likely related to a combination of factors, including high staff turnover rates in the emergency department, poor knowledge of the medication among physicians, and the perception that

**Table 2.** Appropriateness of Prescribed Antibiotic Treatment and Reasons for Inadequacy.

	Total N= 176
Patients with inappropriate treatment, n (%)	126 (71.6)
Number of medication errors	159
Reason for inadequacy, n (%)	
Indication	19 (11.9)
Medication not required	7 (4.4)
Omission of treatment	12 (7.5)
Dosage	135 (84.9)
Underdosing	74 (46.5)
Overdosing	61 (38.4)
Duration	5 (3.1)
Shorter than recommended	0 (0)
Longer than recommended	5 (3.1)
Route of administration	0
Patients undertreated	64 (36.4)
Patients overtreated	45 (25.6)
Mixed patients	17 (9.7)

infectious cervicitis and urethritis are minor conditions compared to other conditions routinely treated in the emergency department.

Most patients were treated with ceftriaxone and azithromycin (83.0%), as recommended by the guideline approved in our center.<sup>8</sup> However, the recommended dose has been doubled from 250 to 500 mg in order to prevent resistance to ceftriaxone.<sup>5</sup> This new recommendation hardly translates into an update of the information contained in the summary of product characteristics, since these provide the information on efficacy that leads to the registration and marketing authorization of the drugs. For this reason, although the updated guidelines recommend an increase in dosage, the summary of product characteristics for ceftriaxone recommends 250 mg.<sup>9</sup> If we had considered the dosage of 250 mg to be correct, however, then 40.3% of prescriptions would have been inappropriate.

In 2004, an article analyzing adherence to treatment of STIs prescribed in emergency departments found that in the case of urethritis and cervicitis, adherence to the recommended antibiotic regimen was 33% and 32%, respectively.<sup>10</sup> Therefore, while these data are slightly better than those reported in our study (28.4%), they are far from optimal. Likewise, a study published in 2013 analyzed the appropriateness of treatment prescribed to adolescents who attended the emergency department for pelvic inflammatory disease. A total of 704 882 episodes were included, and the degree of appropriateness in accordance with the recommendations of the CDC treatment guidelines was only 37.1%.<sup>11</sup> In both studies, the authors reported that the finding of adherence rates lower than those provided in guidelines was associated with high staff rotation in the emergency department and practitioners' poor familiarity with the recommendations.

Nevertheless, given the major public health threat of antibiotic resistance throughout the world, optimizing the use of antibiotics is critical and should be a priority for any healthcare facility.<sup>12</sup> Empirical antibiotic therapy for cervicitis and urethritis is easy to standardize. Thus, one strategy to reduce this high percentage of inadequacy is the use of electronic clinical decision support tools. In 1999, the Institute of Medicine published the report “To Err is Human: Building a safer health system,” which recommended the use of this type of technology as a strategy for increasing patient safety.<sup>13</sup>

Various types of support tools are available, including standardized treatment protocols that are integrated into the electronic prescription program. Based on reported results, pharmacy and emergency departments created an automatic protocol in the electronic prescription program entitled *Empirical management of cervicitis/urethritis*, which includes a single 500-mg intramuscular dose of ceftriaxone and a single 1-g oral dose of azithromycin. Thus, the physician only has to search for the protocol, and, once selected, the medication will be automatically prescribed. If official recommendations change in the future, diffusion of the new recommendations among health professionals will be very simple, because only the antimicrobial treatment included in the protocol will have to be modified. In addition, the protocol includes a reminder to the physician to refer the patient to the microbiology department for follow-up at the STI clinic and to review exudate cultures collected in the emergency department.

The new CDC guidelines published in 2021—after the data collection period of the present study—recommended empirical treatment of gonorrhea and chlamydia with the combination of ceftriaxone and doxycycline rather than ceftriaxone and azithromycin, owing to increased resistance.<sup>14</sup> In our study, we found that 33.3% of patients treated with doxycycline did not collect their medication at the pharmacy department, for this reason, healthcare professionals should be aware of this problem and design strategies to improve medication adherence.

The limitations of the study are those inherent to retrospective studies. The main source of bias lies in the difficulty validating the information obtained from the medical records. However, the study focused on assessing the empirical antibiotic treatment administered, and this information was well recorded in the electronic prescription program. On the other hand, since this is a single-center study, it would be desirable to verify whether our results are similar to those of other emergency departments or whether this is an isolated case in our hospital.

## Conclusions

In conclusion, we found that a high percentage of patients who attended the emergency department for suspected

cervicitis or urethritis received an inappropriate empirical antibiotic regimen. The main reason was undertreatment due to underdosing, mainly of ceftriaxone. An automatic protocol in the electronic program was created to standardize empirical treatment for urethritis and cervicitis in an environment with high staff rotation, such as the emergency department.

## Declaration of Conflicting Interests

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