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ORIGINAL ARTICLE

Antibiotic activity and concentrations in clinical samples from patients with chronic bacterial prostatitis☆

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Abstract

Objectives: Chronic bacterial prostatitis (CBP) is the most common urological disease in patients younger than 50 years, whose long-standing symptoms could be related to an inappropriate therapeutic regimen. The objective was to analyze the sensitivity of microorganisms isolated from patients with CBP and measure the weekly antibiotic concentrations in serum, semen and urine.

Material and methods: For the antibiotic sensitivity study, 60 clinical isolates were included between January 2013 and December 2014 from semen samples from patients with microbiologically confirmed CBP. Broth microdilution was performed on the samples. For the antibiotic concentration study from January to May 2014, urine, blood and semen samples were collected weekly, over 4 weeks of treatment from 8 patients with positive cultures for CBP. The concentrations were measured using ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS).

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Results: The antibiotics fosfomycin and nitrofurantoin had the highest activity (95.2% in both cases). The mean antibiotic concentrations in semen during the 4 weeks studied were as follows: 1.68 mg/L, 8.30 mg/L, 2.61 mg/L, 0.33 mg/L and 2.90 mg/L, respectively, for patients 1 to 5, who were treated with levofloxacin; 1.625 mg/L for patient 6, who was treated with ciprofloxacin; 2.67 mg/L for patient 7, who was treated with ampicillin; and 1.05 mg/L for patient 8, who was treated with doxycycline. Higher concentrations were obtained in the urine samples than in serum and semen, the latter 2 of which were comparable.
Conclusions: Fosfomycin is proposed as the primary alternative to the empiric treatment of CBP due to its high *in vitro* activity. The antibiotic concentration in semen was higher than the minimal inhibitory concentration against the aetiological agent, although microbiological negativisation was not always correlated with a favorable clinical outcome.

PALABRAS CLAVE
Microorganismos;
Prostatitis crónica bacteriana;
Semen;
Orina;
Sangre;
Antibióticos

Actividad y concentraciones de antibióticos en muestras clínicas de pacientes con prostatitis crónica bacteriana

Resumen
Objetivos: La prostatitis crónica bacteriana (PCB) es la enfermedad urológica más frecuente en menores de 50 años, cuya clínica de larga evolución puede estar relacionada con una inadecuada pauta terapéutica. El objetivo fue analizar la sensibilidad de los microorganismos aislados de pacientes con PCB y medir las concentraciones de antibiótico semanalmente en suero, semen y orina.
Material y métodos: Para el estudio de la sensibilidad antibiótica, entre enero de 2013 y diciembre de 2014 se incluyeron 60 aislados clínicos procedentes de muestras de semen de pacientes confirmados microbiológicamente con PCB, y se llevó a cabo por microdilución en caldo. Para el estudio de las concentraciones de antibióticos, entre los meses de enero y mayo de 2014 se recogieron muestras de orina, sangre y semen, semanalmente, durante 4 semanas de tratamiento de 8 pacientes con cultivo positivo para PCB, y se midieron las concentraciones mediante cromatografía de líquidos de ultra alta eficacia acoplada a espectrometría de masas en tándem (UHPLC-MS/MS).
Resultados: Fosfomicina y nitrofurantoína fueron los antibióticos con mayor actividad (95,2% en ambos casos). Las concentraciones medias de antibiótico en semen durante las 4 semanas estudiadas fueron las siguientes: 1,68 mg/l; 8,30 mg/l; 2,61 mg/l; 0,33 mg/l y 2,90 mg/l, respectivamente para los pacientes 1 a 5, que recibieron levofloxacino; 1,625 mg/l para el paciente 6, que recibió ciprofloxacino 2,67 mg/l para el paciente 7, que fue tratado con ampicilina, y 1,05 mg/l para el paciente 8, que recibió doxiciclina. Se obtuvieron mayores concentraciones en las muestras de orina que en suero y semen, siendo comparables estas 2 últimas.
Conclusiones: Fosfomicina se postula como principal alternativa al tratamiento empírico de la PCB por su elevada actividad *in vitro*. La concentración de antibiótico en semen fue superior a la concentración mínima inhibitoria frente al agente etiológico, aunque no siempre se correlacionó la negativización microbiológica con la evolución clínica favorable.

Introduction

Chronic bacterial prostatitis (CBP) is a disease responsible for 5–10% of prostate syndromes, the most common being in men younger than 50.[1,2] It appears mainly as a result of recurrent urinary infections and is characterized by the presence of discomfort in the perineal region along with manifestations of pathological sexual and/or urinary process, which may persist for years. This may be related to an inadequate therapeutic regimen, often based on the use of an empiric antibiotic treatment, alone or associated with α-blockers and/or anti-inflammatories.

The limitations for the diagnosis and classification of CBPs led the *National Institute of Health* of the United States to a consensus meeting on prostatitis in December 1995. The result of that meeting was the creation of a specific system for classification of prostatic syndromes into 4 categories: acute bacterial prostatitis (type I), CBP (type II), chronic pelvic pain syndrome (type III), which in turn is divided into inflammatory (type IIIa) and non-inflammatory (IIIb), and asymptomatic inflammatory prostatitis (type IV). Also, it is necessary to take into account the difficulty of the microbiological diagnosis of CBP, which is based on the fractionated culture of Meares and Stamey, which consists of the sequential culture of the initial fraction and the mean fraction of the urine of clean urination, prostatic fluid, and post-fluid prostatic urine.[3,4] However, there are several studies that propose the simplification of the traditional fractionated culture to the culture of the mean fraction of the urine of clean micturition and the semen/prostatic fluid, showing

similar and even higher sensitivity and specificity data.[5,6] Traditionally, *Escherichia coli* has been considered the main etiological agent of CBP[2,4]; however, in our environment, it is *Enterococcus faecalis*, followed by *E. coli*, as in other studies.[7]

Most guidelines suggest, for treating CBPs, the use of fluoroquinolones for 4–6 weeks or trimethoprim/sulfamethoxazole (SXT) for 4–12 weeks. The use of nitrofurantoin in combination with SXT is also recommended when the treatment of choice fails.[8,9] Recently studies have been published that recommend the use of fosfomycin in the treatment of CBP,[10–12] but without a clear biological basis, since there are few papers that study the concentrations of antibiotics in organic liquids of the genitourinary system,[11,13–15] to establish a real relationship between the minimum inhibitory concentration (MIC) of the antibiotic against the isolated strain and the clinical categorization of the antibiotic for use in the treatment of the patient.

The aim of our study was to propose a pattern of empiric antibiotic treatment based on the analysis of the antibiotic susceptibility of microorganisms isolated from samples of patients diagnosed with CBP, and to know the concentrations of antibiotic (levofloxacin, ciprofloxacin, ampicillin and doxycycline) in blood, semen, and urine during 4 weeks of treatment of CBP patients.

Materials and methods

For the study of antibiotic susceptibility, 60 bacterial clinical isolates were included from a previous study[6] that was carried out between January 2013 and December 2014, in which 761 patients with pain symptoms of more than 3 months of evolution were included, located at the level of the pelvic region, associated or not with sexual or urinary manifestations, compatible with CBPs, treated at the urology consultations of the University Hospital of Granada (Virgen de las Nieves University Hospital). 61 CBP cases were confirmed microbiologically, and sensitivity was studied in 60 of the isolated microorganisms, which were 27 *E. faecalis*, 20 *E. coli*, 3 *Enterobacter* spp., 3 *Klebsiella* spp., 2 *Streptococcus agalactiae*, 2 *Morganella morgannii*, 2 *Citrobacter* spp. and a *Proteus mirabilis*. The broth microdilution method was used using the MicroScan Walkaway (Beckton Dickinson, Sparks, USA) automated system and the antibiotics interpreted were levofloxacin (in the 60 strains), ciprofloxacin, and SXT (in 58) and fosfomycin and nitrofurantoin (in 42). Sensitivity data were interpreted according to the CLSI 2014 criteria.[16] The 2 isolates of *S. agalactiae* were not studied against ciprofloxacin and SXT, since there are no cut-off points for their clinical categorization. It was only possible to analyze 42 isolates against fosfomycin and nitrofurantoin since the latter began to be investigated from November 2013, after one of the first publications on the possible efficacy of fosfomycin in the treatment of CBP.[11]

For the study of antibiotic concentrations between January and May 2014, samples of blood, presemen urine, and semen were collected from 8 patients diagnosed with CBPs in whom a significant microbiological culture had been obtained. These samples were collected in the same act, weekly, for 4 weeks of antibiotic treatment, and in them the levels of levofloxacin (5 patients), ciprofloxacin (one patient), ampicillin (one patient), and doxycycline (one patient) were measured. Patients 1–5 received 500 mg levofloxacin/24 h, their etiologic agent being *E. faecalis* in patients 1, 3 and 4, and *E. coli* in numbers 2 and 5. Patient 6 received 500 mg ciprofloxacin/12 h, the etiologic agent being *E. coli*. Patient 7 received 500 mg ampicillin/8 h for the treatment of CBP caused by *E. faecalis*. Finally, patient 8 was treated with 200 mg doxycycline/24 h, since the etiologic agent was *Ureaplasma urealyticum*. A microbiological and clinical control of the patients was carried out 6 months after the end of the antibiotic treatment. The samples were frozen at −80 °C until processing and the concentration measurement of each antibiotic was performed by ultra high-performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS), using a triple quadrupole analyzer, following the methodology developed by Cazorla-Reyes et al.[17] This procedure is based on a dilution in the case of urinary samples, precipitation of acetonitrile proteins in serum samples, and addition of DL-dithiothreitol (Sigma–Aldrich Química SA, Tres Cantos, Madrid, Spain) to liquefy the samples of semen, followed by determination of the antibiotics under study.

The study protocol was carried out in accordance with the Helsinki Declaration and the 'Ethics and health research commission for hospitals and health care districts'. Each of the patients who participated voluntarily in the project was explained and provided with an informative document of the study in which they participated. This was a non-interventional study, with no additional research to the routine procedures, except for the determination of the antibiotic concentration in the sample. The biological material was used for the standard diagnosis of urinary tract infections, following the prescriptions of the doctors. There was no additional sampling or modification of the Protocol. Data analyses were performed using an anonymous database. Therefore, the approval was considered unnecessary according to the guidelines of our country. The entity that granted permission to access and use the data was the Clinical Management Unit of Infectious Diseases and Clinical Microbiology of the University Hospital Complex of Granada, Spain.

Results

Sensitivity of isolates

Sensitivity data are shown in Table 1. Fosfomycin and nitrofurantoin were the most active antibiotics (95.2% in both cases), while SXT was the least active antibiotic (63.8%). Regarding fluoroquinolones, levofloxacin showed slightly higher activity than ciprofloxacin (78.3% and 75.9%, respectively). The increased activity of levofloxacin is mainly due to the predominance of E. *faecalis* as an etiological agent of CBPs in our country, which shows greater sensitivity to levofloxacin.

Levels of antibiotics in biological liquids

Table 2 and Fig. 1 shows the results obtained when measuring the concentrations in semen, serum, and urine of

Table 1 Sensitivity data to the antibiotics tested.

Levofloxacin (*n* = 60)		Ciprofloxacin (*n* = 58)		Trimethoprim-sulfamethoxazole (*n* = 58)		Fosfomycin (*n* = 42)		Nitrofurantoin (*n* = 42)		
S	R	S	R	S	R	S	R	S	I	R
47	13	44	14	21	37	40	2	40	2	0
78.33%	21.67%	75.86%	24.14%	36.20%	63.80%	95.20%	4.80%	95.20%	4.80%	0%

Table 2 Concentrations of antibiotic (mg/l) in semen, serum and urine determined in each patient.

N.°/measured ATB	N.° sample	Semen	Serum	Urine
1/Levofloxacin	1	1.74	1.98	125.94
	2	1.35	5.74	103.94
	3	21.59	4.96	109.32
	4	1.97	3.40	97.75
2/Levofloxacin	1	5.36	2.50	120.27
	2	10.29	5.83	182.26
	3	15.11	7.60	172.90
	4	2.46	5.34	77.33
3/Levofloxacin	1	0.80	1.11	104.01
	2	4.01	1.54	173.89
	3	2.31	1.45	127.66
	4	3.31	5.89	217.96
4/Levofloxacin	1	0.51	0.64	4.18
	2	0.15	0.63	1.05
	3	–	0.60	0.64
	4	–	0.72	0.87
5/Levofloxacin	1	6.24	4.71	165.44
	2	1.56	1.19	129.50
	3	1.68	1.59	–
	4	2.13	2.00	138.84
6/Ciprofloxacin	1	0.93	2.60	96.39
	2	1.63	2.97	162.11
	3	1.55	2.79	150.50
	4	2.39	2.56	186.50
7/Ampicillin	1	1.25	<0.1	64.97
	2	2.93	<0.1	87.32
	3	4.71	<0.1	88.01
	4	1.80	<0.1	97.21
8/Doxycycline	1	–	<0.1	–
	2	1.09	1.05	29.81
	3	0.95	0.61	21.22
	4	1.10	0.72	25.47

the antibiotic prescribed for each patient, with their evolution. In all cases, higher concentrations were obtained in urine samples than in serum and semen samples. Antibiotic concentrations obtained in serum were comparable, in general, to those obtained in semen. The mean concentrations of antibiotic in semen during the 4 weeks studied were as follows: 1.68 mg/l, 8.30 mg/l, 2.61 mg/l, 0.33 mg/l, and 2.90 mg/l, respectively for patients 1–5, who received levofloxacin; 1.62 mg/l for patient 6, who received ciprofloxacin; 2.67 mg/l for patient 7, who was treated with ampicillin; and 1.05 mg/l for patient 8, who received doxycycline. In patient 4 only levofloxacin concentrations could be studied in the first 2 semen samples.

The clinical and microbiological evolution of these patients is shown in Table 3. In patient 1, the mean concentration of levofloxacin in the semen samples (1.68 mg/l) was higher than the MIC of *E. faecalis* (≤1 mg/l) and the clinical and microbiological evolution was favorable. In patient 2, the mean antibiotic concentration (8.30 mg/l) was higher than the MIC of *E. coli* (≤0.5 mg/l); however, despite achieving the microbiological negativization, the symptoms persisted after antibiotic treatment. In patient 3, the mean

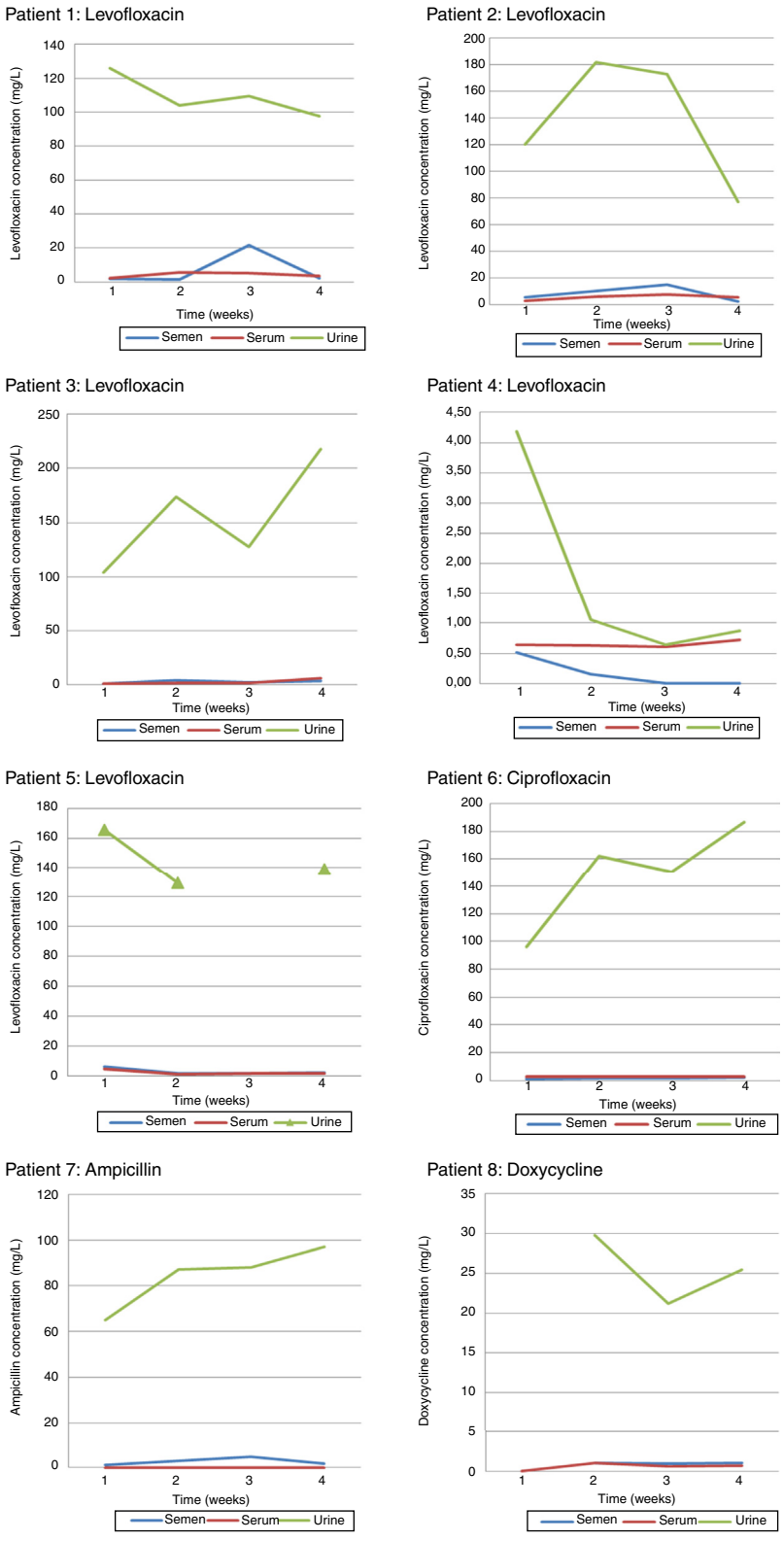

Figure 1 Evolution of the concentration of antibiotics in the patients studied.

antibiotic concentration (2.61 mg/l) was also higher than the MIC of *E. faecalis* (≤1 mg/l) and, although no microbiological control was performed, he showed clinical improvement. In patient 4, the mean antibiotic concentration (0.33 mg/l) was, *a priori*, lower than the MIC of *E. faecalis* (≤1 mg/l). However, it should be taken into account that with the commercial broth microdilution panels of the MicroScan system, we do not know the exact MIC of the antibiotic, so

Table 3 Clinical and microbiological evolution of patients included in the study of antibiotic levels.

Patient	Evolution	
	Clinical improvement	Microbiological negativization
1	Yes	Yes
2	No	Yes
3	Yes	–[a]
4	Yes[b]	Yes
5	No	Yes
6	No	Yes
7	Yes	No
8	Yes	Yes

[a] No microbiological control was performed at 6 months.
[b] Clinically it progressed favorably, but hematospermia continued.

the MIC of levofloxacin in this case could be lower than the concentration of antibiotic, which would explain the favorable microbiological and clinical evolution, in spite of persisting hematospermia. In patient 5, the mean antibiotic concentration (2.90 mg/l) was higher than MIC *versus E. coli* (≤0.5 mg/l), achieving microbiological negativization without showing, however, clinical improvement. In this case, the poor clinical course seems to be related to the diagnosis of a slight urethral stenosis that showed improvement after being treated.

Regarding ciprofloxacin levels, in the semen samples of patient 6, the mean concentration of antibiotic (1.62 mg/l) was higher than MIC *versus E. coli* (≤0.5 mg/l). The mean concentration of ampicillin in patient 7 (2.67 mg/l) was higher than MIC when compared to *E. faecalis* (≤1 mg/l). Finally, the mean concentration of doxycycline in patient 8 was 1.05 mg/l; however, in this case, we did not study the MIC of the antibiotic and, therefore, we do not know the degree of activity against *U. urealyticum*. Taking into account that the patient evolved favorably at both the microbiological and clinical levels, and that the MSCP of tetracycline *versus U. urealyticum* is ≤1 mg/l (S), according to CLSI 2011,[18] the MIC of doxycycline against it should be lower or equal (given its greater antimicrobial activity) and, therefore, the concentrations in semen should be higher than their MIC.

Discussion

CBPs are long-lasting infections and it is very important to know the behavior of the drugs used in their antimicrobial therapy. The measurement of antibiotic concentrations in semen is an indirect method to know or estimate the concentrations reached in the prostate, since between 13 and 33% of the content of the seminal fluid is of prostatic origin, reason why the levels of antibiotic in the prostate are theoretically superior. This information, together with the sensitivity data of the CBP producing strain, allows us to determine the best antimicrobial for the treatment of these infections.

The high rate of relapses during the treatment of CBPs has increased interest in knowing more precisely the ability of antibiotics to penetrate the prostate tissue and, thus, be able to respond to this problem. The study of other antibiotics has also been promoted in the treatment of CBPs, including fosfomycin, which seems to be an alternative to traditional antibiotics because of its high penetration in the prostate[13] and its efficacy demonstrated in *in vivo* studies.[12,19]

Based on the results of the sensitivity profile of the 60 clinical isolates included in this study, fosfomycin and nitrofurantoin were the most active antibiotics. Fosfomycin is a recently studied antibiotic in this condition, so there is not enough data to compare the sensitivity rate that we have obtained with clinical profitability in other studies. It is an antibiotic widely used in other diseases of the urinary tract, such as uncomplicated cystitis and recurrent urinary tract infections, in which it is postulated as a first-choice empiric treatment,[19] also showing excellent sensitivity data against enterobacteria, *Enterococcus* spp., and even multiresistant enterobacteria, understood as such enterobacteria that show resistance to at least 3 families of antibiotics. The high rate of resistance to fluoroquinolones observed in our study (around 25%, slightly lower than that shown by other authors),[10,20] as well as the increase in the incidence of enterobacteria producing extended-spectrum beta-lactamases, has favored the search for other antibiotics, such as fosfomycin, that can address these pathogens. Nitrofurantoin has also proved very high sensitivity, as in other studies[7]; however, it has been documented that nitrofurantoin does not have good prostatic penetration properties and, therefore, it should not be used for the treatment of CBP.[21] Fluoroquinolones, for their part, have been used as the treatment of choice for CBPs due to their excellent pharmacokinetic properties, which make it possible to reach, both in prostatic tissue and in prostatic secretion, high concentrations, and due to their higher activity against formation of biofilms by the bacteria involved.[22] However, the high use of these antibiotics has led to the appearance of resistance to these, so their effectiveness in the empirical treatment of CBP is decreasing.

In addition to the sensitivity profile of the isolated microorganism, a very important aspect to predict the efficacy of an antibiotic is the concentration that it reaches in the site of action, which must be higher than the MIC. This will determine the clinical categorization of the antibiotic, *i.e.*, sensitivity (S), resistance (R), or intermediate sensitivity (I), according to the microbiological sensitivity cut-off points (MSCP) used by EUCAST[23] and CLSI[16] guidelines. Table 4 shows the MSCP of the previous guidelines for levofloxacin, ciprofloxacin, and ampicillin against *E. faecalis* and *E. coli*, respectively. Doxicillin, used for the treatment of CBP by *U. urealyticum* in patient 8, does not have cut-off points against this pathogen, so tetracycline ones (S ≤ 1 mg/l; R > 2 mg/l) have been taken as a reference, according to CLSI,[18] since doxycycline is a tetracycline of superior microbiological generation and activity.

It is important to highlight that the clinical categorization of antibiotics (provided by the MIC of the antibiotic) varies according to the CLSI or EUCAST guideline. This poses a problem for the interpretation of the antibiograms of the microorganisms responsible for CBP since, according to

Table 4 Cut-off points EUCAST and CLSI (2014) for *Enterococcus* spp. and *E. coli*.

	Enterococcus spp.						*E. coli*					
	MIC (mg/l) CLSI			MIC (mg/l) EUCAST			MIC (mg/l) CLSI			MIC (mg/l) EUCAST		
	S	I	R	S	I	R	S	I	R	S	I	R
Levofloxacin	≤2	4	≥8	≤4	–	>4	≤2	4	≥8	≤1	–	>2
Ciprofloxacin	≤1	2	≥4	≤4	–	>4	≤1	2	≥4	≤0.5	–	>1
Ampicillin	≤8	–	≥16	≤4	–	>8	≤8	16	≥32	≤8	–	>8

the guideline used, an antibiotic with the same MIC can be interpreted as sensitive or resistant. Consequently, the absence of a universal criterion for interpreting the MIC of antibiotics adds a further drawback to the standardization of the antibiotic therapy of this disease, since it makes it difficult to choose a suitable dosage to reach sufficient antibiotic concentrations to eradicate the etiological agent. In our study, the concentrations of antibiotics in blood and semen are comparable, and much lower than urine, as in most studies.[14,15] According to the literature, ciprofloxacin reaches concentrations in prostatic tissue, generally 3–10 times higher than serum ones,[13] although some authors detected prostate concentrations only 2-fold higher,[24] levofloxacin levels being higher than those of ciprofloxacin in prostate and semen[25]; the concentrations of doxycycline in prostatic tissue are 40–60% higher than the serum ones[13]; and, finally, prostatic concentrations of ampicillin are generally lower than serum levels.[26] Therefore, the levels of levofloxacin, ciprofloxacin and doxycycline in prostatic tissue of our patients should be higher than those achieved in semen/blood, being sufficient for the eradication of etiological agents. Even so, the microbiological negativization does not always seem to be related to the disappearance of the symptoms. Since it is a chronic inflammatory disease of bacterial origin, the use of anti-inflammatories and/or β-blockers is essential along with the antimicrobial treatment, since the inflammatory process may persist for a long time, even if the etiologic agent has been eradicated. In addition, there may be other underlying diseases, not infectious, responsible for the symptomatology. In the case of ampicillin, the serum concentrations were virtually undetectable, so they cannot be correlated with the seminal ones and it could not be ensured that they were sufficient in prostatic tissue. In fact, microbiological eradication was not achieved in this case.

On the other hand, the studies mentioned above were performed in healthy volunteers, rather than patients with CBP, and it is important to take into account that antibiotic concentrations may vary between these 2 populations due to changes in pH that some biological samples suffer, such as prostate fluid in patients with CBP, as recorded in a review by Wagenlehnern.[27] Thus, our data cannot be compared with those studies, but they do make it possible to perform a preliminary interpretation on the pharmacokinetic processes of these antibiotics in subjects with CBP.

This research work has been carried out with a limited number of patients because many biological samples are needed, and participation in this type of study is complicated. The inclusion of a small number of patients in the study of antibiotic concentrations and of strains tested for MIC studies implies a limitation in the interpretation of the results, since studies with a greater number of patients and strains are necessary to confirm the results obtained. Another limiting factor of the study is the difficult monitoring of adherence to the treatment of patients, which could explain the atypical evolution of the observed concentrations in some cases. Therefore, when commenting the results, the mean concentration of the antibiotic during the 4 weeks studied is more representative. When using presemen urine samples for the study of antibiotic levels, the results obtained in semen could be slightly biased by the small residual amount of antibiotic of urinary origin that could contaminate the urethra. Even so, it is known that these antibiotics reach higher concentrations in the prostate than the seminal and blood ones, so the latter also serve as a reference.

As a conclusion of the study, fosfomycin is postulated as the main alternative in the conventional empirical treatment of CBP, as long as the involvement of other atypical etiologic agents such as genital mycoplasmas has been ruled out. The measurement of antibiotic concentrations, together with the sensitivity profile of the isolated microorganism, provides very useful information for the choice of the most effective antibiotic and for the prognosis of the disease. Finally, although levofloxacin concentrations appear to be sufficiently high in patients, there is not always a relationship between microbiological cure and clinical evolution, which is why it is necessary to carry out more studies and with a greater number of patients to ratify the results obtained. Even so, this preliminary assessment provides very important data about the pharmacokinetic processes that occur during antimicrobial treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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