



Chronic prostatitis caused by extended-spectrum β -lactamase-producing *Escherichia coli* managed using oral fosfomycin—A case report

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ABSTRACT

Prostatitis is a clinical condition of difficult management and with limited antimicrobial options, especially in the setting of antimicrobial resistance. Recurrences are frequent and can be severe. Limited reports support the use of fosfomycin for chronic prostatitis by ESBL-producing bacteria.

We reported a case of a patient with chronic prostatitis caused by ESBL-producing *Escherichia coli* with several relapses after prolonged periods of treatment with broad-spectrum intravenous antibiotic therapy and with recurring urinary symptoms after transurethral prostatic resection. After resolution of the last infection, we performed a long-term eradication antimicrobial treatment with 3 g of fosfomycin once daily, altered to 3 g every 48 h after 10 days due to diarrhea (which resolved with the dose change). After three months with this dosage, fosfomycin was switched to a once-weekly regimen which was maintained for further 9 months. After 9 months of follow-up without antimicrobial treatment, the patient has remained free of urinary symptoms.

Experience with fosfomycin for chronic prostatitis caused by ESBL-producing *E. coli* is limited to three case reports and two case series. Intraprostatic measurements have shown adequate penetration of fosfomycin into prostatic tissue. Accordingly, our report suggests that fosfomycin can be used as eradication therapy in a patient with a prior history of chronic prostatitis by ESBL-producing bacteria with recurring urinary infections after surgical treatment.

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Introduction

Multidrug-resistant bacterial infections, including infections by extended-spectrum β -lactamase (ESBL) producing bacteria, are a growing problem worldwide [1]. Carbapenems are the drugs of reference for ESBL infections [2]. However, due to their high ecological impact, other antibiotics, such as cephalosporins or β -lactam/ β -lactamase inhibitor combinations, are often used as alternatives. Fosfomycin has also shown to be a valid option for infections by ESBL producers [3], including in the setting of complicated urinary tract infections [4], and has anti-biofilm activity [5,6].

Chronic bacterial prostatitis is characterized by prolonged or recurrent symptoms and relapsing bacteriuria, and it complicates a

minority (5–10%) of cases of acute bacterial prostatitis, often occurring without a previous acute infection [7].

Fosfomycin has not been widely used in prostatic infections due to concerns on penetration and effectiveness. However, it has been shown to achieve therapeutic intraprostatic concentrations after oral administration [8]. Limited successful experience has been published on the use of fosfomycin in chronic prostatitis by ESBL-producing bacteria [9–13].

Case report

We describe the case of a 51 years-old Portuguese man whose previous medical history was relevant only for a stable pulmonary nodule under regular follow-up and frequent work-related trips to Angola.

In December 2014 he had a first case of acute urinary tract infection, with dysuria, fever, a white blood cell (WBC) count of 25.880/ μ L, a C-reactive protein of 250.9 mg/L and a prostate-specific antigen (PSA) value of 8.15 ng/mL. He was medicated with 2 weeks of ciprofloxacin 500 mg once daily and improved clinically. A urine sample was collected prior to antibiotherapy and sent for

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culture, which revealed growth of ESBL-producing *E. coli*, resistant to the ongoing therapy with ciprofloxacin and susceptible only to nitrofurantoin, carbapenems and fosfomycin.

Subsequently, between January 2015 and November 2015, the patient had 5 more episodes of urinary symptoms and fever. ESBL-producing *E. coli* with a similar pattern of susceptibility as the one described above was isolated in urine samples in each episode. The first two episodes were managed with oral antibiotics (cefixime 400 mg for one week and prulifloxacin 600 mg for 3 weeks). In the following 3 episodes, the patient was admitted as an inpatient and managed with prolonged periods of intravenous ertapenem (1 g daily for 25, 69 and 85 days).

Ultrasound performed in January 2015 revealed a heterogeneous prostate of 40cc with central hypoechogenic calcified regions. Pelvic magnetic resonance imaging (MRI) performed in August 2015 showed no relevant structural changes in the remaining urinary system except for two simple cysts on the right kidney. Recurrence of infection was interpreted as being caused by persistence of the infectious foci in prostatic calcifications and the patient was referred for transurethral resection of the prostate (TUR-P) in November/2015. During the following 10 months, the patient was free of recurrence of urinary symptoms.

However, since September 2016, the patient developed three further urinary tract infection episodes. He was hospitalized in September due to epididymitis, which was managed with 2 weeks of oral ciprofloxacin 500 mg/day. Afterwards, in December, he was medicated with cefixime (400 mg/day) for 2 weeks as an outpatient due to a new episode of epididymitis. In March 2017, 2 weeks of trimethoprim/sulfamethoxazole were performed due to cystitis. In these episodes, all of the urine samples yielded polymicrobial growth except for one which was positive only for a multisusceptible strain of *Streptococcus agalactiae*.

During the aforementioned period, two urine samples were also sent for culture in the mycobacteriology lab and yielded no mycobacteria growth. *Mycobacterium tuberculosis* nucleic acid amplification testing (NAAT) was performed in both samples and was negative. *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis* NAAT in urine samples was also negative.

The patient presented to our hospital's Infectious Diseases department in March 2017. He had finished his last trimethoprim/sulfamethoxazole course 3 days before his appointment. He was heavily distressed with the impact on daily activities caused by the recurring infections. He was asymptomatic and clinically well. Due to the recurrence of urinary tract infections after prostate resection, and due to the absence of other structural abnormalities in MRI, we concluded that a more effective long-term antimicrobial therapy strategy was necessary for eradication.

After confirmation that the urine was sterile, we started the patient on 3 g oral fosfomycin daily, for a planned duration of 15 days, and a subsequent 3 g every 48 h regimen for 3 months. The patient developed diarrhea, with 2–3 daily liquid dejections. Therefore, on day 10 of treatment, dosing was switched to 3 g every 48 h, with resolution of the diarrhea.

After three months with this dosage, fosfomycin was switched to a once-weekly regimen which was maintained 9 months further, for a total treatment duration of one year. After 9 months of follow-up without fosfomycin or other antibiotics, there was no recurrence of urinary tract infection.

Discussion

Chronic bacterial prostatitis can occur as a complication of an acute prostatitis and is often associated with relapses and with persisting symptoms which impact the quality of life [7,14].

First-line management consists of antimicrobial therapy for a period of 4–6 weeks [7]. However, features such as the presence of prostatic calcifications, the poor penetration of most antimicrobials into prostatic tissue and fluids and the formation of bacterial biofilm favor treatment-resistant and relapsing infections [7].

Prostatic calcifications can function as a sanctuary for bacteria and their presence is associated with relapsing infections [7]. In this setting, patients who have responded to initial antimicrobial therapy may benefit from more prolonged courses or from long-term suppressive therapy with low doses of antibiotics [7]. However, surgery can be an important step in the resolution of infection. A TUR-p approach can help by clearing the bacterial inoculum harbored by calcifications and by reducing post-void residual urine volumes [7,15].

In our case report, TUR-p was certainly an essential step in the removal of the source of the persisting infection, but was followed by recurrences of infection in the genitourinary tract. In the absence of other clear anatomic abnormalities, we assumed that the recurrence of infections was dependent on persistent bacterial colonization of the urinary tract. Therefore, we decided to perform a long-term eradication therapy after clinical and microbiological resolution of the previous infection, which was tailored to be active against prior isolates. ESBL-producing *E. coli* was not the agent of the most recent infections and did not grow in culture after the TUR-p procedure. However, it was the most consistently isolated bacterial agent and the causative agent of most prior infections. Also, a new infection with this agent would be difficult to manage due to limited antimicrobial options.

Biofilm formation occurs in chronic prostatitis, mostly when calcifications are present [16]. *E. coli* isolates causing prostatitis produces biofilm more frequently than those causing other urinary tract infections [17]. Bacteria in prostatic biofilms are difficult to eradicate in part due to their dense extracellular matrix and due to the presence of quiescent cells which can later propagate an inactive infection. Changes in the chemical and immunological changes associated with the chronic immunologic stimulation caused by with biofilms produces an environment propitious to crystallization, calcification and calculus formation [16]. The presence of biofilms is associated with treatment failure and with worse clinical outcomes in chronic prostatitis [9,18].

Fosfomycin has shown to have activity in biofilms produce by gram-negative bacteria, including *E. coli* [6]. Also, a study by Gardiner et al has shown adequate penetration in healthy prostatic tissue [8], which would possibly be even higher in a setting of inflammation.

There is also evidence of effectiveness of fosfomycin in the treatment of ESBL-producing bacteria [19]. A randomized control trial comparing fosfomycin to meropenem in bacteremic urinary tract infections caused by ESBL producers is currently in progress [20].

The use of fosfomycin for chronic prostatitis was evaluated in a series of 15 patients, 5 of which had ESBL-producing *E. coli* as the agent of infection and 6 of which had evidence of prostatic calcifications. Clinical cure rate was 53% with fosfomycin being administered orally in 3 g-doses every 48–72 h for 6 weeks. Four of the 5 patients with infection by ESBL-producing *E. coli* were cured [10]. One other series of 20 patients with chronic prostatitis managed with fosfomycin (3 g daily for one week followed by 3 g every 48 h for 5 additional weeks) included 13 patients with *E. coli* infection, of which 2 were ESBL producers. Cure rate was 85% overall and 73% (10/13) among *E. coli* infections [11].

To the extent of our knowledge, only 3 other cases describing the successful use of oral fosfomycin for ESBL-producing *E. coli* chronic prostatitis have been published: one where 3 g a day of fosfomycin were administered for 12 weeks after an initial failure with 2 weeks of 3 g every 72 h [12]; one where 3 g of fosfomycin

were administered daily for 16 weeks (with an attempted increase in dose to twice daily not tolerated due to diarrhea) [12]; and one where 6g of fosfomycin were given every 72h before TUR-p, followed by 3g of fosfomycin every 72h in combination with doxycyclin for 2 further weeks [9].

One other case report described the use of fosfomycin in the dose of 3g each 48h for 3 months for chronic bacterial prostatitis due to *Raoultella planticola* infection [13]. Diarrhea is the main side effect associated with prolonged treatment with fosfomycin and can be managed with reduction of the frequency of administration [11,12], as was done successfully with our patient.

In conclusion, the worldwide increase in antibiotic resistance complicates management of prostatitis, an already difficult to treat entity on itself. The infection can recur even after a surgical approach and choices of long-term oral antibiotic strategies are limited. Fosfomycin has good antibiofilm activity, has shown to penetrate well into prostatic tissue and has been previously used in the management of chronic bacterial prostatitis.

Although we could not clearly attribute the success of the management of this patient to antimicrobial therapy alone, our eradication strategy with fosfomycin was able to effectively prevent recurrences of urinary tract infection in a patient with a prior history of urinary colonization and infections due to ESBL-producing *E. coli*.

Authors contribution

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. Further approval from the ethical committee was not required.

All authors have no declaration of interest to disclose.

All authors have approved the manuscript and agree to the submission to International Journal of Antimicrobial Agents. We confirm that our article has not been published elsewhere and is not under consideration by another journal.

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