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Cefoxitin-based antibiotic therapy for extended-spectrum β-lactamase-producing Enterobacteriaceae prostatitis: a prospective pilot study

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ABSTRACT

The emergence of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) infections requires re-assessment of therapeutic choices. Here we report the efficacy of cefoxitin-based antibiotic therapy for ESBL-E prostatitis. A prospective study including patients with ESBL-E prostatitis resistant to trimethoprim/sulfamethoxazole and fluoroquinolones from January 2014 to March 2016 was conducted. Cefoxitin was administered by continuous infusion for 3 weeks in the case of acute bacterial prostatitis or 6 weeks in the case of chronic bacterial prostatitis (CBP), with intravenous fosfomycin for the first 5 days. Urological investigations were performed to diagnose underlying urinary tract pathology. Clinical and microbiological efficacy were evaluated 3 months (M3) and 6 months (M6) after the end of therapy. A total of 23 patients were included in the study. The median patient age was 74 years (range 48–88 years). Of the 23 infections, 14 (61%) were CBP and 12 (52%) were healthcare-associated infections. The bacteria involved were *Escherichia coli* in 11 cases, *Klebsiella pneumoniae* in 10 cases and *Klebsiella oxytoca* in 2 cases. Clinical cure was observed in 19/23 patients (83%) at M3 and in 17/22 patients (77%) at M6. Urocultures were sterile in 13/23 patients (57%) at M3 and in 9/19 patients (47%) and M6. Urinary colonisation was observed in 6/19 patients (32%) with clinical cure at M3 and 5/14 patients (36%) with clinical cure at M6. No resistance to cefoxitin was detected. Surgical treatment was required for 7/23 patients (30%). In conclusion, cefoxitin-based antibiotic therapy is suitable for difficult-to-treat ESBL-E infections such as prostatitis.

1. Introduction

Complicated urinary tract infections (cUTIs) are frequent and are associated with an impaired outcome, requiring hospital admissions with a significant medico-economic burden [1].

Among cUTIs, bacterial prostatitis is known to be difficult to treat for many reasons. First, diffusion of antibiotics into the prostate tissue is highly restricted for most molecules [2]. Second, infectious prostatitis in elderly people is strongly associated with an underlying urinary tract pathology, such as benign prostatic hyperplasia, that has to be cured at the same time [3]. Third, management of recurrent cUTI may be associated with the emergence of antimicrobial resistance [4]. For 10 years, the incidence of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) has dramatically increased in France: up to 20% of *Klebsiella pneumoniae* strains and 10% of *Escherichia coli* strains responsible for cUTIs are ESBL-producers [5]. Nowadays, there has been a clear shift of ESBL-E from nosocomial infections towards those originating from a community setting [6]. As a consequence of ESBL-E cUTI treatment, carbapenem consumption has significantly increased [7]. Therefore, carbapenem resistance is rising and should be considered a major public health issue [8]. Consequently, international efforts support the evaluation of new therapeutic strategies, including the use of 'old' molecules for ESBL-E cUTIs [9].

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Cefoxitin is a cephamycin developed in the 1970s that has been used mostly in gastrointestinal surgery prophylaxis [10]. This molecule fulfils all of the conditions to be used in ESBL-E cUTIs. First, it is resistant to hydrolysis induced by ESBL-E [11] and ca. 90% of ESBL-producing *E. coli* are still susceptible to this antibiotic [12]. Second, it is completely excreted via the urinary tract. However, its diffusion into prostate tissue is unknown, unlike that of trimethoprim/sulfamethoxazole (SXT) and fluoroquinolones (FQs) whose diffusion is known to be excellent.

Current French guidelines for acute bacterial prostatitis (ABP) recommend the use of cefoxitin in ESBL-E cUTI resistant to FQs and SXT [13]. However, to the best of our knowledge, the efficacy of cefoxitin in prostatitis has not yet been clearly determined. The aim of this study was to measure the clinical and microbiological efficacy of this antibiotic in ESBL-E prostatitis.

2. Patients and methods

2.1. Patient selection

A prospective monocentric study was conducted in the infectious diseases department of a French teaching hospital from January 2014 to March 2016. All successive patients aged >18 years presenting with ABP or chronic bacterial prostatitis (CBP) due to ESBL-E resistant to both SXT and FQs were included. For inclusion, the patients had to be symptomatic with pollakiuria, burning micturition, dysuria, macroscopic haematuria or bladder outlet obstruction. Fever was required for all ABP cases and for CBP with a urinary catheter. The definition of CBP required a previous infection in the past 3 months with the same strain, despite an adapted antibiotic therapy. Patients with radical prostatectomy and asymptomatic bacteriuria were not included.

2.2. Antimicrobial susceptibility testing

Antibiograms were generated by the disk diffusion method on Mueller–Hinton agar (bioMérieux SA, Marcy-l'Étoile, France) with Bio-Rad antibiotic disks (Bio-Rad, Marnes-la-Coquette, France) and were interpreted according to the recommendations of the Antibiogram Committee of the French Microbiology Society (CA-SFM) using SIRWEB software (i2a, Montpellier, France). Synergy was observed by placing third-generation cephalosporin disks around disks containing clavulanic acid.

According to the CA-SFM 2013 guidelines, a strain was classified as susceptible to cefoxitin if the inhibition zone diameter was ≥22 mm, corresponding to a minimum inhibitory concentration (MIC) of ≤8 mg/L. Susceptibility to cefoxitin was determined at inclusion for all of the involved strains by Etest (bioMérieux SA). Strains of ESBL-E with an MIC strictly higher than 8 mg/L were excluded.

2.3. Cefoxitin treatment

The antibiotic regimen was cefoxitin, in association with intravenous fosfomycin for the first 5 days. Cefoxitin was administered by continuous infusion, with dosages from 2–8 g/day depending on the patient's weight and renal function (Table 1). Regarding the stability of the molecule, cefoxitin was infused continuously for 12 h twice a day [14]. Fosfomycin was used for 5 days in a 4-h prolonged infusion (4 g every 8 h) for patients with normal renal function, with adjusted dosages depending on renal function. Patients with congestive heart failure did not receive fosfomycin. Patients were treated with cefoxitin for 3 weeks in the case of ABP and for 6 weeks in the case of CBP.

When the patient had a urinary catheter-related infection, the material was changed within 3 days from the beginning of antibiotic therapy.

Table 1
Dosage of cefoxitin infusion according to patient weight and renal function.

Creatinine clearance	Weight ≥ 70 kg	Weight < 70 kg
>30 mL/min	8 g/day	6 g/day
10–30 mL/min	6 g/day	4 g/day
<10 mL/min	4 g/day	2 g/day

2.4. Clinical and biological follow-up

The serum concentration of cefoxitin was determined on Day 5 using a validated high-performance liquid chromatography (HPLC) technique coupled with a diode array detector/ultraviolet (DAD-UV). The inhibitory quotient (IQ), defined as the antibiotic serum concentration/MIC ratio, was determined for each patient. Patients were discharged from the infectious diseases department between Day 5 and Day 7 with a peripherally inserted central catheter (PICC) for infusion.

Between Day 10 and Day 14, urological investigations were systematically performed in association with a urologist consultation. In compliance with French guidelines, pelvic and prostatic ultrasound (prostate size measurement, search for urolithiasis, ureteral dilation or prostatic abscess), post-void residual volume and uroflow measurements were made if considered as required by the urologist [13].

2.5. Outcome measurement

The primary goal was the assessment of clinical cure at 3 months (M3) and 6 months (M6) after the end of treatment. Clinical cure was defined as regression of functional urinary symptoms (pollakiuria, burning micturition, dysuria, macroscopic haematuria and bladder outlet obstruction) and absence of fever. Patients with clinical failure at M3 were also considered as failure at M6. The secondary goal was bacteriological cure, defined as a negative urinary culture at M3 and M6. In the case of a positive urinary culture, the antibiotype was used as a surrogate marker for strain distinction when the same bacterium was isolated. So microbiological failure could occur with the same strain (same antibiotype) or with another strain (another species or different antibiotype). If the patient was asymptomatic, a positive urine culture led to the diagnosis of urinary colonisation.

2.6. Ethical approval

As current French recommendations for UTI regarding ESBL-E resistant to both SXT and FQ were followed, the study was considered as non-interventional. In France, at that time only biomedical research required ethical approval, which does not include non-interventional studies according to French law.

2.7. Statistical analysis

Data were analysed using StatView v.4.5 software (SAS Institute Inc., Cary, NC) and statistical significance was established at $\alpha = 0.05$. Continuous variables were compared using the Mann–Whitney non-parametric test, and qualitative variables were compared using the χ^2 or Fisher's exact test when appropriate.

3. Results

A total of 23 patients were included over the 27-month study period. All patients were followed up until 6 months after antibiotic therapy (Fig. 1). The median patient age was 74 years (range

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