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Successful Treatment of Acute Prostatitis Caused by Multidrug-Resistant *Escherichia coli* With Tigecycline Monotherapy

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We present a successful treatment, with tigecycline monotherapy, of acute prostatitis caused by multidrug-resistant *Escherichia coli* harboring an NDM-1 carbapemenase along with a CMY-2 cephalosporinase and a TEM ESBL.

Keywords. CMY-2; NDM-1; prostatitis; TEM ESBL; tigecyclin.

CASE

A 79-year-old patient with known bladder neck sclerosis and subsequent chronic polyuria and nocturia presented to the Department of Urology at Bern University Hospital in March 2018 with progressive worsening of symptoms over the preceding 2 weeks and new-onset premicturition pain without fever. The history was notable for a prostate adenoma treated with transurethral resection of the prostate in 2017 and for chronic renal insufficiency (CKD IIIb) since 2015.

Clinical examination revealed marked prostatic tenderness. Urine, obtained after prostate massage at admission, was nitrite positive, and >40 leucocytes/hpf C-reactive protein and white blood cell count were normal. Culture of urine yielded *Escherichia coli* at 10^4 CFU/mL, resistant to β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, classical tetracyclines, antifolates, fosfomycin, and quinolones (Table 1). Microarray analysis (Check-MDR CT103XL, CheckPoints, Wageningen, the Netherlands) detected genes for an NDM-1 carbapenemase, CMY-2-acquired AmpC, and a TEM 164H extended-spectrum β-lactamase (ESBL).

Table 1. Antibiotic Susceptibilities for *E. coli* From Urine Culture

Antibiotic	Interpretation,[a] MIC in mg/L
Amoxicillin-clavulanate	R
Piperacillin-tazobactam	R
Ceftriaxone	R
Cefepime	SDD (4 mg/L)
Ertapenem	I (0.75 mg/L)
Imipenem	S (0.5 mg/L)
Meropenem	S (0.75 mg/L)
Ceftolozane-tazobactam	R (>256 mg/L)
Ceftazidime-avibactam	R (>256 mg/L)
Aztreonam	S (1.5 mg/L)
Ciprofloxacin	R
Gentamicin	R
Tobramycin	R
Trimethoprim-sulfamethoxazole	R
Minocycline	R (16 mg/L)
Doxycycline	R (>256 mg/L)
Tigecycline	S (0.380 mg/L)[b]
Fosfomycin	R
Colistin	S (0.250 mg/L)[b]

Abbreviations: I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible; SDD, susceptible dose-dependent.

[a]According to Clinical and Laboratory Standards Institute criteria (M100-S28, 2018).

[b]According to European Committee on Antimicrobial Susceptibility Testing criteria (v8.1, 2018)

[c]Antimicrobial susceptibility of the clinical isolate was determined using disc diffusion, and the results were interpreted according to the breakpoints recommended by the Clinical and Laboratory Standards Institute. Minimum inhibitory concentrations were obtained using Etest (bioMérieux, France) and MTS (Liofilchem, Italy).

A diagnosis of acute prostatitis was established. Due to its multidrug resistance (MDR) and the lack of reasonable alternatives (discussed below), tigecycline therapy was started with a loading dose of 100 mg, followed by 50 mg twice daily, and continued for 4 weeks. Full relief from the premicturition pain and improvement of nocturia and polyuria were apparent at day 8 of treatment. Follow-up cultures up to 7 months post- treatment did not detect regrowth of the MDR *E. coli*. Urinalysis after prostate massage, 4 months post-treatment, revealed no persistent pyuria; this had disappeared at treatment day 6.

DISCUSSION

This case complements 3 previous reports of prostatitis treated with tigecycline [1]; all support the drug's effectiveness as monotherapy for prostatitis with MDR *E. coli*.

For the present case, the choice of this regimen reflected several factors, but primarily the lack of good alternatives. Fluoroquinolones, co-trimoxazole, and fosfomycin—as conventional agents for prostatitis—were precluded by resistance. Imipenem and meropenem

Received 24 October 2019; editorial decision 30 December 2019; accepted January 7 2020.

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DOI: 10.1093/ofid/ofz551

were avoided, despite low minimum inhibitory concentrations (MICs), owing to presence of the bla_{NDM} gene. Similar considerations applied for aztreonam (MIC 1.5 mg/L), which is a substrate for CMY-2 and a likely substrate for TEM 164H enzyme that is expected to have ESBL activity [2]. Furthermore, penetration of β-lactams into prostatic tissue is poor, suggesting against their use (and that of aztreonam/avibactam, which would evade all the β-lactamases present). We avoided colistin because of the patient's renal impairment, enhancing the risk of nephrotoxicity, [3] and because of this drug's uncertain prostatic tissue penetration [4]. Eravacycline, a novel tetracycline, has lower MICs than tigecycline for Enterobacteriaceae [5] and might have been an alternative; however, data on prostatic penetration are lacking, and this antibiotic is not yet available in Switzerland.

Prostatitis presents a different challenge to urinary tract infections (UTIs), where any renally excreted antibiotic is potentially therapeutic. Penetration of antibiotics to the prostate occurs by passive diffusion from plasma and depends upon lipid solubility, dissociation constant, and protein binding [6]. Tetracyclines generally have good prostatic tissue and fluid penetration, but they are not appropriate for UTIs [6]. Although there are few data for tigecycline, minocycline, to which it is structurally related, achieves a prostatic tissue/serum ratio of 0.94 ± 0.39 [7]. Such considerations, coupled with a steady-state serum level of *c.* 0.6 mg/L, suggest that adequate area under the curve/MIC ratios (the critical pharmacodynamic parameter for tigecycline [8]) should be achievable, as related to the susceptibility breakpoint (0.5 mg/L) of the European Committee on Antimicrobial Susceptibility Testing [9]. Tigecycline binds to ribosomal 30S subunits with greater affinity than earlier tetracyclines and evades the resistance conferred by acquired efflux and ribosomal protection [8].

To our knowledge, only 3 previous cases of prostatitis treated with tigecycline monotherapy have been reported [1, 10, 11]. All involved ESBL-producing *E. coli*, and, despite significant differences in treatment duration (2, 6, and 22 weeks, respectively), all showed favorable outcomes. Here we achieved microbiological eradication with tigecycline (MIC 0.38 mg/L). Residual nocturia and polyuria after treatment were interpreted in the context of known bladder neck sclerosis.

Tigecycline has a black box warning from the US Food and Drug Administration and is unsuitable for UTIs owing to largely biliary excretion. It has a mixed history as monotherapy in clinical trials, achieving noninferiority to comparators in skin and soft tissue infection (SSTI) [12], complicated Intra-abdominal Infection (cIAI) [13], and community-acquired bacterial pneumonia (CABP) [14], but failing to do so in diabetic foot infection [15] and in the VAP arm of a ventilator-associated penumonia/Hospital-aquired bacterial penumonia (VAP/HABP) trial [16]. It is most often used as a combination agent against MDR pathogens. Although larger trials or case series studies are needed, the present results support the view that prostatitis might be added to the list of infections where use as monotherapy can reasonably be considered, particularly against MDR *E. coli*.

Acknowledgments

Author contributions. Concept and design: E.L.P., D.M.L., C.C., B.B.F.; clinical management: E.L.P., D.M.L., N.B., P.J., N.P., H.J.F., B.B.F.; microbiologic investigation: C.C.; critical reviewing of the manuscript: all authors. All authors have seen and approved the manuscript. All authors contributed significantly to the work.

Financial support. No financial support was required.

Potential conflicts of interest. D.M.L.: advisory boards or ad hoc consultancy Accelerate, Allecra, Antabio, Centauri, Entasis, Meiji, Melinta, Menarini, Mutabilis, Nordic, ParaPharm, Pfizer, QPEX, Roche, Shionogi, T.A.Z., Tetraphase, VenatoRx, Wockhardt, Zambon; paid lectures for Astellas, bioMerieux, Beckman Coulter, Cardiome, Cepheid, Merck/MSD, Menarini, Nordic, Pfizer, Shionogi; relevant shareholdings or options in Dechra, GSK, Merck, Perkin Elmer, Pfizer, T.A.Z., amounting for <10% of portfolio value. All the other authors declare that there are no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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