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Treatment of lower urinary tract infection caused by multidrug-resistant extended-spectrum-β-lactamase-producing *Escherichia coli* with amoxicillin/clavulanate: case report and characterization of the isolate

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Sir,

Extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* are increasingly common. They are assumed to be resistant to all β-lactams and many are also resistant to other antimicrobials. Multidrug-resistant organisms present therapeutic dilemmas, and treatment with intravenous agents is often recommended because of *in vitro* resistance to oral antimicrobials. However, *in vitro* inactivation of ESBLs by oral β-lactamase inhibitors makes their use in minor infections a theoretically attractive option that has not been well studied. We report a case of clinically and microbiologically cured cystitis caused by a multidrug-resistant ESBL-producing *E. coli* using amoxicillin/clavulanate, including microbiological and genetic analysis of the isolate.

A 78-year-old man with a history of prostatic hypertrophy presented to casualty with symptoms of cystitis of 10 days duration. The symptoms included fever, urgency, frequency and dysuria, without haematuria, flank pain and tenesmus. He had recently returned from a trip to India, but did not report any medical problems while travelling. He was completing a 7 day course of oral ciprofloxacin, 250 mg twice daily. His symptoms had not improved. On examination, the patient looked well and was afebrile. Abdominal examination showed mild suprapubic tenderness. Rectal examination revealed a moderately tender prostate. Urinalysis showed pyuria and occult haematuria, and was positive for nitrites. An ultrasound revealed only simple renal cysts and prostatic hypertrophy. The urine culture obtained the week prior had grown $>10^8$ cfu/L *E. coli* with an ESBL phenotype, confirmed using the CLSI method, with co-resistance to fluoroquinolones and sulphonamides. A presumptive diagnosis of cystitis and possible prostatitis was made. Based on his mild symptoms and knowledge of the molecular basis of resistance to β-lactams, the urine was re-cultured and a 6 week trial of oral amoxicillin/clavulanate 500/125 mg thrice daily was prescribed. Although β-lactams are not optimal therapy for acute prostatitis, we hoped to successfully treat it with a long course of therapy. The re-cultured urine also grew $>10^8$ cfu/L *E. coli*. His symptoms of cystitis resolved within 10 days of treatment. Post-treatment urine culture revealed no growth. He remains asymptomatic and without recurrence.

Antimicrobial susceptibilities of the isolate were determined using microbroth dilution and again with the Vitek™ GN-09 card (Table 1). The ESBL phenotype was reconfirmed using the CLSI method. Pulsed-field gel electrophoresis was performed and the analysis of restriction fragment patterns revealed that the organism had a unique fingerprint compared with 28 locally circulating ESBL-producing *E. coli* strains, possibly acquired during his trip to India. PCR and sequencing of *bla*<sub>CTX-M</sub>, *bla*<sub>SHV</sub> and *bla*<sub>TEM</sub> demonstrated that the only β-lactamase gene present was CTX-M-15.

No published reports of clinical and microbiological cure of cystitis caused by multidrug-resistant ESBL-producing *E. coli* exist. *In vitro* susceptibilities of isolates expressing ESBLs have been reported and vary substantially based on genotype, inoculum size and the β-lactamase inhibitor studied. Retrospective studies suggest that β-lactamase inhibitors should not be used for life-threatening infections, but no published data exist for the management of less serious infections. Despite this controversy, some experts recommend amoxicillin/clavulanate as second-line treatment for cystitis caused by ESBL producers. Despite the lack of prospective or retrospective trials, some *in vitro* data supporting this approach exist. *In vitro*, the CTX-M-15 β-lactamase is readily inactivated by tazobactam and clavulanate and less so by sulbactam. Thus, isolates expressing CTX-M-15 may be susceptible to amoxicillin/clavulanate at achievable urine concentrations provided additional β-lactam resistance mechanisms are not present. SHV and TEM ESBLs are also inactivated by clavulanate *in vitro*. Furthermore, urine bactericidal activity developments and clinical impact. *Antimicrob Agents Chemother* 2003; 47: 2385–92.


from volunteers given a single 500/125 mg dose of amoxicillin/clavulanate has been tested against multiple SHV ESBL producers, some with amoxicillin/clavulanate MICs of 64 mg/L. For all strains tested, bactericidal activity was maintained up to 8 h post-dosing. Physiological concentrating may explain this observation. A pharmacodynamic study showed peak amoxicillin urine concentration between 647 and 1547 mg/L and peak clavulanate concentration between 150 and 439 mg/L at 2–4 h following an oral dose of 250/125 mg. The urinary half-life of amoxicillin was 65 min and that of clavulanate was 50 min. Based on this study, the urinary concentration of amoxicillin/clavulanate would exceed the MIC for our isolate for >75% of the dosing interval, which may explain why our patient experienced long-term clinical cure and microbiological eradication of the organism despite in vitro resistance to amoxicillin/clavulanate (Table 1). Furthermore, the higher dose we prescribed would have resulted in an even higher urinary concentration. Physiological concentrating of amoxicillin/clavulanate does not occur in prostate tissue, and cure in the face of in vitro resistance suggests that prostatitis may not have been present.

Prospective studies are urgently needed to address the management of cystitis caused by ESBL producers. Given the theoretical inactivation of ESBLs by clavulanate, the physiological concentration of the agent in urine and this evidence of cure, it may be reasonable to consider amoxicillin/clavulanate for the treatment of outpatients with uncomplicated cystitis caused by ESBL-producing E. coli when first-line oral agents cannot be used.

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**References**


