Treatment Options for Urinary Tract Infections Caused by Extended-Spectrum B-Lactamase-Producing Escherichia coli and Klebsiella pneumoniae

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INTRODUCTION

Increased utilization of antibiotics has contributed to greater resistance among pathogenic bacteria. The prevalence of such organisms has created challenges for practitioners treating bacterial infections. One of the most frequently encountered infections in both inpatient and outpatient settings is urinary tract infections (UTIs). *Escherichia coli* is the most commonly isolated uropathogen.[1] Both *E. coli* and *Klebsiella pneumoniae, another uropathogen,* are capable of producing extended-spectrum β-lactamases (ESBL) which result in resistance to many antibiotics that are typically used in the treatment of UTIs. An analysis of inpatient urinary isolates in the United States found rates of ESBL-producing *E. coli* (ESBL-EC) and *K. pneumoniae* (ESBL-KP) to be 6.8% and 10.3%, respectively.[2]

ANTIBIOTICS REVIEW

Carbapenems are considered the most reliable treatment for infections caused by ESBL-producing bacteria.[3] Despite their utility, resistance has emerged, placing a focus on finding alternative antibiotics for UTIs so that carbapenems can be reserved for more serious infections.[4,5] Antimicrobials that may prove useful for this purpose include nitrofurantoin, fosfomycin, amikacin, cefepime, and piperacillin/tazobactam. These non-carbapenem treatment options for UTIs caused by ESBL-EC and ESBL-KP will be reviewed.

Nitrofurantoin, a commonly used oral agent for cystitis treatment, possesses activity against *E. coli*, but it is not reliably active against *K. pneumoniae*.[6,7] Tasbakan *et al.* conducted a retrospective study of the efficacy of nitrofurantoin for the treatment of ESBL-EC cystitis.[8] All isolates were susceptible to nitrofurantoin. The study included 75 patients who did not have fever or leukocytosis, but 81% of whom had complicated urinary tract infections. All patients received nitrofurantoin (macrocrystals) 50 mg every 6 hours for 14 days. Symptom resolution occurred in 69% of patients and follow-up cultures obtained 7-9 days after treatment completion were negative in 68%. Despite the use of the extended treatment duration, the rate of success observed was limited, but suggests a potential alternative therapy.

Fosfomycin is another oral agent with potential for treatment of cystitis caused by ESBL-producing microorganisms.[9] It possesses in-vitro activity against both ESBL-EC (97% susceptible) and, to a lesser degree, ESBL-KP (81% susceptible).[10] Pullukcu *et al.* conducted a retrospective cohort study of 52 patients to evaluate the efficacy of fosfomycin in the treatment of susceptible ESBL-EC cystitis.[11] All included patients were afebrile and had a normal white blood cell count prior to initiation of therapy. The majority of the patients had complicated cystitis (69%). All patients received fosfomycin 3 g every 48 hours for a total of 3 doses. Pre-treatment symptoms resolved in 94% of patients at 7-9 days after the completion of treatment and 79% of patients had negative repeat urine cultures at that time. These results were consistent with those found by Rodriguez-Baño *et al.* who evaluated patients with cystitis caused by ESBL-EC.[12] That study found that 93% (26/28) of patients treated with a single 3 g dose of fosfomycin had resolution of their pre-treatment symptoms without recurrence for 4 weeks. Fosfomycin can be considered for cystitis caused by ESBL-EC, but its utility against ESBL-KP has not been established.

There is limited evidence supporting the use of amikacin in UTIs caused by ESBL-producing bacteria, but in vitro susceptibility to amikacin was reported to be 89% for ESBL-EC and 59% for ESBL-KP.[2] Amikacin monotherapy is effective for the treatment of cystitis and pyelonephritis caused by non-ESBL-producing bacteria.[13] In a pooled analysis of 3 prospective, multicenter, randomized controlled trials, 93% (51/55) of patients treated for uncomplicated or complicated UTIs with amikacin 7.5 mg/kg twice daily achieved microbiologic success. All bacterial isolates included in this evaluation were susceptible to amikacin. A benefit of amikacin is that high urinary concentrations are achieved since 94-98% of unchanged drug is recovered in the urine at 24 hours.[14]

There has been much debate over the utility of cefepime for infections caused by ESBL-producing bacteria. Compared to the previously discussed agents, urinary isolates of ESBL-EC and ESBL-KP are far less susceptible to cefepime, 22.5% and 33.4% respectively.[2] Also, much of the evidence evaluating cefepime use for ESBL-producing organisms has focused on patients with bacteremia.[15] The findings from these studies suggest that lower MICs (≤ 1 mcg/mL) and possibly higher cefepime doses are associated with favorable outcomes.[15-16] Of note, a retrospective chart review described 3 patients who were successfully treated with cefepime for UTIs caused by ESBL-producing Enterobacteriaceae (1 ESBL-EC and 2 ESBL-KP).[17] All isolates had a cefepime MIC ≤ 1 mcg/mL. Cefepime is primarily excreted unchanged, so high concentrations are achieved in the urine.[18] Given these findings and the new lower breakpoints established by Clinical and Laboratory Standards Institute Performance Standards for Antimicrobial Susceptibility Testing, cefepime may prove to be a valuable treatment option for UTIs when the pathogen is susceptible.[19]

Another treatment option for ESBL-EC and ESBL-KP UTIs is piperacillin/tazobactam. Bouchillon *et al.* showed piperacillin/tazobactam susceptibility among urinary isolates from hospitalized patients in the United States to be 81.7% for ESBL-EC and 31.3% for ESBL-KP.[2] Piperacillin/tazobactam is also largely eliminated renally, with 68% of piperacillin and 80% of tazobactam excreted in the urine as unchanged drug.[20] Although there is a paucity of data for the use of piperacillin/tazobactam for UTIs caused by ESBL-producing bacteria, the evidence appears favorable.[21] Two small studies (6 and 14 patients) reported 100% treatment success with the use of piperacillin/tazobactam for UTIs (type of ESBL-producing organisms not specified).[22,23] Based on these limited results, piperacillin/tazobactam may have utility for these infections.

IN PIPELINE

In addition to the antibiotics discussed, there are a few new combinations in development that have potential to be very efficacious for ESBL-EC and ESBL-KP UTIs. One is ceftazidime/avibactam, which has shown a high degree of in vitro activity against these pathogens.[24,25] It is important for providers to be aware of the evidence for antibiotic use for UTIs caused by ESBL-producing bacteria. Understanding of these agents can help healthcare practitioners be better stewards of antibiotic usage and hopefully lessen the burden of carbapenem resistance.

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