

CASE REPORT

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Novel β -lactam/ β -lactamase Inhibitor Combinations in the Treatment of Elderly Patients with Complicated Urinary Tract Infections

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Urinary tract infection is a common health problem in elderly patients. In addition, urinary tract infection can be associated with increased morbidity and mortality and cause a significant healthcare burden. Furthermore, the increase of antimicrobial resistance in this clinical condition has negatively impacted the outcome of elderly patients with urinary tract infection. More and more mechanisms of antimicrobial resistance, such as including extended-spectrum-lactamases, AmpC- β -lactamase, and carbapenemases have developed and largely limited the options of appropriate antibiotics. All these facts trigger the urgent need of new agents to enhance our antibiotic armamentarium in this critical situation.

Keywords: β -lactam/ β -lactamase, inhibitor combination, urinary tract infection

To the Editor

Urinary tract infection is a common healthy problem in elderly patients (1,2). In addition, urinary tract infection can be associated with increased morbidity and mortality and cause a significant healthcare burden (1,3). Furthermore, the increase of antimicrobial resistance in this clinical condition has negatively impact the outcome of the elderly patients with urinary tract infection (3). More and more mechanisms of antimicrobial resistances, such as including

extended-spectrum-lactamases, AmpC- β -lactamase, and carbapenemases have developed (4) and largely limited the options of appropriate antibiotics. All these facts trigger the urgent needs of new agent to enhance our antibiotic armamentarium in this critical situation.

Recently, several novel β -lactam/ β -lactamase inhibitor combinations, including ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, aztreonam/avibactam, imipenem/cilastatin/relebactam, ceftarolin/avibactam

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cefepime/zidebactam and meropenem/nacubactam have been investigated to overcome the threaten of multidrug resistant organisms (5). Three of them - ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam have been evaluated in the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis (APN) in phase 3 studies (6-8). However, the clinical efficacy of these novel β -lactam/ β -lactamase inhibitor combinations for treating cUTI among elderly patients remains unclear. Therefore, the data of elderly patients from these three studies extracted (6-8) and did an integrated analysis to assess their usefulness in the treatment of elderly patients with cUTIs.

A RECAPTURE trial by Wagenlehner et al compared ceftazidime/avibactam with doripenem for treating cUTI/APN (6). ASPECT-cUTI trial by Wagenlehner et al compared ceftolozane/tazobactam with levofloxacin in the treatment of cUTI/APN (7). TANGO-I trial by Kaye et al compared the clinical efficacy and tolerability of meropenem/vaborbactam and piperacillin/tazobactam in the treatment of cUTI/APN (8). All three trials were randomized, double-blind, multicenter, and multinational studies (6-8)(Table-1).

Overall success-composite outcome of clinical cure and microbial eradication for the microbiologic modified intention-to-treat (mMITT) population was extracted as the primary outcome. Modified intent-to-treat (MITT) population was defined as all intent-to-treat patients who received at least one dose of study drug and microbiological MITT (mMITT) population was defined as MITT patients who met the disease definition of cUTI/APN and had a baseline pathogen.

Overall, 598 elderly patients with cUTI/APN were included in this analysis. 286 and 312 patients received novel β -lactam/ β -lactamase inhibitor combinations and comparators, respectively. The overall success rates of novel β -lactam/ β -lactamase inhibitor combinations and comparators were 71% (203/286) and 64.7% (202/312), respectively. No significant difference in terms of overall success between novel β -lactam/ β -lactamase inhibitor combinations was observed (odds ratio [OR], 1.68; 95% confidence interval [CI], 0.76 to 3.58; $I^2=67$). In the pooled analysis of two studies reported the clinical efficacy in the subgroups - 65-74 years and 75 years and older, we found the similar trends. For patients aged 65-74 years, the overall success rates of novel β -lactam

Table-1. Characteristics of included studies

Study - Published year	Study design	Study duration	No of patients		Dose regimen	
			Study	Control	Study	Control
<i>Wagenlehner et al, 2015 (ASPECT-cUTI)</i>	Randomized, double-blind, multicenter trial	2011-2013	100	99	Ceftolozane-tazobactam (1000 mg/500 mg) every 8 hours	Levofloxacin 750 mg everyday
<i>Wagenlehner et al, 2016 (RECAPTURE)</i>	Randomized, double-blind, multicenter trial	2012-2014	124	136	Ceftazidime-avibactam 2000 mg/500 mg every 8 hours	Doripenem 500 mg every 8 hours
<i>Kaye et al, 2018 (TANGO I)</i>	Randomized, double-blind, multicenter trial	2014-2016	62	77	Meropenem-vaborbactam (2 g/2 g) every 8 hours	Piperacillin-tazobactam (4g/0.5g) every 8 hours

/ β -lactamase inhibitor combinations and comparators were 72.9% and 69.4% (OR, 1.1; 95% CI, 0.58 to 2.11; $P=0$), respectively. For patients aged 75 years and older, the overall success rates of novel β -lactam/ β -lactamase inhibitor combinations and comparators were 70% and 70.7%, respectively (OR, 1.85; 95% CI, 0.22 to 15.45; $P=56$).

In this study, we demonstrated the clinical efficacy of novel β -lactam/ β -lactamase inhibitor combinations was noninferior to comparators in the treatment of cUTI/APN among elderly patients. The non-inferiority of novel β -lactam/ β -lactamase inhibitor combinations to comparators was found in both overall elderly population and subgroup analysis. These findings could be supported by previous in vitro studies (9,10), in which novel β -lactam/ β -lactamase inhibitor combinations show potent activity against most of Gram-negative bacteria from patients with UTI including high potencies against multidrug-resistant organisms. Therefore, it should suggest that novel β -lactam/ β -lactamase inhibitor combinations could play a significant role for treating elderly patients with cUTI/APN.

However, this study had several limitations. First, the numbers of enrolled patients and study were limited. Second, we did not perform a more detail analysis, such as the usefulness of novel β -lactam/ β -lactamase inhibitor combinations for antibiotic-resistant organism, and for different types of infections – cUTI or APN. Third, safety profile remains another important concern, however, we did not assess the tolerability of these agents in the elderly patients. Further large-scale study is warranted to clarify these issues.

In conclusion, novel β -lactam/ β -lactamase inhibitor combinations exhibit comparable

efficacy with comparator in elderly patients with cUTI/APN. Novel β -lactam/ β -lactamase inhibitor combinations may be considered as one potential therapeutic option in this clinical entity.

Conflict of Interest

The authors declare that they have no conflict of interests.

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