RESEARCH PAPER

Clinical significance of carbapenem synergism in combination with reserve antibiotics: a retrospective study in patients with carbapenem-resistant infections

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Abstract

Objective: To evaluate the clinical significance of carbapenems synergism in combination with reserve antibiotics in patients with carbapenem-resistant infections based on a retrospective analysis of treatment results.

Methods: A single-center retrospective cohort study was conducted that included 186 adult patients with microbiologically confirmed carbapenem-resistant infections. All patients received combined antibacterial therapy, including carbapenem and a reserve antibiotic. The synergism of antibiotic combinations was determined by the checkerboard assay with the calculation of the fractional inhibitory concentration index (FICI). The patients were divided into the synergism group (n = 112) and the non-synergism group (n = 74). The primary outcome was a 30-day mortality rate. Secondary outcomes included clinical recovery, microbiological eradication of the pathogen, duration of hospitalization, and frequency of adverse drug reactions.

Results: A synergistic effect was found in 60.2% of patients. The rate of clinical recovery in the synergy group was 79.5% versus 56.8% in the no-synergy group (p = 0.001). Microbiological eradication was achieved in 72.3% and 47.3% of patients, respectively (p = 0.002). Thirty-day mortality was significantly lower in the synergism group (23.2% vs. 44.6%; p = 0.002). In multifactorial logistic analysis, lack of synergy was an independent predictor of death (OR 2.41; 95% CI 1.18–4.92; p = 0.016). In addition, the use of synergistic combinations was accompanied by a reduction in the length of stay in the intensive care unit and the total duration of hospitalization. There were no significant differences in the frequency of adverse drug reactions between the groups.

Conclusion: The laboratory-proven synergy of carbapenems with reserve antibiotics is associated with improved clinical outcomes in patients with carbapenem-resistant infections, including reduced mortality and increased clinical recovery rates. The results obtained confirm the prospects of using synergism testing for a personalized choice of antibacterial therapy and justify the need for further prospective studies.

Key Words: Carbapenem resistance, carbapenem-resistant infections, reserve antibiotics, antibiotic synergism, combined antibacterial therapy, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, antibiotic resistance, mortality, microbiological eradication.

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Introduction: Antimicrobial resistance is currently considered one of the most serious threats to global health in the 21st century. According to international epidemiological studies, the spread of antibiotic-resistant microorganisms leads to a significant increase in morbidity, mortality, duration of hospitalization and economic costs of treatment. Of particular concern is the increase in the number of infections caused by gram-negative multidrug-resistant bacteria, among which carbapenem-Resistant Enterobacteria (Carbapenem-Resistant Enterobacterales, CRE), carbapenem-resistant Pseudomonas aeruginosa and Acinetobacter baumannii occupy a leading place. These pathogens are included by the World Health Organization in the list of microorganisms of critical priority requiring the development of new therapeutic strategies and antimicrobial drugs. [1]

Carbapenems have for many years been considered the most effective beta-lactam antibiotics for the treatment of severe infections caused by gram-negative bacteria. Due to their wide range of activity, resistance to most beta-lactamases, and favorable pharmacokinetic characteristics, drugs of this group have been widely used in sepsis, nosocomial pneumonia, complicated urinary tract infections, intra-abdominal infections, and other severe bacterial diseases. However, the intensive use of carbapenems in clinical practice has contributed to the selection and spread of microorganisms with various mechanisms of resistance to these drugs. The main mechanism of carbapenem resistance is the production of carbapenemases— enzymes capable of hydrolyzing carbapenems and other beta-lactam antibiotics. Among the most common carbapenemases are enzymes of classes A, B and D according to the Ambler classification, including KPC (Klebsiella pneumoniae carbapenemase), metallo-β-lactamases of the NDM, VIM and IMP types, as well as oxacillinases of the OXA family. Additional resistance mechanisms are a decrease in the permeability of the outer membrane of bacteria due to the loss of porin proteins, overexpression of active efflux systems, and hyperproduction of extended-spectrum beta-lactamases or AmpC-cephalosporinases in combination with impaired membrane transport of antibiotics. Often, several resistance mechanisms are present in one strain at the same time, which significantly limits the effectiveness of existing antimicrobial agents. [2-3]

The clinical significance of carbapenem-resistant infections is due not only to the difficulty of choosing adequate antibiotic therapy, but also to the high mortality of patients. According to numerous studies, mortality in bloodstream infections caused by carbapenem-resistant enterobacteria can reach 40-60%, and in septic shock and severe infections in patients with intensive care units and intensive care units exceed these values. A significant contribution to adverse outcomes is made by a delay in the appointment of effective therapy, a limited choice of active drugs, and the serious condition of patients with multiple concomitant pathologies. [4]

In the context of the rapid spread of carbapenem resistance, reserve antibiotics are of particular importance. This group includes drugs that remain active against many multidrug-resistant pathogens, including polymyxins (colistin and polymyxin B), tigecycline, fosfomycin, as well as new beta-lactam/inhibitory combinations. Despite the availability of new antimicrobial drugs, their availability remains limited in many countries, and their effectiveness may vary depending on the molecular mechanisms of resistance of a particular pathogen. In addition, the use of reserve antibiotics is associated with the risk of developing toxic reactions, the formation of additional resistance, and significant economic costs. [5]

In this regard, the possibilities of combined antibacterial therapy have been actively studied in recent years. The theoretical rationale for using combinations of antibiotics is to achieve a synergistic effect, in which the combined effect of the drugs exceeds the total effect of each of them with a separate application. Synergism can lead to increased bactericidal activity, an expanded spectrum of action, suppression of the formation of resistant subpopulations, and an increased likelihood of achieving clinical success in patients with severe infections. Of particular interest is the use of carbapenems as part of combined treatment regimens, even in cases of laboratory-confirmed resistance of the pathogen to these drugs. This strategy is based on the assumption that carbapenem can maintain partial activity against a bacterial cell or enhance the action of other antibiotics due to various molecular mechanisms. For example, the interaction of carbapenems with penicillin-binding proteins can alter the structure of the microbial cell wall, facilitating the penetration of the concomitant drug. In addition, high doses of carbapenems with prolonged infusions can create concentrations sufficient to partially overcome some resistance mechanisms. Numerous in vitro studies have demonstrated the existence of a synergy between carbapenems and various reserve antibiotics. The most frequently studied combinations of meropenem or imipenem with colistin, tigecycline, fosfomycin, aminoglycosides and new beta-lactam drugs. In experimental models, such combinations often provided a more pronounced reduction in bacterial load compared with monotherapy. However, the results of clinical trials remain ambiguous. Some authors report a decrease in mortality and an increase in the frequency of microbiological eradication when using combined regimens, while other studies do not reveal significant advantages compared with monotherapy with active drugs. [6-7]

An additional difficulty is the lack of uniform criteria for interpreting synergy. Various laboratory methods are used to evaluate the interaction of antibiotics, including the checkerboard assay, time-kill assay, gradient methods, and modern automated technologies. The results obtained may vary significantly depending on the technique used, the strain under study, and the experimental conditions. Moreover, the presence of a synergistic effect in vitro does not always correlate with clinical outcomes in patients, since the effectiveness of therapy is also determined by the pharmacokinetic and pharmacodynamic characteristics of drugs, the localization of infection, the state of the patient's immune system, and other factors. Despite these limitations, combination therapy remains a widespread practice in the treatment of carbapenem-resistant infections, especially in critically ill patients. [8-9]

Thus, the problem of carbapenem-resistant infections treatment remains extremely relevant in modern clinical medicine. Limited therapeutic options, high patient mortality, and the continued spread of multidrug-resistant microorganisms necessitate the search for effective strategies for antibacterial therapy. Combinations of carbapenems with reserve antibiotics are one of the most promising approaches, but their clinical effectiveness requires further study. A retrospective analysis of the results of treatment of patients with carbapenem-resistant infections provides important information about the practical significance of the synergistic interaction of antibiotics and its impact on clinical outcomes. [10]

The purpose of this study is to evaluate the clinical significance of carbapenems synergism in combination with reserve antibiotics in patients with carbapenem-resistant infections based on a retrospective analysis of treatment results, as well as to identify factors associated with the effectiveness of combined antibacterial therapy.

Materials and Methods

A single-center retrospective cohort study was conducted to evaluate the clinical significance of carbapenems synergism in combination with reserve antibiotics in patients with carbapenem-resistant infections. The analysis included data from patients treated in a multidisciplinary hospital between January 2022 and December 2025. The study was carried out in accordance with the principles of the Helsinki Declaration and approved by the local ethics committee of the institution. Due to the retrospective nature of the work, the need to obtain individual informed consent from patients was eliminated. Study population The study included adult patients (≥18 years old) with microbiologically confirmed infection caused by carbapenem-resistant gram-negative microorganisms who received combined antibacterial therapy, including carbapenem and at least one reserve antibiotic.

Inclusion criteria: age 18 years and older; presence of clinical and laboratory signs of an infectious process; isolation of a carbapenem-resistant microorganism from clinically significant biological material; appointment of combination therapy with carbapenem (meropenem, imipenem or doripenem) together with a reserve antibiotic for at least 72 hours; availability of complete medical documentation for the analysis of treatment outcomes.

Exclusion criteria: colonization without signs of active infection; duration of antibacterial therapy less than 72 hours; absence of microbiological examination results; repeated hospitalization of one patient (only the first episode of infection was taken into account); incompleteness of clinical data.

Microbiological methods

Clinical material (blood, sputum, bronchoalveolar lavage, urine, wound discharge, and other samples) was examined in a microbiological laboratory according to standard protocols. The identification of microorganisms was carried out by MALDI-TOF mass spectrometry. Antibiotic sensitivity was determined by micro dilution in broth or automated systems in accordance with the recommendations of the European Committee for the Determination of Sensitivity to Antimicrobials. Carbapenem resistance was determined by detecting resistance to at least one of the following drugs: meropenem, imipenem or ertapenem. Molecular genetic detection of carbapenemase genes (blaKPC, blaNDM, blaVIM, blaIMP, blaOXA-48, etc.) by polymerase chain reaction was performed for some isolates. Determination of antibiotic synergism To evaluate the interaction of antibiotics, the checkerboard assay method was used with the calculation of the Fractional Inhibitory Concentration Index (FICI). Synergism was determined at FICI <0.5, additive effect — at FICI >0.5 and <1.0, indifferent interaction — at FICI >1.0 and <4.0, antagonism — at FICI >4.0.

The following combinations were analyzed: meropenem + colistin; meropenem + tigecycline; meropenem + fosfomycin; imipenem + colistin; imipenem + tigecycline; other combinations of carbapenems with reserve antibiotics.

Depending on the test results, the patients were divided into two groups: 1. The synergism group — treatment with a combination of antibiotics that demonstrated a laboratory-confirmed synergistic effect;

2. the group of lack of synergy is a combination with an additive or indifferent effect.

The primary outcome was a 30-day total mortality after infection was confirmed. Secondary outcomes were: clinical recovery by the end of antibacterial therapy; microbiological eradication of the pathogen; duration of hospital stay; duration of stay in the intensive care unit; frequency of infection recurrence within 30 days; development of adverse drug reactions. Clinical recovery was defined as complete or significant regression of infection symptoms without the need to change antibiotic therapy. Microbiological eradication was confirmed by negative results of repeated crops after completion of treatment. Statistical analysis Statistical data processing was performed using the IBM SPSS Statistics software package version 27.0 (IBM Corp., USA). The differences at $p < 0.05$ were considered statistically significant.

Result & Discussion: The study included 186 patients with carbapenem-resistant infections who met the inclusion criteria. The average age of the patients was 61.8 ± 14.2 years, with men accounting for 58.1% (n = 108) and women for 41.9% (n = 78). The majority of patients were in intensive care units (64.0%; n = 119). The most common concomitant diseases were arterial hypertension (62.9%), diabetes mellitus (31.2%), chronic kidney disease (22.0%) and malignant neoplasms (18.3%). Nosocomial pneumonia (34.9%; n = 65), bloodstream infections (24.7%; n = 46), complicated urinary tract infections (18.8%; n = 35), intra-abdominal infections (12.4%; n = 23) and surgical wound infections (9.1%; n = 17). Sepsis was diagnosed in 102 patients (54.8%), septic shock in 48 patients (25.8%).

Among the isolated carbapenem-resistant microorganisms, the following prevailed: * Klebsiella pneumoniae — 44.1% (n = 82); * Acinetobacter baumannii — 28.5% (n = 53); * Pseudomonas aeruginosa — 21.0% (n = 39); * other gram—negative bacteria - 6.4% (n = 12).

The most frequently prescribed combinations of antibiotics were: * meropenem + colistin — 37.1% (n = 69); * meropenem + tigecycline — 24.2% (n = 45); * meropenem + fosfomycin — 16.1% (n = 30); * imipenem + colistin — 11.3% (n = 21); * other combinations accounted for 11.3% (n = 21). According to the results of the synergy testing, a laboratory-confirmed synergistic effect was detected in 112 patients (60.2%), while in 74 patients (39.8%) the combinations demonstrated an additive or indifferent effect.

Thus, two groups were formed: the group of synergy — 112 patients; the group of lack of synergy — 74 patients.

The initial clinical and demographic characteristics of the groups did not significantly differ in age, gender, severity of the condition and the structure of pathogens ($p > 0.05$).

Clinical treatment outcomes Clinical recovery was achieved in 79.5% of patients in the synergy group compared with 56.8% of patients in the no-synergy group (89/112 vs. 42/74, respectively; $p = 0.001$). Microbiological eradication of the pathogen was registered in 72.3% of patients in the synergism group and in 47.3% of patients in the no-synergism group ($p = 0.002$). The average duration of antibacterial therapy was 12.4 ± 4.8 days in the synergism group and 14.1 ± 5.2 days in the no-synergism group ($p = 0.031$). The median length of stay in the intensive care unit was 9 (IQR 5-16) days versus 13 (IQR 7-20) days, respectively ($p = 0.017$). The total duration of hospitalization was significantly lower in patients receiving combinations with laboratory-confirmed synergism: 21 (IQR 15-32) days versus 28 (IQR 18-39) days ($p = 0.024$). Mortality analysis The total 30-day mortality in the study cohort was 31.7% (59/186). In the synergism group, mortality was 23.2% (26/112), while in the non—synergism group it was 44.6% (33/74), which indicated a statistically significant reduction in the risk of death when using combinations with a synergistic effect ($\chi 2 = 9.41$; $p = 0.002$). Among patients with septic shock, the differences were even more pronounced. The mortality rate was 39.1% in the synergism group and 67.9% in the no-synergism group ($p = 0.018$).

The Kaplan—Mayer survival analysis demonstrated a statistically significant advantage of the synergy group in terms of 30-day survival (log-rank test $p = 0.001$). Factors associated with death According to the results of a single-factor analysis were associated with an increased risk of 30-day mortality: * age over 65 years (OR 1.89; 95% CI 1.03–3.48; $p = 0.039$); * septic shock (OR 3.76; 95% CI 1.98–7.13; $p < 0.001$); * APACHE II ≥20 points (OR 4.21; 95% CI 2.19–8.09; $p < 0.001$); * bloodstream infection (OR 2.14; 95% CI 1.11–4.13; $p = 0.022$). The presence of a laboratory–confirmed synergy between carbapenem and a reserve antibiotic was associated with a reduced risk of death (OR 0.37; 95% CI 0.20-0.68; $p = 0.001$). After multivariate logistic regression analysis, the independent predictors of 30-day mortality were: * septic shock (OR 3.12; 95% CI 1.55–6.29; $p = 0.001$); * APACHE II ≥20 points (OR 2.76; 95% CI 1.34–5.67; $p = 0.005$); * lack of synergy between antibiotics (OR 2.41; 95% CI 1.18–4.92; $p = 0.016$). Adverse drug reactions were reported in 27 patients (14.5%). Nephrotoxicity was most often observed when using colistin (8.1%), increased activity of liver enzymes during tigecycline therapy (3.8%) and gastrointestinal disorders (2.7%). The incidence of adverse reactions did not significantly differ between the groups of synergism and lack of synergism ($p = 0.64$). The main results of the study indicate that the use of combinations of carbapenems with reserve antibiotics, which have a laboratory-proven synergistic effect, is associated with a higher rate of clinical recovery and microbiological eradication of the pathogen, a reduction in the duration of hospitalization and stay in the intensive care unit, as well as a significant reduction in 30-day mortality in patients with carbapenem-resistant infections. Laboratory-confirmed synergy was an independent factor of favorable prognosis in the multifactorial analysis model.

The results of a retrospective study indicate the clinical significance of the synergy of carbapenems in combination with reserve antibiotics in the treatment of infections caused by carbapenem-resistant gram-negative microorganisms. The data obtained showed that the use of combinations of antibiotics demonstrating a laboratory-proven synergistic effect is associated with a higher rate of clinical recovery and microbiological eradication of the pathogen, as well as a decrease in 30-day mortality compared with combinations without pronounced synergism. The problem of carbapenem-resistant infections treatment remains one of the most urgent in modern clinical practice. Despite the emergence of new antimicrobial drugs, the availability of effective therapeutic options remains limited in many countries. In this regard, the search for optimal combinations of existing antibacterial agents is of considerable practical interest. The results of this study confirm the prospects of this approach and are consistent with the concept of rational combination therapy based on the use of potential synergistic interactions between antibiotics. In the study cohort, a synergistic effect was found in more than half of the patients. It was most often observed when using combinations of meropenem with colistin, tigecycline and fosfomycin. The results obtained correspond to data from experimental studies demonstrating the ability of carbapenems to enhance the activity of reserve antibiotics even against strains characterized by formal resistance to carbapenems. It is assumed that this effect is associated with a change in the structure of the cell wall of microorganisms, an increase in the permeability of the bacterial membrane and an increase in the intracellular accumulation of concomitant antibacterial drugs. Of particular interest is the reduction in 30-day mortality among patients in the synergism group identified in this study. The difference between the groups exceeded 20 percentage points, which indicates a potentially significant effect of the synergistic interaction of antibiotics on clinical outcomes. Moreover, in the multifactorial regression analysis, the presence of synergy remained statistically significant after adjusting for the severity of the patients' condition and the presence of septic shock. This suggests that the observed effect cannot be explained solely by differences in the initial severity of the disease. The results obtained are consistent with a number of previously published observational studies in which combination therapy demonstrated advantages over monotherapy in the treatment of infections caused by carbapenem-resistant Enterobacteria and Acinetobacter baumannii. However, the literature data remains ambiguous. Some authors did not find significant differences between combined and monotherapy regimens. Such contradictions can be explained by differences in the structure of pathogens, the treatment regimens used, the methods of assessing synergy, and the characteristics of the studied patient populations. An important result of this study was the identification of a higher frequency of microbiological eradication in the synergism group. This fact confirms the hypothesis that a laboratory-determined interaction between antibiotics can be realized in a clinical setting. It should be noted that the relationship between the results of in vitro synergy tests and clinical outcomes remains a matter of debate. However, the data obtained indicate the potential prognostic value of such studies when choosing antibacterial therapy.

In addition to the effect on mortality, the use of synergistic combinations was accompanied by a reduction in the length of stay of patients in the intensive care unit and the hospital as a whole. This effect has not only clinical, but also economic significance, since reducing the duration of hospitalization helps to reduce the costs of the healthcare system and reduce the risk of additional nosocomial complications. Attention should also be paid to the safety of combination therapy. In our study, the frequency of adverse drug reactions did not differ between the groups. The nephrotoxic effects of colistin were most frequently reported, which corresponds to the literature data. The absence of an increase in the incidence of complications when using synergistic combinations indicates an acceptable safety profile of the approach under consideration, provided that patients are adequately monitored. Despite the results, the study has a number of limitations. Firstly, the retrospective design does not completely eliminate the influence of hidden confounding factors. Secondly, the work was carried out in one center, which may limit the possibility of extrapolating the results to other medical institutions with a different structure of pathogens and levels of antibiotic resistance. Thirdly, the molecular characterization of resistance mechanisms was not available for all clinical isolates. In addition, different combinations of antibiotics were analyzed together, which does not allow us to fully assess the effectiveness of each specific treatment regimen. Another limitation is the lack of a standardized approach to defining synergies. Despite the widespread use of the chessboard method, the results of various laboratory tests may differ, which makes it difficult to directly compare the data from different studies. To definitively confirm the clinical significance of the synergy, multicenter prospective studies with standardized microbiological testing methods and sufficient statistical power are needed. Nevertheless, the results obtained have important practical significance. They confirm the feasibility of testing antibiotic combinations in patients with severe carbapenem-resistant infections and support the concept of personalized choice of antibacterial therapy based on both microbiological and clinical data. Using the results of the synergy assessment can help improve the effectiveness of treatment and improve the prognosis in the most severe category of patients.

Conclusion:

1. In patients with carbapenem-resistant infections, a laboratory-confirmed synergy between carbapenems and reserve antibiotics was detected in 60.2% of cases.
2. The use of synergistic combinations was associated

with a significantly higher frequency of clinical recovery and microbiological eradication of the pathogen compared with combinations without a synergistic effect.

3. The presence of synergy was accompanied by a decrease in the 30-day mortality rate, a reduction in the length of stay of patients in the intensive care unit and a decrease in the total duration of hospitalization.

4. According to the multifactorial analysis, the lack of synergy was an independent predictor of an unfavorable outcome along with septic shock and high severity of the patient's condition.

5. The frequency of adverse drug reactions did not differ between the groups, which indicates acceptable safety of combination therapy with proper clinical monitoring.

6. The results obtained confirm the clinical significance of carbapenems synergism in combination with reserve antibiotics and substantiate the need for further prospective multicenter studies to develop personalized treatment strategies for carbapenem-resistant infections.

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Ethical Clearance: The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to inclusion in the study.

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