

Review Article

Antibiotic synergy as a strategy for combating multidrug-resistant bacteria: a review of mechanisms and clinical implications

Alaa Mohammed Malki^{1*}, Rana Abdulrahim Alaeq², Ahlam Ayidh Alosaimi³,
Mawaddah Mohsen Ageeli⁴, Ghadah Mohammed Alshehri⁴, Riyadh Othman Shati⁵,
Tahani Jubran Almalki⁶, Abdulrahman Abdulmalek Almalki⁷, Khulod Nawaf Alotaibi⁸,
Khalid Abdullah Alsaedi⁹, Abdulla Mubarak Alheddi¹⁰

¹Department of Infectious Diseases, East Jeddah Hospital, Jeddah, Saudi Arabia

²College of Applied Medical Sciences, Taibah University, Medina, Saudi Arabia

³Pharmacy Department, AlQuwayiyah General Hospital, Al Quwayiyah, Saudi Arabia

⁴Department of Cardiology, Prince Faisal bin Khalid Cardiac Center, Abha, Saudi Arabia

⁵Department of Internal Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia

⁶Pharmacy Department, Ministry of Defence – Armed Forces Hospital, Khamis Mushait, Saudi Arabia

⁷College of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia

⁸Compliance Assist Administration, Compliance Third West Office, Al Duwadimi, Saudi Arabia

⁹Pharmacy Department, King Abdullah Medical City, Mecca, Saudi Arabia

¹⁰Department of Internal Medicine, Salmaniya Medical Complex, Manamah, Kingdom of Bahrain

Received: 01 September 2023

Accepted: 16 September 2023

*Correspondence:

Dr. Alaa Mohammed Malki,

E-mail: A.m.malki1409@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Multidrug-resistant bacteria (MDRB) are a global concern due to their resistance to multiple antibiotics. The rise of MDRB is attributed to factors like antibiotic misuse and horizontal gene transfer. Limited treatment options led to increased morbidity, mortality, and healthcare costs. MDRB spreads within healthcare and community settings, posing risks to vulnerable populations. Urgent efforts are needed to combat MDRB, including antibiotic synergy, which enhances therapeutic efficacy. Synergy disrupts bacterial processes, improves penetration and intracellular accumulation, and inhibits resistance mechanisms. It is crucial in treating biofilm-associated infections. Methods like checkerboard assays and time-kill assays assess synergistic effects, while high-throughput screening enables rapid identification. The rise of multidrug resistance has prompted urgent calls for concerted efforts to address this global health crisis. Antibiotic synergy broadens treatment options, allows dose reduction, and addresses biofilm infections. Careful implementation is necessary to minimize resistance and drug interactions. Successful case studies highlight the potential of antibiotic synergy against MDRB.

Keywords: MDRB, Antibiotic synergy, Treatment efficacy, Resistance mechanisms, Biofilm-associated infections

INTRODUCTION

Multidrug-resistant bacteria (MDRB) have emerged as a significant global concern in recent years, posing a grave threat to public health and healthcare systems worldwide. These bacteria, commonly referred to as superbugs, are

strains that have developed resistance to multiple classes of antibiotics, rendering them difficult or even impossible to treat using conventional antibiotic therapies.¹ The rise of MDRB has been attributed to several factors, including the misuse and overuse of antibiotics, inadequate infection control measures, and the horizontal transfer of resistance genes among bacterial populations.²

One of the primary consequences of multidrug resistance is the limited availability of effective treatment options for bacterial infections. Infections caused by MDRB are associated with increased morbidity, mortality, and healthcare costs.³ Patients affected by these infections often experience prolonged hospital stays, delayed recovery, and higher rates of treatment failure. Furthermore, the spread of MDRB within healthcare settings poses a significant risk to vulnerable populations, such as immunocompromised individuals, elderly patients, and those undergoing invasive medical procedures.

MDRB are not confined to a specific geographical region but have become a global phenomenon. They can be found in hospitals, long-term care facilities, community settings, and even in the environment. The rapid global movement of people and goods facilitates the dissemination of multidrug-resistant strains across borders, making it a shared concern for countries worldwide.^{4,5} Additionally, the impact of MDRB extends beyond human health, affecting veterinary medicine, agriculture, and food production.⁶

The rise of multidrug resistance has prompted urgent calls for concerted efforts to address this global health crisis. Strategies such as antimicrobial stewardship, infection prevention and control measures, and the development of novel antibiotics or alternative treatment modalities are being pursued to combat MDRB.⁷ One such measure includes the application of antibiotic synergy in such clinical scenarios.

Antibiotic synergy is being explored as a potential solution to combat MDRB due to its ability to enhance therapeutic efficacy beyond what can be achieved with single antibiotics alone.⁸ The emergence and spread of MDRB have significantly limited the effectiveness of traditional antibiotic therapies, leading to treatment failures and increased morbidity and mortality rates. In this context, antibiotic synergy offers a promising approach to overcome resistance mechanisms and improve treatment outcomes. The objective of the paper is to review the mechanisms underlying antibiotic synergy and discuss its clinical implications in MDRB infections.

LITERATURE SEARCH

This study is based on a comprehensive literature search conducted on June 25, 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed antibiotic synergy as a strategy for combating MDRB 1

infections. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

One key advantage of antibiotic synergy is its ability to target different cellular processes or pathways within bacteria.⁹ Combining antibiotics with distinct mechanisms of action can disrupt multiple vital functions simultaneously, making it more challenging for bacteria to develop resistance. By targeting different cellular processes, antibiotic synergy can enhance the overall bactericidal activity and prevent the emergence of resistance against the individual drugs. This cooperative action increases the effectiveness of treatment, particularly against multidrug-resistant strains that have developed intricate resistance mechanisms. Furthermore, antibiotic synergy can enhance the penetration and intracellular accumulation of antibiotics within bacteria.¹⁰ Some antibiotic combinations work synergistically by improving the ability of one drug to penetrate the bacterial cell wall and facilitating the entry of the other drug. This enhanced penetration enables greater exposure of bacteria to the antibiotics, increasing their effectiveness against resistant strains that may have developed mechanisms to limit antibiotic entry. Additionally, certain combinations can promote the intracellular accumulation of antibiotics, allowing for higher concentrations within bacteria and better eradication of intracellular pathogens.¹¹

Another important aspect of antibiotic synergy is its potential to inhibit antibiotic resistance mechanisms employed by bacteria.¹² Some combinations can act synergistically to inhibit efflux pumps or enzymes responsible for antibiotic degradation or modification. By simultaneously targeting these resistance mechanisms, antibiotic synergy can overcome or delay the development of resistance, making it a valuable strategy for combating MDRB. Moreover, antibiotic synergy can play a critical role in addressing biofilm-associated infections.¹³ Biofilms, complex communities of bacteria encased in a self-produced matrix, are notoriously resistant to antibiotic treatment. By combining antibiotics with complementary actions, such as agents that disrupt biofilm architecture or enhance antibiotic penetration through the matrix, antibiotic synergy can effectively target and eradicate biofilm-associated pathogens.

Combining antibiotics that target different cellular processes can disrupt multiple pathways in bacteria, leading to enhanced bacterial killing.¹⁴ Bacteria possess various cellular processes that are essential for their survival and growth, such as cell wall synthesis, protein synthesis, DNA replication, and metabolism.^{15,16} When different antibiotics with distinct mechanisms of action are used together, they can simultaneously interfere with multiple cellular processes, causing a more significant disruption to bacterial homeostasis and increasing the likelihood of bacterial killing. This synergy occurs

because the combined effects of the antibiotics exceed the additive effects of each drug alone, leading to enhanced bacterial eradication. Certain antibiotic combinations can enhance penetration into bacterial cells or promote intracellular accumulation, improving their effectiveness against resistant bacteria.¹⁰ Some bacteria employ mechanisms to limit antibiotic entry into their cells, such as reducing the permeability of their cell membranes or activating efflux pumps that actively remove antibiotics from the cell. By combining antibiotics that have different cell entry mechanisms or that can bypass these resistance mechanisms, the overall penetration into bacterial cells can be improved.¹⁷ For example, one antibiotic may disrupt the cell membrane, allowing easier entry for another antibiotic that targets intracellular processes. This enhanced penetration ensures greater exposure of the bacteria to the antibiotics, increasing their efficacy against resistant strains.

Synergistic combinations can also inhibit resistance mechanisms employed by bacteria, such as efflux pumps or enzymatic inactivation, thereby overcoming resistance.¹⁸ Efflux pumps are cellular transporters that actively pump antibiotics out of the bacterial cell, reducing their intracellular concentrations and rendering them less effective. Some antibiotic combinations can inhibit or block these efflux pumps, preventing the expulsion of the drugs and allowing for higher intracellular concentrations.¹⁹ Similarly, certain combinations can inhibit enzymatic inactivation of antibiotics by bacterial enzymes, preserving the activity of the drugs and overcoming resistance mechanisms.²⁰ Antibiotic synergy is particularly valuable in combating biofilm-associated infections. Biofilms are complex communities of bacteria embedded within a self-produced matrix, making them highly resistant to antibiotic treatment.²¹ Synergistic combinations can target different stages of biofilm formation, disrupting the attachment of bacteria to surfaces, inhibiting matrix production, or enhancing the penetration of antibiotics through the biofilm matrix.²² By addressing multiple aspects of biofilm formation and stability, antibiotic synergy can effectively target and eradicate biofilm-associated pathogens that are notoriously difficult to eliminate using monotherapy.

Checkerboard and microdilution assays are commonly used to determine the interaction between antibiotics and assess their synergistic effects.²³⁻²⁵ In these assays, different concentrations of two or more antibiotics are combined in a matrix format, with varying concentrations of each antibiotic along the rows and columns. Bacterial cultures are then added to each well, and the growth inhibition or bacterial killing is measured. The combination effect is determined by comparing the growth inhibition of the combination with the expected additive effect of the individual antibiotics. Synergy is observed when the combination effect is greater than the sum of the effects of the individual antibiotics.

Time-kill assays provide insights into the bactericidal activity of antibiotic combinations over time, helping to identify synergy.²⁵ In these assays, bacteria are exposed to antibiotics either alone or in combination, and samples are taken at specific time points to measure bacterial viability. The reduction in bacterial colony-forming units (CFUs) over time is evaluated, allowing the determination of the bactericidal activity of the antibiotics. Synergy is observed when the combination demonstrates a more rapid and significant reduction in bacterial CFUs compared to the individual antibiotics.

The E-test and gradient diffusion methods enable the determination of antibiotic concentration gradients to identify optimal synergistic combinations.^{25,26} In the E-test, an antibiotic gradient strip containing a predefined concentration range is placed on an agar plate inoculated with bacteria. As the antibiotic diffuses from the strip into the agar, a concentration gradient is established. The point of intersection between the elliptical inhibition zone and the strip corresponds to the minimal inhibitory concentration (MIC). By placing two or more E-test strips on the same plate, different combinations of antibiotics can be evaluated to determine the optimal concentration gradient for synergistic effects.

High-throughput screening techniques, such as robotic systems or automated platforms, allow for the rapid screening of numerous antibiotic combinations to identify synergistic interactions.²⁷ These techniques employ microtiter plates with a large number of wells, each containing a different antibiotic combination. The growth or viability of bacteria is assessed using automated imaging or measurement systems. By systematically testing a vast array of combinations, high-throughput screening enables the identification of potential synergistic interactions and the optimization of antibiotic combinations for enhanced efficacy against MDRB.

Antibiotic synergy has the potential to broaden the range of bacterial species or infections that can be effectively treated, including those caused by multidrug-resistant pathogens.¹⁸ By combining antibiotics with different mechanisms of action, the synergistic effect can overcome resistance mechanisms that a single antibiotic might not be able to tackle alone. This expanded coverage is particularly crucial in the context of MDRB, where conventional antibiotics may be ineffective due to the presence of multiple resistance mechanisms. Antibiotic synergy offers the opportunity to target these pathogens using combinations that can inhibit or bypass these resistance mechanisms, thereby improving treatment outcomes.

Combining antibiotics with different mechanisms of action can also enable dose reduction, minimizing individual drug toxicity and associated side effects.²⁸ In some cases, synergistic combinations allow for lower concentrations of each individual antibiotic to be used while achieving the desired therapeutic effect. This dose

reduction can help mitigate the toxicity and side effects associated with high antibiotic doses. By combining antibiotics that act through different pathways, the overall effectiveness can be enhanced, allowing for lower individual doses and reducing the risk of adverse reactions.

Despite the potential benefits of antibiotic synergy, several challenges must be addressed to ensure its effective and safe implementation. One concern is the risk of increased antibiotic resistance development.²⁹ The use of combination therapy may exert selective pressure on bacteria, potentially leading to the emergence of resistance to both antibiotics simultaneously. Close monitoring and surveillance of resistance patterns are essential to identify any emergence of resistance and adjust treatment strategies accordingly.

Another challenge is the potential for drug interactions when combining multiple antibiotics. Some combinations may exhibit antagonistic interactions, where the combined effect is less than the sum of the individual effects.³⁰ Additionally, drug interactions can lead to increased toxicity or reduced efficacy. Careful consideration and evaluation of potential drug interactions are necessary when designing antibiotic synergy regimens.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a well-known multidrug-resistant pathogen associated with a range of infections, including skin and soft tissue infections, pneumonia, and bloodstream infections.³¹ Antibiotic synergy has been explored as an approach to enhancing the effectiveness of treatment against MRSA. Several studies have demonstrated successful applications of antibiotic synergy in combating MRSA infections.³²⁻³⁵ One example of antibiotic synergy against MRSA involves the combination of a β -lactam antibiotic, such as oxacillin or cefoxitin, with an inhibitor of cell wall synthesis, such as a β -lactamase inhibitor like clavulanic acid or tazobactam.³⁶ MRSA strains often produce β -lactamases, enzymes that inactivate β -lactam antibiotics. By combining a β -lactam antibiotic with a β -lactamase inhibitor, the activity of the β -lactamase is blocked, allowing the β -lactam antibiotic to exert its bactericidal effects effectively. This synergy has been observed in vitro and in animal models, demonstrating enhanced killing of MRSA and improved treatment outcomes. Another example of antibiotic synergy in MRSA involves the combination of a β -lactam antibiotic with a non- β -lactam antibiotic, such as a fluoroquinolone or an aminoglycoside.³⁷ This combination targets different cellular processes, such as cell wall synthesis and protein synthesis, leading to synergistic bactericidal effects against MRSA. Studies have shown that these combinations exhibit enhanced killing of MRSA compared to monotherapy with either antibiotic alone.

Extended spectrum β -lactamase producing *Enterobacteriaceae* (ESBL) are MDRB that produce

enzymes called extended-spectrum β -lactamases, which confer resistance to a broad range of β -lactam antibiotics, including penicillins and cephalosporins.³⁸ Antibiotic synergy has shown promise in overcoming resistance in ESBL-producing *Enterobacteriaceae*. One example of antibiotic synergy against ESBL-producing *Enterobacteriaceae* involves combining a β -lactam antibiotic, such as ceftazidime or cefepime, with a β -lactamase inhibitor, such as avibactam or tazobactam.³⁹ The β -lactamase inhibitor prevents the inactivation of the β -lactam antibiotic, allowing it to exert its antimicrobial activity effectively. This combination has demonstrated enhanced activity against ESBL-producing *Enterobacteriaceae* in vitro and in clinical studies, providing an effective treatment option for infections caused by these multidrug-resistant pathogens.

Overall, these studies illustrate the successful applications of antibiotic synergy in combating MDRB such as MRSA and ESBL-producing *Enterobacteriaceae*. By combining antibiotics with different mechanisms of action, the synergistic effect can overcome resistance mechanisms and enhance treatment outcomes. These findings highlight the potential of antibiotic synergy as a valuable strategy in the fight against multidrug-resistant pathogens.

CONCLUSION

Antibiotic synergy offers a promising approach to combating MDRB. By targeting different cellular processes, enhancing penetration, inhibiting resistance mechanisms, and addressing biofilm-associated infections, antibiotic synergy has shown efficacy against pathogens such as MRSA and ESBL-producing *Enterobacteriaceae*. However, cautious implementation is necessary due to the risk of increased antibiotic resistance and potential drug interactions. Close monitoring, surveillance of resistance patterns, and evaluation of drug interactions are essential. With further research, antibiotic synergy has the potential to revolutionize treatment outcomes and contribute to the global fight against antimicrobial resistance.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Alanis AJ. Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Research. 2005;36(6):697-705.
2. Serwecińska L. Antimicrobials and antibiotic-resistant bacteria: a risk to the environment and to public health. Water. 2020;12(12):3313.
3. Colomb-Cotinat M, Lacoste J, Brun-Buisson C, Jarlier V, Coignard B, Vaux S. Estimating the morbidity and mortality associated with infections due to multidrug-resistant bacteria (MDRB), France,

2012. Antimicrobial Resistance Infect Control. 2016;5(1):1-11.
4. AMR NGHRUoGSo. Whole-genome sequencing as part of national and international surveillance programmes for antimicrobial resistance: A roadmap. BMJ Global Heal. 2020;5(11):e002244.
5. Suk JE, Semenza JC. Future infectious disease threats to Europe. Am J Publ Heal. 2011;101(11):2068-79.
6. Pérez J, Contreras-Moreno FJ, Marcos-Torres FJ, Moraleda-Muñoz A, Muñoz-Dorado J. The antibiotic crisis: How bacterial predators can help. Computational Structural Biotechnol J. 2020;18:2547-55.
7. Zilahi G, Artigas A, Martin-Loeches I. What's new in multidrug-resistant pathogens in the ICU? Anna Intensive Care. 2016;6(1):1-11.
8. Sun W, Weingarten RA, Xu M, Southall N, Dai S, Shinn P et al. Rapid antimicrobial susceptibility test for identification of new therapeutics and drug combinations against multidrug-resistant bacteria. Emerging Microbes Infect. 2016;5(1):1-11.
9. Worthington RJ, Melander C. Combination approaches to combat multidrug-resistant bacteria. Trends in biotechnology. 2013;31(3):177-184.
10. Bolla J-M, Alibert-Franco S, Handzlik J, Chevalier J, Mahamoud A, Boyer G et al. Strategies for bypassing the membrane barrier in multidrug resistant Gram-negative bacteria. FEBS letters. 2011;585(11):1682-90.
11. Shang D, Liu Y, Jiang F, Ji F, Wang H, Han X. Synergistic antibacterial activity of designed Trp-containing antibacterial peptides in combination with antibiotics against multidrug-resistant *Staphylococcus epidermidis*. Frontiers in Microbiol. 2019;10:2719.
12. Chawla M, Verma J, Gupta R, Das B. Antibiotic potentiators against multidrug-resistant bacteria: discovery, development, and clinical relevance. Frontiers in Microbiol. 2022;13.
13. Pervin Z, Hassan MM. Synergistic therapeutic actions of antimicrobial peptides to treat multidrug-resistant bacterial infection. Rev Res Med Microbiol. 2021;32(2):83-89.
14. Gupta A, Saleh NM, Das R, Landis RF, Bigdeli A, Motamedchaboki K et al. Synergistic antimicrobial therapy using nanoparticles and antibiotics for the treatment of multidrug-resistant bacterial infection. Nano Futures. 2017;1(1):015004.
15. Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. Nature Rev Microbiol. 2010;8(6):423-35.
16. Mc Dermott PF, Walker RD, White DG. Antimicrobials: modes of action and mechanisms of resistance. Int J Toxicol. 2003;22(2):135-43.
17. Allahverdiyev AM, Kon KV, Abamor ES, Bagirova M, Rafailovich M. Coping with antibiotic resistance: combining nanoparticles with antibiotics and other antimicrobial agents. Expert review of anti-infective therapy. 2011;9(11):1035-52.
18. Liu Y, Tong Z, Shi J, Li R, Upton M, Wang Z. Drug repurposing for next-generation combination therapies against multidrug-resistant bacteria. Theranostics. 2021;11(10):4910.
19. Pagès J-M, Amaral L. Mechanisms of drug efflux and strategies to combat them: challenging the efflux pump of Gram-negative bacteria. Biochimica et Biophysica Acta (BBA)-Proteins Proteomics. 2009;1794(5):826-33.
20. Wright GD. Antibiotic adjuvants: rescuing antibiotics from resistance. Trends Microbiol. 2016;24(11):862-71.
21. Uruén C, Chopo-Escuin G, Tommassen J, Mainar-Jaime RC, Arenas J. Biofilms as promoters of bacterial antibiotic resistance and tolerance. Antibiotics. 2020;10(1):3.
22. Hemmati F, Rezaee MA, Ebrahimzadeh S, Yousefi L, Nouri R, Kafil HS et al. Novel strategies to combat bacterial biofilms. Molecular Biotechnol. 2021;63(7):569-86.
23. Ozseven AG, Ozseven L. Do different interpretative methods used for evaluation of checkerboard synergy test affect the results? Mikrobiyoloji Bulteni. 2012;46(3):410-20.
24. Saiman L. Clinical utility of synergy testing for multidrug-resistant *Pseudomonas aeruginosa* isolated from patients with cystic fibrosis: 'the motion for'. Paediatric respiratory reviews. 2007;8(3):249-55.
25. White RL, Burgess DS, Manduru M, Bosso JA. Comparison of three different in vitro methods of detecting synergy: time-kill, checkerboard, and E test. Antimicrobial agents and chemotherapy. 1996;40(8):1914-8.
26. Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. Paper presented at: Mayo Clinic Proceedings. 2012.
27. Zhu M, Tse MW, Weller J, Chen J, Blainey PC. The future of antibiotics begins with discovering new combinations. Ann N York Academy Sci. 2021;1496(1):82-96.
28. Cheng Y-S, Williamson PR, Zheng W. Improving therapy of severe infections through drug repurposing of synergistic combinations. Curr Opinion Pharmacol. 2019;48:92-8.
29. Bueno J. Antimicrobial adjuvants drug discovery, the challenge of avoid the resistance and recover the susceptibility of multidrug-resistant strains. J Microb Biochem Technol. 2016;8(3):169-76.
30. ilancioglu K, Unlu O. Multidrug resistance stimulated antagonistic antibiotic interactions. Rom J Leg Med. 2017;25(4):331-6.
31. Gajdács M. The continuing threat of methicillin-resistant *Staphylococcus aureus*. Antibiotics. 2019;8(2):52.
32. Bao M, Zhang L, Liu B, Li L, Zhang Y, Zhao H et al. Synergistic effects of anti-MRSA herbal extracts combined with antibiotics. Future Microbiol. 2020;15(13):1265-76.

33. Foster TJ. Can β -lactam antibiotics be resurrected to combat MRSA? Trends Microbiol. 2019;27(1):26-38.
34. Sakagami Y, Mimura M, Kajimura K, Yokoyama H, Linuma M, Tanaka T et al. Anti-MRSA activity of sophoraflavanone G and synergism with other antibacterial agents. Letters Applied Microbiol. 1998;27(2):98-100.
35. Zuo G-Y, Li Y, Wang T, Gen-Chun W, Yun-Ling Z, Wei-Dong P. Synergistic antibacterial and antibiotic effects of bisbenzylisoquinoline alkaloids on clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA). Molecules. 2011;16(12):9819-26.
36. Fatima H, Goel N, Sinha R, Khare SK. Recent strategies for inhibiting multidrug-resistant and β -lactamase producing bacteria: A review. Colloids and Surfaces B: Biointerfaces. 2021;205:111901.
37. Bassetti M, Righi E, Viscoli C. Novel β -lactam antibiotics and inhibitor combinations. Expert Opinion Investigational Drugs. 2008;17(3):285-96.
38. Sawa T, Kooguchi K, Moriyama K. Molecular diversity of extended-spectrum β -lactamases and carbapenemases, and antimicrobial resistance. J Intensive Care. 2020;8:1-13.
39. Van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation β -lactam/ β -lactamase inhibitor combinations. Clin Infectious Diseases. 2016;63(2):234-41.

Cite this article as: Malki AM, Alaeq RA, Alosaimi AA, Ageeli MM, Alshehri GM, Shati RO et al. Antibiotic synergy as a strategy for combating multidrug-resistant bacteria: a review of mechanisms and clinical implications. Int J Community Med Public Health 2023;10:3885-90.