

Combination Therapy: A Vital Weapon Against Resistance

Chen Wei*

Department of Emerging Infectious Diseases, Tsinghua University, China

Introduction

The escalating crisis of antimicrobial resistance necessitates innovative and robust therapeutic strategies to safeguard global public health. Combination therapy has emerged as a particularly promising avenue, offering a multifaceted approach to combat pathogens that have developed resistance to single-agent treatments. This strategy leverages the power of simultaneously targeting microbes through multiple mechanisms, which can significantly enhance treatment efficacy and crucially, reduce the likelihood of resistance developing further [1]. The synergistic effects observed when specific drug combinations are employed are a cornerstone of this approach, suggesting that the combined impact of drugs can be greater than the sum of their individual effects. Furthermore, combination therapy holds the potential for reduced dosages of individual agents, which can lead to fewer adverse side effects for patients, thereby improving tolerability and adherence [1]. A critical aspect of rationally designing effective combination regimens lies in a deep understanding of the complex resistance mechanisms employed by pathogens. This knowledge allows for the selection of drugs that can effectively bypass or overcome these defenses [1]. However, the complexity of predicting synergistic interactions remains a significant challenge, with the potential for antagonistic effects, where combinations may prove less effective than expected, posing a hurdle to widespread adoption [1]. Another vital consideration in optimizing combination therapy involves understanding the pharmacokinetic and pharmacodynamic profiles of the drugs involved. This profiling is essential to determine the appropriate dosing, timing, and routes of administration to achieve the desired therapeutic outcome while minimizing toxicity [2]. The emergence of highly resistant pathogens, such as carbapenem-resistant Enterobacteriaceae (CRE), presents an urgent global health threat, often requiring combination therapy as a last resort [3]. Research into specific drug pairings against CRE aims to identify combinations that demonstrate synergistic activity and can effectively bypass known resistance mechanisms, highlighting the urgent need for novel therapeutic strategies [3]. Fungal infections, particularly those caused by resistant *Candida* species, are also increasingly difficult to treat, prompting investigations into combination therapies to enhance the activity of existing antifungals and overcome resistance [4]. This involves combining different classes of antifungals to achieve synergistic activity against resistant fungal strains, a crucial factor in improving patient survival [4]. The slow pace of novel antibiotic development further underscores the importance of combination therapy as an attractive strategy to prolong the clinical utility of existing antimicrobial agents [5]. Understanding the molecular basis for synergy is key, exploring how different drugs can interfere with overlapping resistance pathways or create a more potent antimicrobial effect through mechanisms not fully understood by traditional methods [5]. Tuberculosis (TB), a persistent global health problem, is further complicated by the rise of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains, making combination therapy the indispensable cornerstone of treatment [6]. This field involves reviewing evolving drug regimens to overcome resistance, considering new drug development and

optimal combinations for various resistance patterns, a complex task requiring tailored treatment approaches [6]. Beyond bacterial infections, viral infections such as HIV and influenza are also managed with combination therapies to prevent resistance. Combining antiviral drugs with different targets effectively suppresses viral replication and reduces the emergence of resistant viral strains, emphasizing the importance of adherence and strategic drug sequencing [7]. Emerging strategies also explore novel combinations, such as the use of bacteriophages in conjunction with antibiotics for bacterial infections. The rationale here is that phages can lyse bacteria, potentially increasing their susceptibility to antibiotics or reducing the overall bacterial load, thereby overcoming resistance mechanisms [8]. The application of advanced computational tools, such as artificial intelligence (AI) and machine learning (ML), is revolutionizing the discovery of synergistic drug combinations. These technologies can analyze vast datasets of drug interactions and resistance mechanisms to identify promising combinations that might not be apparent through conventional research methods, accelerating the development of effective treatments [9]. The substantial economic impact of antimicrobial resistance further emphasizes the need for effective solutions like combination therapy, which is not only a scientific endeavor but also an economic and public health imperative [10]. Addressing challenges in development, implementation, regulatory hurdles, and cost-effectiveness requires global collaboration to ensure that combination therapies are accessible and widely adopted [10].

Description

The application of combination therapy represents a powerful strategy in the ongoing battle against antimicrobial resistance, offering a means to combat pathogens through simultaneous targeting of multiple mechanisms [1]. This approach has demonstrated significant potential to enhance treatment efficacy, diminish the likelihood of resistance emergence, and even re-sensitize strains that have become resistant to previously effective drugs [1]. Key findings from research highlight the synergistic effects achievable with certain drug combinations, where the combined action exceeds the sum of individual drug activities, and the possibility of reduced dosages leading to fewer patient side effects [1]. A crucial element in the successful design of combination regimens is a thorough understanding of pathogen resistance mechanisms, enabling a more rational and targeted therapeutic approach [1]. Nevertheless, the inherent complexity in predicting synergistic interactions and the potential for antagonistic effects remain significant challenges in this field [1]. Moreover, optimizing combination therapy necessitates a detailed examination of pharmacokinetic and pharmacodynamic properties to ensure that drug regimens are both effective and safe [2]. This includes careful consideration of how drugs are absorbed, distributed, metabolized, and excreted, as well as their effects on the body over time, to achieve optimal therapeutic outcomes and minimize adverse events [2]. The escalating threat posed by carbapenem-resistant Enterobacteriaceae (CRE) often compels the use of combination therapy as a treatment of last

resort, prompting extensive research into various drug pairings to improve patient outcomes [3]. Studies specifically investigating combinations against CRE detail observed synergistic effects and explore how resistance mechanisms can be circumvented, underscoring the critical need for innovative therapeutic solutions [3]. In the realm of fungal infections, particularly those caused by resistant *Candida* species, combination therapy is being actively investigated to amplify the activity of existing antifungal agents and overcome resistance mechanisms [4]. This involves strategically combining different classes of antifungals to achieve synergistic activity against resistant strains, a vital step in improving patient survival rates [4]. The slow rate of novel antibiotic development makes combination therapy an increasingly attractive strategy for extending the lifespan and utility of existing antimicrobial drugs [5]. Research into the molecular underpinnings of synergy explores how diverse drugs can disrupt overlapping resistance pathways or collectively exert a more potent antimicrobial effect, a complex interplay that requires further elucidation [5]. Tuberculosis (TB) continues to be a significant global health challenge, with the emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains complicating treatment efforts. Combination therapy remains the fundamental pillar of TB management, and ongoing reviews focus on evolving drug regimens to surmount resistance, including the development of new drugs and optimizing combinations for specific resistance patterns [6]. The management of viral infections, such as HIV and influenza, also increasingly relies on combination therapies to effectively prevent the development of drug resistance [7]. By combining antiviral drugs that target different aspects of the viral life cycle, it is possible to suppress viral replication more effectively and reduce the emergence of resistant strains, emphasizing the importance of patient adherence and strategic sequencing of treatments [7]. Innovative approaches are also being explored, such as the combination of bacteriophage therapy with antibiotics for bacterial infections [8]. The proposed mechanism involves phages lysing bacteria, thereby potentially increasing their susceptibility to antibiotics or reducing the overall bacterial burden, which could help overcome established resistance [8]. The field of drug discovery is being significantly advanced by the application of artificial intelligence (AI) and machine learning (ML) in predicting synergistic drug combinations [9]. These computational tools can analyze vast amounts of data on drug interactions and resistance mechanisms to identify promising therapeutic combinations that might be missed by traditional research methods, accelerating the discovery pipeline for new treatments [9]. The substantial economic burden associated with antimicrobial resistance underscores the critical role of combination therapy as a vital solution [10]. Developing and implementing these therapies involves navigating various challenges, including regulatory pathways, demonstrating cost-effectiveness, and fostering global collaboration, making it not merely a scientific pursuit but also a public health and economic imperative [10].

Conclusion

Combination therapy is a critical strategy for combating antimicrobial resistance by simultaneously targeting pathogens through multiple mechanisms. This approach enhances efficacy, reduces resistance development, and can re-sensitize resistant strains. Key benefits include synergistic effects, potential for reduced side effects, and the rational design of regimens based on understanding resistance mechanisms. However, predicting synergy and avoiding antagonism remain challenges. Pharmacokinetic and pharmacodynamic profiling are essential for optimizing combination therapy. Specific drug combinations are being explored for challenging infections like those caused by carbapenem-resistant Enterobacteriaceae and resistant fungal strains. The slow pace of new drug development makes combination therapy vital for prolonging the utility of existing drugs. Research is delving into

the molecular basis of synergy, while artificial intelligence is accelerating the discovery of effective combinations. Combination therapy is also crucial for managing viral infections and is being explored in novel strategies like phage-antibiotic combinations. The economic impact of resistance necessitates these advanced therapeutic approaches, requiring global collaboration for their development and implementation.

Acknowledgement

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Conflict of Interest

None.

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***Address for Correspondence:** Chen, Wei, Department of Emerging Infectious Diseases, Tsinghua University, China, E-mail: chen.wei@tsiedu.cn

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