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Combating CRE: Combination Therapy's Promising Future

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Introduction

The escalating global health crisis posed by carbapenem-resistant Enterobacteriaceae (CRE) necessitates a comprehensive understanding of therapeutic strategies to combat these formidable pathogens. Recent research has predominantly focused on the comparative efficacy of various combination therapies against CRE infections, moving beyond monotherapeutic approaches that often prove insufficient [1]. The emergence of polymyxin-based combination regimens has shown significant promise, particularly in addressing severe bloodstream infections caused by resistant strains like Klebsiella pneumoniae, with specific adjunctive agents demonstrating a notable reduction in mortality [2]. Furthermore, the evaluation of novel therapeutic agents and their synergistic potential in combination with existing drugs is a critical area of investigation. For instance, the combination of ceftazidime-avibactam with aztreonam has been systematically reviewed and shown to yield high clinical cure rates and favorable outcomes, especially against infections driven by carbapenemase-producing Enterobacteriaceae [3]. The role of older antibiotics, such as fosfomycin, is also being re-examined in the context of combination therapy, revealing its potential value, particularly in treating urinary tract infections caused by CRE [4]. The development of new antibiotic classes and formulations, such as meropenem-vaborbactam, has further expanded treatment options, with studies indicating superior efficacy and safety profiles compared to older agents like polymyxin B for CRE bloodstream infections [5]. A broader overview of the current therapeutic landscape underscores the importance of combining different classes of antibiotics, including beta-lactam/beta-lactamase inhibitors and novel agents, to effectively manage CRE [6]. In vitro studies have also contributed to our understanding by assessing the synergistic effects of various combinations against extensively drug-resistant Enterobacterales, highlighting the need for phenotypic susceptibility testing to guide treatment [7]. The application of established antibiotics like tigecycline within combination regimens is also being explored, with careful consideration given to dose optimization and potential side effects to maximize efficacy and safety [8]. The utility of newer agents, such as plazomicin, a novel aminoglycoside, in combination therapy for complicated urinary tract infections caused by CRE is also being investigated, showing promising results in terms of clinical success and bacterial eradication [9]. Finally, a deeper understanding of the pharmacokinetic and pharmacodynamic (PK/PD) properties of these combination therapies is crucial for optimizing their effectiveness, as synergistic interactions are often essential to overcome complex resistance mechanisms and improve patient outcomes [10].

Description

The landscape of antimicrobial therapy for carbapenem-resistant Enterobacteriaceae (CRE) is rapidly evolving, with a significant shift towards combination strategies to overcome widespread resistance mechanisms. One key area of research involves exploring the comparative efficacy of diverse antibiotic combinations. Studies indicate that while monotherapies frequently fail against CRE, carefully designed combinations, incorporating both novel and established agents, lead to improved treatment outcomes. This approach leverages synergistic interactions between different drug classes to enhance bacterial killing [1]. A notable advancement has been the investigation of polymyxin-based combination regimens, particularly for severe infections like carbapenem-resistant Klebsiella pneumoniae bloodstream infections. Research has demonstrated that the addition of agents like rifampicin to polymyxins can significantly reduce mortality, underscoring the critical role of synergy in overcoming carbapenem resistance [2]. The development and evaluation of newer therapeutic agents have also played a pivotal role. For instance, a systematic review and meta-analysis evaluated the effectiveness of ceftazidime-avibactam in combination with aztreonam for CRE infections. The findings revealed high clinical cure rates and favorable outcomes, especially for infections involving specific resistance mechanisms, suggesting this combination as a valuable therapeutic option [3]. Furthermore, the utility of older antibiotics is being reassessed within combination frameworks. Fosfomycin, in particular, has shown promise when used in combination therapy against CRE, demonstrating particular efficacy in treating urinary tract infections and highlighting potential synergistic effects [4]. The introduction of novel fixed-dose combinations has also provided new avenues for treatment. Meropenem-vaborbactam, for example, has been compared to polymyxin B for CRE bloodstream infections, with meropenem-vaborbactam exhibiting superior clinical cure rates and lower mortality, positioning it as a promising alternative with a better efficacy and safety profile [5]. The overall current landscape of CRE treatment emphasizes the strategic use of combination therapies. This includes combinations of beta-lactam/beta-lactamase inhibitors, polymyxins, and newer agents like ceftazidime-avibactam and meropenem-vaborbactam, with a strong emphasis on understanding the specific resistance mechanisms of the infecting organism to guide optimal therapy selection [6]. In vitro studies are instrumental in identifying potential synergistic combinations. Research assessing combinations against extensively drug-resistant Enterobacterales has shown promising results with combinations like meropenem with colistin or tigecycline, reinforcing the importance of phenotypic susceptibility testing for guiding therapeutic strategies against highly resistant strains [7]. The role of specific agents like tigecycline in combination therapy is also being refined. Studies examining high-dose tigecycline in combination regimens for CRE infections have noted its efficacy but also highlighted the need for careful dose optimization and monitoring due to potential gastrointestinal side effects [8]. Novel agents are also being integrated into combination strategies. Plazomicin, a new aminoglycoside, has been evaluated in combination for complicated urinary

tract infections caused by CRE, demonstrating high rates of clinical success and bacterial eradication, indicating its potential utility in combating CRE [9]. Finally, a deeper understanding of the pharmacokinetic and pharmacodynamic (PK/PD) properties of these combination therapies is essential. This knowledge is crucial for achieving target drug concentrations and leveraging synergistic effects to overcome resistance mechanisms and improve clinical outcomes in CRE infections [10].

Conclusion

Carbapenem-resistant Enterobacteriaceae (CRE) infections pose a significant therapeutic challenge, leading researchers to explore combination therapies as a primary strategy. Studies highlight the failure of monotherapies and the improved outcomes achieved with strategic antibiotic combinations, including novel agents and older drugs. Key insights focus on understanding resistance mechanisms, optimizing dosing, and leveraging drug synergy. For instance, polymyxin-based combinations have shown reduced mortality, while ceftazidime-avibactam plus aztreonam and meropenem-vaborbactam demonstrate high clinical cure rates. Fosfomycin and plazomicin are also showing promise in combination for specific infections like UTIs. Pharmacokinetic and pharmacodynamic considerations are crucial for maximizing the effectiveness of these complex regimens, emphasizing the need for tailored therapy based on pathogen resistance profiles. Adjunctive therapies and careful patient monitoring are also important aspects of successful CRE treatment.

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Conflict of Interest

None.

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