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REVIEW

Clinical translation of polymyxin-based combination therapy: Facts, challenges and future opportunities

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Summary The emergence and spread of multidrug resistant Gram-negative bacteria has led to a resurgence in the clinical use of polymyxin antibiotics. However, the prevalence of polymyxin resistance is on the rise at an alarming rate, motivating the idea of combination therapy to sustain the revival of these "old" antibiotics. Although ample evidence in favor of combination therapy has emerged, it seems impracticable and confusing to find a promising combination from the diverse reports or gain adequate information on the efficacy and safety profile. With a stagnating discovery pipeline of novel antimicrobials, there is a clear need to fill the knowledge gaps in translating these basic research data to beneficial clinical practice. In this review, we examined the factors and ambiguities that stand as major hurdles in bringing polymyxin combination therapy to bedside care, highlighting the importance and urgency of incorporating translational research insights into areas of difficulty. We also discussed future research priorities that are essential to gather the necessary evidence and insights for promoting the best possible use of polymyxins in combination therapy.

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Introduction

In the past decades, with an increasing threat from multidrug-resistant (MDR) and even pan drug-resistant microorganisms worldwide, the concern of untreatable infections has grown more grave. In the face of a waning discovery pipeline of novel antibiotics, clinicians more often have to revive some 'old' antibiotics that were developed 50—70 years ago.[1,2] A typical case is the resurgence of polymyxin antibiotics, despite previous concerns for their nephrotoxicity and neurotoxicity.[3,4] Polymyxins (colistin and polymyxin B) have now become the last-line defense against intractable infections caused by multidrug resistant Gram-negative bacteria (GNB), especially *Klebsiella pneumonia* (*K. pneumonia*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Acinetobacter baumannii* (*A. baumannii*).[5,6] Considering the daunting challenges in the battle against infectious diseases, a critical issue is how to prevent the loss of these potentially life-saving agents. In fact, although relatively low, the incidence of polymyxin resistance has unfortunately been on the rise.[7,8]

As a potential strategy to surmount bacterial resistance and strengthen treatment efficacy, combination therapy has received growing attention where polymyxins are combined together with one or more other antibiotics.[9,10] Literature reports on this topic have been growing, but it appears difficult to gain a definite message to guide the clinical practice of polymyxin-related antimicrobial therapy.[11—13] In this review, we examine the major factors and knowledge gaps that stand as the roadblocks in the clinical application of polymyxin-based combination therapy. We also outline potential steps needed to drive this critical field forward and discuss the conceptual and technical progresses that may help overcome the complexities. Although this review is not intended for a comprehensive coverage of all the data and issues concerning polymyxin-based combination therapy, we hope that it could provide a timely glimpse into the major points deserving consideration in clinical translation.

Ambiguities in the practice of polymyxin-based combination therapy

Although a large body of data, especially those from *in vitro* synergy studies, has claimed superior antimicrobial efficacy of polymyxin in combination therapy, the translation to the clinical practice is fraught with uncertainties and difficulties at several levels. Firstly, the reports from preclinical studies are varied in terms of the combination agent and antimicrobial outcome (Table 1). As discussed by recent systematic analyses,[14,15] synergy rates from studies examining the *in vitro* combination of polymyxins and carbapenems are inconsistent to a large extent, depending on many factors such as the testing method, type of antibiotic, and bacteria subtype. Secondly, despite the largely appealing efficacy of antibacterial synergy from preclinical studies, few solid evidence could be found from the clinical data, thus raising ambiguities on the efficacy and benefit of combination therapy versus monotherapy.[16] As shown in Table 2, although the *in vitro* synergy of colistin-rifampicin combination was well-confirmed against multidrug resistant (MDR) -*A. baumannii*,[17] latest results from the first large, randomized, controlled prospective study on colistin plus rifampicin against ventilator-associated pneumonia caused by MDR-*A. baumannii* reported that 30 day mortality in the 210 patients was not reduced by addition of rifampicin to colistin.[18] Similarly, despite the superior antimicrobial efficacy of colistin-glycopeptides combination *in vitro*[19] and *in vivo*,[20] a retrospective study looking at the effectiveness of colistin-vancomycin combination on severe infections caused by carbapenem-resistant *A. baumannii* reported no added benefits but significantly increased risk of renal failure.[21] Thirdly, the heterogeneity and discrepancy among the mixed findings, coupled with the still rudimentary knowledge on the pharmacokinetic-pharmacodynamic/toxicodynamic (PK-PD/Tox) relationships of polymyxins,[6] give confusions to clinicians when designing polymyxin-based combination therapy. For instance, in the treatment regimen for *K. pneumonia* carbapenemase-producing *K. pneumonia* (KPC-Kp) infections, current clinical studies gave discordant recommendations on the necessity of including a carbapenem in combination therapy.[22—24] This controversy means that solid evidence supporting which antibiotics to use and the optimal combination regimen for the treatment of KPC-Kp infections are actually limited. Together, from the perspective of translational research, these uncertainties and challenges have become the major obstacles for bringing polymyxin-based combination regimens to better management of MDR bacterial infections and improved patient outcomes in the clinic. There is clearly an urgent need to identify the multiple factors plaguing the translation of polymyxin combination therapy from the research bench to the bedside, and more importantly, inspire more concerted efforts for overcoming these hurdles.

What are key issues deserving attention in clinical translation?

In vitro evaluation of antibacterial synergy

For the assessment of *in vitro* antimicrobial effects involving polymyxins, the inherent flaw of the disc diffusion method has been long recognized.[25] Also, for other assays, it has been acknowledged that the testing conditions (e.g., addition of surfactants or not) and procedures (e.g., gradient diffusion or dilution) are closely correlated with the susceptibility readouts for polymyxins.[26] These confounding issues could largely compromise the validity in the test for polymyxin-related combination therapy, which need to be addressed by an international consensus of reference test method.[7] Before this is established, when determining the minimum inhibitory concentration (MIC), special care is needed on many factors, such as the use of surfactants, cation concentrations[27] and bacterial strains[28] to avoid result that is possibly an artifact of the specific assay. For clinical laboratories, how to select the "right" assay to strengthen the predictive accuracy is another practical concern. As shown in Table 1, to assess polymyxin-related antimicrobial synergy, chequerboard (broth microdilution, agar dilution), E test, and time-kill methodologies are commonly used.[29] However, it is notable that synergy