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Colistin monotherapy vs. combination therapy: evidence from microbiological, animal and clinical studies

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ABSTRACT

Colistin is commonly the last resort for treatment of infections caused by multidrug-resistant Gram-negative bacteria. In clinical practice, it is frequently used as combination therapy in order to improve its antibacterial activity, despite the consequent increase in toxicity. The available evidence from various studies (microbiological, animal and clinical studies, retrieved from the PubMed and Scopus databases) regarding the comparative effectiveness of colistin monotherapy and colistin combination therapy was evaluated. Most of the microbiological studies examined colistin monotherapy vs. combinations with rifampicin (nine studies) or carbapenems (three studies) for *Pseudomonas aeruginosa* or *Acinetobacter baumannii* infections. A synergistic effect was detected in all the studies examining the combination of colistin and rifampicin, whereas carbapenems exhibited a synergistic effect in two of three studies. Most of the animal studies examined colistin monotherapy vs. combinations with rifampicin, carbenicillin, piperacillin and imipenem for treatment of *P. aeruginosa*, *A. baumannii* or *Escherichia coli* infections. Mortality rates were significantly lower in the combination treatment arm in three of six relevant studies. However, data from the small number (four) of relevant human studies suggest non-inferiority of colistin monotherapy as compared with combination therapy. In conclusion, microbiological studies suggest superiority of colistin combination treatment, which is in contrast to preliminary data from studies in humans. Results from animal study data are equivocal. There is an urgent need for appropriately designed and powered clinical trials addressing this apparently controversial situation.

Keywords *Acinetobacter baumannii*, bacteraemia, carbapenem, *Escherichia coli*, *Klebsiella pneumoniae*, multiple drug resistance, pneumonia, polymyxins, *Pseudomonas aeruginosa*, rifampicin

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INTRODUCTION

The mounting prevalence worldwide of infections caused by multidrug-resistant (MDR) Gram-negative bacteria, in particular *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, is causing substantial concern [1]. The lack of novel antimicrobials for Gram-negative infections under development, especially for the treatment of infections due to *P. aeruginosa*, has forced clinicians to reappraise the clinical value of colistin, a polymyxin antibiotic discovered *c.* 60 years ago [2–5].

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Colistin is a multicomponent polypeptide antibiotic, composed mainly of colistin A and colistin B; its use was limited by its renal toxicity, and it was replaced in the 1970s by antibiotics considered to be less toxic. Pharmacokinetic and pharmacodynamic information on colistin is limited, perhaps due to the moderate clinical interest in polymyxins during the 1980s and 1990s and the difficulties in accurately measuring colistin and colistimethate sodium separately in biological samples [3].

More recently, colistin has increasingly been used as salvage therapy [2,6] in combination with one or more antibacterials for the treatment of severe infections in critically ill patients [7]. Despite the fact that polymyxins have been available for over 50 years, *in vitro* pharmacodynamic, animal or clinical studies regarding the

pharmacokinetic parameters (maximal concentration (C_{max})/MIC, area under the curve/MIC (AUC/MIC), and proportion of time/MIC (%*T*/MIC)) of colistin formulations are scarce [8]. In clinical practice, colistin is usually administered at 8-h intervals.

The medical community has shown great interest in the comparative benefit, if any, of combination therapy vs. monotherapy in the treatment of Gram-negative and Gram-positive bacterial infections. Several studies have questioned the clinical superiority of combination therapy and have addressed the issues of the increased toxicity and the increased cost related to combination treatment regimens [9–13]. However, in severe infections caused by MDR Gram-negative pathogens, most clinicians would currently have reservations about colistin monotherapy. Moreover, a major concern regarding colistin monotherapy is the potential problem of heteroresistance among Gram-negative bacterial populations exposed to colistin alone [8,14]. Currently, there is a dearth of data regarding the clinical value of combination therapy and the clinical impact of heteroresistance. An overview of data from *in vitro*, animal and clinical studies regarding the efficacy and effectiveness of colistin combinations vs. colistin alone is presented in this review. This brief synopsis of relevant data may contribute to an evaluation of whether the superiority of colistin combinations, as compared with colistin alone, as depicted in *in vitro* studies, is maintained and verified in animal and, most importantly, in clinical studies.

MICROBIOLOGICAL STUDIES COMPARING COLISTIN MONOTHERAPY AND COMBINATION THERAPY

In vitro studies comparing colistin alone and colistin in combination with other antibiotics were considered to be relevant to the focus of this review. A search of the PubMed and Scopus databases yielded 16 relevant studies [15–30]. The search terms used were colistin, polymyxin or colimycin, *in vitro* study, *Acinetobacter*, *Pseudomonas*, *Stenotrophomonas maltophilia*, and *Klebsiella*. One study [20] was excluded because it referred to polymyxin B. Data retrieved from relevant studies are presented in Table 1.

In all these studies, susceptibility to colistin was previously evaluated by determination of MICs. The activity of the combination of colistin and other agents was evaluated using the checkerboard microbroth dilution method in six studies [15,16,23,25–27]. Concentration–time–kill curves were used in nine studies [17–19, 21–23,27,28,30]. In one investigation, an Etest study was also performed [30].

The antimicrobial agents combined with colistin were rifampicin [15,16,18–19,21,23,26,28,29], azithromicin [17,24,26], imipenem [27], meropenem [17,26], gentamicin [17], piperacillin [17], ciprofloxacin [17,22,24], co-trimoxazole [19,24], ceftazidime [22,24], doxycycline [26], minocycline [30], and the histatin derivative P-113 [25], i.e. a combination of polypeptides. However, the antimicrobials most frequently combined with colistin were rifampicin (ten studies) and carbapenems (four studies).

The most commonly studied organism was *P. aeruginosa* (8/13 studies [17,21–27]). In one study, Rynn *et al.* found that the addition of colistin to other antipseudomonal agents produced a smaller area under the bactericidal killing curves, and hence a greater killing effect on *P. aeruginosa*, than monotherapy [17]. This effect was independent of the colistin concentration (0.5 and 5 mg/L, respectively). In another study, two MDR strains, which were colistin-susceptible, were studied using a time–kill assay [22]. The combination of colistin and ceftazidime was synergistic, with only slight superiority of the combination with colistin at C_{max} 18 mg/L as compared to the combination with colistin at C_{max} 6 mg/L. Ciprofloxacin added to colistin did not enhance antibiotic activity.

Tascini *et al.* compared colistin plus rifampicin with colistin alone in seven MDR *P. aeruginosa* strains on which colistin alone had no bactericidal effect and after 6 h was unable to counteract bacterial growth [23]. They found that, in combination with rifampicin, colistin became bactericidal and the effect was prolonged for 12 h. Moreover, the combination resulted in synergy in six of seven strains. Synergy between colistin and rifampicin was also confirmed by Timurkaynak *et al.* in five MDR *A. baumannii* strains [26].

However, results were equivocal when carbapenems were added to colistin [26,27] in the case of MDR *P. aeruginosa*. Indeed, in one study [26], colistin plus meropenem was additive in two of