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Short Communication

Non-inferiority of colistin compared with standard care for the treatment of ventilator-associated pneumonia

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ABSTRACT

This study examined the literature on the treatment of ventilator-associated pneumonia (VAP) using colistin or standard care (SC). Based on this clinical material, a meta-analysis was conducted and a non-inferiority test was performed. Studies were selected for inclusion based on the following criteria: (a) patients with VAP; (b) experimental arm based on intravenous or aerosolized colistin; and (c) control arm based on SC. The meta-analysis employed a fixed-effect model, and the endpoint was the rate of clinical response. No pre-specified non-inferiority threshold for the upper boundary of the 95% confidence interval was adopted; instead, the intention was to perform a retrospective evaluation of whether the threshold suggested by the results was acceptable on clinical grounds.

In total, eight controlled studies were included. The pooled risk ratio was 1.019 for colistin compared with SC (95% confidence interval 0.895–1.16); this result corresponds to a non-significant 1.9% increase in cure rate with colistin compared with SC (range +16% to −10.5%). Heterogeneity was minimal (0%). The post-hoc non-inferiority threshold for colistin compared with SC was −10.5% in terms of relative cure rate (pooled risk ratio = 0.895). This margin was considered to be acceptable on clinical grounds.

This analysis found that colistin can play a role in the treatment of VAP, particularly when given as a combination of aerosolized and intravenous drug.

1. Introduction

Only 11 new antibiotics were approved between 1998 and 2014, and no new classes of antibiotics have been approved since 1987 [1]. In this framework, revisiting the therapeutic role of 'old' agents is worthwhile. At least two meta-analyses [2,3] have shown that aerosolized colistin [alone or in association with intravenous (IV) colistin] is more effective than the IV form given alone. On the other hand, no conclusive information is available regarding whether colistin (irrespective of its route of administration) is more or less effective for the treatment of ventilator-associated pneumonia (VAP) than other antibiotics compared with standard care (SC). In particular, two meta-analyses [3,4] found no significant difference between either aerosolized or IV colistin and SC in patients with VAP.

However, no evidence of difference is not the same as evidence of no difference [5]. As such, an equivalence analysis or a non-inferiority analysis is warranted to explore this issue further.

This study re-examined the literature on the treatment of VAP reported in the two meta-analyses by Florescu et al [3] (six trials) and Gu et al [4] (six trials). A non-inferiority study was undertaken based on this clinical material.

2. Methods

2.1. Study design

The analysis was designed to test the non-inferiority of colistin compared with SC. For this purpose, a series of clinical studies comparing colistin (IV or aerosolized) with SC was retrieved from two published meta-analyses [2,3]. The decision to rely on published papers [2,3] to identify the pertinent clinical studies was in line with the observation that an excessive number of overlapping meta-analyses are being published [6]. No pre-specified non-inferiority threshold for the upper boundary of the 95% confidence interval (CI) was adopted; instead, the intention was to perform a retrospective evaluation of whether or not the threshold suggested by the results was acceptable on clinical grounds.

2.2. Literature search and inclusion criteria

No original literature search was conducted. Eligible studies were those reported in the two meta-analyses mentioned above (fig. 2 of Reference 3 and fig. 2 of Reference 4). From an analysis of eligible

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Table 1
Characteristics of the eight studies included in the meta-analysis.

First author	Year/location	Study design	Population	No. of patients	Infecting organism	Colistin administration route	Treatment given to controls	Dosage of colistin	Type of nebulizer
Betrosian et al [9]	2008/Greece	RCT	Adult ICU patients with MDR VAP	28 (15/13)	*A. baumannii*	IV colistin alone	IV ampicillin/sulbactam	9 MIU/day divided into three doses for 8–10 days	—
Garnacho-Montero et al [10]	2003/Spain	PC	Adult ICU patients with MDR VAP	35 (21/14)	*A. baumannii*	IV colistin alone	IV mipenem/cilastatin	2.5–5.0 mg/kg/day divided into three doses with adjustment for renal function	—
Kallel et al [11]	2007/Tunisia	CC	Adult ICU patients with PDR VAP	120 (60/60)	*A. baumannii*, *P. aeruginosa*	IV colistin alone	IV imipenem/cilastatin	6 MIU/day divided into three doses for 14 days	—
Lu et al [12]	2012/France	PC	Adult ICU patients with MDR VAP	165 (43/122)	*A. baumannii*, *P. aeruginosa*	AS colistin alone	IV beta-lactam	6 MIU/day divided into three doses for 14 days or until successful weaning from mechanical ventilation	Vibrating plate nebulizer (Aeroneb Pro, Aerogen Nektar Corp., Galway, Ireland)
Rios et al [13]	2007/Argentina	RC	Adult ICU patients with MDR VAP	61 (31/30)	*A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *S. maltophilia*	IV colistin alone	IV imipenem/cilastatin	5 mg/kg/day for 14 days, doses were corrected in patients with renal failure	—
Zalts et al [14]	2013/Israel	RC	Adult ICU patients with CR VAP	98 (66/32)	*A. baumannii*	IV colistin alone	IV ampicillin/sulbactam	6 MIU/day divided into three doses for 7–10 days; doses were corrected in patients with renal failure	—
Nakwan et al [15]	2011/Thailand	RC	Neonates with MDR VAP	15 (8/7)	Drug-resistant *A. baumannii*	AS colistin (combined with IV colistin in two cases); concurrent IV antibiotics were given	IV cefoperazone/sulbactam or meropenem or ceftazidime/amikacin	8 mg/kg/day divided into two daily doses over 4–14 days	Servo Ultra Nebulizer in the SERVO-i ventilator (Maquet, Solna, Sweden)
Rattanaumpawan et al [16]	2010/Thailand	RCT	Adults with Gram-negative VAP	100 (51/49)	*A. baumannii*, *P. aeruginosa*, *K. pneumoniae*	AS colistin; concurrent IV antibiotics were given	IV standard antibiotics	4.5 MIU/day divided into two doses over 4 to 14 days	Jet or ultrasonic nebulizer

A. baumannii, *Acinetobacter baumannii*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *K. pneumoniae*, *Klebsiella pneumoniae*; *S. maltophilia*, *Stenotrophomonas maltophilia*; RCT, randomized controlled trial; ICU, intensive care unit; MDR, multi-drug-resistant; VAP, ventilator-associated pneumonia; IV, intravenous; MIU, million international units; PC, prospective cohort; CC, case–control; PDR, pan-drug-resistant; AS, aerosolized; RC, retrospective cohort; CR, carbapenem-resistant.