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Combination antibiotic therapy versus monotherapy for *Pseudomonas aeruginosa* bacteraemia: A meta-analysis of retrospective and prospective studies

Yangmin Hu[a], Leiqing Li[b], Wenlu Li[a], Huimin Xu[a], Ping He[a], Xiaofeng Yan[a], Haibin Dai[a,*]

[a] *Department of Pharmacy, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China*
[b] *Department of Intensive Care Unit, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China*

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ABSTRACT

The choice of antibiotic monotherapy or combination therapy to treat *Pseudomonas aeruginosa* bacteraemia is controversial. The aim of this review was to compare both types of therapy to determine which delivers the best outcome for *P. aeruginosa* bacteraemia. We systematically searched electronic bibliographic databases, including PubMed, Ovid EMBASE and The Cochrane Library, for clinical studies that compared combination therapy with monotherapy in the treatment of *P. aeruginosa* bacteraemia. Eligible articles were analysed using Stata®/SE software v.12.0. Stratification analysis was conducted by study design and treatment type. Publication bias was assessed using Begg's funnel plot and Egger's test. Ten studies (eight retrospective and two prospective) involving 1239 patients were analysed. We found no difference between combination therapy and monotherapy when the data were combined (odds ratio = 0.89, 95% confidence interval 0.57–1.40; $P = 0.614$) or when data were analysed in subgroups. Neither combination therapy nor monotherapy treatment appears to have a significant effect on mortality rates in patients with *P. aeruginosa* bacteraemia. Further studies evaluating the effects of combination therapy or monotherapy in more specialised cases, such as when encountering a multidrug-resistant organism, are necessary.

1. Introduction

Pseudomonas aeruginosa is a common pathogen that is implicated in a wide variety of nosocomial infections [1]. Hospital mortality rates associated with *P. aeruginosa* bacteraemia are reported to be >20% in recent studies [2]. Inappropriate use of empirical antibiotic therapy has been identified as an independent contributor to the high hospital mortality rate of *P. aeruginosa* bacteraemia [3–5].

Combination empirical antimicrobial therapy directed against Gram-negative bacteria may be a more appropriate treatment approach than monotherapy [4,5]. It has been suggested that inappropriate antimicrobial treatment of *P. aeruginosa* bacteraemia can be minimised by using combination treatment, at least until susceptibility results are known [5]. Utilising two antipseudomonal drugs of different classes helps to guarantee that the patient receives at least one drug to which the pathogen is sensitive [5–8].

Previous studies involving potential treatments for *P. aeruginosa* bacteraemia have varied in how they defined appropriate antimicrobial therapy. Moreover, they did not specifically examine the effect of administering combination antimicrobial agents [9,10]. Despite the advantages of combination empirical therapy, there is no evidence for the benefits of using combination therapy over monotherapy for the treatment of *P. aeruginosa* infection [7,11–13]. In this meta-analysis, we assess the mortality rates of patients with *P. aeruginosa* bacteraemia treated with adequate combination therapy versus adequate monotherapy.

2. Methods

2.1. Study identification

We searched for relevant studies using the PubMed, Ovid EMBASE and The Cochrane Library databases up to March 2013 using the following search terms: 'bacteremia' and '*Pseudomonas aeruginosa*', 'antibiotic' and 'monotherapy' or 'combination therapy'. References from clinical trials were searched manually to identify potentially relevant studies. Only studies published in English were considered. Abstracts and full-text articles were included. Study inclusion criteria were: (a) studies that compared the effects of combination therapy with monotherapy; (b) independent retrospective or prospective studies; (c) studies in which

* Corresponding author. Tel.: +86 571 8778 3891; fax: +86 571 8778 3891.
E-mail address: haibindai@zju.edu.cn (H. Dai).

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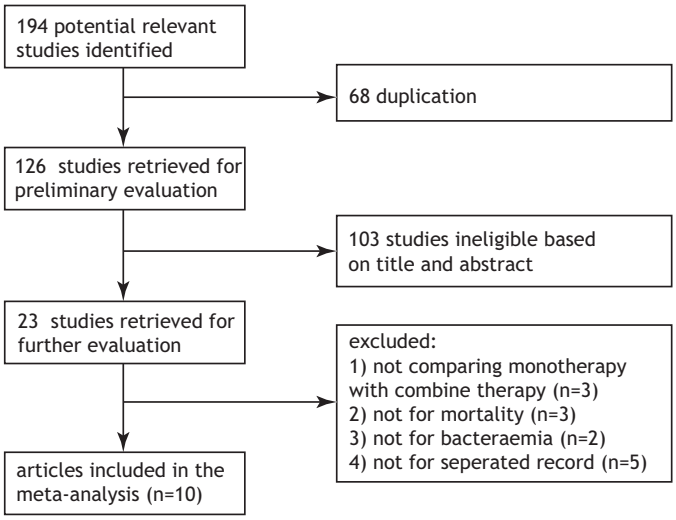

Fig. 1. Flowchart of included studies and the selection process.

appropriate therapy included at least one antipseudomonal agent, which was continued or commenced after antibiogram results were reported [7]; and (d) outcome of mortality was reported by the study.

2.2. Data extraction and quality assessment

Two researchers independently reviewed the included studies and extracted the relevant information from each study. Disagreement between the two reviewers was resolved by discussion until consensus was reached. The following variables were extracted from each study, if available: first author's surname; publication year; study design type; setting; patients; therapy type; drugs; mortality outcome; numbers of different groups; and odds ratio (OR) with 95% confidence intervals (CIs) of outcomes. The study quality was assessed using the nine-star Newcastle–Ottawa Scale for assessing the quality of non-randomised studies in meta-analyses (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

2.3. Statistical methods

Statistical analysis was conducted using Stata®/SE v.12.0 (StataCorp. LP, College Station, TX). For each study, ORs with 95% CIs were retrieved from the paper to estimate mortality outcomes. Heterogeneity across studies was assessed by Cochrane χ^2 Q statistic and the I^2 statistic. A random-effects model was applied when heterogeneity was assumed ($P < 0.1$ or $I^2 > 50\%$) [14,15]; otherwise, a fixed-effects model was used. Evaluation of how using either a fixed-effects or random-effects model may alter the results was also performed. Egger precision weighted linear regression tests and Begg's funnel plots were used to test potential publication bias [16]. The meta-analysis results were also stratified by study design type and therapy type.

3. Results

A total of 194 articles were identified in the initial search. After reviewing their titles, 23 articles were identified as being potentially eligible for inclusion (Fig. 1). The abstracts of all 23 articles were reviewed. If deemed eligible, the full-text papers were then retrieved and reviewed (Fig. 1). Thirteen studies were excluded from further analysis for various reasons: three studies were excluded because they did not compare monotherapy with combination therapy, three were excluded because their evaluated outcomes did not include mortality, two were excluded because patient infections were not caused by bacteraemia, and five were excluded because they did not distinguish separate records regarding *P. aeruginosa* bacteraemia from other infections. Thus, 10 eligible studies, involving 1239 patients, were included in the meta-analysis [5,7,11–13,17–21], including 8 retrospective cohort studies [5,7,11–13,18,20,21] and 2 prospective cohort studies [17,19]. Two of these focused on appropriate empirical therapy and eight focused on definitive therapy. Three studies were conducted in the USA [5,17,20], three were conducted in Europe [7,11,18], three were conducted in Asia [13,19,21] and one was conducted across different continents [12] (Table 1). According to the Newcastle–Ottawa Scale, the 10 included studies were rated as being of good or excellent quality (score range 6–9; Table 1).

Owing to the observed heterogeneity ($P = 0.011$; $I^2 = 58.2\%$) across the 10 included studies, a random-effects model was used to analyse them (Fig. 2). There was no difference between combination therapy and monotherapy when the studies were combined (OR = 0.89, 95% CI 0.57–1.40; $P = 0.614$). When meta-analysis was performed by study design type and therapy type, there was also no significant difference between monotherapy and combination therapy (Table 2). Graphical inspection through Begg's funnel plot and quantitative evaluation through Egger's test ($P = 0.553$) did not reveal any evidence of publication bias (Fig. 3).

4. Discussion

In this meta-analysis, we systematically reviewed 10 studies comparing combination therapy with monotherapy for *P. aeruginosa* bacteraemia. By extracting data for definitive antibiotic treatment and appropriate empirical therapy, all-cause mortality associated with *P. aeruginosa* bacteraemia was analysed. We found no significant differences in all-cause mortality between combination therapy and monotherapy for *P. aeruginosa* bacteraemia. This result indicates that neither definitive combination therapy nor appropriate empirical combination therapy offers independent additional benefits.

Despite the high mortality rates in patients with *P. aeruginosa* bacteraemia, it is still not clear how best to treat the infection [22]. Hilf et al. [17] suggested that combination therapy was superior to monotherapy for patients with *P. aeruginosa* bacteraemia; however, 86% of patients (37/43) receiving monotherapy in that study received only an aminoglycoside, which is no longer considered an optimal therapy owing to its association with increased mortality [3,18,19]. Another meta-analysis compared the use of β-lactam monotherapy versus β-lactam in combination with an aminoglycoside, in immunocompetent patients with sepsis [23]. No advantage for using combination therapy was found for all-cause mortality or treatment failures in the subgroup of patients with *P. aeruginosa* infections. In contrast, a related meta-analysis focused on the relationship between combination therapy and reduced mortality rates in patients with Gram-negative bacteraemia, revealing a significantly reduced mortality after combination therapy in a subgroup analysis of *P. aeruginosa* bacteraemia [24]. However, owing to the poor quality and heterogeneity of the studies included in these meta-analyses, convincing clinical data are sparse, and studies often vary in their findings [22,24,25]. The most recent meta-analysis examined the use of a β-lactam plus an aminoglycoside or fluoroquinolone combination versus β-lactam monotherapy for *P. aeruginosa* infections [26]. As previously shown, a subgroup analysis (five studies) of *P. aeruginosa* bacteraemia showed no significant differences in mortality rates between monotherapy and combination therapy.

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