Combination Therapy Versus Monotherapy In The Treatment Of *Stenotrophomonas Maltophilia* Infections: A Systematic Review And Meta-Analysis

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Abstract

Background: *Stenotrophomonas maltophilia* is a multidrug-resistant bacteria that is difficult to treat in hospitals around the world. It has become a public health issue, as well as being linked to a high mortality rate. Several studies have shown a variety of treatment and clinical outcomes; however, the efficacy of combination therapy remains limited. Therefore, the purpose of this study is to investigate the effect of monotherapy and combination therapy for *S. maltophilia* infections on mortality outcome.

Methods: We performed a systematic review and meta-analysis of combination therapy versus monotherapy in the treatment of *S. maltophilia* infections on mortality as a clinical outcome. Electronic databases, including Cochrane Library, PubMed, EMBASE, ClinicalTrials.gov, Scopus, and OpenGrey, were systematically searched from the inception of the database until September 3, 2021.

Results: Of which 6,524 articles identified, a total of 13 studies and 2 cohort studies were included for systematic review of combination therapy and meta-analysis, respectively. The systematic review of combination antimicrobial therapy had been showed clinically desirable outcome on mortality in *S. maltophilia* infection, especially in complex or severe infection. In the fixed-effects meta-analysis of the cohort study, monotherapy was surprisingly shown to have statistically significant effects on the decreased risk of mortality (hazard ratio 1.42; 95% confidence interval, 1.04-1.94).

Conclusions: Our results found that the combination antimicrobial therapy had been showed clinically desirable outcome on mortality in *S. maltophilia* infection and monotherapy has a trend toward improved better outcome than combination therapy on mortality for the treatment of *S. maltophilia* infections. A longitudinal study that further explores this association is warranted.

Trial registration: This study was registered with the trial registration number ID: 210843 under the international prospective register of systematic reviews (PROSPERO: www.crd.york.ac.uk/PROSPERO).

Background

Stenotrophomonas maltophilia is an aerobic Gram-negative bacteria that can causes various opportunistic infections in humans [1]. An emerging multi-drug resistant of this organism in hospitals worldwide because *S. maltophilia* is intrinsically resistant to various classes of antibiotics, including beta-lactam agents and aminoglycosides and has developed itself through multiple resistance mechanisms. The main mechanism of resistances of this organism relies on the presence in its chromosome of genes encoding efflux pumps and antibiotic inactivating enzymes [2]. The recommendation of treatment *S. maltophilia*, which is resistant to first line therapy was various combinations of antimicrobial agents. These regimens have been surveyed in order to overcome resistance or to attain synergism. Combinations of 2-3 old agents with good susceptibility or with new antibiotics such as telavancin have demonstrated synergistic effects to *S. maltophilia*. Hence, antimicrobial resistance is become a large problem to treat *S. Maltophilia* [3]. This is challenging the clinicians to treat and It has become a public health concern and associated with a high mortality rate in *S. maltophilia* infection [4]. The prevalence of *S maltophilia* infection in Asia, Europe and, Latin America that had been reported by worldwide surveillance and multi-center studies were 1.68%, 1.0%, and 0.8%, respectively [3].

To date, trimethoprim-sulfamethoxazole and fluoroquinolones have been considered as the treatment of choice for *S. maltophilia* infections. In data of sub-group analyses in bacteremia patients showed no statistically significant difference between fluoroquinolones and trimethoprim-sulfamethoxazole [5]. Several studies were demonstrated various treatment and clinical outcomes. However, the efficacy of combination therapy are still limited and no report has been established to prove the efficacy. Therefore, our purpose is to investigate the effect of monotherapy and combination therapy for *S. maltophilia* infections on mortality outcome.

Methods

We performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This study was registered with the trial registration number ID: 210843 under the international prospective register of systematic reviews (PROSPERO: www.crd.york.ac.uk/PROSPERO).

Data sources and search strategy

We searched for articles from these electronic databases: The Cochrane Library, PubMed, Embase, Scopus, ClinicalTrials.gov, and OpenGrey databases for relevant articles published from inception of the databases to September 3, 2021. Medical Subject Heading (MeSH) were applied as applicable. Reference lists of related articles were explored. The search strategy was carried out with the following keywords: “*Stenotrophomonas maltophilia*”, “mortality”, “therapeutics”, and “anti-bacterial agents” with slight adjustments depended on the database. There was no study design and language restriction.

Study selection

We included studies: 1) that were performed in adult patients (age ≥ 18 years old) who infected with *S. maltophilia* in any sources of infection; 2) that presented the results as odds ratio (OR), risk ratio (RR), hazard ratio (HR), or the number of mortality, and with a 95% confidence interval (95%CI) or p-value; 3) in which patients received combination as the exposure group; 4) in which patients received monotherapy as a comparator. Animal studies and those studies not presented as original research, such as reviews, comments, editorials, expert opinions, surveys, letters, conference meeting abstracts, case reports, case series, systematic reviews and meta-analyses, were excluded.

Data extraction and quality assessment

Two independent authors (NC and WR) examined the search results according to the study selection criteria. Details of each study were extracted and tabulated, including study design, patient population, co-morbidity, severity, reported mortality, type of infection, percentage of polymicrobial infection, method of bacterial identification and funding source. Data for mortality according to antibiotic treatment were extracted from the published article. The number of cases treated with each antibiotic treatment and associated mortality were recorded. Risk of bias in non-randomized studies of interventions (ROBINS-I) assessment tool was used for quality evaluation of the included studies, all of which were retrospective cohort or case-control studies.

Definition and outcome measures

The primary outcome was a mortality of *S. maltophilia* infections treated by monotherapy or combination therapy. The term “mortality” was primarily used for data searching. The term “30 day mortality” was defined as the death in 30 days with any causes of mortality. The term “In-hospital mortality” was defined as the number of patients who died during hospital admission. A combination therapy was used as a comparator drug against monotherapy. A combination therapy means using 2 or more antibiotics to treat *S. maltophilia* infections. A monotherapy means using only 1 antibiotic to treat *S. maltophilia* infections.

Statistical analysis

Unadjusted ORs and 95%CI were calculated between monotherapy or combination therapy for each individual study. The pooled OR and 95% CI were calculated using a random-effects model (Mantel-Haenszel method). Statistical heterogeneity between studies were assessed using a χ^2 -test ($p < 0.10$ was defined as indicating significant heterogeneity), and I^2 was used to indicate the degree of heterogeneity (0%-25% low heterogeneity, 25%-50% moderate heterogeneity, 50%-75% substantial heterogeneity, 75%-100% considerable heterogeneity). Publication bias was assessed by the funnel plot method and Egger's test. Review Manager for Windows, version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used for meta-analysis and R- 3.3.1 for Windows (RStudio, Boston, MA, USA) was used for Egger's test.

Subgroup and sensitivity analysis

Subgroup analyses were performed in this studies. We classified into 7 categories as the following: model of meta-analysis, age, day on ventilator, ICU length of stay, Hospital length of stay, Immunocompromised status and Severity score. Adjusted ORs and 95%CI were calculated among these categories. Statistical heterogeneity were assessed using a I^2 was used to indicate the degree of heterogeneity (0%-25% low heterogeneity, 25%-50% moderate heterogeneity, 50%-75% substantial heterogeneity, 75%-100% considerable heterogeneity) and p-value ($p < 0.10$ was defined as indicating significant heterogeneity)

Results

Search results and included study characteristics

The study selection process is presented in Figure 1. Thirteen and 2 studies [6-18,19,20] were included in the systematic review and final meta-analysis, respectively. We did not contact the authors of 1 study, which had enough information in the original publications. We have contacted the corresponding author of 1 study to request additional data but did not receive replies from the authors more than 3 months. Characteristics of the studies included are summarized in Table 1.

Of 6,524 articles, a total of 13 case reports and case series were identified by the literature search with a total of 50 participants were included for systematic review of combination therapy. The studies were published in 1998-2020. The summarized data is shown in Table 1. The systematic review of combination antimicrobial therapy had been showed clinically desirable outcome on mortality in *S. maltophilia* infection, especially in complex or severe infection such as peritonitis, meningitis, ventilator-associated pneumonia, infective endocarditis and bacteremia had the survival rate of treatment was 100%, 100%, 100%, 70% and 50%, respectively. However, we discovered that hemorrhagic pneumonia caused by *S. maltophilia* infection had 100% death rate even though treat with combination antimicrobial therapy.

We performed systematic review and meta-analysis to compare the regimen of combination therapy versus monotherapy in the treatment of *S. maltophilia* infections. Of 6,524 articles, 2 cohort studies were identified by the literature search with a total of 740 participants were included for meta-analysis. Of which 25 studies met outcome measures, 4 were inappropriate comparison, 5 were *in-vitro* studies, and 14 were comment, letter, review, case report, case series or editorial reports. Finally, 2 full-text articles were included for synthesis of this systematic review and meta-analysis [19, 20]. The studies were published in 2019.

Quality assessment

Overall of included studies were used ROBINS-I assessment tool for quality assessment. The results showed moderate risk of bias of both included studies. The data is shown in Table 2.

Mortality

In the random effect model meta-analysis of the cohort study, monotherapy was surprisingly shown to have statistically significant effects on the decreased risk of mortality (hazard ratio 1.42; 95% confidence interval, 1.04-1.94) in *S. maltophilia* infections as showed in Figure 2 There is no evidence of publication bias, according to Egger's test (p-value = 0.182) and Begg's test (p-value= 0.602).

Subgroup and sensitivity analysis

In addition, we performed subgroup-analysis simultaneously to explore the trend of some interesting factors that probably affected on mortality of *S. maltophilia* infections. The model, age, day on ventilator, ICU length of stay, hospital length of stay, immunocompromised status and severity score were analyzed. The data showed all factors for subgroup analysis had similar trend with major data analysis. Hence, the model, age, day on ventilator, ICU length of stay, hospital length of stay, immunocompromised status and severity score would rather monotherapy in patients who infected with *S. maltophilia* with no heterogeneity (I^2 value=0 for all factors). The detail of data was shown in Figure 3.

Discussion

Monotherapy such as fluoroquinolones and trimethoprim-sulfamethoxazole have been used for *S. maltophilia* infections as potential antibiotics since the 1980s [5]. However, some studies had been shown the potential combination regimens of antibiotic but they literally were controversial and lack of summarized data that monotherapy or combination therapy, which one is better? This study is the first systematic review and meta-analysis evaluating the best regimen to treat *S. maltophilia* infections. Among these, two studies were designed to compare the clinical efficacy of monotherapy and combination therapy, showing that monotherapy was better than combination therapy on mortality outcomes according to the analyses. In another hand of subgroup analysis, showing all of factors (the model, age, day on ventilator, ICU length of stay, hospital length of stay, immunocompromised status, and severity score) favored the monotherapy than combination therapy that similar with major outcome. The possible causes which support this outcome might cause by synergy activity of adverse drug event in combination antibiotic group that accelerate the rate of mortality. Moreover, in treating severe patients who infected with *S. maltophilia* had potential to use combination antibiotic and had high risk of death, simultaneously. Hence, We hypothesize the possible reasons indicated monotherapy has a trend toward improved better clinical outcome than combination therapy might caused by less severity and adverse drug reactions in monotherapy group.

In treating *S. maltophilia* infections with monotherapy even though our study showed desirable clinical outcome than combination therapy, but many studies of systematic review reported the use of combination therapy has been recommended in patients suffering from severe or complex infection such as bacteremia, infective endocarditis, ventilator-associated pneumonia and meningitis [7, 8, 13, 14, 16, 18].

The limitation of this study that there were small number of included studies to draw a conclusion and these 2 included studies were not a randomized controlled trial which is the best study design with minimized bias.

Conclusion

In conclusion, systematic review evaluating 13 non-randomized studies revealed the combination antimicrobial therapy had been showed clinically desirable outcome on mortality in *S. maltophilia* infection, especially in complex or severe infection. The meta-analysis of our results found that monotherapy has a trend toward improved better outcome than combination therapy on mortality for the treatment of *S. maltophilia* infections. A longitudinal study that further explores this association is warranted

Declarations

Ethical approval and consent to participate.

The systematic review or meta-analysis is exempt from ethics approval because it collecting and synthesizing data from the previous studies. In addition, patient data are anonymized and data are available in the public domain so that ethical permission is not needed. The authors followed applicable EQUATOR Network (<http://www.equator-network.org>) guidelines during the conduct of research project.

Consent for publication

The authors all agreed to the publication of this manuscript.

Availability of data and materials

The datasets used and analyzed during the study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None received.

Author's contributions

AP and SK conceived and designed the study. NC and WR searched for articles and extracted and managed data. AP, SK, NC, and WR performed data analysis. AP and TP wrote the paper. All authors contributed to drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Tables

Due to technical limitations, tables 1-2 are only available as a download in the Supplemental Files section.

Figures

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizes the study selection process.

Figure 2

Forest plot presenting the HRs of mortality of patients with *Stenotrophomonas maltophilia* infections compared between combination therapy and monotherapy.

Figure 3

Forest plot presenting the HRs of sub-group analysis of patients with *Stenotrophomonas maltophilia* infections compared between combination therapy and monotherapy.

Supplementary Files

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- [Tables.docx](#)