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REVIEW

Empirical mono- versus combination antibiotic therapy in adult intensive care patients with severe sepsis — A systematic review with meta-analysis and trial sequential analysis

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Summary *Objectives:* To assess benefits and harms of empirical mono- *vs.* combination antibiotic therapy in adult patients with severe sepsis in the intensive care unit (ICU).
Methods: We performed a systematic review according to the Cochrane Collaboration methodology, including meta-analysis, risk of bias assessment and trial sequential analysis (TSA). We included randomised clinical trials (RCT) assessing empirical mono-antibiotic therapy versus a combination of two or more antibiotics in adult ICU patients with severe sepsis. We exclusively assessed patient-important outcomes, including mortality. Two reviewers independently evaluated studies for inclusion, extracted data, and assessed risk of bias. Risk ratios (RRs) with 95% confidence intervals (CIs) were estimated and the risk of random errors was assessed by TSA.
Results: Thirteen RCTs ($n = 2633$) were included; all were judged as having high risk of bias. Carbapenems were the most frequently used mono-antibiotic (8 of 13 trials). There was no difference in mortality (RR 1.11, 95% CI 0.95–1.29; $p = 0.19$) or in any other patient-important outcomes between mono- *vs.* combination therapy. In TSA of mortality, the Z-curve reached the futility area, indicating that a 20% relative risk difference in mortality may be excluded between the two groups. For the other outcomes, TSA indicated lack of data and high risk of random errors.
Conclusions: This systematic review of RCTs with meta-analysis and TSA demonstrated no differences in mortality or other patient-important outcomes between empirical mono-

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vs. combination antibiotic therapy in adult ICU patients with severe sepsis. The quantity and quality of data was low without firm evidence for benefit or harm of combination therapy.

Introduction

It is estimated that approximately 10% of all admissions to the intensive care unit (ICU) are due to severe sepsis, and that even more patients develop the syndrome during their ICU stay.[1] Despite advances in diagnostics and treatment, one in three patients with sepsis die.[1,2]

Sepsis is triggered by microbial infection, which is why initial management includes mechanical removal of the infectious source (source control), cultures, and early administration of appropriate antimicrobial therapy.[3] Empirical combination antibiotic therapy for treatment of severe sepsis is a matter of debate.[4] The proposed rationale for using a combination of two or more different antimicrobials includes a broader empirical coverage with a higher likelihood of targeting the causative organism, a possible decreased risk of developing resistance to the antibiotics used, and a potential synergistic effect increasing the efficacy of bacterial eradication.[4] However, the quality of the evidence supporting empirical combination antibiotic therapy is weak and does not include high quality randomised clinical trials (RCTs).[5]

In recent years, several systematic reviews and meta-analysis have sought to summarise existing evidence on empirical combination antibiotic therapy in sepsis.[6–10] However, existing systematic reviews are conflicting and hampered by methodological limitations, including trial heterogeneity, statistical heterogeneity, high risk of systematic errors, and high risk of random errors.[11] Consequently, equipoise exists.

Therefore, we aimed in this systematic review of RCTs with meta-analysis and trial sequential analysis (TSA) to assess patient-important benefits and harms of empirical mono- *vs.* combination antibiotic therapy in patients with severe sepsis admitted to the ICU. We hypothesised that patients in the ICU with severe sepsis may benefit from empirical combination antibiotic therapy, since they have a high disease burden and, therefore, a high *a priori* risk of adverse outcome.

Methods

We followed the recommendations published by the Cochrane Collaboration,[12] and prepared the systematic review according to the PRISMA (Preferred, Reporting Items for Systematic Reviews and Meta-Analysis) statement.[13] The protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO, no. CRD42015016965), prior to the conduct of the review.

Eligibility criteria

Eligible trials were RCTs assessing empirical mono-antibiotic therapy versus a combination of two or more antibiotics in adult ICU patients with severe sepsis or septic shock. Trials were permitted to have more than one combination group. Exclusion criteria were trials in animals, trials in paediatric patients, trials not reporting patient-important outcome measures,[14] trials where both groups received empirical combination antibiotic therapy, trials assessing non-empirical treatment, quasi-randomised trials, cross-over trials, observational studies, and trials in patients not admitted to an ICU. To minimize language bias, publications in all languages were included.

Search strategy

We framed the following research question: "Is empirical combination antibiotic therapy superior to single antibiotic therapy in adult ICU patients with severe sepsis or septic shock?" A population, intervention, comparator and outcomes based question and literature search was created[15] (Electronic Supplementary Material (ESM) 1).

We searched PubMed (January 1947 to February 2016), EMBASE (January 1980 to February 2016) and the Cochrane Library (February 2016). Following pilot-tests of different search strategies, we used the following search strategy: (sepsis OR septicaemia OR septic shock OR critically ill OR intensive care OR severe) AND (antibiotic* OR lactam OR quinolone OR cephalo* OR carbapen* OR aminoglyc*) AND (combination OR duplicate OR mono*). References from included trials and relevant systematic reviews were hand-searched for additional trials.

Study selection

Two authors (FS and MHM) independently reviewed all titles and abstracts identified in the literature search. Trials deemed obviously irrelevant were excluded, and the remaining trials were evaluated in full text (Fig. 1). Disagreements were resolved by discussion.

Data extraction

Two authors (FS and MHM) independently screened the identified references and extracted data using a data extraction form. The extracted data included trial design, characteristics of patients included, interventions *i.e.* antibiotics used and outcomes. Two study authors were contacted for additional information.[16,17]

Risk of bias assessment

Two authors (FS and MHM) independently assessed the risk of systematic errors (bias) of the included trials as advised by the Cochrane Collaboration.[12] The following seven risk of bias domains were assessed: random sequence generation, allocation concealment, blinding of personnel and