

Is de-escalation of antimicrobials effective? A systematic review and meta-analysis



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ARTICLE INFO

Article history:

Received 1 March 2016

Received in revised form 16 May 2016

Accepted 4 June 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

De-escalation therapy

Systematic review

Meta-analysis

SUMMARY

Background: De-escalation therapy is a strategy used widely to treat infections while avoiding the use of broad-spectrum antimicrobials. However, there is a paucity of clinical evidence to demonstrate the effectiveness and safety of de-escalation therapy compared to conventional therapy.

Methods: A systematic review and meta-analysis was conducted on de-escalation therapy for a variety of infections. A search of the MEDLINE (via PubMed), EMBASE, and Cochrane Library databases up to July 2015 for relevant studies was performed. The primary outcome was relevant mortality, such as 30-day mortality and in-hospital mortality. A meta-analysis was to be conducted for the pooled odds ratio using the random-effects model when possible. Both randomized controlled trials and observational studies were included in the analysis.

Results: A total of 23 studies were included in the analysis. There was no difference in mortality for most infections, and some studies favored de-escalation over non-de-escalation for better survival. The quality of most studies included was not high.

Conclusions: This review and analysis suggests that de-escalation therapy is safe and effective for most infections, although higher quality studies are needed in the future.

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1. Introduction

The provision of effective antimicrobial therapy in a timely manner and of an appropriate spectrum is one of the mainstays of the treatment of infectious diseases.^{1,2} However, this has led to the widespread use of broad-spectrum antibiotic therapy for the empirical treatment of infections, which may have contributed to the increase in a variety of drug-resistant organisms.

De-escalation therapy is an approach aimed at balancing the effective treatment of patients with infections and the prevention of an increase in antimicrobial resistance. It allows the use of broad-spectrum antimicrobials as empirical therapeutic agents, but these are replaced by agents with the narrowest possible spectrum immediately upon identification of the causative organisms and the results of antimicrobial susceptibility testing.³ Thus failure of the initial therapy of each given infectious disease is avoided by use of broad-spectrum antibiotics, and they can then

be discontinued so that antibiotic pressure to select resistant organisms is minimized.

The premise justifying the de-escalation strategy is clinical efficacy and safety that is non-inferior to therapy without de-escalation. However, there is a paucity of clinical evidence to demonstrate the equivalence or non-inferiority of de-escalation therapy compared to conventional therapy. A recent meta-analysis on de-escalation therapy for adults with sepsis, severe sepsis, or septic shock by the Cochrane Collaboration sought to include randomized controlled trials (RCTs), but not a single such study could be found to include in the analysis.⁴ However, it should not be concluded that de-escalation has no value. The Cochrane Collaboration did not examine infections other than sepsis and they did not include clinical studies other than RCTs. The inclusion of observational studies in meta-analyses might impair the quality of the study, but meta-analyses using observational studies have provided clinically robust and useful information. In fact, observational studies may even provide important additional information or higher-quality evidence than available RCTs for certain health care problems.⁵

Therefore, a systematic review and meta-analysis was conducted on de-escalation therapy for a variety of infections, not only

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for sepsis and its related complications, while allowing observational studies to be included in the analysis.

2. Methods

The primary objective was to evaluate the efficacy and safety of de-escalation therapy compared to antimicrobial therapy without de-escalation for a variety of infections by measuring the all-cause mortality for a certain duration.

De-escalation was defined as a change in the initially appropriate antimicrobial therapy from an empirical broad-spectrum characteristic to a narrower-spectrum one (either by changing the antimicrobial agent or by discontinuing an eventual antimicrobial combination, or both) according to culture results or for other clinical reasons.^{6–8}

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement⁹ and the Meta-analysis Observational Studies in Epidemiology (MOOSE) guidelines.¹⁰

2.1. Search strategy and study selection

A search of the MEDLINE (via PubMed), EMBASE, and Cochrane Library databases up to July 2015 for relevant studies was performed. The reports retrieved were also screened manually for further potentially relevant articles. No language restriction was applied. The search strategy is provided in the Appendix.

2.2. Study eligibility criteria

Two investigators (GO and KI) independently screened all citations by title and abstract. The same investigators then screened the studies retrieved independently. Disagreements regarding inclusion were resolved by discussion or by consulting a third investigator (AD).

Any comparative studies such as RCTs, quasi-experimental designs, and observational studies that assessed the effectiveness of the de-escalation therapy strategy were included. Attempts were made to contact the authors of the studies if necessary.

The primary outcome was 28–30-day mortality, in-hospital mortality, or other types of mortality if necessary. All-cause mortality was included, but infection-specific mortality was not, since the aim was to evaluate the overall risk/benefit of de-escalation, taking into account potential factors such as the toxicity of the medications. A meta-analysis of studies with the same clinical diagnosis and outcomes was to be conducted if possible.

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach for estimating the quality of evidence was used, utilizing GRADEpro to assess each study.^{10,11} The completed evidence summaries and GRADE assessments were discussed by the investigators. The confidence in the estimate of effect was categorized into four levels, ranging from very low to high.

2.3. Data synthesis and analysis

For the data synthesis, meta-analyses of dichotomous outcomes were conducted using Mantel–Haenszel methods with the random-effects model to provide the odds ratio (OR), utilizing Review Manager, version 5.3 (The Nordic Cochrane Center and the Cochrane Collaboration, Copenhagen, Denmark). All statistical tests were two-sided, and a *p*-value of <0.05 was considered to be statistically significant.

Heterogeneity was measured and expressed as I^2 , the percentage of total variation across studies due to between-study heterogeneity rather than chance, with suggested thresholds for

low ($I^2 < 49\%$), moderate ($I^2 = 50–74\%$), and high ($I^2 > 75\%$) values.^{12–14} The funnel plot for mortality was examined visually to assess publication bias.

3. Results

3.1. Literature flow

A total of 12 627 articles were identified in the electronic search of the databases (1862 articles from MEDLINE via PubMed, 573 articles from the Cochrane Library, and 10 192 articles from EMBASE). After removing duplicate articles, 10 607 remained. The titles and abstracts of these articles were screened and it was possible to retrieve 90 full-text articles and conference abstracts. Eleven further articles were found after reviewing the reference lists of the articles retrieved. Forty-five comparative studies were then selected out for full-text review. Studies were excluded for the following reasons: no relevant clinical outcomes or the outcomes were not evaluated for de-escalation ($n = 8$), no full text data were obtainable ($n = 8$), duplication of published articles and conference abstracts ($n = 3$), and the antimicrobial change was not actually de-escalation by definition ($n = 3$). The remaining 23 articles were reviewed for this study (Figure 1).

3.2. Community-acquired pneumonia (CAP)

Two studies concerning de-escalation for CAP were found. Kothe et al. conducted a multi-center prospective observational study in Germany from 2003 to 2005.¹⁵ They mainly analyzed the outcome data of CAP based on patient age groups. However, it was possible to calculate the outcome (30-day mortality) according to de-escalation status. Among 2647 patients who participated in the study, 114 (4%) received de-escalation treatment, whereas the remaining 2533 (96%) received conventional treatment without de-escalation.

Carugati et al. analyzed data on hospitalized patients with bacteremic CAP in 35 countries.¹⁶ Among 289 patients whose initial antimicrobial therapy was considered appropriate on admission, 165 (57%) received de-escalation therapy and 96 (43%) remained on the initial treatment.

The combined 30-day mortality after meta-analysis was significantly lower in the de-escalation group (Figure 2; OR 0.50, 95% confidence interval (CI) 0.29–0.87).

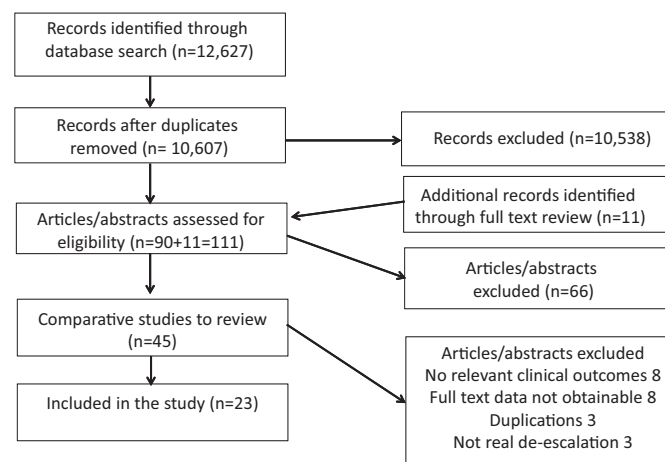


Figure 1. Summary of evidence search and selection.

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