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

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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.

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) statement[9] 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).

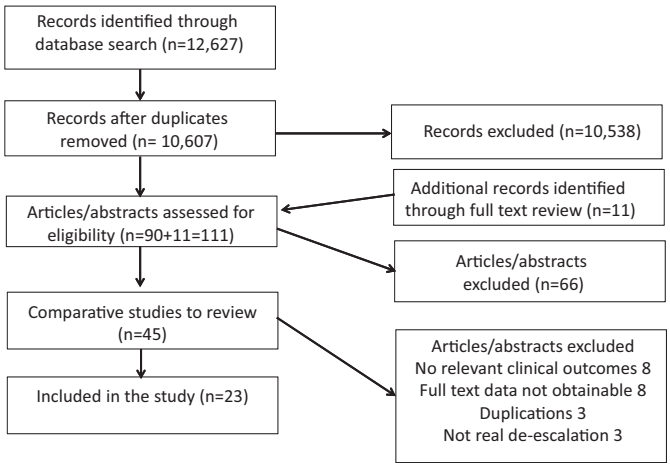

Figure 1. Summary of evidence search and selection.

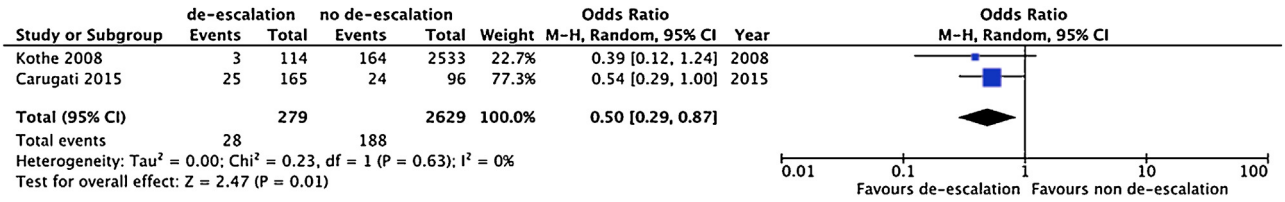

Figure 2. Forest plot of 30-day mortality for community-acquired pneumonia (CI, confidence interval).

3.3. Hospital-acquired pneumonia (HAP)

Kim et al. conducted a prospective open-label randomized clinical trial at a medical intensive care unit (ICU) in South Korea.[17] Patients who were diagnosed and then admitted to the ICU were enrolled, and were randomized to either a de-escalation group or a non-de-escalation group. There was no difference in overall hospital mortality between the groups (44.2% vs. 34.6%, $p = 0.316$). This study was peculiar since the initial empirical antimicrobials differed between the de-escalation group and the non-de-escalation group. There were more multidrug-resistant organisms detected after treatment in the de-escalation group, and mortality from methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia was also higher in the de-escalation group.

Khasawneh et al. conducted a retrospective observational study for bacteremic HAP at a hospital in the USA.[18] There was no difference in overall hospital mortality between groups (9.0% vs. 25.9%, $p = 0.09$).

Meta-analysis combining these two studies also did not show a statistical difference in in-hospital mortality between the de-escalation group and the non-de-escalation group (Figure 3; OR 0.75, 95% CI 0.14–3.96). The studies included showed high heterogeneity ($I^2 = 75\%$).

3.4. ICU-acquired pneumonia

Three studies investigating the effectiveness of de-escalation for pneumonia that developed in the ICU were found. Most were cases of ventilator-associated pneumonia (VAP), but not all of them. Therefore, ICU-acquired pneumonia was analyzed as a different entity, and VAP is discussed separately (see below).

Álvarez-Lerma et al. designed a prospective multi-center observational study in 24 ICUs of Spanish general hospitals.[19] A total of 244 patients were enrolled with diagnostic criteria developed by the US Centers for Disease Control and Prevention.[20] Most patients (83.5%) were on mechanical ventilation. Among the five groups of patients in this study, group III represented non-de-escalation therapy and group IV represented de-escalation therapy.

Joung et al. conducted a retrospective observational study in the medical and surgical ICU of a tertiary care university hospital in South Korea.[21] The diagnostic criteria were the same as those used by Álvarez-Lerma et al. More than 90% of the patients were on mechanical ventilation. Both pneumonia-related and overall mortality at day 30 were reported to be significantly lower in the de-escalation group ($p = 0.03$ and $p = 0.04$, respectively), but it was not possible to find an actual number of deaths with regard to overall in-hospital mortality, and thus it was not possible to include this study in the meta-analysis.

Knaak conducted a retrospective observational study in an ICU at a tertiary care academic medical center in the USA.[22] Both pneumonia diagnosed in the ICU and in those transferred to the ICU after diagnosis of health care-associated pneumonia (HCAP) were included in the study, with adequate diagnostic criteria.

The combined meta-analysis favored de-escalation to decrease in-hospital mortality (Figure 4; OR 0.34, 95% CI 0.17–0.68).

3.5. Ventilator-associated pneumonia (VAP)

Kollef et al. designed a prospective observational study on VAP in 20 ICUs in the USA.[23] De-escalation occurred in 22.1% of the patients.

Giantsou et al. also conducted a prospective observational study on VAP at a university hospital in Greece.[24] De-escalation occurred in 40.5% of the patients.

Joffe et al. performed a secondary analysis in a multi-center trial of patients with VAP randomized to bronchoscopy or endotracheal aspirate cultures.[25] Among patients with a positive culture from the lower respiratory tract, the majority went through de-escalation. Both 28-day mortality and in-hospital mortality were measured as outcomes.

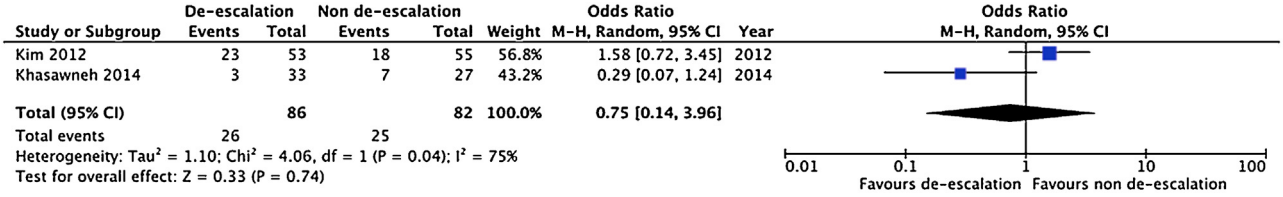

Figure 3. Forest plot of in-hospital mortality for hospital-acquired pneumonia (CI, confidence interval).

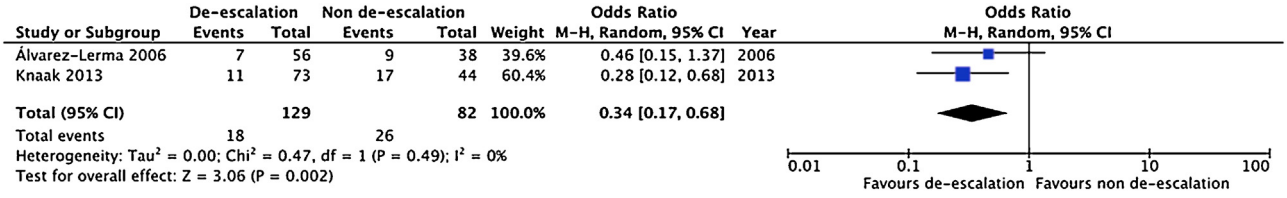

Figure 4. Forest plot of in-hospital mortality for ICU-acquired pneumonia (CI, confidence interval).

Eachempati et al. conducted a retrospective observational study on VAP diagnosed by quantitative bronchoalveolar lavage at a surgical ICU in the USA.[26]

Meta-analyses of both 28-day mortality and in-hospital mortality did not show a statistical difference between de-escalation therapy and non-de-escalation therapy (Figure 5; OR 0.49, 95% CI 0.07–3.32 and OR 0.88, 95% CI 0.54–1.44, respectively). High heterogeneity was observed in the analysis of 28-day mortality (I^2 = 92%).

3.6. Bacteremia

Shime et al. published two retrospective observational studies on this subject, based on positive blood cultures, at a university medical center in Japan.[27,28] The first concerned bacteremia diagnosed between 2004 and 2009, and there was no difference in in-hospital mortality between the de-escalation group and the group of those whose antimicrobials were unchanged or escalated (1% vs. 5%, p = 0.20).[27] The second study concerned bacteremia caused by specific Gram-negative bacilli (SPACEs; *Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, and *Enterobacter*), diagnosed between 2006 and 2011 at the same institution. Again, there was no difference in in-hospital mortality between the de-escalation group (0/28 patients) and the non-de-escalation group (2/11 patients) (p = 0.20).[28]

Since there was an overlap in the period observed in these two studies at the same institution, with different clinical entities evaluated, it was not possible to combine them.

3.7. Urinary tract infection (UTI)

Khasawneh et al. conducted a retrospective observational study on bacteremic UTI at a hospital in the USA.[29] UTI was diagnosed based on positive blood cultures, urine cultures, and a review of the medical records. There was a trend in in-hospital mortality favoring the de-escalation group (1/34 patients) over the non-de-escalation group (6/31 patients) (p = 0.06).

3.8. Sepsis with bloodstream infection (BSI)

Koupetori et al. conducted a prospective multi-center observational study on sepsis/BSI in 31 hospitals in Greece.[30] Both community-acquired and hospital-acquired infections were included in the study. Inclusion criteria were (1) age ≥18 years, (2) systemic inflammatory response syndrome (SIRS), and (3) presence of BSI. There were two study periods over which the effectiveness of antimicrobial treatment was observed (2006–2009 and 2010–2013). Although Kaplan–Meier survival analysis demonstrated significantly prolonged survival for the de-escalation group during the latter period, Cox regression analysis after adjustment for disease severity showed no difference in mortality between the de-escalation group and non-de-escalation group for both periods (hazard ratio (HR) 2.48, 95% CI 0.75–8.12 and OR 0.69, 95% CI 0.28–1.69, respectively).

3.9. Severe sepsis and/or septic shock

Garnacho-Montero et al. performed a prospective observational study enrolling patients admitted to the ICU of a university hospital in Spain with severe sepsis and septic shock.[31] A propensity score-adjusted multivariable analysis was performed, and the OR for overall mortality adjusted by propensity score favored de-escalation (adjusted OR 0.55, 95% CI 0.32–0.98).

Leone et al. conducted a multi-center open-label randomized non-inferiority trial on severe sepsis at nine ICUs in France.[32] The de-escalation group had a significantly longer time between sepsis and inclusion in the study (mean 3.2 days vs. 2.7 days, p = 0.05), but patients in the non-de-escalation group were significantly older (mean 57.9 years vs. 66.8 years, p = 0.003). There was no difference in 90-day mortality between the de-escalation group and the non-de-escalation group (31% vs. 23%, p = 0.35). There was no difference in other outcomes, such as length of ICU stay.[33]

The meta-analysis of 90-mortality did not show superiority for either treatment group (Figure 6; OR 0.96, 95% CI 0.51–1.79). There was moderate heterogeneity among the studies included (I^2 = 51%).

3.10. Severe sepsis among neutropenic patients

Mokart et al. investigated neutropenic patients after chemotherapy with severe sepsis or septic shock in an ICU in France, conducting a prospective observational study.[34] De-escalation was performed in 44 patients, whereas 57 patients did not undergo de-escalation. The ICU mortality was 23%. Six patients died after going through de-escalation during neutropenia, two patients died de-escalated after recovering from neutropenia, and 15 patients without de-escalation also died. De-escalation was not associated with the hazard of death within the first 30 days (HR 0.51, 95% CI 0.20–1.33), or within the 1 year post ICU discharge (HR 1.06, 95% CI 0.54–2.08).

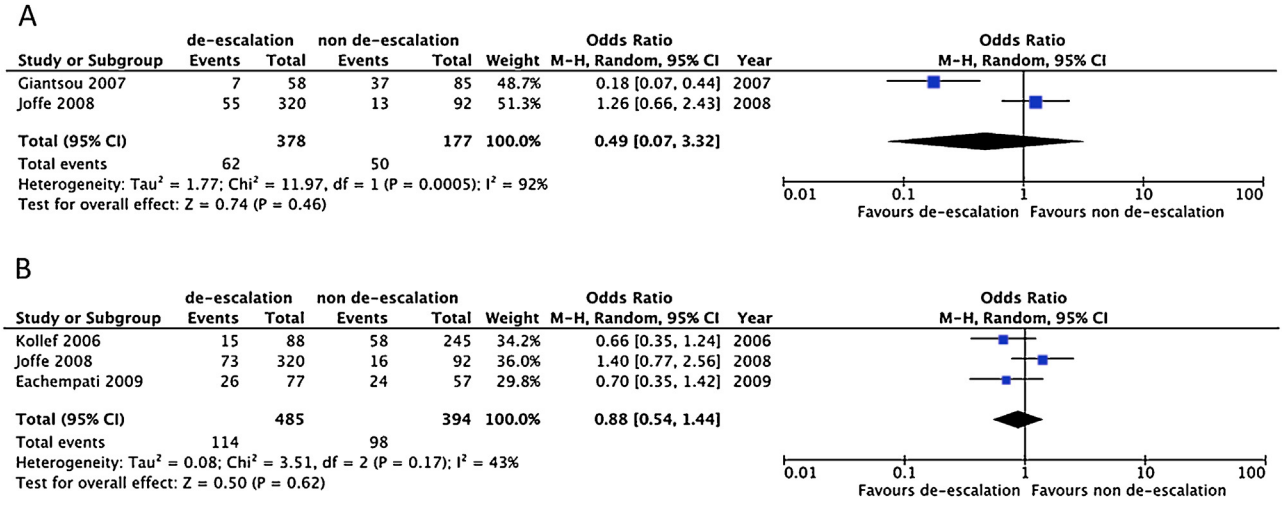

Figure 5. Forest plot of 28-day mortality (A) and in-hospital mortality (B) for ventilator-associated pneumonia (CI, confidence interval).

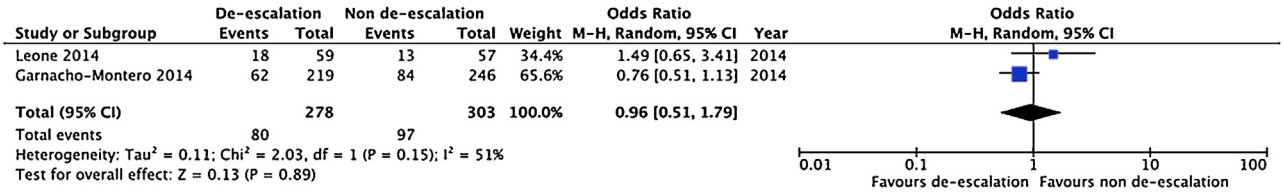

Figure 6. Forest plot of 90-day mortality for severe sepsis and septic shock (CI, confidence interval).

3.11. Patients in the ICU

Morel et al. conducted a retrospective observational study in an ICU of a teaching hospital in France.[35] All patients who were treated with empiric antimicrobials were included irrespective of the origin and severity of the suspected infection.

De Waele et al. also performed a retrospective observational study in a surgical ICU in a university hospital in Belgium.[36] All patients receiving more than one dose of meropenem as empirical therapy were included in the analysis.

Gonzalez et al. conducted a retrospective observational study at a medical ICU in a university hospital in France.[37] A variety of infections were included in the analysis and there were no protocols for the administration of empirical antimicrobials.

Meta-analyses of both ICU-mortality and in-hospital mortality showed no difference between the de-escalation group and the non-de-escalation group (Figure 7; OR 0.67, 95% CI 0.26–1.73 and OR 0.85, 95% CI 0.52–1.38, respectively).

3.12. Pneumococcal bacteremia

Cremers et al. conducted a retrospective study on pneumococcal bacteremia at two hospitals in the Netherlands.[38] A total of 275 cases were analyzed and the majority of them had accompanying pneumonia (229 cases, 83.3%). In-hospital mortality was significantly lower in the de-escalation group than in the non-de-escalation group (6.3% vs. 15.4%, $p = 0.021$). However, after adjusting for potential confounders, de-escalation was not associated with decreased in-hospital mortality (OR 0.55, 95% CI 0.20–1.51, $p = 0.242$).

3.13. De-escalation from carbapenems

Lew et al. evaluated the effectiveness of de-escalation from carbapenems at an academic hospital in Singapore.[39] A retrospective observational study was conducted from 2011 to 2012, when there was high endemicity of multidrug-resistant Gram-negative bacteria in the region. Their antimicrobial stewardship program recommended de-escalation for health care-associated or hospital-acquired infections upon susceptibility testing results, and they evaluated data based on acceptance or rejection of their recommendation. Neither 30-day mortality nor in-hospital mortality differed between the de-escalation group and the non-de-escalation group (12.3% vs. 14.6%, $p = 0.58$, and 15.2% vs. 17.7%, $p = 0.58$, respectively). The strength of this study was that it restricted patients to those for whom de-escalation was recommended by the antimicrobial stewardship program team, taking various factors such as contraindications to certain antimicrobials into consideration.

For each meta-analysis, no significant funnel plot asymmetry was found (results not shown).

A GRADE evidence profile was produced through quality assessment (Table 1). The majority of studies included in this systematic review were of 'low' or 'very low' quality, mostly because they were observational in design.

4. Discussion

A total of 23 studies evaluating the effectiveness and safety of de-escalation therapy for a variety of infections were identified. For critical outcomes such as in-hospital mortality, de-escalation appeared equally effective or even better than therapy that did not involve de-escalation . Meta-analysis suggested that de-escalation may improve mortality in both community-acquired and ICU-acquired pneumonia (Figures 2 and 4). However, the quality of the studies used in these analyses was generally low.

Despite this, fairly high quality studies were identified; there were two RCTs[17,32] and one observational study with a propensity score analysis.[31] Although the study by Kim et al. had the problem of different empirical regimens used in the two groups,[17] the RCT by Leone et al.,[32] as well as the propensity score analysis by Garnacho-Montero et al.,[31] suggested that de-escalation after

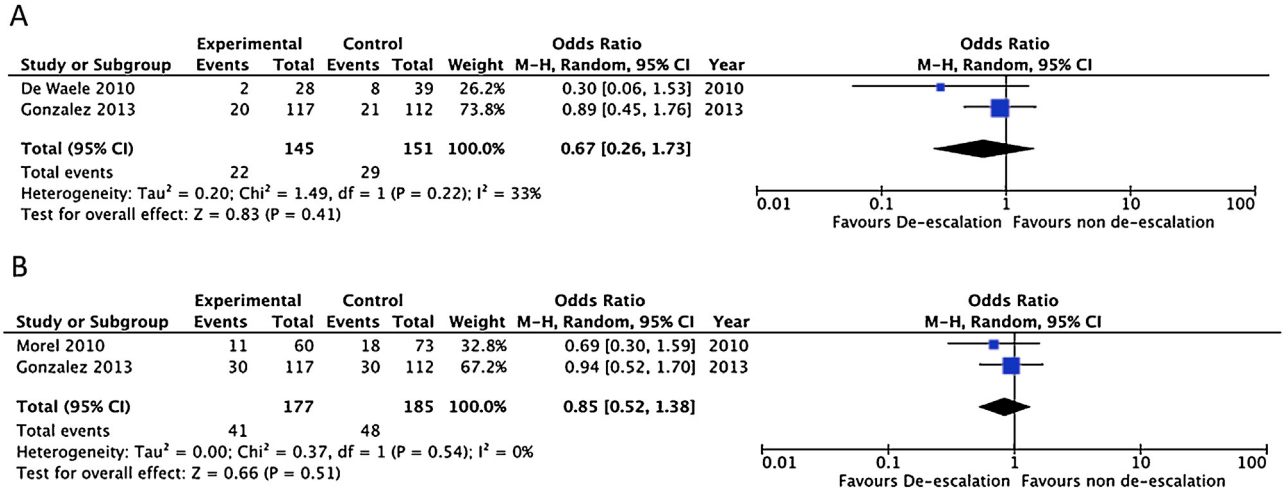

Figure 7. Forest plot of ICU mortality (A) and in-hospital mortality (B) for infections in the ICU (ICU, intensive care unit; CI, confidence interval).

Table 1
GRADE evidence profile for de-escalation therapy

Quality assessment							Number of patients De-escalation/ non-de-escalation	Relative effect (95% CI)	Quality	Importance
Number of studies [Ref.]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
30-day mortality for community-acquired pneumonia										
2 [15,16]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	279 cases/2629 controls	OR 0.50 (0.29–0.87)	Low	Critical
In-hospital mortality for hospital-acquired pneumonia (RCT)										
1 [17]	Randomized trials	Serious[c]	Not serious	Not serious	Serious[d]	All plausible residual confounding would suggest a spurious effect, while no effect was observed	54 cases/55 controls	OR 1.41 (0.65–3.05)	Moderate	Critical
In-hospital mortality for hospital-acquired pneumonia (bacteremic, observational)										
1 [18]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	33 cases/27 controls	OR 0.29 (0.07–1.24)	Low	Critical
In-hospital mortality for ICU-associated pneumonia										
2 [19,22]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	129 cases/82 controls	OR 0.34 (0.12–0.68)	Low	Critical
In-hospital mortality for ventilator-associated pneumonia										
3 [23,25,26]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	485 cases/394 controls	OR 0.88 (0.54–1.42)	Low	Critical
28-day mortality for ventilator-associated pneumonia										
2 [24,25]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	378 cases/177 controls	OR 0.49 (0.07–3.32)	Low	Critical
In-hospital mortality for bacteremia										
1 [27]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	79 cases/122 controls	OR 0.25 (0.03–2.10)	Low	Critical
In-hospital mortality for Gram-negative bacteremia (SPACEs)										
1 [28]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	28 cases/11 controls	OR 0.07 (0.00–1.52)	Low	Critical
In-hospital mortality for severe sepsis and septic shock										
1 [31]	Observational studies	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding would suggest a spurious effect, while no effect was observed[e]	219 cases/246 controls	OR 0.55 (0.32–0.98)	Moderate	Critical
90-day mortality for severe sepsis and septic shock (RCT)										
1 [32]	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	59 cases/57 controls	HR 1.31 (0.64–2.67)	High	Critical

Table 1 (*Continued*)

Quality assessment							Number of patients De-escalation/ non-de-escalation	Relative effect (95% CI)	Quality	Importance
Number of studies [Ref.]	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
90-day mortality for severe sepsis and septic shock (observational study)										
1 [32]	Observational studies	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[e]	219 cases/246 controls	OR 0.55 (0.34–0.87)	Moderate	Critical
30-day mortality for severe sepsis among neutropenic patients										
1 [34]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	44 cases/57 controls	HR 0.51 (0.20–1.33)	Low	Critical
ICU mortality for ICU infections										
2 [36,37]	Observational studies	Serious[a]	Not serious	Not serious	Serious[d]	All plausible residual confounding would reduce the demonstrated effect[b]	145 cases/151 controls	OR 0.67 (0.26–1.73)	Very low	Critical
In-hospital mortality for ICU infections										
2 [35,37]	Observational studies	Serious[a]	Not serious	Not serious	Serious[d]	All plausible residual confounding would reduce the demonstrated effect[b]	177 cases/185 controls	OR 0.85 (0.52–1.38)	Very low	Critical
In-hospital mortality for pneumococcal bacteremia										
1 [38]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	126 cases/149 controls	OR 0.55 (0.20–1.51)	Low	Critical
30-day mortality after carbapenem use for health care-associated or hospital-acquired infections										
1 [39]	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[b]	204 cases/96 controls	OR 0.82 (0.40–1.65)	Low	Critical

CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; ICU, intensive care unit; SPACEs, *Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, and *Enterobacter*; HR, hazard ratio.

[a] Observational study.

[b] De-escalation group could have a better prognosis to begin with.

[c] Open-label; initial empirical antimicrobials differed between the groups.

[d] Diagnostic criteria not clear.

[e] Factors unidentified in propensity score analysis might exist.

sepsis and septic shock might be clinically useful. These studies indicated that de-escalation did not impair the mortality outcome and thus may be an important option to maintain clinical effectiveness for infections while avoiding the overuse of broad-spectrum antimicrobials.

A recently published systematic review and meta-analysis combined studies on infections occurring in the ICU.[40] Although the random-effects model of meta-analysis allows various types of study to be included, and this may produce statistically significant findings, the present authors considered it clinically important to treat different clinical entities differently so that clinicians can apply the findings to their own practice. For example, when managing infectious diseases, clinicians usually treat neutropenic patients differently from those who are not .[41]

There are several limitations in these analyses. First, the overall quality of the studies included in the analyses was not high. Although the inclusion of observational studies in a systematic review and meta-analysis is justifiable, and may even improve the quality of the analysis,[5,10,42] these should be of good quality to yield more reliable results. Second, although it was sought to identify all studies relevant to this systematic review and meta-analysis, there may be studies that were not identified in the thorough search. Third, there are many other types of infectious disease, such as cholangitis, infective endocarditis, and septic arthritis; however relevant studies on these infections were not found. Further RCTs and observational studies of better quality are needed to overcome these limitations.

In conclusion, available studies in regard to de-escalation and its impact on mortality were identified and it was found that de-escalation appears safe and effective for certain infectious diseases. Further studies are needed to confirm these findings and to apply them to other types of infection.

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Conflict of interest: The authors declare that there are no conflicts of interest.

Appendix

Search of MEDLINE via PubMed

#1 (De-escalation) OR (De escalation) OR (Deescalate) OR (Narrow spectrum) OR (Narrow-spectrum) or (Narrower spectrum) OR (Tailoring) OR (Tailor) OR (Downgrading) OR (Discontinue) OR (Discontinuing)

#2 (Anti-Bacterial agents [Mesh]) OR (Antibiotic therapy) OR (Anti Bacterial) OR (Antibacterial) OR (Anti-Mycobacterial) OR (Bactericidal) OR (Antifungal agents [Mesh]) OR (Anti-fungal) OR (Antifungic) OR (Anti-fungic) OR (Fungicides) OR (Chemotherapies) OR (Chemotherapy) OR (Drug therapies) OR (Drug therapy [Mesh]) OR (Pharmacotherapies) OR (Pharmacotherapy)

#3 (Adequacy) OR (Adequate) OR (Extended-spectrum) OR (Appropriate) OR (Empiric) OR (Empirical) OR (Broad-spectrum) OR (Broad spectrum)

#1 AND #2 AND #3

Search of EMBASE

#1 'antiinfective agent[emtree]' OR 'anti bacterial' OR ('antibiotic' OR 'antibiotic'/exp) OR antibioitic AND ('therapy' OR 'therapy'/exp OR therapy) OR (anti AND bacterial) OR antibacterial OR bactericidal OR 'anti mycobacterial' OR (anti AND mycobacterial) OR antimycobacterial OR 'antibiotics' OR 'antibiotics'/exp OR antibiotics OR 'antibiotic' OR 'antibiotic'/exp OR antibiotic OR bacteriocidal OR bacteriocides OR 'antifungal' OR 'antifungal'/exp OR antifungal OR 'anti fungal' OR antifungic OR 'anti fungic' OR fungicides OR chemotherapies OR 'chemotherapy' OR 'chemotherapy'/exp OR chemotherapy OR ('drug' OR 'drug'/exp OR drug AND therapies) OR ('drug' OR 'drug'/exp OR drug AND ('therapy' OR 'therapy'/exp OR therapy)) OR pharmacotherapies OR 'pharmacotherapy' OR 'pharmacotherapy'/exp OR pharmacotherapy

#2 adequacy OR adequate OR 'extended spectrum' OR appropriate OR empiric OR empirical OR 'broad spectrum' OR (broad AND ('spectrum'/exp OR spectrum))

#3 narrow AND ('spectrum'/exp OR spectrum) OR 'narrow spectrum' OR (narrower AND ('spectrum'/exp OR spectrum)) OR 'narrower spectrum' OR 'narrowered spectrum' OR (narrowered AND ('spectrum'/exp OR spectrum)) OR (de AND escalation) OR narrowing OR deescalate OR 'de escalation' OR 'adjustment'/exp OR adjustment OR adjust OR tailoring OR tailored OR tailor OR downgrading OR discontinue OR discontinuing OR switch$

#1 and #2 and #3

Search of Cochrane Library

#1 de-escalation OR (De escalation) OR Deescalate OR (Narrow spectrum) OR Narrow-spectrum or (Narrower spectrum) OR Tailoring OR Tailor OR Downgrading OR Discontinue OR Discontinuing

#2 (Anti-Bacterial agents) OR (Antibiotic therapy) OR (Anti Bacterial) OR Antibacterial OR Anti-Mycobacterial OR Bactericidal OR (Antifungal agents) OR Anti-fungal OR Antifungic OR Anti-fungic OR Fungicides OR Chemotherapies OR Chemotherapy OR (Drug therapies) OR (Drug therapy) OR Pharmacotherapies OR Pharmacotherapy

#3 Adequacy OR Adequate OR Extended-spectrum OR Appropriate OR Empiric OR Empirical OR Broad-spectrum OR (Broad spectrum)

#1 AND #2 AND #3

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