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Review

# Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis

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ABSTRACT

Antibiotic de-escalation is an appealing strategy in antibiotic stewardship programmes. We aimed to assess its safety and effects using a systematic review and meta-analysis. We included randomized controlled trials (RCTs) and observational studies assessing adults with bacteraemia, microbiologically documented pneumonia or severe sepsis, comparing between antibiotic de-escalation and no de-escalation. De-escalation was defined as changing an initially covering antibiotic regimen to a narrower spectrum regimen based on antibiotic susceptibility testing results within 96 hours. The primary outcome was 30-day all-cause mortality. A search of published articles and conference proceedings was last updated in September 2015. Crude and adjusted ORs with 95% CI were pooled in random-effects meta-analyses. Sixteen observational studies and three RCTs were included. Risk of bias related to confounding was high in the observational studies. De-escalation was associated with fewer deaths in the unadjusted analysis (OR 0.53, 95% CI 0.39–0.73), 19 studies, moderate heterogeneity. In the adjusted analysis there was no significant difference in mortality (adjusted OR 0.83, 95% CI 0.59–1.16), 11 studies, moderate heterogeneity and the RCTs showed non-significant increased mortality with de-escalation (OR 1.73, 95% 0.97–3.06), three trials, no heterogeneity. There was a significant unadjusted association between de-escalation and survival in bacteraemia/severe sepsis (OR 0.45, 95% CI 0.30–0.67) and ventilator-associated pneumonia (OR 0.49, 95% CI 0.26–0.95), but not with other pneumonia (OR 0.97, 95% CI 0.45–2.12). Only two studies reported on the emergence of resistance with inconsistent findings. Observational studies suggest lower mortality with antibiotic susceptibility testing-based de-escalation for bacteraemia, severe sepsis and ventilator-associated pneumonia that was not demonstrated in RCTs.
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## Background

Bloodstream infections and pneumonia requiring hospitalization are responsible for significant morbidity and mortality, with mortality rates ranging between 27% and 54% [1,2]. Numerous studies have pointed to the importance of appropriate empiric antibiotics in reducing mortality for severe infections [3,4]. This had led to the widespread use of broad-spectrum drugs as first-line treatment, potentially contributing to the increase in bacterial resistance to antibiotics since, without intervening, empirical therapy is frequently continued. Several strategies have evolved to limit the appearance and spread of such organisms, among them antibiotic de-escalation [5,6].

De-escalation (also termed streamlining) refers to tailoring of empirical antibiotic treatment to the susceptibilities of the bacteria isolated, selecting the narrowest spectrum antibiotic. It can follow any empirical treatment, but is also applied with a policy of initial broad-spectrum treatment mainly in intensive-care units (ICUs). De-escalation might be easier to implement in antibiotic stewardship programmes than interventions targeting empirical antibiotics [5,7]. More information is available at the latter time-point, the patient's course is known and there is time for discussion and consideration. Promoting de-escalation entails increasing awareness among all antibiotic prescribers and education regarding antibiotic hierarchy or local preferences for targeted antibiotic treatment.

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A Cochrane review published in 2013 found insufficient evidence to recommend for or against de-escalation in adults with sepsis after a review of the literature failed to reveal randomized controlled trials (RCTs) testing the intervention [8]. RCTs constitute the reference standard design to assess such an intervention. However, as de-escalation has been appraised in many observational studies, systematically reviewing them and appraising the risk of bias in observational studies might prove useful to guide practice and further research. We aimed to assess the outcome of de-escalation therapy in patients with bloodstream infections, severe sepsis and pneumonia.

## Materials and methods

We included RCTs and prospective or retrospective observational studies, conducted in non-ICU and ICU settings. Patients, interventions, comparisons and outcomes are summarized in the Supplementary material (Table S1). We included adults 18 years of age and older with pneumonia, bacteraemia and severe sepsis/septic shock with microbiologically documented infections, who received appropriate empirical antibiotic treatment. Bloodstream infections had to be defined as clinically significant using valid definitions to exclude contaminants and pneumonia had to be defined using valid clinical and microbiological definitions [9].

The studies had to compare de-escalation therapy versus continued empiric antibiotic therapy. De-escalation was defined as changing an initially appropriate (covering) antimicrobial therapy to a narrower spectrum regimen based on culture results within 96 hours. A narrower spectrum regimen was defined as downgrading from a broad spectrum to a narrower spectrum agent within the same antibiotic class, changing a broad-spectrum antibiotic to a narrower-spectrum antibiotic of a different class (e.g. vancomycin to oxacillin), or discontinuation of one or more drugs of a combined regimen. Downgrading antibiotics from a broad to a narrow spectrum necessitates a hierarchy of antibiotics; we documented whether a hierarchy was used and accepted the study definitions for de-escalation and antibiotic hierarchy, as long as defined by antibiotic susceptibility testing and compatible with our definitions. We separated between studies in which empiric antibiotic treatment was intentionally broad-spectrum and those that did not specifically direct the empirical regimen.

The primary outcome assessed was all-cause mortality at 30 days. If not reported, we used all-cause mortality at the end of study follow up. Secondary outcomes included clinical failure, as defined in the study, examined at the end of treatment; duration of hospital and ICU stay; duration of antibiotic treatment; resistance development and superinfections, defined as secondary clinically significant infections developing within a 30-day follow up. Antibiotic resistance development was assessed as isolation of bacteria resistant to the antibiotics given to the patient in clinical or surveillance samples; and as isolation of MDR bacteria of epidemiological significance that were not present initially, including: extended-spectrum β-lactamase-producing bacteria, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterobacteriaceae* and carbapenem-resistant *Enterobacteriaceae*. We assessed adverse effects of antibiotic therapy, including nausea or vomiting, rash, antibiotic-associated diarrhoea, renal failure and hepatotoxicity and *Clostridium-difficile* infection.

We conducted a broad search for randomized and observational studies in PubMed, The Cochrane Library from inception until September 2015, and conference proceedings for the last 3 years of the ECCMID and ICAAC. In addition, we examined the bibliographies of identified trials as well as previous systematic reviews. No restrictions on language, date of publication or publication status were applied. We tailored the following search string by database: (blood stream infection OR bloodstream infection OR bacteremia OR sepsis OR septic shock OR pneumonia) AND (de-escalation OR de-escalate OR streamlining OR streamline OR targeted OR targeting OR narrowing OR narrow) AND (antibiotic OR antibiotics).

We applied the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI, http://bmg.cochrane.org/cochrane-risk-bias-assessment-tool-non-randomized-studies-interventions-acrobat-nrsi) to both observational studies and RCTs, addressing the outcome of all-cause mortality. The tool includes signalling questions in seven domains of bias, to which the responses are yes, probably yes, probably no and no. RCTs could achieve low risk of bias for all domains, depending on randomization methods. Low risk of bias in an observational study implies that it is comparable to a well-performed RCT. We tailored the tool to our review (see Supplementary material, Appendix S1).

Two reviewers independently applied inclusion/ exclusion criteria and extracted all data. Data were compared and differences were resolved by discussion. We extracted crude mortality rates and adjusted effect estimates in observational studies. For continuous outcomes we computed means and standard deviations from the data reported in the study using methods specified in the Cochrane Handbook and Wan *et al.* [10,11].

Adjusted risk ratios were converted to odds ratios and the hazard ratio reported in one trial was assumed to represent the risk ratio following the proportional hazards assumption. We compiled crude ORs or absolute mean differences using a random effects meta-analysis and adjusted ORs (or ORs computed from RCTs) using an inverse variable random effects meta-analysis. Heterogeneity was assessed using a chi-square test ($p < 0.1$) and the $I^2$ test (>50%). Analyses were conducted in Review Manager 5.3 [12].

## Results

Our literature review identified 558 potential articles for evaluation. Of these, 19 fulfilled review eligibility criteria and were included in the analysis [13–31] (Fig. 1). One study contributed to two analyses of different, non-overlapping periods in the study [24]. The studies comprised a total of 3973 patients, all adults, with a study mean or median age between 51 and 71 years. Eight studies enrolled patients with bacteria, two addressed severe sepsis or septic shock in the ICU and 14 studies enrolled patients with pneumonia (Table 1). Four studies included community-acquired infections only [14,17,25,29], eight included exclusively hospital-acquired infections [13,19,22,23,27,28,30,31] and six studies included both [15,18,20,21,24,26]. De-escalation was performed according to MDI in all of the included studies and was defined variably (see Supplementary material, Table S2): ten defined de-escalation by narrowing the spectrum and 13 by stopping one or more drugs of a combination. In five studies on hospital-acquired pneumonia de-escalation was performed from a broad-spectrum empirical regimen [13,19,22,30,31]. All-cause mortality was reported in all studies. The majority (11) reported 28- to 30-day all-cause mortality, whereas the others reported on in-hospital, in-ICU, 90 days [26] or in relation to completion of antibiotic treatment [13].

### *Risk of bias assessment*

Three trials were randomized [17,22,26], whereas the remainder were observational studies. The RCTs did not score low risk of bias for all items, one trial failing to match groups for important confounders [26] and two open-label trials did not report on co-interventions [17,26] (Fig. 2). Overall, 11/19 studies reported on pre-defined important confounders (age, renal function baseline