Impact of antimicrobial de-escalation on mortality: a literature review of study methodology and recommendations for observational studies

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Impact of antimicrobial de-escalation on mortality: a literature review of study methodology and recommendations for observational studies

Inger Van Heijl [a,b], Valentijn A. Schweitzer [b], Paul D. Van Der Linden [a], Marc J.M. Bonten[b,c] and Cornelis H. Van Werkhoven [b]

aDepartment of Clinical Pharmacy, Tergooi Hospital, Hilversum/Blaricum, The Netherlands; bJulius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands; cDepartment of Medical Microbiology, University Medical Centre Utrecht, Utrecht, The Netherlands

ABSTRACT

Introduction: The safety of de-escalation of empirical antimicrobial therapy is largely based on observational data, with many reporting protective effects on mortality. As there is no plausible biological explanation for this phenomenon, it is most probably caused by confounding by indication.
Areas covered: We evaluate the methodology used in observational studies on the effects of de-escalation of antimicrobial therapy on mortality. We extended the search for a recent systematic review and identified 52 observational studies. The heterogeneity in study populations was large. Only 19 (36.5%) studies adjusted for confounders and four (8%) adjusted for clinical stability during admission, all as a fixed variable. All studies had methodological limitations, most importantly the lack of adjustment for clinical stability, causing bias toward a protective effect.
Expert opinion: The methodology used in studies evaluating the effects of de-escalation on mortality requires improvement. We depicted all potential confounders in a directed acyclic graph to illustrate all associations between exposure (de-escalation) and outcome (mortality). Clinical stability is an important confounder in this association and should be modeled as a time-varying variable. We recommend to include de-escalation as time-varying exposure and use inverse-probability-of-treatment weighted marginal structural models to properly adjust for time-varying confounders.

1. Introduction

Empirical antimicrobial therapy of suspected bacterial infections often includes broad-spectrum antibiotics to ensure coverage of multiple potential pathogens. According to antimicrobial stewardship principles, empirical treatment should be de-escalated when possible to reduce antimicrobial pressure and antimicrobial resistance [1]. In a systematic review, de-escalation of empirical antimicrobial therapy compared to the continuation of empirical treatment was associated with a relative risk reduction of 56% (95% CI 34%-70%) for mortality, which was based on one randomized controlled trial (RCT) and 19 observational studies [2]. However, the RCT [3] demonstrated no difference in mortality between de-escalation and continuation. A total of 116 patients with severe sepsis admitted to an ICU were included and de-escalation was not statistically significantly associated with mortality with an adjusted HR of 1.7 (95% CI 0.79–3.49, p = 0.18) [3]. The trial had relatively small sample sizes resulting in imprecise effect estimates. Therefore, the evidence of safety of de-escalation is largely based on observational data reporting a reduction in mortality. We postulate that the mortality reduction based on interpretation of observational data could reflect a true causal effect if narrow-spectrum antibiotics are more effective or safer than broad-spectrum antibiotics, i.e. if they cause less (ultimately

fatal) side effects. We consider the first hypothesis (more effective) unlikely because generally the antimicrobial spectrum and activity of narrow-spectrum antibiotics are entirely included in the spectrum and activity of broad-spectrum antibiotics. For specific pathogens, narrow-spectrum antibiotics can potentially be more effective than broad-spectrum antibiotics, such as penicillin for *Staphylococcus aureus* infections although the level of evidence is low [4]. However, this is not likely to result in a mortality reduction of 56% as seen in the aforementioned systematic review. The second (fewer side effects) might hold for less severe outcomes such as duration of hospitalization or complications such as *Clostridioides difficile* infection, but is considered unlikely or of indiscernible size for mortality. If not causal, the observed mortality reduction may reflect residual confounding by indication, meaning that, even after adjustment for measured confounders, the prognosis of those in whom antimicrobial therapy is de-escalated is more favorable compared to those continuing or escalating the antibiotic treatment due to differences in unmeasured patient characteristics.

In this paper, we review the methodology used in observational studies on the effect of de-escalation of empirical antimicrobial therapy on mortality, followed by an expose of causal effects that need to be taken into account in the

Table 1. Study populations.

Study population	N = 52 (%)
Community-acquired pneumonia	5 (9.6)
Hospital-acquired or ventilator-associated pneumonia	12 (23.1)
Healthcare-associated pneumonia	1 (1.9)
Pneumonia (acquisition not specified)	4 (7.7)
Urinary tract infection	2 (3.8)
Intra-abdominal infections	1 (1.9)
Skin infections	1 (1.9)
Bloodstream infections	10 (19.2)
Severe sepsis and/or septic shock	5 (9.6)
Critically ill patients	2 (3.8)
Neutropenic fever	2 (3.8)
Any infection in severe aplastic anemia patients	1 (1.9)
Any infections treated with specific antibiotic classes	6 (11.5)

study of de-escalation. Finally, we provide recommendations for the design and analysis of antibiotic de-escalation studies.

2. General characteristics of observational studies evaluating de-escalation and mortality

A PubMed search was done until October 2019 to find all studies evaluating the effect of de-escalation of empirical antimicrobial therapy on mortality. We used the search strategy described by Schuts et al. [2] (Appendix 1). In addition, we checked all other available systematic reviews and meta-analyses for missed publications [5–9]. We selected papers evaluating the effect of de-escalation on mortality (as primary or secondary outcome), which yielded 52 observational studies [10–61]. The heterogeneity in study populations between the studies was large (Table 1). Eighteen studies (34.6%) were done in an ICU setting, the remaining in a non-ICU hospital setting.

A retrospective design was used in 34 (65.4%) of the studies. The majority was performed in a single center (n = 42; 80.8%). Mortality differences were reported as crude estimates in 33 (63.5%) studies. In the other studies multivariable analyses (n = 19; 36.5%) were used to adjust for potential confounders;

11 (21.1%) used logistic regression, 1 (1.9%) used Poisson regression and 7 (13.5%) used Cox proportional hazard regression. The effect estimates obtained in these multivariable analyses are depicted in Figure 1, clustered by study population. Studies that did not present an OR, HR, or RR in their article [45,50,56] are not included. The confidence intervals between the different studies per study population overlap largely and the point estimates are mostly in favor of de-escalation. This means that the individual studies yield comparable results. In the next section, we will discuss the limitations in the methodology used in observational de-escalation studies.

3. Methodological limitations in de-escalation studies

Several limitations were identified in the methodology of observational studies regarding the association between de-escalation of empirical antimicrobial therapy on mortality after evaluating
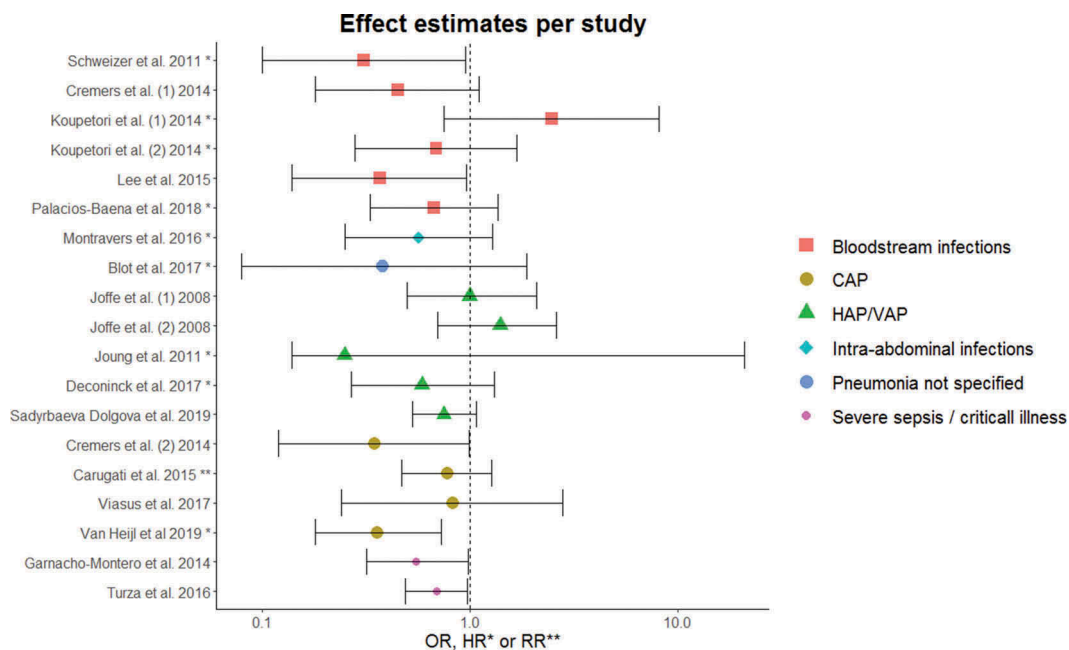
Figure 1. Adjusted effect estimates for the association between de-escalation of empirical antimicrobial therapy and mortality. Koupetori (1) and (2) are effect estimates from different time periods (resp. 2006–2009 and 2010–2013). Joffe (1) and (2) are effect estimates from culture-positive and culture-negative patients, respectively. Joung et al. reported an effect estimate for non-de-escalation; we calculated the inverse effect estimate for de-escalation which results in an aHR of 0.25 (95% CI 0.14–21). Note that this confidence interval seems incorrect, as it is asymmetric on a log scale, which also was the case for the reported confidence interval. We contacted the corresponding author to verify this; however, we received no response.

the abovementioned studies. For 33 studies solely reporting crude estimates on mortality, we confine ourselves by stating that they suffer from severe confounding by indication and are of no use for a causal inference. For the remaining we discuss studies that adjusted for potential confounders (N = 19) [15,20,21,27,28,31,33,34,40,43,45–47,50,53,56,57,60,61]. For the purpose of this review, we focus on three main issues: (1) lack of adjustment for the patients' clinical course, (2) modeling de-escalation as a fixed variable, and (3) modeling time-varying confounders as fixed variables.

All studies adjusted for baseline characteristics as potential confounders, which are measured from the time point the patient is enrolled in the study. In Table 2 we have summarized all the potential confounders used in the studies, categorized by type of baseline factor.

Although these studies used multiple baseline characteristics as potential confounders, this is probably insufficient to adjust for confounding by indication. Our previous study, which aimed to quantify the potential confounding effect of clinical stability during hospital stay on the estimated impact of de-escalation on mortality in patients with CAP, suggests that clinical stability in de-escalated patients is likely to explain the lower mortality observed in patients after de-escalation [61]. This was done by simulating a variable representing clinical stability on day 3, using data on prevalence and associations with mortality from the literature. Therefore, it is important to not only include confounders measured at the time of admission, but also confounders that occur during hospital stay. This is intuitive because the decision to de-

escalate is made several days after initiation of empirical therapy and is influenced by clinical stability during hospital stay and available culture results. As clinical stability is also a strong prognostic factor, not including this in the analysis inevitably results in biased effect estimates in favor of de-escalation. Only four studies adjusted for clinical stability or a similar variable indicating the clinical course up to the time of de-escalation [20,28,40,50] (Table 2). Three of these studies included patients admitted to an ICU; Joung et al. included APACHE II score (used in ICU [62]) and modified CPIS (used for VAP [63]) at day 5 [20]. Garnacho Montero et al. included SOFA score (used in ICU [64]) at culture result day [28] and Montravers included SOFA score at day 3 [40]. Parameters to establish clinical stability during admission are measured (and registered) more regularly in ICU than in non-ICU populations. So, it is probably more convenient to collect such data and to adjust for variables representing clinical stability during admission in ICU populations. The fourth de-escalation study that included a variable predictive for the clinical course was performed in a population with and without admission at ICU, and included PBS (used in bloodstream infections [65]) at day 3 after the start of antibiotic treatment [50]. Although there are specific criteria for clinical stability in patients with CAP [66], which have been used in studies evaluating iv to oral switches [67,68], these have not been used in de-escalation studies.

Another limitation in observational de-escalation studies is that de-escalation is analyzed as a time-fixed variable, which applies to all 19 studies that corrected for confounders. For

Table 2. Summary of all potential confounders used in individual studies.

Variable group	Variables used	Frequency (n = 19)	Reference
Baseline disease severity	APACHE II score, CPIS score, SOFA score, PSI score, A-DROP, Pitt bacteremia score, CPIS score, ICU admission before onset, mechanical ventilation before onset, presence of sepsis or septic shock.	17 (90%)	[19,20,27,30,32,33,39,42,44–46,49,52,55,56,59,60]
Comorbidities	No. of comorbidities, Charlson index, McCabe classification, or specific type of comorbidity.	14 (74%)	[14,20,26,30,33,42,44,45,49,52,55,56,59,60]
Demographics	Age, gender, BMI, previous use of antibiotics, previous hospitalization, nursing home residence.	12 (63%)	[14,20,27,39,44–46,52,55,56,59,60]
Antibiotic therapy	(In)appropriateness of initial therapy, time to appropriate therapy, monotherapy vs. combination therapy, specific type (or rank) of antibiotic therapy.	11 (58%)	[19,20,26,27,32,42,44,46,55,59,60]
Type of infection	Acquisition; Community- or nosocomial or specific focus, timing of onset.	8 (42%)	[20,27,42,45,52,55,56,59]
Hospital or department of admission	Type of hospital/department.	5 (26%)	[26,27,44,56,59]
Disease severity during admission	Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU day 5, modified Clinical pulmonary infection score (CPIS) at ICU day 5, sequential organ failure assessment (SOFA) score at culture result day, SOFA score at ICU day 3, Pitt bacteremia score (PBS) at day 3 after start of antibiotic treatment.	4 (21%)	[19,27,39,49]
Laboratory results	Creatinine, hemoglobin, pH, blood urea nitrogen, sodium, glucose, hematocrit, partial pressure of oxygen	3 (16%)	[33,45,60]
Timing of admission	Certain year, season or day (week/weekend).	3 (16%)	[26,44,60]
Health behavior	Smoking	2 (11%)	[44,60]
Medical imaging	Presence of pleural effusion	2 (11%)	[44,60]
Medication use	Use of specific medication or other therapies; steroids, blood transfusion, albumin, immunoglobulins, NSAIDs, Proton pump inhibitors/H_2 receptor antagonists, protease inhibitors, anticoagulants.	2 (11%)	[42,44]
Signs and symptoms	Tachycardia, altered mental status, respiratory rate, systolic blood pressure, temperature, heart rate	2 (11%)	[52,60]
Other	Specific surgery	1 (5%)	[39]
	Pneumococcal vaccination	1 (5%)	[52]
	Injury Severity Score (ISS)	1 (5%)	[55]
	Invasive procedures	1 (5%)	[59]

* Sorted from most to least commonly used baseline factors as confounders.

example, in one patient, de-escalation occurs at day 3 of hospital admission, and then survival time until day 3 is incorrectly counted as survival time for the de-escalation group, when in fact these patients were not exposed to de-escalation until day 3. Not adjusting for time-varying exposures results in immortal time bias (also termed time-dependent bias) [69] in favor of the de-escalated group. This can be intuitively understood as too much survival time being incorrectly classified as survival time for de-escalation. In only one study de-escalation was included as a time-varying variable in the analysis, but unfortunately without adjustment for confounders [32].

A third common limitation is analyzing all possible confounders as time-fixed variables. Some confounders, such as clinical stability, differ over time with different trajectories for different patients. Such variables, when analyzed as time-fixed confounders, lead to biased estimates, as explained in the next sections. The four studies that correct for a variable indicating the clinical course up to the time of de-escalation mentioned above [20,28,40,50] have included this variable in a time-varying way. For example, in the study from Montravers et al. [40], clinical improvement is defined as a > 2 points decrease in SOFA score on day 3 compared to day zero or a SOFA score of 0 points. Patients that died or were discharged alive within the first 3 days were excluded from the analysis. In the multivariable analysis, clinical improvement was included as a confounder. De-escalation was analyzed after 48 h. The difference in SOFA score was assessed at day 3, which is usually the day when empirical therapy is evaluated and when culture results are available, and most de-escalation decisions are taken. This approach adjusts for clinical improvement; however, still clinical stability is reached at different points in time for individual patients so including it as a real time-varying confounder will be more appropriate. This causes collider stratification bias, i.e. adjusting for a variable that may occur after escalation, which we will elaborate on in section 4.

In summary, all studies evaluating the effects of de-escalation have methodological limitations, most importantly the lack of adjustment for the clinical course, ignoring time-varying exposure, and ignoring the time-varying nature of some confounders. In the next section, we provide a proposal to study the causal effect of de-escalation on mortality.

4. Expert opinion

To study the causal effect of de-escalation on mortality we first need to consider all variables that might influence this association. We will first propose causal diagrams, also called directed acyclic graphs (DAGs) visualizing the causal associations, after which we will provide recommendations for future studies with observational data.

4.1. Proposal of a DAG for studying the causal effect of de-escalation on mortality

In observational data, it is important to adjust for confounding. The preferred method to identify confounders is to use prior knowledge. In recent years, DAGs have been increasingly used to identify confounders (i.e. common causes of the exposure and the outcome) [70,71]. In Figure 2 a simple DAG is depicted on the

relation between exposure and outcome with one confounder. All DAGs consist of variables connected by arrows that represent direct causal effects (which can denote positive or negative associations) and they are acyclic because arrows always go in one direction and a causal path is not allowed to go back to its origin [70]. Not adjusting for confounder C, in Figure 2, will bias the causal association between exposure E and outcome O. This pathway from E to O through C is also called a 'backdoor path' which is a non-causal pathway. When adjusting for confounder C this 'backdoor path' is closed (and so is the non-causal pathway). If both arrows from C to E and from C to O were directed to C, then C is not a confounder but a collider (Figure 3), which is a variable caused by both exposure (E) and outcome (O). When adjusting for a collider, a 'backdoor path' (or a non-causal pathway) is *introduced* rather than closed, which causes bias rather than to solve it. It is therefore essential to distinguish confounders from colliders, for example, with a DAG, because it is important to adjust for confounders and not for colliders. Of note, a collider can also exist through a proxy or precursor of the outcome as we will see later. Finally, in Figure 4 the effect of exposure (E) can be mediated through an intermediate (M) on outcome (O). Adjustment for intermediates is not necessary; there is no 'backdoor path' because M is on the causal pathway of E to O. Researcher may wish to adjust for intermediates if they are explicitly interested in the relative contribution of distinguished causal pathways, rather than estimation of the main causal effect, but this is beyond the scope of the current paper.
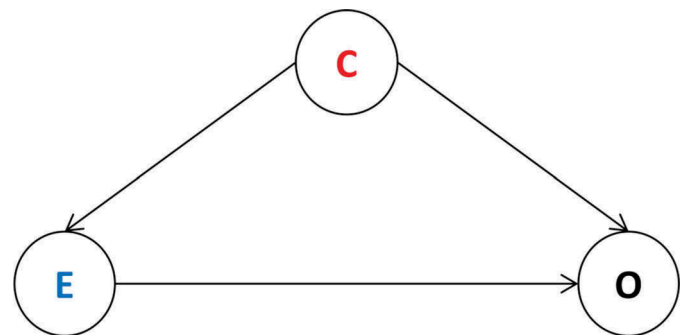
Figure 2. An example of a causal diagram (or DAG). E = exposure, O = outcome, and C = confounder. For example, in the relationship between alcohol consumption (E) and lung cancer (O), smoking (C) is highly correlated with alcohol consumption and also a cause of lung cancer.
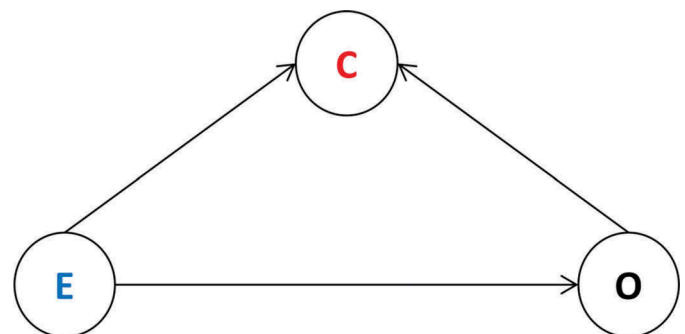

Figure 3. DAG with a collider. E = exposure, O = outcome, and C = collider. For example, in the relationship between obesity (E) and cardiovascular disease (O), there are also other risk factors for cardiovascular disease (C). E and C both are causes of cardiovascular disease, which makes C a collider.
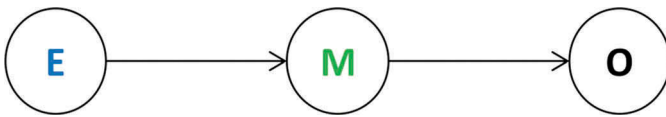
Figure 4. DAG with an intermediate. E = exposure, O = outcome, and M = intermediate. For example, statins (E) reduce cholesterol in the blood (M), and thereby lower the risk for a stroke (O).

For estimating the causal relationship between de-escalation of empirical therapy and mortality, we consider the following aspects essential: (1) the exposure de-escalation is time-varying, i.e. exposure of individual patients is set at different points in time and (2) confounders can be time-fixed or time-varying. Examples of time-fixed confounders are patients' comorbidity and severity of disease at presentation (more examples are presented in Table 2). Examples of time-varying confounders are culture results and clinical stability. After a certain time period, culture results become available (pathogen detection) and clinical stability can be reached; the values of these variables change over time and influence the decision for de-escalation. In Figure 5 we present the DAG in which all important factors involved in the association of de-escalation of empirical therapy on mortality are depicted. E is exposure, which is the change of empirical antimicrobial therapy; either de-escalation, escalation, or continuation. Exposure is time-varying presented as E_1 (exposure day 1) and E_t (exposure day t), which occurs after the start of empirical therapy (A) at the day of admission. Also, exposure (E) influences future clinical stability (C) and is associated with outcome O. O is the outcome which is mortality. The other variables in this diagram are fixed or time-varying confounders in the association between exposure E and outcome O. B is a collection of time-fixed confounders, such as comorbidities and disease severity. B influences empirical therapy (A), the unknown pathogen (P_0), clinical stability at day 0 (C_0), and mortality (O). B is very disease specific and researchers should take efforts to identify all variables relevant to the disease and setting

of investigation prior to commencing the study. Both P and C are time-varying confounders, as mentioned above, representing pathogen detection and clinical stability. P_0 is the unknown pathogen and P_1 and P_t are day 1 and day t, when the culture results could be available and the pathogen is possibly detected. P_0 influences clinical stability at day 0 (C_0) and mortality (O). P_1 and P_t influence exposure (E) by the decision to de-escalate, escalate, or continue treatment. C_0 is clinical stability at the day of admission, C_1 and C_t are clinical stability determined on day 1 and day t. Clinical stability (C) influences mortality (O). For simplification we only used E_1, P_1, and C_1 measured at day 1, all other admission days are presented as E_t, P_t, and C_t. There is one important issue to add to the already complicated causal relationship between de-escalation (E) and mortality (O), which is clinical stability not only being a time-varying confounder, but also a mediator and collider in the association between de-escalation (E) and mortality (O). Firstly, it is a confounder because it is a cause of future exposure (E) (the decision to de-escalate or not) and is also a prognostic factor for the outcome (O) mortality. For example, in the figure C_1 influences E_1 and O, either directly or through C_t. Secondly, clinical stability at a certain day (C_t) is influenced by past exposure (E_1; de-escalation or continuation of empirical therapy) and is a risk factor for mortality (O); it is, therefore, an intermediate between E1 and O. At the same time, C_t is also influenced by clinical stability from the previous day (C_1) and is, therefore, also a collider.

The tackle these complicated relationships we provide methodological recommendations for future studies for how to deal with this and other important limitations in the next section.

4.2. Methodological recommendations for observational (de-escalation) studies

For future observational studies, we provide the following recommendations.
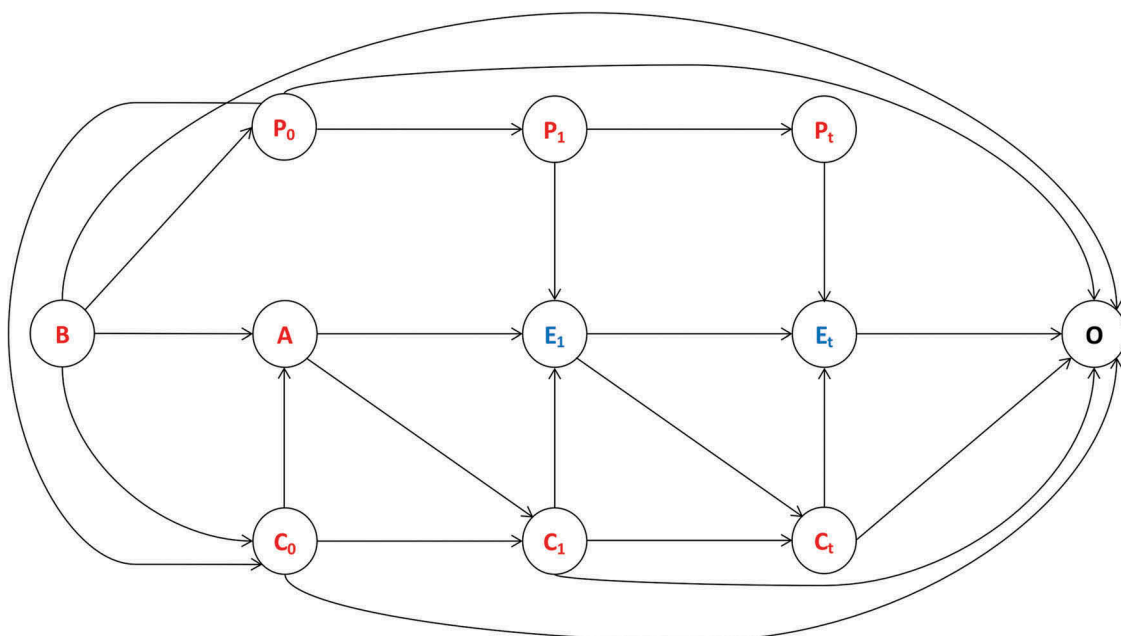
Figure 5. A directed acyclic graph (DAG) for the causal relationship between de-escalation of empirical antimicrobial therapy and mortality. Exposure (E) = change or continuing antimicrobial therapy. Outcome (O) = mortality. Time-fixed confounder (A) = empirical therapy. Other time-fixed confounders (B) = e.g. comorbidities and disease severity. Time-varying confounders (P) = pathogen detection and (C) = clinical stability. The numbers 0 and 1 are day 0 and day 1, all other admission days are presented as t.

First, the exposure variable (de-escalation) has to be included as a time-varying variable to prevent immortal time bias (also called time-dependent bias). The difference between time-fixed and time-varying exposures has been nicely explained by Munoz-Price et al. Antibiotic exposure is often available in patients' medical records and can, therefore, be determined on a daily basis. Cox proportional hazard models can be used to adjust for time-varying exposures [69].

Second, in our opinion, important fixed confounders to consider in the analyses are patient demographics, disease severity score, comorbidities, and (appropriate) empirical antimicrobial therapy, all measured at baseline. These are based on our summary in Table 2 and can all be considered as common causes of exposure and outcome. Also, source control (which was never included in the observational studies) should be considered. Still, it is the responsibility of the researcher to choose the appropriate confounders. Some of these will be specific for different infectious diseases. For example, source control can be relevant for abdominal infections and pneumonia but not for urinary tract infections. It is beyond the scope of this paper to elaborate further on this topic. Drawing a causal diagram can be extremely helpful to determine which variables are to be considered a confounder; however, a limitation of DAGs is that they cannot easily visualize interactions, which can be a relevant part of causal inference.

Thirdly, it is inappropriate to exclusively include confounders measured at the time of admission. Confounders that change over time, and are both associated with the outcome, and influence the decision for de-escalation, such as clinical stability, should also be included. Clinical stability, as a concept, is not easily measured. To the best of our knowledge, there are criteria defined by the Infectious Diseases Society of America (IDSA) for non-ICU hospitalized patients with CAP but not for other populations [72]. Clinical stability in CAP patients is reached when temperature ≤37.8℃, heart rate ≤100 beats/min, respiratory rate ≤24 breaths/min, systolic blood pressure ≥90 mm Hg, arterial oxygen saturation ≥90%, or pO_2 ≥60 mm Hg on room air. For the switch to oral treatment, two variables are added: ability to maintain oral intake and normalized mental status. For disease entities where such criteria are not established, researchers should determine criteria for clinical stability. The availability of accepted criteria does not exclude the researchers' responsibility to critically consider which other factors (e.g. oral food intake) determine the decision for de-escalation, as these can vary locally. Clinical stability should be modeled as a time-varying confounder because individual patients become clinical stable at different time points.

A complicating factor is that clinical stability is influenced by past exposure; de-escalation or continuation of empirical antimicrobial therapy may influence the clinical stability of a patient during the subsequent hospital stay, for example, by clinical deterioration after de-escalation. As a result, conventional Cox proportional hazard models may provide biased estimates caused by adjustment for an intermediate and a collider (collider-stratification bias), as explained in the previous section [73,74]. For time-varying confounders that are influenced by past exposure, G-methods are proposed [75]. The G-methods comprise three statistical causal methods: G-computation algorithm formula, G estimation of a structural nested model, and inverse-probability-of-treatment weighted (IPTW) marginal structural models (MSM) [75]. Recently, statistical software has also become available for other methods, such as the 'gfoRmula' and 'DTReg' package in R. For IPTW MSM, statistical software is available [76] and the model will provide correct estimates for associations between de-escalation of empirical antimicrobial therapy and mortality, provided that the model assumptions are met. MSM was first introduced by Robins and Hernán [74], interested readers may also consider the more accessible introductions to these models [76–78], or the more technical tutorial of Daniel et al. [79]. Space prohibits an elaborate discussion on these model assumptions.

Ideally, clinical stability is determined daily until patients are not at risk for the exposure (de-escalation) anymore, which is after the last day of antibiotic therapy (or after hospital discharge or death). A disadvantage of current MSM implementations in statistical software is that exposure can occur only once, and the model cannot incorporate escalation after prior de-escalation (it could be done, but you have to do this by hand, requiring statistical expertise). Alternatively, researchers might simply report the crude proportion of escalations occurring after de-escalation. Unfortunately, in real-life situations, missing data in the daily measurements of clinical stability may occur, for which in most circumstances multiple imputation is the recommended approach.

Obviously, the better alternative to avoid confounding by indication is a trial in which randomization for de-escalation or continuation is performed when patients are clinically stable and/or culture results are known. However, clinical trials are time-consuming and expensive, not all indications can be studied in a trial, and not all at the same time, making observational studies, when performed correctly and with the right data, valuable alternatives until trial data become available. When planning a randomized trial, such observational studies can be useful to generate hypotheses and inform the design of the trial.

4.3. Conclusion

The current evidence base on the safety of de-escalation of empirical antimicrobial therapy contains one RCT and 52 observational studies that suffer from various methodological limitations. Future observational studies could be improved by using advanced statistical analyses such as IPTW MSM to adjust for the time-varying exposure of de-escalation and the time-varying confounding effect of clinical stability during hospital stay.

4.4. Five-year view

In the next 5 years, researchers and clinicians should establish a standardized definition for de-escalation and clinical stability for specific infections, particularly outside the ICU, which should be developed as a continuous score rather than a binary variable. Also, an important goal is to determine the causal effect of de-escalation on mortality either by well-designed RCTs or by observational studies using appropriate methodology, such as MSM.

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Declaration of Interest

Reviewer Disclosures

ORCID

Inger Van Heijl http://orcid.org/0000-0002-0160-715X
Valentijn A. Schweitzer http://orcid.org/0000-0001-9640-7291
Paul D. Van Der Linden http://orcid.org/0000-0003-1564-2041
Cornelis H. Van Werkhoven http://orcid.org/0000-0002-0626-4635

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