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EDITORIAL COMMENTARY

Antimicrobial De-escalation: What's in a Name?

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Keywords. de-escalation; antibiotics; resistance.

In this issue of *Clinical Infectious Diseases,* Tabah et al [1] performed a systematic review of antimicrobial de-escalation (ADE) focusing on the definition, determinants of clinical outcomes, and antimicrobial resistance. They strictly selected studies that defined ADE as a narrowing or "streamlining" of the initial empiric antimicrobial regimen. They concluded that ADE was more commonly performed when broad-spectrum and/or appropriate initial therapy was prescribed, when multiple antimicrobial agents were used, and in the absence of multidrug-resistant (MDR) pathogens. Overall, ADE had a protective effect on mortality, largely because the determinants of ADE are markers for good clinical responses to the empirically prescribed antibiotics. These investigators also observed that none of the studies reviewed were designed to assess the impact of ADE on subsequent emergence of resistance.

We should not be surprised by the findings of this analysis. ADE is simply a clinical approach to empiric antibiotic treatment that attempts to balance the need for appropriate initial therapy with the need to limit unnecessary antimicrobial exposure to curtail the emergence of resistance [2]. When specific risk factors for antibiotic resistance are identified in individuals with serious or life-threatening infection—for example, patients at risk for healthcare-associated pneumonia in the intensive care unit—broad-spectrum antimicrobials are typically recommended [3].

Historically, the goal for clinicians has been to understand local patient characteristics that increase the risk for infection due to MDR pathogens above a threshold where broader empiric antibiotics would be needed. However, in the face of rising resistance the focus has shifted in many centers toward excluding patients at minimal risk for MDR bacteria, thus limiting unnecessary use of broad-spectrum agents. The basic problem with these risk-based approaches is that investigators attempting to validate them have demonstrated limited precision for these models when applied to independent populations, indicating again that local ecology and case mix drive MDR rates in different regions and countries [4–6]. Therefore, the currently used risk estimates for MDR infection will always result in the overtreatment or undertreatment of significant numbers of patients.

Another problem with using the term "antimicrobial de-escalation" is that it focuses the clinician on simply narrowing the antibiotic regimen. As Tabah et al [1] have shown, there is no good evidence that ADE directly results in less emergence of resistance. The duration of antibiotic therapy is known to be an important determinant of antimicrobial resistance and is not intrinsically part of the ADE definition. Several investigations of ventilator-associated pneumonia (VAP) have demonstrated that courses of antibiotic therapy beyond 7 days result in greater subsequent colonization or infection with MDR pathogens [7, 8]. However, even a few days of antibiotic exposure can promote collateral damage by altering intestinal flora in favor of colonization with MDR bacteria [9]. Short courses of antibiotic therapy have been shown to be effective in a wide spectrum of infections [10], yet it is also important to recognize that short courses of antibiotics are most likely to be clinically effective when the selected agents are appropriate for the causative pathogen(s) based on susceptibility testing [8] and can result in treatment failures when not dosed adequately owing to patient factors, such as augmented renal clearance [11]. Treatment failures resulting from inadequate antibiotic dosing has emerged as an important problem affecting critically ill infected patients [12–14].

The dosing of antibiotics is not generally considered to be part of ADE. Conventional antibiotic doses as recommended in package inserts are unlikely to optimize patient outcomes or suppress the emergence of resistance in critically ill patients because of extensive pharmacokinetic variability and altered pharmacodynamics [15–17]. Consequently, individualization of antibiotic dosages with therapeutic drug monitoring (TDM) has been advocated. Unfortunately, it is still rare to use TDM for antimicrobial agents other than vancomycin, aminoglycosides, and voriconazole [18]. TDM for β-lactams, carbapenems, ciprofloxacin, and linezolid can be accomplished by several methods to optimize delivery and minimize toxicity [19]. Recent studies have demonstrated the ability of TDM to optimize antibiotic dose adjustments in the setting of continuous renal replacement therapy due to excess serum antibiotic

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concentrations [20] as well as during treatment of MDR *Pseudomonas aeruginosa* with fluctuating renal function [21]. It seems logical that future development of cost-effective TDM technologies should be an important focus of attention.

A strategy for circumventing the need for TDM is to develop novel platforms for antibiotic delivery to the infection site in order to maximize therapeutic efficacy and minimize systemic toxicity. The clearest example of this is the administration of aerosolized antibiotics for VAP. Clinical failure in the treatment of VAP is common and often attributable to the high prevalence of MDR pathogens and poor pulmonary perfusion of intravenous antibiotics [22, 23]. The lung is also one of the major sites for emergence of MDR organisms, in part because of longer required durations of antibiotic therapy, especially for MDR nonfermenting gram-negative bacilli [8, 11].

Palmer and Smaldone [24] demonstrated that aerosolized antibiotics were successful in eradicating existing MDR bacteria and reducing the emergence of subsequent resistance from systemically administered antibiotics. Advances in the design of aerosol generators have allowed for the delivery of high antibiotic concentrations into the lung. Niederman et al [25] studied an investigational drug-device combination (BAY41-6551) of amikacin formulated for inhalation, using a primary end point 25 times the minimum inhibitory concentration of 256 μg/mL, representing a tracheal aspirate amikacin maximal concentration ≥6400 μg/mL. Response rates for this end point were 50% for amikacin delivered every 12 hours. Similarly, the administration of 300 mg/120 mg amikacin/fosfomycin combination to mechanically ventilated adults using an investigational vibrating mesh nebulizer achieved tracheal aspirate amikacin concentrations of 12 390 μg/g and fosfomycin concentrations of 6174 μg/g [26]. The results of ongoing randomized trials in VAP are eagerly awaited.

Conventional microbiologic procedures typically require several days for isolation, identification, and antimicrobial susceptibility testing of bacteria from clinical samples delaying ADE. Several rapid microbiologic diagnostic platforms (RMDPs) have been introduced and evaluated, including the LightCycler SeptiFast Test (Roche), peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) (AdvanDx), matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) (VITEK MS; bioMérieux), polymerase chain reaction (PCR) combined with electrospray ionization MS (PCR/ESI-MS) (Abbott Ibis Biosciences), and DNA-based microarray platforms (Prove-it sepsis assay [Mobidiag] and the Verigene gram-positive blood culture assay [Nanosphere]). In addition, automated microscopy methods such as the ID/AST system (Accelerate Diagnostics) are in development, using both genomic and phenotypic technologies to provide rapid pathogen identification and antimicrobial susceptibilities.

Clinical studies have demonstrated the potential utility of RMDPs to advance the goals of ADE. Huang et al [27] performed a quasi-experimental study to analyze the impact of MALDI-TOF MS in conjunction with an antimicrobial stewardship program (ASP) in patients with bloodstream infections. The use of MALDI-TOF MS significantly decreased time to organism identification and improved time to effective antibiotic therapy. The mortality rate, length of intensive care unit stay, and rate of recurrent bacteremia were significantly lower with the intervention. Similarly, the PCR-based GeneXpert methicillin-resistant *Staphylococcus aureus* and *S. aureus* (MRSA/SA) diagnostic platform (Cepheid) was studied, demonstrating that for methicillin-susceptible *Staphylococcus aureus* bacteremia the mean time to initiation of appropriate therapy decreased from 49.8 to 5.2 hours and the duration of unnecessary drug therapy was reduced by 61 hours per patient [28].

Perez et al [29] used MALDI-TOF MS to develop a rapid ASP and found that hospital lengths of stay and hospital costs were significantly reduced with this intervention. Other studies have confirmed the potential utility of these techniques [30–32]. However, current limitations in the application of RMDPs still need to be overcome. A recent study comparing PCR/ESI-MS and molecular beacons found isolates of *Klebsiella pneumoniae* that did not have detectable carbapenemase genes yet were carbapenem resistant by susceptibility testing [33]. They also observed that for piperacillin-tazobactam the probability of accurately identifying resistance was only approximately 0.80.

In summary, we should consider ADE to be part of broader ASPs. The ultimate rationale or justification for the use of ADE and ASPs in the intensive care unit is that antibiotic therapy affects not only the treated patient but also patients in the surrounding environment by promoting resistance. However, we need to continue to develop more cost-effective and widely applicable tools that facilitate clinicians' and hospitals' ability to successfully carry out these important processes.

Notes

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REVIEW ARTICLE

A Systematic Review of the Definitions, Determinants, and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit

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Antimicrobial de-escalation (ADE) is a strategy to reduce the spectrum of antimicrobials and aims to prevent the emergence of bacterial resistance. We present a systematic review describing the definitions, determinants and outcomes associated with ADE. We included 2 randomized controlled trials and 12 cohort studies. There was considerable variability in the definition of ADE. It was more frequently performed in patients with broad-spectrum and/or appropriate antimicrobial therapy ($P = .05$ to $.002$), when more agents were used ($P = .002$), and in the absence of multidrug-resistant pathogens ($P < .05$). Where investigated, lower or improving severity scores were consistently associated with ADE ($P = .04$ to $<.001$). The pooled effect of ADE on mortality is protective (relative risk, 0.68; 95% confidence interval, .52–.88). Because the determinants of ADE are markers of clinical improvement and/or of lower risk of treatment failure this effect on mortality cannot be retained as evidence. None of the studies were designed to investigate the effect of ADE on antimicrobial resistance.

Keywords. de-escalation; stewardship; streamlining; resistance.

Antimicrobial de-escalation (ADE) of antimicrobial therapy is a strategy proposed to allow for the rational use of broad-spectrum antimicrobial therapy as the empiric treatment for infections and minimize the overall exposure to these broad-spectrum agents. The need for prompt, effective antimicrobial therapy for patients with known or suspected infections is widely accepted. This principle leads to the use of very broad-spectrum antimicrobial therapy to increase the odds that all suspected potential pathogens are adequately treated. However, the potential drawback is selection of multidrug-resistant (MDR) organisms.

ADE is widely recommended in the management of antimicrobial therapy in intensive care unit (ICU) patients [1–3]. The Surviving Sepsis Campaign guidelines [2] describe and recommend the process for selecting antimicrobial therapy as (1) commencement of antimicrobials within the first hour, (2a) antimicrobial therapy broad enough to cover all likely pathogens, and (2b) daily reassessment for potential ADE.

A recent Cochrane review found "no adequate, direct evidence as to whether ADE of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis or septic shock" [4]. With this background, we performed a systematic search for evidence supporting ADE in ICUs. Our aims were to review and analyze (1) the definitions used for ADE, (2) the determinants and factors associated with ADE, (3) the effects of ADE on outcomes, and (4) the impact of the strategy on antimicrobial usage, bacterial resistance and costs.

METHODS

Methods of the analysis and inclusion criteria were specified in advance and registered through PROSPERO (CRD42013006944; registered 23 December 2013).

Search Strategy

A search of MEDLINE (1966–2014), EMBASE (all years), and the Cochrane library was conducted to identify suitable publications using the following search terms: (*antibiotics* OR *antimicrobials* OR *antibacterials*) AND (*de-escalation* OR *de-escalate* OR *narrowing* OR *step-down* OR *stepdown* OR *streamline*) AND (*ICU* OR *intensive care* OR *critical care* OR *septic shock* OR *severe sepsis* OR *sepsis*). The searches were limited to studies fully published in the English language. The resulting outputs were combined, excluding duplicate results. Abstracts were scanned for suitability and the full text retrieved for all

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potentially relevant studies. Bibliographies and reference lists were reviewed to identify additional relevant studies. Conference, congress, and scientific meeting abstracts were not included. A MEDLINE alert was created to remain informed of any new studies being published with the same search string and was stopped on 1 September 2015.

Study Content Inclusion Criteria

The following inclusion criteria were used to assess the retrieved studies: (1) ADE of antimicrobial therapy, (2) an intensive care setting, and (3) application of any intervention or provision of substantial epidemiological data to judge the effects or determinants of ADE. Studies that did not include antibacterial agents were not included. Studies that reported ADE of antimicrobials as part of the results but did not provide specific information on the reasons, modalities or effects of such ADE were also excluded from the review.

Quality Inclusion Criteria

Each study was independently evaluated by 2 reviewers (A. T. and M. O. C.) using quality inclusion specifications derived from the Cochrane Effective Practice and Organization of Care (EPOC) Review Group [5]. We included uncontrolled before-and-after, case-control, and cohort studies if they met the criteria of measurement and reporting of potential confounding variables between periods or patient groups. Any disagreement between the 2 reviewers was resolved after asking the opinion of 2 other reviewers (J. S. and J. R. Z.). The quality of included studies was appraised using the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) [6], and a modified version (provided in the Supplement) of the Newcastle-Ottawa Scale for case-control and cohort studies [7]. The scale was modified to match the specifics of this review after 3 rounds of discussions to reach agreement between 5 investigators (A. T., M. O. C., J. G. M., J. S., and J. R. Z.). It included 3 domains with 7 questions, for a maximum of 8 points.

Data Analysis and Statistical Methods

Three reviewers (A. T., J. G. M., and J. S.) independently appraised each included study. Interrater agreement was calculated with free marginal κ statistics [8]. The relative risk (RR) ratio with 95% confidence intervals (CIs) was calculated to assess the association between ADE and mortality rates. Heterogeneity among studies was evaluated using the χ^2 test based on the Cochran Q statistic and quantified by the I^2 value [9]. Because the level of heterogeneity indicated a moderate level of diversity in the results of the studies, pooled RRs were calculated using both the fixed-effects model and the random-effects model proposed by DerSimonian and Laird [10], with the Egger test used for publication bias. Relevant factors associated with performing ADE versus non-ADE at the level of significance of 5% were extracted from each publication. Factors influencing rates of ADE versus escalation were excluded. Data and *P* values are reported as from original publications. All analyses were conducted using Stata 12.1 software (StataCorp).

RESULTS

Search Results, Grading, and Study Quality

The results of our search strategy are detailed in Figure 1. The 14 included studies are summarized in Table 1. Two open-label randomized trials were included. One compared initial broad-spectrum antimicrobials (a carbapenem and a glycopeptide) with a strategy excluding these. Appropriateness of initial empiric antibiotic therapy differed between the groups (75.9% vs 48.0%; $P = .04$) [18]. Because this trial compared the effectiveness of 2 different empiric antimicrobial therapy strategies, and not the safety or effectiveness of ADE, it was excluded from further analysis. The other study randomized ADE and a continuation strategy in 120 patients treated with antibiotics for severe sepsis in 9 ICUs [23]. Aside from the open-label design, the main risks of bias were a low inclusion rate and an imbalance in baseline characteristics between the 2 groups, including the initial use of broad-spectrum antibiotics, age, severity scores, and site of infections.

Grading showed "almost perfect" interrater agreement among the 3 reviewers ($\kappa = 1$), both studies being nonblinded, with complete outcome, no selective reporting, and the other risks of bias as described above. The grading for the 12 cohort studies is detailed in Table 1; mean grades ranged from 4 to 7, with "substantial" interrater agreement among reviewers ($\kappa = 0.61$; 95% CI, .51–.71). One study was multicentric [11], 4 were prospective [11, 12, 21, 22]. Five investigated ADE exclusively in patients with a respiratory tract infection [11–13, 16, 20]. Three included patients with severe sepsis or septic shock [17, 21, 22]. Two studies reported ADE in an unselected population [15, 19], 2 included exclusively patients with cancer or neutropenia [21, 24], and 1 included only cases with empiric carbapenem therapy [14]. The reported ADE rate ranged from 34% to 62%.

Definitions

There was no uniform definition of ADE (Table 2). In some studies ADE was evaluated only in case of "very" broad empiric therapy, whereas in others ADE was assessed irrespective of initial antimicrobial therapy. ADE was always described as narrowing or "streamlining" the spectrum of antimicrobials, with a ranking of agents' spectra of activity provided in 4 of the 13 studies [12, 16, 20, 23]. Ten studies provided either a specific day or range of 2–5 days after initiation of broad-spectrum empiric therapy for which ADE had to occur [11–17, 19, 20, 23, 24]. ADE included decreasing the number of antimicrobials in 13 studies [11–13, 15–17, 19–24]. Four studies included shortening the duration of antimicrobial therapy in the definition of ADE [15, 16, 19, 24].

Leone and colleagues [23] used the concept of a "pivotal" antimicrobial, usually an extended-spectrum β-lactam, together with an agent used to treat methicillin-resistant *Staphylococcus*

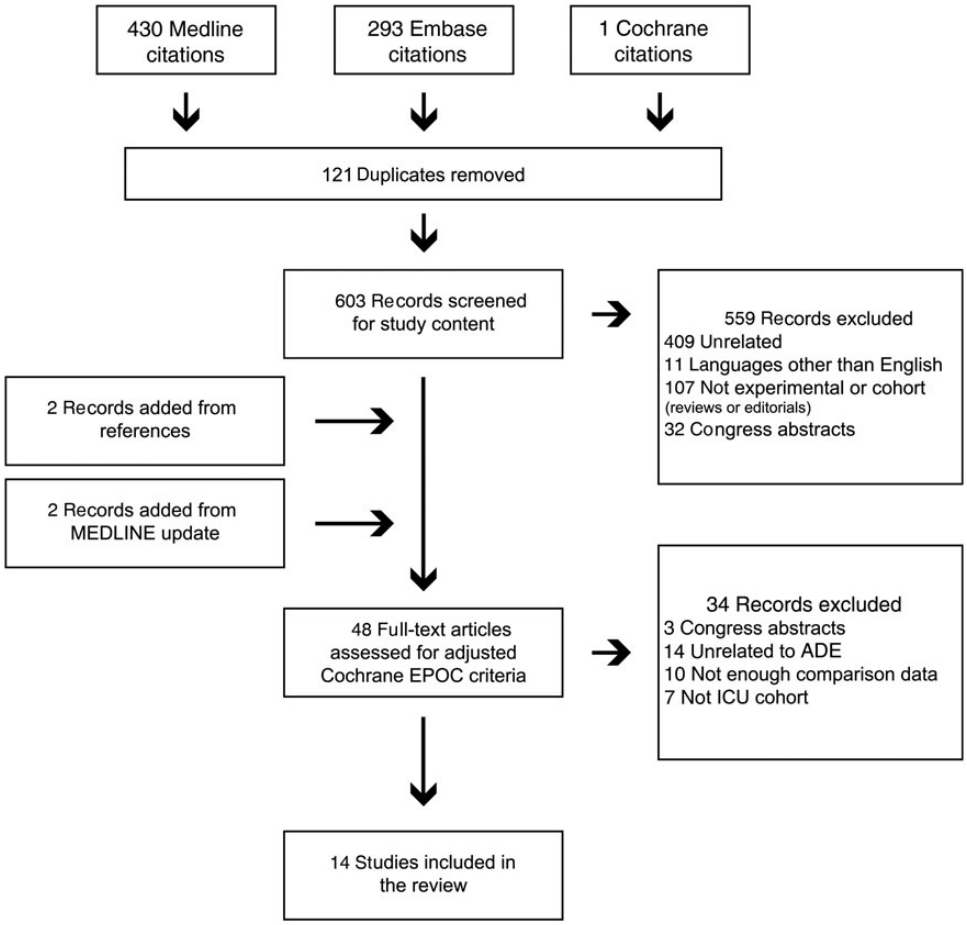

Figure 1. Flow chart detailing study extraction and selection. Abbreviations: ADE, antimicrobial de-escalation; EPOC, Effective Practice and Organization of Care; ICU, intensive care unit.

aureus (MRSA) and a "companion" antimicrobial (aminoglycoside or fluoroquinolone or macrolide). ADE was defined as switching from the pivotal antibiotic to a narrower agent, stopping the companion antibiotic at day 3 of therapy, and ceasing anti-MRSA therapy when not required. None of the studies described the ADE (vs non-ADE) status as rated by blinded investigators.

Factors Associated With ADE

Microbiological documentation [14, 17, 21], such as a positive blood culture [22] or the use of invasive sampling in ventilator-associated pneumonia [12], and initially appropriate antimicrobial therapy were consistently correlated with ADE ($P = .05$ to .002) [13, 15, 17, 19, 21, 22] (summary in Table 3, full report in the Supplement). Likewise, an initial empiric broad-spectrum treatment [19, 21], compliance with guidelines to start antipseudomonal β-lactams in neutropenic patients ($P = .01$) [21], or the use of several agents and companion drugs were all correlated with ADE ($P = .002$) [15].

A lower baseline severity [11, 24] or clinical resolution at the time of culture results (when ADE can be considered) increased the rate of ADE. Garnacho-Montero et al [22] reported lower Sepsis-related Organ Failure Assessment (SOFA) scores at the moment of ADE ($P = .04$), Knaak et al [20] and Paskovaty et al [24] both reported a higher delta SOFA score (surrogate for improvement in organ failures) ($P < .001$ and .002, respectively), and Joung et al [16] reported lower modified Clinical Pulmonary Infection Score (CPIS) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores at day 5 ($P = .03$ and .002), all occurring more frequently in the ADE group. Likewise, recovery from neutropenia was associated with ADE ($P = .05$) in a cohort of neutropenic sepsis [21].

Conversely, infection with an MDR pathogen significantly reduced the likelihood of ADE in 4 studies ($P < .05$) [11, 14, 15, 19]. Polymicrobial infections ($P < .05$) [20, 22], multiple concomitant infections ($P = .02$) [24], and infections with a high risk of undiagnosed pathogens, such as intra-abdominal infections, were associated with non-ADE ($P = .02$) [14, 22] or escalation ($P < .01$) [22].

Outcomes After ADE

Based on the primary end point of ICU length of stay and a noninferiority margin of 2 days, the recent RCT did not demonstrate noninferiority of the ADE strategy [23]. There was a

Table 1. Summary of Included Studies

Authors	Year	ICU Patient Cohort	Sites, No.	Patients, No.	Study Design	Duration of Follow Up	End Points Measured	Reported ADE Rate, %	Study Quality Grade, Mean[b]
Alvarez-Lerma et al [11]	2006	Nosocomial pneumonia treated with imipenem	24	244	Prospective observational	7–9 d after end of therapy	Clinical resolution of pneumonia; attributable and all-cause mortality	52[a]	5/8
Giantsou et al [12]	2007	VAP	1	143	Prospective observational	15 and 28 d after diagnosis	Duration of ICU and total hospital stay; all-cause mortality	41	4/8
Eachempati et al [13]	2009	Surgical patients with VAP	1	138	Retrospective observational	ICU admission	Recurrence of pneumonia; all-cause mortality	57	4/8
De Waele et al [14]	2010	Surgical patients treated with meropenem	1	113	Retrospective observational	ICU admission	All-cause mortality	42	5/8
Morel et al [15]	2010	All ICU patients started on empiric antibiotic therapy (excluding patients with bone marrow aplasia)	1	116	Retrospective observational	ICU admission	Infection recurrence; duration of ICU stay; all-cause mortality	45	6/8
Joung et al [16]	2011	ICU-acquired pneumonia	1	137	Retrospective observational	14 and 30 d after diagnosis	Attributable and all-cause mortality	32	6/8
Heenen et al [17]	2012	Hospital-acquired severe sepsis	1	169	Retrospective observational	ICU admission	All-cause mortality	81[a]	5/8
Kim et al [18]	2012	Hospital-acquired pneumonia	1	109	Randomized controlled trial	14 and 28 d after diagnosis	Length of ICU stay; all-cause mortality; emergence of MDR bacteria	50	NA
Gonzalez et al [19]	2013	Suspected infections	1	229	Retrospective observational	ICU, hospital, 28 d and 12 mo after admission	ICU-acquired infection; length of ICU stay; all-cause mortality; emergence of MDR bacteria	51	7/8
Knaak et al [20]	2013	HCAP, HAP, and VAP	1	113	Retrospective observational	Hospital admission	Length of ICU stay; in-hospital mortality; total cost of ICU stay	62	5/8
Mokart et al [21]	2014	Neutropenic patients with severe sepsis	1	101	Prospective observational	ICU, 30 d and 12 mo after ICU discharge	All-cause mortality	44	6/8
Garnacho-Montero et al [22]	2014	Patients with severe sepsis or septic shock	1	628	Prospective observational	ICU, hospital, and 90 d after admission	All-cause mortality	35	7/8
Leone et al [23]	2014	Patients with severe sepsis	9	116	Randomized controlled trial	ICU, 28 and 90 d after admission	Length of ICU stay; No. of ICU-free days; No. of superinfections; 90-d survival rate	51	NA
Paskovaty et al [24]	2015	Patient with cancer and severe sepsis	1	105	Retrospective observational	ICU, hospital, 28 d after admission	Length of ICU and hospital stay; all-cause mortality	58	5/8

Abbreviations: ADE, antimicrobial de-escalation; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MDR, multidrug-resistant; NA, not applicable; VAP, ventilator-associated pneumonia.

[a] Where this subgroup is reported by the authors, ADE rates are reported for the population with adequate antimicrobial therapy and a ADE possibility.

[b] Grades based on a modified version (provided in the Supplement) of the Newcastle–Ottawa Scale for case-control and cohort studies [7].

higher rate of superinfections requiring antimicrobial therapy in the ADE group (27% vs 11%; $P = .03$), of which 44% were due to the initial pathogen.

Two cohort studies looked at a follow-up of 7–14 days [11, 16]. The others followed up the patients for the duration of either ICU or hospital admission or for ≥28 days. Data comparing mortality rates between ADE and non-ADE groups, involving a total of 1688 patients, are reported in Figure 2. The pooled estimate of mortality showed a protective effect of ADE (RR, 0.68; 95 CI, .52–.88) with moderate heterogeneity ($I^2 = 44.2\%$). We did not find significant publication bias (Figure 3; Egger test $P = .08$; bias estimate, −1.54; 95% CI, −3.30 to .22).

Outcomes varied from similar response [11] and mortality [13–15, 19, 21, 24] rates to a decrease in length of stay [12, 24]

Table 2. Definition of Antimicrobial De-escalation in Included Studies

Authors	Year	Initial Broad-Spectrum Therapy (If Specific Antimicrobials Described)	Definition of ADE			Negative Cultures Included in ADE	Ranking of Agents	ADE to Occur on or Before Specified Day of Therapy
			Decrease No. of Antimicrobials	Narrow Spectrum	Shorten (or Cease) Therapy			
Alvarez-Lerma [11]	2006	Imipenem ± aminoglycoside ± glycopeptide	Yes	Yes	No	No	Not ranked	Between 3rd and 5th d
Giantsou et al [12]	2007	No specific antimicrobials described	Yes	Yes	No	No	Carbapenem > extended-spectrum penicillin > fluoroquinolone + aminoglycoside > nonantipseudomonal β-lactam	3rd d
Eachempati et al [13]	2009	Monthly rotation of empiric therapy (cefepime, levofloxacin, imipenem or meropenem, piperacillin-tazobactam)	Yes	Yes	No	No	Not ranked	Between 2nd and 3rd d
De Waele et al [14]	2010	Meropenem	No	Yes	No	No	Not ranked	3rd d
Morel et al [15]	2010	No specific antimicrobials described	Yes	Yes	Yes	No	Not ranked	Before 5th d for reducing number of antibiotics, before 3rd d for early cessation
Joung et al [16]	2011	No specific antimicrobials described	Yes	Yes	Yes	Yes	Carbapenem > piperacillin-tazobactam > cefepime or 3rd generation cephalosporin	Specified for negative cultures: discontinuation before 5th d if >48 h of defervescence
Heenen et al [17]	2012	No specific antimicrobials described	Yes (including antifungal)	Yes	No	No	Not ranked	5th d after diagnosis
Kim et al [18]	2012	ADE group: imipenem + vancomycin; non-ADE group: empiric antimicrobials according to national guidelines for nosocomial pneumonia	Yes	Yes	No	Yes	Not ranked	3rd to 5th d
Gonzalez et al [19]	2013	No specific antimicrobials described	Yes	Yes	Yes	Yes	Not ranked	Specified when no obvious infectious site: discontinuation before 4th d if favorable clinical evolution/ alternative diagnosis
Knaak et al [20]	2013	Piperacillin-tazobactam + levofloxacin + vancomycin	Yes	Yes	No	No	Gram negative: carbapenem > piperacillin-tazobactam > cefepime > fluoroquinolone; gram-positive: vancomycin > nafcillin or cefazolin	Within 24 h of culture results
Mokart et al [21]	2014	No specific antimicrobials described	Yes (including antifungal or antiviral)	Yes	No	No	Not ranked	Not specified
Garnacho-Montero et al [22]	2014	No specific antimicrobials described	Yes	Yes	No	Yes	Not ranked	Once culture results were available
Leone et al [23]	2014	No specific antimicrobials described (antimicrobials termed either "pivotal" or "companion")	Yes	Yes	No	No	Carbapenem > piperacillin-tazobactam or ceftazidime or cefepime or ertapenem > ticaricllin > 3rd-generation cephalosporin > aminopenicillin + clavulanate > aminopenicillin or methicillin	When antibiogram available; for "companion" antimicrobial: ceased on 3rd d
Paskovaty et al [24]	2015	No specific antimicrobials described	Yes	Yes	Yes	Yes	Not ranked	By d 5

Abbreviation: ADE, antimicrobial de-escalation.

Table 3. Factors Associated With Antimicrobial De-escalation

Factors Associated With ADE
Positively associated
Initially appropriate empiric antimicrobial therapy
Broad-spectrum empiric therapy
Compliance with national prescribing guidelines
Treatment with multiple and "companion" antimicrobials
Positive microbiological cultures
Lower severity of illness scores at
Baseline
Time of ADE
Day 5 of therapy
Negatively associated
Isolation of a multiresistant pathogen
Polymicrobial infections
Intra-abdominal infections

Abbreviation: ADE, antimicrobial de-escalation.

and mortality rates [12, 16, 17, 20, 22]. None of the studies reported a worse survival with the ADE strategy. All publications lacked a precise description as to how the outcome was assessed. Furthermore, confounders such as an incompletely described cohort [12], an imbalance in patient characteristics at baseline [15, 23], or "at the moment of ADE" [16, 20] introduced high risk of bias.

Adjustment and multivariable analysis on the effect of ADE on outcome were provided in 5 publications [11, 16, 21, 22, 24]. In a cohort of neutropenic sepsis, ADE had no influence on 30-day (hazard ratio [HR], 0.51; 95% CI, .20–1.33) or 1-year mortality rates [21]. Two studies accounted for severity at the moment where ADE was considered. After adjustment with a propensity score, Garnacho-Montero et al [22] showed that ADE was protective (odds ratio [OR], 0.55; $P = .022$). Higher SOFA scores on the day of culture results (OR, 1.11; $P < .001$), septic shock (OR, 1.70; $P = .043$), and inadequate empiric antimicrobial therapy (OR, 2.03; $P = .03$) were all independently associated with mortality. In a cohort of patients with ICU-acquired pneumonia, after adjustment with a Cox model, severity scores (APACHE II and CPIS) at day 5 were the only independent predictors of pneumonia-related and all-cause mortality [16].

Effect of ADE on the Duration of Antimicrobial Therapy

To avoid misinterpreting the effect of ADE on the duration of antimicrobial therapy, we excluded studies that allowed for shortening or discontinuation of therapy as part of the definition of ADE in this part of the analysis [15, 16, 19, 24]. Four studies compared the duration of antimicrobial therapy between ADE and non-ADE groups [11, 21–23]. There was no

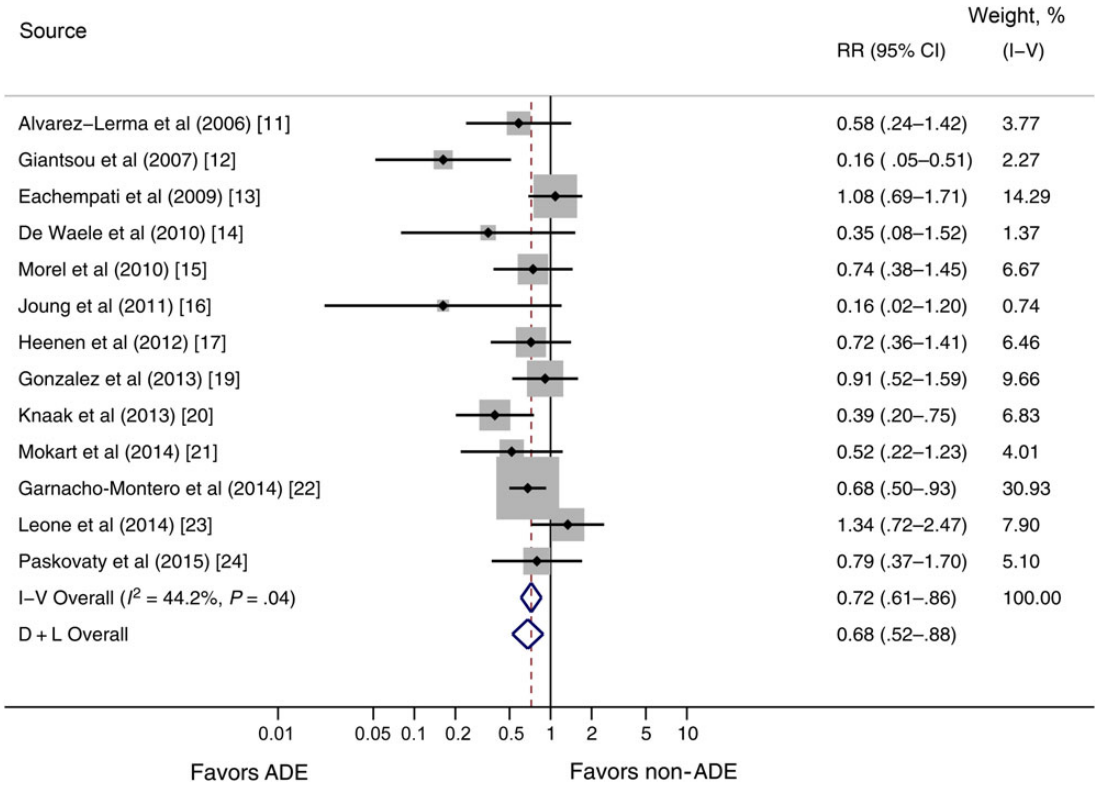

Figure 2. Difference in patient mortality rates between antimicrobial de-escalation (ADE) and non-ADE. Heterogeneity $\chi^2 = 21.52$ ($df = 12$); $P = .04$; $I^2 = 44.2\%$ (variation in RR attributable to heterogeneity). Test of RR = 1: $z = 3.72$; $P < .001$. Abbreviations: CI, confidence interval; D + L, random-effects model proposed by DerSimonian and Laird [10]; I-V, inverse variance; RR, relative risk.

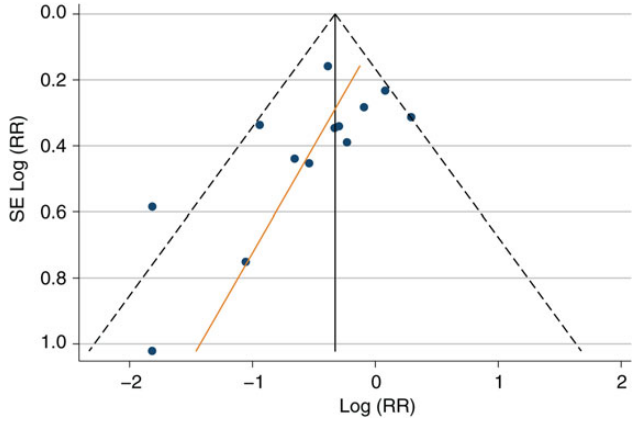

Figure 3. Funnel plot with pseudo 95% confidence intervals (CIs) (Egger test $P = .08$; bias estimate value, −1.54; 95% CI, −3.30 to .22). There is no evidence to reject the null hypothesis that there is no bias in the studies presented. Abbreviation: RR, relative risk.

reduction in antibiotic days with ADE. One study reported an increase in the duration of therapy with ADE (9 vs 5 days; $P = .005$) [21].

Effect of ADE on Microbiological Flora and Antimicrobial Resistance

None of the studies were designed to investigate the effect of ADE (or non-ADE) on the acquisition of MDR bacteria. Gonzalez and colleagues did not show any difference in the carriage or ICU-acquired infections with MDR bacteria between the 2 groups [19]. Leone et al [23] reported that no effect on local ecology at day 8 was found.

Cost Analysis

Two studies reported lower costs in patients with ADE [11, 20]. This was explained not by a higher market price for broad-spectrum antimicrobial therapy but by an overall decrease in expenses due to the same factors that tend to increase the rate of ADE, such as lower severity or clinical improvement [20]. In turn, this led to shorter ICU and hospital stays for patients in the ADE group, further contributing to lower costs associated with this cohort [11].

DISCUSSION

In this systematic review we found a paucity of studies looking at the effect of a ADE strategy on duration of antimicrobial therapy, emergence of resistance or costs. We found an association between ADE and better patient outcomes. We describe a high risk of bias in the cohort studies. Most importantly, because this effect was not confirmed in the only available RCT, these data should not be read as a causal association between ADE and outcomes.

ADE was variably defined across the studies, making comparability problematic. There are inherent difficulties in defining ADE. Weiss and a group of French-speaking experts [25] used a Delphi method to propose a definition of ADE. They provided a 6-rank classification of β-lactams according to their spectrum and resistance promoting potential. Reaching a consensus for the ranking of ureidopenicillins and carboxypenicillins, third- and fourth-generation antipseudomonal cephalosporins required 4 Delphi rounds, highlighting the difficulty in ranking drugs even within a single class of antimicrobials. Madaras-Kelly and colleagues [26] developed a spectrum score and calculated piperacillin-tazobactam at a higher value and broader spectrum than those for imipenem or meropenem, opposite to the findings from Weiss et al [25]. Leone et al [23] have provided a pragmatic definition of ADE with the concept of pivotal antibiotic, on which ADE efforts focus, together with cessation of companion antibiotics if they are not required.

We found that ADE was associated with reduced mortality. However, the clinical and statistical heterogeneity in our meta-analysis questions the validity of this result. We found heterogeneity in study design and populations, in the definition of ADE, and in the adjustment for confounding variables. Where investigated, improving severity scores are associated with an increased rate of ADE [16, 20, 22, 24]. In the cohort with the largest weight, the authors attempted to minimize bias by performing a propensity score adjusted multivariable analysis. Although it is a state-of-the-art statistical adjustment, it is not possible to exclude an interaction with clinical improvement, because it is a determinant for both mortality rate and performance of ADE [22]. In patients with improving severity scores, it is not known how many were already microbiologically and/or clinically cured. For those patients, ADE may not have influenced outcome. As such, outside of a randomized setting, ADE could be considered a marker of clinical improvement, whereas the reluctance to narrow the antimicrobial spectrum may indicate deterioration.

The ADE strategy is advocated to limit the emergence of resistance to antimicrobial therapy. Although resistance emergence has been studied for shortening treatment [27], to date there is no evidence of this for ADE because none of the published studies was designed to evaluate this variable. Broad-spectrum antimicrobials have been associated with resistance among gastrointestinal tract flora [28]. Although, intuitively, it seems that giving a narrower-spectrum antibiotic might reduce the emergence of resistance, this remains to be investigated. The increased number of superinfections with ADE in a randomized trial [23], of which 44% were due to the initial pathogen, might be related to the higher risk of nonachievement of pharmacokinetic/pharmacodynamic targets with narrow-spectrum compared with broad-spectrum antimicrobials found in simulation studies [29].

ADE has been investigated as the simple component of care to decrease antimicrobial spectrum based on culture results. However, it is dependent on multiple other factors, such as risk, severity and improvement, site of infection, adequacy of

source control, and factors that will vary with each treatment, microorganism, patient, and institution. As such, ADE should be regarded as a process part of the global antimicrobial stewardship approach, inclusive of other elements such as the route and mode of administration and the total duration of antimicrobial therapy.

The main limitation of this work resides in its initial concept to provide more information than the available meta-analysis and to allow for the inclusion of cohort studies. Inferring an effect on outcomes from such studies is associated with a high risk of accepting bias. In addition, limiting the inclusion to studies published in English may have introduced further bias. Furthermore, because we did not include studies that limited their analysis to only antifungal or antiviral drugs, our findings are not applicable to those classes of antimicrobials.

In conclusion, there is no uniform definition of ADE. It is more commonly performed in patients with improving severity scores and those receiving broad-spectrum antimicrobials. ADE did not reduce the total duration of antimicrobial treatment costs or length of stay. The effects of ADE on bacterial resistance have not been adequately investigated. Although the pooled estimate shows a protective effect of ADE on mortality, there is too much bias to retain this result as evidence for a direct beneficial effect. This leads us to conclude that equipoise remains and a large cluster-randomized trial is required to assess the effect of the ADE strategy on the bacterial ecosystem, on MDR carriage, and on patient outcomes.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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