Review Article

Antimicrobial stewardship programmes focused on de-escalation: a narrative review of efficacy and risks

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Background and Objective: Multi-drug resistance is an increasing problem and is associated with increased morbidity and mortality. High levels of antimicrobial consumption and broad-spectrum antimicrobial use are associated with antimicrobial resistance (AMR). Studies have shown substantial antimicrobial use across intensive care units (ICUs) worldwide. International guidelines advise antibiotic de-escalation (ADE) as part of an antimicrobial stewardship programme (ASP). ADE is a strategy to decrease the spectrum of the empirical antimicrobial therapy, with the aim to reduce the ecological impact on the patient's microbiome and reduce the emergence of AMR. Our aim was to provide an insight into the latest developments on ADE in the intensive care setting.

Methods: PubMed was searched using the terms 'antibiotic de-escalation' and 'antimicrobial stewardship' up to and including November 2021.

Key Content and Findings: Evidence to date is limited, ADE appears to be a safe intervention. The evidence is inconclusive regarding resistance development. Concerns regarding increased duration and superinfections with an ADE approach are unproven with studies finding mixed results. ADE should not be used as a sole quality indicator as this could encourage empiric broad-spectrum antimicrobial overuse.

Conclusions: ADE appears safe. Evidence is inconclusive regarding resistance development but data to date is limited. ADE should be used alongside other antimicrobial stewardship (AMS) measures. These include appropriate empirical therapy, guided by local guidelines considering local epidemiology and host factors, optimal dosing, regular review of antimicrobial therapy with clinical progress and microbiology results, with de-escalation as soon as feasible and early cessation where appropriate, and infection control measures.

Keywords: Antimicrobial de-escalation; antimicrobial stewardship programme (ASP); antimicrobial stewardship (AMS); resistance

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Introduction

Since the early 20th century antibiotics have effectively reduced the morbidity and mortality associated with infectious diseases. Effective antimicrobials are crucial to protect against a range of infections and allow complex surgery to be carried out safely. However, the global rise in antimicrobial resistance (AMR) is a major concern and the World Health Organization (WHO) has declared AMR as one of the top ten worldwide public health threats affecting humanity (1). The use of large volume broad spectrum antibiotics coupled with poor infection control practices

are major driving forces behind increasing numbers of resistant bacteria in the healthcare setting (2-4). Treating multidrug resistant (MDR) organisms is a huge challenge and is associated with high morbidity and mortality (5). In 2015, the World Health Assembly adopted a global action plan on AMR, with one of the five objectives outlined being "to optimize the use of antimicrobial medicines in human and animal health" (6). The WHO recommended the set-up of antimicrobial stewardship programmes (ASP) (6). Antimicrobial stewardship (AMS) encompasses a broad approach tackling the timely and appropriate selection in terms of choice, dose, duration and route of antimicrobials, regular review of the antimicrobials with clinical progress, biomarkers and culture results, and wide-ranging infection control measures to reduce the risk of transmission of MDR organisms. Antibiotic de-escalation (ADE) is a strategy to discontinue one or more combination empiric antimicrobials or replacing a broad-spectrum antimicrobial with a narrower spectrum agent with the aim to reduce selection pressure on antibiotics and emergence of MDR organisms. ADE is recognised internationally as a key component of AMS (7,8).

In this narrative review, we aim to provide an insight into the latest developments on ADE in the intensive care setting. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-6/rc).

Methods

PubMed was searched for reviews, meta-analyses, randomised control trials (RCTs) and observational studies with the terms 'antibiotic de-escalation' and 'antimicrobial de-escalation' both with and without 'intensive care', and 'antimicrobial stewardship', including articles up to November 2021. Publications with ADE-related outcomes were included. Bibliographies of relevant papers were also reviewed, and applicable articles hand-picked.

Setting the scene

Antibiotics are widely used in intensive care units (ICUs), with a prospective international point prevalence study collecting data from 1,265 ICUs worldwide finding that 71% of all ICU patients were receiving an antimicrobial (9). The average antibiotic consumption calculated as defined daily doses per 1,000 patient-days has been estimated to be three times higher in ICU patients than in ward patients [1,563/1,000, 95% confidence interval (CI): 1,472–1,653 in ICU patients versus 586/1,000, 95% CI 540–632 hospital-wide] (10). The DIANA study (11), a prospective cohort study in ICUs across 28 countries, found empiric choice included combination therapy (i.e., more than one antimicrobial) in 50% and carbapenem use in 26% of cases. Only 16% underwent ADE within 3 days, this increased to 21% by day 5. This highlights the importance of multidisciplinary engagement in providing an optimal AMS in an ICU setting. *Figure 1* shows the factors contributing to good AMS in critical care.

The need for prompt and effective antimicrobial therapy in patients with confirmed or suspected sepsis is well acknowledged. A large retrospective multicentre study in the United States evaluating antibiotic timing and mortality in patients with sepsis in the emergency department demonstrated that for every hour delay in antibiotic administration there was an increase in absolute mortality of 0.3% (95% CI: 0.01–0.6%; P=0.04) and 1.8% (95% CI: 0.8–3.0%; P=0.001) for sepsis and septic shock respectively (12). Two single centre cohort studies also demonstrated an association between antibiotic delay and increased mortality in the treatment of sepsis. One study calculated a 15% increase in mortality [hazard ratio (HR) =0.79, P=0.0092] for every hour delay in antibiotic administration from triage (13). Another study highlighted a significant reduction in mortality when antibiotics were given within an hour of triage [mortality 19.5% versus 33.2%; odds ratio (OR) 0.30, 95% CI: 0.11–0.83; P=0.02] (14). The Surviving Sepsis Campaign guidance (15) updated in 2021 states that "for adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within 1 hour of recognition". Early and adequate empirical antimicrobial coverage are critical in patients with community or hospital onset sepsis. The empirical choice needs to cover the likely causative organisms, often resulting in usage of broad-spectrum antimicrobials. Excessive use of broad-spectrum antimicrobials selects for resistant organisms (16). A timely de-escalation of broad-spectrum therapy, reviewed with relevant microbiology results and clinical progress, constitutes an important part of antimicrobial therapy (17). A before and after study found advice from an infectious disease physician was significantly correlated with antimicrobial modifications (P=0.004) and antimicrobial discontinuation (P≤0.001) (18).

ADE usually makes up part of an ASP. The definition of ADE across studies is not consistent but there now appears

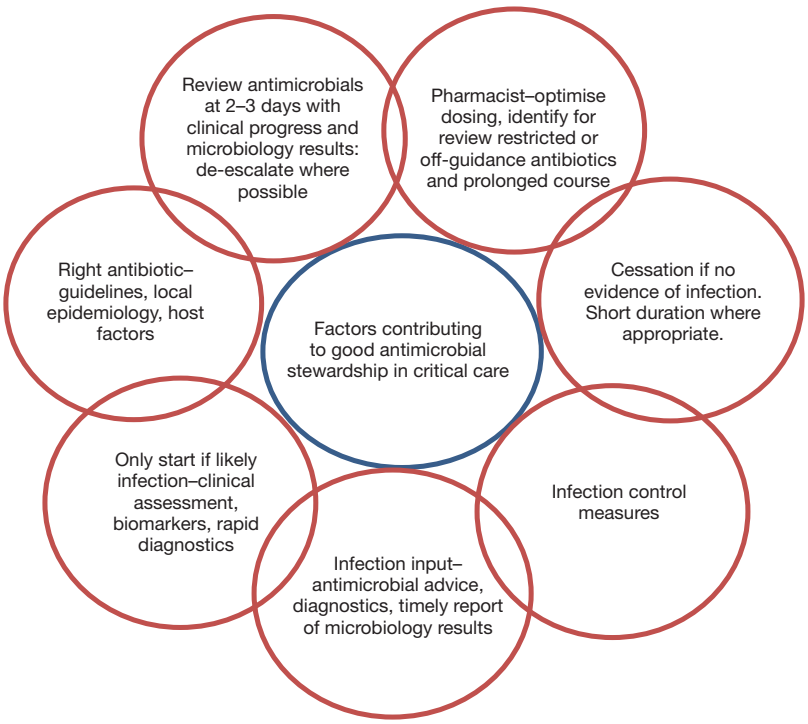

Figure 1 Factors contributing to good AMS in critical care. AMS, antimicrobial stewardship.

to be consensus that ADE is defined as: (I) stopping one or more components of combination antimicrobial therapy; and/or (II) changing from a broad-spectrum antimicrobial to an agent with a narrower spectrum (19). This strategy aims to reduce the development of AMR by decreasing exposure to broad-spectrum antimicrobials without compromising patient outcomes (20). Factors positively correlated with ADE include microbiological documentation, use of invasive sampling in ventilator-associated pneumonia, lower baseline severity or clinical resolution at time of culture positivity. Factors inversely correlated with ADE include infection with an MDR pathogen, polymicrobial infection and infection with low probability of microbiological findings such as intra-abdominal infections (18). *Figure 2* depicts the factors positively (up arrow) and negatively (down arrow) correlated with ADE.

Despite attempts to classify antibiotics by their spectrum and ecological consequences, this has proven difficult. A French De-escalation Study Group (22) used a Delphi process with 28 expert participants to classify beta-lactam antibiotics according to spectrum and risk of resistance development. Despite several Delphi rounds, they were unable to reach consensus on piperacillin-tazobactam, third generation cephalosporins with anti-pseudomonal activity and fourth generation cephalosporins. A group from the United States (23) calculated numerical scores for 27 antibiotics according to antimicrobial activity spectrum. To validate the scoring system twenty antibiotic regimen changes were assessed by a group of experts and the change in spectrum score calculated. Change in spectrum score was not significantly correlated with mean expert opinion. The ranking of antibiotics is considerably different between the two scoring systems, including disagreement on which antibiotic has the most detrimental ecological impact-highlighting the complexity of classifying antibiotics into groups based on their ecological consequences.

Effect of ADE on development of resistant bacteria

Increased antibiotic consumption is associated with increased resistance (24). A single centre cohort study of 7,118 adult patients diagnosed with sepsis or septic shock demonstrated an increased risk of resistance development with each additional day of exposure to piperacillin-tazobactam, cefepime and meropenem (25). In the ICU setting increased use of a particular class of antibiotic is associated with increased resistance to that class (26,27).

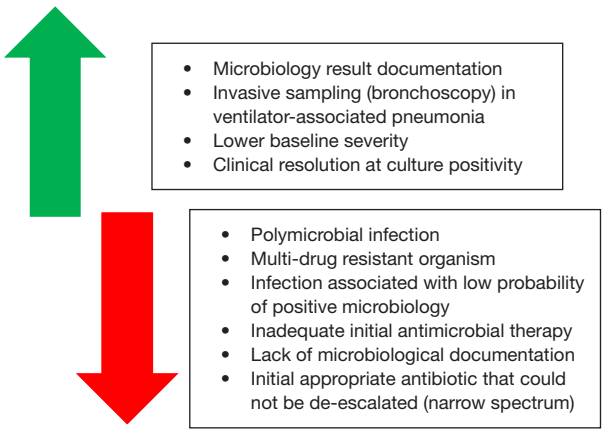

Figure 2 Factors positively and negatively correlated with antibiotic de-escalation (19,21).

Various studies have been conducted looking at the effect of various antimicrobials on the faecal microbiota. In murine models when comparing ceftriaxone and piperacillin-tazobactam both significantly reduced the faecal microbial diversity, but this was more marked and prolonged in the ceftriaxone group (28). There is, to date, a lack of clinical data regarding the impact of ADE and emergence of resistance. The few studies that looked at AMR as an outcome reported no or very limited effect of de-escalation on the individual's or local prevalence of MDR bacteria. The DIANA study (11) found a trend towards reduced MDR acquisition in the ADE group compared to the "no change" group (7.5% and 11.9% respectively, P=0.06) but this was not statistically significant. De Bus *et al.* (29) analysed 478 anti-pseudomonal beta-lactam prescriptions in tertiary ICUs. They found the risk of resistance emergence at day 14 was not lower in the de-escalation group; however, the de-escalation group was associated with a longer duration of treatment which may have confounded this. An evaluation of 182 ventilator-associated pneumonias found a trend towards reduced acquisition of extended spectrum beta-lactamase producing Enterobacterales in the de-escalation group (1.4% versus 8.2%, P=0.07), although this did not reach statistical significance (30). Another retrospective single centre observational study of 229 ICU patients treated for sepsis showed an increase in carriage of MDR bacteria in the ADE group but again this did not reach statistical significance (15.3% in ADE group and 10.7% in non-ADE group, P=0.1). In addition to MDR gram-negative bacteria this study included *methicillin-resistant Staphylococcus aureus* (MRSA), *coagulase negative Staphylococci* and inherently resistant bacteria such as *Enterococci* in their MDR description which may have affected results (21). Finally, a prospective study evaluating ASP guided carbapenem de-escalation found a significant lower incidence of carbapenem-resistant *Acinetobacter baumani* in the ADE group [4/204 (2.0%) versus 7/96 (7.3%), P=0.042] (31).

When considering de-escalation, one needs to consider the ecological effect of the new antimicrobial choice. In a double-blinded clinical trial, patients with complicated intra-abdominal infection requiring surgery were randomised to piperacillin-tazobactam or ertapenem. Rectal swabs at baseline and at the end of therapy were assessed for the acquisition of Enterobacterales resistant to the antimicrobial used, and 8/122 (6.6%) of the piperacillin-tazobactam group and 0/122 (0%) of the ertapenem group (P=0.007) developed resistance to the chosen antibiotic (32). Piperacillin-tazobactam and third generation cephalosporins both impact on microbiome diversity and are often considered a stepdown from a carbapenem. Armand-Lefévre *et al.* showed that ICU patients who received a short duration (1–3 days) of imipenem had increased risk of imipenem-resistant gram-negative bacilli (OR 5.9, 95% CI: 1.5–25.7) (33). Reducing exposure to broad spectrum antibiotics should be promoted. However, if a short duration of broad-spectrum antimicrobials can contribute to resistance development, a switch to a different antimicrobial with a differing spectrum may have a cumulative insult on the microbiome.

In summary, the data available on the impact of ADE on emergence of resistance is inconclusive. Although expert opinion suggests for short treatment courses (5–7 days) that there may be no benefit to performing ADE once microbiology culture results are available (34), in our view, the ecological impact on selective pressure would still warrant de-escalation where possible even if this does not affect the outcome of that particular patient. Again, for prolonged treatment (more than 5–7 days) ADE should be performed as early as feasible, and within 24 hours of definitive culture and antibiogram results (35).

The effect of ADE on clinical outcomes

Mortality

Three meta-analyses published in 2016 looked at 30-day mortality in patients with and without ADE. The meta-analysis from Tabah *et al.* (19) included 14 studies that

evaluated de-escalation in a critical care setting. The pooled estimated mortality favoured de-escalation [relative risk (RR) 0.68, 95% CI: 0.52–0.88]. Paul *et al.* (36) included almost four thousand patients in their analysis focused on patients with pneumonia and blood stream infections (BSI). There was no difference in mortality between the de-escalation group and the control group on the adjusted analysis (OR 0.83, 95% CI: 0.59–1.16). Ohji *et al.* (37) looked at mortality in different patient groups. In both community-acquired pneumonia (CAP) and pneumonia acquired on ICU, the 30-day mortality rate was significantly lower in the de-escalation group compared to the control group (OR 0.50, 95% CI: 0.29–0.87; OR 0.34, 95% CI: 0.17–0.68 respectively). There were no significant differences in the calculated 30-day mortality rate across the two groups for ventilator-associated pneumonia, BSI, urinary tract infection and septic shock. They commented on the lack of good quality studies. The DIANA study attempted to control for potential confounding factors and found no difference in mortality between ADE and "no change" patients (11). Observational studies have shown that an ADE approach in patients with community-acquired BSI is safe with a potential trend towards reduced mortality (38,39). A non-blinded RCT of 120 patients comparing ADE versus continuation therapy found no significant difference in 90-day mortality (31% versus 23% respectively, P=0.35). It is a small sample size and may not be adequately powered to show a difference (40). Studies are heterogenous and high-quality data is lacking. The observational studies are prone to inclusion bias due to lack of adjustment for clinical stability.

Although to our knowledge no recent meta-analysis has been published in this area, no study has shown increased mortality with an ADE approach, suggesting it is a safe intervention in most patients. Current guidelines advise a review of antimicrobial therapy at 48–72 hours with relevant microbiology results and clinical progress and stop or de-escalate where appropriate (15,16).

Length of ICU and hospital stay

The non-blinded RCT from Leone and colleagues showed similar ICU length of stay (LOS) across the de-escalation and continuation groups (9 versus 8 days, P=0.71) (40), results hampered by imbalances between groups. Most observational studies report no change in ICU and/or hospital LOS (21,30,41). A meta-analysis (36) of studies evaluating ADE in pneumonia and BSI showed no significant difference in ICU or hospital LOS, and a more recent meta-analysis examining de-escalation in patients with pneumonia in ICU demonstrated a significant decrease in hospital LOS with ADE (mean reduction 5.96 days, 95% CI: 8.39–3.52 days) but again comments on the low-quality evidence (42).

Studies have limitations and low-quality evidence, but ADE does not appear to have a measurable impact on LOS.

Duration of antimicrobial therapy

Observation studies that reported on duration of therapy found mixed results. Three studies showed similar antibiotic treatment durations (30,43,44), two showed ADE was associated with longer treatment duration (29,45) and one study found ADE decreased the duration of antimicrobial therapy (46). The ADE group in the RCT had an increased total duration of antimicrobial therapy but similar initial duration of treatment (40). In the studies where ADE was associated with a longer duration of therapy, the authors hypothesised that clinicians perceive narrower spectrum antibiotics to be of low risk of harm.

An expert panel recommends particular attention to antimicrobial therapy duration in patients undergoing ADE (35). Shortening the duration of antimicrobial therapy reduces the emergence of resistance (47) so is an important consideration alongside de-escalation.

Longer courses (7–14 days) of antimicrobial therapy do not necessarily improve patient outcomes and may increase risk of MDR bacteria and adverse events such as *Clostridium difficile* infection (48-50). In our view short course antibiotic therapy has been shown to be effective and safe in several infections, including CAP, ventilator-associated pneumonia, urinary tract infections, intra-abdominal infections with adequate source control and certain BSIs (49,51-53).

Risks of ADE strategy

Superinfections

The RCT from Leone *et al.* (40) assessing ADE versus continuation of empirical treatment in 120 patients across nine ICUs in France showed an increased incidence of superinfections, although this did not impact on mortality or LOS. Superinfections were defined by the occurrence of an additional infection with an identified pathogen requiring introduction of new antimicrobial treatment. A total of 27% (16/59) in the ADE group versus 11%

(6/57) in the continuation group, P=0.03, but numbers are small, and results should be treated with caution; 44% (7/16) of episodes in ADE group and 67% (4/6) episodes in the continuation group were due to the initial pathogen. Two studies in patients with pneumonia, one prospective observational study (43) and one secondary analysis of a multicentre study (54) found no difference in superinfection rates between ADE and continuation groups.

Empiric broad spectrum antimicrobial therapy overuse

De Waele *et al.* (55) cautioned against using ADE as a quality improvement (QI) indicator—this would discourage empiric narrow-spectrum antibiotic choice as broad-spectrum or combination therapy would score more favourably on a QI when later undergoing de-escalation, but in practice would be poorer AMS. This may lead to overuse of empiric broad spectrum antimicrobials.

A systematic review by Schuts *et al.* showed that when empiric therapy complied with guidelines, the RR reduction in mortality was 35% (56). An observational cohort study involving 1,756 patients from three hospitals in Norway found 30-day mortality and in-hospital mortality were lower in the guideline adherent group, compared to the non-adherent group (OR 0.48, P=0.003 and OR 0.46, P=0.001 respectively) (57).

It is important to optimise empirical antimicrobial choice through access to and compliance with local infection guidelines, guided by up-to-date local resistance data. Treatment for patients with community acquired infections with an identified source who are antibiotic-naive with no risk factors for resistant organisms should follow local guidance. A prospective multicentre study from Australia identified microbiological aetiology in 46% (404/885) of patients admitted with CAP. Only 5.4% had an infection that would not be adequately treated with a combination of penicillin plus either a macrolide or doxycycline. Most of these patients had risk factors for unusual organisms such as chronic obstructive pulmonary disease, extensive co-morbidities, and residence in long-term care facilities. *Streptococcus pneumoniae* and *Legionella pneumophila* were associated with severe disease and ICU admission, but both would typically be covered by the empiric regimen (58). In the United Kingdom where penicillin resistance *pneumococci* are rare, benzylpenicillin or amoxicillin remains pivotal treatment for community-acquired lobar pneumonia including in severe disease (59,60). A retrospective study of 1,995 adult patients admitted to four hospitals in the United States with CAP found despite adjustment for multiple confounders broad-spectrum antibiotics were associated with increased mortality (OR 4.6, 95% CI: 2.9–7.5; P<0.001) (61) (*Table 1*).

Use of ADE in culture negative infection

A retrospective single centre study of 229 patients with community acquired infection showed no mortality difference in those who underwent de-escalation (21). Cowley and colleagues' retrospective study of culture-negative hospital acquired pneumonia found stopping the anti-MRSA agent whilst continuing or de-escalating the pivotal antibiotic did not influence mortality or treatment failure and reduced acute kidney injury incidence (62). In a single centre non-blinded randomised trial into empiric treatment of pulmonary infiltrates patients with a clinical pulmonary infection score (CPIS) of 6 or less were randomised to receive standard therapy (physician choice of antimicrobial and duration) or experimental therapy (ciprofloxacin monotherapy, subsequently stopped at day 3 if CPIS remained <6). Antibiotics were continued at day 3 in 90% (38/42) in the standard therapy group versus 28% (11/39) in the experimental group (P=0.0001). Mortality and LOS were similar despite shorter duration of treatment. AMR emergence and/or superinfections were picked up in respiratory and other cultures taken 7–28 days after initial therapy developed in 35% (14/37) of the standard therapy group versus 15% (5/37) of the experimental therapy group (P=0.017) (47), suggesting that if there is no apparent evidence of infection, continuing antimicrobial therapy causes more harm.

Given our experience prior to the COVID-19 pandemic (63), our centre recently adopted using biomarkers such as procalcitonin as an AMS tool in COVID-19 patients. We found this can successfully lead to stoppage of antibiotics in over 50% (14/25) of cases without negatively impacting on patients' outcome, ICU or hospital LOS (64). These are real life experiences, and we need more studies to assess the impact of these biomarkers on ADE and patients' outcome.

Conclusions

An ASP focused on ADE aims to decrease development of resistant organisms and minimise ecological consequences by reducing exposure to broad-spectrum antimicrobials. Data on the impact of de-escalation on the microbiome and emergence of resistant organisms is inconclusive. There

Table 1 Summary of effect of ADE on different outcomes

Advantages	No difference	Disadvantages
Resistance development	LOS	Duration of antimicrobial therapy
Evidence is limited and inconclusive	Meta-analyses, RCT, observational studies—no effect	Mixed results from observational studies (3 no effect, 2 ↑duration and 1 ↓duration)
Several studies—no effect		RCT—↑ total duration
2 studies—trend towards ↓MDR bacteria		
1 study—↓carbapenem-resistant *Acinetobacter*		
Mortality		Superinfections
1 meta-analysis—↓mortality		RCT—↑ superinfections
1 meta-analysis—↓mortality in CAP and ICU associated pneumonia (but not other groups)		2 studies found no difference
1 meta-analysis (BSI and pneumonia)—no effect		Empiric broad-spectrum antimicrobial overuse
Observational studies trend towards ↓mortality (but possible bias)		Theoretical risk but if ADE used as part of a multi-AMS approach alongside local guidelines risk is minimal

ADE, antibiotic de-escalation; MDR, multi-drug resistant; CAP, community acquired pneumonia; ICU, intensive care unit; BSI, blood stream infection; LOS, length of stay; RCT, randomised control trial; AMS, antimicrobial stewardship.

remains a need to establish the real impact of ADE on resistance development. Evidence to date is heterogenous and low quality but suggests that narrowing the antibiotic spectrum is safe. As well as potentially reducing the acquisition of MDR bacteria one retrospective observational study from Singapore (Lew *et al.*, 2015) showed significantly reduced incidence of diarrhoea [9/204 (4.4%) versus 12/96 (12.5%), P=0.015] and fewer adverse drug reactions [11/204 (5.4%) versus 12/96 (12.5%), P=0.037] in the carbapenem de-escalation group compared to continuation group (31). A case-control study (Armand-Lefèvre *et al.*, 2013) showed resistance development can occur early (after 1–3 days) (33) and two consecutive antimicrobial agents with differing spectrums may have a cumulative deleterious effect on the microbiome. There are mixed results from studies regarding risk of superinfections and effect of ADE on duration of therapy. Using ADE as a QI indicator could encourage overuse of broad-spectrum empiric treatment and is not recommended. Please find the studies included in this review which had outcomes on ADE in Table S1.

Antimicrobial consumption, irrespective of antibiotic class, is linked to AMR. Decreasing antibiotic exposure should be a priority of ASP, and ADE can help reduce broad-spectrum exposure and reduce selective pressure but should not be used alone. Well-designed studies are needed to understand the benefits and risks of de-escalation of antimicrobial therapy in ICU patients. An ASP should include a wide range of measures including optimising empiric therapy with infection site specific guidelines, up to date local resistance data and assessment of host factors, including risk of resistant or atypical pathogens, optimising pharmacokinetics and pharmacodynamics of chosen therapy, a review at day 2–3 with relevant microbiology results and clinical progress and early cessation of antibiotics in unproven infection and ADE where feasible, and efforts to reduce the duration of antimicrobial therapy where appropriate. Involvement of an infection specialist is beneficial and rapid diagnostics may play an increasing role.

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Footnote

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Supplementary

Table S1 The main characteristics of studies that had outcomes on the effect of antibiotic de-escalation, by section

Reference	First author	Publication year	Study type	Effect of ADE
Effect of ADE on development of resistance				
(11)	De Bus	2020	Prospective observational	Trend towards ↓
(29)	De Bus	2016	Retrospective observational	No difference
(30)	Weiss	2016	Retrospective observational	Trend towards ↓
(21)	Gonzalez	2013	Retrospective observational	Trend towards ↑
(31)	Lew	2015	Prospective observational	↓
Effect of ADE on clinical outcomes: mortality				
(11)	De Bus	2020	Prospective observational	No difference
(19)	Tabah	2016	Meta-analysis	↓ mortality
(36)	Paul	2016	Meta-analysis	No difference
(37)	Ohji	2016	Meta-analysis	No difference (VAP, BSI, UTI, septic shock). ↓ mortality CAP
(38)	Shime	2011	Observational study	No difference (trend towards ↓ mortality)
(39)	Lee	2017	Observational study	No difference (trend towards ↓ mortality)
(40)	Leone	2014	RCT	No difference
Effect of ADE on clinical outcomes: length of stay (LOS)				
(30)	Weiss	2016	Retrospective observational	No difference
(21)	Gonzalez	2013	Retrospective observational	No difference
(36)	Morel	2010	Retrospective observational	No difference
(40)	Leone	2014	RCT	No difference
(41)	Paul	2016	Meta-analysis	No difference
(42)	Ambaras Khan	2018	Meta-analysis	↓ LOS
Effect of ADE on clinical outcomes: duration of antimicrobial therapy				
(29)	De Bus	2016	Retrospective observational	↑ duration
(30)	Weiss	2016	Retrospective observational	No difference
(40)	Leone	2014	RCT	No difference initial duration but ↑ overall
(43)	Álvarez-Lerma	2006	Prospective observational	No difference
(44)	Trupka	2017	Observational, cross-over	No difference
(45)	Mokart	2014	Observational	↑ duration
(46)	Li	2018	Retrospective observational	↓ duration
Risks of ADE strategy: superinfections				
(40)	Leone	2014	RCT	↑
(43)	Álvarez-Lerma	2006	Prospective observational	No difference
(54)	Joffe	2008	Multicenter observational	No difference
Risk of ADE strategy: empiric broad spectrum antimicrobial treatment overuse				
			Theoretical risk: no data at present	

ADE, antibiotic de-escalation; VAP, ventilator-associated pneumonia; BSI, blood stream infection; UTI, urinary tract infection; CAP, community-acquired pneumonia; RCT, randomised control trial; LOS, length of stay.

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