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NARRATIVE REVIEW

Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions—a viewpoint of experts

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Abstract

Antimicrobial de-escalation (ADE) is defined as the discontinuation of one or more components of combination empirical therapy, and/or the change from a broad-spectrum to a narrower spectrum antimicrobial. It is most commonly recommended in the intensive care unit (ICU) patient who is treated with broad-spectrum antibiotics as a strategy to reduce antimicrobial pressure of empirical broad-spectrum therapy and prevent antimicrobial resistance, yet this has not been convincingly demonstrated in a clinical setting. Even if it appears beneficial, ADE may have some unwanted side effects: it has been associated with prolongation of antimicrobial therapy and could inappropriately be used as a justification for unrestricted broadness of empirical therapy. Also, exposing a patient to multiple, sequential antimicrobials could have unwanted effects on the microbiome. For these reasons, ADE has important shortcomings to be promoted as a quality indicator for appropriate antimicrobial use in the ICU. Despite this, ADE clearly has a role in the management of infections in the ICU. The most appropriate use of ADE is in patients with microbiologically confirmed infections requiring longer antimicrobial therapy. ADE should be used as an integral part of an ICU antimicrobial stewardship approach in which it is guided by optimal specimen quality and relevance. Rapid diagnostics may further assist in avoiding unnecessary initiation of broad-spectrum therapy, which in turn will decrease the need for subsequent ADE.

Keywords: Antimicrobial, Antibiotic, De-escalation, Antimicrobial stewardship, Antimicrobial resistance, Sepsis

Introduction

Antimicrobial de-escalation (ADE) is a strategy to decrease the spectrum of the empirical antimicrobial regimen a few days into the treatment [1]. Multiple definitions have been used in the past but there appears to be consensus that ADE refers to stopping one or more components of combination therapy, changing an antimicrobial for another molecule with a narrower spectrum or a combination thereof (Fig. 1) [2]. Table 1 provides an overview of the terminology commonly used in this context.

ADE was introduced in the intensive care unit (ICU) at the beginning of the century with the rationale that it may prevent the harm from (extremely) broad-spectrum empirical regimens [3]. Those were becoming increasingly necessary due to the emerging and mounting phenomenon of antimicrobial resistance (AMR) [4].

Many studies have looked at ADE in the ICU. Most were observational and published from centers with a particular interest in antimicrobial stewardship programs (ASP). ADE appears to be safe, but while improved

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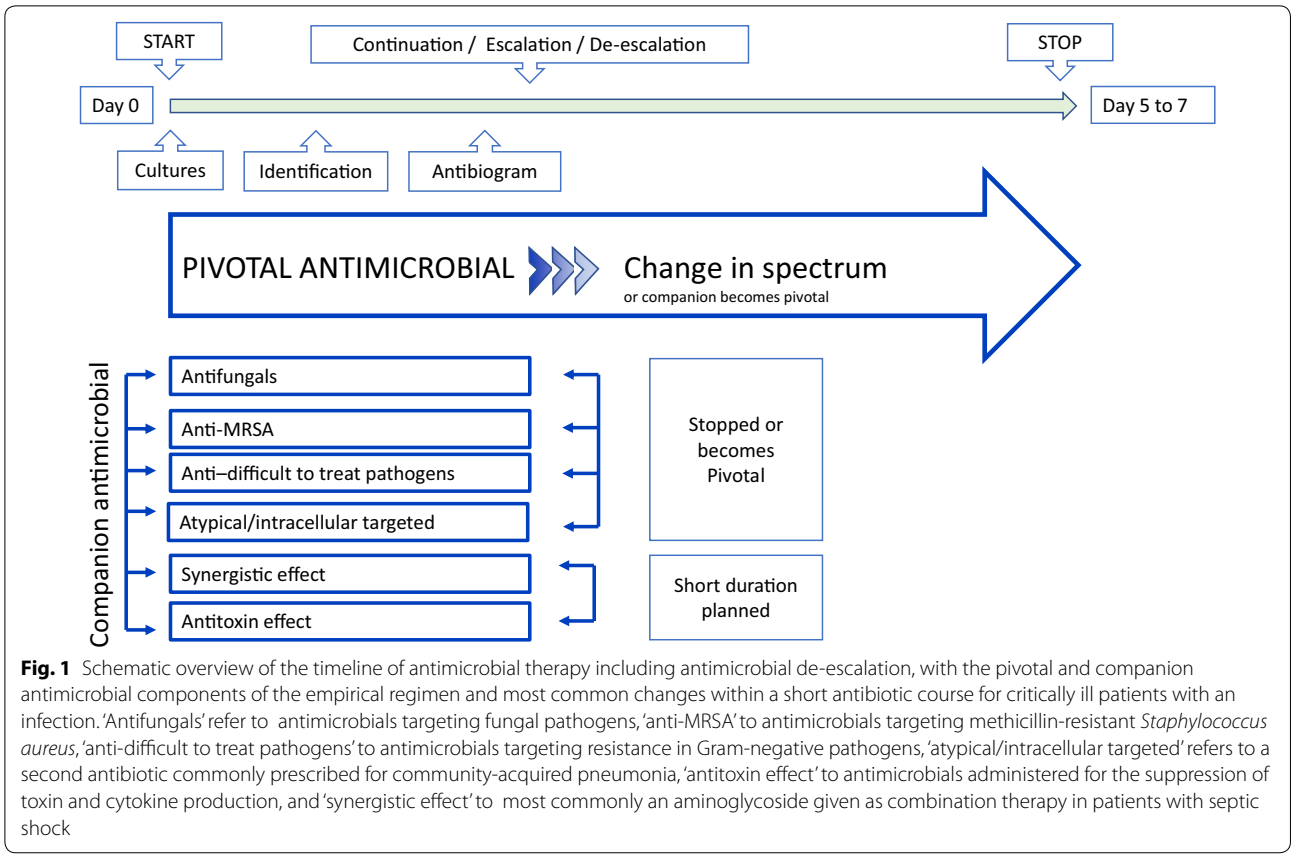


Fig. 1 Schematic overview of the timeline of antimicrobial therapy including antimicrobial de-escalation, with the pivotal and companion antimicrobial components of the empirical regimen and most common changes within a short antibiotic course for critically ill patients with an infection. 'Antifungals' refer to antimicrobials targeting fungal pathogens, 'anti-MRSA' to antimicrobials targeting methicillin-resistant *Staphylococcus aureus*, 'anti-difficult to treat pathogens' to antimicrobials targeting resistance in Gram-negative pathogens, 'atypical/intracellular targeted' refers to a second antibiotic commonly prescribed for community-acquired pneumonia, 'antitoxin effect' to antimicrobials administered for the suppression of toxin and cytokine production, and 'synergistic effect' to most commonly an aminoglycoside given as combination therapy in patients with septic shock

Table 1 Definition of terms

Terms	Definition
Adequate antimicrobial therapy	Antimicrobial therapy active against the pathogen responsible for infection, administered at the dose, route and mode in accordance to best current practices
Broad-spectrum therapy	Antimicrobial therapy aimed at covering all relevant pathogens potentially causing the infectious episode
Narrow-spectrum therapy	Antibiotic with activity exclusively against one specific pathogen or a more limited group of pathogens
Combination therapy	Two or more antibiotics aimed at 1. covering the identified or suspected pathogen(s) with more than one antibiotic to hasten pathogen clearance using antimicrobials with different mechanisms of action or 2. broadening antimicrobial spectrum
Ecological impact	Collateral effects of the antimicrobials administered to the patient, including downstream effects on the patient's microbiota favouring the acquisition, selection and overgrowth of multidrug-resistant bacteria
Pivotal antibiotic	Antibiotic that is central to the regimen, usually a beta-lactam antibiotic for Gram-negative severe infections
Companion antibiotics	Antibiotics added to the regimen to broaden the spectrum to pathogens not covered by the pivotal agent. Commonly glycopeptides and/or aminoglycosides, which are interrupted most of time after a short exposure (3 days)

outcomes are frequently reported, selection bias is prevalent: ADE is more frequently used in patients who are clinically improving [5]. We should be careful not to infer causation between ADE and improved clinical outcomes [1].

Regardless of the definition used or the intervention studied, it should be very clear that overall antimicrobial consumption is linked to AMR, irrespective of the class of antibiotics. Decreasing antibiotic exposure should, therefore, be the priority of any ASP [6].

In this manuscript, we aim to highlight recent insights into ADE, its value in ASPs and the practical application as well as discuss the controversies and

pitfalls related to the topic. For an overview of recent studies, we refer to the ESICM/ESGCIP position statement on this topic [2].

What do we expect from ADE?

ADE aims to reduce broad-spectrum antimicrobial exposure, and as a result decrease the emergence of AMR, without impairing patient outcomes [5]. A randomised clinical trial comparing continuation or de-escalation of the pivotal or main antimicrobial found a decrease in broad-spectrum antimicrobial use in the de-escalation group, while the mortality rate was similar in both groups [7]. Reducing antimicrobial exposure is essential in any ASP, as antimicrobial use has an important impact on the gut where overgrowth of organisms resistant to antimicrobials significantly impacts the intestinal microbiome.

Inadequate empirical therapy has been associated with an increased mortality rate in septic shock [8]. ADE indirectly legitimises the use of broad-spectrum empirical therapy, as it suggests that—once the causative pathogen has been identified and the susceptibility is known—therapy can be scaled down. Therefore, ADE would limit any further harm to the microbiome, inflicted by broad-spectrum agents and would thus allow for a broad-spectrum empirical safety net as well as for the application of antimicrobial stewardship principles. Observational studies and meta-analyses have suggested improved outcomes associated with ADE [9, 10], but as mentioned before, any causal effect is not likely to be present.

Finally, as discussed elsewhere, ADE may be associated with cost saving, since it allows reducing the use of expensive antimicrobials for short durations and using older and less expensive drugs for the continuation of treatment [5].

The dark side of de-escalation

ADE was welcomed as a remedy to mitigate the effects of empirical broad-spectrum agents with the assumption that short courses of those agents have little impact on the development of AMR. However, this assumption has given us an unwarranted sense of safety that ADE would prevent the ecological consequences of extremely broad-spectrum empirical antimicrobial treatment regimens. These regimens are often considered lifesaving and necessary in patients with severe infections especially in the setting of high prevalence of AMR. Recent research, however, has clearly shown that AMR appears earlier than expected in the course of treatment, probably within the first few days [11]. Thus, ADE should not be used as an excuse for the indiscriminate prescription of broad-spectrum antimicrobial regimens.

When analysing the influence of this sense of safety that ADE has on our prescribing behaviour, we need to consider two other issues. First, although none of the involved studies was designed to assess its effect on total duration of therapy, ADE has been associated with an increase in the total duration of antimicrobial therapy [1]. There may be multiple possible explanations for this finding, including potential "errors in counting total days of therapy" and the perception that narrow-spectrum antimicrobials are harmless and can be continued for longer periods of time [12]. Second, the risk of using ADE as an excuse to continue antimicrobials in the absence of infection is likely to cause more harm than stopping all antimicrobials alltogether. On one hand, narrower agents will still cause the emergence of AMR, and on the other, continuing antimicrobials in the absence of infection may decrease the quality of diagnostic decision-making [13]. Finally, the broad- and narrower spectrum antimicrobials may differ in their pharmacokinetics resulting in insufficient concentrations at the site of infection and PK/PD target attainment, often with a disadvantage for narrow-spectrum antibiotics [14].

ADE is often presented as an effective strategy to reduce AMR, but no direct associations were found between ADE and ecological impact in ICU patients. In an observational comparative study, De Bus et al. did not find associations between de-escalation and emergence of multidrug-resistant (MDR) pathogens [15]. Similar findings were reported in a randomised clinical trial comparing ADE and continuation of the pivotal antimicrobial [7]. Small but significant differences in carbapenem-resistant *Acinetobacter* spp. colonisation were observed after carbapenem de-escalation [16]. Large numbers of patients are probably required to find a difference in terms of AMR, suggesting a limited overall ecological impact. In brief, the level of evidence showing that ADE reduces AMR is low.

ADE, at least for the pivotal agent, is defined by the switch from a broad-spectrum antimicrobial to a narrower spectrum antimicrobial. However, "grading" of antimicrobials according to spectrum is not an easy task. A French group proposed a six-rank consensual classification of beta-lactam antibiotics. Despite several Delphi rounds, no consensus was reached to differentiate piperacillin/tazobactam, ticarcillin/clavulanic acid, fourth-generation cephalosporin and antipseudomonal third-generation cephalosporin. The group could not find an agreement on the delay within which ADE should be performed and on whether or not the shortening of antimicrobial therapy duration should be included in ADE definition [17]. In parallel, a group of experts from the US developed a numerical score to measure the spectrum of antimicrobial regimens [18]. The classification that was obtained using a Delphi consensus procedure based on clinical scenario's differed from the one reported by the

French group. Piperacillin–tazobactam was the worst ecological antimicrobial for the US group, whereas imipenem was selected by the French group. This discrepancy underlines how difficult it is to assess the ecological impact of antimicrobials, and thereby to define ADE.

Is two (always) better than one?

ADE implicitly involves the use of more than one antimicrobial: either the number of antimicrobials is reduced in patients who receive combination antimicrobial therapy initially, or patients are administered two different antimicrobials sequentially. Although we generally assume that ADE is beneficial, there may also be downsides to the use of multiple antimicrobials, even for short periods of time.

First, when one antimicrobial is replaced by another with a narrower spectrum, it should be considered that two antimicrobials may cause more harm than one. For example, when empirical treatment with meropenem is switched to levofloxacin, this may be considered as narrowing of the spectrum, but that patient is exposed to two courses of short duration antimicrobial therapy with a different —and potentially—cumulative damaging effect on the microbiome. Short exposure to broad-spectrum antimicrobials already results in early disruption of intestinal microbiome [19]. It has been demonstrated that as little as 1 day of exposure to imipenem is enough to result in AMR [11]. For each day of additional exposure to cefepime or piperacillin/tazobactam, the risk of MDR emergence increases with 8% [20]. Furthermore, antibiotics have been found to persist for up to 48 h at low concentrations after discontinuation [21] and these low concentrations are at high risk for the emergence of resistance.

Second, combining antimicrobials in empirical therapy aims at broadening the spectrum of therapy, reducing AMR or creating synergy between drugs; although this was documented in experimental studies, the latter two effects were never confirmed in vivo. While the reduced number of antimicrobials after ADE may appear advantageous, one should question the true need for multiple antimicrobials in the first place [22]. Better risk stratification, the use of rapid diagnostic techniques and the use of surveillance cultures are all strategies that could avoid the use of multiple antimicrobials empirically [23].

Finally, the impact of combining different antibiotic classes on the intestinal flora is largely unknown [24]. Recent studies have shown differential effects according to the antimicrobial activity against anaerobes, with a four times higher risk of gut colonisation with ceftriaxone resistant Gram-negative bacteria after being exposed to anti-anaerobe antimicrobials [25]. A better insight into the effect of different antimicrobials is needed to understand the dynamics that are relevant in ADE.

The role of ADE in ASP: taking a broader perspective

In most practice guidelines for ASP, ADE appears as a recommended stewardship objective [26]. In the US, a survey showed that prior authorisation for selected antimicrobials, antimicrobial reviews with prospective audit and feedback, and guideline development were common strategies in ASPs [27], while ADE was not explicitly reported as a major component. In a French survey, reassessment of antimicrobial prescriptions, but not specifically ADE, appears as a major element of ASP for most respondents [28]. In nine Dutch hospitals, ADE was not yet included in ASP, although responders disclosed that the intervention was required in the future program [29].

Of the two most evidence-based ASP interventions (post-prescriptional review and prior authorisation [26]), post-prescriptional review (which may include ADE) gained some advantage over the latter because of its larger effect on reducing antimicrobial use [30]. In the light of pitfalls of ADE mentioned before, post-prescriptional review by an expert remains essential for good antimicrobial practice. However, reviewing antimicrobial use only after prescription may equally stimulate unnecessary initial broad-spectrum empirical treatment.

It is becoming increasingly clear that duration of therapy can be reduced to 5–7 days for most infections in ICU patients [31], with specific exceptions such as some pathogens (e.g. *S. aureus*), patient conditions (immunosuppression) or inadequacy of source control. This development certainly questions the indication for ADE. If cultures become available 48–72 h after the start of therapy, what is the expected benefit of changing well-instituted therapy for 2 more days? Apart from the considerations discussed earlier, getting ADE done properly in daily practice (collect cultures, correctly interpret cultures, instigate change of therapy in concordance with prescribers, prevent a time gap without effective antimicrobial therapy, adapting dose due to different PK properties of new antimicrobial, etc.) can be a challenge with little apparent benefit.

However, this does not mean in any way that cultures should not be taken. For many reasons other than ADE (such as potentially inappropriate therapy, duration of therapy, MIC determination, complications, follow-up, epidemiology), appropriate sampling remains pivotal to ASPs in ICU.

Rapid diagnostics (different molecular technology sepsis panels, metagenomics), another component of ASP, undoubtedly will change the way we will use antimicrobials in the future. For example, an observational retrospective

study suggested that the use of a rapid test detecting MRSA within the first hour after bronchial sampling was associated with a reduction of empirical vancomycin or linezolid [23]. An ongoing multicentre randomised clinical trial evaluates the use of a rapid diagnostic test detecting early the presence of ESBL in patients with suspected infections to *Enterobacteriaceae* [32]. Rapid diagnostics would also give more opportunities for watchful waiting and not start broad-spectrum antimicrobial therapy, thereby eradicating ADE practice in subgroups of patients [33]. Especially in patients without shock, this could probably be done safely. Unfortunately, there are still a lot of uncertainties regarding the use of these tests to allow their routine use in septic ICU patients.

Individualisation of antimicrobial treatment based on risk assessment and rapid diagnostics may be a less appealing strategy in institutions with high resistance rates. It is certainly easier to avoid carbapenems in hospitals where AMR rates are low. Moreover, rapid diagnostic techniques are often unavailable in low- and middle-income countries where an already higher resistance burden leads to a vicious circle of increasing AMR and indiscriminate broad-spectrum empirical treatment. In these settings where control of AMR is most urgently needed [34]—in spite of its limitations—ADE may still be felt as one of the few options to decrease broad-spectrum antimicrobial use. Counterintuitively, promoting ADE may cause an increase in broad-spectrum antibiotic use as an unexpected side effect in these settings [35].

The risks of using ADE as a performance indicator

ADE has been proposed repeatedly as an important objective for ASP in hospitals. It has been selected in a RAND-modified Delphi procedure among experts as 1 of 14 key quality indicators (QI) to measure and improve appropriate use in hospital [36] and clinimetric properties have been tested in a large group of hospitalised patients [37, 38]. Furthermore, it has been associated with reduced mortality, hospital length of stay and cost reduction in a systematic review, although the lack of a clear definition hampers interpretation of this association [39]. As a result, ADE has become an essential quality metric to evaluate the success of an ASP. For measurement purposes, "appropriate ADE" has been operationalised as the number of patients in whom empirical antimicrobials have been changed to a less broad-spectrum regimen (numerator) divided by all patients who were started on empirical therapy on admission (denominator). The score of the indicator is expressed as a percentage. In routine hospital practice, performance on key QIs is regarded as increasingly important as hospitals are often publicly and financially punished by healthcare authorities or health insurance companies if they do not meet expectations. As ASPs are now considered essential for the quality and safety of hospital care, it is likely that QIs related to ASP will come under increasing scrutiny in the following years. A higher percentage of "appropriate ADE" will be regarded as one of the elements of a more successful implementation of an ASP.

However, due to the ongoing discussion about the definition of appropriate ADE, it remains extremely difficult to judge and compare hospitals on this specific QI: when is ADE actually considered appropriate, which are definitions and cut-off points? Here are two examples of how misinterpretation and unwanted effects of mandatory ADE reporting could play out:

1. If broad-spectrum antimicrobial therapy is prescribed for a patient with nosocomial pneumonia, e.g. with meropenem and vancomycin and it is changed by simply stopping vancomycin on day 2, this will count as ADE, even if the pivotal antimicrobial (meropenem) remains unchanged. This (undesirable) course of events would still be considered ADE and add to a higher percentage of hospital-wide "appropriate ADE".
2. On the other side, patients who are prescribed (relatively) narrow-spectrum antimicrobial therapy (e.g. starting with flucloxacillin for a suspected *S. aureus*-related skin and soft tissue infection) and need not be changed once cultures become available, are 'punished' as no ADE has taken place while best medical practice has been followed.

In summary, it becomes easy to achieve good QI results while performing poor antimicrobial stewardship. Even worse, starting narrower spectrum therapy is discouraged and broad-spectrum empirical is encouraged (as this will increase ADE performance metrics). A high performance on a QI for ADE may only reflect an overuse of empirical broad-spectrum antimicrobials. Clearly, the opportunities to de-escalate are largely determined by empirical therapy and, therefore, using ADE as an isolated quality measure should be discouraged.

Microbiological sample interpretation: not so simple

Identifying the pathogen responsible for infection is critical for ADE, which relies on an accurate interpretation of microbiological results in the context of clinical presentation of infection. A crucial necessity is to obtain cultures from relevant sites before antibiotics are administered, as the absence of cultures or negative cultures has been associated with non-ADE [1]. The challenge and complexity of this process in routine practice are often underestimated in recommendations

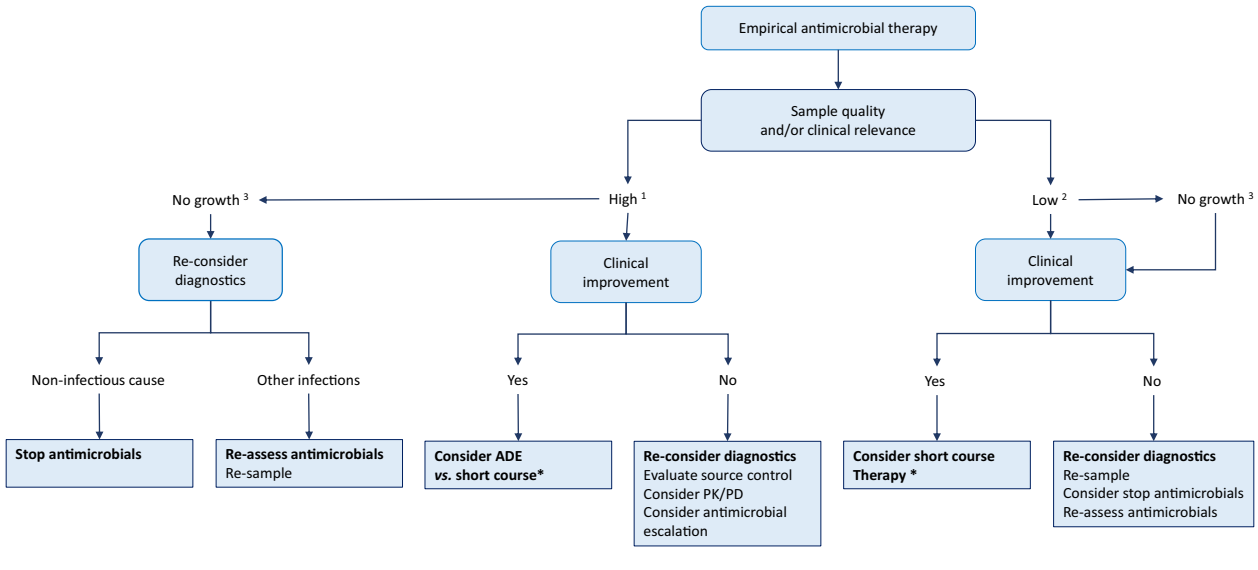
and guidelines. First, all samples are not equal: samples obtained from sterile sites have a different role compared to samples obtained from superficial sites: e.g. positive blood cultures are more relevant than samples collected from skin wound or through a drain. In this context, respiratory samples are the most challenging to interpret in the absence of quantitative cultures or other diagnostic approaches that allow discrimination between infection and colonisation. Clearly, defining ventilator-associated pneumonia as well as hospital-acquired pneumonia remains difficult and may be an obstacle to ADE. Second, infective pathogens should be discriminated from colonising pathogens, in the absence of accurate biomarkers. Third, all pathogens are not equal: identification of *S. aureus* is more significant than that of coagulase-negative Staphylococci, although this should be modulated by the clinical context. In brief, there are some situations in which the confidence in a sample and its clinical relevance are higher compared to some other situations. Here, the resulting strategy will rely strongly on the microbiological result.

To resolve this issue, an excellent interaction between intensivists, surgeons, radiologists, microbiologists and infectious diseases physicians is required. While ADE is sometimes conducted in patients in whom no microbiological samples were available [1], obtaining samples before initiating any antimicrobial treatment should be a general rule, and the quality and relevance of these samples are critical.

In the meantime: de-escalate or not?

Our purpose is not to exclude ADE as a part of ASP's, and we remain convinced that ADE has great value. As discussed above, until the validation and large-scale use of rapid diagnostic techniques is a reality, ADE—or rather streamlining antimicrobial therapy—will remain essential. Based on the microbiological results available and clinical course of the patient, we recommend a clinical strategy that integrates ADE while acknowledging the inherent limitations of this approach.

The planned duration of antimicrobial therapy is also to be considered when antimicrobial therapy is re-evaluated (Fig. 2). For short courses of antimicrobial therapy (5 days or less), continuing the empirical treatment, if appropriate, can avoid sequential use of different antimicrobials and thus multiple impacts on the microbiome. Another option, which should always be considered is stopping the antimicrobial treatment. Indeed, in patients who are improving, e.g. in whom the SOFA score decreased during the first 48–72 h, the need for continuing treatment beyond day 3 should be debated for a significant number of infections. A seminal randomised clinical trial suggested that, in patients with non-severe



[1] High:
Blood culture (pathogens not considered as colonization),
Samples collected in an identified focus (computed tomography scan, surgery),
Samples collected in a focus responding to all criteria used for the clinical definition of a given infection
In relation with the clinical picture
[2] Low: Positive culture without clinical picture or samples from drain or no relevant site or no relevant culture
[3] Samples were collected before antibiotics were given
*According to practice guidelines

Fig. 2 Antimicrobial management strategies integrating antimicrobial de-escalation in clinical practice

pulmonary infiltrate, a course of 3 days of ciprofloxacin was as efficient as a prolonged treatment [40]. The feasibility of ultra-short course of antimicrobial treatments has been suggested in an observational study comparing 259 patients with ventilator-associated pneumonia treated for 1–3 days and 1031 treated for > 3 days, the outcomes of two groups being similar [41]. For longer courses of antimicrobial therapy (7 days or more), ADE should probably be a recommended strategy, particularly if high-quality and clinically relevant samples are available. Its presumed effects on AMR and cost are relevant in these conditions. For intermediate-duration antimicrobial therapy (5–7 days), decisions should be tailored according to institutional ASP recommendations.

Ranking antibiotics according to the local epidemiology and available drugs probably is more important than trying to obtain an international consensus on how antibiotics should be classified.

In patients with confirmed infection and who are deteriorating, a single integrated recommendation is impossible. In our opinion, the first step is to rule out other—infectious and non-infectious—causes of shock. The second step is to confirm the adequacy of source control and dosing of antimicrobial(s). Only then, the empirical antimicrobial treatment can be either maintained, escalated, de-escalated or stopped.

In patients with negative cultures, another cause of organ dysfunction should be considered. If the mechanism is non-infectious, the antimicrobial treatment can be stopped; if another source of infection is found, new samples are required, and antimicrobials should be adapted to the new clinical picture.

Conclusion

In conclusion, ADE has become more clearly defined and understood, but until now, a demonstrable impact on AMR is lacking. ADE should not be used as a 'carte blanche' for the unrestricted use of (very-) broad empirical antimicrobial therapy and it is important to recognize that it may have unexpected and unwanted side effects. The impact of ADE on the microbiome needs further study while one should consider that sequential exposure to two different antimicrobials may not necessarily be better than to one. We advocate against the use of ADE as a QI in the ICU.

In the meantime, ADE should clearly be regarded as an important component of ASPs. When applying ADE, planned duration of therapy, as well as sample quality and relevance need to be incorporated in the decision-making process. Efforts should also be aimed at optimising empirical therapy, which may reduce the need for ADE later on; this is where rapid diagnostic techniques may have an important role.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no competing interests.

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