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EDITORIAL

De-escalation of Antimicrobials: Current Updates

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INTRODUCTION

There has been a paradigm shift in how antimicrobials are prescribed from 'start low and go slow' to 'go hard and go home'.[1] This has led to the prescribing of empirical broad-spectrum antimicrobials to target the suspected pathogens. Thus, timely antimicrobial de-escalation (ADE) or narrowing of antimicrobial therapy has become ever more essential in preventing the development of antimicrobial resistance (AMR).

Although 'Antimicrobial De-escalation' is often used, it lacks a uniform definition. It is defined differently by different authors; for example, Kollef MF proposed ADE as beginning treatment with an empirical broad-spectrum antimicrobial therapy, aiming to cover the probable infectious agent and narrowing down therapy by either changing the antimicrobial agent or discontinuing an antimicrobial combination.[2] Some consider shortening the duration of antimicrobial therapy also a part of ADE.[3,4] In short, ADE is a strategy that allows for the rational use of broad-spectrum antimicrobial therapy as the empiric treatment initially and minimizes the overall exposure. Agency for Healthcare Research and Quality (AHRQ) recommends *Four Moments o Antimicrobial Decision Making*, which are critical: when considering to prescribe an antimicrobial, just before initiating the antimicrobial therapy, on the subsequent day of initiation, and lastly, deciding on the appropriate duration of treatment.[5] ADE as a therapeutic intervention can be applied prospectively during the third and the fourth moments of such decision-making while monitoring the patient's clinical response to prescribed antimicrobials. The prospective nature of ADE may be more accepted by physicians than restrictive strategies such as formulary restriction. Each time, one must weigh the risk-benefit for the betterment of the patient population. Hence, practising ADE in real-world situations is a tedious/tricky task for the scientific community.

CURRENT UPDATES

ADE has been associated with numerous benefits, such as a decrease in antimicrobial-related adverse events and costs, decreased selection pressure and the emergence of AMR without compromising patient outcomes.[6] Considering the benefits of ADE, it is widely recommended for routine practice in ICU settings even though robust evidence is scarce for or against ADE.[5-8] Most of the evidence from clinical studies is based on observational studies conducted on healthcare-associated infections, especially hospital-acquired pneumonia. A Cochrane review (2013) that evaluated the effectiveness and safety of ADE in adults diagnosed with sepsis, severe sepsis or septic shock (n= 493 studies) found no adequate, direct evidence for the safety or efficacy of ADE.[9] Another systematic review (2020) found low evidence for the safety of ADE and recommended it in patients requiring long-term antimicrobial therapy.[10] Further, more than 45 randomized controlled trials (RCTs), including their meta-analyses that compared the efficacy and safety of

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short-course over longer courses of antibiotic therapy for the treatment of community-acquired and nosocomial pneumonia, acute exacerbation of chronic bronchitis and sinusitis, complicated urinary and intra-abdominal infections, Gram-negative bacteraemia, acute bacterial skin infections, osteomyelitis, and septic arthritis, found shorter course therapy to be non-inferior to longer courses.[11] Most recent Surviving Sepsis Campaign Guideline (2021) recommends daily assessment for possible ADE over using fixed durations of therapy and early discontinuation of all antimicrobial therapy if the infection is ruled out.[7] Another RCT (2024) in patients with bacteraemia caused by Enterobacterales found de-escalation from antipseudomonal beta-lactams to non-pseudomonal antibiotics to be similar in clinical efficacy.[12] Hence, ADE does not seem to cause patient harm, and well-designed RCTs will provide more robust evidence in the future.

In contrast to the contemporary evidence on the benefits of ADE, the actual rates of its practice are low and differ based on definitions used and the severity of illnesses. DIANA study revealed an ADE rate of only 16% in critically ill patients.[13] Low rates of ADE in clinical practice could be due to the natural propensity of clinicians not to change antimicrobial regimens that have proven to be effective. Other possible reasons could be poor microbiological laboratory support, lack of local guidelines, or scarcity of evidence on ADE efficacy and safety.

Factors that are positively associated with ADE practice include microbiological documentation of pathogen(s), initial appropriate empirical antimicrobial therapy, proper infective diagnosis, restricted usage of multiple, companion, or redundant antimicrobials, baseline severity of illness, timely monitoring the clinical responses, clinical improvement at the time of culture reports, and compliance with guidelines or local antibiogram of antimicrobial prescription. Conversely, detecting a multidrug-resistant pathogen, polymicrobial infection, multiple concurrent infections, or infections with a substantial risk of undiagnosed pathogens, e.g., intra abdominal infections, were negatively associated with ADE.[14] All these factors are directly or indirectly associated with ADE or escalation of therapy in actual practice.

DE-ESCALATION METHODS

There are several strategies for implementing ADE in different hospital settings based on the above primal factors of when to stop, switch, or change antimicrobials.

1. Right infective diagnosis is the first strategy of AMSP. If there are no documented signs of infection, or sepsis, or inflammatory signs that can be explained by non-infective diagnosis, stopping antimicrobial therapy must be considered as a de-escalation strategy.
2. Appropriate culture-guided de-escalation becomes pivotal as it is incredibly challenging to de-escalate antimicrobial therapy without microbial documentation of pathogen and culture sensitivity reports.
3. Switching from irrational broad-spectrum therapy or reductant antimicrobials to rational antimicrobials by following local antibiogram and national/international guidelines is a major de-escalation strategy, and this is to be assessed daily.
4. Practising a short course of antimicrobial therapy using evidence-based medicine against various diseases at the right time during follow-up is a crucial de-escalation intervention.
5. Syndromic multiplex polymerase chain reaction (PCR) panels help in the early molecular diagnosis of infectious AMR pathogens. However, its role in de-escalation before the availability of the culture sensitivity report has yet to be established. In the near future, it can be one of the promising strategies.[15]
6. Similarly, screening methicillin-resistant *Staphylococcus aureus* (MRSA) through nasal swab PCR in suitable patients and, if found negative, stopping their empirical coverage is a good strategy, but it needs local research and implementation.[16]
7. Similarly, the role of biomarkers (e.g., procalcitonin, galactomannan, etc.) of various infections is yet to be proven as a De-escalation intervention but can be tried and researched.

There are no evidenced parameters to measure ADE outcomes. However, as studied before, few basics apply to assess therapeutic interventions, such as clinical cure, mortality benefit, cost-effectiveness, hospital stay, and serious adverse events.

LIMITATIONS

Switching from a broad-spectrum antimicrobial agent to a narrower-spectrum antimicrobial is considered as de-escalation. However, this classification of antimicrobials according to a spectrum is a challenging

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task. In infections where shorter courses of antimicrobial therapy are recommended, switching a broad-spectrum antimicrobial agent to a narrow spectrum exposes the patient to two different antimicrobial agents and their side effects and effects on the microbiome. The assumption that short courses of antimicrobial therapy have a limited impact on the development of AMR is challenged by recent research showing that AMR can appear even within the first few days of antimicrobial treatment.[17] Thus, ADE should not be used as an excuse for the indiscriminate use of various antimicrobials in a patient.

Microbiological documentation of infection by cultures is critical in ADE. However, the interpretation of microbial data is more complex. Infective pathogens need to be differentiated from non-pathogens, such as colonizers, commensals, or contaminants. No one knows when these colonizers or commensals turn into pathogens in a patient, nor is there any significant evidence. Samples obtained from sterile sites have a different role than samples obtained from superficial sites. Many newer antimicrobials do not have minimum-inhibitory concentration (MIC) cut-offs. Therefore, how the prescriber can plan to de-escalate these antimicrobials needs to be clarified. Furthermore, no de-escalation strategies for antimicrobial treatments exist in medical or surgical prophylaxis cases. Considering these limitations, we can say the ADE strategy has a long way to go before evidence sets in.

CONCLUSIONS

ADE is the need of the hour to tackle antimicrobial overuse and its devastating consequences. Among the *Four Moments of Antimicrobial Decision Making,* ADE can be implemented in the last two moments, i.e., reviewing de-escalation daily after the initiation and deciding the exact duration of the antimicrobial therapy. ADE can be practised through various ways: stopping antimicrobial therapy when the non-infective diagnosis is more likely, targeted culture-guided treatment, switching to rational/non-redundant antimicrobials based on local/national/international guidelines, switching to short course therapy where indicated, and changing empirical treatment based on proper infective diagnosis with the help of molecular testing including PCR and biomarkers such as pro-calcitonin, galactomannan, etc. However, more clinical research is needed on ADE strategies and their outcomes to be effective and safe.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTION

PKP: Conceptualization; Writing the draft; Review and editing; Approving

VT: Writing the draft; Reviewing; Approving

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