

## Reduction of Antimicrobial Resistance and Limiting Use of Antibiotics by the Application of De-escalation and Streamlining: A Review Update

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### Abstract

De-escalation is a critical component that lies at the center of antimicrobial stewardship programs. It is a clinically effective concept in reducing infection with drug resistant isolates. Although there is significant and serious shortfalls like establishment of the real impact of de-escalation on antimicrobial resistance development; it is now well demonstrated that there is no harm for patients, whether it genuinely improve clinical outcomes. Further studies are needed to establish the most effective tools to implement de-escalation, particularly in terms of providing clear guidelines to clinicians to enable them to be confident in applying this maneuver in our country. It is interesting that this concept of de-escalation is now being explored in different types of infection. [*Journal of National Institute of Neurosciences Bangladesh, July 2020;6(2): 140-142*]

**Keywords:** De-escalation; Streamlining; Antibiotic stewardship program; Antimicrobial resistance

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### Introduction

Antibiotic resistant strains are more and more prevalent day by day<sup>1</sup>, whereas, availability of new antibiotic agents is becoming exceptional. The fight against multidrug resistant (MDR), extensively drug resistant (XDR) and pandrug resistant (PDR) bacteria in health-care facilities is a national priority that involves the whole community and especially intensive care units (ICUs) as they can be considered 'factories' for creating, disseminating, and amplifying resistance to antibiotics<sup>2-3</sup>. More than two-thirds of cases of ICU-acquired bacteremia are caused by MDR and XDR bacteria<sup>4</sup>. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), Glycopeptide-resistant enterococci (VRE), extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae (ESBL) and Gram-negative bacteria resistant to carbapenems are increasing at an alarming rate. Rational use of antibiotics along with

cross-transmission prevention is a crucial part of a strategy aiming at reducing the selection pressure. However, the total effect of antibiotic pressure is due to a direct effect on the individual who receives the antibiotic agent, however, also to the indirect impact on the transmissibility of resistant and susceptible strains within an entity such as an ICU<sup>5</sup>. Many studies demonstrated the link between antibiotic use and antibiotic resistance, both at a unit<sup>6-8</sup> and at an individual level on the infecting flora and on the gut microbiota<sup>6,9-10</sup>. However, the intensity of the effect is very difficult to evaluate because of the numerous uncontrolled factors and methodological issues, such as absence of regular screening of the patient's gut flora<sup>6</sup>.

In Bangladesh, antibiotics are available over the counter since dispensing is not restricted to prescription only<sup>11</sup>. Evidence suggests, resistance pattern shows remarkable changes if any antibiotic is

used for a short time in the locality and withdrawn for some time<sup>12</sup>. For effective and optimum antibiotic prescribing, a fundamental understanding on Microbiology is required based on national and local information of their efficacy<sup>13-14</sup>. Antibiotics need to be given early to infected people, properly using aggressive initial dosing and stopping early when possible. Besides, antimicrobial stewardship programs involving pharmacists, physicians and other healthcare providers should be established as antibiotic resistance increases<sup>15</sup>. Hospital can utilize these information or data by evaluating and formulating a policy in infection control practices. De-escalation forms one of the key features of the new treatment paradigm (Table 1)<sup>16</sup>.

Table 1: Key Principles of the New Treatment Paradigm

- Get effective antibiotic selection right first time
- Base antimicrobial selection, both empiric and targeted, on knowledge of local susceptibility patterns
- Use broad-spectrum antibiotics early
- Optimize the antibiotic dose and route of administration
- Administer antibiotics for the shortest possible duration
- Adjust or stop antibiotic therapy as early as possible to best target the pathogen(s) and remove pressure for resistance development (ie, de-escalation)

### De-escalation

Although it is often necessary to initiate a broad-spectrum antimicrobial regimen in patients with severe sepsis, continuing an overly broad regimen contributes to antimicrobial resistance and does not improve patient outcomes. The terms de-escalation and streamlining describe the practice of using culture results as a basis for switching from broad-spectrum or multiple antimicrobials to narrower spectrum or targeted therapy (Table 2)<sup>16</sup>. It may also include changing administration from the intravenous to the oral route, or discontinuing antimicrobials if infection has been ruled out. De-escalation and streamlining may also include narrowing the antimicrobial selection when cultures are negative.

If a patient is receiving antimicrobial therapy for *Pseudomonas aeruginosa* and it is not identified in cultures, de-escalation to an agent without activity against *Pseudomonas aeruginosa* is usually appropriate. Also, if a patient is empirically started on vancomycin specifically for methicillin-resistant *Staphylococcus aureus* and it has not been cultured, it

would be reasonable to discontinue or substitute the vancomycin. Other examples include changing ceftriaxone to penicillin for a susceptible *Streptococcus pneumoniae* isolate, vancomycin to cloxacillin for methicillin-susceptible *Staphylococcus aureus*, or ciprofloxacin to ampicillin for cystitis caused by a susceptible *Escherichia coli*<sup>17</sup>.

Table 2: Practical Clinical Bedside Approach to de-escalation

1. Every patient with severe sepsis on antibiotic therapy should have the need for this considered and formally documented every day
2. No later than day 3, a full assessment of investigation results and clinical progress should be performed and a positive decision should be captured to: Stop the treatment (eg, no infection is present) Narrow the spectrum of the therapy Reduce the number of antibiotics being used, for example, there is redundancy in the therapy or such clinical progress that multiple agents active against the same pathogen(s) are not necessary Not to de-escalate, for example, the specific reason for not de-escalating is documented (eg, lack of microbiology results, lack of clinical improvement)
3. Every day thereafter a positive decision to stop, change, or continue the therapy should be made against specific reasons
4. At every assessment the goal is to stop the therapy, or elements of the therapy, unless a positive and persuasive need for their continuation exists

### Evidence from Clinical De-Escalation Studies

A recent study has been explored the practical application of de-escalation, where data from 113 intensive care unit (ICU) meropenem prescriptions were evaluated. De-escalation was defined as the administration of an antibiotic with a narrower spectrum within 3 days of the start of meropenem. The study found a trend toward a lower mortality rate in patients who had been de-escalated<sup>18</sup>.

There are several more studies<sup>19-23</sup> suggesting that clinical outcome may actually be improved where de-escalation is practiced whereas, continued potent, broad-spectrum empiric therapy may be intrinsically detrimental in some patients. A meta-analysis/meta-regression demonstrated that empiric combination therapy in serious infections can be detrimental in patients at low risk of mortality even while providing significant clinical benefit in high-risk patients<sup>24</sup>. Patients who have already responded to potent, broad-spectrum antimicrobial therapy are similarly at a low risk of death and

therefore may derive more harm than benefit from continued broad-spectrum therapy where de-escalation is not implemented, perhaps as a consequence of the modest but measurable toxicity/side effects of such regimens<sup>17</sup>.

### Advantages of De-escalation

- Can decrease antimicrobial exposure and costs
- Uses reports that are already generated by the microbiology laboratory
- Allows for discontinuation of potentially toxic antimicrobials like vancomycin, aminoglycosides and use of agents with a better safety profile<sup>17</sup>.

### Conclusion

Recommendations to de-escalate treatment may not be accepted because of physicians' reluctance to change therapy if the patient is improving, regardless of culture results. Moreover, the ability to assess a patient's therapy for de-escalation and streamlining depends on appropriate initial cultures being performed. However, still there is clearly an overwhelming need for well-constructed de-escalation studies to identify whether short- and/or long-term benefits are truly associated with this strategy in terms of modifying the risk of resistance development.

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