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Outcomes of Antimicrobial De-escalation with Emphasis on Antimicrobial Utilisation in a Tertiary Care Hospital at South India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Research and literature on antimicrobial de-escalation are often confined to assessment of safety and efficacy of de-escalation for patients with infection and, not antimicrobial utilization. Evidence suggests that the key intervention to stop further emergence of antimicrobial resistance (AMR) is to optimize antimicrobial de-escalation and improve antimicrobial stewardship (AMS) practices. An audit of antibiotic use in infection and measuring antibiotic consumption is the basic area of an Antimicrobial stewardship AMSP. This study aimed to assess the clinical outcomes of antibiotic de-escalation on length of stay (LOS), days on IV antibiotics, along with antibiotic utilization and duration of antibiotic therapy.

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Methods: This prospective observational study included in-patients with antibiotic prescriptions. Data collected included patient demographics, empiric, de-escalated or non-de-escalated antibiotic regimens, microbiological reports and final diagnoses were collected. The outcomes of de-escalation and non-de-escalation were compared. Statistical analysis was done using SPSS software and the *p* value < 0.05% was considered significant.

Results: Out of the 360 patients, 226 patients were de-escalated and 134 patients had their therapy non-de-escalated. The de-escalated population had a shorter LOS (mean: 4 days vs. 6 days, *p* <.05), shorter DOT (mean: 11.3 days vs. 13.9 days, *p* = .05), and fewer days on IV antibiotics (median: 3 days vs. 5 days, *p* = .05) compared to the non-de-escalated group.

Conclusion: De-escalation resulted in a:

- Reduction of 2.6 DOT (Days of Therapy) units of antimicrobial use (*p* value= .05), despite similar durations of antimicrobial therapy (LOT).
- Reduction of 2 days of intravenous antimicrobial (*p* value= .05).

Reduction of 1.7 days in the Length of hospital Stay (*p* value < .05).

Keywords: Antimicrobial stewardship; de-escalation; antimicrobial resistance; antimicrobial utilization.

1. INTRODUCTION

Antimicrobial resistance (AMR) is a growing global threat, necessitating urgent strategies to optimize antimicrobial use and curb its spread. One key intervention in this effort is antimicrobial de-escalation. De-escalation options include the following: adjustment of the antibiotic treatment according to the microbiological culture results or susceptibility of the isolated pathogen such as broad-spectrum antibiotics to narrow spectrum antibiotics or targeted therapy; clinical response such as intravenous to oral antibiotics, discontinuation of the treatment, the conversion of combined therapy to monotherapy [1]. This approach reduces the number of antibiotics being used, thereby minimizing the potential for side effects and antibiotic resistance while still effectively treating the infection. Each of these de-escalation strategies aims to optimize patient outcomes while promoting responsible antibiotic use [2]. Although much research has focused on the safety and efficacy of de-escalation in treating infections, there is a paucity of literature examining its impact on antimicrobial utilization—a critical component of antimicrobial stewardship programs (AMSPs).

Antimicrobial de-escalation aims not only to treat infections effectively but also to reduce the exposure to broad-spectrum antibiotics, thereby limiting the emergence of resistant strains [3]. Analyzing antibiotic consumption through metrics such as Days of Therapy (DOT) and Length of Therapy (LOT) provides valuable insights into the effectiveness of AMSPs in optimizing antimicrobial use [4]. Despite its significance, the impact of de-escalation on these metrics remains underexplored in many settings, particularly in tertiary care hospitals in South India [5-7].

This study addresses this gap by evaluating the clinical outcomes of antimicrobial de-escalation, specifically focusing on Length of Stay (LOS), days on intravenous (IV) antibiotics, and overall antibiotic utilization. By comparing de-escalated and non-de-escalated patient groups, this research aims to highlight the benefits of de-escalation in improving clinical outcomes and optimizing antibiotic use in a tertiary care hospital in South India.

2. METHODOLOGY

2.1 Study Design and Participants

The study was conducted at a tertiary-care hospital, having a prospective observational study design, that included 360 in-patients who had antibiotic prescriptions, for a period of five months (March 2023- July 2023). A prospective observational study design was chosen considering the study duration, feasibility and ethics related factors. Also a prospective design allows to include additional information during the study period. As there exists a clinical equipoise for de-escalation of antimicrobial therapy, a prospective observational design can be of value in such cases. However this study design poses the risk of selection bias due to the research being carried out in a single tertiary care hospital that may limit the diversity of patient population. Also the variations in clinician practices such as the timing and criteria for IV to oral antibiotic switch or the decision to de-escalate based on clinical scenario may give rise to confounding bias.

Length of Stay (LOS), Number of days on IV Antibiotic Therapy, Days of Therapy (DOT), an advanced antimicrobial stewardship metric, was calculated to quantify and compare antimicrobial use in both groups. The duration of antimicrobial use was expressed as Length of Therapy (LOT).

The formula used for calculating the sample size was,

Sample size n = [DEFF*Np(1-p)]/ [$(d^2/Z^2_{1-\alpha/2}$*(N-1)+p*(1-p)]

The estimated sample size was verified using the OpenEpi Software Version 3.01. The estimated sample size of the total study population was 360 patients during the study period with a CI= 95%, and a Margin of error of + 5%.

Participants were divided into two groups for comparison:

- De-escalated group
- Non-de-escalated group

The following outcome parameters were compared between the groups:

- Days of Therapy (DOT)
- Length of Therapy (LOT)
- Length of stay (LOS)
- Number of days on IV Antibiotic Therapy

Days of therapy (DOT), an advanced antimicrobial stewardship metric was calculated to quantify and compare antimicrobial use in the de-escalated and non-de-escalated group. The duration of antimicrobial use was expressed as Length of therapy (LOT).

2.2 Data Collection

Data such as patient demographics, empiric, de-escalated or non-de-escalated antibiotic regimens, microbiological reports, final diagnosis were collected and documented.

The required patient data were collected from medical records, initially entered in paper-based data collection forms and then entered in Excel sheets. To maintain data integrity and accuracy, a research manual was prepared and followed accordingly.

Eligibility criteria:

• **Inclusion criteria**

➢ In-patients of any age and gender.
➢ In-patients prescribed with one or more antimicrobials.

• **Exclusion criteria**

➢ In-patients who receive antimicrobials as surgical prophylaxis.
➢ In-patients who receive antimicrobials as prophylaxis for Hospital
acquired infections.
➢ In-patients who have no antimicrobials in their prescription

2.3 Statistical Analysis

Descriptive and inferential statistics were conducted using SPSS version 29.00. A P-value < 0.05 was considered significant.

Descriptive Statistics:

- Categorical variables were summarized using frequency and proportion.
- Continous variables were summarized using mean and standard deviation or median and interquartile range (IQR; 25th – 75th percentile) depending in the distributional symmetry.

Inferential Statistics:

- Characteristics and outcomes of patients in the de-escalated and non-de-escalated groups were compared using the Mann-Whitney U test, Pearson's Chi-Square test, or Fisher's Exact test.

3. RESULTS

As per the inclusion criteria, 360 patients were included in the study. Out of which 226 patients had their therapy de-escalated and 134 patients with non- de-escalated therapy.

The patient characteristics such as Age and Time of switch between the escalated and de-escalated population were analyzed using the Mann-Whitney U test and the other characteristics, gender, type of infection and culture status were analyzed using the Chi-square test respectively.

On comparing the age characteristics of the de-escalated and non- de-escalate groups, the non-de-escalated group had a significantly higher median age, with a *p*-value of 0.023. While analysing the percentage of males and females among the de-escalation and non- de-escalation

Table 1. Characteristics of patients in the De-escalated and Non- de-escalated groups

Characteristics	Total	De-escalated	Non- de-escalated	*p* value (2 sided)
Age, median (Q1, Q3), years	59.0 (33, 73)	57.0(24, 73)	63.0 (41,74)	0.023
Gender, n (%)				
Male	168(46.7)	104(46.2)	64(47.5)	0.206
Female	192(53.3)	122(53.9)	70(52.2)	
Type of Infection, n (%)				
Respiratory tract infection	130(36.1)	78(34.7)	52(38.5)	
Gastro-intestinal Infection	63(17.5)	40(17.8)	23(17)	
Urinary Tract infection	49(13.6)	31(13.8)	18(13.3)	< 0.01
Skin and Soft tissue Infection	47(13.1)	29(12.9)	18(13.3)	
Acute Undifferentiated Febrile Illness	45(12.5)	33(14.7)	12(3.8)	
Systemic Infections	26(7.2)	14(6.2)	12(8.9)	
Culture status, n (%)				
Positive culture	115(46.9)	67(58.3)	48(41.7)	< 0.01
Negative culture	245(68.1)	159(64.9)	86(35.1)	
Time of switch (days), mean (SD)	4.0 (1.8)	4.0(1.7)	4.1(2.1)	0.75

groups, no significant differences were observed. (*p*-value = 0.206).

Regarding the type of infections, a statistically significant difference was found between the de-escalated and non- de-escalated groups (*p*-value < 0.01). And no significant difference was seen considering the time of switch to de-escalation or non- de-escalation among the two groups.

Outcomes stratified by the study group are shown in the Table 2. In the univariate analysis, Days of Therapy, Length of Stay, Length of Therapy and Number of days on IV Antibiotic Therapy, among the de-escalated and non- de-escalated group were analyzed. To further assess the association between the de-escalation and non- de-escalation, Absolute risk difference or Attributable risk was estimated with 95 % CI for the given outcomes. All the outcome parameters were statistically analyzed using Mann-Whitney U test.

The study group that had their empiric antibiotic therapy de-escalated had a significantly shorter Days of Therapy compared to the non-de-escalated group [mean (SD), 11.3 (6 .9) versus 13.9 (10.9) days, *p*-value = 0.006), with absolute risk being 2.6 % lower (95 % CI, 1.7% to 3.5%).

Similarly, the study group that de-escalated showed a significantly shorter Length of Stay than the non- de-escalated [mean (SD), 4.5 (2.5) versus 6.2 (4.0) days] with a *p*-value < 0.001, showing an absolute risk reduction of 1.7% (95% CI, 1.4% to 2.0%). Another outcome, Length of Therapy (LOT) did not differ significantly between the two study groups [mean (SD), 8.6 (3.7) versus 9.1 (5.7) days, *p*-value = 0.59]. However, there is 0.5% risk reduction (95% CI, 0.03 to 0.9%) for Length of Therapy in the de-escalated group.

The outcome on Number of Days on IV Antibiotic therapy differed between the two study groups, [median (Q1, Q3), 3 (2 – 5) versus 5 (3 – 7), *p*-value = 0.004], as the non- de-escalated group had prolonged IV antibiotic therapy than the de-escalated group. De-escalation group showed an absolute risk reduction of 2% (95% CI, 1.7% to 2.3%).

Hence the de-escalation was associated with reduced Days of Therapy (DOT), Length of hospital stay (LOS) and number of days on IV antibiotics compared to the non- de-escalation group, but no significant impact was found in in Length of Therapy.

Hence de-escalation showed absolute risk reductions of 2.6 % (95 % CI, 1.7% to 3.5%) for prolonged Days of Therapy, 1.7% (95% CI, 1.4% to 2.0%) for prolonged length of stay, 2% (95% CI, 1.7% to 2.3%) for increased number of days on IV antibiotic therapy. Even though the two study groups did not show any statistical significance in terms of Length of Therapy, the absolute risk reduction was is 0.5% (95% CI, 0.03 to 0.9%) for the de-escalation group.

Table 2. Outcomes of De-Escalation and Non- De-Escalation in the Study Groups

Outcomes	Total	De-escalated	Non- de-escalated	*p* value (2 sided)	Absolute Risk Difference (95% CI)
DOT, mean (SD)	12.3 (8.6)	11.3 (6.9)	13.9 (10.9)	0.006	**- 2.6 (-1.7 to -3.5)**
LOS, mean (SD)	5.1 (3.3)	4.5 (2.5)	6.2 (4.0)	< 0.001	**- 1.7 (-1.4 to -2.0)**
LOT, mean (SD)	8.8 (4.5)	8.6 (3.7)	9.1 (5.7)	0.59	**- 0.5 (-0.003 to -0.9)**
Number of Days on IV Antibiotic therapy, median (Q1, Q3)	4 (2-6)	3 (2-5)	5 (3-7)	0.004	**- 2 (-1.7 to -2.3)**

DOT: Days of therapy (days)
LOS: Length of Stay (days)
LOT: Length of therapy (days)

4. DISCUSSION

This study was done, considering the need to evaluate the impact of antimicrobial de-escalation on antimicrobial consumption (Days of Therapy) and other parameters such as Length of Therapy (LOT), length of hospital stay (LOS) and the days of intravenous antibiotics in patients admitted to the hospital with infections, comparing them with those who do not undergo de-escalation.

The largest group of patients treated with antimicrobials were the elderly, between the age group of 61-70 years with a percentage of 18.9%. The gender-wise distribution had the largest female population, 192 patients (53.3%). Respiratory Tract Infections were the most common type of infection observed,130 patients (36.1%). The most dominant past medical condition was found to be Type 2 Diabetes Mellitus (26.3%). On determining the distribution of the antimicrobials prescribed, the largest group of the population was de-escalated, 226 patients (62.8%). The empirical treatment had 17% of Escalations, 65% of De-Escalation and the continuation was found to be 18%, based on the clinical stability.

Different patterns in de-escalation were observed. One of the patterns was the narrowing of antibiotic spectrum from the broad spectrum. Positive culture reports led to the de-escalation of broad-spectrum antibiotics to a narrower one. Therefore, the presence of culture data itself be it positive or negative, may lead to the de-escalation of antimicrobial therapy. The switching of narrower spectrum antibiotics from broad-spectrum was studied by Ching Chi Lee et al., whose results convey that the non-de-escalated group in whom broad spectrum antimicrobials was not narrowed down had a decrease in the adverse effects/complications but however leading to antimicrobial resistance in the long run [8]. This thereby proves that de-escalation of broad-spectrum antibiotics to a narrower spectrum is needed. The reason for the culture-based de-escalations in this study were mostly due to the occurrence of the organism, E. coli finding similarity with the Svetlana Sadyrbeva Dolgova S et al., study revealing decreased length of hospital stay in de-escalated patients whereas, 68% of cases de-escalated in their study with K. pneumoniae and E. coli involved ESBL producing organisms [1]. De-escalation in this was also due to the occurrence of another organism K. pneumoniae. The remaining de-escalations were the conversion from IV to oral routes. This finding stands unique in our study since there is no abundant literature supporting this pattern conveying that the future study editions should include IV to oral transition while simultaneously assessing the other de-escalation types.

On analysing outcomes between the two groups, the Days of therapy (DOT) and length of stay (LOS) were comparatively less in the de-escalated group than that of the escalated [11.3 versus 13.9 (*p* value 0.006) for DOT and 4.5 versus 6.2 (*p* value < 0.001) for LOS]. The shorter LOS observed in the de-escalated group is consistent with studies by Viasus et al. and Svetlana Sadyrbeva Dolgova S et al., which found that de-escalation strategies led to reduced hospital stays due to faster clinical improvement [9,1]. Similarly, the Length of therapy (LOT) and IV antibiotic therapy duration was also found to be lower in the de-escalated population when compared to that of the non-de-escalated ones [8.6 versus 9.1 (*p* value 0.59) for LOT and 3 versus 5 (*p* value 0.004) for IV antibiotic therapy duration] proving that the difference in DOT, LOS, and the number of days

for which the patient was on IV antibiotic therapy were found to be statistically significant meaning that the group that was de-escalated had significantly reduced quantity of antimicrobial consumption(DOT), shorter Length of Hospital stay, and number of days on IV antibiotic therapy when compared to the non-de-escalated group, emphasizing the importance of de-escalation and its impact on patients' health and therapy. Similar results were obtained in a study by Deigo Viasus et al., where de-escalated patients had significantly lower lengths of stay and IV antibiotic therapy days, and the reduction in DOT in the de-escalated group aligns with their findings that de-escalation led to significantly shorter DOT in patients with community-acquired pneumonia [9]. Also, the study by Ching Chi Lee et al. demonstrated that de-escalation of broad-spectrum antibiotics reduced the overall duration of therapy and minimized adverse effects [8]. The reduced number of days on IV antibiotic therapy in the de-escalated group aligns with the findings of studies by Viasus et al. and Ching Chi Lee et al., highlighting the importance of transitioning from IV to oral therapy as part of de-escalation [9,8]. However, the decreased LOT, which is the total duration of antimicrobial therapy, was nearly similar between the two study groups, i.e., the LOT was not statistically significant, signifying that the empiric therapy, whether deescalated or non-de-escalated, did not have any impact on the number of days for which the patient consumed the antibiotics making it similar to the study of Kuang Yuan et al., where both de-escalated and non-de-escalated groups had similar lengths of therapy or the total duration of antimicrobial therapy [10].

Despite having similar length of antimicrobial therapy for both the groups, none of the available literature attributed a reason explaining the overall outcome. However, our study stands unique in attributing the decrease in quantity of antibiotic use (DOT), as an added advantage favouring the de-escalation group, explaining the decreased risk of antimicrobial resistance related to the decreased exposure or utilization of antimicrobials in the de-escalated patients, comparatively with the non-de-escalated patients.

5. CONCLUSION

The de-escalated patients had a lesser day of hospitalization and IV antibiotics, indicating early attainment of clinical stability. Despite nearly similar durations of antimicrobial therapy (LOT), the quantity of antimicrobial utilization (DOT) was less for the de-escalated group [11.3 versus 13.9], highlighting that, de-escalated patients used lesser number of antimicrobial agents during the course of therapy. Therefore, we suggest de-escalation as a feasible option in patients with relevant microbiological investigations and clinical stability, to curb further emergence of AMR.

6. LIMITATIONS

- Confounding Variables: The study could not fully control for all potential confounding variables, which may influence the results.
- Need for Further Research: Larger, multi-center studies with longer follow-up are needed to confirm these findings and assess broader applicability.
- Multivariate Analysis: The study did not perform multivariate analysis to adjust for multiple confounders simultaneously, which could provide a more comprehensive understanding of the factors influencing outcomes.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

We hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Authors got ethical clearance from the faculty of Ethics Committee of the Fortis Healthcare.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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