



Research Article

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

Zhang Yong^{1*}¹Changzhou University, Changzhou 213164, China

*zhangy@gmail.com


Article Info

Keywords: Antimicrobial stewardship, de-escalation, antimicrobial resistance, antimicrobial utilization

Received: 30 August 2024

Accepted: 25 November 2024

Published: 27 December 2024

 © 2024 by the author's. The terms and conditions of the Creative Commons Attribution (CC BY) license apply to this open access article.

Abstract

Background: Research and literature about antimicrobial de-escalation frequently focus on evaluating the safety and efficacy of de-escalation in infected patients, rather than on antibiotic utilisation itself. Evidence indicates that the primary intervention to prevent the further evolution of antimicrobial resistance (AMR) is to enhance antimicrobial de-escalation and refine antimicrobial stewardship (AMS) techniques. An audit of antibiotic use in infections and the assessment of antibiotic consumption constitutes the fundamental aspect of Antimicrobial Stewardship Programs (AMSP). This study sought to evaluate the clinical consequences of antibiotic de-escalation concerning length of stay (LOS), duration of intravenous antibiotics, as well as antibiotic utilisation and therapy duration.

Methods: This prospective observational study encompassed in-patients receiving antibiotic prescriptions. Data gathered encompassed patient demographics, antibiotic regimens (empiric, de-escalated, or non-de-escalated), microbiological findings, and final diagnoses. The results of de-escalation and non-de-escalation were analysed. Statistical analysis was conducted with SPSS software, with a p value of less than 0.05% deemed significant.

Results: Among the 360 patients, 226 underwent therapy de-escalation, whereas 134 experienced non-de-escalation of their treatment. The de-escalated population exhibited a reduced length of stay (mean: 4 days vs. 6 days, $p < .05$), a shorter duration of therapy (mean: 11.3 days vs. 13.9 days, $p = .05$), and fewer days on intravenous antibiotics (median: 3 days vs. 5 days, $p = .05$) in comparison to the non-de-escalated group.

Conclusion: Deescalation yielded a: Reduction of 2.6 Days of Therapy (DOT) units of antibiotic usage (p value = 0.05), despite comparable lengths of antimicrobial treatment (LOT). Reduction of two days of intravenous antibiotic therapy (p value = 0.05). Decrease of 1.7 days in hospital length of stay (p value $< .05$).

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

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 $n = [DEFF * N_p(1-p)] / [(d^2/Z^2(1-\alpha/2*(N-1)+p*(1-p))]$

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).

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.

Statistical Analysis

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

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)	< 0.01
Gastro-intestinal Infection	63(17.5)	40(17.8)	23(17)	
Urinary Tract infection	49(13.6)	31(13.8)	18(13.3)	
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

Descriptive Statistics:

- Categorical variables were summarized using frequency and proportion.
- Continuous 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-escalated 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 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 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 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., [8] 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.,[1] 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. [9] and Svetlana Sadyrbeva Dolgova S et al., [1] which found that de-escalation strategies led to reduced hospital stays due to faster clinical improvement [1, 10]. 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.,[9] 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 [10]. 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.[10] and Ching Chi Lee et al.,[8] highlighting the importance of transitioning from IV to oral therapy as part of de- escalation [8, 10]. 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 [9].

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.

References

- [1] S. Sadyrbaeva-Dolgova, P. Aznarte-Padial, J. Pasquau-Liaño, M. Expósito-Ruiz, M. Á Calleja Hernández, C. Hidalgo-Tenorio, et al. Clinical outcomes of carbapenem de-escalation regardless of microbiological results: A propensity score analysis. *Int J Infect Dis*, 85. DOI:80–87, 2019. doi: 10.1016/j.ijid.2019.04.034. PMID: 31075508.
- [2] J. J. De Waele, J. Schouten, B. Beovic, A. Tabah, and M. Leone. Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions - a viewpoint of experts. *Intensive Care Med.*, 46(2):236–244, 2020. doi: 10.1007/s00134-019-05871-z. PMID: 32025778. PMCID: PMC7224113.
- [3] E. S. Tanzarella, S. L. Cutuli, G. Lombardi, F. Cammarota, A. Caroli, E. Franchini, et al. Antimicrobial de-escalation in critically ill patients. *Antibiotics*, 13(4):375, 2024. doi: 10.3390/antibiotics13040375. DOI.
- [4] O. Ibrahim and R. Polk. Antimicrobial use metrics and benchmarking to improve stewardship outcomes. *Infect Dis Clin North Am*, 28. DOI:195–214, 2014. doi: 10.1016/j.idc.2014.01.006.
- [5] S. S. Chowdhury, A. S. Sastry, S. Sureshkumar, A. Cherian, S. Sistla, and D. Rajashekar. The impact of antimicrobial stewardship programme on regulating the policy adherence and antimicrobial usage in selected intensive care units in a tertiary care center-a prospective interventional study. *Indian journal of medical microbiology*, 38(3-4):362–70, 2020.
- [6] P. Rupali, P. Palanikumar, D. Shanthamurthy, J. V. Peter, S. Kandasamy, N. G. Zacchaeus, H. Alexander, P. Thangavelu, R. Karthik, O. C. Abraham, and J. S. Michael. Impact of an antimicrobial stewardship intervention in india: evaluation of post- prescription review and feedback as a method of promoting optimal antimicrobial use in the intensive care units of a tertiary-care hospital. *Infection Control Hospital Epidemiology*, 40(5):512–9, 2019.
- [7] M. Campion and G. Scully. Antibiotic use in the intensive care unit: optimization and de-escalation. *Journal of Intensive Care Medicine*, 33(12):647–55, 2018.
- [8] C. C. Lee, C. C. Wang, J. L. Lee, J. L. Wang, C. H. Lee, Y. P. Hung, M. Y. Hong, H. J. Tang, and W. C. Ko. Clinical benefits of antimicrobial de-escalation in adults with community-onset monomicrobial escherichia coli, klebsiella species and proteus mirabilis bacteraemia. *Int J Antimicrob Agents*, 50(3):371–376, 2017. doi: 10.1016/j.ijantimicag.2017.03.024. PMID: 28694235. Epub 2017 Jul 8.
- [9] D. Viasus, A. F. Simonetti, C. Garcia-Vidal, J. Niubó, J. Dorca, and J. Carratalà. Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia. *J Antimicrob Chemother*, 72(2):547–553, February 2017. doi: 10.1093/jac/dkw441. PMID: 27798219. Epub 2016 Oct 20.
- [10] K. Y. Lew, T. M. Ng, M. Tan, S. H. Tan, E. L. Lew, L. M. Ling, B. Ang, D. Lye, and C. B. Teng. Safety and clinical outcomes of carbapenem de-escalation as part of an antimicrobial stewardship programme in an esbl- endemic setting. *J Antimicrob Chemother*, 70(4):1219–25, 2015. doi: 10.1093/jac/dku479. PMID: 25473028. Epub 2014 Dec 3. DOI.