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## Antimicrobial De-Escalation (ADE) and its Correlation with Clinical Cure and Mortality of Critically Ill Patients at a Tertiary Care Hospital

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### ABSTRACT

**Background:** To estimate how often ADE of an empirically prescribed antimicrobial therapy is performed in the critical ill patients and the pattern of de-escalation and To determine the effect of ADE on day-7 clinical cure and 28-day mortality following initiation of empirical therapy.

**Method:** In a prospective observational study conducted from november 2022 to January 2024, researchers examined how antimicrobial de-escalation (ADE) affected clinical outcomes in adult ICU patients who were receiving empirical antimicrobial treatment for bacterial infections. ADE was defined in two ways: either by discontinuing an antimicrobial when combination therapy was used or by replacing an antimicrobial to narrow its spectrum within the first three days of treatment. To account for time-dependent confounding factors, inverse probability (IP) weighting was applied in estimating the effect of ADE on the likelihood of clinical cure.

**Result:** The study included 200 patients from ICUs of HAH hospital. Combination therapy was used for 50% of these patients, and 26% received carbapenems. Within the first three days of empirical therapy, 16.5% of patients underwent antimicrobial de-escalation (ADE), 63.5% had no change, and 21% experienced changes other than ADE.

**Conclusion:** Antimicrobial de-escalation (ADE) was used infrequently among critically ill patients with infections. The observational data indicated that ADE did not appear to negatively affect clinical cure rates compared to situations where no ADE was applied. Nevertheless, there is likely residual confounding that may influence these findings.

**Keyword:** Antimicrobial de-escalation , Intensive care unit , Bacterial infection , Empirical therapy , Clinical cure.

## INTRODUCTION

Antimicrobial de-escalation (ADE) is a treatment strategy pursuing early adequate antimicrobial therapy as well as a reduction in the overall use of broad-spectrum agents, with the aim to contain subsequent emergence of multidrug resistance Kollef MH (2001). De-escalation may be achieved through replacement of a broad-spectrum antimicrobial by an antimicrobial agent with a narrower spectrum or a lower ecological impact or by discontinuation of one or more antimicrobials of empirical combination therapy (Tabah A et al., 2019). Internationally, ADE is recognized as a key component of antimicrobial stewardship (Ruiz J et al., 2018)

The intensive care studies have provided more insight in the global epidemiology of infections and antimicrobial use in critically ill patients, however, international studies mapping complete antimicrobial treatment courses in intensive care unit (ICU) patients are unavailable at present Vincent JL et al., 1995). Many observational studies and few randomized controlled trials (RCT) have evaluated ADE and the impact thereof on patient outcome (Paul M et al., 2016) whereas, systematic reviews have indicated a positive influence of ADE on mortality (Leone M et al., 2014). The decision to de-escalate a treatment is a multi-layered decision that relies not only on microbiological data but also on clinical stability, the severity of the illness at the time of admission to the EMW did not influence our decision to change treatment, as the SOFA scores were not significantly different between the groups. However, patients with negative SOFA scores tended to de-escalate more frequently than the others (Silvia Corcione et al., 2021).

Early administration of broad-spectrum, empiric antimicrobial therapy reduces mortality and improves outcomes in patients with severe sepsis and septic shock. However, broad spectrum therapy favours the emergence of drug-resistance and adds excessively to the costs of care. De-escalations refers to a strategy whereby clinicians either discontinue or change to a narrower spectrum antimicrobial drug and is usually carried out after culture results become available. The objective of this study was to identify variables associated with de-escalation failure (Nawal Salahuddin et al., 2016) .

De-escalation of empirical antimicrobial treatment based on culture results and discontinuation of redundant combination medication are strongly advised in terms of antimicrobial stewardship.

De-escalation at the bedside involves employing a beta-lactam antibiotic with a narrower spectrum of action wherever possible, or removing one antibiotic from the prescription combination. De-escalation attempts to lessen the spread of multidrug-resistant organisms by decreasing the usage of broad spectrum antibiotics. Studies based on observation revealed that this tactic was secure. On the other hand, de-escalation of antimicrobial drugs for individuals with sepsis, severe sepsis, or septic shock lacks sufficient, direct data (Marc Leone et al., 2014)

## MATERIAL AND METHODS

### Study Design

This is a random sample prospective observational study, conducted in the Intensive Care Unit (ICU) of Hamdard Institute of Medical Sciences & Research and Associated HAHC Hospital, New Delhi. The study is conducted as per GCP-ICH guidelines after due approval from the Institutional Ethics Committee (IEC) and obtaining informed written patient consent.

### Duration of Study

Patient enrolment will be carried out for 12 months with a follow-up of 28 days. Data analysis is for another 3 months. Thus, the total study period is of 16 months, from the date of commencement.

### Study Participants

All adult patients above 18 years of age, admitted in ICU and started on antimicrobial agents will be included in the study after meeting the following eligibility criteria.

#### ***Inclusion criteria:***

- Age 18 years and above.
- Patients of any gender.
- Patients admitted in ICU (medical, cardiac and surgical).
- Patients started on empirical antimicrobial therapy in the ICU or no more than 24 h prior to ICU admission, to treat any suspected bacterial infection.
- Patients consenting to participate in the study (directly or through LAR)

#### ***Exclusion criteria:***

- Patients in neonatal/ pediatric ICU or post-operative ward.
- Patients started on antimicrobial treatment without collection of sample for blood culture
- Patients receiving antimicrobial agents prophylactically (for prevention of infection in high risk/ surgical patients).
- Patients receiving antiviral or anti tubercular drugs.
- Patients not consenting or able to consent for the study participation.

### Methodology

Critically ill patients admitted in the medical ICU and started on antimicrobials for treatment of suspected infection will be screened for the inclusion and exclusion criteria.

- Demographic and baseline characteristics of patients receiving empirical antimicrobial therapy initiated in the ICU (or no more than 24 h prior to ICU admission) collected in a structured.
- Severity of illness evaluated using Acute Physiology and Chronic Health Evaluation (APACHE) II (Knaus WA et al., 1985) and Simplified Acute Physiology Score (SAPS) II (Le Gall JR et al., 1983) on the day of inclusion in the study (day-0).
- Sequential Organ Failure Assessment (SOFA) (Vincent JL et al., 1996) and APACHE II scores will be evaluated on day-0 as well as day-3.
- Different microbiological samples (urine/endotracheal aspirate/pus) from other sources is evaluated in an attempt to establish the source of each patient's infection.

- Empirical antibiotic therapy is prescribed by the treating physician, as per the hospital antimicrobial policy.
- Patients is followed up to 21 days or discharge from the hospital, whichever is earlier.
- Patient microbiological and infection data (source, causative pathogen, relapse and emergence of MDR pathogens) is collected from the day-0 until day-21.
- Empirical antimicrobial therapy related data is collected from the day-0 until day-21. Additional antimicrobial therapy following study inclusion and antimicrobial-free days will be assessed on day 21.
- Patients reviewed clinically after 72 hours, with available culture and other lab reports. Though most cultures show growth signal in <48 hrs, time duration of 72hrs was chosen for allowing enough time for species identification and sensitivity.
- The study population categorized into 3; based on the first modification of antimicrobial treatment course; made between day-0 and day-3 by the treating physician, namely: “**no change**” (empirical therapy maintained without modification between); “**ADE**”, “**other change**” .
- Indications for stopping, switching or addition of each antimicrobial agent is recorded.
- The need for supportive therapy, number of days in the ICU and hospital, ICU mortality recorded until day-21.
- The treating clinician assess the clinical response of the patient for the initial infection on day-7.

### **Data Collection**

Well-structured data collection form designed to capture the study data systematically under five domains: patient demographic and baseline characteristics; microbiological and infection characteristics, empirical antimicrobial therapy and ADE characteristics; factors effecting ADE practices and ADE outcomes will be used.

#### **I. Patient Demographic & Baseline Characteristics**

- Age (years) ,Gender, Duration of hospital stay (days) prior to empirical antimicrobial therapy, Duration of ICU stay (days) prior to empirical antimicrobial therapy, Previous hospitalization (<6 months), Previous antimicrobial intake (<6 months), Definitive Diagnosis, Admission category (Medical , Surgical) ,Admission diagnosis(Cardiovascular/Gastrointestinal/Hematological/Metabolic/Neurological/ Pregnancy related / Renal/genito-urinary/Respiratory/Trauma/Skin/Others).

#### **II. Microbiological and Infection Characteristics**

Microbiologically documented infection, Microorganisms isolated (patient samples obtained on admission to ICU), MDR organisms isolated, Bacteremia , Polymicrobial infection , Source of infection (Abdominal/Cardiovascular/Respiratory/Skin/Urogenital/Catheter-related/ Other/Unknown) , Septic shock , SOFA > 1 (day-0).

#### **III. Empirical Antimicrobial Treatment & ADE Characteristics**

Pattern of antimicrobial use, Monotherapy ,Combination therapy , Duration of AMA treatment, Addition of AMA after inclusion in study, Inappropriate empirical antimicrobial prescription, Patient category based on antimicrobial modification **ADE**, **No Change**, **Other Change**

## Statistical Analysis

Descriptive statistics will be analysed with the SPSS version 17.0 software. Frequencies (percentages) is reported as descriptive summary statistics for categorical variables; and medians/interquartile range (IQR) (25th to 75th percentile) and mean  $\pm$  SD for continuous variables. Distributional differences for categorical patient outcomes are evaluated using Pearson Chi-squared test or Fisher's exact test when appropriate.  $P < 0.05$  is considered statistically significant. Risk ratios is reported for binary variables, along with 95% confidence intervals (CIs). Unadjusted outcome analyses is also performed comparing ADE and "no change" patients, "other change" and "no change" patients.

## RESULT

A total of 200 ICUs in HAH hospital new delhi. Infectious disease specialists, microbiologists and clinical pharmacists joined regular multidisciplinary staff meetings in 28%, 24% and 22% of centers, respectively. Local ADE guidelines were used in 16.5% of patient in this centers. Baseline methicillin resistance of the *S. aureus* isolates was 10% in the participating ICUs; vancomycin resistance of the *enterococcus* species isolates 0% .ESBL production was reported in 11% of *enterobacteriaceae* isolates, whereas carbapenemase production was reported in 1%.

ADE guidelines were followed in this hospital. Mean age was 48 **Table 1,figure 1**. Mean number of days in the Duration of hospital stay is mean of 8 and Duration of icu stay mean of (4.08 $\pm$ 2.06 days) **Table 3**. around 44.5% has taken antimicrobial drugs previously **table 4**. The patient characteristics with diagnosed with cardiovascular disease 145,GI 131 , haematological 90 , Metabolic 75, neurological 88, pregnancy related 31, renal 32, respiratory 111, trauma 114, skin 99, others 45 **table 5**. As seen in APACHE II SCORE, SOFA SCORE and SAPS II SCORE gradually increases from day 7 to day 21 **table 6, table 7 & table 8(figure 2, figure 3, figure 4)**. During the first 3 days, empirical antimicrobial therapy was de-escalated in 16.5% (33/200) and not changed in 62.5% (125/200). In 21% (42/200) of patients, another treatment change was performed **table 9**. Nine percent (21/200) of patients died during the first 7 days of therapy. Microbiologically documented infection were seen in 111 patient **table 10** .ADE consisted mainly of discontinuation of one or more components of Monotherapy was prescribed in 43(87/200 and Combination therapy was prescribed in 56%(113/200) and of empirical courses **table 11**. The most frequently prescribed agents were anti-pseudomonal penicillins in combination with a beta-lactamase inhibitor, carbapenems and third-generation cephalosporins in 29.6%, 26% and 19.3% of patients, respectively. Combination therapy treatment 2 antimicrobial agent (79) , 3 antimicrobial agent (26) , 4 antimicrobial agent (6) , 5 antimicrobial agent (2) **table 12**. Association of empirical antimicrobial therapy with treatment therapy **Antipseudomonal penicillins+ $\beta$ -lactamase inhibitor** (monotherapy 35,combination 41), **Carbapenems** (monotherapy

23,combination 27) , **Penicillins+ $\beta$ -lactamase inhibitor**(monotherapy 12,combination 23) , **Fluoroquinolones** (monotherapy 07,combination 14) , **Glycopeptides** (monotherapy 10,combination 08) **table 13,figure 5.**

Table 1: Age distribution

| Age group           | Frequency<br>(n=200) | Percentage<br>(%) |
|---------------------|----------------------|-------------------|
| <b>≤30 years</b>    | 47                   | 23.5%             |
| <b>31-40 years</b>  | 23                   | 11.5%             |
| <b>41-50 years</b>  | 34                   | 17%               |
| <b>51-60 years</b>  | 33                   | 16.5%             |
| <b>&gt;60 years</b> | 63                   | 31.5%             |
| <b>Mean age</b>     | 48.85±18.62 years    |                   |

Figure 1: Age group distribution

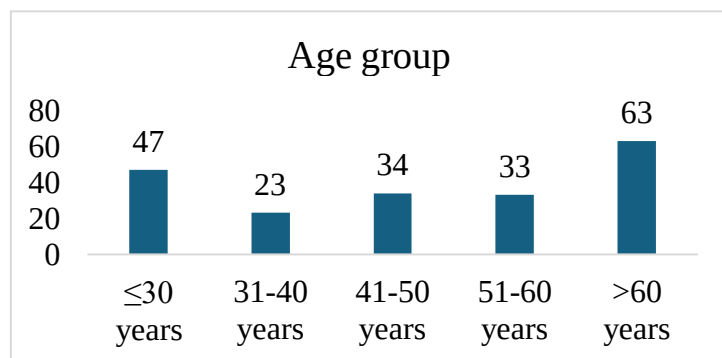


Table 2: Gender

| Gender        | Frequency (n=200) | Percentage (%) |
|---------------|-------------------|----------------|
| <b>Male</b>   | 121               | 60.5%          |
| <b>Female</b> | 79                | 39.5%          |

Table 3: Duration of Hospital Stay

| Duration of hospital stay | Frequency (n=200) | Percentage (%) | ICU stay       | Percentage(%) |
|---------------------------|-------------------|----------------|----------------|---------------|
| 1-5 days                  | 72                | 36%            | 84             | 42%           |
| 6-10 days                 | 55                | 27.5%          | 83             | 41.5%         |
| >10 days                  | 73                | 36.5%          | 33             | 16.5%         |
| Mean                      | 8.04±4.54 days    |                | 4.08±2.06 days |               |

Table 4: Previous antimicrobial intake

| Previous antimicrobial intake | Frequency (n=200) | Percentage (%) |
|-------------------------------|-------------------|----------------|
| Yes                           | 89                | 44.5%          |
| No                            | 111               | 55.5%          |

Table 5: Diagnosis

| Diagnosis            | Frequency (n=200) | Percentage (%) |
|----------------------|-------------------|----------------|
| Cardiovascular       | 145               | 72.5%          |
| Gastrointestinal     | 131               | 65.5%          |
| Haematological       | 90                | 45%            |
| Metabolic            | 75                | 37.5%          |
| Neurological         | 88                | 44%            |
| Pregnancy related    | 31                | 15.5%          |
| Renal/Genito-urinary | 32                | 16%            |
| Respiratory          | 111               | 55.5%          |
| Trauma               | 114               | 57%            |
| Skin                 | 99                | 49.5%          |
| Others               | 45                | 22.5%          |

Table 6: APACHE II score

| APACHE II | Mean± SD    | P value |
|-----------|-------------|---------|
| Baseline  | 27.82±10.16 |         |
| At 3 days | 28.56±9.34  | 0.448   |

|                   |            |       |
|-------------------|------------|-------|
| <b>At 7 days</b>  | 29.45±5.54 | 0.047 |
| <b>At 14 days</b> | 29.65±6.67 | 0.033 |
| <b>At 21 days</b> | 30.13±8.56 | 0.014 |

Figure 2: APACHE II score

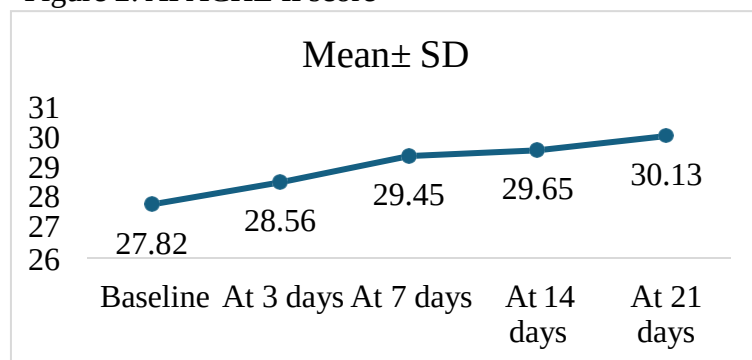


Table 7: SOFA score

| <b>SOFA score</b>       | <b>Mean ± SD</b> | <b>P Value</b> |
|-------------------------|------------------|----------------|
| <b>On ICU admission</b> | 14.29±5.49       |                |
| <b>At 3 days</b>        | 14.70±4.34       | 0.407          |
| <b>At 7 days</b>        | 15.23±3.56       | 0.042          |
| <b>At 14 days</b>       | 15.42±5.12       | 0.033          |
| <b>At 21 days</b>       | 15.99±6.78       | 0.006          |

Figure 3: SOFA score

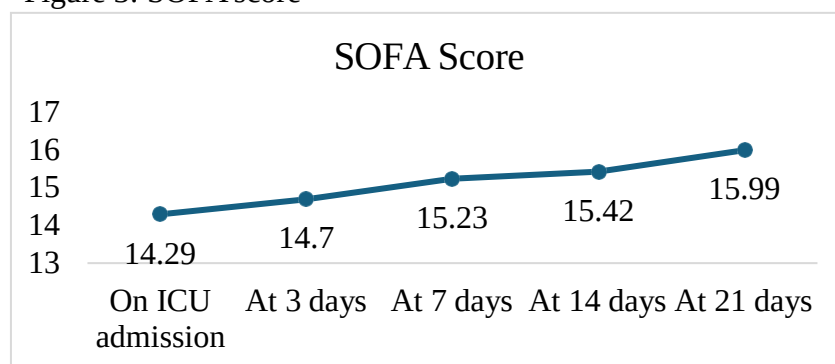


Table 8: SAPS II Score

| <b>SAPS II Score</b> | <b>Mean ± SD</b> | <b>P Value</b> |
|----------------------|------------------|----------------|
|----------------------|------------------|----------------|

|                         |             |       |
|-------------------------|-------------|-------|
| <b>On ICU admission</b> | 44.34±12.34 |       |
| <b>At 3 days</b>        | 46.25±13.45 | 0.139 |
| <b>At 7 days</b>        | 47.11±14.76 | 0.042 |
| <b>At 14 days</b>       | 47.65±14.34 | 0.013 |
| <b>At 21 days</b>       | 47.98±15.12 | 0.008 |

Figure 4: SAPS II Score

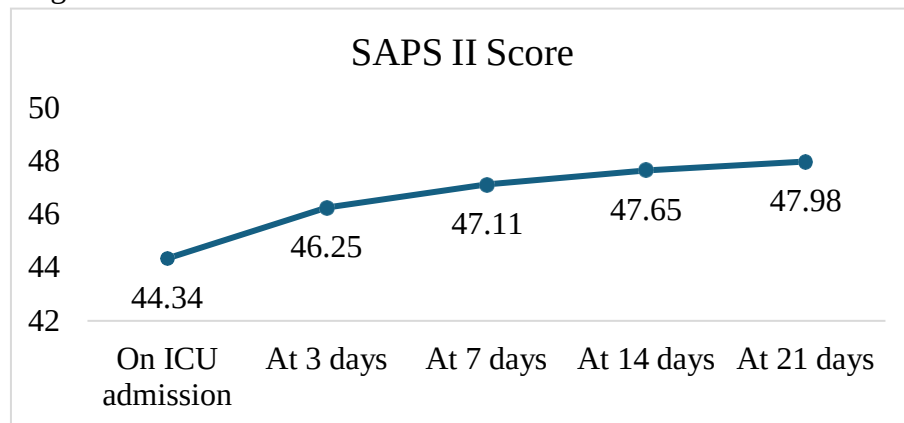


Table 9: Empirical antimicrobial therapy

| <b>Empirical antimicrobial therapy</b> | <b>Frequency (n=200)</b> | <b>Percentage (%)</b> |
|----------------------------------------|--------------------------|-----------------------|
| <b>ADE</b>                             | 33                       | 16.5%                 |
| <b>No Change</b>                       | 125                      | 62.5%                 |
| <b>Other Change</b>                    | 42                       | 21%                   |

Table 10: Microbiologically documented infection

| <b>Microbiologically documented infection</b> | <b>Frequency (n=200)</b> | <b>Percentage (%)</b> |
|-----------------------------------------------|--------------------------|-----------------------|
| <b>Positive</b>                               | 111                      | 55.5%                 |
| <b>Negative</b>                               | 89                       | 44.5%                 |

Table 11: Combination therapy treatment

| <b>Empirical therapy treatment</b> | <b>Frequency (n=113)</b> | <b>Percentage (%)</b> |
|------------------------------------|--------------------------|-----------------------|
| <b>1 Antimicrobial agents</b>      | 87                       | 43.5%                 |
| <b>2 Antimicrobial agents</b>      | 79                       | 69.91%                |

|                               |    |        |
|-------------------------------|----|--------|
| <b>3 Antimicrobial agents</b> | 26 | 23.01% |
| <b>4 Antimicrobial agents</b> | 6  | 5.31%  |
| <b>5 Antimicrobial agents</b> | 2  | 1.77%  |

Table 12: Empirical antimicrobial therapy

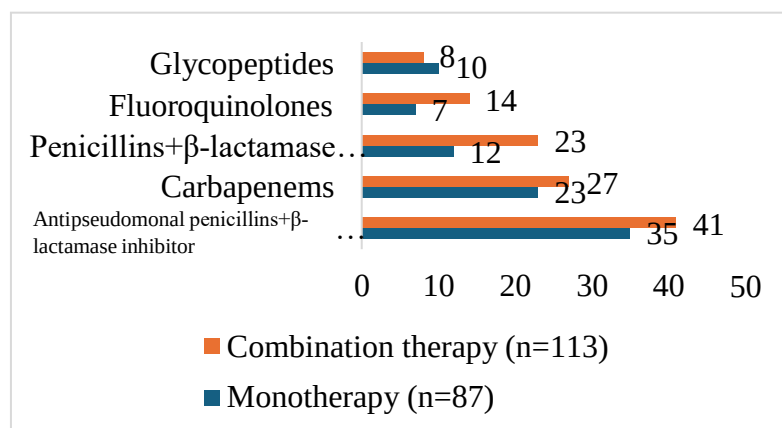
| <b>Empirical antimicrobial therapy</b>                                    | <b>Frequency (n=200)</b> | <b>Percentage (%)</b> |
|---------------------------------------------------------------------------|--------------------------|-----------------------|
| <b>Antipseudomonal penicillins+<math>\beta</math>-lactamase inhibitor</b> | 76                       | 38%                   |
| <b>Carbapenems</b>                                                        | 50                       | 25%                   |
| <b>Penicillins+<math>\beta</math>-lactamase inhibitor</b>                 | 35                       | 17.5%                 |
| <b>Fluoroquinolones</b>                                                   | 21                       | 10.5%                 |
| <b>Glycopeptides</b>                                                      | 18                       | 9%                    |

Table 13: Association of empirical antimicrobial therapy with treatment therapy

| <b>Empirical antimicrobial therapy</b>                                    | <b>Monotherapy (n=87)</b> | <b>Combination therapy (n=113)</b> | <b>P value</b> |
|---------------------------------------------------------------------------|---------------------------|------------------------------------|----------------|
| <b>Antipseudomonal penicillins+<math>\beta</math>-lactamase inhibitor</b> | 35                        | 41                                 | 0.480          |
| <b>Carbapenems</b>                                                        | 23                        | 27                                 |                |
| <b>Penicillins+<math>\beta</math>-lactamase inhibitor</b>                 | 12                        | 23                                 |                |
| <b>Fluoroquinolones</b>                                                   | 7                         | 14                                 |                |
| <b>Glycopeptides</b>                                                      | 10                        | 8                                  |                |

Figure 5: Association of empirical antimicrobial therapy with treatment therapy

Antipseudomonal



## DISCUSSION

Antimicrobial de-escalation (ADE) is a treatment strategy pursuing early adequate antimicrobial therapy as well as a reduction in the overall use of broad-spectrum agents, with the aim to contain subsequent emergence of multidrug resistance Kollef MH (2001). De-escalation may be achieved through replacement of a broad-spectrum antimicrobial by an antimicrobial agent with a narrower spectrum or a lower ecological impact or by discontinuation of one or more antimicrobials of empirical combination therapy (Antonelli M et al 2001) Internationally, ADE is recognized as a key component of antimicrobial stewardship (Tabah A 2016 and Garnacho-Montero J 2015)

Information on how often ADE is performed in everyday practice on a world-wide scale is lacking. Whereas the extended prevalence of infection in intensive care studies provided more insight in the global epidemiology of infections and antimicrobial use in critically ill patients; international studies mapping complete antimicrobial treatment courses in intensive care unit (ICU) patients are unavailable at present (Silva BN 2013 and Tabah A 2019).

Many observational studies and few randomized controlled trials (RCT) evaluated ADE and the impact thereof on patient outcome. RCTs have been unable to show convincing evidence that ADE is definitely safe, while systematic reviews have indicated a positive influence of ADE on mortality.(Kollef MH, Barlam TF 2016 and Rhodes A 2017). Controversies regarding the safety of ADE nonetheless still exist as various definitions were used, and antimicrobials were predominantly de-escalated in patients with microbiologically confirmed infections and a favorable clinical course. As such, observational studies are prone to bias (Ruiz J et al., 2018).

Many studies reported ADE rates between 25 and 81%.(Kollef MH 2001 and Tabah A 2016) Studies with higher percentages of ADE often included patients with lower severity of illness compared to our study or focused on patients in whom ADE was possible due to the broadness of the empirical spectrum and the susceptibility pattern of the causative pathogens (Kollef MH 2001 and Vincent JL 1995) Other studies included only patients with specific types of infections or pathogens (Vincent J-L 2009 and Guo Y 2016). These were usually single-center studies, conducted in centers with a special interest in antimicrobial stewardship. Instead, we studied ICU patients and included all empirical antimicrobial therapies, independent of culture results, and therefore provide a more realistic picture of ADE in routine clinical practice.

The present study was aimed to evaluate Antimicrobial De-Escalation (ADE) and its Correlation

### with Clinical Cure and Mortality of Critically Ill Patients at a Tertiary Care Hospital

In our study, the mean age of study was  $48.85 \pm 18.62$  years. The most common age group was  $\geq 60$  years (31.5%) followed by  $\leq 30$  years (23.5%), 31-40 years (18.5%), 41-50 years (17%), and 51-60 years (16.5%). In our study, 60.5% of patients were male and 39.5% of patients were female. Male to female ratio was 1.53:1. In a study by **Bus et al**, total of 1495 patients were available for analysis (online supplement 6). Median age was 65 (IQR 51–75) years, 61.5% were male and 66.6% were medical admissions. Patients were colonized with MDR pathogens prior to initiation of empirical antimicrobial therapy in 11.5% (Paul M et al 2016) In a study by **Corcione et al**, the study population consisted of 336 patients admitted to EMW, of which 58% (194) were male. The median age of all patients was 70 years (IQR: 60–80). During the preceding six months, 73.8% (248) of patients had at least one previous hospitalization, and half of those (51%) received antibiotics at that time. An active underlying malignancy was recorded in 44% of patients. The mean length of hospital stay was 17 days (Leone M et al., 2014)

In a study by **Pedroso et al**, there was no significant difference between patients who received EAT and the ATGBC with respect to sociodemographic characteristics such as age, sex, and ethnicity (van Heijl I et al., 2019).

In our study, the most common duration of hospital stays  $>10$  days (36.5%) followed by 1-5 days (36%) and 6-10 days (27.5%). In our study the most common duration of ICU stay was 1-3 days (42%) followed by 1-6-10. days (41.5%) and  $> 10$  days (16.5%). 52% of patients had previous hospitalization. 44.5% of patients had previous antimicrobial intake. 53% of patients had a diagnosis. In a study by **Bhattula et al**, Empiric antibiotic combinations were used in 43.8%. Third generation Cephalosporins were used in 32%, BL-BLI combinations in 36% and Carbapenems in 22.2%. Vancomycin was a part of combination in 25.9% of the episodes.<sup>17</sup> In a study by **Salahuddin et al**, Empiric therapy was appropriate in 57% cases. The median ICU length of stay was 6 days (IQR 4–43) with a 28-day survival rate of 71% (281 patients) (Battula V et al., 2021).

In our study, the most common diagnosis was cardiovascular (72.5%) and gastrointestinal (65.5%) followed by hematological (45%), metabolic (37.5%), neurological (44%), and skin (49.5%) hypertension was the most common comorbidities (%) followed by DM (45.5%), CAD (37.5%), and CVD (35%).

In our study, 77% of patients had mechanical ventilation on ICU admission. In our study, 37.5% of patients had catheterization on ICU admission. In this study, 22.5% of patients had immunosuppression status In this study, 35.5% of patients were previous steroids therapy.

In our study, there was no significant change in APACHE II score from baseline till 3 days. However, started significantly increasing from day 7 to day 21. In our study, there was no significant change in SOFA score from baseline till 3 days. However, started significantly increasing from day 7 to day 21. In our study, there was no significant change in SAPS II Score from baseline till 3 days. However, started significantly increasing from day 7 to day 21. In a study by **Salahuddin et al**, three hundred and ninety-five patients were included in the study; 194 (49%) were female, mean age of  $52.4 \pm 12$  years; mean APACHE II and SAPS II scores were  $24 \pm 7.8$  and  $45 \pm 19.7$ . Three hundred and thirty-three (84.3%) patients were admitted from within the hospital, 58 (14.7%) were admitted from the emergency department, and 4 (1%) came as

interhospital transfers via MEDEVAC (Battula V et al., 2021).

In our study, 16.5% of patients had ADE, 21% of patients had other changed, and 62.5% of patients had no changes. In our study, the most common infection was abdominal (77.48%) followed by Cardiovascular (40.54%), Respiratory (21.62%), Skin (38.74%), Uro-genital (10.81%), Catheter-related (9.91%). In a study by **Zhao et al**, with 53 (11.2%) in the ADE group, 173 (36.6%) in the No Change group, and 247 (52.2%) in the Other Change group (Silvia Corcione et al., 2021). Previous study reported ADE rates between 25 and 81% (Antonelli M et al 2001). Study with higher percentages of ADE often included patients with lower severity of illness compared to our study or focused on patients in whom ADE was possible due to the broadness of the empirical spectrum and the susceptibility pattern of the causative pathogens (Vincent JL et al., 1995). Other studies included only patients with specific types of infections or pathogens (Vincent J-L 2009 and Guo Y 2016).

In our Study, the most common therapy treatment was 2 antimicrobial agents (69.91%) followed by 3 antimicrobial agents (23.04%), 4 antimicrobial agents (5.31%), 5 antimicrobial agents (1.77%). In our study, the most common antimicrobial therapy was Antipseudomonal penicillins+ $\beta$ -lactamase inhibitor (38%) followed by Carbapenems (25%), Penicillins+ $\beta$ -lactamase inhibitor (17.5%), Fluoroquinolones (10.5%), and Glycopeptides (9%). In a study by **Roper et al** The most common indication for antibiotics was pneumonia (50.9%). Piperacillin/tazobactam was the most common empirically selected pivotal antibiotic (71.7%). One hundred and six patients (61.3%) had appropriate cultures drawn for the diagnosed infection, and most patients had cultures obtained on the day antibiotics were initiated. Respiratory cultures were only obtained in 58% of patients with pneumonia, and this was not statistically different between those who did and did not undergo de-escalation. MRSA PCR utilization for the purpose of vancomycin de-escalation was higher in the de-escalation population ( $p = 0.016$ ), and positivity for the MRSA PCR was low in both groups. Only 15% of patients had their antibiotics managed by an Infectious Disease team (Pedroso JVM et al., 2021).

In a study by **Ruiz et al**, total antimicrobial DDD/100 patient-days consumption was reduced from 380.6 to 295.2 ( $-22.4\%$ ;  $p = 0.037$ ). Antimicrobials in which the AMS programme had a significant impact were penicillins plus  $\beta$ -lactamase inhibitors, linezolid, cephalosporins, and aminoglycosides. A noticeable reduction was also observed in carbapenems, quinolones, and antifungal agents, although no significant differences were obtained. On the other hand, a non-significant increase of reduced-spectrum penicillins was observed. Antimicrobial global spending after one year of AMS programme was reduced by D 119.636 compared with the previous control year (D 520.186 vs. D 400.550;  $p = 0.012$ ) (Garnacho-Montero J et al., 2015).

In our study, 10.5% of patients were expired. In a study by **Zhao et al**, the 14-day mortality rates in the three groups were 9.4%, 11.6%, and 21.9% (Silvia Corcione et al., 2021). In a study by **Corcioner et al**, the overall in-hospital mortality rate was 21%, and it was significantly lower among the ADE group than the continuation group (16% vs. 25%  $p = 0.003$ ). The univariate analyses of factors associated with ADE (Leone M et al., 2014). In a study by **Pedroso et al**, 49 deaths were reported, resulting in a mortality rate of 53.8%. Mortality for patients who continued receiving EAT was 56.9% vs. 48.5% for patients receiving ATGBC (van Heijl I et al., 2019).

## CONCLUSION

An Antimicrobial Stewardship Program (ASP) focused on Antimicrobial De-escalation (ADE) aims to limit the development of resistant organisms and mitigate environmental impacts by reducing the use of broad-spectrum antimicrobials. Current evidence on how de-escalation affects the microbiome and the emergence of resistant organisms is mixed and inconclusive. There is still a need to clearly understand the true effects of ADE on resistance development. Although existing data is varied and of low quality, it generally suggests that narrowing the antibiotic spectrum is safe. Consumption of antimicrobials, regardless of class, is associated with antimicrobial resistance (AMR). Reducing antibiotic use should be a key goal of ASP, and while ADE can help lower broad-spectrum exposure and lessen selective pressure, it should not be used in isolation. Comprehensive studies are needed to assess the benefits and risks of de-escalating antimicrobial therapy in ICU patients. An effective ASP should incorporate a range of strategies, including optimizing empirical therapy based on infection site guidelines, using current local resistance data, considering host factors and risks of resistant or atypical pathogens, and optimizing the pharmacokinetics and pharmacodynamics of selected treatments. Additionally, it should involve reviewing therapy on days 2–3 with relevant microbiology results and clinical progress, ceasing antibiotics in cases of unproven infection and feasible ADE, and reducing the duration of therapy when appropriate. Consulting with an infection specialist and utilizing rapid diagnostics can also be beneficial.

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