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# De-Escalation of Broad-Spectrum Antibiotics After Relevant Culture Reports in Medical Ward Patients Audit from A Tertiary Care Hospital in South India

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**Abstract**: Prolonged and improper usage of antibiotics has been shown as a main reason for the emergence of multidrug-resistant pathogens.Antimicrobial stewardship (AMS) programs have been shown to reduce the antibiotics usage and the rate of emergence of resistance. De-escalation of antimicrobials is an important component of AMS. AMS programmes require regular auditing and feedback for proper implementation and continuous improvement. Hence we did this clinical audit with the main aim of estimating the de-escalation rates and identifying the possible reasons for non-de-escalation in our centre. Case sheets of the patients admitted between 1st October 2020 to 31st December 2020 were screened during discharge for data for de-escalation and reasons for non-de-escalation. Cefeprazone-sulbactum (32%) was commonly used empirical monotherapy in the audited period. De-escalation rate after positive culture reposts was 28%. Serious clinical illness (36%) was found to be the most common reason for non-de-escalation. De-escalation was not done in nearly 25% of eligible instances without a proper justification.

**Keywords**: Antimicrobial Stewardship, De-Escalation, Antibiotics, Antimicrobial Resistance, AMS and Broad Spectrum Antibiotics

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## 1. INTRODUCTION

Antimicrobial resistance is a problem of global significance. [1] Worldwide there has been a constant increase in the prevalence of infections caused by multidrug resistant (MDR) pathogens[2,3,4]. Infections with MDR pathogens are often complicated to treat and are associated with significant mortality[5,6,7] Prolonged and improper usage of antibiotics has been shown as the main reason for the emergence of multidrug-resistant pathogens [8,9] Also, prevalence of infections due to MDR pathogens like MRSA (methicillin resistance staphylococcus) has been reported to be alarmingly high in low-middle income countries as compared to high-income countries [9]. This has prompted the medical community to formulate and implement antibiotic stewardship (AMS) programs and proper utilization of antimicrobials[9,10,11]. AMS strategies include antibiotic pre authorization, antibiotic usage monitoring, involvement of multi-disciplinary teams (physicians, clinical pharmacists. Infection control nurses), periodic education of health care providers etc. AMS programmes have been shown to reduce antibiotics usage [12,13,14], and the rate of emergence of resistance among microbes by various authors. [15,16]. De-escalation of antimicrobials has been recommended as an important component of AMS without affecting the clinical outcome of patients[17,18]. De-escalation could be one or more of switching over to a narrow-spectrum antibiotic from a broad-spectrum one, reducing the number of antibiotics or changing to oral from an intravenous route. Despite this variation in the exact meaning of de-escalation, implementation in any form, has been shown to improve clinical outcomes and reduce the emergence of resistance [19,20] Guidelines recommend sending appropriate microbiological culture tests before empirical antibiotic therapy. major advantages of this practice lie in increased chances of identifying the causative organism in sepsis and, more importantly, deescalating antibiotics to ones that directly address the organism. Hence microbiological culture reports guide the physicians for implementing appropriate de-escalation [21]. world-wide de-escalation rates have widely varied between 20 and 70 percent among the reports, and till now there is no bench mark rate, derived at, or recommended for it [2,4]. AMS programmes require monitoring the antimicrobial usage through regular auditing and feedback for effective implementation[22]. Antimicrobial resistance including carbapenem resistance has been shown to be very high and increasing in developing counties including India as compared to western counterparts [3,9]. Major health care facilities in India have in house AMS programmes, yet there is a huge lag in monitoring and reporting the effectiveness of these programmes[23]. The monitoring, auditing, and reporting the usage of broad-spectrum antibiotics helps to identify the rates and reasons for inappropriate use along with the reasons for non-de-escalation in appropriate circumstances[21,22]. Hence, we did a clinical audit in our center to estimate the de-escalation rates of empirical broad-spectrum antibiotics and identify possible reasons for non-de-escalation. Here we are reporting the results of a clinical audit conducted on antibiotic usage and de-escalation rates highlighting the possible causes for non-de-escalation from our tertiary care medical center in south India.

## 2. MATERIALS AND METHODS

This audit was conducted from 1st October 2020 to 31st December 2020.

### *2.1. Study Setting and Study Population*

Case sheets of patients at least 18 years old admitted during this period in the medical wards of our center were screened during discharge and data was collected from them. Case sheets were included for data collection based on the following inclusion and exclusion criteria

### *2.2. Inclusion Criteria*

- Patients who are at least 18 years old admitted in medical wards for whom empirical broad-spectrum antibiotic(s) had been started for suspected infection
- Patients should have a positive microbiological culture report from any of the microbial samples (urine pus etc)
- Patients should have been discharged from the hospital after clinical recovery.

### *2.3. Exclusion Criteria*

- Patients less than 18 years of age
- Patients who died in the course of hospital stay.
- Patients who did not have positive microbiological culture reports
- Patients who were started on empirical antibiotics other than those defined as broad spectrum by us.

All case sheets were screened for the following parameters using the data collection sheet

1. Empirical broad-spectrum antibiotics used
2. Sample of the culture and the organism grown in the culture
3. De-escalation, whether done or not
4. Reason for not deescalating
5. Data collection sheet

**PROFORMA FOR ESTIMATING THE FREQUENCY OF DE-ESCALATION OF BROAD-SPECTRUM ANTIBIOTICS IN MEDICAL WARD PATIENTS**

**Hospital Id-**
**Age - Sex-**
**Date of Admission-**
**Date of Discharge /Death-**
**Diagnosis-**
**Comorbidities-**
**Emperical Antibiotic Started** (Date)--
**Culture Report(S)** (Date)
Sample - 1. 2. 3.
Organism(s) -
Colony count-

**DE-ESCALATION DONE**
Yes (date, antibiotic)-
No (reason)-

**TOTAL DURATION OF ANTIBIOTICS**
Empirical antibiotics -
Deescalated choice –

**IN-HOSPITAL PROGNOSIS**
Recovered
Expired (cause of death)

### *2.4. Case Definitions*

A positive (significant) microbiological culture report from a

sample (i.e., urine, blood etc) in a patient in whom empirical broad-spectrum antibiotic had been started was counted as an "instance". If two or more different samples (i.e., blood and urine) had been taken from the same patient and were reported positive, each was counted as a separate instance. Each such instance was considered as an opportunity for de-escalation of antibiotics. Broad spectrum antibiotics were defined as monotherapy with either 3rd generation cephalosporin or above, piperacillin-tazobactam, carbapenems, vancomycin and linezolid [4,5,13]. These antibiotics were classified as restricted antibiotics in our hospital AMS program and required senior physician's authorization for usage. The usage of more than one antibiotic for broadening the antimicrobial spectrum was also classified as broad-spectrum antibiotics in our audit. De-escalation was defined as changing to narrow spectrum antibiotic or reducing the number of antibiotics within 24 hrs of obtaining positive microbiological culture reports[2,19,21]. Antibiotic change after that was not considered as de-escalation. Positive cultures or instances of patients who died in the hospital course were excluded from the study. Reasons of de-escalation were classified into four groups after screening

#### *2.4.1. Serious Clinical Illness*

This included instances where de-escalation was not done because of poor clinical condition (lack of improvement, clinical deterioration, and organ dysfunction which precluded the use of narrow-spectrum antibiotics (i.e., amikacin in renal failure).

#### *2.4.2. Polymicrobial Infection*

This included instances where more than one organism was isolated from a single sample or different samples of single patient.

#### *2.4.3. Resistant Organism*

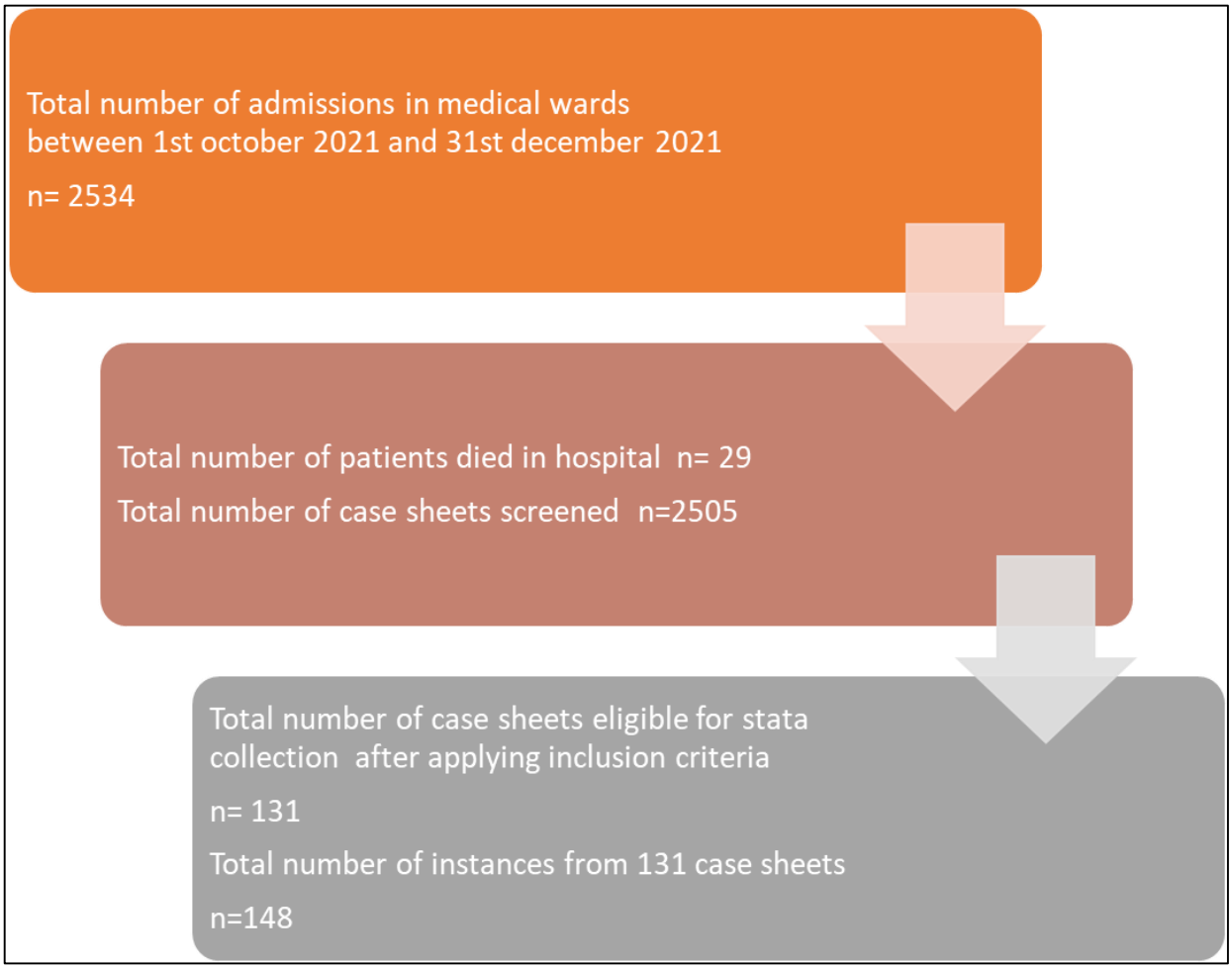
This included instances where the isolated organism was resistant to the available narrow-spectrum antibiotics where the physician had to continue the broad-spectrum coverage or had to escalate into a broader spectrum antibiotic

#### *2.4.4. Consultants' Choice*

Instances where there was no proper reason identified for not deescalating the empirical antibiotics and were grouped under consultants' choice.

At the end of screening, there were 131 eligible case sheets with 148 instances which were taken for analysis

### *2.5. Data Collection Flow Chart*



## 3. STATISTICAL ANALYSIS

Data were tabulated and analyzed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Inorder to describe the data, frequency analysis, and percentage analysis were used for categorical variables, while median with interquartile range (IQR) were used for continuous variables. Chi-Square test was used to find out the significance in categorical data. Fisher's Exact Test was used if the expected cell frequency was less than 5 in 2×2 tables. The probability value of .05 was considered as a significant level in the above statistic tools.

### *3.1 Ethical Statement*

The clinical audit protocol was approved by institutional ethics committee 2(1EC2) of Sri Ramachandra institute of higher education and research (SRIHER), Chennai. Appropriate ethical principles were followed according to the 1964 declaration of Helsinki during the collection and storage of data.

## 4. RESULTS

**Table 1: Baseline characteristics compared between de-escalation and non-de-escalation groups.**

| Variable | De-escalation | Non -de-escalation | P value | Over all |
|---|---|---|---|---|
| Median age in years (IQR) | 56(46-62) | 58(49-66) | | 58 (49-65) |
| Male | 22(27%) | 60(73%) | .34 | 82(100%) |
| Female | 17(35%) | 32(65%) | .34 | 49(100%) |
| Number of "instances" | 42(28%) | 106(72%) | | 148(100%) |
| Diabetes mellitus | 25(32%) | 53(68%) | .20 | 78(100%) |
| Hypertension | 25(32%) | 52(68%) | .20 | 77(100%) |
| Coronary artery disease | 1(17%) | 5(83%) | .51 | 6(100%) |
| Cerebrovascular disease | 2(20%) | 8(80%) | .54 | 10(100%) |
| Chronic kidney disease | 0(0%) | 3(100%) | .55 | 3(100%) |
| Thyroid disorders | 1(13%) | 7(87%) | .30 | 8(100%) |
| Connective tissue diseases | 0(0%) | 1(100%) | 1 | 1(100%) |
| Malignancy | 1(50%) | 1(50%) | .49 | 2(100%) |

Out of 131 case sheets screened 82 case sheets were from male patients and 49 were from female patients (Table 1). There were 148 over all eligible instances from the screened case sheets. (Table1). Median age of the patients in the de-escalation group was 56 years while that of non-de-escalation group was 58 years. De-escalation happened in 28% (42) instances. Diabetes mellitus 78/148(60%) and hypertension 77/148(59%) were the most common co morbidities prevalent in both the groups. The other comorbidities prevalent were cerebrovascular desease 10/148(7%), coronary artery desease 6/148(4%), thyroid disorders 8/148(5%), and malignancy 2/148(1%).However, there were no significant difference in the prevalence of various co morbidities among them. (Table 1)

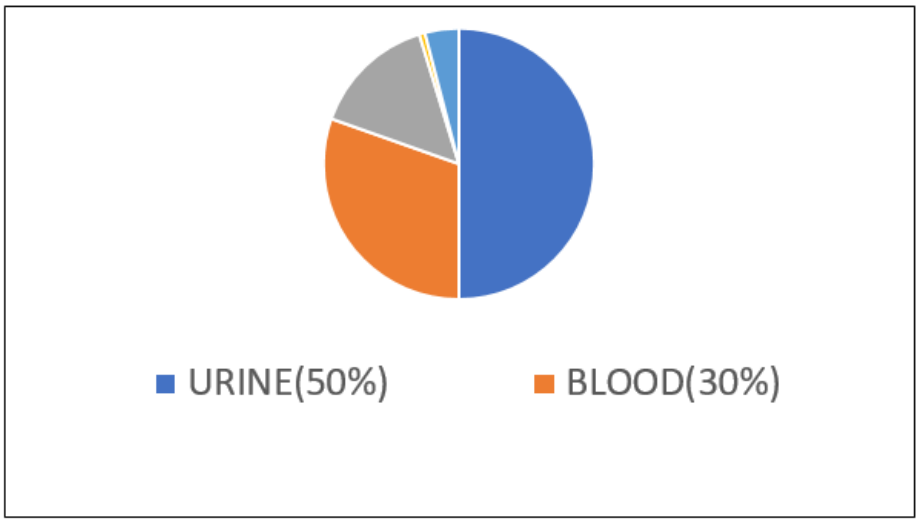



**Fig 1: Total number of samples n=148(100%)**

Among the culture samples (Figure 1), which were positive 74 (50%) were urine samples. The next common sample was blood 45(30%) followed by pus samples 22(15%) from various sites. There were 6 (15%) sputum samples and one (1%) pleural fluid sample, which had positive microbiological results.

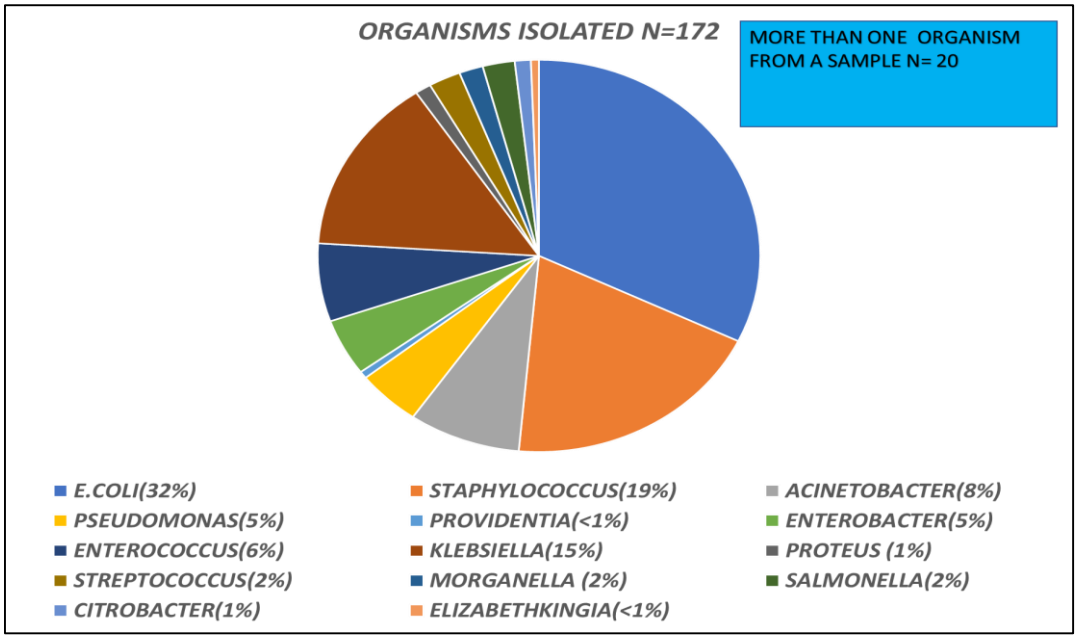



**Fig 2 Spectrum of the Organisms Isolated from the Culture Samples**

The total number of organisms isolated from the culture specimens were 172(100%). The most common organism isolated from the cultures was *Escherichia coli(E.coli)* (32%) followed by *staphylococcus sps ( species)*(19%) and *klebsiella sps* (15%)( FIGURE 2). The prevalence rate of other organisms was less than 10% (Figure 2). More than one organism was isolated from about 20 samples (Figure 2)

**Table 2 - Antibiotics Empericaly used as Monotherapy or in Combination**

| EMPERICAL ANTIBIOTIC | NO OF INSTANCES (142) | PERCENTAGE (100%) |
|---|---|---|
| CEFEPERAZONE-SULBACTUM | 45 | 32% |
| PIPERACILLIN-TAZOBACTUM | 38 | 27% |
| CEFTRIAXONE | 21 | 15% |
| CEFOTAXIME | 7 | 5% |
| MEROPENEM | 20 | 14% |
| VANCOMYCIN | 3 | 2% |
| LINEZOLID | 3 | 2% |
| CEFTAZIDIME | 1 | 1% |
| POLYMIXIN | 4 | 3% |
| TOTAL | 142 | 100% |
| MORE THAN ONE ANTIBIOTIC | 20 | 14% |

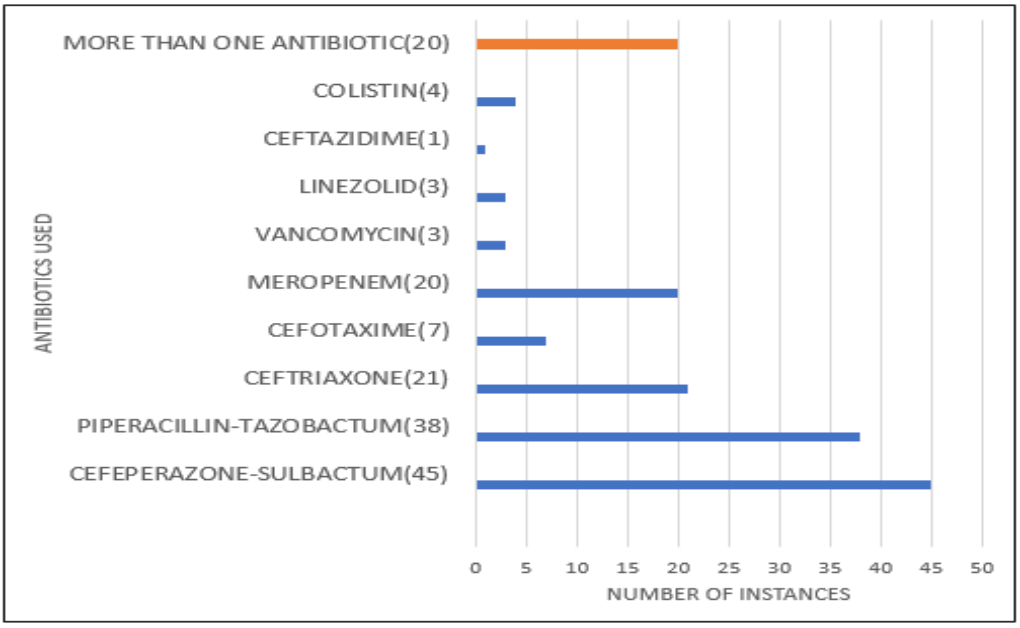



**Fig 3: Antibiotics empericaly used as monotherapy or in combination n=142(100%)**

Cefeprazone-sulbactum n=45 (32%) was the most preferred empirical monotherapy in the audited period. Piperacillin-tazobactum n=38(27%) was the following commonly used monotherapy either alone or in combination. (Table 2). Another third-generation cephalosporin, ceftriaxone n=21 (15%) and the carbapenem, meropenem n=20 (14%) were used in similar rates (Table 2). The other antibiotics used either alone or in combination in less than 10% of instances were cefotaxime, polymyxin, vancomycin, linezolid, and ceftazidime (Table 2, Figure 3). More than one antibiotic was used in 20(14%) of instances.

**Table 3: Antibiotics Empericaly Used only in Combination**

| EMPERICAL ANTIBIOTIC | NO OF INSTANCES (20) | PERCENTAGE (100%) |
|---|---|---|
| CIPROFLOXACIN | 2 | 10% |
| LEVOFLOXACIN | 1 | 5% |
| DOXYCYCLINE | 2 | 10% |
| CLOXACILLIN | 2 | 10% |
| AOMOXYCILLIN-CLAVULANIC ACID | 9 | 45% |
| CLINDAAMYCIN | 4 | 20% |
| TOTAL | 20 | 100% |

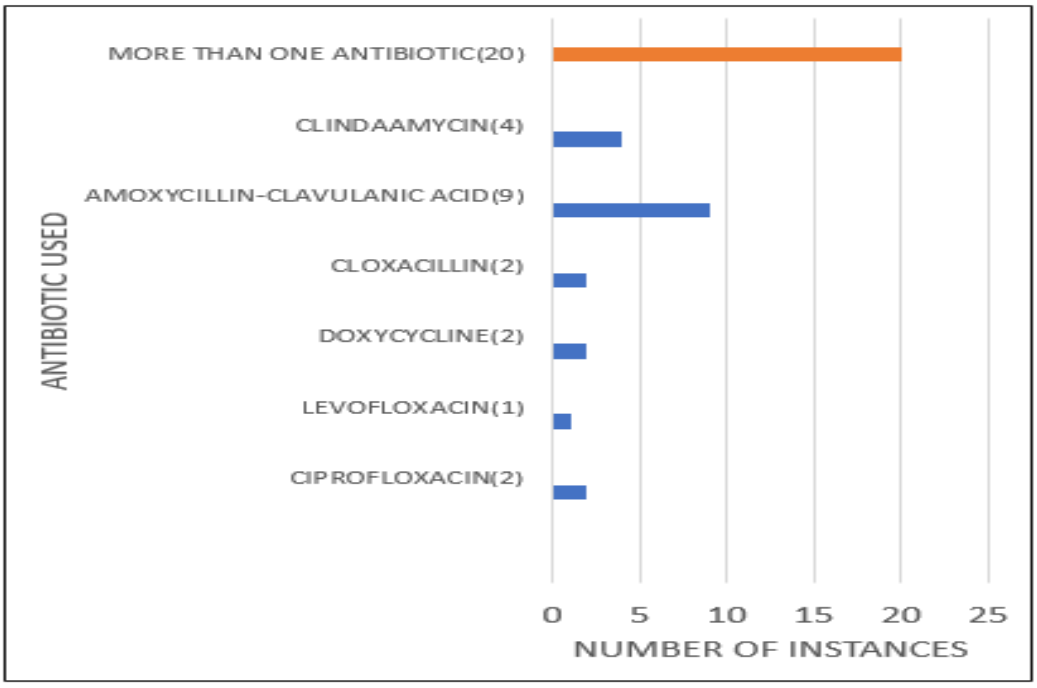



**Fig 4-Antibiotics Empericaly Used Only in Combination N=20(100%)**

Among the antibiotics used only in combination empirical therapy, amoxicillin and clavulanic acid n=9 (45%) were the most prevalent. Other less frequently used antibiotics were clindamycin n=4 (20%), cloxacillin n=2 (10%), doxycycline n=2(10%), levofloxacin n=1 (5%) and ciprofloxacin n=2 (10%) (Table 3, Figure 4).

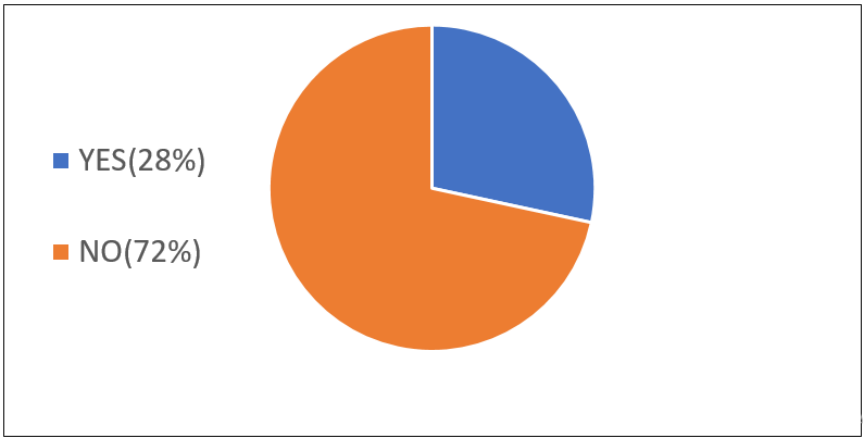



**Fig 5: Frequency of De-Escalation N=148(100%)**

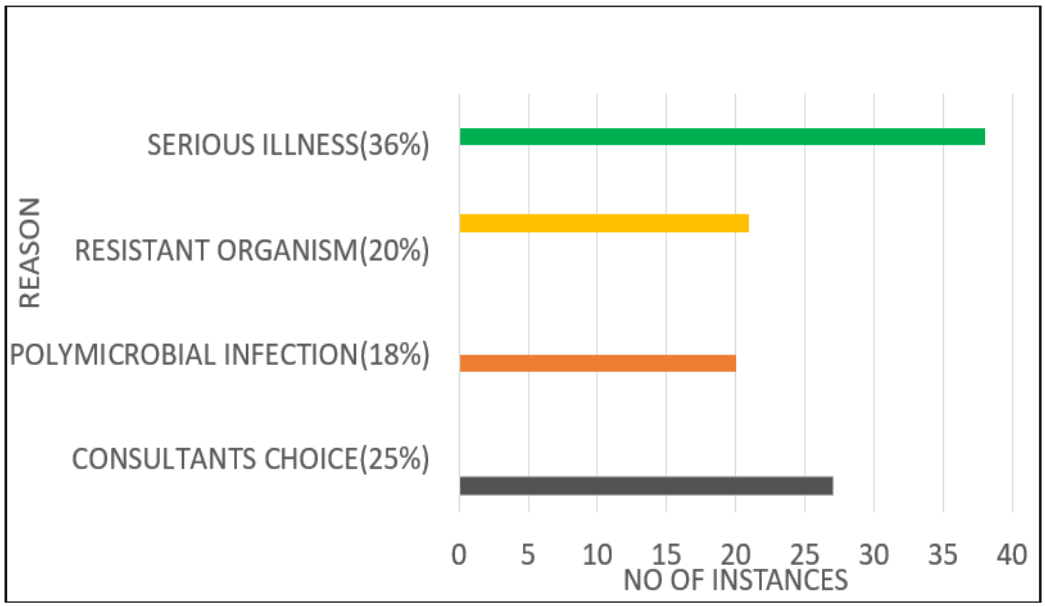



**Fig 6: Reasons for Not Deescalating N=106(100%)**

In our study the de-escalation rate after positive culture reposts was 42/148 (28%) (Figure 5). On analyzing the reasons for not deescalating, serious clinical illness 38/106 (36%) was found to be the most common reason (Figure 6). The prevalence of multi drug resistant organism21/106 (20%) and the presence of polymicrobial infection 20/106 (18%) were the other reasons (Figure 6). However, in 27/106 (25 %) of the instances de-escalation was not done by the consultant without an identifiable reason. (Figure 6).

## 5. DISCUSSION

The main objective of our audit was to estimate the de-escalation rates of broad-spectrum antibiotics in our center, a tertiary care hospital, and to identify the reasons for non-de-escalation. Analysing the reasons for non de.escalation would be crucial in formulating strategies for improving antibiotic de-escalation rates. After the screening process, we have included 148 eligible instances from 131 case sheets (Table-1). On comparing the baseline characteristics between the instances of de-escalation and non-de-escalation, there were no significant differences (Table 1). Among the culture-positive instances 50 percent were from urine samples, followed by blood (Fig 1). The culture positivity rate is usually high in urinary samples of patients with symptomatic UTI than that of septicaemia patients [2]. in the report from AIIMS India urine cultures and endotracheal tube cultures have been shown to yield slightly more positive results than that of blood.[3]. It is known that blood culture yields can be as low as 50 % even in sepsis patients. [12,17]. This could be the reason for more instances from urine samples in our audit. Since urine samples were the major instances (50 %) in our audit, Gram negative pathogens were isolated more in frequency with *E.coli* being the commonest (32%) followed by *klebsiella species* (15%) (Fig 2). *Staphylococcus sps.* were the most grama positive pathogen isolated from the specimens. The study by V. Pérut et al[21] in the hospitalized patients, including all wards, the pathogenic spectrum was similar to our audit (e coli 27%, *klebsiella sps.*(10%) and *staphylococcus sps.* (17%). in the report from Brazil [2] on septic shock patients, again gram-negative pathogens *E coli* and *klebsiella sps*. were the commonly isolated ones, with *staphylococci* were the most frequently isolated gram-positive bacteria. Gram negative pathogens, particularly *E coli* seems to be the most common isolated organism across medical wards in patients with serious infections. Ceferazone-sulbactum along and piperacillin-tazobactum were the most commonly used antibiotics for empirical treatment as a monotherapy (Table1, Fig 3). considering the fact that 50 percent of instances were urine cultures (Fig 1) which are likely to harbour extended spectrum beta lactamase (ESBL) producing organisms [9]the usage of these two antibiotics appears reasonable.[14]. In the study from a teaching hospital in France, ceftriaxone and piperacillin-tazobactum were the commonly used antibiotics for empirical treatment of suspected sepsis.[21] A hospital-based study on urinary tract infections reported that ceftriaxone along with piperacillin-tazobactum and meropenem were the most commonly used empirical antibiotics[5]. Since our audit has 50 % urine culture instances, the empirical antibiotics usage is similar. At times two or more antibiotics are combined to provide broad spectrum antimicrobial coverage in empirical treatments [3,8,24] and more so in prolonged intensive care settings [19]. The usage of combination therapy might be as high as 42% to 60%, depending upon the study population [19,21]. The de-escalation strategy includes reducing the number of antibiotics based on the culture reports apart from switching from broad spectrum antibiotics to a narrow-spectrum one. In our audit there were 20(14%) instances of combined antibiotic therapy which were eligible for de-escalation (Table 1, Fig 3)). we have found that the de-escalation rate is about 28% in our audit. (Fig 5). World-wide there Is a large variation in the reported de-escalation rates mainly because of the heterogenous study population and study settings [2,4,13,17], and it varied between 10 and 70 percent in the reported studies [2,4]. There has been no bench mark yet for de-escalation rates as the criteria for de-escalation varied among the studies[19,25,26] In an intensive care unit (ICU) setting from Brazil [2], it has been reported to be 44% which went up to more than 70% in the study from united states which included even non critically ill patients.[4]. The latter showed no difference of de-escalation between culture positive and culture negative patients[4]. Most of these studies have included de-escalation, even in culture-negative patients considering the clinical improvement. Considering this variation our de-escalation rates after the positive culture reports appear slightly lesser. On auditing the instances, we found that physicians were hesitant to deescalate when the

patient is very sick or seriously ill (36%) (Fig 6). It is often difficult to de-escalate when the patient's clinical condition is deteriorating. Most earlier studies have also shown that de-escalation was performed only in clinically improving patients i.e., afebrile for more than 24 hours, resolved hypoxia etc, irrespective of the culture reports [2,14]. Hence this number is unlikely to change with AMS as clinical improvement often defines the adequacy of the treatment. In about 20 % of instances, physicians were unable to deescalate because of the microbiological evidence of resistant organisms (Fig 6). It's well known that the prevalence of multidrug resistant organisms is quite high in developing countries like India.[9] since about 50 % of instances were urine samples with likely organisms being ESBL-producing Enterobacteriaceae, the chances of de-escalation in these patients are very low unless the possibility of contamination or colonization is considered [2]. Hanan Alshareef et al in their study on urinary tract infections, reported the high prevalence of MDR pathogens as an important reason for non-de-escalation[5]. Resistant organisms predicted non-de-escalation in the study by F A Khasawneh et al as well[26]. Polymicrobial infections are often hard to treat in hospital setting. Majority of them harbour resistant organisms. [12,27]. The antibiotic regimen is chosen to reasonably address the multiple organisms grown in culture and the complicated pathogenesis like biofilms to be considered [27,28]. Physicians may have to maintain the broader antibiotic coverage even in suspected polymicrobial infections [12]. Polymicrobial infections were the reason for non-de-escalation in 18 % of instances (Fig 6). The usage of alternate strategies like antimicrobial peptides [28] with evaluation and validation of an antimicrobial policy in polymicrobial infections might help in reducing this rate. In our audit 25 % of instances did not have a proper reason for non-de-escalation (Fig 6). The consultant preferred to continue the broad-spectrum antibiotic after the positive culture report, even though a narrow spectrum antibiotic was available from the culture report. This area provides a significant opportunity for the implementation of comprehensive AMS, including physician education, stringent antimicrobial policy, time out on antibiotic therapy, multidisciplinary team involvement, regular audit and feedback, which has been shown to improve the de-escalation rates by many authors. [20,21,29].

## 6. STRENGTHS OF THE STUDY

As far as we know, this is the first study to report antibiotic usage and de-escalation rate from this part of the country. The reasons for non- de-escalation and the opportunities for improvement have been analysed in this study.

## 7. LIMITATIONS

This study included only instances from medical ward patients. Therefore, the rationale of empirical regimen was not analysed. Instances where the patients die during hospital stay were excluded from the study. Hence the impact of de-escalation could not be analysed.

## 8. CONCLUSION

Cefeprazone-sulbactum and piperacillin-tazobactum are the two most frequently used antibiotics for empirical treatment in medical ward patients. The de-escalation rate after the relevant culture reports in medical ward patients is about 28%. This rate appears low, considering the fact that the study included instances from both critical as well as non-critical patients. The most common reason for non-de-escalation is the poor clinical status of the patient. Polymicrobial infections contribute significantly to non-de-escalation, where a uniform antimicrobial policy might help out. De-escalation was not done in nearly 25% of eligible instances without a proper reason. This gap provides an opportunity for stringent implementation of AMS program and improving de-escalation rates.

## 9. AUTHORS CONTRIBUTION STATEMENT

Dr sathyamurthy Conceived and designed the analysis. Dr.sathyamurthy and Dr. Rajkumar collected the data and performed the analysis. Dr.sathyamurthy wrote the manuscript with the help of Dr.rajkumar.

## 10. CONFLICT OF INTEREST

Conflict of interest declared none.

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