



Antibiotic De-Escalation Practices in Gram Negative Bacteremia

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ABSTRACT

Introduction: Gram negative bacteremia is a global health problem. It is a huge challenge to the physicians because of the rapidly emerging resistance to multiple drugs among the microorganisms. Empirical use of broad-spectrum antibiotics is an important step in treating patients with gram negative sepsis. De-escalation is an integral part of Antimicrobial Stewardship programme.

Methodology: it is a Descriptive study done in Hospitals Affiliated to Manipal University which was conducted from September 2016 to July 2018. Adults ≥ 18 years with culture proven gram negative bacteremia were included in the study and excluded patients who died before the culture reports are available.

Results and Discussion: During the study period, 300 patients with positive blood cultures were identified. Of which patients with non eligible pathogens (n=99) and patients who died before culture reports are available and polymicrobial organisms (n=45) were excluded. 156 patients were analysed. Out of 156 patients, antibiotics were de-escalated in 38 patients (24.4%), and not de-escalated in 118 (75.6%). Among 118 patients, antibiotics were escalated in 67 (42.9%) and not changed in 51 (32.7%). There was no difference in mortality rates between de-escalation and non-de-escalation group. ($p=1.00$)

Conclusion

In our study, rate of de-escalation was 24% among patients with gram negative bacteraemia. This is of concern as we enrolled patients who were candidates for de-escalation based on blood culture reports. Training programmes must be conducted at regular intervals in hospitals to increase awareness about the benefits of de-escalation among all antibiotic prescribers. De-escalation is a simple tool to combat AMR.

Keywords: Sepsis, Bacteremia, Antimicrobial Stewardship, De-escalation.

I. INTRODUCTION

Gram negative bacteremia is a global health problem. It is a huge challenge to the physicians because of the rapidly emerging resistance to multiple drugs among the

microorganisms [1]. Mortality due to Gram negative bacteraemia ranges from 12-38% [2]. The most important Gram-negative organisms in the hospital setting includes *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* which represent 28 % of all microorganisms and 71 % of total Gram negative organisms involving healthcare acquired infections [3]

Antimicrobial therapy for gram-negative bacteraemia can be divided into two distinct treatment phases with unique approaches: empiric therapy and directed therapy. Empiric therapy is drugs given when an infection is suspected but not yet confirmed. Definitive therapy is drugs given when the clinician has confirmed the type of infection, causative pathogen, and pathogen antimicrobial susceptibilities[4]

Empirical use of broad-spectrum antibiotics is an important step in treating patients with gram negative sepsis. The 'spectrum' of antibiotic refers to the number of pathogens against which it is effective. In patients with septic shock, delay in administration of appropriate antibiotic is associated with up to a 7.6% absolute increase in mortality per hour.[5] Early initiation of broad-spectrum antibiotics is considered the standard of care according to Surviving Sepsis Guidelines. The choice of antibiotics should take into account the patient's history, comorbidities, clinical syndrome, health care exposures, and previous culture results in addition to local resistance patterns. However, the use of broad-spectrum antibiotics has some problems i.e. antibiotic-related side effects, cost issues and the emergence of resistance. [6] Rational use of antibiotics is more important to prevent the emergence of multidrug resistant (MDR) bacteria which can lead to therapeutic deadlock, especially in ICUs.

Antimicrobial Stewardship (AMS) is an activity that includes appropriate selection, dosing, route and duration of antimicrobial therapy. AMS when combined with infection control program can limit the emergence and transmission of antimicrobial resistant bacteria. De-escalation is an integral part of Antimicrobial Stewardship



programme.[7] 'Antibiotic de-escalation refers to the practice of starting with a broad-spectrum empiric antibiotic regimen, designed to avoid inadequate therapy, combined with a commitment to change from broad-spectrum to narrow-spectrum therapy and from multiple agents to fewer medications and if possible even a single agent'.[8] Surviving sepsis guideline has not only championed the need for early usage of appropriate empirical broad spectrum antimicrobials but it has highlighted the importance of de-escalation when the causative agent has been identified.[9] Antibiotic de-escalation is one of the strategies recommended to avoid selection of MDR isolates. There are hardly any studies in India documenting antibiotic de-escalation practices in gram negative bacteremia, hence the need for this study.

II. MATERIALS AND METHODS

Study type- Descriptive study

Study setting- Hospitals Affiliated to Manipal University(KMC Attavar, KMC Ambedkar circle)

Duration of data collection- The study was conducted from September 2016 to July 2018.

Inclusion criteria:

Adults ≥ 18 years with culture proven gram negative bacteremia.

Exclusion criteria:

Patients who died before the culture reports are available.

Patients with typhoid and polymicrobial infections.

Sampling method: Study participants were selected by non probability sampling.

Sample size estimation:

The sample size of 156 was calculated based on expected proportion of de-escalation as 39% based on previous study [11], relative precision as 20%, power as 80% and Confidence Interval 95% (CI). Formula used for sample size calculation was : $n = 4pq/d^2$

Data collection:

The following patient details were collected using a proforma: socio demographic data, presence of comorbid illness, implicated bacteria, antibiotic sensitivity profile, initial empiric antibiotic used. SOFA score was calculated on the day when blood culture was drawn. The patient's need for admission to intensive care was noted. Information about antibiotic de-escalation or the lack of it and mortality was collected.

Patients who are treated empirically with broad-spectrum antibiotics or an antibiotic regimen

consisting of multiple agents were considered as candidates for de-escalation.

Opportunities for de-escalation were assessed. De-escalation was evaluated once, the culture sensitivity reports are available.

Study definitions

A broad-spectrum antibiotic is defined as a third or fourth-generation cephalosporin, extended-spectrum penicillin, or a carbapenem.[10] Antibiotic strategies once culture results are available were classified as: "no change" (empirical therapy was maintained without modification), "escalation of therapy" (the switch to or addition of an antibiotic with a broader spectrum), and "de-escalation" (switch to a drug class resulting in a less broad spectrum of coverage).[6]

Appropriate antibiotic- Antimicrobial therapy was considered appropriate when atleast one of the antibiotics had an in vitro activity against the identified microorganism

III. STATISTICAL ANALYSIS

Continuous data was expressed as mean (SD), and was compared using the Mann-Whitney U-test. Categorical data was expressed as counts and percentages, and compared using the chi-square test. A p value of <0.05 was considered statistically significant.

IV. RESULTS:

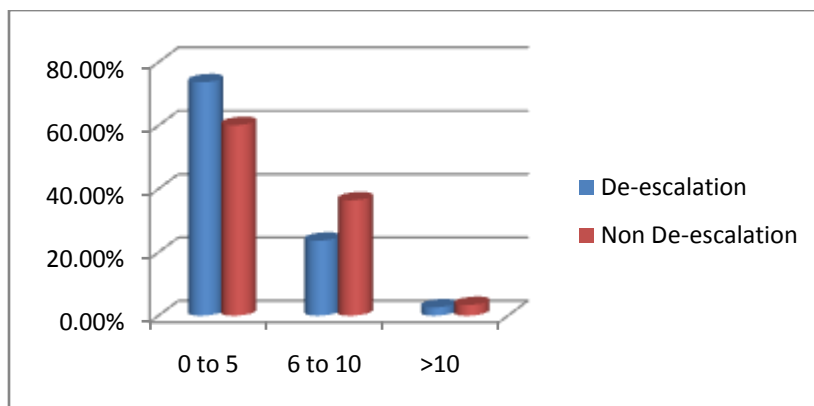
During the study period, 300 patients with positive blood cultures were identified. Of which patients with non eligible pathogens (n=99) and patients who died before culture reports are available and polymicrobial organisms(n=45) were excluded. 156 patients were analysed. Majority of the patients 74 (47.4%) in our study belonged to the age group of more than 60 years. Mean age was 57.78 ± 13.57 years. Majority of our patients were males 85 (54.5%).

The commonest gram negative organism in our study was *Escherichia coli* 94(60.3%). *Klebsiella*, *Pseudomonas*, *Acinetobacter* were also isolated from blood cultures in our study and the common comorbidities seen in our study was hypertension 84(55.1%) and diabetes 83(53.2%). Majority of the patients 99 (63.5%) in our study had SOFA score of <5 . In our study 87 (55.8%) patients required ICU care. Various combinations of antibiotics was used in our study. Out of 156 patients, Piperacillin / Tazobactam was the most used antibiotic 58 (37.2%). Carbapenems were used in 33 (21.2%).



Out of 156 patients, antibiotics were de-escalated in 38 patients (24.4%), and not de-escalated in 118 (75.6%). Among 118 patients, antibiotics were escalated in 67 (42.9%) and not

changed in 51 (32.7%). Majority of patients in de-escalation group had SOFA score <5 which is same as in non-de-escalation group.



Among 156 patients in the study population 141 (90.4%) were alive and 15 (9.6%) died during the study period. Out of 94 (60.25%) patients who had E.coli bacteremia 9 (5.7%) died.

Among patients with SOFA score of 0-5, most of them were alive and majority of patients with SOFA score >10 died. Among 38 patients in whom antibiotics were de-escalated, 35 (92.1%) were alive. There was no difference in mortality between both the groups.

V. DISCUSSION

In our study de-escalation rate was 24%. The mean age was 57.78 ± 13.7 years. Majority 85 (54.5%) were males. Mean SOFA score was 4.96 ± 2.586 . There was no difference in mortality rates between de-escalation and non-de-escalation group. ($p=1.00$)

Shime et al. [11] conducted a study on de-escalation practices in immunocompetent patients presenting with bacteraemia due to antibiotic-sensitive pathogens at Kyoto Prefectural University of Medicine in Japan. They included both gram negative and gram positive pathogens in their study. E coli was the commonest organism in their study. Out of 201 candidates, antimicrobial therapy was deescalated in 79 (39%) and remained unchanged or was escalated in 122 (61%) patients. Shime et al. conducted another study in Japan wherein they analysed de-escalation practices in the treatment of bacteraemia caused by specific gram-negative bacilli (SPACEs; Serratia, Pseudomonas, Acinetobacter, Citrobacter, and Enterobacter). In their study de-escalation was done in 57% of patients. They also concluded that there was no significant difference in in-hospital

mortality between the de-escalation group and the non-de-escalation group. [12] De-escalation was associated with significantly lower costs of antimicrobial therapy in their study. Khasawneh et al. [13] conducted a study in West Texas on bacteraemia due to urinary tract infections. De-escalation was done in 34 (45%) patients. Resistance to fluoroquinolones, bacteria other than Escherichia coli and discharge to long-term care facilities predicted failure to de-escalate antibiotics. The same study showed a trend in in-hospital mortality favoring the de-escalation group (1/34 patients) over the non-de-escalation group (6/31 patients) but it was not statistically significant ($p = 0.06$). Khasawneh et al. [10] analysed de-escalation practices for bacteremic HAP in USA. They included both gram positive and gram negative organisms in their study. Among the 60 patients who were eligible for de-escalation, physicians failed to de-escalate antibiotics in 27 cases (45.0%). Discharge to a long-term care facility predicted failure to de-escalate antibiotics, while an infectious diseases consultation was significantly associated with antibiotic de-escalation. The average daily cost of antibacterial therapy in the de-escalation group was \$25.7 compared with \$61.6 in the group where de-escalation was not implemented. The difference in mean length of hospital stay and mortality between the two groups was not statistically significant. Carugati et al. [14] analysed de-escalation practices in patients with bacteremic CAP. They included both gram positive and gram negative organisms. Two hundred and sixty-one bacteraemic CAP patients were included. Gram-positive bacteria were responsible for 88.1% of the cases (Streptococcus pneumoniae, 75.9%).



Gram-negative bacteria were responsible for 7.3% of the cases. DET was performed in 165 patients (63.2%). The N-DET group was characterized by a more severe presentation at admission. After adjustment for confounders, DET was not associated with an increased risk of 30-day mortality.

A Cochrane review done by Silva et al [15] in 2013 concluded that there was no sufficient evidence to recommend for or against de-escalation in adults with sepsis. Paul et al [16] in their meta-analysis have mentioned that observational studies showed lower mortality following antibiotic de-escalation (culture guided results) among patients with bacteraemia, pneumonia or severe sepsis, whereas RCTs favored no de-escalation. Ohji et al [17] conducted a systematic review and meta-analysis on de-escalation therapy for a variety of infections. A total of 23 studies evaluating the effectiveness and safety of de-escalation therapy were identified. They concluded that de-escalation may improve mortality in both community-acquired and ICU acquired pneumonia. However, they also mentioned that quality of the studies used in their analyses was generally low.

Our study has some limitations. It is a single center study. We included patients with Gram negative bacteremia. So our results cannot be applied for gram positive organisms. Our institute caters predominantly to an urban population. We did not assess de-escalation practices in other Gram negative bacteremia like Salmonella typhi. We did not assess factors influencing de-escalation. Data regarding infection relapse or long-term mortality was not captured. We did not collect data about

side effects of antibiotics. We did not collect details about intravenous to oral antibiotic switch.

VI. CONCLUSION

In our study, rate of de-escalation was 24% among patients with gram negative bacteraemia. This is of concern as we enrolled patients who were candidates for de-escalation based on blood culture reports. Training programmes must be conducted at regular intervals in hospitals to increase awareness about the benefits of de escalation among all antibiotic prescribers. De-escalation is a simple tool to combat AMR. Hospitals must try to identify the reasons that impair the decision towards de-escalation so that steps can be taken to curb the clinician's reluctance to adopt de escalation strategy.

Summary

We evaluated 156 patients with Gram negative bacteremia.

- Mean age of our study population was 57.78 ± 13.57 years.
- Majority of patients in our study were males 85 (54.5%).
- Escherichia coli was the most common organism isolated in our study 94 (60.3%)
- De-escalation rate in our study is 38 (24.4%)
- Mortality rate in our study is 15 (9.6%)
- There was no significant difference in the outcome among the de-escalated and non-de-escalated group.

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Ethical clearance:



**MANIPAL
UNIVERSITY**
Institutional Ethics Committee
Kasturba Medical College, Mangaluru
(Reg. No. ECR/541/Inst/K/A/2014)

Communication of the Decision of the Institutional Ethics Committee


Wednesday 28th September, 2016

IEC KMC MLR 09-16/233

Protocol title	:	Antibiotic de-escalation practices in gram negative bacteremia
Principal Investigator	:	Dr. Dodda Vasanthi
Guide/Co-Guide/Co-Investigators	:	Dr. Deepak R. Madi
Name & Address of Institution	:	Department of Medicine Kasturba Medical College Mangalore
New / review	:	New
Date of review (DD/M/YYYY)	:	28/09/2016
Decision of the IEC ➤ Approved ➤ Pending ➤ Revision ➤ Rejected	:	Approved from 28/09/2016
Remarks	:	Approved for the study period as mentioned in protocol

Please Note*

- Inform IEC immediately in case any Adverse events and Serious adverse event
- Inform IEC in case of any amendments to the protocol, change of study procedure, site and Investigator and premature termination of study with reasons along with summary.
- Final & Yearly Reports to be submitted to IEC.
- Members of IEC have right to monitor the study with prior intimation.
- A copy of the consent document to be given to the study participant giving the consent.


Dr. Shalini Shenoy
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BIBLIOGRAPHY

- [1]. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, [1]pathogens and outcomes. *Expert Review of Anti-Infective Therapy* 2012;10(6):701-06.
- [2]. Bouza C, López-Cuadrado T, Saz-Parkinson Z, Amate-Blanco JM. Epidemiology [2]and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011). *BMC Infect Diseases* 2014;14:3863.
- [3]. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2009–2010. *Infect Control Hosp Epidemiology* 2013;34:1–14
- [4]. Kang CI, Kim SH, Park WB. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrobial Agents Chemotherapy* 2005; 49:760- 66.
- [5]. Kumar A , Roberts D , Wood KE , et al . Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589–96.
- [6]. Garnacho-Montero J, Escoresca-Ortega A, Fernández-Delgado E. Antibiotic de-escalation in the ICU: how is it best done? *CurrOpin Infect Dis* 2015;28:193-8.
- [7]. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship *Clin Infect Dis* 2007; 44:159-77.
- [8]. Niederman MS. De-escalation therapy in ventilator-associated pneumonia. *CurrOpin Crit Care* 2006;12:452–57.
- [9]. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock:2012 *Crit Care Med* 2013; 41:580–37
- [10]. Khasawneh F, Ahmed S, Jaffri SF, Mahmood T, Mehmood M, Karim A. Safety and feasibility of antibiotic de-escalation in bacteremic pneumonia. *Infect Drug Resist* 2014;7:177–82.
- [11]. Shime N, Satake S, Fujita N. De-escalation of antimicrobials in the treatment of bacteraemia due to antibiotic-sensitive pathogens in immunocompetent patients. *Infection* 2011;39(4):319-25.
- [12]. Shime N, Kosaka T, Fujita N (2013) De-escalation of antimicrobial therapy for bacteraemia due to difficult-to-treat Gram-negative bacilli *Infection* 41:203–210.
- [13]. Khasawneh FA, Karim A, Mahmood T, Ahmed S, Jaffri SF, Tate ME, et al. Antibiotic de-escalation in bacteremic urinary tract infections: potential opportunities and effect on outcome *Infection* 2014;42:829–34.
- [14]. Carugati M, Franzetti F, Wiemken T, Kelly R, Peyrani P, Blasi F, et al. De-escalation therapy among bacteraemic patients with community-acquired pneumonia. *Clin Microbiol Infect* 2015;21. 936.e11-8.
- [15]. Silva BN, Andriolo RB, Atallah AN, Salomão R. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. *Cochrane Data-base Syst Rev* 2013;3:CD007934.
- [16]. M. Paul, Y. Dickstein, A. Raz-Pasteur Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis *CMI* 2016;22:960-67
- [17]. Ohji G, Doi A, Yamamoto S, et al. Is de-escalation of antimicrobials effective? A systematic review and meta-analysis 2016 ;49:71-9