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# Efficacy Ratio Based Comparison of Susceptible Minimum Inhibitory Concentration of Antibiotics in *E. coli* Isolates of Bacteremia-A Retrospective Study

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## ABSTRACT

*Introduction: It is necessary to compare the susceptible minimum inhibitory concentrations (MIC) of different antibiotics to choose the appropriate one. Direct comparison of MICs cannot be done since the breakpoints are different for each antibiotic. In this scenario Efficacy ratio(ER) of an antibiotic can be determined.This is the ratio between the susceptible breakpoint and the susceptible MIC of the specific antibiotic. The therapeutic efficacy is directly proportional to the ER value. ER is a significant factor in antimicrobial agent selection and a very useful tool in planning the empirical therapy.*

*Aim: To calculate the Efficacy ratio of susceptible minimum inhibitory concentrations of antibiotics in E.coli isolates of bacteremia and select the appropriate antibiotic for treatment.*

*Materials and methods: Retrospectively study the Vitek 2 derived susceptible minimum inhibitory concentrations of E.coli isolates from bacteremia and determines the Efficacy ratio.*

*Result: Amikacin had the Highest ER 8 for 88% of isolates. Tigecycline (100%), colistin (97%), imipenem (94%), Meropenem (100%), Meropenem (100%), Gentamycin (88%), Piperacillin tazobactzm (97%) all had ER of 4. Cotrimoxazole (100%), Cefepime (92%), Cefoperazone sulbactam (91%) had ER of 2. Ertapenem (100%), Ceftriaxone (100%), Ciprofloxacin (100%), Amoxyclav (40%), Cefuraxime (92%), had ER of 1. Ampicillin ER was 1 and 4 with only 3 isolates in each category.*

*Conclusion: Selecting the antibiotic based on MIC value is advantageous for positive treatment outcome and prevention of resistant subpopulation. The antibiotics with High degree of susceptibility are preferred for more effective treatment for which calculating ER value is of immense help and it is to be correlated with the type of infection, side effects, frequency of drug administration etc.*

**Key words:** Efficacy ratio, *E. coli*, Bacteremia, Antibiotic selection, Antibiotic resistance

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## INTRODUCTION

The antibiotics if not chosen appropriately may fail to render the desired outcome in infectious diseases. Hence it is essential not only to select the right antibiotic but also to use it wisely so that it accomplishes its therapeutic effect to the maximum. The Antibiotic sensitivity testing by the time tested disc diffusion method is immensely helpful in treating various types of infections. Still there has to be a more accurate selection of antibiotic in treating the patients who are critically ill such as gram negative bacteremia. For this purpose the MIC of the antimicrobial agent plays an important role [1].

The MIC interpretation grants us the understanding of degree of susceptibility or the resistance pattern of the organism to the antibiotics. Degree of susceptibility adds significant deeper knowledge to the epidemiological study as well. If the MIC is well below the susceptible breakpoint value the organism would not develop resistant subpopulation. This makes the strain highly

susceptible to the antibiotic because the drug can attain the therapeutic concentration effectively. Therefore the data of degree of susceptibility of a bacterium to various antibiotics in a hospital is valuable in designing antibiotic policies [1-3]. In therapeutic aspect it is necessary to compare the MICs of different drugs to choose the appropriate one. While comparing the degree of susceptibility between the antibiotics, direct comparison of MICs cannot be done since the breakpoints are different for each antibiotic. In this scenario Efficacy ratio(ER) of an antibiotic can be determined. This is the ratio between the susceptibility breakpoint and the MIC of the specific antibiotic. The therapeutic efficacy is directly proportional to the ER value. ER is a significant factor in antimicrobial agent selection and a very useful tool in planning the empirical therapy [4].

In this study we conducted a retrospective analysis of the MIC patterns of the *E. coli* isolates from blood cultures in our ICU and calculated the ER for the susceptible antibiotics in order to formulate the antibiotic policy. As there are no cumulative MIC related information's available in literature for Bacteremia our study of the bacteremia causing organism *E. coli* which is one of the leading causative organisms of sepsis [5] and its MIC pattern will be of advantage in developing empirical antibiotic policies in other centers as well.

## MATERIALS AND METHODS

This study was conducted at Sree Balaji Medical College and Hospital in Chennai, South India. It is a retrospective study. The blood samples of patients clinically suspected to have blood stream infection were included in the study. The samples were collected in BacT/ALERT bottles and incubated for upto 5 days in BacT/ALERT automated system. When the bottles flagged they were subculture manually. Next day the colonies were processed in VITEK 2 for identification and AST. The cards used for detecting MIC were N280 and N281. The interpretations were

**Table 1: Susceptible ranges of minimum inhibitory concentration of antibiotics and number of susceptible *E. coli* isolates.**

| Antibiotic | Susceptible Ranges of Minimum inhibitory concentration of antibiotics | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | <=0.25 n(%) | <=0.5 n(%) | <=1 n(%) | <=2 n(%) | <=4 n(%) | <=8 n(%) | <=16 n(%) | <=20 n(%) | Number of Susceptible isolates |
| Ampicillin | | | | 3 (50) | | 3(50) | | | 6(15) |
| Amoxyclav | | | | 6 (30) | 6(30) | 8(40) | | | 20(50) |
| Amikacin | | | | 31 (88) | 2(6) | 1(3) | 1(3) | | 35(88) |
| Ciprofoxacin | 8 (100) | | | | | | | | 8 (20) |
| Ceftriaxone | | | 15 (100) | | | | | | 15(37) |
| Cefuraxime | | | 1(8) | | 11(92) | | | | 12(30) |
| Cotrimoxazole | | | | | | | | 25(100) | 25(62) |
| Ertapenem | | 36(100) | | | | | | | 36(90) |
| Cefepime | | | 20 | 2(8) | | | | | 22(55) |
| Gentamycin | | | 30 | 2(6) | 2(6) | | | | 34(85) |
| Imipenem | 32(94) | | 2(6) | | | | | | 34(85) |
| Meropenem | 34 (100) | | | | | | | | 34(85) |
| Cefoperazone sulbactam | | | | | | 30 (91) | 3(9) | | 33(82) |
| Colistin | | 38(97) | | 1(3) | | | | | 39* (100) |
| Tigecycline | | 40(100) | | | | | | | 40(100) |
| Piperacillin tazobactam | | | | | 31(97) | 1(3) | | | 32(80) |

* Intermediate level of breakpoint was taken into account for Colistin as per CLSI guidelines

**Table 2: Efficacy ratio of antibiotics and the percentage of Susceptible *E. coli* isolates.**

| Antibiotic | Sensitive n(%) | Intermediate n(%) | Resistant n(%) | Efficacy ratio = Susceptible breakpoint/ Susceptible MIC value observed | | | |
|---|---|---|---|---|---|---|---|
| | | | | ER =1 | ER=2 n(%) | ER=4 n(%) | ER=8 n(%) |
| Ampicillin | 6(15) | 2(5) | 32(80) | 3(50) | | 3(50) | |
| Amoxyclav | 20(50) | 6(15) | 14(35) | 8(40) | 6(30) | 6(30) | |
| Amikacin | 35(88) | 0 | 5(12) | 1(3) | 1(3) | 2(6) | 31(88) |
| Ciprofoxacin | 8 (20) | 2(5) | 30(75) | 8(100) | | | |
| Ceftriaxone | 15(37) | 0 | 25(63) | 15(100) | | | |
| Cefuraxime | 12(30) | 3(8) | 25(62) | | 11(92) | | 1(8) |
| Co-trimoxazole | 25(62) | 0 | 15(38) | | 25(100) | | |
| Ertapenem | 36(90) | 0 | 4(10) | 36(100) | | | |
| Cefepime | 22(55) | 8(20) | 10(25) | 2(8) | 20(92) | | |
| Gentamycin | 34(85) | 0 | 4(15) | 2(6) | 2(6) | 30(88) | |
| Imipenem | 34(85) | 1(3) | 5(12) | 2(6) | | 32(94) | |
| Meropenem | 34(85) | 1(3) | 5(12) | | | 34(100) | |
| Cefoperazone sulbactam | 33(82) | 2(5) | 5(13) | 3(9) | 30(91) | | |
| Colistin | - | 39(97) | 1(3) | 1(3) | | 38(97) | |
| Tigecycline | 40(100) | 0 | | | | 40(100) | |
| Piperacillin tazobactam | 32(80) | 1(3) | 7(17) | | 1(3) | 31(97) | |

based on CLSI and EUCAST 2021 guidelines. The blood culture isolates of *E. coli* were included in this study from January 2021 to January 2022 and their MIC patterns were analysed. The Vitek 2 system and BacT/ALERT system's quality controls were meticulously followed as per the manufacturer's instructions. Efficacy ratio was calculated as the ratio between the susceptibility breakpoint and the MIC of the specific antibiotic and analysed.

## RESULTS

The total number of *E. coli* isolates was 40. The susceptible Minimum inhibitory concentration pattern of the *E. coli* isolates and the total number of susceptible organisms were as per the following Table 1. To compare the degree of susceptibility of antibiotics we determined the efficacy ratio by dividing the susceptibility breakpoints by MIC of the particular antibiotic observed. The highest ER was noted for Amikacin(ER=8). The most sensitive Tigecycline was with the ER of 4 for all isolates. The carbapenems Imipenem and Meropenem were of ER 4. Among them the highly sensitive Ertapenem's ER was low as 1. With regards to Piperacillin tazobactam 97% of isolates were with ER 4.Colistin's ER was also 4 when the intermediate breakpoint was used for calculating ER. Cefoperazone sulbactam was having ER of 3 for 91% of isolates.Gentamycin was having ER of 3 for 88% of isolates. Co-trimoxazole and Cefepime also showed ER 2 for 100% and 92% respectively. Ceftriaxone showed ER of 1 for 100% of susceptible isolates. Table 2 shows Efficacy ratio of antibiotics and the percentage of Susceptible *E. coli* isolate.

## DISCUSSION

In our study, the *E. coli* isolates' antimicrobial data analysis by ER based on Susceptible MIC patterns showed considerable susceptibility (ER4) to Imipenem, Meropenem, Amikacin (ER8) and even Co-trimoxazole (ER2) which correlates with the study conducted by Di Carlo P et al. [4]. Piperacillin tazobactam has added value in treatment as it has ER 4 similar to Sabu et al. [5]. Cefoperazone sulbactam sensitivity pattern is of concern as the ER is 2 and none of the isolates are having higher ER. Ceftriaxone shows low level of sensitivity with ER1. It is to be used with caution for future resistance development and treatment failure.

Colistin and Tigecycline which are considered as last resort antibiotics in severe infections were showing 100 and 95 percentage of susceptibility with ER4 though the intermediate level of breakpoint was taken into account for Colistin as per CLSI guidelines. As the micro broth dilution is the acceptable method for Colistin MIC value detection, Vitek 2 results were considered for theoretical ER analysis in our study. Ampicillin, cefuroxime and fluoroquinoles are showing high degree of resistance and their ER is also low similar to Xiao Shuzhen et al. [6]. ER value helps in selecting the right antibiotic within the class of antibiotic too. For example in Carbapenems though Ertapenem had the highest number of sensitive isolates its ER was 1.Meropenem was having higher ER 3 for more isolates(100%) than Imipenem(94%). So Meropenem was suggested as the preferable choice for *E. coli* bacteremia in our center. Among the aminoglycosides Amikacin had ER of 8 and suggested as a good choice while selecting between other drugs of same class.

ER adds information about the susceptible drug to be used as mono or in combination with other drugs. As per the Sabu et al. [5] it was suggested to clinicians that drugs with ER>=2 to be used for monotherapy depending on other attributes of the antibiotic and clinical correlation. But needs combination therapy with other antibiotics if the ER<=2 to prevent resistant subpopulation development in our center. When ER is 1 or <=2 judicious use to be strictly followed as we suggested this for Cefoperazone sulbactam.

## CONCLUSION

Selecting the antibiotic based on MIC value is advantageous for positive treatment outcome and prevention of resistant subpopulation. The antibiotics with High degree of susceptibility are preferred for more effective treatment for which calculating ER value is of immense help and it is to be correlated with the type of infection, side effects, frequency of drug administration etc.

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