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Original Article

# Microbiological Efficacy of Meropenem–ethylenediaminetetraacetic Acid Combination as Compared to Meropenem in a Tertiary Care Intensive Care Unit

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## Abstract

**Background:** With the global epidemic of sepsis on the rising trend and gram negative sepsis being one of the most common cause of increasing morbidity and mortality in developing nations like India, it becomes imperative to understand the role of combination antibiotics in controlling this burden. **Aim and Methodology:** In this study, we recognized the potential therapeutic role of Meropenem combined with EDTA against a clinical endemic isolate of multi-drug resistant extended spectrum beta-lactamases (ESBLs) producing pathogens was investigated. The E-test strips studied the antimicrobial susceptibility of the pathogens and were applied to check for in-vitro sensitivity to Meropenem and combination of Meropenem and Ca-EDTA. **Result:** The MIC value of Meropenem-EDTA (0.25) was less than 50% of that of Meropenem (2.45) in sensitive isolates. **Conclusion:** Meropenem in unification with EDTA can exhibit more potent antimicrobial activity against ESBL producing pathogens than just Meropenem or EDTA alone.

**Key words:** Antimicrobial resistance, Combination therapy, Gram-negative pathogens, *In vitro* study, Sepsis, Synergy

## INTRODUCTION

Sepsis is a serious infection and remains a common cause of mortality and morbidity in developing, scantily-resourced countries such as India. It occurs in 2% of all hospitalizations in developed countries with 6–30% of those affected belonging to intensive care unit (ICU patients) and places a huge burden physically and financially worldwide.[1] The global estimates approximate around 25000 USD and 50000 USD. With over 8.7% increase in sepsis patients per year in the US, the problem is now a global epidemic.

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In developing countries such as India, which holds one of the highest disease burdens in the world, reflective studies claim that 12% of adults (1–51%) of those diagnosed with acute febrile illness will have bacteremia. The most affected being the younger individuals and the liable organisms likely to be Gram-negative and atypical pathogens.[1,2]

Delays in providing effective antimicrobial therapy, in cases of severing septic shock, increase the risk of dying by approximately 10% for every hour of delay - making it crucial to initiate antimicrobial therapy at an appropriate time depending on the location of the patient and the suitability of the antimicrobial treatment. This criticality poses a significant challenge as antimicrobial resistance (AMR) is on the rise and poses a significant threat toward achieving favorable outcomes.[1]

### AMR and Emergence of Extended-spectrum Beta-lactamases (ESBLs)

Many studies have suggested that almost 2 million cases of infection with resistant bacteria are reported in the

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US every year leading to $20 billion incremental direct health-care costs. Recently, the European Medicine Agency and European Centre for Disease Prevention and Control reported a toll of 25,000 deaths per year as a direct consequence of a multidrug-resistant infection with total costs of EUR 1.5 billion.[3,4]

The studies by the Indian Network for Surveillance of AMR group reported a prevalence of 41% with methicillin-resistant *Staphylococcus aureus*(MRSA). High prevalence of Gram-negative bacterial resistance has also been reported and India is being one of the largest consumers of antibiotics; the effectiveness of several antibiotics is threatened by the emergence of resistant microbial pathogens.[4]

The path to antibiotic development is challenged at every step by the emerging AMR. The emergence of MRSA-resistant *Pseudomonas aeruginosa* has already compromised the most effective treatments. Urgent threats with Clostridium difficile, Carbapenem-resistant *Enterobacteriaceae*, and drug-resistant *Neisseria gonorrhoeae* have also been reported by the U.S. CDC.[4]

A disquieting example is the spread of New Delhi metallo-beta-lactamase 1, a transmissible genetic element encoding resistance genes against most known beta-lactam antibiotics, from its emergence in New Delhi, India, in 2008.[3]

β-lactamase production by several Gram-negative and Gram-positive organisms is possibly one of the most significant single mechanisms of resistance to penicillins and cephalosporins. It was earlier believed that cephalosporin was immune to attack by β-lactamases, but it was surprising to find that cephalosporin-resistant *Klebsiella* spp., as among the clinical isolates - the mechanism of this resistance was the production of ESBLs.[5,6]

ESBLs are plasmid mediated, which have the ability to hydrolyze β-lactam antibiotics. ESBL-producing organisms exhibit coresistance to many classes of antibiotics, resulting in the limitation of therapeutic options.[5]

### Minimum Inhibitory Concentration (MIC) and Combination Antibiotics to Fight AMR

The MIC is the lowest concentration (μg/mL) of an antibiotic that inhibits the growth of a given strain of bacteria.[7] A quantitative method of susceptibility testing and MIC helps determine which class of antibiotic is most effective. This information can lead to an appropriate choice of an antibiotic that will increase the chances of treatment success and help in the fight to slow antibiotic resistance.[8]

Infections caused by ESBL-producing pathogens are problematic because, when coresistance to other antimicrobial class is present, limited antibiotic options are available. At present, imipenem or meropenem is considered as a drug of choice for infections caused by ESBL-producing pathogens. However, the selective pressure from increasing use of carbapenems will lead to the development of carbapenem-resistant microbes.[9]

The objectives of this study were to understand the outcomes of patient with various agents in the treatment of ESBL-producing bacteremia and to evaluate the efficacy of meropenem and ethylenediaminetetraacetic acid (EDTA) combination against ESBLs.

## MEROPENEM–EDTA IN FIGHTING ESBL PRODUCTION

### Materials and Methods

#### *Hospital Setting*

This observational and prospective study was conducted for a period of 3 months, from February 15, 2018, to May 15, 2018. 94 patients in the ICU of W. Pratiksha Hospital, Gurgaon, India, were listed to be a part of the inquiry aging from 18 to 80 years.

Medical and surgical patients in the ICU were included in the study, and for the purposes of this study, patients who were immunocompromised, pregnant, HIV positive, and bone marrow transplantation were excluded from the study.

#### *Study Design*

Two groups of patients were created:

1. Who were admitted for the 1st time in the past 1 year ($n = 56$) and
2. Who have been admitted before, in the past 1 year ($n = 34$).

During these 3 months, blood, urine, and sputum (including endotracheal and tracheostomy tube) samples were collected and sent to microbiology laboratory for routine and culture-sensitivity pattern [Figure 1].

#### *Microbiological Efficacy of Meropenem–EDTA Combination*

Blood cultures were tested positive for 15 patients, the most common being *Escherichia coli* ($n = 7$) followed by *Klebsiella pneumoniae* ($n = 5$), followed by *P. aeruginosa* ($n = 3$), *Candida albicans* ($n = 2$), *Acinetobacter baumannii* ($n = 1$), and *Ralstonia pickettii* ($n = 1$) [Figure 2].

Urine cultures were tested positive for 27 patients, the most common being *K. pneumoniae* ($n = 12$), followed by *E. coli* ($n = 9$), and *C. albicans* ($n = 6$) [Figure 3].

Sputum cultures were tested positive for 15 patients, the most common being *E. coli* ($n = 9$), followed by *P.*

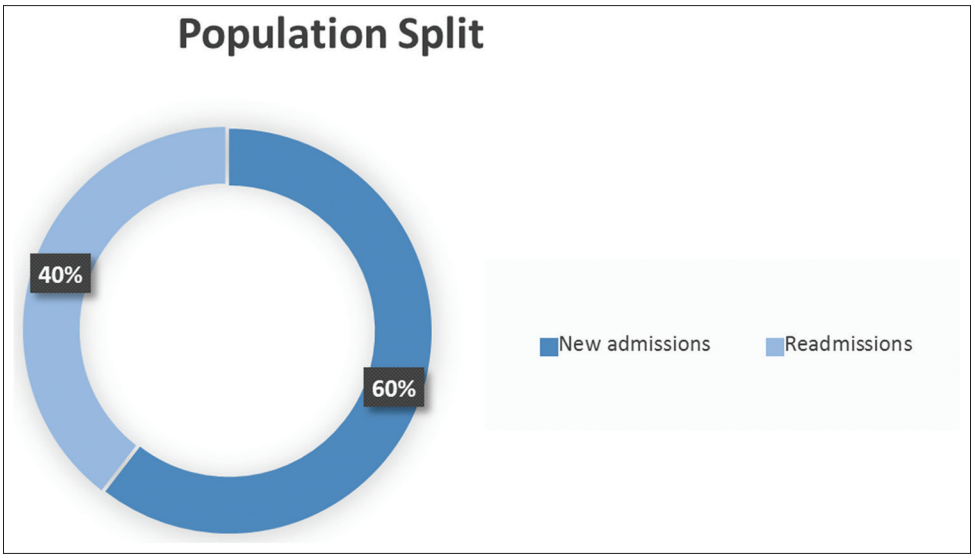


**Figure 1: Percentage of population as new and re-admissions in the ICU**

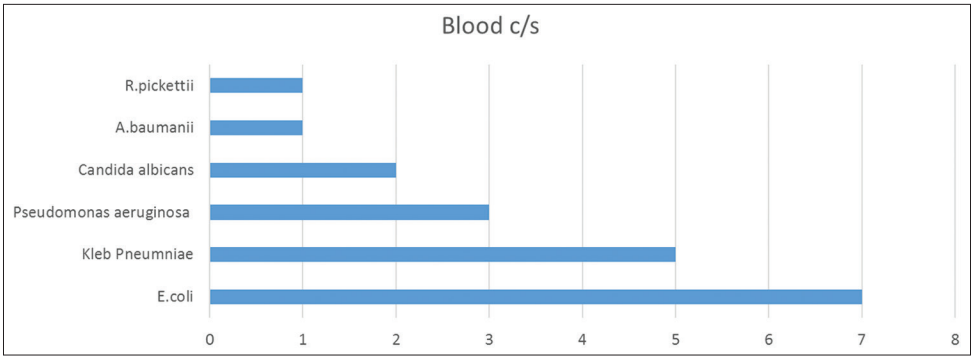


**Figure 2: Common organisms which tested positive in the blood cultures of the patients**

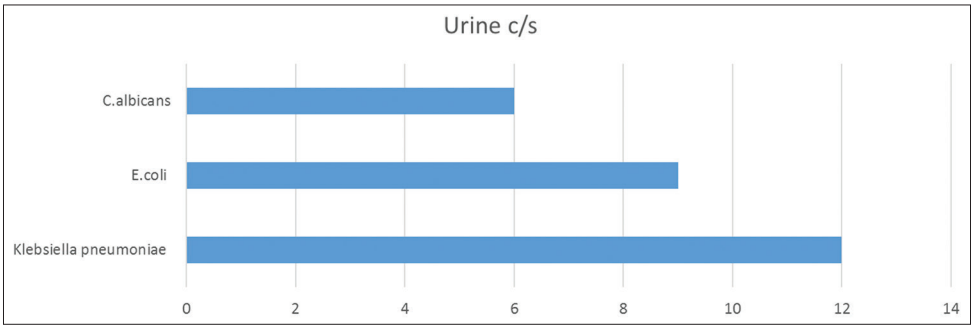


**Figure 3: Common organisms which tested positive in the urine cultures of the patients**

*aeruginosa* ($n$ = 2), *S. aureus* ($n$ = 2), and *Candida tropicalis* ($n$ = 2) [Figure 4].

### MIC Values for Meropenem–EDTA Combinations

Cultures showed 51 isolates in total, which were ESBL-producing bacteria. Further, E-strips were applied to check for *in vitro* sensitivity to meropenem and combination of meropenem and Ca-EDTA, of which, 14 were meropenem-resistant isolates and showed sensitivity to meropenem–EDTA [Figure 5].

The MIC value of combination for meropenem–EDTA was reported to be 50% less than that of meropenem in sensitive isolates ($n$ = 29) and intermediate sensitive ($n$ = 8) isolates, $P < 0.005$. The mean MIC value of meropenem in such patients ($n$ = 37) was 2.45 MIC and that of combination was 0.25 [Figure 6].

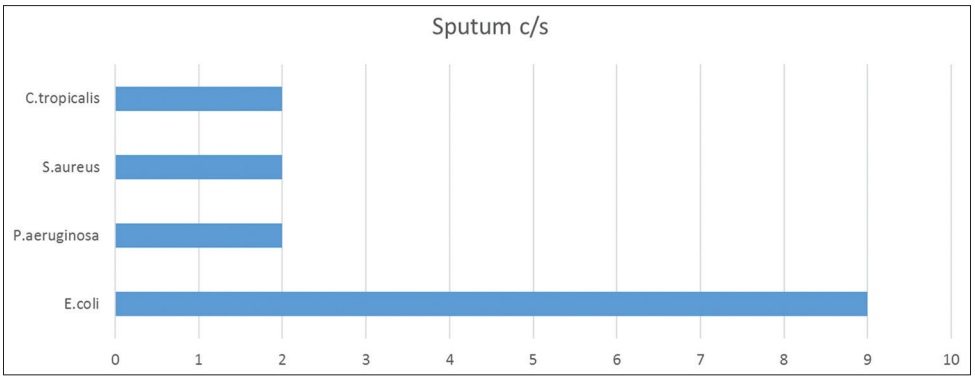


**Figure 4: Common organisms which tested positive in the sputum culture of the patients**

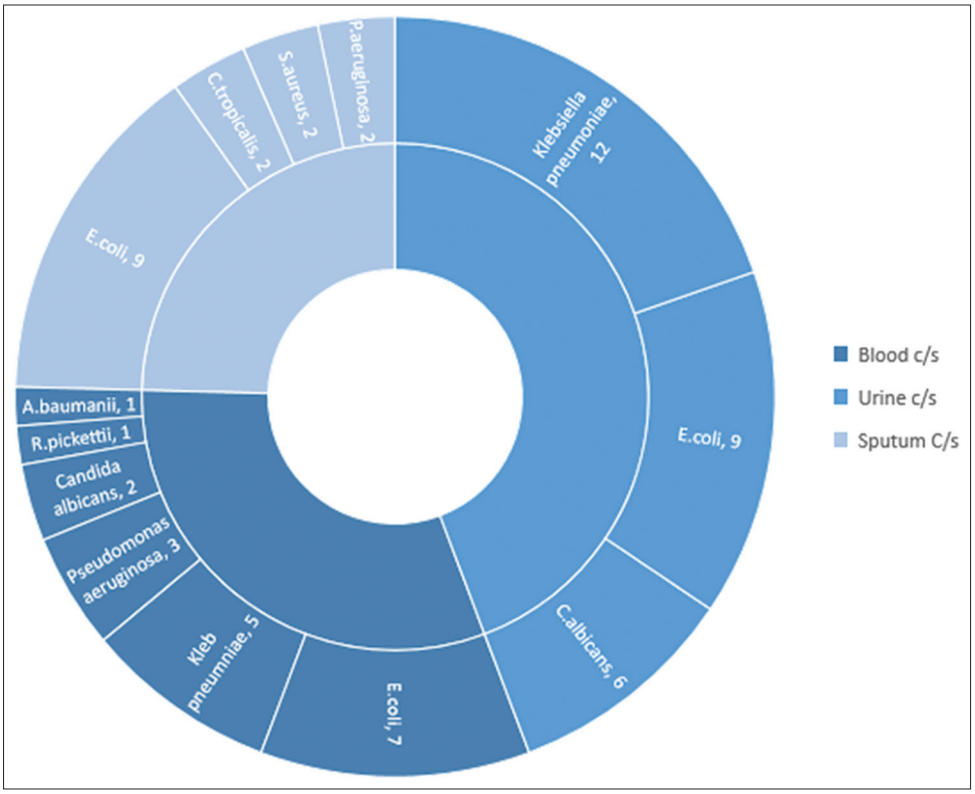


**Figure 5: Most common pathogenic organisms isolated from the admitted patients**

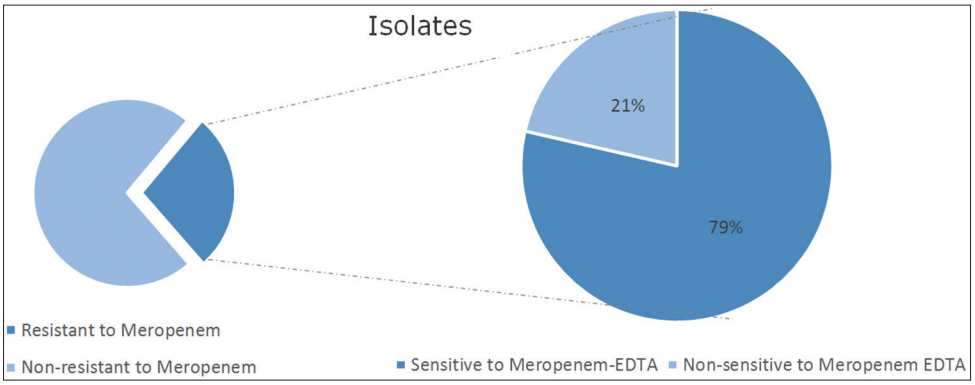


**Figure 6: Division of pathogens sensitive to Meropenem and Meropenem-EDTA combination**

## DISCUSSION

ESBLs are well known for their resistance to many commonly used antimicrobial agents and pose a major problem for clinical therapeutics. Initially restricted to hospital-acquired infections, they have also been isolated from infections in outpatients. Major outbreaks involving ESBL strains have been reported from all over the world, thus making them emerging pathogens.[11,12,13]

Of all the available beta-lactams, carbapenems are the most effective and reliable as they are highly resistant to the hydrolytic activity of all ESBL enzymes, due to the trans-6 hydroxyethyl group.[14,15]

In the retrospective study, the combination of meropenem and EDTA resulted in a sustained synergistic bactericidal effect lasting for at least 12 h. However, we found that the meropenem–EDTA combination regimen significantly improved the survival rate of those infected with ESBLs, compared with those treated with either drug alone. Meropenem plus EDTA was effective against our multiresistant isolate of ESBLs. Given the limitations of small size and being a retrospective study, our report may lack the power to discriminate real difference in the outcome. Further study is warranted to establish the therapeutic roles of meropenem and EDTA combination in the treatment of infections caused by ESBL-producing pathogens.

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