

EFFICACY OF TEBIPENEM AND MEROPENEM WITH ADJUVANT COMBINATIONS AGAINST DRUG RESISTANT GRAM NEGATIVE BACILLI

a) BRIEF OUTLINE :

Antimicrobial resistance (AMR) is an overriding public health concern of 21st century. As per WHO, AMR is one among the top ten causes of mortality in the world. It is coming in a way of effective treatment and prevention of infections. Multidrug Resistant (MDR) organisms are now responsible for most of the life threatening infections including sepsis. Therapeutic options for treatment of MDR organisms are very limited and we are reaching a “NO ANTIBIOTIC ERA.” In this critical situation, Carbapenems remain one among the few effective antibiotics against these drug resistant bacteria. At the same time oral carbapenems, with similar efficacy are in the limelight. To inspect their potency against MDR organisms with respect to injectable carbapenems is need of the hour. Mindful of this, we are keen to know the oral Tibepenem’s action against these MDR bacteria. However, emergence of carbapenem resistant organisms have incapacitated the efficacy of carbapenems. There is an urgent need for the development of set of tactics to combat these organisms. Increasing the efficacy of available antibiotics is one such approach. In that light antibiotic adjuvants are important tools. Many effective adjuvant combination with Meropenem were proved effective in-vitro and in animal studies. Here, we urge to find effective adjuvants to Meropenem against clinically isolated Carbapenem resistant gram negative bacilli in our institution.

b) OBJECTIVES:

- To test the efficacy of Tebipenem against Gram negative bacilli isolated from different clinical samples.
- To compare the efficacy of Meropenem with different adjuvants like Aspergillomarasmine A, Bismuth nitrate, Daunorubicin (DNR) and 5- Flurouracil against clinically isolated carbapenem resistant Gram negative bacilli.

c) BRIEF METHODOLOGY:

- Gram negative bacilli isolated from different clinical samples will be subjected to antibiotic susceptibility testing by Kirby Bauer’s disc diffusion method according to the CLSI guidelines. Additionally Tebipenem, Ertapenem and Meropenem will also be included in the panel.

- Carbapenem resistance exhibited by the isolates will be further confirmed by broth micro dilution method according to the CLSI guidelines.
 - Carbapenem resistant isolates will be further subjected to check for the efficacy of adjuvants, in enhancing sensitivity to carbapenems. Antibiotic – Adjuvant combinations used will be Meropenem - Aspergillomarasmine A, Bismuth nitrate, Daunorubicin (DNR) and 5-Flurouracil.
 - These combinations will be analysed in detail with respect to Fractional Inhibitory Concentration Index of each adjuvant, effect on bacterial metabolism and effect on expression of carbapenemase producing genes in the organisms.
 - Fractional Inhibitory Concentration Index: FICI of each adjuvant can be calculated According to the Clinical and Laboratory Standards Institute (CLSI) guideline (M45-A2). FICI of adjuvants and Meropenem will be determined by checkerboard assays with two-fold serial dilution of drugs in final volumes of 100 μ L, to create an 8 \times 8 matrix. After 18 h incubation at 37°C with bacterial suspension OD600 nm will be measured. FICI will be calculated as per the formula.
 - The metabolic state of bacteria affects their antibiotic susceptibility. Adjuvant which can alter bacterial metabolic status, enhance respiratory activity and foster the production of ATP and ROS, will eventually sensitize bacteria to antibiotic killing.
 - Using FICI of adjuvants and Meropenem, effect on bacterial metabolism can be checked by
 - i. NAD⁺/NADH determination using NAD⁺/NADH Assay Kit
 - ii. ATP measurement using Enhanced ATP Assay Kit
 - iii. Oxygen consumption rate quantification - OCR Plate Assay Kit
 - iv. Measurement of ROS and SOD activity - Total Superoxide Dismutase Assay Kit
 - Tests will be performed and analysed as per manufacturer's instructions.
 - Inhibition of the carbapenemase enzyme by the adjuvant can be checked by enzyme inhibition assay and RT-PCR assay.
- d) ANTICIPATED OUTCOME:** Invention of effective adjuvant to Meropenem. With that strengthening of antibiotic pipeline by reviving the capability of existing antibiotics.
- e) TIMELINE:** Two years.