



Antibacterial Synergy: An Imperative Need

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Abbreviation

CFU: Colony Forming Unit; FIC: Fractional Inhibitory Concentration; GII: Growth Inhibitory Index; MIC: Minimum Inhibitory Concentration.

Antibiotics stand as the mainstay of treatment against life-threatening infection, to humans, with bacterial pathogen. However, the acquirement and dissemination of bacterial antibiotic resistances add up to a havoc threat to modern medicine, and hence, in the absence of alternate antibiotic-based treatment regimen, antibacterial combination is employed progressively in order to get augmented effect of conventionally used existing antibiotics against antibiotic resistant strains [1-3], following *in vitro* experimentations [1,2,4]: agar dilution checkerboard, time-kill studies and double disk synergy test.

In checkerboard agar dilution [2], the factors considered include: MICs (determined from the lowest concentrations of the test antibiotics), FICs (determined from the highest dilution of an antibiotic in combination with the other, i.e. this is MIC of antibiotic A in combination with antibiotic B, or vice versa) that sanction no visible growth of the test bacterial strains, and FIC indices (FIC index = $\frac{FIC \text{ of antibiotic A}}{MIC \text{ of antibiotic A alone}} + \frac{FIC \text{ of antibiotic B}}{MIC \text{ of antibiotic B alone}}$).

The FIC indices of ≤ 0.5 , > 4 and $0.5 - 4$ are defined respectively as the synergistic, antagonistic, or additive interaction between the test antibiotics [4]. In time-kill studies, synergism has been defined as $2 \log_{10}$ decrease in CFU/ml from combined action (of two test antibiotics) compared to its most active component after 24h incubation [1,2], while the antagonism has been defined as $2 \log_{10}$ increase in CFU/ml between the combination and either drug alone; intermediate results were interpreted as addition [4].

The double disc synergy tests are performed broadly using the protocol described by Leclercq, *et al.* [4], and the synergism are labeled as strong, weak or absent, based upon the alteration of zones of inhibition of bacterial growth following incubation for 24h at 37°C. To interpret the interaction between two antibacterial agents against test bacteria, following disc diffusion method, report is available on the determination of GII, which is calculated using the following equation:

$$GII = \frac{ZDI \text{ in combination of two test agents}}{\text{Total of ZDIs of the two agents in single action}}$$

where ZDI denotes zone diameter of inhibition [5]; following this protocol, synergistic, additive (or indifference) and antagonistic activities between the agents are defined with GIIs of > 0.5 , 0.5 and < 0.5 , respectively. The GII interpretative method is corroborated with the synergistic activity defined in terms of increment of ZDIs from combined action [5,6].

The application of antibiotics in combination, in need, that constituted a clinically successful therapeutic regimen [7,8], has later been proven by *in vitro* investigation [1]. Therefore, the therapeutic trial to corroborate the synergistic action of two antibiotics *in vitro* help establish cost-effective treatment regimen of life-threatening bacterial infection to humans, in developing countries, like India, 'keeping at bay' the need for costly newer generation of antibiotics in order to combat bacterial antibiotic resistances [1,2,9,10]. Finally, we have to learn to leave with the bacterial antibiotic resistances by stopping the misuse of antibiotics through their (antibiotics) judicious application.

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