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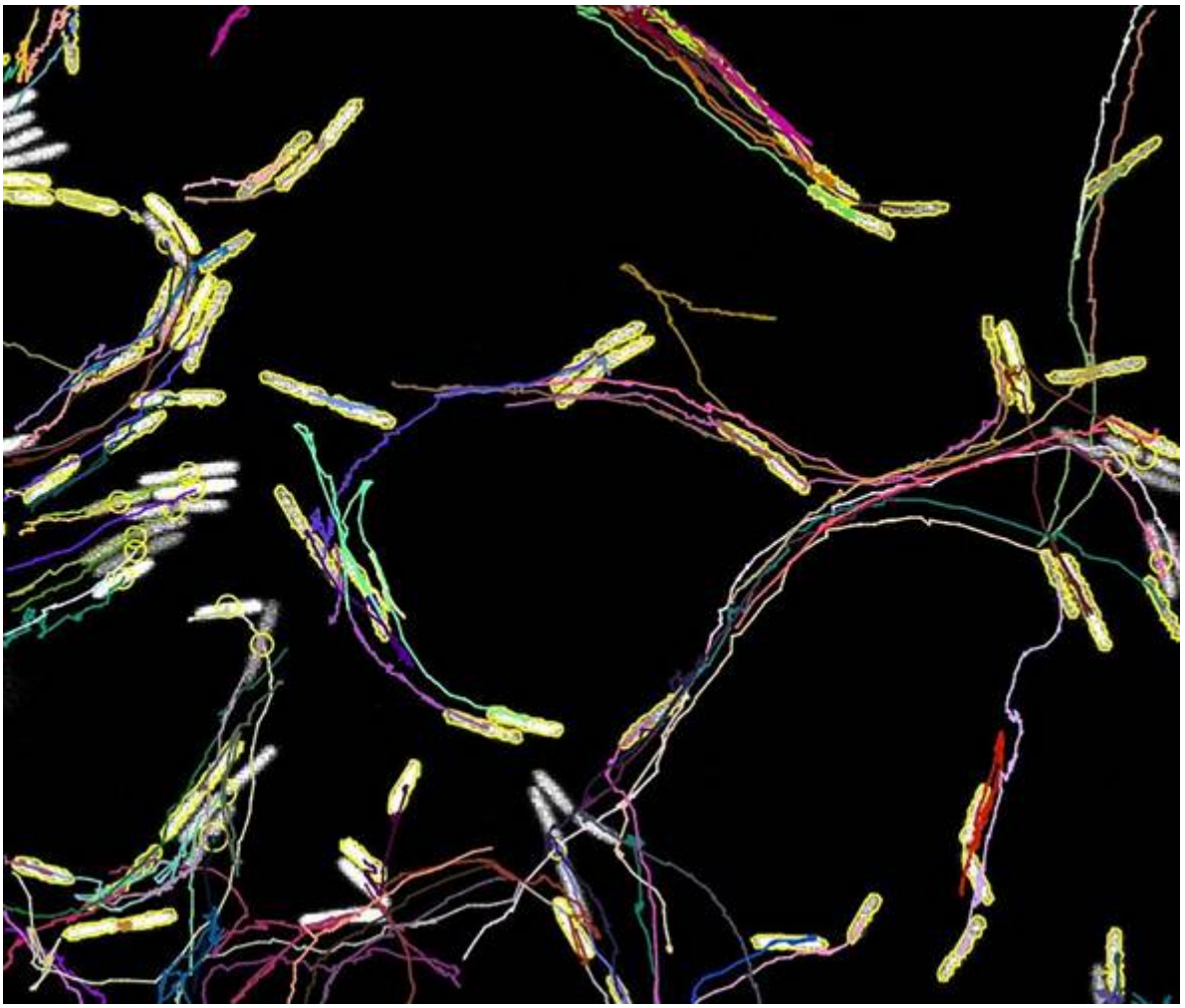

Foto: Se hace camino al andar. Celeste Dea. 1er puesto. Concurso fotográfico SAMIGE 20 años.

POTENTIATION STUDIES OF CIPROFLOXACIN AND MEROPENEM BY MONOTERPENE 1,8-CINEOLE ON CLINICAL ISOLATES OF *Klebsiella pneumoniae* IN PLANKTONIC GROWTH

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The Enterobacteriaceae family includes high clinical relevance species such as *K. pneumoniae*, which causes urinary tract infections, bacteremias, pneumonia and neurological infections. This pathogen produces ?-lactamases of broad spectrum and is resistant to several antibiotics. For this reason, the World Health Organization has included *K. pneumoniae* on the list for the urgent development of new therapeutic alternatives. In recent years, plant derived compounds have been proposed as new alternatives to fight infections caused by bacteria. Previously, we have shown that the monoterpene 1,8-cineole (1,8-C) is effective against multi-drug-resistant *K. pneumoniae* clinical strains both in planktonic and biofilm states. This phytochemical is a main component of essential oils in most plant leaves as *Rosmarinus officinalis*. This study addresses the antimicrobial effect of 1,8-C in combination with antibiotics commonly used in the clinic to treat *K. pneumoniae* infections. Ciprofloxacin (CIP) and meropenem (MER) used to treat *K. pneumoniae*-related infections were investigated to explore potential synergistic effects against a clinical isolate of *K. pneumoniae* from a patient with urinary infection. For this purpose, minimal inhibitory concentrations (MIC) for each antimicrobial were determined by measuring bacterial growth (OD_{600nm}) through the broth microdilution method using MH medium supplemented with 0.5% Tween 80 to better solubilize the phytochemical. Subsequently, fractional inhibitory concentrations of each antibiotic in combination with 1,8-C were tested on *K. pneumoniae* growth using chequerboard assays and fractional inhibitory concentration index (FICI) was calculated to examine the combinational effect of the drugs using the following formula: FIC of drug = MIC in combination / MIC alone; FIC index = FIC of CPR + FIC of 1,8-C. For a synergistic interaction, the FIC index was taken as ? 0,5. For additive, the FIC index was taken 0,5 ? FIC ? 1,0; 1,0 ? FIC ? 2,0 for indifferent, and for antagonism, the FIC index was more than 4,0. Results showed that CIP, MER and 1,8-C MIC values were 0.062 ? g/ml, 0.312 ?g/ml, and 20.0 mg/ml, respectively. The most remarkable synergistic effect occurred when the bacteria was exposed to 0.014 ?g/ml CIP in combination with 10.0 mg/ml 1,8-C, observing a 97% growth inhibition after 24 h and a FICI of 0,351, whereas CIP and 1,8-C alone showed 3% and 50% inhibition each. Besides, the combination of MER (0.120 ?g/ml) and 1,8-C (5.0

mg/ml) inhibited 57% of bacterial growth (FICI of 0,756) but only 44% and 6% when tested alone. Therefore, our results indicate that the phytochemical enhances the antimicrobial effect of both CIP and MER on planktonic cultures of *K. pneumoniae*. Altogether, these findings support the hypothesis that 1,8-C is a promising antibiotic-enhancer phyto-compound for K. pneumoniae infections.

Palabras clave: 1,8-cineole - Enterobacteriaceae - Ciprofloxacin - Meropenem - synergistic effects.