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# In Vitro Synergistic Activity of Colistin-Based Antimicrobial Combinations against Extensively Drug-Resistant (XDR) *Acinetobacter baumannii* from a Tertiary Hospital in Greece †

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## 1. Background

Over the past years, *Acinetobacter baumanni* has emerged as a serious nosocomial pathogen especially due to its extensively resistant antimicrobial profile. Colistin is currently used as one of the last resort agents to treat the related infections but resistance because of monotherapy has increasingly been reported. We evaluated the in vitro susceptibility of colistin-based antimicrobial combinations against extensively drug-resistant (XDR) *A. baumannii* isolates from a tertiary hospital in Northern Greece.

## 2. Materials

One hundred *A. baumannii* single clinical isolates with resistance to carbapenems and colistin between March and October 2021 were included in the study; 46 were isolated from blood, 41 from bronchoalveolar secretions, 6 from urine, 3 from central lines, 3 from skin and soft tissues and 1 from cerebrospinal fluid. Antimicrobial susceptibility testing was performed by Vitek2 (bioMérieux, France) whereas tigecycline, rifampicin, daptomycin were tested with MIC test strip (Liofilchem, Italy) and colistin with broth microdilution method (Liofilchem, Italy). MIC range, MIC50, MIC90 and resistance rates were calculated according to EUCAST breakpoints. The MIC test strip fixed ratio method was used for the synergistic activity for three antimicrobial combinations of colistin with either meropenem or rifampicin or daptomycin. The results were interpreted using fractional inhibitory concentration index (FICI). 'Synergy', 'additivity', 'indifference' and 'antagonism' were interpreted when the FICI was ≤0.5, >0.5–≤1, >1–≤4 and >4, respectively.

## 3. Results

All the studied strains displayed high rates of resistance to major classes of antimicrobials (>97%) with 100% resistance to colistin (Table 1). MIC50/MIC90 (mg/L) for tigecycline were 3/6, for ampicillin/sulbactam 32/32, for rifampicin 6/32 and for daptomycin 256/256. All 100 isolates were tested for colistin-meropenem combination exhibiting 87% synergy (FICI range = 0.00078–0.5) while 13% additivity (FICI range = 0.56–0.84). Although rifampicin and daptomycin are typically inactive against Gram-negative bacteria, higher rates of synergy were observed using colistin-rifampicin combination with 93.75% (75/80) synergy (FICI range = 0.002–0.47), 3.75% (3/80) additivity (FICI range = 0.56–0.62)

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and 2.5% (2/80) indifference (FICI range = 1–1.42). Colistin-daptomycin combination was tested in 30 isolates resulting in 90% (27/30) synergy (FICI range = 0.017–0.42), and 10% (3/30) additivity (FICI range = 0.51–0.76).

**Table 1.** Antimicrobial profile of *Acinetobacter baumannii* isolates. NA: not applicable.

| Antibiotic | Number of Strains Tested | MIC Range (mg/L) | $MIC_{50}$ (mg/L) | $MIC_{90}$ (mg/L) | Resistance (%) |
|---|---|---|---|---|---|
| Meropenem | 100 | 8–16 | 16 | 16 | 100 |
| Imipenem | 100 | 8–16 | 16 | 16 | 100 |
| Ciprofloxacin | 36 | 4 | 4 | 4 | 100 |
| Amikacin | 36 | 4–64 | 64 | 64 | 97.22 |
| Gentamicin | 35 | 1–16 | 16 | 16 | 97.14 |
| Trimethoprim/Sulfamethoxazole | 36 | 0.75–320 | 320 | 320 | 97.22 |
| Ampicillin/Sulbactam | 67 | 16–32 | 32 | 32 | NA |
| Colistin | 100 | 4–64 | 16 | 16 | 100 |
| Tigecycline | 97 | 0.05–8 | 3 | 6 | NA |
| Rifampicin | 81 | 2–256 | 6 | 32 | NA |
| Daptomycin | 30 | 256 | 256 | 256 | NA |

## 4. Conclusions

In vitro colistin-based combinations with either rifampicin or daptomycin or meropenem resulted in high synergy rates rendering them a valuable option for the treatment of colistin-resistant *A. baumannii* infections.