

Bactericidal Activity of Multiple Combinations of Tigecycline and Colistin against NDM-1 producing Enterobacteriaceae

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Introduction:

- The therapeutic options against NDM-1 producing *Enterobacteriaceae* are limited.
- Colistin and tigecycline are both agents where many strains still have MICs below the clinical breakpoint.
- Tigecycline and colistin act on bacterial cell by different mechanisms
- There is a potential scope for both antagonism as well as synergism.

Methodology:

- Bactericidal activity of tigecycline(TGC), Colistin sulphate(CS), and Colistin methanesulfonate(CMS) by time-kill methodology
- 8 well characterised strains of NDM-1 producing Enterobacteriaceae were used (Table 1)
- Pharmacokinetically achievable free drug serum concentrations were used.
- The following concentrations reflecting peak (C_{max}), steady-state (C_{ss}), and trough (C_{min}) concentrations expressed in mg/L were used respectively for TGC (0.17, 0.04, 0.025), CS (2.5, 0.17, 0.1) and CMS (8.1, 2.7, 2.1).
- A 4x4 drug exposure matrix of TGC with CS and CMS were used along with growth control (GC) at 0, 1, 3, 6, 12, and 24 hr time-points.

Results:

- The comparative mean TKC of individual antimicrobial agent at different concentrations are shown in Fig 1a, 1b and 1c.
- AUBKC for TGC showed a modest but significant inhibitory effect only at C_{max} . Fig 2a.
- CS and CMS showed good antimicrobial activity at all concentrations Table 2.
- Combinations of TG with CS did not produce significant synergism at any concentrations. Fig.2b.
- Trough-level (C_{min}) combinations of TG with CS showed antagonistic effect, and this was statistically significant ($p < 0.05$)
- Combinations of TG with CMS produced high AUBKC at all combinations (i.e. antagonism), Fig.2c.
- Based on "classic" interpretive criteria, there was no synergism between TGC and CS or CMS.

Table 2. Mean log change in CFU at 3hour time point

| Second drug | TGC 0 mg/L | TGC0.02 mg/L | TGC0.04 mg/L | TGC0.17 mg/L |
|-------------|------------|--------------|--------------|--------------|
| CS | | | | |
| 0 mg/L | +1.10 | +1.10 | +0.94 | +0.79 |
| 0.10 mg/L | -2.97 | -1.69 | -2.00 | -2.76 |
| 0.16 mg/L | -3.19 | -2.06 | -2.71 | -2.88 |
| 0.29 mg/L | -3.26 | -2.56 | -3.18 | -3.43 |
| CMS | | | | |
| 0 mg/L | +0.89 | +0.69 | +0.82 | +0.76 |
| 2.1 mg/L | -2.61 | -1.98 | -1.82 | -1.81 |
| 2.7 mg/L | -2.72 | -2.10 | -2.07 | -2.11 |
| 8.5 mg/L | -3.38 | -2.38 | -2.16 | -3.26 |

TG-CS-CMS trough conc. comparison

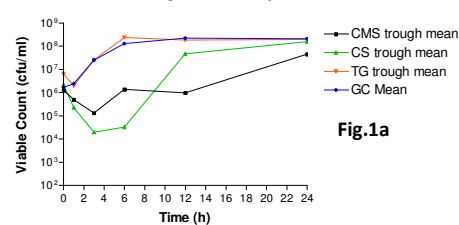


Fig.1a

TG-CS-CMS Peak conc. comparison

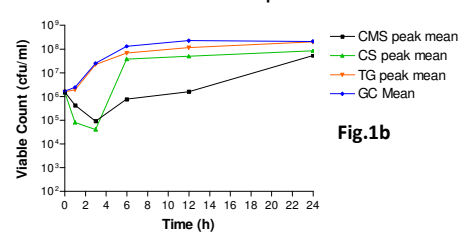


Fig.1b

TG-CS-CMS ss conc. comparison

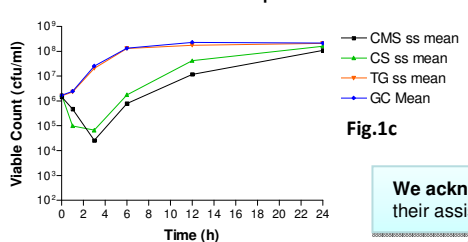


Fig.1c

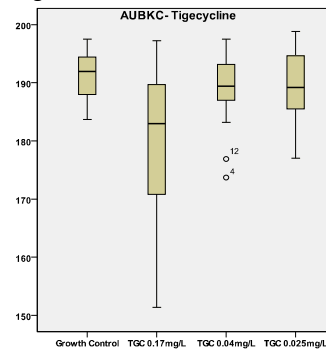
Discussion:

The results of this novel study show that, the addition of TG to either CS or CMS did not produce any bactericidal benefit in terms of significant synergism at all concentrations tested, based on both AUBKC and >2log kill difference criteria. Instead there was some evidence of antagonism at the combinations of lower concentrations, especially against isolates with low colistin MIC. These findings have important therapeutic implications in the management of patients with infections caused by NDM-1 producing *Enterobacteriaceae*.

Table 1 MICs of the isolates

| Isol. No. | Isolate ID | TGC MIC | Colistin MIC |
|-----------|----------------------|---------|--------------|
| 1 | <i>E. coli</i> | 0.25 | 0.38 |
| 2 | <i>E. coli</i> | 0.38 | 0.38 |
| 3 | <i>K. pneumoniae</i> | 3 | 0.38 |
| 4 | <i>K. pneumoniae</i> | 1.5 | 0.125 |
| 5 | <i>K. oxytoca</i> | 0.25 | 0.094 |
| 6 | <i>K. oxytoca</i> | 0.25 | 0.125 |
| 7 | <i>K. pneumoniae</i> | 0.38 | 0.094 |
| 8 | <i>K. pneumoniae</i> | 0.38 | 0.125 |

Fig.2a



Conclusion:

- Addition of tigecycline to colistin does not produce synergistic effect.
- Instead it may cause antagonism at lower concentrations, especially against isolates with low colistin MIC.

We acknowledge Sharon Tomaselli and Donna Nicholls for their assistance in carrying out laboratory experiments.

Fig.2b AUBKC- Colistin sulphate & Tigecycline

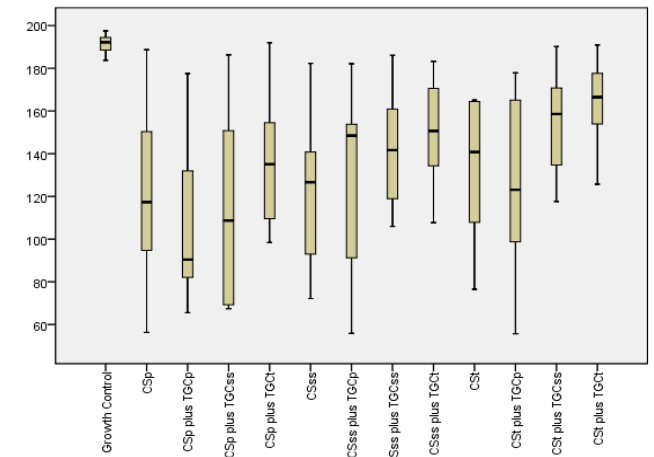


Fig.2c AUBKC- Colistin methanesulfonate & Tigecycline

