Combination Cefuroxime and Sulopenem is active in vitro against *Mycobacterium abscessus*.

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Background

- ***Mycobacterium abscessus*** (Mab) is a highly drug-resistant nontuberculous mycobacteria (NTM).
- Efforts to discover new treatments for Mab infections are accelerating with a focus on cell wall synthesis proteins (L, D-transpeptidases, Ldt_{Mab1-5}, and D, D-carboxypeptidase) that are targeted by combination β-lactam antibiotics.
- The US Food and Drug Administration (FDA) has granted Qualified Infectious Disease Product (QIDP) to the oral and intravenous (IV) formulations of Sulopenem (SUL), Figure 1. Data on SUL *in vitro* activity against Mab is currently unavailable.
- Here, we evaluated activity of SUL alone and in combination with Cefuroxime monohydrate (CEF) against representative clinical isolates belonging to the Mab complex. Both CEF and SUL are available in oral formulation and can be considered as oral step-down therapy.

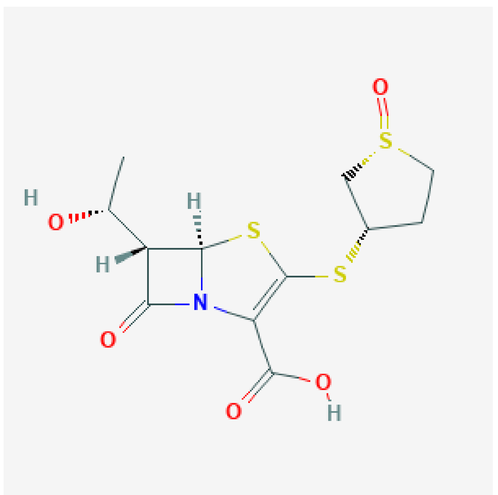


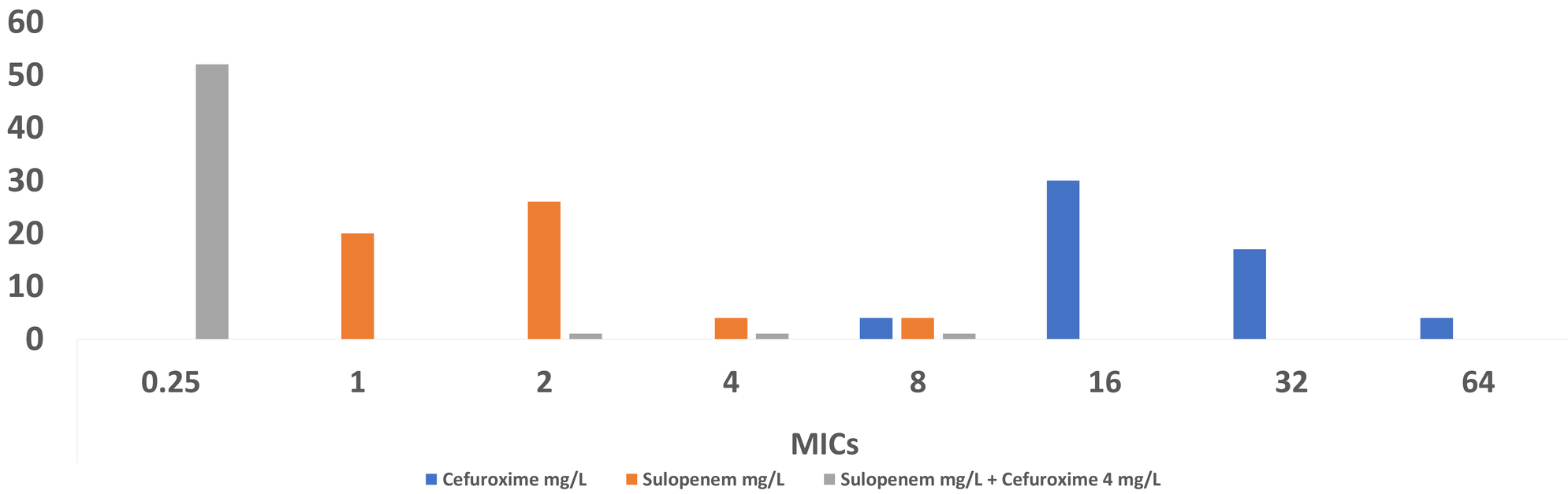
Figure 1: Chemical composition of Sulopenem

Methods

Minimum inhibitory concentrations (MICs) of SUL and CEF alone and in combination were determined using microdilution. Approximately 5 x 105 colony-forming units (CFU) per milliliter were inoculated into Middlebrook 7H9 broth supplemented with 10% (vol/vol) oleic albumin dextrose catalase and 0.05% (vol/vol) Tween 80. CEF was added at fixed concentration of 4 µg/mL to serial dilutions of SUL. Mab isolates were incubated with test agents at 30 ˚ C for 48 h, and MIC was defined as lowest antibiotic concentration that prevented visible bacterial growth.

Results

Figure 2. MIC distributions of cefuroxime monohydrate, sulopenem, sulopenem with 4 µg/ml cefuroxime monohydrate against 55 Mab clinical strains



- Fifty-five clinically derived and previously characterized isolates were tested in these assays.
- MIC_{50} and MIC_{90} of CEF is 16 and 32 ug/ml; MIC50 and MIC90 of SUL is 2 and 4 ug/ml, the range of MICs are as follows: CEF (8 → 64 ug/ml); SUL (1→8 ug/ml); and SUL and CEF at fixed 4 ug/ml (< 0.25 → 4 ug/ml).
- Combination SUL and CEF lowered MIC to < 0.25 ug/ml in 52 clinical isolate (Figure 2).

Conclusion

- Our results support the emerging hypothesis that dual β-lactam therapy is a promising strategy in the treatment of serious Mab infections.
- Investigating the biochemical rationale for this combination will support the application to clinical trials.

Acknowledgements

This work was supported by Roe Green Grant for Travel Medicine at University Hospital Cleveland Medical Center