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Sulbactam-durlobactam (SUL-DUR) in Vitro Dose Response Studies With and Without Imipenem or Meropenem Against Carbapenemase-Producing *Acinetobacter baumannii* Utilizing the Hollow-Fiber Infection Model

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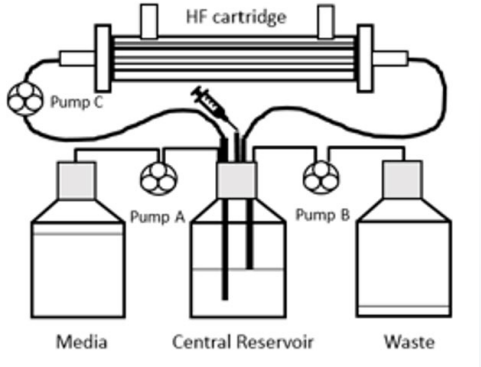
Background

- SUL-DUR is a β-lactam/β-lactamase inhibitor combination in development for the treatment of *Acinetobacter baumannii-calcoaceticus* Complex (ABC), a cause of severe infections associated with substantial mortality.
- A global, Phase 3 trial was conducted to evaluate the safety and efficacy of SUL-DUR versus colistin for patients with ABC infections, including carbapenem-resistant and multidrug-resistant (MDR) strains.
- Since SUL-DUR is pathogen-focused, imipenem/cilastatin was added as background therapy in the Phase 3 trial to treat any non-ABC, co-infecting Gram-negative pathogens.
- In in vitro susceptibility studies, SUL-DUR is a more potent combination than IPM-DUR against ABC. Triple combinations of SUL-IPM-DUR had similar activity compared to SUL-DUR except for a subset of isolates with MICs > 4 µg/mL, the preliminary breakpoint for SUL-DUR.



Goal

- This study evaluated the efficacy of SUL-DUR dosage regimens with or without imipenem (IPM) or meropenem (MEM) against carbapenem-resistant *A. baumannii* with different SUL-DUR susceptibilities using an in vitro hollow fiber infection model (HFIM).

Results: MIC and Pharmacodynamic Summary of *A. baumannii* Isolates Tested in HFIM

MIC summary of carbapenem-resistant *A. baumannii* strains used in HFIM

Isolate	β-lactamase content	MIC (μg/mL)				
		SUL	DUR	SUL + 4 μg/mL DUR	SUL: IPM (1:1) + 4 μg/mL DUR	SUL: MEM (1:1) + 4 μg/mL DUR
ARC3486	ADC-30; TEM-1; OXA-66; OXA-72	16	>64	0.5	0.5	0.5
ARC5955	ADC-82; TEM-1; OXA-23; OXA-66	64	>64	8	4	4
ARC5950	ADC-11; OXA-23; OXA-69	64	>64	8	8	8

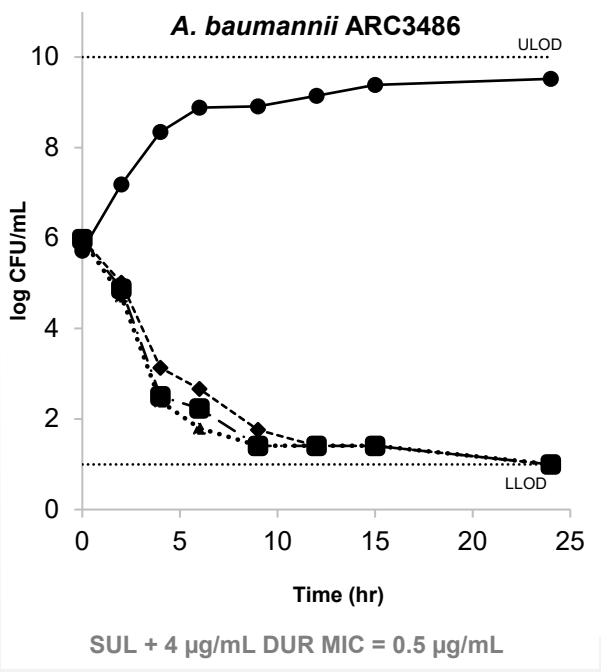
Addition of a carbapenem to SUL-DUR did not have large effects on MIC values

Pharmacodynamic summary of SUL, SUL-DUR, and SUL-DUR + Carbapenem regimens in HFIM

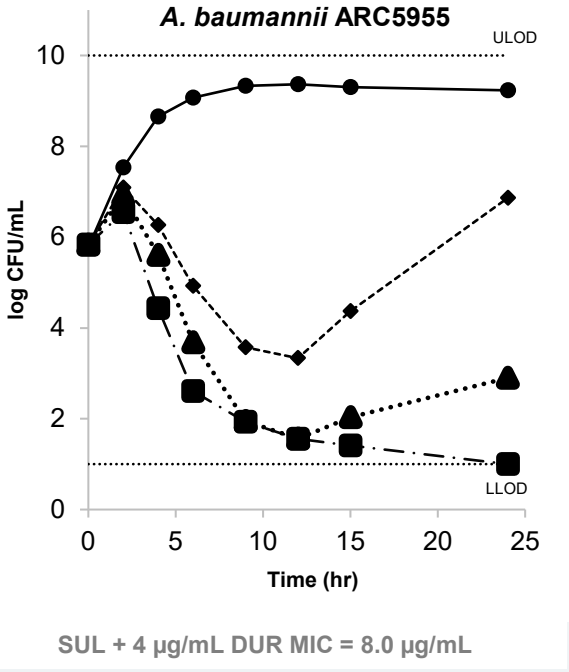
Isolate	Dose	Regimen	24h change of bacterial burden (CFU/mL)			
			SUL alone	SUL-DUR	SUL-DUR + IPM	SUL-DUR + MEM
ARC3486	1 g each	q6h	+3.30	-4.98*	-4.98*	-4.98*
ARC5955	1 g each	q6h	+3.25	+1.03	-4.83	-2.94
ARC5950	1 g each	q6h	+3.21	+1.24	-5.03*	-5.03*

*bacterial burden reached the lower limit of detection in the HFIM

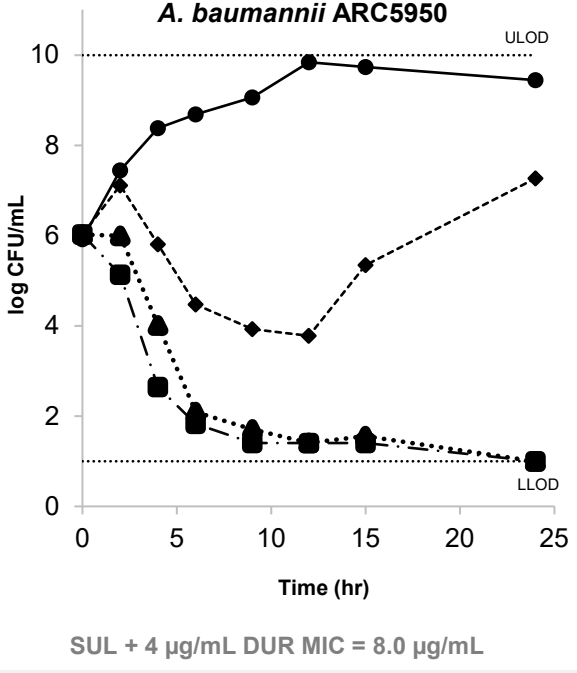
Results: Rapid, Bactericidal Activity Is Observed For SUL-DUR and SUL-DUR + Carbapenem Combinations Against MDR *A. baumannii*



SUL + 4 µg/mL DUR MIC = 0.5 µg/mL



SUL + 4 µg/mL DUR MIC = 8.0 µg/mL



SUL + 4 µg/mL DUR MIC = 8.0 µg/mL

1 g Durlobactam + 1 g Sulbactam QID | 1 g Durlobactam + 1 g Sulbactam + 1g Imipenem QID | 1 g Durlobactam + 1 g Sulbactam+ 1g Meropenem QID | Growth Control

*average of N=2 experiments

Conclusions

- Using HFIM, SUL-DUR had robust efficacy against ARC3486, a carbapenem-resistant *A. baumannii* isolate susceptible to SUL-DUR, based on a preliminary breakpoint criteria of 4 µg/mL
  - Addition of a carbapenem had no impact on SUL-DUR efficacy against this isolate
- For strains ARC5955 and ARC5950 (SUL-DUR MIC values of 8 µg/mL) SUL-DUR 1g/1g treatment did not result in cidal activity by 24 hr, with net +1 log growth observed for both isolates in the HFIM.
  - This is likely due to insufficient %T>MIC exposure of sulbactam to cover an MIC of 8 µg/mL based upon the exposures observed in the SUL-DUR 1g/1g regimen
  - For these *A. baumannii* strains that fall outside the SUL-DUR susceptibility range, improvement of activity was observed in the presence of a carbapenem when co-administered at clinical exposures
- Imipenem and meropenem showed similar activity when administered in combination with SUL-DUR
- If approved, SUL-DUR could be an important treatment option for infections caused by ABC including carbapenem-resistant and multidrug-resistant strains