**Introduction**

- *Mycobacterium abscessus* (Mab) is the most multidrug-resistant, rapid growing mycobacteria, responsible for major pulmonary infections worldwide (1).
- Current regimens including parenteral administrations of cefoxitin (FOX) in combination with amikacin and clarithromycin raise compliance problems and are frequently associated with high failure and development of resistance.
- Intratracheal administration (nebulization) of FOX offers a biopharmaceutical advantage over intravenous administration (2).
- FOX is known to degrade in vitro (3). Consequently, time-kill assays performed up to more than a week and MIC interpretation over 3 days give a de facto misleading impression of the true extent of FOX activity.

**Purpose**

- To study the impact of FOX in vitro stability on time-kill curve data using pharmacokinetic/pharmacodynamic (PK/PD) type modeling approach.

**Materials/Methods**

1. **M. abscessus** CIP104536
2. FOX MIC: 8 mg/L
3. Time kill-kinetics analysis
4. Up to 8 days
5. Concentration measurement using LC-MS/MS
6. Bacterial count

**Results & Discussion**

- No effect for initial FOX concentration < MIC
- An initial CFU decay followed by regrowth > MIC
- Regrowth depends on the increasing FOX initial concentration

**Fig. 2: Schematic diagram of final PK/PD type model**

- **Growth inhibition model** with single homogeneous bacterial population (S)
- FOX is bacteriostatic against Mab (4)
- FOX Degradation → first order process ($t_{1/2}: 1.5$ days)

**Materials/Methods**

- Log$_{10}$(CFU/mL)
- Time (days)

**Fig. 3: FOX time-kill curves against Mab. Initial concentrations of FOX are in mg/L. (A) First set, (B) Second set**

- **Observed bacterial counts (circles)** Medium (black continuous line) 80% Prediction interval (black dotted line)

**Conclusion & perspective**

- This study suggests that FOX dosing regimens used in clinic for the treatment of *M. abscessus* are not sufficient to reduce the bacterial burden.
- FOX by nebulization may allow to achieve high concentration at infection site.
- Also FOX in combination using nebulization could resolve this situation.

**References**

1. Lee et al., *Emerg Infect Dis*, 2015
2. Mehta et al., *ECCMID* 2018, P2204