In vitro evaluation of novel bi- or tri-antibiotic combinations against clinical isolates of *Mycobacterium abscessus*

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P-210

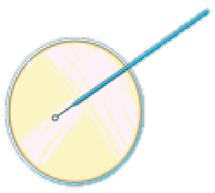
Introduction

- ***Mycobacterium abscessus*** (Mab) is an emerging pathogen, intrinsically resistance to many antimycobacterial drugs (1).
- **Current treatment is limited to combination** of intravenous **amikacin** (AMK), and **cefoxitin** (FOX) **with** oral **clarithromycin** (CLR). In most cases, it is associated with treatment failure (2).
- FOX is known to degrade *in vitro* with the degradation half-life of 1.5 days which may lead to misinterpretation of time-kill results (3).
- Recent reports demonstrate intrinsic **resistance to CLR** in Mab clinical isolates. Fluoroquinolones, rifamycins, linezolid or clofazimine can be added when standard therapy is ineffective (4,5).

Purpose

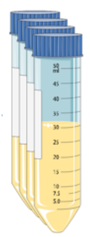
To evaluate the ***in vitro*** **efficacy of several combinations against clinical isolates of Mab** including FOX and AMK and replacing CLR to avoid the induced resistance.

Material & Methods

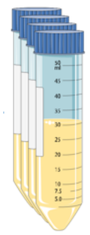


Mycobacterium abscessus

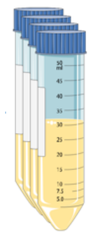
- ✓ Reference strain: CIP104536
- ✓ Clinical isolates:
  - Ma1611 (CLR resistant isolate from CHU, Poitiers)
  - T28 (multidrug resistant MDR- isolate from Lariboisière Hospital, Paris)



Time-kill curves (TKC) up to 8 days
Antibiotic alone
against all isolates

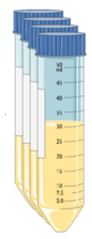


FOX + AMK
TKC:
Bi-combinations against CIP104536
(*data are not shown*)



FOX + AMK + 3rd antibiotic

No tri-combination active against the highly AMK resistant T28 isolate



FOX (@ MIC of T28) + 2nd antibiotic
TKC: Bi-combinations against T28

Table I: Antibiotics used for combination TKC, containing cefoxitin and amikacin combined with 3rd antibiotic

	3rd antibiotic	concentrations used for 3rd antibiotic
FOX + AMK	+ CIP	4 mg/L
	+ MXF	4 mg/L
	+ LZD	8 mg/L
	+ CLO	2 mg/L
	+ RFB	2 mg/L
	+ RIF	16 mg/L
	+ CLR	1 mg/L

Results

1. Susceptibility test of single antibiotics

Table II: Susceptibility data for different Mab isolates tested by broth microdilution (4)

Antibiotics	MIC breakpoints			MICs (mg/L)		
	S	I	R	CIP 104536	Ma1611	T28
FOX	<16	32	>128	8	8	64
AMK	<16	32	>64	32	16	>1024
CIP	<1	2	>4	4	4	8
MXF	<1	2	>4	4	4	16
LZD	<8	16	>32	8	8	256
RIF			>1	16	16	256
CLR	<2	4	>8	1	16	>256
CLO	ND			2	16	4
RFB				2	2	16

S, susceptible; I, intermediate; R, resistance; ND, not determined

2. Effect of several antibiotics alone and in tri-combination against CIP104536

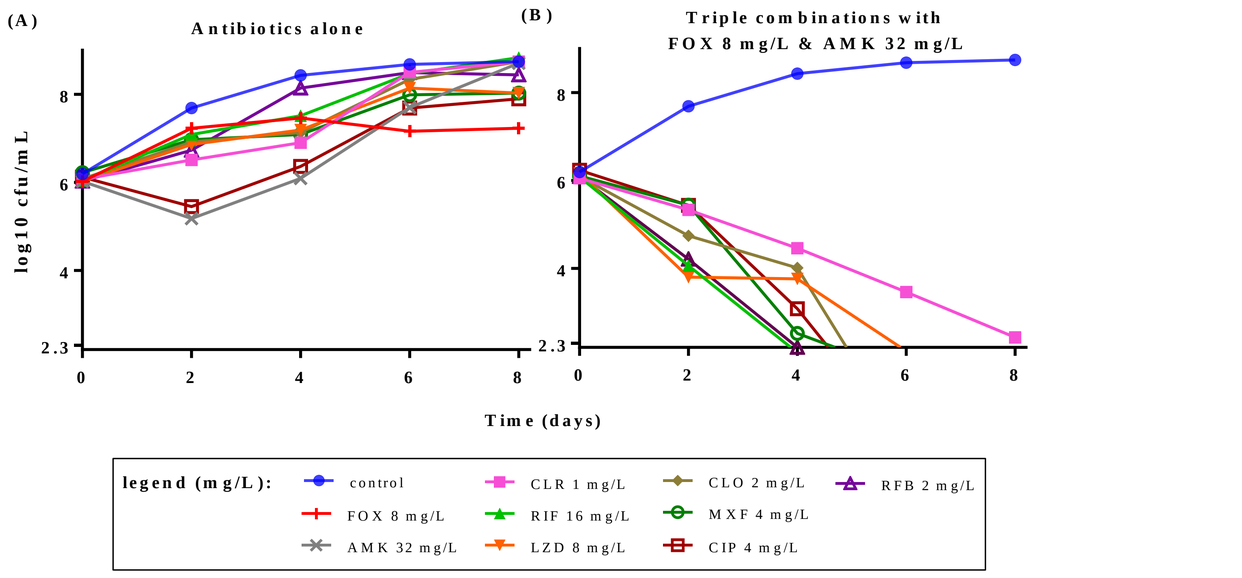


Fig. 1: (A) Activity of antibiotics alone and (B) Tri-combination of cefoxitin and amikacin with a 3rd antibiotic.

3. Effect of several combinations against Mab strain

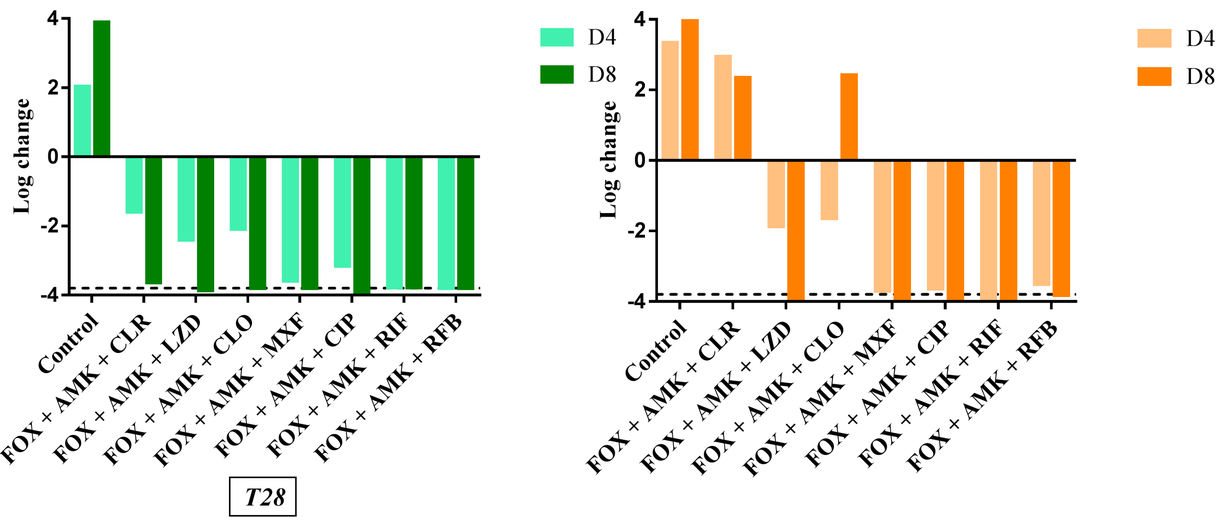


Fig. 2: *In vitro* activity of various tri-combinations against Mab (A) CIP104536 (B) Ma1611 and (C) T28. Log change was calculated using respective positive control data. For Comparision purpose, results are compared at day 4 and day 8.

- ✓ Tri-combinations including CLO or CIP were active against CIP104536 but inactive against Ma1611.
- ✓ Almost all tested triple combinations were inactive against T28.

4. Effect of several combinations against T28 isolate

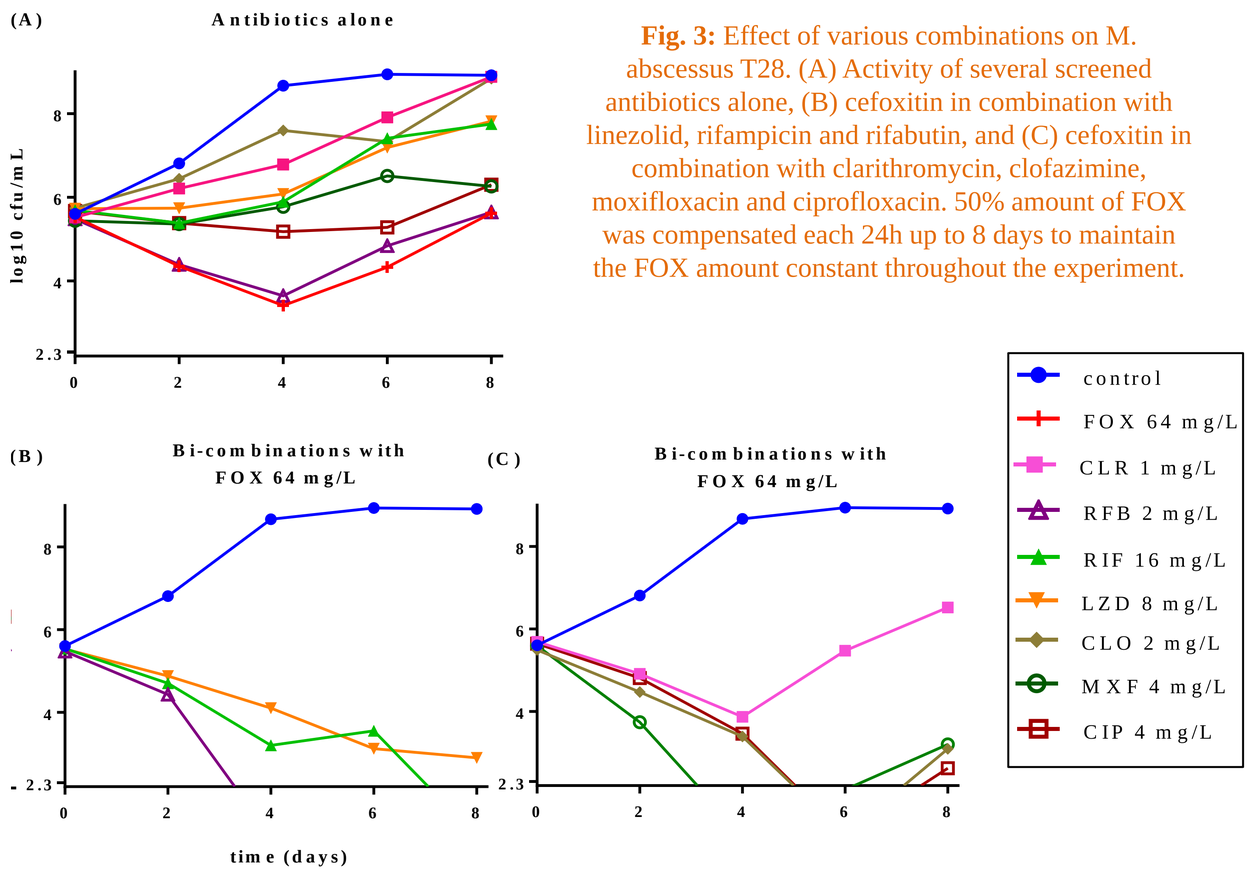


Fig. 3: Effect of various combinations on M. abscessus T28. (A) Activity of several screened antibiotics alone, (B) cefoxitin in combination with linezolid, rifampicin and rifabutin, and (C) cefoxitin in combination with clarithromycin, clofazimine, moxifloxacin and ciprofloxacin. 50% amount of FOX was compensated each 24h up to 8 days to maintain the FOX amount constant throughout the experiment.

- ✓ T28 was highly resistant to AMK because of A1408G mutation of the *rrs* gene encoding rRNA 16S. FOX alone was not much efficient. FOX with RFB bi combination was the most active bi-combination against T28.

Conclusion & Perspectives

- ❖ Tri-combinations were highly efficient against Mab CIP104536 and intermediate to susceptible clinical isolate Ma1611 but not against MDR isolate T28.
- ❖ The synergy between FOX and rifamycins suggests a potent role of this combinations that may warrant further optimization of treatment regimen for the treatment of *M. abscessus* pulmonary infections.

References

(1) Nessar et al., JAC, 2012
(2) Lee et al., Emerg Infect Dis, 2015
(3) Mehta et al., AAC, 2019
(4) Oh et al., JAC, 2014
(5) Griffith et al., IDSA, 2007
(6) NCCLS, 2003

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