Novel treatments of *Mycobacterium abscessus* infection based on dual β-lactam combinations

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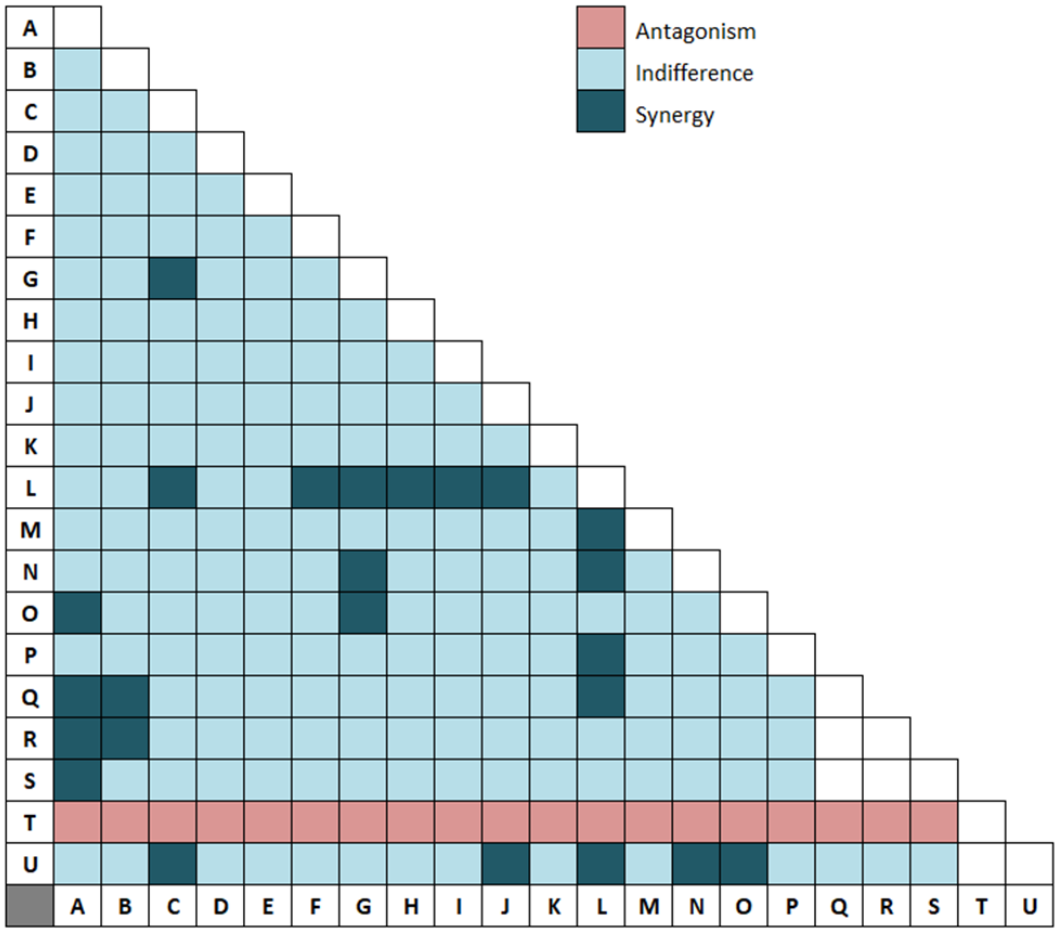
Checkerboard assay

β-lactam class	Drug	MIC (ug/ml)
Cephalosporins	Cefadroxil	256
	Cefprozil	256
	Cefuroxime	256
	Cefixime	256
	Cefibuten	256
	Cefdinir	64
	Cefditoren	256
	Cefpodoxime	256
	Cefoxitin	64
Carbapenems	Ertapenem	256
	Meropenem	32
	Imipenem	8
	Doripenem	16
	Biapenem	16
	Tebipenem	256
Penem	Faropenem	256
Rifamycins	Rifabutin	32
	Rifapentine	128
	Rifampin	128
β-lactamase Inhibitors	Clavulanate	256
	Avibactam	256



Synergistic β-lactam combinations

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Drug combination	MIC of single drug (µg/mL)	MIC in combination (µg/mL)
Cefuroxime	256	32
Avibactam	256	5
Biapenem	16	4
Avibactam	256	4
Cefoxitin	64	9
Imipenem	8	1
Cefditoren	256	26
Imipenem	8	1
Imipenem	8	2
Doripenem	16	2
Cefuroxime	256	33
Cefditoren	256	44
Cefditoren	256	26
Biapenem	16	4
Cefdinir	64	9
Imipenem	8	2
Cefuroxime	256	30
Imipenem	8	2
Cefpodoxime	256	28
Imipenem	8	2
Imipenem	8	2
Biapenem	16	3
Imipenem	8	2
Avibactam	256	64

Drug combination	MIC of single drug (µg/mL)	MIC in combination (µg/mL)
Tebipenem	256	28
Avibactam	256	5
Ertapenem	256	64
Avibactam	256	4
Ertapenem	256	19
Imipenem	8	2
Imipenem	8	1
Faropenem	256	29
Imipenem	8	2
Rifabutin	32	3
Cefadroxil	256	40
Tebipenem	256	48
Cefditoren	256	64
Tebipenem	256	32
Cefadroxil	256	48
Rifabutin	32	6
Cefadroxil	256	64
Rifapentine	128	16
Cefadroxil	256	64
Rifampin	128	32
Cefprozil	256	64
Rifabutin	32	8
Cefprozil	256	64
Rifapentine	128	32

Drug resistance frequency

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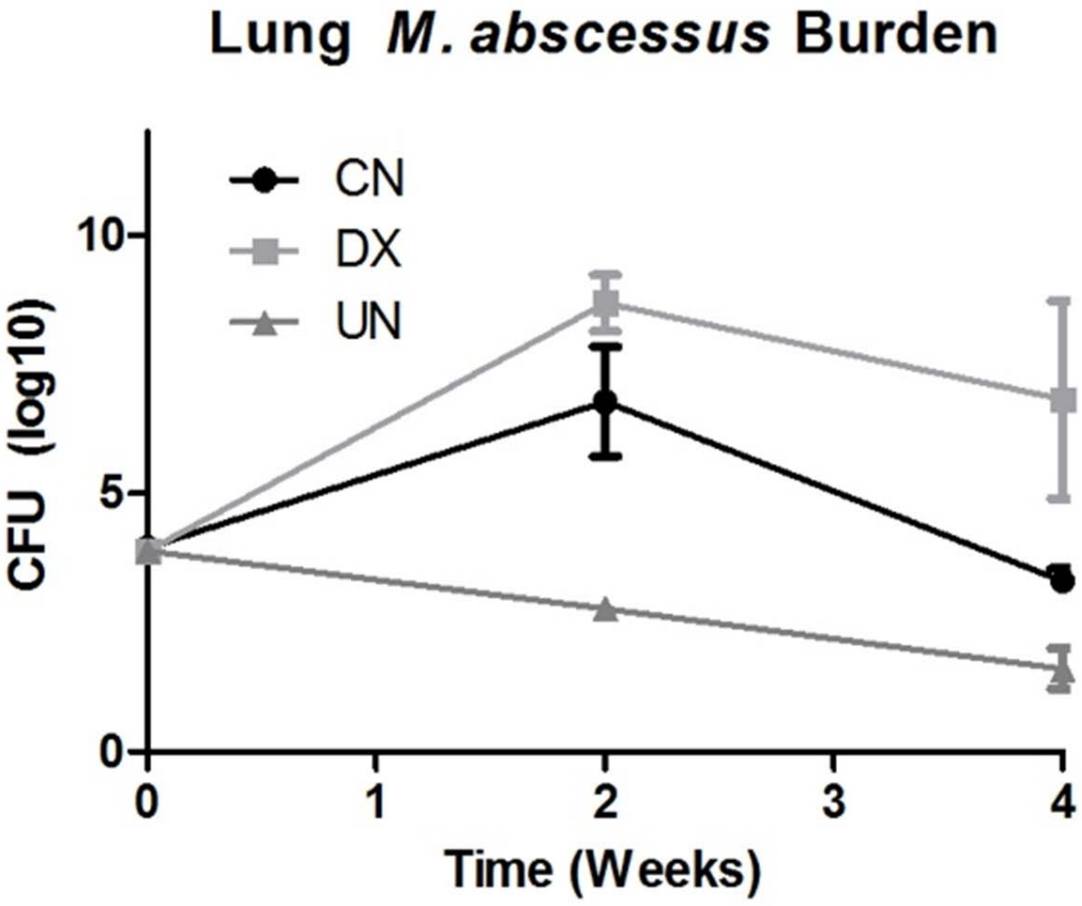
Drug combination	Resistance frequency	
	Individual drugs	Combination
Cefuroxime Avibactam	$> 2 \times 10^{-6}$ --	$< 1 \times 10^{-10}$
Biapenem Avibactam	8.9×10^{-8} --	3.3×10^{-9}
Cefoxitin Imipenem	$> 2 \times 10^{-6}$ 1.9×10^{-7}	$< 1 \times 10^{-10}$
Cefditoren Imipenem	$> 2 \times 10^{-6}$ 1.9×10^{-7}	$< 1 \times 10^{-10}$
Imipenem Doripenem	1.9×10^{-7} 9.9×10^{-8}	9.1×10^{-9}
Cefuroxime Cefditoren	$> 2 \times 10^{-6}$ $> 2 \times 10^{-6}$	$< 1 \times 10^{-10}$
Cefditoren Biapenem	$> 2 \times 10^{-6}$ 8.9×10^{-8}	$< 1 \times 10^{-10}$
Cefdinir Imipenem	7.8×10^{-9} 1.9×10^{-7}	$< 1 \times 10^{-10}$
Cefuroxime Imipenem	$> 2 \times 10^{-6}$ 1.9×10^{-7}	$< 1 \times 10^{-10}$
Cefpodoxime Imipenem	$> 2 \times 10^{-6}$ 1.9×10^{-7}	$< 1 \times 10^{-10}$
Imipenem Biapenem	1.9×10^{-7} 8.9×10^{-8}	1.1×10^{-9}
Imipenem Avibactam	1.9×10^{-7} --	$< 1 \times 10^{-10}$

Drug combination	Resistance frequency	
	Individual drugs	Combination
Tebipenem Avibactam	1.1×10^{-7} --	$< 1 \times 10^{-10}$
Ertapenem Avibactam	8.3×10^{-8} --	$< 1 \times 10^{-10}$
Ertapenem Imipenem	8.3×10^{-8} 1.9×10^{-7}	4.3×10^{-9}
Imipenem Faropenem	1.9×10^{-7} $< 1 \times 10^{-10}$	$< 1 \times 10^{-10}$
Imipenem Rifabutin	1.9×10^{-7} $< 1 \times 10^{-10}$	$< 1 \times 10^{-10}$
Cefadroxil Tebipenem	$> 2 \times 10^{-6}$ 1.1×10^{-7}	1.3×10^{-8}
Cefditoren Tebipenem	$> 2 \times 10^{-6}$ 1.1×10^{-7}	$< 1 \times 10^{-10}$
Cefadroxil Rifabutin	$> 2 \times 10^{-6}$ $< 1 \times 10^{-10}$	$< 1 \times 10^{-10}$
Cefadroxil Rifapentine	$> 2 \times 10^{-6}$ $< 1 \times 10^{-10}$	$< 1 \times 10^{-10}$
Cefadroxil Rifampin	$> 2 \times 10^{-6}$ $> 2 \times 10^{-6}$	$< 1 \times 10^{-10}$
Cefprozil Rifabutin	$> 2 \times 10^{-6}$ $< 1 \times 10^{-10}$	$< 1 \times 10^{-10}$
Cefprozil Rifapentine	$> 2 \times 10^{-6}$ $< 1 \times 10^{-10}$	$< 1 \times 10^{-10}$

Aerosolized *M. abscessus* infection in mice



Maggioncalda et al. *BioRxiv*. 2018.