

Efficacy of NXL 104, a Novel Broad Spectrum β -lactamase Inhibitor, in Combination with Ceftazidime in Murine Septicaemia and Pneumonia

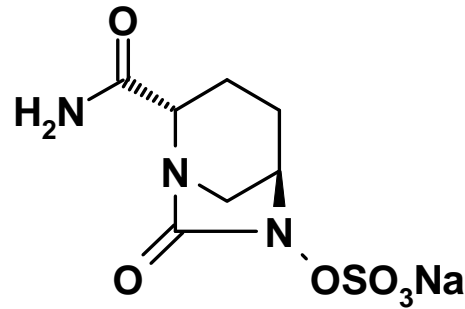
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- NXL 104 is a novel β -lactamase inhibitor which has been shown *in vitro* to inhibit both class A and C β -lactamases.



- Efficacy of CAZ/NXL 104 (ratio 4/1) compared to CAZ alone, was evaluated against CAZ^R *Enterobacteriaceae* in murine septicemia and pneumonia models.

Efficacy of CAZ/NXL104 (4/1 ratio) in mouse septicaemia* after parenteral dosing

Strains	Reference	β -lactamase	Drug	MIC (mg/l)	ED50 (mg/kg)
<i>K. pneumoniae</i>	283IP35	SHV-2	CAZ	256	>90
			CAZ/NXL104	0.5	29
			TAZOCILLIN	32	>90
	283IP10	SHV-4	COAMOXICLAV	64	>90
			CAZ	>64	>50
			CAZ/NXL104	1	5
<i>E. coli</i>	250BE1	SHV-4	TAZOCILLIN	8	>50
			COAMOXICLAV	8	20
			CAZ	>64	>50
			CAZ/NXL104	2	16
<i>E. cloacae</i>	293GR8	AmpC	TAZOCILLIN	16	39
			COAMOXICLAV	8	49
			CAZ	64	>90
	P99	AmpC	CAZ/NXL104	1	<10
			TAZOCILLIN	16	>90
			COAMOXICLAV	>64	>90
<i>C. freundii</i>	261GR3	AmpC	CAZ	64	>90
			CAZ/NXL104	1	14
			TAZOCILLIN	64	>90
	261GR6	AmpC	COAMOXICLAV	>64	>90
			CAZ	64	>50
			CAZ/NXL104	2	<5
261GR6	AmpC	TAZOCILLIN	32	>50	
		COAMOXICLAV	>64	>50	
		CAZ	64	>50	

*Mice (n=10) infected intraperitoneally; SC treatments given immediately and 4 hours post-infection

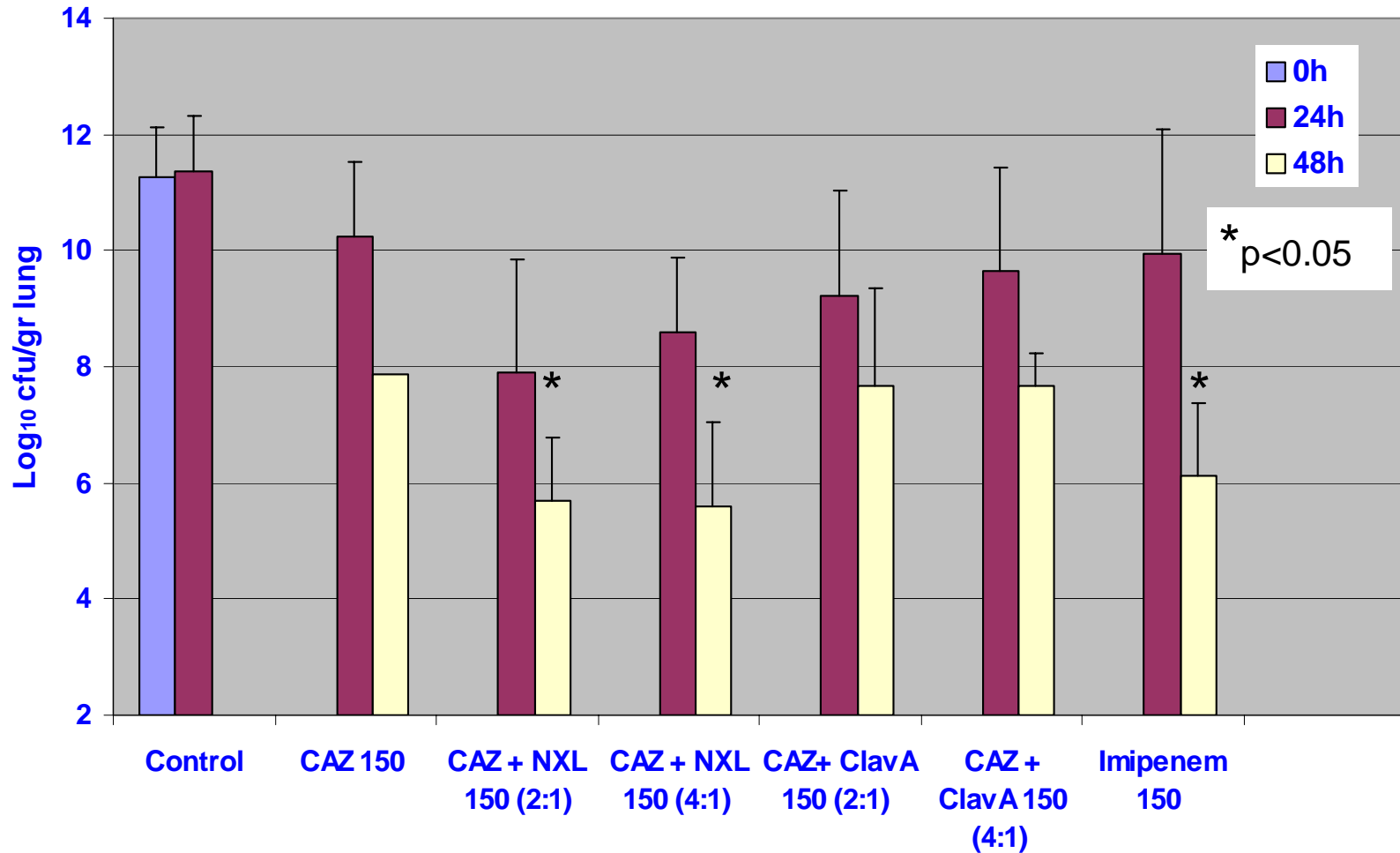
Experimental Pneumonia - Protocol

- Female Swiss (OF1) mice (6-7wks) were immunosuppressed with 150 mg/kg cyclophosphamide (i.p) 3 days prior to- and 6- hours before infection.
- A transient neutropenia ($1000/\text{mm}^3$) is induced and renders mice susceptible to infection with CAZ-resistant bacterial strains.
- Anesthetised mice were intratracheally infected with *K. pneumoniae* strains ($\sim 10^8$ to 10^9 cfu in 50 μl volume).
- Mice develop bacteraemic pneumonia and fatal disease within 2 to 4 days.
- Lung bacterial burden 16 – 18 hours post-infection: 10^{11} to 10^{13} cfu/gr lung

Experimental Pneumonia - Protocol

- Subcutaneous treatment was initiated 16-18 hours post-infection t.i.d for two days.
- Groups of 20–30 infected mice were treated with either:
 - CAZ - 150 mg/kg
 - CAZ + NXL104: 2/1
 - CAZ + NXL104: 4/1
 - CAZ + Clavulanic acid: 2/1
 - CAZ + Clavulanic acid: 4/1
 - Imipenem/Cilastatin: 150 mg/kg
- A group of 20 control mice received only saline at the indicated time.
- *In vivo* efficacy monitored using:
 - Bacterial lung clearance at 24- and 48- hours post-treatment

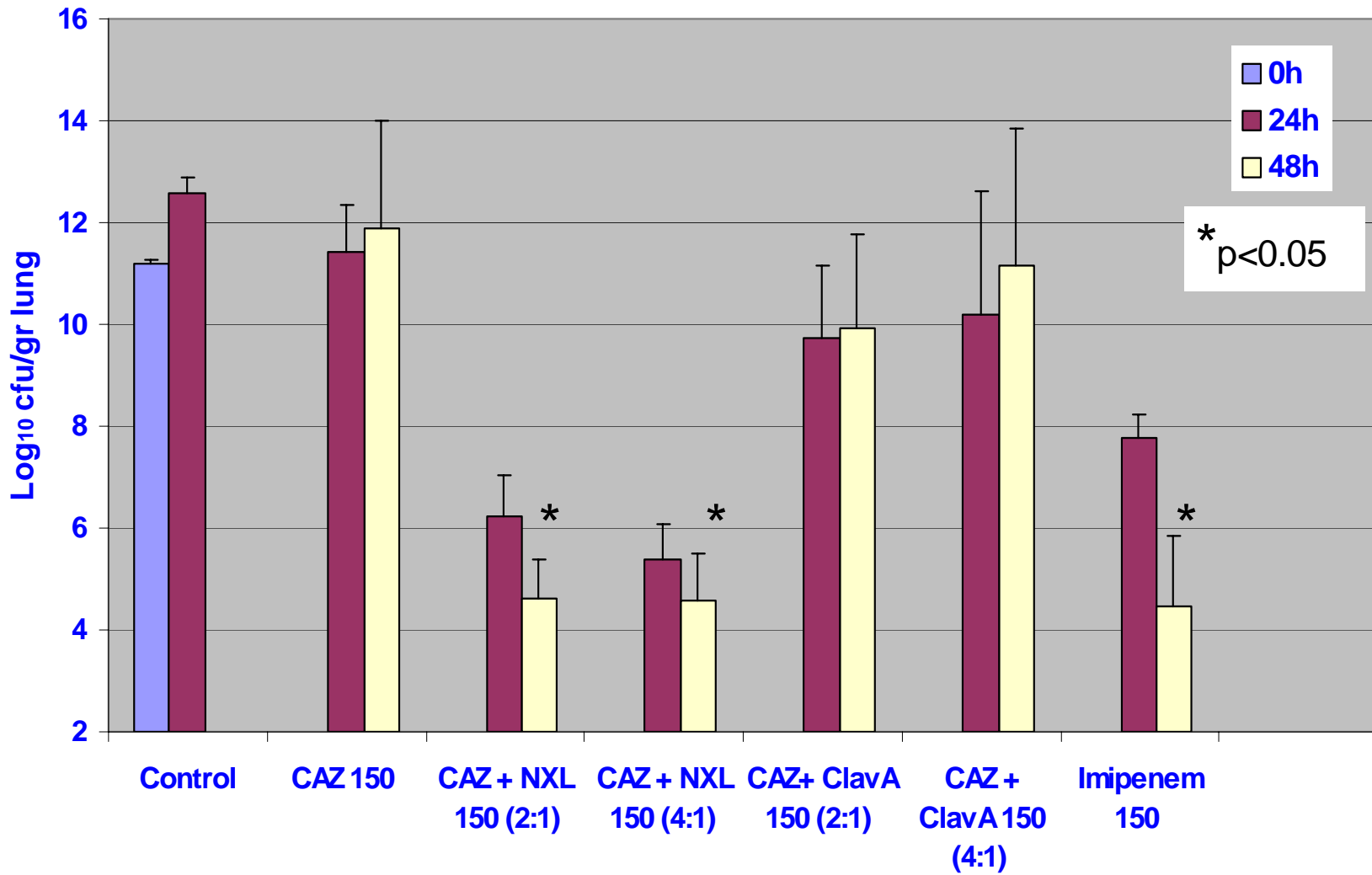
Lung counts of *K. pneumoniae* 283KB4 - AmpC



MICs (μg/ml): CAZ:>256; CAZ/NXL:4; CAZ/ClaA:128; Imipenem:1

Subcutaneous treatment initiated 16-18 hours post-infection t.i.d (every 8 hours) for two days.

Lung counts of *K. pneumoniae* 283KB5 - AmpC + Class A



MICs ($\mu\text{g/ml}$): CAZ:32; CAZ/NXL:1; CAZ/ClaA:8; Imipenem:1

Subcutaneous treatment initiated 16-18 hours post-infection t.i.d (every 8 hours) for two days.

Conclusion

- NXL 104 restored the activity of CAZ against CAZ^R *Enterobacteriaceae* species including class A and importantly class C β -lactamase producers in mouse infection models:
 - Septicaemia: ED50 range <5-29 mg/kg compared to >90 mg/kg CAZ
 - Pneumonia: both 2/1 and 4/1 ratio of CAZ/NXL104 demonstrated similar efficacy with a significant 3 to 6 –log reduction in lung bacterial counts compared to CAZ alone or CAZ/clavulanic acid.