

## Supplementary material- Figure S1

**Supplementary Figure S1.** In vitro antimicrobial spectrum for newer antibiotics used for nosocomial pneumonia. *Each colour is based on current reported in vitro antibiotic susceptibility rates; these rates are indicative and may differ in different reports depending on cohorts and cut-offs used (EUCAST versus CLSI), and as new real-world in vitro sensitivity data arise constantly.*

Antibiotic-susceptibility rate			
81-	61-	41-	≤ 40%

	Enterobacterales					<i>Pseudomonas aeruginosa</i>				<i>Acinetobacter baumannii</i>
<i>Main resistance mechanism</i>	Ambler Class A	Ambler Class A	Ambler Class B	Ambler Class C	Ambler Class D	AmpC de-repression	Efflux Pump Over-expression	Deficient OprD expression	MBLs^	CRAB
<i>Antibiotic</i>	ESBLs	KPC	MBLs^		OXA-48 like					
Ceftolozane-tazobactam				~						
Ceftazidime-avibactam										
Meropenem-vaborbactam										
Imipenem-cilastatin-relebactam&										
Cefiderocol*			VIM	NDM#					^*	*

Sulbactam-durlobactam										
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**ESBL:** extended-spectrum  $\beta$ -lactamase (e.g. **SHV:** sulphydryl variable  $\beta$ -lactamase; **TEM:** named from the parental enzyme found in the blood of a Greek patient called Temoniera; **CTX-M:** cefotaxime- $\beta$ -lactamases); **MBL:** metallo- $\beta$ -lactamase (e.g. **VIM:** Verona-integron-mediated metallo- $\beta$ -lactamase; **IMP:** imipenemase-type carbapenemase; **NDM:** New Delhi metallo- $\beta$ -lactamase); **CRAB:** Carbapenem-Resistant *Acinetobacter baumannii*.

<sup>&</sup>The activity against OXA-48-producing strains is mostly that of imipenem; relebactam hardly enhances the activity of imipenem against OXA-48 (it has been reported to provide weak potentiation against some OXA-48 producing isolates of *Klebsiella pneumoniae*).

~ Ceftolozane developed to be more hydrolysis-resistant against Pseudomonas-derived AmpC compared to previous cephalosporins, however, much less is known about ceftolozane-tazobactam's activity against Enterobacterales-derived AmpC (tazobactam provides weaker protection against AmpC hydrolysis compared to newer beta-lactamase inhibitors) – in a study it has been reported that only 19% of *Enterobacter cloacae* were sensitive to ceftolozane-tazobactam.

<sup>#</sup>42–59% cefiderocol nonsusceptibility in NDM-producing clinical isolates reported in some cohorts.

<sup>^</sup>Enhanced stability does not always correlate with efficacy; <sup>\*</sup>A combination of mechanisms, e.g.  $\beta$ -lactamases, mutations affecting expression or function of siderophore receptors and mutations affecting expression/function of porins or efflux pumps can increase cefiderocol strain resistance. Antibiotic heteroresistance is a phenotype in which a bacterial isolate contains subpopulations of cells showing a substantial reduction in antibiotic susceptibility compared with the main population. Cefiderocol heteroresistance was detected in carbapenem-resistant bacteria, including *Acinetobacter baumannii* (59%), *Klebsiella* spp (30%), *Pseudomonas aeruginosa* (9%), and *Stenotrophomonas maltophilia* (48%), but its clinical importance remains unclear.

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