

Table S1. Pertinent regression parameters of dose-response curves for intracellular and extracellular activity of antibiotics against PAO1 strain ^a.

Antibiotic	Extracellular activity ^c					Intracellular activity ^a				
	E_{min}^d	E_{max}^d	EC_{50}^e	C_s^f	R^2	E_{min}^d	E_{max}^d	EC_{50}^e	C_s^f	R^2
GEN	3.66 (3.20 to 4.11)	>-4.5	0.63 (0.47 to 0.84)	0.46	0.98	2.76 (2.44 to 3.08)	-1.59 (-1.96 to -1.23)	3.30 (2.18 to 4.99)	5.70	0.96
AMK	3.70 (3.01 to 4.39)	>-4.5	1.20 (0.79 to 1.82)	0.69	0.94	3.78 (3.33 to 4.22)	-2.17 (-2.79 to -1.55)	2.04 (1.32 to 3.14)	3.53	0.89
TOB	4.28 (2.76 to 5.81)	>-4.5	0.69 (0.42 to 1.14)	0.55	0.90	2.99 (2.63 to 3.36)	-1.02 (-1.38 to -0.65)	3.64 (2.26 to 5.86)	10.69	0.88
Aminoglycosides ^g	3.83 (3.37 to 4.28)	>-4.5	0.74 (0.57 to 0.98)	0.56	0.93	3.34 (3.04 to 3.64)	-1.31 (-1.62 to -1.00)	2.12 (1.51 to 2.98)	5.40	0.84
MXF	4.04 (3.21 to 4.87)	>-4.5	1.97 (1.40 to 2.77)	1.28	0.94	2.75 (2.49 to 3.01)	-2.87 (-3.11 to -2.64)	1.10 (0.85 to 1.42)	1.05	0.98
LVX	3.94 (3.00 to 4.88)	>-4.5	1.82 (1.11 to 2.98)	1.37	0.90	3.45 (2.86 to 4.04)	-3.22 (-3.58 to -2.88)	0.49 (0.30 to 0.79)	0.48	0.95
CIP	4.66 (3.49 to 5.82)	>-4.5	1.09 (0.74 to 1.60)	0.98	0.93	3.15 (2.39 to 3.90)	-2.66 (-3.02 to -2.29)	2.15 (1.22 to 3.77)	2.55	0.92
Fluoroquinolones ^g	4.10 (3.57 to 4.63)	>-4.5	1.61 (1.29 to 2.00)	1.21	0.94	3.02 (2.65 to 3.39)	-2.88 (-3.13 to -2.63)	1.00 (0.73 to 1.36)	1.04	0.91
TIC	3.24 (3.01 to 3.47)	>-4.5	0.54 (0.33 to 0.75)	1.27	0.97	2.53 (2.33 to 2.73)	-1.44 (-1.71 to -1.17)	0.59 (0.43 to 0.82)	1.04	0.96
PIP	3.87 (3.46 to 4.27)	>-4.5	1.94 (1.37 to 2.76)	1.29	0.97	2.96 (2.64 to 3.28)	-1.13 (-1.41 to -0.85)	0.26 (0.17 to 0.40)	0.68	0.96
TZP	3.69 (3.22 to 4.15)	>-4.5	1.85 (1.22 to 2.86)	1.36	0.94	2.50 (2.27 to 2.74)	-0.91 (-1.22 to -0.61)	0.56 (0.33 to 0.95)	1.54	0.95
FEP	3.97 (3.15 to 4.79)	>-4.5	1.29 (0.81 to 2.04)	0.93	0.92	3.14 (2.62 to 3.66)	-1.52 (-1.93 to -1.11)	0.75 (0.42 to 1.34)	1.56	0.93
CAZ	3.51 (3.01 to 4.00)	>-4.5	1.97 (1.40 to 2.78)	1.45	0.96	3.13 (2.56 to 3.69)	-1.33 (-1.67 to -1.00)	0.31 (0.19 to 0.53)	0.74	0.85
ATM	3.87 (3.43 to 4.31)	-4.36 (-5.02 to -3.69)	1.67 (1.18 to 2.36)	1.48	0.92	2.92 (2.62 to 3.22)	-0.75 (-0.99 to -0.52)	0.20 (0.14 to 0.30)	0.79	0.96
MER	4.62 (3.17 to 6.06)	>-4.5	1.02 (0.55 to 1.89)	0.74	0.92	2.65 (2.17 to 3.13)	-1.57 (-1.80 to -1.34)	0.36 (0.23 to 0.57)	0.61	0.94
IMI	4.23 (3.62 to 4.85)	>-4.5	0.77 (0.47 to 1.25)	0.63	0.97	2.80 (2.42 to 3.19)	-1.07 (-1.33 to -0.81)	0.74 (0.47 to 1.17)	1.95	0.92
DOR	3.51 (2.77 to 4.26)	>-4.5	1.98 (1.34 to 2.94)	1.51	0.93	2.11 (1.72 to 2.51)	-1.33 (-1.60 to -1.08)	1.21 (0.74 to 1.98)	1.91	0.95
β -lactams ^g	3.77 (3.57 to 3.98)	>-4.5	1.58 (1.37 to 1.83)	1.16	0.93	2.74 (2.60 to 2.88)	-1.23 (-1.34 to -1.11)	0.44 (0.36 to 0.53)	0.98	0.90
CST	3.81 (2.75 to 4.87)	>-4.5	1.78 (1.08 to 2.95)	1.25	0.92	2.84 (2.50 to 3.18)	-1.04 (-1.22 to -0.86)	0.94 (0.63 to 1.40)	2.52	0.92

^a Data are based on a 24-h post-phagocytosis exposure. Regression parameters were calculated using all data from antibiotic concentrations of 10^{-2} to 10^3 to times the MIC. The parameters described in the table were derived from analysis of the curve shown in Fig 5. See Table S2 and 3 for statistical analyses

^b Determined in THP-1 macrophages with an initial phagocytosed inoculum of about 10^6 CFU/mg of protein.

^d Log CFU decrease at 24 h from the corresponding original inoculum, as extrapolated for an infinitely large antibiotic concentration. Samples yielding less than -5 log CFU were considered below the detection level.

^e extracellular concentrations (total drug; in multiples of the MIC) causing a reduction of the inoculum halfway between the initial (E_0) and the maximal (E_{max}) values, as obtained from the Hill equation.

^f Static concentration, i.e., the extracellular concentration (total drug; in multiples of the MIC) resulting in no apparent bacterial growth (number of CFU identical to the initial inoculum), as calculated from the Hill equation of the concentration-response curve.

^g reproduced from Table 2; data from all antibiotics within the class were used to fit a single curve

Table S2: statistical analyses of EC₅₀ presented in Table S1

Black and dark gray cells compare parameters for extracellular and intracellular activity of individual antibiotics (black) or classes as a whole (dark grey) (***, $p < 0.01$; NS, not significant).

Colored cells compare antibiotics within a same class (orange: aminoglycosides; green: β -lactams; blue: fluoroquinolones) or classes as whole among them (yellow). Light and dark colors correspond to statistical analysis for extracellular and intracellular activities, respectively (*: $p < 0.05$; NS: not significant).

EC ₅₀		Antibiotics																		
		AMIN.	GEN	AMK	TOB	Blact	TIC	PIP	TZP	FEP	CAZ	ATM	MEM	IMI	DOR	FQ	LVX	MOX	CIP	CST
Antibiotics	AMIN.	***	NS	NS	*	*										*				*
	GEN	NS	***	NS	NS															
	AMK	NS	*	NS	NS															
	TOB	NS	NS	*	***															
	Blact	NS				NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS				NS
	TIC					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	PIP					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	TZP					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	FEP					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	CAZ					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	ATM					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	MEM					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	IMI					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	DOR					NS	NS	NS	NS	NS	NS	NS	NS	NS	NS					
	FQ	NS				NS										NS	NS	NS	NS	NS
	LVX															NS	NS	NS	NS	
	MOX															NS	NS	NS	NS	
	CIP															NS	NS	NS	NS	
	CST	NS				NS										NS				NS

Table S3: statistical analyses of E_{max} presented in Table S1

Black and dark gray cells compare parameters for extracellular and intracellular activity of individual antibiotics (black) or classes as a whole (dark grey) (***, p< 0.01; NS, not significant).

Colored cells compare antibiotics within a same class (orange: aminoglycosides; green: β-lactams; blue: fluoroquinolones) or classes as whole among them (yellow). Light and dark colors correspond to statistical analysis for extracellular and intracellular activities, respectively (*: p<0.05; NS: not significant; NA: not applicable [because E_{max} > detection limit]).

E _{max}		Antibiotics																		
		AMIN.	GEN	AMK	TOB	Blact	TIC	PIP	TZP	FEP	CAZ	ATM	MEM	IMI	DOR	FQ	LVX	MOX	CIP	CST
Antibiotics	AMIN.	***	NS	*	NS	NS										*				NS
	GEN	NA	***	NS	*															
	AMK	NA	NA	***	NS															
	TOB	NA	NA	NA	***															
	Blact	NA				***	NS	NS	NS	NS	NS	*	NS	NS	NS	*				NS
	TIC					NA	***	NS	*	NS	NS	*	NS	NS	NS					
	PIP					NA	NA	***	NS	NS	NS	*	NS	NS						
	TZP					NA	NA	NA	***	*	*	NS	*	NS	*					
	FEP					NA	NA	NA	NA	***	NS	*	NS	*	NS					
	CAZ					NA	NA	NA	NA	NA	***	*	NS	NS	NS					
	ATM					NA	NA	NA	NA	NA	NA	***	*	NS	*					
	MEM					NA	NA	NA	NA	NA	NA	NA	***	NS	NS					
	IMI					NA	NA	NA	NA	NA	NA	NA	NA	***	NS					
	DOR					NA	NA	NA	NA	NA	NA	NA	NA	NA	***					
	FQ	NA				NA										***	NS	NS	NS	*
	LVX															NA	***	NS	*	
	MOX															NA	NA	***	NS	
	CIP															NA	NA	NA	***	
	CST	NA				NA										NA				***

Figure S1. Influence of the time on the rate and extent of activity of antibiotics against extracellular and intracellular *P. aeruginosa* PAO1 upon incubation at a fixed extracellular concentration corresponding to their MIC in broth (open symbols and dotted lines) and to their maximal concentration (total drug) observed in humans after administration of conventional doses (C_{max} ; closed symbols and plain lines). The ordinate shows the change in the number of CFU (log scale) per mL for extracellular bacteria or per mg of cell protein for intracellular bacteria. The plain horizontal line corresponds to a bacteriostatic effect (no change from initial inoculum) and the dotted horizontal line shows the limit of detection ($-4.5 \log_{10}$ CFU decrease). Values are means \pm standard deviations ($n = 3$); when not visible, error bars are smaller than the symbols.



