Dose Optimization of Colistin Combinations against Carbapenem-Resistant *Acinetobacter baumannii* from Chinese Hospital-acquired Pneumonia Patients Using *In Vitro* PK/PD Model

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Key words: *Acinetobacter baumannii*, carbapenem resistance, colistin, meropenem, combination therapy, PK/PD modeling

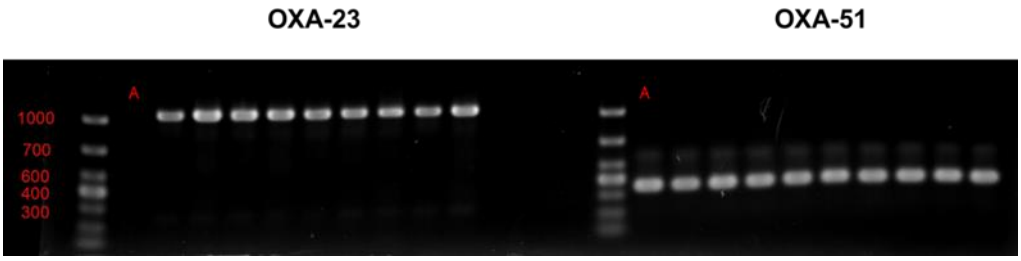

Fig. S1 PCR results of *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{OXA-51}}$ for MDR *A. baumannii* and ATCC19606 (A).

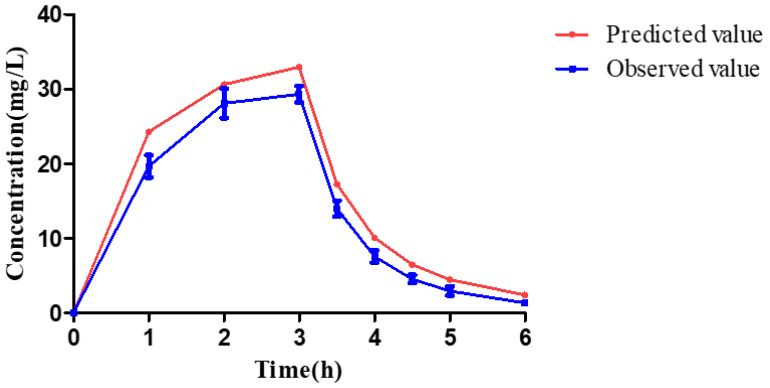

Fig. S2 Concentration-time curves of meropenem dosed at 2 g with 3-h infusion.

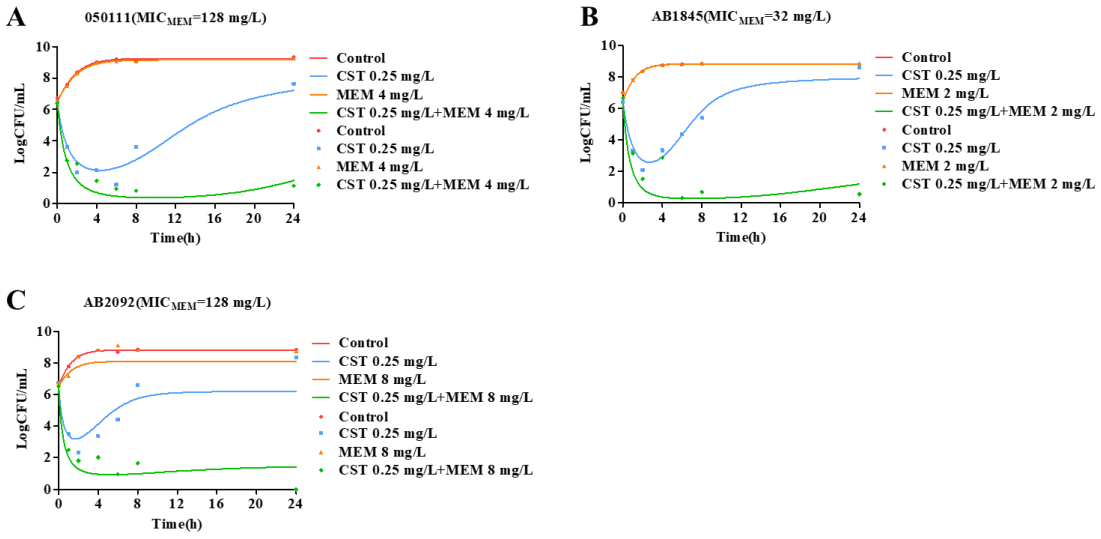

Fig. S3 Observed (symbols) and model fitted (lines) viable counts for the static time-kill experiments with meropenem or colistin alone and in combination against *A. baumannii* 050111(A), AB1845(B) and AB2092(C). CST, colistin; MEM, meropenem.

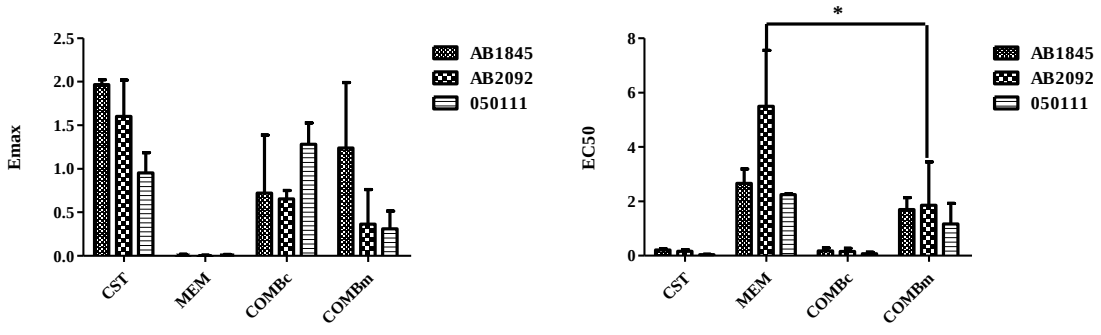

Fig. S4 Comparison of estimated parameters E_{max} and EC_{50} for the three strains in the static time-kill study. CST and MEM represent colistin and meropenem parameters in monotherapy; COMBc and COMBm represent colistin and meropenem parameters in the combination therapy (*: p<0.05).

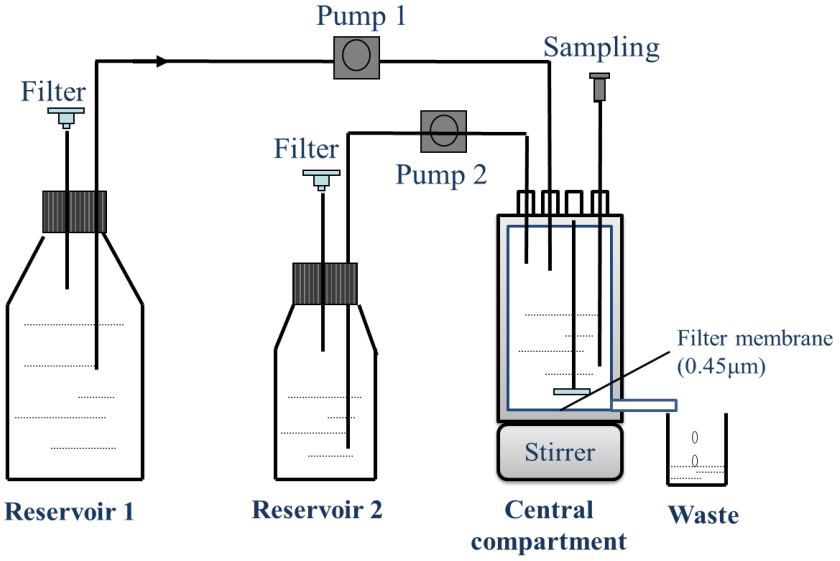

Fig. S5 Schematics of the *in vitro* PK/PD model. The volume of culture medium in central compartment was 200 mL. Bacterial solution was filtered by 0.45-μm membrane to prevent bacterial loss. The peristaltic pump was digitally controlled by a computer using WinLIN 3.2 software (Cole-Parmer Co. Ltd.). The flowing rate was regulated by section-divided modulation to mimic plasma drug concentrations in patients.

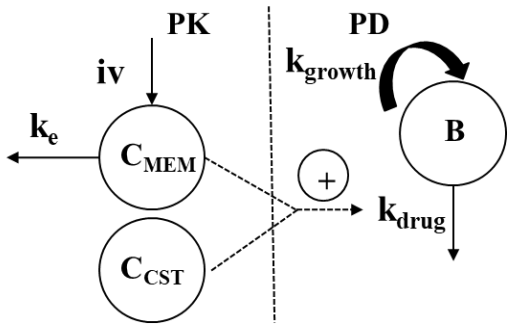

Fig. S6 Schematics of the pharmacokinetic/pharmacodynamic (PK/PD) model characterizing the killing effect of colistin and meropenem.

Table S1. MICs of ATCC19606 and clinical CRAB isolates

Strain		ATCC 19606	050111	020411	120211	070311	070411	080411	080511	AB 1845	AB 2092
MIC (mg/L)	CST	1	0.5	1	0.5	0.5	0.5	1	0.5	0.5	1
	MEM	0.5	128	32	32	32	64	32	32	32	128
	RIF	2	4	4	4	2	2	4	4	4	8
	FOF	64	128	64	128	128	128	128	128	128	>128
	MIN	<0.125	4	8	2	1	1	0.5	2	4	8

CST, colistin; MEM, meropenem; RIF, rifampicin; FOF, fosfomycin; MIN, minocycline; MIC, minimum inhibitory concentration.

CLSI breakpoints: CST, S: ≤2mg/L, R: ≥4mg/L, MEM, S: ≤2mg/L, I: 4mg/L, R: ≥8mg/L; MIN, S: ≤4mg/L, I: 8mg/L, R: ≥16mg/L.

Table S2. Synergistic effects of each combination against 9 clinical isolates.

Combination	Number of strains			Synergy rate
	Synergy	Indifference	Antagonism	（%）
CST-MEM	4	5	0	44
CST-RIF	5	4	0	56
CST-FOF	1	8	0	11
CST-MIN	3	6	0	33

CST, colistin; MEM, meropenem; RIF, rifampicin; FOF, fosfomycin; MIN, minocycline

Synergy rate（%）= No. of strains showing synergy / total number of strains

Table S3. Observed and predicted concentrations of meropenem dosed at 2 g with 3-h infusion

Time(h)	Predicted concentration (mg/L)	Measured concentration (n=3) (mg/L)
0	0	0.04±0.05
1	24.3	19.7±1.07
2	30.6	28.1±1.39
3	32.9	29.3±0.9
3.5	17.2	14.0±0.76
4	10.0	7.58±0.58
4.5	6.5	4.56±0.4
5	4.5	2.96±0.43
6	2.4	1.36±0.11

Table S4. Parameter estimates for the static time-kill study

Parameter	**Explanation**	***A. baumannii* 050111**	***A. baumannii* 1845**	***A. baumannii* 2092**
$k_{growth}(h^{-1})$	rate constant of bacterial net growth	0.692	0.986	0.984
$B_{max}(\log_{10}CFU/mL)$	bacterial count in the stationary phase	9.27	8.84	8.81
$E_{max\_CST}(h^{-1})$	maximum achievable kill rate constant by colistin	4.09	1.07	9.01
EC_{50_CST}(mg/L)	colistin concentration that results in 50% of E_{max}	0.489	0.0141	0.364
$E_{max\_MEM}(h^{-1})$	maximum achievable kill rate constant by meropenem	0.014	0.719	0.16
EC_{50_MEM}(mg/L)	meropenem concentration that results in 50% of E_{max}	4.00	7.01	2.40
γ_{CST}	hill factor for colistin	1.73	2.72	4.13
γ_{MEM}	hill factor for meropenem	30.6	5.54	1.24×10^{-7}
f	maximal adaptation factor	7.82	40.7	0.561
k	rate of adaptation	0.0667	0.575	1.70

Int	parameter describing drug interaction	5.53	9.99	2.50
Fval(%)	residual error fraction	1.38	3.43	2.77

Table S5. Pharmacokinetic parameters of meropenem

Parameter	Explanation	Dose	
		0.5 g	**1 g or 2 g**
k_e (h^{-1})	elimination rate constant	1.39	1.34
V_1 (L)	volume of central compartment	13.7	13.8
V_2 (L)	volume of peripheral compartment	5.49	5.97
k_{12} (h^{-1})	speed constant from central compartment to peripheral compartment	0.506	0.323
k_{21} (h^{-1})	speed constant from peripheral compartment to central compartment	1.26	0.750