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Drug Combinations To Prevent Antimicrobial Resistance

防控抗微生物耐药性的药物组合研究

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Abstract

Background

Antimicrobial resistance (AMR) has been a serious threat to human health, and combination therapy is proved to be an economic and effective strategy for fighting the resistance. However, the abuse of drug combinations conversely accelerates the spread of AMR. In our previous work, we concluded that the mutant selection indexes (SIs) of one agent against a specific bacterial strain are closely related to the proportions of two agents in a drug combination. To discover probable correlations, predictors and laws for further proposing feasible principles and schemes guiding the AMR-preventing practice, here, three aspects were further explored.

Methods

The mathematical and statistical analyses were performed for the experimental data published by us or collected from the literature, and the results were further verified and improved by anitibotic exposure experiments.

Results

MRSA isolates	MIC (μg/mL)					FICI		
	RM[b]	DC	VM	OX	FF	RM/DC	VM/OX	VM/FF
01	0.13	0.25	1.00	1.00	64	0.26–0.50	0.75–1.25	1.00–1.25
02	0.13	0.13	2.00	2.00	32	0.28–0.38	1.00–1.50	1.25–1.50
03	32	0.13	0.50	2.00	32	0.53–0.75	1.25–1.50	1.00–1.25

Table 1. Minimal inhibitory concentrations (MICs) of five agents and fractional inhibitory concentrationIndices (FICIs) of three combinations against three clinical MRSA isolates. " The data of FICI were publishedas an abstract of oral presentation at ISAAR&ICIC 201742, bRM: roxithromycin, DC: doxycycline, VM:vancomycin, FF: fosfomycin, OX: ofloxacin.

MRSA isloates	Combinations[a]	$MIC_{99\%}$s Alone	MPCs Alone	MPCs in combinations[c]						
				8:1	4:1	2:1	1:1	1:2	1:4	1:8
01	RM/DC	0.04/0.17	0.21/2.56	0.09/0.01	0.10/0.02	0.07/0.03	0.08/0.08	0.03/0.05	0.04/0.15	0.01/0.12
	VM/OX	0.32/0.92	15.4/25.6	4.56/0.57	9.01/2.25	4.44/2.22	2.72/2.72	1.79/3.58	1.44/5.76	0.73/5.84
	VM/FF	0.32/6.92	15.4/1000	4.56/0.57	3.57/0.89	4.44/2.22	3.54/3.54	8.70/17.4	4.36/17.4	4.38/35.0
02	RM/DC	0.07/0.10	0.16/2.00	0.08/0.01	0.07/0.02	0.05/0.03	0.05/0.05	0.04/0.09	0.03/0.13	0.02/0.16
	VM/OX	1.79/1.12	16.0/19.2	8.88/1.11	7.04/1.76	5.97/2.99	2.88/2.88	2.83/5.67	1.40/5.60	1.67/13.4
	VM/FF	1.79/8.01	16.0/1000	9.36/1.17	9.22/2.30	4.50/2.25	4.61/4.61	3.77/7.55	5.76/23.0	2.25/18.0
03	RM/DC	0.28/0.04	256/0.39	2.64/0.33	1.34/0.34	0.86/0.43	0.41/0.41	0.20/0.41	0.11/0.42	0.07/0.56
	VM/OX	0.21/1.25	15.0/8.00	1.76/0.22	4.40/1.10	2.04/1.02	2.00/2.00	1.49/2.99	0.77/3.07	0.53/4.24
	VM/FF	0.21/10.3	15.0/256	4.48/0.56	7.04/1.76	4.34/2.17	5.44/5.44	4.25/8.50	4.25/17.0	4.28/32.2

Table 2. MICoggs and MPCs of antimicrobial agents alone and their MPCs in combinationsd. aMost data werepublished as an abstract of oral presentation at ISAAR&ICIC 201742, PRM: roxithromycin, DC: doxycycline,VM: vancomycin, FF: fosfomycin, OX: ofloxacin. MPCs of two antimicrobial agents in three combinations withseven different proportions.

Concentration Range	Regression Equation (Equation Number)	r	$r_{0.995}$ (179)	R^2
0.0312~1024 (μg/mL)	$y = 16.025x$ (7)	0.980 **	0.20	0.9622
	$y = 0.00006x^3 - 0.0710x^2 + 25.5154x$ (8)	0.9837 **		0.9677
	$y = 0.9351x + 1.2373$ [b] (9)	0.8414 **		0.7079
0.0414~1873 (μM/L)	$y = 18.743x$ (10)	0.9354 **		0.8750
	$y = 0.000004x^3 - 0.0142x^2 + 29.8848x$ (11)	0.9528 **		0.9079
	$y = 0.922x + 1.2588$ [b] (12)	0.8737 **		0.7633

[a]: r, correlation coefficient; $r_{0.995}$ (179) was the critical values when the significant levels α were set as 0.01; using r-test, the very significant difference ($P < 0.01$) was marked as **; R^2 was coefficient of determination. [b]: x and y were respectively taken from the natural logarithm ($\log_{10}$) of MIC and MPC for their more intuitive correlation.

Table 3. Regression equations between the MIC (x) and the corresponding MPC (y), of antimicrobialagents against pathogenic bacteria (n = 181) a.

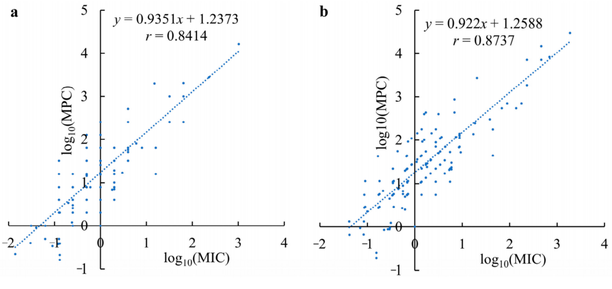

Figure 1. Correlations between the natural logarithm (log10) of MIC and that of MPC. (a), the concentration units of the MIC and MPC were μg/mL; (b), the concentration units of the MIC and MPC were μM/L.

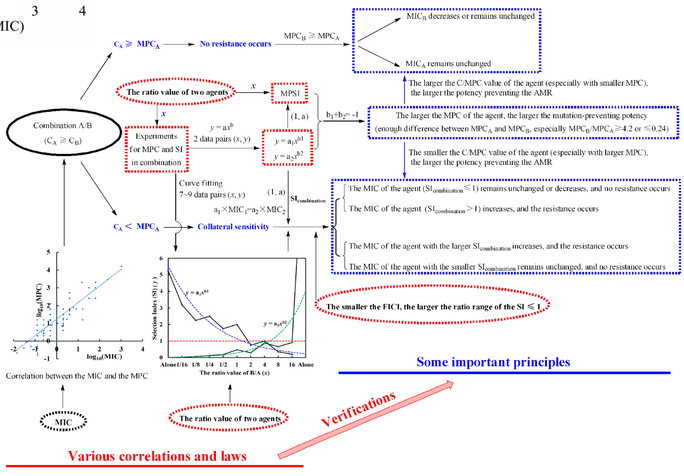

Figure 2. Diagram of the mutation-preventing effects and the resistant trajectories for drug combinations with different concentrations and ratios of two agents. Combination A/B consists of agents A and B, and CA and CB are the applied concentrations of agents A and B, respectively; MIC, mini - mal inhibitory concentration; MPC, mutant prevention concentration; FICI, fractional inhibitory concentration index; MPSI, mutation - preventing selection index; SIcombination, the SI in combination of two agents; setting CA larger than or equal to CB, and MPCB larger than or equal to MPCA.

Conclusion

A preliminary framework for antimicrobial combinations preventing AMR was proposed for subsequent improvement research and clinic popularization, and some similar conclusions were also speculated for triple or multiple drug combinations.

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