In vitro activity of fidaxomicin and other antibiotics against *Clostridium difficile* isolates from a university teaching hospital in China

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1. Introduction

1.1 CDI major clone.

Europe and North America: Ribotype 027
Asia including China: Ribotype 017
Ribotype 017 strains showed higher resistance rates against clindamycin, erythromycin, levofloxacin, rifampicin, rifaximin and tetracycline.

1.2 CDI therapy

Metronidazole and vancomycin are the mainstay options for CDI treatment.
Metronidazole and vancomycin are associated with treatment failure (affecting 3%~18% of patients) and disease recurrence (~30%).
There is no oral formulation of vancomycin for CDI treatment in China.

1.3 Limited studies

Fidaxomicin is a new macrocyclic bactericidal antibiotic against *C. difficile*.
Little is known about the in vitro activity of fidaxomicin against *C. difficile* isolates from China

2. Materials and methods

2.1 Bacterial isolates
101 toxigenic isolates from PUMCH

2.2 Toxin genes detection: tcdA, tcdB, cdtA, cdtB

2.3 Multilocus sequence typing (MLST)
adk, atpA, dxr, glyA, recA, sodA and tpi

2.4 Antimicrobial susceptibility testing
agar dilution method

3. Results

3.1 MICs of fidaxomicin, metronidazole, vancomycin, tigecycline, moxifloxacin

Toxin type (n)	Antimicrobial agent	MIC (mg/L) range	MIC_{50}	MIC_{90}	GM	R %
Overall total (101)	fidaxomicin	0.032-1	0.25	0.5	0.227	-
	metronidazole	0.125-1	0.25	0.5	0.345	0
	vancomycin	0.25-2	0.5	1	0.579	0
	tigecycline	0.016-0.5	0.032	0.064	0.041	0
	moxifloxacin	0.5-64	2	16	3.22	34.7
A+B+CDT- (51)	fidaxomicin	0.064-1	0.25	0.5	0.241	-
	metronidazole	0.125-0.5	0.5	0.5	0.346	0
	vancomycin	0.25-2	0.5	1	0.605	0
	tigecycline	0.016-0.5	0.032	0.064	0.041	0
	moxifloxacin	1-16	1	8	1.77	15.7
A-B+CDT- (20)	fidaxomicin	0.032-0.5	0.25	0.5	0.171	-
	metronidazole	0.125-1	0.25	1	0.354	0
	vancomycin	0.25-1	0.5	1	0.518	0
	tigecycline	0.032-0.064	0.032	0.064	0.042	0
	moxifloxacin	1-64	16	64	17.753	85.0
A-B-CDT- (24)	fidaxomicin	0.064-0.5	0.25	0.5	0.258	-
	metronidazole	0.125-0.5	0.25	0.5	0.324	0
	vancomycin	0.25-1	0.5	1	0.5	0
	tigecycline	0.032-0.5	0.032	0.157	0.043	0
	moxifloxacin	1-16	2	16	2.748	29.2

3.2 MICs results of 6 A+B+CDT+ *C. difficile* isolates

Strain No.	MIC (mg/L) fidaxomicin	metronidazole	vancomycin	tigecycline	moxifloxacin	MLST
40	0.25	1	2	0.016	32	1
301	1	1	1	0.032	16	1
235	1	1	2	0.032	16	1
2	0.125	0.125	0.5	0.032	1	5
5	0.25	0.125	0.5	0.032	1	5
196	0.064	0.125	0.5	0.032	2	5

3.3 Molecular characterization of the 28 moxifloxacin-resistant strains

Isolate	Toxin genotype	MLST	Moxifloxacin MIC (mg/L)	Amino acid substitution GyrA	GyrB
40	A+B+CDT+	1	32	Thr82→Ile	
235	A+B+CDT+	1	16	Thr82→Ile	
301	A+B+CDT+	1	16	Thr82→Ile	
119	A-B+CDT-	3	16	Thr82→Ile	
232	A-B+CDT-	3	8		Asp426→Asn
603	A-B+CDT-	3	16	Thr82→Ile	
604	A-B+CDT-	8	8		Asp426→Asn
608	A-B+CDT-	8	8	Thr82→Ile	
612	A-B+CDT-	8	8	Thr82→Ile	
211	A-B+CDT-	35	16	Thr82→Ile	
308	A-B+CDT-	35	16	Thr82→Ile	
8	A-B+CDT-	37	16	Thr82→Ile	
77	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
88	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
268	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
276	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
303	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
327	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
377	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
402	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
610	A-B+CDT-	37	16	Thr82→Ile	Ser366→Ala
4	A-B+CDT-	81	64	Thr82→Ile	Ser366→Ala, Asp426→Val
10	A-B+CDT-	81	64	Thr82→Ile	
83	A-B+CDT-	81	64	Thr82→Ile	Ser366→Ala, Asp426→Val
96	A-B+CDT-	81	64	Thr82→Ile	
103	A-B+CDT-	81	64	Thr82→Ile	Ser366→Ala, Asp426→Val
150	A-B+CDT-	81	64	Thr82→Ile	Ser366→Ala, Asp426→Val
218	A-B+CDT-	81	64	Thr82→Ile	Ser366→Ala, Asp426→Val

4. Conclusions

4.1 Fidaxomicin is fully active against all C. difficile isolates tested, which shows promise as a new drug for treating Chinese CDI patients.

4.2 The gyrA and gyrB mutations were the principal mechanism conferring fluoroquinolone resistance in *C. difficile* in the present study. All the moxifloxacin-resistant isolates carried a mutation either in gyrA or gyrB or both.

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