Susceptibility of *Clostridium difficile* to alternative agents

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Introduction

Clostridium difficile is a leading cause of nosocomial diarrhoea worldwide and is associated with high rates of morbidity and mortality. A 35-fold increase in the reported incidence of *C.difficile* Infection (CDI) in the United Kingdom over the last decade has been associated in part with the emergence of the highly virulent strain PCR-ribotype 027. Recommended empiric therapy for CDI is currently metronidazole or oral vancomycin but as rates of relapse and re-infection increase, new pharmacological approaches are needed.

Rifaximin is a semi-synthetic poorly absorbed rifamycin which reaches high levels in the gastro-intestinal tract after oral administration and is therefore pharmacologically attractive as a potential treatment of CDI. Successful treatment of CDI with rifaximin has been reported[3] and although not used extensively in the UK, is used more frequently elsewhere in Europe[1].

This study aimed to investigate the antimicrobial susceptibilities of *C.difficile* strains to some less commonly used agents.

Methods

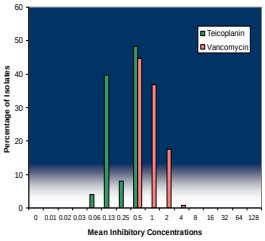
276 *C.difficile* isolates from 38 different ribotypes (of known susceptibility to vancomycin and metronidazole) submitted to the UK Anaerobe Reference Unit between 2001 and 2011 were tested. Susceptibility was assessed by agar dilution MIC by the CLSI method for rifaximin, rifampicin, fusidic acid and teicoplanin.

Ribo-type	Rifampicin		Rifaximin		Teicoplanin		Fusidic acid	
	Range	MIC 90	Range	MIC 90	Range	MIC90	Range	MIC90
001	<0.002 –32	<0.002	<0.002 – >32	0.008	0.06-0.5	0.25	0.06-2	1
027	<0.002 – >32	0.004	<0.002 – >32	0.008	0.125-0.5	0.25	0.125-1	1
078	<0.002 – 0.004	<0.002	<0.002 – 0.008	0.008	0.06-1	0.25	0.06-2	1
106	<0.002 – >32	<0.002	<0.002 – 0.008	0.008	0.06-1	0.5	0.03-2	2
Other	<0.002 – >32	<0.002	<0.002 – >32	0.008	0.06-1	0.25	0.03->128	1

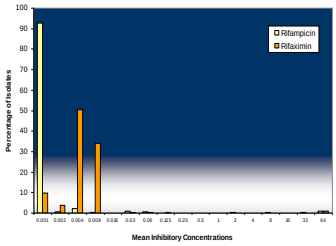
Table: range and MIC90 of C.difficile isolates from 2000-2011 by ribotype

Results

- Summary MIC data presented by ribotype are shown in the *table*. The "Other" category consisted of 110 isolates from 34 less common ribotypes.
- The great majority of isolates were susceptible to all of the agents tested, irrespective of ribotype or indeed year of isolation.
- The one isolate resistant to vancomycin (MIC 4 mg/L) remained sensitive to teicoplanin (MIC 0.25 mg/L).
- Isolates were 4-8 times more sensitive to teicoplanin than vancomycin (*graph 1*).
- Isolates were more sensitive to Rifampicin than Rifaximin (*graph 2*).
- Two isolates were resistant to both rifampicin and rifaximin (MIC 32mg/L);four isolates were resistant to rifampicin but remained sensitive to rifaximin; one isolate was intermediate to rifampicin (MIC 8mg/L) but resistant to rifaximin (MIC 64mg/L).
- Ribotypes with reduced susceptibility to rifampicin included 001 (1 of 49 tested (2%)), 027 (2 of 48 tested (4%)), and 012 (1 of 3 tested). The two isolates with reduced susceptibility to rifampicin but not rifaximin were ribotypes 012 and 027.



Graph 1: Population Density Chart Showing MICs of *C.difficile* Isolates to Teicoplanin and Vancomycin from 2000-2006



Graph 2: Population Density Chart Showing MICs of *C.difficile* Isolates to Rifampicin and Rifaximin from 2000-2011

Discussion

- A low overall resistance rate to rifampicin (1.8%) and rifaximin (1%) is reported which is lower than previously quoted rates of 2.7%-7.5%[1,4] .
- Discordance between rifampicin and rifaximin susceptibility has implications for the development of susceptibility testing in routine clinical laboratories.
- Of the common ribotypes tested here in significant numbers, 027 was more resistant to rifampicin (4%). This is much lower than previously quoted levels of rifampicin resistance in ribotype 027 (26%) in one institution which may have occurred due to clonal expansion in the context of a clinical outbreak[4].
- Further characterization of these discordant strains such as *rpoB* gene sequencing will be important in determining mechanism of resistance.

Conclusions

- Isolates of *C. difficile* from across the UK collected between 2000 and 2011 appear sensitive to rifampicin, rifaximin, teicoplanin, and fusidic acid.
- They may therefore be effective alternative agents in the treatment of severe CDI.
- Rifampicin susceptibility does not always correlate with rifaximin susceptibility.
- The mechanism of this differential susceptibility is yet to be determined.

References
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