Rapid Susceptibility Testing of Cefiderocol Directly From Positive Blood Cultures Using a MicroFluidic Agar-Diffusion Assay

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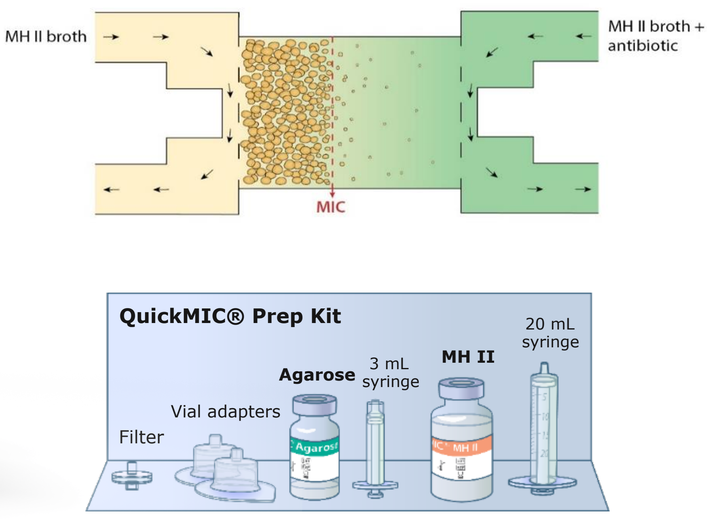
Introduction

The increasing prevalence of carbapenemase-producing Enterobacterales (CPE) has significant implications as treatment options are very limited for these strains. In recent years, a few new antibiotics active against CPE have been introduced, including the siderophore cephalosporin cefiderocol. Cefiderocol uses an iron-dependent drug delivery system, which poses challenges for AST. Iron-depleted CAMHB is recommended for BMD, while the Kirby-Bauer method should be performed using standard Mueller–Hinton agar. The QuickMIC rapid AST system uses microfluidic agarose diffusion analogous to the Kirby-Bauer method. This study aimed to evaluate whether the QuickMIC system can be used to rapidly provide MIC-values for cefiderocol from colony suspension or directly from positive blood culture.

Methods

22 genetically well-characterized CPE isolates (Fig. 2) were tested on QuickMIC from direct colony suspensions. Six strains were also tested from spiked blood cultures. A prototype cefiderocol-containing cassette was run in the QuickMIC system with standard CAMHB or with iron-depleted CAMHB and minimum inhibitory concentration (MIC) results were compared with reference BMD using iron-depleted CAMHB. We assessed the essential/categorical agreement for all strains and stratified by carbapenemase type.

The QuickMIC® system gives precise MIC values in 2-4 hours directly from positive blood cultures



Media: CAMHB vs. iron-depleted CAMHB

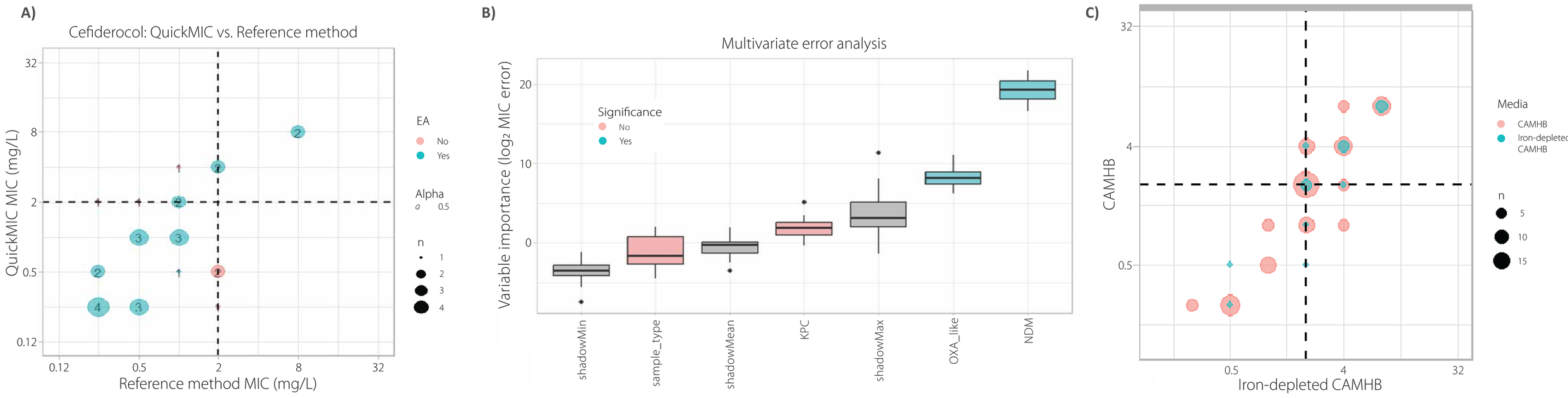


Figure 1 | a) Correlation between QuickMIC rapid AST using standard CAMHB, both from colony suspension and blood, with reference BMD using iron-depleted CAMHB. b) Multivariate variable importance analysis using the Boruta method. Blue variables are deemed statistically important compared to the best randomized predicting variable (shadowMax). Red variables are deemed statistically not important for the outcome variable (log2 MIC error), since they perform equal to or less than shadowMax – notably sample type. KPC, OXA-like and NDM groups include all subtypes. c) Correlation between MIC-values obtained from QuickMIC runs with or without iron-depleted CAMHB

Results

The QuickMIC prototype cassette yielded reportable MIC-values for all tests (n=28), with MIC results available on average in 3h27min. There was no difference in time-to-result between colony suspension and positive blood culture (avg. 3h26min vs. 3h30min, respectively). Overall essential and categorical agreement was 81.8/90.9%, respectively, varying depending on genetic context. The overall bias was low, at 12.8 (0.6/60 for colony/positive blood culture, respectively). Multivariate analysis indicated mainly blaNDM to be associated with poor agreement, with no significant difference based on sample type.

ESBL-CARBA enzyme	N	EA	CA
*bla*KPC-2, *bla*NDM-5	1	0.0	100.0
*bla*KPC-3, *bla*NDM-5	1	100.0	100.0
*bla*NDM-1	2	100.0	100.0
*bla*NDM-5	7	71.4	71.4
*bla*OXA-181	2	50.0	100.0
*bla*OXA-181, *bla*NDM-5	1	100.0	100.0
*bla*OXA-244	5	100.0	100.0
*bla*OXA-48	2	100.0	100.0
*bla*OXA-484	1	100.0	100.0
Overall	**22**	**81.8**	**90.9**

Figure 2 | Overview of cefiderocol essential and categorical agreement stratified by ESBL-CARBA enzyme and overall for the 22 strains.

Conclusions

- Cefiderocol AST may be feasible using the QuickMIC platform
- Results within ~3.5 h for carbapenemase-producing E.coli
- Iron-depleted culture media is indicated to not be necessary

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