Activity of cefiderocol (CFDC), ceftazidime-avibactam (CZA), and eravacycline (ERV) against carbapenem-resistant (CR) *E. coli* isolates from the US: Clonal Background, Resistance Genes, and Co-Resistance

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Background
Carbapenem resistance is emerging in *E. coli*, including its multidrug-resistant ST131-H398 carbapenemase (KPC)-producing isolates. Here, we tested agents against 403 U.S. clinical isolates, from surveillance systems encompassing multiple data across the U.S. and Minnesota (MN), in relation to phylogenetic origin and key resistance genes.

Methods
203 U.S. clinical *E. coli* isolates, confirmed as non-susceptible to 1 carbapenem (2012–2017; median year 2014), were obtained from MN laboratories (n=62; diverse U.S. locales; median year, 2013) and MN Dept. of Health (N=141; diverse counties; median, 2015), and 201 Surveillance isolates from 6 U.S. sites (60; diverse sites, median year, 2015-2017; median year, 2014), were obtained from JMI Laboratories (n=62; diverse U.S. locales; median year, 2013) and MN Department of Health (N=141; diverse counties; median, 2015). Sources divided evenly between urosepsis (50%) and "other" (50%), i.e., bowel (1%), respiratory (1%), abdominal (1%), and wound (8%).

Resistance
CFDC, CZA, and ERV were all highly active vs. ST131 and its clonal subgroups (100% susceptible).

Results
Among 203 molecularly characterized CR organisms. Accordingly, we tested these agents against CR *E. coli* clinical isolates, from surveillance systems encompassing multiple data across the U.S. and Minnesota (MN), in relation to phylogenetic origin and key resistance genes.

For CFDC, iron $\leq 0.06$ for 98% (P < 0.001) and $> 128$ for 12% (80% overall), with MICs ranging from 0.001 to 256 min. For TGC, iron $\leq 0.06$ for 98% (P < 0.001) and $> 128$ for 12% (80% overall), with MICs ranging from 0.001 to 256 min. For CZA, iron $\leq 0.06$ for 98% (P < 0.001) and $> 128$ for 12% (80% overall), with MICs ranging from 0.001 to 256 min. For ERV, iron $\leq 0.06$ for 98% (P < 0.001) and $> 128$ for 12% (80% overall), with MICs ranging from 0.001 to 256 min.

For CFDC, CZA, and ERV were highly active overall, more so than all other agents except TGC and CST.

Per carbapenem susceptibility (per FDA TGC breakpoints) for CFDC [69% (95% CI: 64%–74%)] and CZA [47% (95% CI: 43%–51%)] were significantly lower against NDM isolates (87%), exceeded only by CST (100%) and TGC (94%).

Conclusions
CFDC, CZA, and ERV were highly active overall, more so than all other agents except TGC and CST.

Per carbapenem susceptibility varied by phylogroup.

CFDC, CZA, and ERV percent susceptibility was 100% against ST131-H398 and H398c; percent susceptibility was lower against NDM vs. other resistance genotypes.

Implications
CFDC, CZA, and ERV are promising new treatment options in the U.S. for infections caused by CR *E. coli* – including several multidrug-resistant STs, notably ST131-H398 and H398c.

ERV was highly active against NDM isolates (87%), exceeded only by CST (100%) and TGC (94%).

References

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