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Are Vancomycin Non-Susceptible *Clostridioides difficile* Strains Emerging?

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To the Editor—We read with concern the report by Darkoh and colleagues describing vancomycin resistance in *Clostridioides difficile* isolates recovered from patients in Houston, Texas, and Nairobi, Kenya [1]. The authors suggested that vancomycin resistance, which they found to be common, may lead to therapeutic failure for patients infected with *C. difficile* and that routine antimicrobial susceptibility testing (AST) should be expanded. The authors report that 26% of *C. difficile* toxin gene-positive patients in Houston and 67% of sequential hospitalized patients in Nairobi with acute diarrhea had growth on primary screening media containing 4 μg/mL vancomycin. This alarmingly high proportion of a vancomycin resistant phenotype exceeds initial treatment failure rates reported in the literature [2], calling into question the reliability of these findings.

We noted several limitations to the investigators' laboratory methods. The incorporation of antibiotics in screening media is an established practice in certain cases to facilitate isolation and selection of an organism with well-defined resistance (eg, vancomycin-resistant enterococci) [3]. However, use of this method to define a previously uncharacterized form of resistance, as implemented by Darkoh et al, is concerning. Exposing *C. difficile* to low levels of vancomycin may artificially induce resistance [4]. Also, in contrast to the broth microdilution (BMD) and gradient diffusion strip AST methods performed by these investigators, the Clinical and Laboratory Standards institute (CLSI) recommends agar dilution as the reference AST method for *C. difficile* because BMD results were shown to be more variable than agar dilution [5]. When CLSI-recommended agar dilution AST has been performed on large contemporaneous sets of *C. difficile* isolates from North America, much lower proportions of isolates with a vancomycin minimum inhibitory concentration (MIC) ≥4 μg/mL were observed [6-8]. Among the 536 isolates, Darkoh et al. selected 10 of 194 isolates (MIC >4 μg/mL) for whole genome sequencing and submitted the data

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to National Center for Biotechnology Information (NCBI). Of the 9 isolates that passed NCBI's quality control metrics, the following sequence types (STs) were represented: 3 ST1, associated with ribotype (RT)027, 2 ST53, 1 ST8 (RT002), 1 ST34 (RT056), 1 ST42 (RT106), and 1 ST43 (RT054) [9]. Several of these ribotypes are commonly seen in US surveillance data without similarly high MICs when using reference agar dilution AST [7]. The lack of ST convergence with vancomycin phenotype in geographically disparate regions does not suggest clonal expansion as a basis for emergence of resistance.

Due to insufficient data correlating vancomycin MIC with clinical outcomes, CLSI doesn't publish a vancomycin breakpoint for *C. difficile* but instead provides an epidemiological cutoff value [10]. An association between MIC and outcome was found in an experimental mouse model of infection; however, the 50% mortality rate in mice infected with vancomycin-susceptible *C. difficile* and treated with vancomycin does not recapitulate experience treating human *C. difficile* infection [1,2]. Unfortunately, no details are provided by Darkoh et al. concerning the clinical course of patients. Until results from reference agar dilution AST, performed according to CLSI isolation and testing methods [5], are made available for these isolates, their findings should be interpreted with caution.

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