Clinical Infectious Diseases
CORRESPONDENCE

Can *Clostridium innocuum* Masquerade as *Clostridioides difficile?*

To the Editor—Darkoh et al [1] recently described high-level vancomycin resistance (≥32 μg/mL) in *Clostridioides difficile* isolates that were recovered from Houston, Texas, and Nairobi, Kenya. The authors concluded that *C. difficile* isolates with a reduced susceptibility to vancomycin are circulating within a broad population. They further concluded that the increasing presence of these isolates with reduced vancomycin susceptibility may result in therapeutic failures, thus calling for increased screening for *C. difficile* vancomycin resistance [1]. The authors report that 38% of the 536 stool samples acquired from patients with acute diarrhea had *C. difficile* growth on a screening medium containing 4-μg/mL vancomycin. These results are counter to previously reported vancomycin minimum inhibitory concentration (MIC) data from clinically relevant *C. difficile* isolates [2].

The investigators used a screening media that included vancomycin to select for isolates with an elevated vancomycin MIC (≥4 μg/mL) [1]. These methods have been well described for the selection of vancomycin-resistant enterococci, but there is a lack of evidence for identifying resistant *C. difficile* [3]. In addition, while Slanetz and Bartley medium was used to control for enterococcal contamination, there is no indication as to Darkoh et al controlled for additional vancomycin-resistant anaerobic organisms [1].

To replicate the findings in their report, and as part of an ongoing epidemiologic study, we cultured 10 stool specimens from patients that were positive for *C. difficile* by real-time polymerase chain reaction (PCR) to taurocholate-cefoxitin-cycloserine-fructose agar (TCCFA) and to TCCFA plus 4 μg/mL vancomycin (TCCFA-V). These stool specimens were collected from patients in the Chicago area between 1 September and 7 October 2022. All 10 specimens were positive for *C. difficile* using TCCFA, which was confirmed via matrix-assisted laser desorption/ionization (MALDI) or restriction endonuclease analysis. However, there was no growth of *C. difficile* using the TCCFA-V medium. Instead, we identified *Clostridium innocuum* from 4 of the 10 stool specimens, using the TCCFA-V medium confirmed with MALDI.

We subsequently determined the vancomycin MIC against *C. innocuum,* using the Clinical and Laboratory Standards Institute–recommended agar dilution method [4]. The vancomycin MIC against all 4 of these *C. innocuum* was ≥32 μg/mL. *C. innocuum* is an emerging stool pathogen that has been associated with diarrheal illnesses and is intrinsically resistant to vancomycin owing to the chromosomal genes *racemase* and $ddl_{C.\ innocuum}$ [5, 6]. In addition, the phenotypic appearance of *C. innocuum* is similar to that of *C. difficile* on a blood agar plate, which could lead to misidentification (Figure 1).

Our results confirm previous findings that stool specimens can be coinfected by *C. difficile* and *C. innocuum* [7]. While Darkoh et al reported that PCR was performed to confirm the identification of *C. difficile*, it is unclear whether the isolates that underwent PCR were retrieved from the vancomycin screening plates or the standard *C. difficile* culture medium used [1]. While *C. difficile* isolates with moderately elevated MICs (4–8 μg/mL) have been reported, particularly in the epidemic BI/027/NAP1/ST1 strain, there are no corroborated data to suggest high-level resistance (eg, MICs ≥32 μg/mL) [8]. We caution against the use of unvalidated screening methods and bring to attention to the possibility of misidentifying other vancomycin-resistant organisms, such as *C. innocuum*.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the US Department of Veteran Affairs.

Financial support. This work was supported by the National Center for Advancing Translational Sciences, National Institutes of Health (grant 5KL2TR002387-05; support to A. M. S. and the Institute for Translational

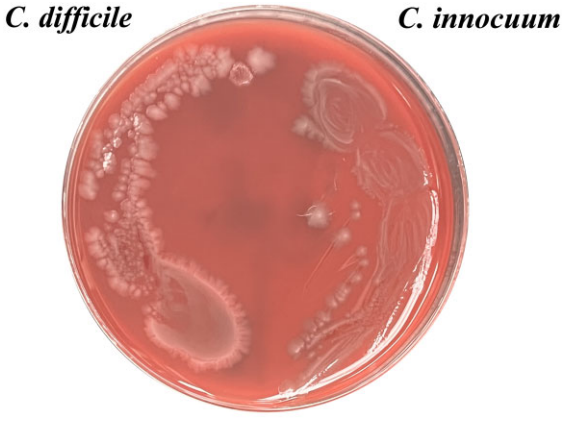

Figure 1. Culture of *Clostridioides difficile* (*left*) and *Clostridium innocuum* (*right*) on blood agar plate.

Published online 17 May 2022

Medicine) and the US Department of Veterans Affairs Research Service (support to S. J.).

Potential conflicts of interest. A. M. S. reports payment or honoraria for CME activity for *C difficile* from the Academy for Continued Healthcare Learning. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Andrew M. Skinner,[1,2] Laurica Petrella,[1] Stacey Spandoni,[1] Fidel Serna-Perez,[1] and Stuart Johnson[1,2]

[1]Department of Research and Medicine, Edward Hines Jr Veterans Administration Hospital, Hines, Illinois, USA; and [2]Loyola University Medical Center, Department of Medicine, Maywood, Illinois, USA

References

1. Darkoh C, Keita K, Odo C, et al. Emergence of clinical *Clostridioides difficile* isolates with decreased susceptibility to vancomycin. Clin Infect Dis **2022**; 74: 120–6.
2. Snydman DR, McDermott LA, Thorpe CM, et al. Antimicrobial susceptibility and ribotypes of *Clostridium difficile* isolates from a phase 2 clinical trial of ridinilazole (SMT19969) and vancomycin. J Antimicrob Chemother **2018**; 73: 2078–84.
3. Suwantarat N, Roberts A, Prestridge J, et al. Comparison of five chromogenic media for recovery of vancomycin-resistant enterococci from fecal samples. J Clin Microbiol **2014**; 52: 4039–42.
4. Clinical and Laboratory Standards Institute. Methods for antimicrobial susceptibility testing of anaerobic bacteria. Approved standard—ninth edition. Wayne, PA: Clinical and Laboratory Standards Institute, **2018**.
5. Chia JH, Wu TS, Wu TL, et al. *Clostridium innocuum* is a vancomycin-resistant pathogen that may cause antibiotic-associated diarrhoea. Clin Microbiol Infect **2018**; 24:1195–9.
6. Cherny KE, Ozer EA, Kochan TJ, Kociolek LK. Complete genome sequence of *Clostridium innocuum* strain ATCC 14501. Microbiol Resour Announc **2020**; 9:e00452-20.
7. Cherny KE, Balaji A, Mukherjee J, et al. Identification of *Clostridium innocuum* hypothetical protein that is cross-reactive with *C. difficile* anti-toxin antibodies. Anaerobe **2022**; 102555. doi:10.1016/j.anaerobe.2022.102555.
8. Thorpe CM, McDermott LA, Tran MK, et al. U.S.-based national surveillance for fidaxomicin susceptibility of *Clostridioides difficile*-associated diarrheal isolates from 2013 to 2016. Antimicrob Agents Chemother **2019**; 63: e00391-19.

Correspondence: A. M. Skinner, Loyola University Medical Center, 2160 S First Ave, Maywood, IL 60153 (Andrew.Skinner@lumc.edu).

Clinical Infectious Diseases® 2022;75(7):1268–9

https://doi.org/10.1093/cid/ciac377

Cost-Effective Treatment of *Clostridiodes difficile* Infection

To the Editor—From a cost-effectiveness point of view, Rajasingham et al conclude that the preferred regimen for treatment of *Clostridiodes difficile* infection (CDI) is fidaxomicin for nonsevere CDI, vancomycin for severe CDI, fidaxomicin for first recurrences, and fecal microbiota transplant for subsequent recurrences [1]. This is based on the premise that individuals and payers are willing to pay $31 751 dollars per quality-adjusted life-year (QALY), the incremental cost of this regimen over using metronidazole for nonsevere CDI and vancomycin for severe CDI and for all recurrences.

The methodology of this study appears to be sound. However, the authors assume that any intervention that costs less than $100 000 per QALY is cost-effective. They do not provide an explanation for this cutoff, which is at the upper end of the amounts typically chosen for such analyses [2]. When the cost per QALY that individuals and payers would be willing to pay was first derived in the early 1990s, there were limited ultraexpensive drugs and technologies. The number of ultraexpensive drugs and technologies that clinicians can recommend is rapidly increasing. If we choose to adopt any that meet this broad definition of "cost-effective," there will be limited incentive for manufacturers to decrease prices and the cost of healthcare will increase beyond what even the wealthiest of nations can afford.

Note

Potential conflicts of interest. J. L. R. reports data safety board payment from Westat. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Joan L. Robinson

Department of Paediatrics, University of Alberta, Edmonton, Alberta, Canada

References

1. Rajasingham R, Enns EA, Khoruts A, Vaughn BP. Cost-effectiveness of treatment regimens for *Clostridioides difficile* infection: an evaluation of the 2018 Infectious Diseases Society of America guidelines. Clin Infect Dis **2020**; 70:754–62.
2. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoecon Outcomes Res **2008**; 8: 165–78.

Correspondence: J. L. Robinson, 3-556 ECHA, 11405-87 Ave NW, Edmonton AB Canada T6G 1C9 (jr3@ualberta.ca).

Clinical Infectious Diseases® 2022;75(7):1269

https://doi.org/10.1093/cid/ciac369

A Review of Infectious Diseases Guidelines' Incorporation of Economic Evidence

To the Editor—The cost of diagnostics and treatment can significantly impact access and quality of care. As healthcare costs continue to rise in the United States, economic evaluation and cost-effectiveness studies can guide societal decisions about adopting clinical innovations. Clinical guidelines panels have the opportunity to incorporate economic evidence into guideline recommendations. The recent update to the *Clostridioides difficile* infection (CDI) guidelines, which recommended fidaxomicin as first line, and to consider bezlotoxumab for cases of recurrent CDI, elicited concern that economic considerations were not sufficiently incorporated into decision making [1]. Our objective was to identify how infectious diseases guidelines incorporate economic evidence or cost considerations when providing recommendations.

We reviewed all available (N = 29) Infectious Diseases Society of America (IDSA) guidelines for incorporation of economic factors, including "cost," "economic," "price," "insurance," and "dollars." All studies mentioned cost at least once, but fewer incorporated it into recommendations, and fewer still had explicit methodological statements about how economic evidence was incorporated into panel decision making (Figure 1). Qualitative review of guideline text revealed that the panels would cite the cost of certain therapies, but not others, as a consideration, but rarely cited formal cost-effectiveness studies.

Guidelines that included statements in methods sections indicated that guidelines panels may consider cost as a factor, but rarely made explicit how this factor was weighted and when it was applied. Notable exceptions were the hepatitis C virus treatment guidelines, which included a dedicated economic section, and the tuberculosis and nontubercular mycobacterial guidelines, which included an evaluation rubric that included costs and resource utilization [2–4].

While economic factors are rightfully never the primary consideration for guidelines panels, these findings suggest opportunities for more consistently and systematically incorporating economic evidence into infectious diseases guidelines. For conditions in which resource constraints are likely to be major considerations for the field, guidelines documents can follow the example of the hepatitis C guidance and include a dedicated section. For most conditions, guidelines panels should follow an explicit methodology for appraising economic evidence and incorporating value into recommendations. Both the American Society of Clinical Oncology and the American College of Cardiology/American Heart Association have published frameworks to guide the consistent review, appraisal, and incorporation of economic evidence [5, 6].