Reply to McDonald

TO THE EDITOR—We thank Dr McDonald for his interest in our work and concur that the role of particular ribotypes in the clinical outcome of Clostridium difficile infection (CDI) is complex [1]. Our study identified several factors that predicted severe CDI in unadjusted analysis, including ribotype 027/078 (Table 2 in our article) [2]. We agree that including intermediate white blood cell (WBC) counts in our final model (Table 4 in our article) may have potentially attenuated direct effects of ribotype on outcome. In Table 3 of our article, we show, however, that adjustment for any of the significant predictors rendered ribotype 027/078 effect on CDI severity nonsignificant [2], indicating that WBC count was not required for the conclusions drawn in our study.

To directly address the possibility that WBC count was influenced by ribotype-specific host responses requires temporal patient data, including treatment, which we did not collect. To indirectly address this issue, we performed additional analyses for our combined dataset (N = 412 cases with complete data) in the following 4 contexts:

1. We added abnormal WBC count (<4000 or >12,000 cells/mL) to the definition of severe CDI.
2. We determined whether ribotype 027/078 predicted an abnormal WBC count.
3. We excluded both WBC count and albumin levels from the analysis, as is appropriate if they are potentially confounded.
4. We again added abnormal WBC to the severe CDI definition and excluded albumin level from the analysis.

Ribotype 027/078 was not significant in any of these contexts (adjusted analyses). Although these results do not exclude the possibility raised by McDonald, they do add support to our original conclusion that predictors other than ribotype may be more important in explaining the variability of CDI severity. We did not explore the influence of treatment on outcome, so the influence of ribotype was either not strong enough to overcome these effects or they were relatively minor.

Why the incidence and severity of CDI increased in the early 2000s remains unclear. However, epidemic spread of clonal pathogens need not result from advantageous phenotypes (toxin production, sporulation, antibiotic resistance, etc). Such population expansions may result simply by chance, as transmission rates overcome clonal interference. Temporal fluctuations in ribotype prevalence support a “drift” scenario [3]. Such fluctuations suggest that many ribotypes reach a high local prevalence, which would increase transmission and potentiate a high global
prevalence. This phenomenon does not necessitate strong selection, although increased antibiotic resistance suggests that strong selective pressure from fluoroquinolones and other antimicrobials has been important [4, 5].

As noted by McDonald, the prevalences of both 027 CDI cases and severe outcome are declining in apparent synchrony. However, both declines have occurred in light of heightened surveillance, improved diagnostics, more effective/aggressive infection control practices and therapies, and the popularization of antimicrobial stewardship. Correlations among these shifting practices, ribotype prevalence, and clinical outcome are understudied and require more data from properly designed studies that recognize the potential role of chance (null hypothesis). As 027 prevalence wanes in Europe [6], it appears that the C. difficile population is changing back to a more even distribution. These are exciting times in C. difficile epidemiology, but the complexity of ribotype-specific influences on disease progression and/or severity remains mottled.

Notes

Financial support. This work was supported by the National Institutes of Health (U19 AI090871 to V. B. Y. and D. M. A.).

Potential conflicts of interest. All authors: No reported 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.

Seth T. Walk,1,2 Dejan Micic,1 Andrzej T. Galecki,1,3,4 Mary A. M. Rogers,1 Laraine Washer,1,5 Duane W. Newton,6,7 Preeti N. Malani,1,2,9 Vincent B. Young,1,2,8 and David M. Aronoff1,2,8

1Department of Internal Medicine, 2Division of Infectious Diseases, 3Division of Geriatric Medicine, 4Department of Biostatistics, 5Department of Infection Control and Epidemiology, 6Clinical Microbiology Laboratories, 7Department of Pathology, and 8Department of Microbiology, University of Michigan Health System, and 9Veterans Affairs Ann Arbor Healthcare System, Geriatric Research Education and Clinical Center, Ann Arbor, Michigan

References


Correspondence: David Aronoff, MD, Department of Internal Medicine, Division of Infectious Diseases, University of Michigan Health System, 5510-E MSRB I, 1150 W Medical Center Dr, Ann Arbor, MI 48109-5680 (daronoff@umich.edu).

Clinical Infectious Diseases 2013;56(6):907–8 © The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cis1003