Understanding Increased Mortality in *Clostridium difficile*–Infected Older Adults

To the Editor—

> As people get older, they have more things wrong with them. And the more things they have wrong with them, the more likely they are to die. —Katalin Koller and Kenneth Rockwood [1]

We read with great interest the study by Walker et al examining the impact of *Clostridium difficile* infection (CDI) on 14-day attributable mortality [2]. The authors drew conclusions about *C. difficile* genotype-specific mortality, noting higher attributable mortality for clades 2 (ribotype 027) and 5 (ribotype 078) [2]. Although the statistical methods appear to be adequate, the presentation of the results adopted by the investigators does not fully support their conclusions.

The authors report unadjusted and adjusted *P* values (Table 1 [2]) for the factor "type of test," indicating that the 7 levels (EIA [enzyme immunoassay]–positive, culture-negative; EIA-positive, not cultured; clade 1, etc) had significantly different hazard ratios for mortality compared to the reference (EIA-negative) [2]. The authors concluded that mortality was significantly different between clades (worse for clades 2 [ribotype 027] and 5 [ribotype 078]), but the *P* values pertained to level-wise comparisons to the EIA-negative cases and not between-clade comparisons. Similarly, the *P* values shown in Walker et al's Figure 3 represented differences compared to EIA-negative cases (ie, 1.00) and not between clades [2]. Thus, it is unclear whether any significant between-clade differences exist after adjustment for host factors. We agree that CDI, regardless of *C. difficile* clade, resulted in increased mortality compared to patients with non-CDI diarrhea. However, determining

clade-wise differences requires head-to-head comparisons (clade 1 vs clade 2, etc), which were not conducted.

Although not compared statistically, Figure 1*C* suggests that any increased mortality among clade 2 cases versus clades 1 or 3 was limited to patients ≥75 years old [2]. Frailty and comorbidities pose significant risks for death in older adults [1, 3]. Therefore, efforts to quantify clade-specific effects on mortality need to control for these factors. It is notable that data in the authors' Figure 4 revealed lower serum sodium levels among clade 2 [2]. Because hyponatremia is associated with a number of chronic diseases [4] and is independently associated with mortality [5, 6], this lab abnormality might have been an indicator of comorbidity imbalance among clade 2–infected patients.

Studies relating pathogen genotype with clinical outcome are challenging when different genetic lineages infect distinct patient populations [7]. Although clade 2 strains are more prevalent in older adults and older adults are more likely to die from CDI, it remains unproven whether these 2 observations are causally related. Strain typing remains an important tool for epidemiology, but the role of such methods in guiding treatment remains absent [8]. Future studies that attribute significant differences in patient mortality to different *C. difficile* genotypes should adjust for patient age and underlying comorbidities, and should identify a genotype-specific virulence factor. Whole genome sequencing may help unmask currently unknown microbial determinants of disease severity that can be leveraged to improve CDI prevention and therapy.

Notes

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Seth T. Walk,[1] Dejan Micic,[2] Andrzej T. Galecki,[2,4,5] Vincent B. Young,[2,3,6] and David M. Aronoff[2,3,6]

[1]Department of Microbiology, Montana State University, Bozeman; and [2]Department of Internal Medicine, [3]Division of Infectious Diseases, [4]Division of Geriatric Medicine, [5]Department of Biostatistics, and [6]Department of Microbiology, University of Michigan Health System, Ann Arbor

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

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