Virulence and Clinical Outcomes in Clostridium difficile Infection: A Complex Business

To the Editor—The epidemiology of Clostridium difficile infection (CDI) and role of particular strain types in clinical outcome is complex. Walk et al conclude that the polymerase chain reaction (PCR) ribotypes 027 and 078 are not independent predictors of severe outcome when adjusted by the patient’s leukocyte count and albumin level [1]. Although the albumin level more clearly reflects underlying host status, a leukocyte count measured within 72 hours of CDI diagnosis reflects both underlying host status and any strain-specific host response to infection that may exist. Adjustment for an intermediate such as leukocytosis does not necessarily estimate a direct effect, in this case between strain type and outcome; unmeasured confounders in the relationship between leukocytosis and outcome may lead to the direct effect between strain type and outcome being obscured [2]. An important potential confounder in the relationship between leukocytosis (and therefore strain type) and outcome that was not included in the study by Walk et al is the treatment that patients received. Given recent guidelines [3], it is likely treatment decisions were influenced by the finding of leukocytosis; more intensive treatment would hopefully attenuate the association between leukocytosis and outcome and thereby obscure any direct effect of strain type on outcome. Contrary to both the discussion by Walk et al and the accompanying editorial by Barbut and Rupnik [4], there is compelling, albeit inconsistent, epidemiologic evidence for 027 being more virulent than many other strains, at least from a public health, if not clinical, standpoint. The emergence of 027 as a cause of epidemic and endemic CDI has been temporally associated in multiple regions with apparent increases in disease burden and severity [5, 6]; declines in these outcomes have also been temporally associated with decline in the prevalence of 027 [7]. In a large national survey adjusted by age but not by treatment or other host factors, more severe outcomes were associated with 027 [8]. Compared with other strains, PCR ribotype 027 has a higher infection-to-colonization ratio [9], and, most recently, this strain has been associated with a poorer response to therapy and higher recurrence rate—an effect observed across treatment types and despite lack of demonstrable resistance in vitro [10]. Nonetheless, no association between 027 and more severe clinical outcome has been identified in the several studies highlighted by both Walk et al [1] and
Barbut and Rupnik [4]. Some of this inconsistency may reflect small sample sizes and the multiple confounders present; however, as pointed out by Barbut and Rupnik, additional consideration should be given to interactions between strain type and environmental factors, including predisposing antibiotic and other medication use (eg, proton pump inhibitor). Where we can currently most agree is that 027 and 078 strain status does not add to host leukocyte count and serum albumin level in predicting clinical outcomes among patients treated for CDI in the study hospital. Further studies that control for the therapy received will be necessary to extend this conclusion to other patient populations.

Notes

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