Building a Better Crystal Ball for Predicting Complications of *Clostridium difficile* Infection

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(See the Major Article by Abou Chakra et al on pages 1781–8.)

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Clostridium difficile infections (CDIs) quickly reemerged at the turn of the century to become one of the major nosocomial infections in North America. The history of this epidemic has been well documented [1] and was associated with the dissemination of two very closely related, fluoroquinolone-resistant strains of *C. difficile* described by various typing methods as North American pulse field gel electrophoresis type 1, restriction endonuclease assay type BI, or polymerase chain reaction ribotype 027 (hereafter referred to as the 027 strains) [2, 3]. Along with an increased incidence, CDI caused by the epidemic 027 strains has been more severe than that associated with many other ribotypes, and these isolates appear to be more virulent in vitro and in animal models [1, 4, 5]. This feature of more severe and complicated CDI associated with 027 isolates has garnered significant interest, both in terms of research and clinical care.

An explosion of new diagnostic, preventive, and therapeutic strategies has accompanied the global reemergence of CDI. Diagnostic modalities have evolved over a short period of time, moving from the labor intensive practices of stool culture and cell culture–based toxin detection to faster and cheaper enzyme immunoassay–based toxin assays and onward to more sensitive nucleic acid amplification testing [6]. Controversy persists around the optimal diagnostic strategy [7, 8]. Efforts at infection control and prevention have resulted in myriad new approaches for removing spores from healthcare environments, using probiotics, and searching for an effective vaccine [9, 10]. As for treatments, we have moved away from the one-size-fits-all approach of oral metronidazole to a host of available oral agents such as vancomycin and fidaxomicin, and many investigational agents are in the clinical trials pipeline [11]. What is more, the use of immunological agents, probiotics, and fecal microbiome transplant has expanded therapeutic options well beyond traditional antimicrobial approaches [11].

Current guidelines suggest that therapies for CDI should be tailored for each patient based on the severity of colitis, in hopes of preventing complications such as admission to an intensive care unit (ICU), colon surgery, or death [12, 13]. Thus, with the flurry of therapeutic interventions at hand, healthcare providers require evidence-based guidelines and simple clinical decision support tools to apply these practices in the right circumstances. Given the high cost of providing care for those with CDI [14], in the modern era of value-based healthcare delivery (maximizing quality per unit cost), such guidelines and tools are imperative. A central question in CDI management, for which evidence-based guidance would be useful, is, "What factors predict a complicated course of CDI in my patient?" In general, predictors of "standard" complications from CDI (eg, death, ICU admission, or the need for surgery) have included old age, vital sign derangements, renal insufficiency, hypoalbuminemia, leukopenia or leukocytosis, and the presence of 027 strains [15–18]. However, differences in study design and outcomes studied have made firm conclusions difficult, and there remains doubt and confusion about the best clinical prediction rules for treating CDI and (hopefully) preventing complications [15].

Prospective studies of CDI are now helping to refine clinical prediction rules for CDI. As an example, a recently published prospective study of nearly 400 acute CDI patients derived (and externally validated in pilot fashion) a prediction rule incorporating age, admission due to diarrhea, diagnosis within the ICU, recent abdominal surgery, and hypotension as

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independent predictors of a complications such as death, ICU admission, and/or colectomy [16]. However, the impact of strain type was not assessed. In this issue of *Clinical Infectious Diseases*, Abou Chakra and colleagues present the results of a much larger (1380 patients), multicenter, prospective study designed to identify predictors of complicated CDI that might be used for deriving an accurate clinical prediction rule [19]. A strength of their study was the inclusion of not only patient-level data available to most clinicians but also strain-level data about the infecting ribotype of *C. difficile* [19]. These investigators report that complications of CDI are best predicted by older age (≥80 years), vital sign derangements (tachycardia, tachypnea), and laboratory abnormalities (leukocytosis/leukopenia, elevated urea nitrogen, and high C-reactive protein). Despite the higher frequency of complications among patients infected with 027 strains, ribotype was not one of the stronger predictors of adverse outcomes in a multivariable analysis [19]. This was somewhat surprising, given that during the study period (2005–2008), 52.4% of all cases were associated with 027 strains [19]. However, Rao et al similarly reported that infection by 027 strains was significantly associated with complicated disease but was not as strong a predictor as host-level data [20].

What appears to be coming into focus for CDI is that host features are the strongest predictors of adverse outcomes, and robust clinical prediction rules should be built accordingly. The challenge now is to show prospectively that any decision rule improves patient care and avoids overuse of limited healthcare resources (ie, enhances value). It is likely that data from the Abou Chakra et al study will be incorporated into such decision support tools, or they will help refine existing models [19]. The need to rule in or rule out the *C. difficile* 027 ribotype remains uncertain, particularly as non-027 strains with increased virulence emerge [21]. Moving forward, studies that prospectively validate clinical prediction rules should consider addressing the question of what additional benefit occurs based upon knowing the strain ribotype, if such data are available.

Risk assessment for the individual patient is likely to be improved as we expand our understanding of genetic determinants of virulence in *C. difficile* and develop the capacity to analyze large amounts of data that incorporate both patient-level clinical information and bacterial whole-genome sequencing (WGS) data matures. Studies of WGS in *C. difficile* are already providing useful information about virulence [21]. An added benefit of WGS is the capacity to assess antimicrobial resistance potential [22].

Along with the rise in antimicrobial-resistant pathogens, infections caused by *C. difficile* are a major nosocomial threat to health in developed nations. Community-onset disease is also a growing concern [23]. Prevention is the answer: prevention of both the onset and the complications of CDI. Given the high cost of care and evidence that treatment should be individualized, the need for robust clinical decision support tools is greater than ever. The study by Abou Chakra and colleagues [19] is likely to impact the development and validation of prediction rules that improve the value-based delivery of CDI care.

Notes

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