COMMENTARY

# *Clostridium difficile*: The More We Learn, the Less We Know

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(See the article by Kamboj et al[18] on pages 8–15.)

*Clostridium difficile* has become known as a pathogen responsible for a considerable number of avoidable healthcare-acquired infections. Acquisition is traditionally thought to involve the ingestion of spores from the contaminated healthcare environment by patients whose normal bowel flora is altered by antibiotics.[1] While the majority of these patients remain asymptomatic, some develop diarrhea, further contaminating the environment and serving as a source of ongoing transmission.[1,2] Clabots et al[3] demonstrated that the rate of *C. difficile* acquisition is linearly correlated with length of hospital stay, lending further support to the role of the hospital environment as an important reservoir of *C. difficile*. Thus, prevention efforts have relied largely on measures aimed toward reducing the risk of environmental spread within the healthcare setting such as contact precautions and environmental disinfection, as well as antimicrobial stewardship.[4]

For many years, *C. difficile* was generally regarded as an inconvenient but readily treatable cause of antibiotic-associated diarrhea. In 2003, however, this organism was afforded new respect with the recognition of the North American Pulsed Field type 1 (NAP1)/PCR ribotype 027 strain.[5] This strain became epidemic in several countries and was associated with dramatic increases in healthcare-acquired infection, morbidity, mortality, and metronidazole treatment failures compared with previously described with *C. difficile*.[6–9] Public inquiries attributed patient deaths during these epidemics to deficiencies in nursing and medical care, infection control practices, administrative responsiveness, and resource allocation.[10,11] Media reports of these outbreaks used harsh and litigious language, describing the pathogen as deadly, healthcare providers as villains, and patients as victims.[12] These reports were followed by demands for transparency around *C. difficile* infection in hospitals.[13]

In the wake of these events, *C. difficile* has become synonymous in the public perception with dirty hospitals, poor management, and noncompliant healthcare providers. Outbreaks have led to successful litigation against healthcare organizations, and criminal charges have been considered in at least one instance.[14] The threat of sanctions and loss of financial reimbursement for patients who develop *C. difficile* infection during their hospital stay has led to a heightened focus by healthcare administrators on unit-level healthcare-onset *C. difficile* infection (HO-CDI) rates and accountability. One study found that public reporting was associated with a substantial reduction HO-CDI rates and attributed this reduction to quality improvement efforts by individual healthcare organizations.[15] Consumer groups are now using HO-CDI data to rate hospital performance.[16,17]

In this issue of *Infection Control and Hospital Epidemiology*, an article by Kamboj et al[18] serves as a caution against using HO-CDI rates as a healthcare system performance measure. Using multilocus sequence typing (MSLT), the authors characterized toxigenic strains of *C. difficile* from the stools of a large cohort of patients admitted to a stem-cell transplant unit. In this high-risk patient population, 26% of patients were found to be colonized with a toxigenic strain of *C. difficile* at the time of admission; 75% of these colonized patients later developed *C. difficile* infection with an identical strain to the one they were carrying at the time of admission. Considerable diversity was observed among *C. difficile* isolates in this population, suggesting multiple potential sources of acquisition. The HO-CDI rate, as defined by standard surveillance definitions, was very high on the study unit (3.6 per 1,000 patient days). Conversely, this study found microbiologic evidence of nosocomial acquisition in only 21% of cases, and only half of those had an epidemiologic link to an earlier patient with identical strain type. Thus, healthcare acquisition could be established in only a very small proportion of cases. The authors conclude that most cases of *C. difficile* infection in this inpatient population represent development of disease in asymptomatic carriers rather than transmission within the inpatient setting.

This is not the first study to call into question the belief that *C. difficile* infection is largely acquired through environmental reservoirs within the healthcare setting. Eyre et al[19] used whole-genome sequencing of isolates from a large cohort of inpatients with *C. difficile* infection to demonstrate that only 35% of patients were genetically related to an earlier case of *C. difficile* infection. Furthermore, in nearly half of these genetically related cases (46%), there was no epidemiologic evidence of hospital transmission. These authors also identified a diversity of strains suggesting multiple sources of transmission. A large population-based study in the United

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States estimated that only 24% of all *C. difficile* infections are acquired during hospital admission, while the rest may be linked to outpatient healthcare settings or community acquisition.[20] It has been postulated that food, animals, and healthy infants could serve as community reservoirs for this pathogen,[21,22] though epidemiologic studies have failed to confirm any of these as important sources of infection in humans.[23] While we lack full knowledge of the reservoirs of *C. difficile*, there is growing evidence that colonization in the community can lead to the subsequent development of *C. difficile* infection in the setting of antibiotic use, proton pump inhibitor use, or hospital admission.[18,24–26]

The current study by Kamboj et al[18] along with the earlier study by Eyre et al[19] demonstrate that current surveillance definitions and laboratory methods are too crude to accurately attribute *C. difficile* acquisition to a particular healthcare setting or inpatient unit. Failure to take into account the carrier state and to determine genetic relatedness of *C. difficile* strains leads to false attribution of *C. difficile* based on epidemiologic data alone. This poses a dilemma for healthcare epidemiologists who find themselves wielding blunt instruments with which to measure the effectiveness of their infection control programs, identify outbreaks, and evaluate control efforts. Furthermore, traditional *C. difficile* infection prevention methods focused on contact precautions, environmental disinfection, reduction of overcrowding, and hand hygiene may have limited impact on HO-CDI rates in the absence of an epidemic strain. There is further concern that the gains made in strengthening infection control, environmental cleaning, and hand hygiene programs in the wake of the NAP1 strain may be lost as healthcare decision makers begin to understand the implications of these findings.

Patients deserve high-quality healthcare and transparency around healthcare-acquired infections. Nonetheless, increasing evidence indicates that the relationship between HO-CDI rates (as currently measured), and the effectiveness of interventions in the healthcare setting is not as straightforward as it seemed in the past. Much more work is needed to understand the evolving epidemiology of *C. difficile* and to determine which interventions will have the greatest population-wide impact on *C. difficile*-related morbidity and mortality. In the meantime, healthcare epidemiologists have a responsibility to help administrators, governments, and the public understand that traditional definitions and detection methods will almost certainly overestimate the burden of HO-CDI and that the use of HO-CDI rates to measure the performance of healthcare organizations has important limitations.

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