Reducing the Incidence of *Clostridium Difficile* Infections: Can We Do It?

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Although *Clostridium difficile* infections (CDI) have long been recognized as the cause of antibiotic-associated diarrhea and colitis,[1] fulminant presentations with septic shock, toxic megacolon, and the need for emergent colectomies were rare until the hypervirulent NAP1/BI/027 strain[5] emerged at the center of several outbreaks of unprecedented severity in 2004-2005.[2-4]

Since then, *Clostridium difficile* (*C.difficile)* has become endemic in the US, Canada, and Europe, causing significant morbidity, mortality, and cost. The 30-day CDI mortality in a study of 12 Canadian hospitals was 6.9%,[4] whereas the attributable mortality one year after the initial CDI was as high as 16.7% in Quebec.[6] The average CDI-related hospital cost in Massachusetts was $10,212 in 2000. Patients who developed CDI in the hospital had their average stay prolonged by 2.95 days, and their hospital charges increased by a mean of $13,675.[7]

CDI have also contributed to re-hospitalization. A study of care transitions in Rhode Island shows that 2.6% of sampled Medicare patients discharged from the hospital during July 2008- June 2009 were readmitted within 30 days with a CDI diagnosis. The great majority of these readmissions occurred among patients of advanced age, with 46.5% of patients age 85 and over (unpublished data).

These data highlight an important, if uncomfortable, truth: *C.difficile*, a pathogen once difficult to isolate in the microbiology lab, has become even more difficult to eradicate from the healthcare setting. Why are CDI so persistent, and what can be done to reduce their rates?

Infection Control Challenges

CDI present several unique challenges for infection control:

1. Persistence of environmental *C. difficile* spores.

Spores can survive in the environment for months to years,[8] and alcohol-containing disinfecting products will not kill the spores.[9] Therefore, effective environmental cleaning, especially when *C. difficile* is hyperendemic, is notoriously difficult. Moreover, epidemic *C. difficile* strains seem to be hyper-sporulating, compared to non-epidemic strains.[10] Nosocomial CDI transmission originating from a contaminated environment or from improperly cleaned medical equipment (such as rectal thermometers or bedpans) has been repeatedly demonstrated.[11,12]

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2. Asymptomatic carriers – a persistent reservoir of infection and potential transmission.

Although many patients develop typical clinical manifestations when they are infected with *C. difficile*, potentially more patients who acquire this pathogen remain asymptomatic. For example, according to a cohort study conducted over 11 months in a medicine ward, 63% of the 83 patients who became colonized with *C. difficile* during their hospital stay remained asymptomatic.[8] These asymptomatic patients served as the source of *C. difficile* transmission to their hospital roommates, who later developed symptomatic CDI with identical molecular strains. This study also evidenced substantial *C. difficile* transmission from asymptomatic carriers to their immediate hospital room environment, as well as to the hands of their healthcare workers.[8] Similar findings were reported in a study of **long-term care (LTC)** residents, where *C. difficile* spores from the skin of asymptomatic carriers were easily transferred to investigators' hands.[13] Since most hospitals do not screen for asymptomatic *C. difficile* carriage, and contact precautions are instituted only for symptomatic patients with CDI, colonized patients remain an unidentified reservoir of ongoing nosocomial transmission.

3. Lack of specific infection control policies in other healthcare settings, with potential for increasing CDI influx into the hospital and/or the community.

Since CDI affect primarily elderly people, and the majority of the patients hospitalized today are older and sicker than in the past,[14] more and more patients are discharged to acute rehabilitation centers and nursing homes after a CDI diagnosis.[15] Many of these patients still harbor *C. difficile* and may develop symptomatic CDI shortly after arrival. A study of nosocomial *C. difficile* acquisition found that 82% of the patients infected with *C. difficile* during their hospital stay still had positive cultures at discharge, and the majority of these patients were discharged to a LTC facility.[8] While most hospitals have relatively stringent infection control policies related to CDI and other hospital-acquired pathogens, equivalent infection control policies may not be feasible outside the hospital, and may not always exist in LTC facilities. In fact, in a recent study of CDI-related infection control policies and practices among 418 LTC facilities in Iowa, the majority (77.5%) of facilities did not test for CDI unless residents had severe diarrhea; less than half (42%) of the facilities had a specialized protocol to identify residents with CDI; and more than a third (41.5%) of the facilities did not place residents in private rooms once CDI symptoms occurred.[16] The potential for further *C. difficile* dissemination within the LTC facility setting and back into

the hospital can be significant. *C. difficile* dissemination into patients' homes and into the community after discharge from healthcare institutions is possible and deserves further study.

4. Difficulties in diagnosing CDI, leading to delays in the institution of contact precautions, and increased potential for nosocomial transmission.

a) *Insensitive diagnostic modalities.* The low-sensitivity of the **enzyme immunoassays (EIA)** routinely used for toxin detection in most hospitals and clinical laboratories can delay CDI diagnosis. While these tests are technically easy, produce results within hours, and are inexpensive, the proportion of false negative results can reach 10-20%,[17] requiring repeated samples. More sensitive diagnostic modalities for toxin detection, such as cell cytotoxicity assays or PCR, are more expensive, and not widely available in the clinical setting.

b) *Atypical presentations in patients with cognitive decline.* CDI is easily suspected in patients who report typical diarrheal symptoms after exposure to antimicrobials and/or contact with the healthcare setting. However, the diagnosis may remain more elusive in elderly patients with cognitive impairment, who are unable to verbalize their symptoms, and are often brought to the hospital due to increased confusion, fever, and/or leukocytosis. An abnormal urine analysis may prompt empiric antibiotics for a presumed urinary tract infection. CDI is later suspected when diarrheal symptoms become evident after admission, but the delay in diagnosis and the initial lapse in contact precautions can increase the amount of exposure and nosocomial transmission to other vulnerable patients.

c) *CDI in patients without typical risk factors for this disease.* Patients who present from the community without the traditional risk factors associated with CDI represent another group in whom the diagnosis may not be initially suspected. For example, recent reports of CDI among healthy peripartum women,[18] or among otherwise healthy patients without recent healthcare contact,[18] underscore the importance of considering this diagnosis even in populations previously thought to be at low risk for CDI.

5. Propensity for multiple recurrences, despite adequate treatment.

Recurrent CDI occurs in up to 25% of patients.[17] Recently, there have been reports of even more frequent CDI recurrences, affecting at least 50% of the elderly patients treated with metronidazole both in Canada,[19] as well as in Texas.[20] Recurrences after therapy with vancomycin have also been reported.[21] The pathophysiology of multiple relapsing CDI is not fully understood. Some authors attribute it to the persistence of *C. difficile* spores within the colon that may have escaped adequate antibiotic pressure during therapy.[22] The host immune responses to CDI are likely important as well. For example, asymptomatic carriers and patients who only experience a single, brief CDI episode have higher levels of antitoxin antibodies, compared to patients who develop recurrent CDI.[23] Exposure to antibiotics during or after CDI treatment seems to be a major risk factor in triggering CDI recurrences.[24]

6. Unmodifiable risk factors.

The majority of the risk factors associated with CDI reflect the fragile health of many patients hospitalized. Advanced age, a bedridden state, immunodeficiency (including chemotherapy-associated), multi-morbidity, gastrointestinal surgery,[17] and tube feeding[25] are not easily modifiable, increasing vulnerability to infection. Additional risk factors, such as frequent and multiple antibiotic exposures, prolonged hospitalizations, and perhaps the use of proton pump inhibitors[26] may be modifiable in part. Although all antibiotics (including metronidazole) have been associated with CDI, the recent epidemic appears to have been driven by the overuse of fluoroquinolones, as evidenced by higher level of fluoroquinolone resistance among recent *C. difficile* isolates.[2]

Potential Solutions

Infection control efforts aim to provide practical solutions to some of the challenges listed above, as follows:

1. Environmental *C. difficile* cleaning. The 2010 IDSA and SHEA CDI guidelines recommend the use of bleach-containing cleaning products for environments where *C. difficile* is endemic since these products appear reliably sporicidal compared with other disinfectants.[21]

2. Asymptomatic carriage. Efforts to reduce asymptomatic *C. difficile* carriage have been disappointing. A randomized placebo-control trial found no difference in *C. difficile* carriage rates among patients treated with metronidazole versus those treated with placebo.[27] Although patients treated with oral vancomycin were more likely to clear *C. difficile* initially, the majority became re-colonized by day 70 of follow-up.[27] Therefore, no guidelines support the treatment of asymptomatic carriers, or screening for asymptomatic carriage at hospital admission.

3. Early CDI diagnosis. Maintaining a high index of suspicion in patients with recent hospitalizations and antibiotic exposure could avoid unnecessary morbidity and nosocomial transmission. Teaching patients and their caregivers at the time of hospital discharge how to recognize and report early CDI symptoms may avoid further clinical deterioration and reduce re-hospitalization rates.[28] Empiric CDI treatment and contact precautions should be instituted early. In cases where there is a strong suspicion for CDI, clinicians should not be deterred by a negative toxin-detection EIA test, given the suboptimal sensitivity of this assay. Further diagnostic confirmation can be sought using more sensitive diagnostic modalities, if clinically available. Sometimes, resolution of symptoms after empiric CDI treatment provides evidence in support of the suspected diagnosis.

4. CDI-related infection control policies in other healthcare settings. Enacting feasible policies in LTC facility and short-stay rehabilitation centers is especially important, given the increased transit of patients with CDI diagnosis and/or CDI risk factors between different facilities and the community.

5. Management of multiply relapsing CDI. Treating patients with recurrent infections remains frustrating, although the recently tested human monoclonal antibodies to *C. difficile* toxins as well as *C. difficile* vaccines in development[29] hold promise.[30] Until newer therapies such as

these or others enter the market, the treatment will largely remain focused on prolonged tapers and/or pulsed regimens of oral vancomycin. Patients with CDI who require ongoing or frequent antibiotic administration for concurrent infections are at risk for CDI recurrences.[21] In these instances, we have found it clinically useful to extend the duration of oral vancomycin treatment beyond the cessation of all other antimicrobials, particularly when non-modifiable host risk factors for CDI were also present. The effectiveness of probiotics as an adjunctive CDI therapy in preventing further CDI recurrences remains limited.[21]

6. Judicious use of antibiotics. Antibiotic exposure is perhaps the most important modifiable risk factor that can reduce the incidence of CDI. Antibiotic stewardship programs that encourage clinicians to minimize the number, frequency, and duration of antimicrobial use can reduce CDI rates in institutions where *C. difficile* is endemic or epidemic.[31] The approach is likely to be particularly successful when it complements infection control measures aimed at decreasing horizontal *C. difficile* transmission.

7. Hand hygiene. Correct hand washing technique is, arguably, the most effective, yet simplest method of reducing horizontal *C. difficile* transmission within healthcare institutions, and its value in preventing infections has been repeatedly proven.[32] Paradoxically, the compliance among healthcare workers is disconcertingly low. At this time, it is unclear whether complete eradication of *C. difficile* from the healthcare environment will ever be achievable. It is, however, clear that achieving 100% compliance with hand-hygiene is 100% within our control. It is, in fact, "in our hands."

Conclusions

We can reduce the incidence of *C. difficile* infections in the healthcare setting. Increasing our compliance with basic infection control policies, instituting specific measures aimed at eradicating environmental spores, and promptly initiating *C. difficile* treatment as soon as symptoms develop can greatly decrease the *C. difficile* burden in the healthcare environment. Increasing our communication between different healthcare settings and providers during transitions of care, and teaching patients and caregivers to recognize and report relapsing *C. difficile* early can reduce the burden of readmissions due to this pathogen.

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The authors and/or significant others have no financial interests to disclose.

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