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Looking to the Future: Vertical vs. Horizontal Prevention of *Clostridium difficile* Infections

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Multidrug-resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, carbapenem-resistant *Enterobacteriaceae*, and *Clostridium difficile* all share certain epidemiologic characteristics: transmission via direct and indirect contact, colonization preceding infection by days to months, and a greater number of asymptomatically colonized than infected patients. For each of these MDROs, colonized patients may serve as an important source for healthcare transmission. Active surveillance (AS) to identify colonized patients has been used to prevent the transmission of MDROs by focusing isolation and/or decolonization efforts. In the case of *C. difficile* infection (CDI), AS has not been attempted largely because there has not been a feasible method for detecting colonized patients and the role of colonized patients in overall transmission has not been well defined. In this issue, Curry et al. cast additional light on the role of asymptomatic colonization in *C. difficile* transmission leading to hospital-associated CDI (HA-CDI: defined as hospital-onset cases plus community-onset within 12 weeks of previous discharge and no intervening hospital stay).[1, 2]

First, an important incidental finding was that among 114 AS cultures performed on patients 8 or more days before their first positive toxin assay (when they were symptomatic), 10 cultures from 7 patients were positive for isolates highly related to the isolate recovered later from the patient's first toxin-positive stool. Previous studies suggest incubation periods less than 3–7 days and the prevailing disease model is one that sustained asymptomatic colonization paradoxically reduces patient's risk for subsequent CDI through boosting of serum antibodies to toxins A and B.[3–6] Although intriguing, this finding by Curry et al. does not necessarily challenge that model nor is it sufficient to provoke revision in current surveillance definitions.[2] The total number of patients in whom the prior cultures were performed was not reported; however, assuming a similar ratio of cultures to patients (i.e. 10:7) for all 114, less than 10% of evaluable CDI patients had incubation periods over 7 days--possibly representing the 'trailing off' of a skewed normal distribution of incubation periods with a median less than 3 days and a somewhat larger mean.

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The main conclusion of the report by Curry et al., namely that at least 29% of HA-CDI results from transmission from asymptomatic carriers, is sensitive to several important factors. First, the study setting was a tertiary hospital with a seasoned infection control program focused on containing transmission from CDI patients. An average rate of 5.6 HA-CDI cases/10,000 patient days (2006–12) supports the assertion of an effective program at interrupting transmission from CDI cases,[7] especially given the hospital's tertiary care status with intensive antibiotic exposures. Hospitals with less effective infection control would have a higher proportion of all cases resulting from transmission from CDI patients.

A recent study in England found only about 25% of CDI cases result from ward-based transmission from a prior CDI patient.[8] However, that result was limited by the use of a toxin A and B enzyme immunoassay (EIA) as the diagnostic assay. Although the cell cytotoxin neutralization assay used by Curry et al. is more sensitive than an EIA, it is still less sensitive than a nucleic acid amplification test (NAAT). Because of its increased sensitivity, it is likely that use of a NAAT for diagnosis would result in a higher proportion of CDIs linked to previous NAAT-defined CDIs.

In contrast, more extensive and comprehensive AS testing would increase the proportion of CDIs traced to previously colonized patients. Use of swabs collected for vancomycin-resistant enterococcus screening was an efficient use of resources by Curry et al. but only 24.9% of all admissions during the 117-day study period were screened for asymptomatic carriage.[1] Had a larger proportion of all inpatients, including those with more CDI-directed risk factors (e.g. patients >65 y.o. readmitted from home or nursing home after a recent inpatient stay in which antibiotics were administered) been subjected to AS, a larger number of colonized patients would have been identified and likely a larger proportion of all CDIs would have been linked back to colonized patients.

Even where 29% or more of new HA-CDI cases are confirmed to be the result of transmission from colonized patients, there are several hurdles to overcome before AS can be used in CDI prevention. First is the need to rapidly detect colonization. Although Curry et al. previously demonstrated accurate detection of colonization through use of a broth amplification culture followed by commercial NAAT, the pre-amplification incubation could last as long as 72 hours, calling into question the utility of the approach.[9] While existing commercial diagnostics could be refined or new ones developed to improve the rapid, sensitive detection of nearly all colonized patients, currently available NAATs may serve a useful purpose even without broth pre-amplification. For example, currently available NAATs alone may reliably detect a subset of colonized patients with higher organism loads who are more contagious as reflected by skin and environmental contamination.

Once colonized patients are identified, special precautions will be needed to reduce transmission from these patients to other susceptible patients. In the case of other MDROs this has most commonly entailed isolating colonized patients using Contact Precautions. However, criticism has been leveled at AS partly for this reason.[10] It may be more cost effective to apply broad, 'horizontal' approaches to prevent all MDROs and healthcare-associated infections, such as improved hand hygiene for all patients, over a more

burdensome ‘vertical’ approach such AS-directed isolation of all specific MDRO-colonized patients.

However, because of its uniqueness as a spore-forming cause of healthcare-associated infection, AS-directed special precautions may have particular relevance for *C. difficile* compared to other MDROs. For example, enhanced cleaning with a *C. difficile* sporicidal disinfectant and the use of gloves for patient care are more efficacious than standard methods at reducing environmental and hand contamination, respectively.[11–13] Thus one approach would be to perform enhanced environmental cleaning, possibly along with the use of gloves for all patient care, for patients colonized with *C. difficile*.

It also appears that limiting colonized patient movement, or at least employing enhanced precautions and cleaning when a colonized patient does need to go to non-ward locations, may be another key strategy. Whether linked to a prior colonized or infected patient, transmission frequently occurs across different ward locations.[1, 8] Although some of this may reflect carriage of *C. difficile* spores from ward to ward by either contaminated hands of healthcare personnel or contaminated reusable medical equipment, cross transmission may be occurring frequently, especially from those asymptotically colonized, in non-ward locations (e.g. emergency departments, physical therapy, or diagnostic imaging).

Even if its spore-forming status strengthens the case for using a vertical approach of AS-focused precautions to reduce *C. difficile* transmission, there are several special horizontal approaches to consider. One possible approach on particular ward locations with high rates of colonization and infection is universal gloving along with enhanced cleaning and environmental disinfection. Perhaps in the future, improved hand hygiene and environmental disinfection products can be developed that better remove or deactivate spores and yet can be used more broadly. Regardless, another important horizontal approach, the importance of which cannot be overstated, is antibiotic stewardship. Because reducing unnecessary antibiotic exposures decreases the risk of colonization and infection by a number of MDROs, especially CDI, a highly effective stewardship intervention could easily overshadow the impact of further reducing *C. difficile* transmission through AS-focused measures.[14] A third possible horizontal approach with rapidly broadening evidence base in the prevention of CDI is the use of probiotics in patients receiving antibiotics.[15, 16] However, thus far there is not a similar level of evidence for probiotics preventing colonization or infection from MDROs other than *C. difficile*.

Regardless of what becomes the future role for vertical vs. horizontal measures to reduce CDI, Curry et al. have done a good job highlighting the importance of better understanding the epidemiology of *C. difficile* colonization and infection in healthcare settings.

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