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Uncovering the Role of Antibiotics in the Transmission of Multidrug-resistant Organisms

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Conventional wisdom has suggested two distinct categories of epidemiologic risk factors in the development of *Clostridium difficile* infection (CDI): factors that increase the risk of transmission of *C. difficile* and factors that disrupt the patient's lower intestinal microbiota, a major host defense against infection. This host defense function may be best understood in terms of the expression of these microorganisms collective and representative genome, known as the microbiome. Although antibiotics appear to be the major disruptive force of the microbiome in hospitalized patients, there is evidence that other medications such as proton pump inhibitors and antidepressants, as well as chronic conditions such as obesity[1], may also be associated with microbiome disruption and/or CDI. In addition to increasing the risk for infection, the microbiome disruption from antibiotics may also increase *C. difficile* transmission via increased likelihood of asymptomatic colonization and, once colonized, increasing clonal expansion and domination of the microbiota by *C. difficile*. Meanwhile, there is increasing evidence pointing to the importance of asymptomatic carriers in the transmission of *C. difficile* in hospitals. However, few studies have examined the epidemiology of antibiotics effecting transmission of *C. difficile* between patients, something Brown et al have addressed in this issue of JAMA Int Med.[2]

This study examined an individual acute care hospital cohort over 4 years, capturing both individual level risk factors such as age, gender, previous admission, and inpatient medication exposures including but not limited to antibiotic exposures. In addition, average characteristics of the ward or unit population over the 46-month study period were recorded including mean age and antibiotic, chemotherapeutic, and antacid medications in days of therapy (DOT)/100 patient-days, as well as mean feeding tube use. Other ward and unit-level risk factors included patient density and hand hygiene compliance. Multivariable models and, most importantly, a multilevel model, were constructed in which patient factors and ward factors were examined together in regard to their increasing risk of CDI.

The major finding was that each 10% increase in overall ward or unit antibiotic exposure was independently associated with a 34% increase in CDI. Other previously described patient risk factors found to be associated with individual CDI risk in the multilevel model

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included age and antibiotic, chemotherapy, and feeding tube exposures in the preceding 7 days.

The main finding of this study shows how antibiotics, by impacting the microbiomes of a subset of patients across a population (here patients on wards or units of a hospital), puts the entire population, including those who do not receive antibiotics, at increased risk via increased transmission. The converse is also true, if unnecessary antibiotic use is decreased through improved stewardship it will lead to a proportionate decrease in CDI. This same indirect effect of disrupting the microbiome of neighboring patients, rendering them more at risk for asymptomatic colonization and, once colonized, at increased risk for transmission, may be an important role for antibiotics in the epidemiology of a number of other multidrug-resistant organisms including carbapenem-resistant enteeobacteriaceae and vancomycin-resistant enterococci.

Given the importance of understanding how antibiotics can increase the risk of transmission and thereby potentially impact the health of neighboring patients, future studies should focus on improving our understanding through two main improvements in study design. One is to adjust for colonization pressure defined as the proportion of patients already colonized or infected with *C. difficile* at the time of admission to the ward or unit. Although ideally this would be accomplished by active surveillance testing on admission, this is a practice not currently recommended in the control of CDI. However, it appears likely, though not proven, that the rate of CDI with onset in the first 48 hours of admission correlates with asymptomatic colonization rates across inpatient settings; such prevalence of CDI on admission is an important factor for risk adjusting rates of hospital-onset CDI.[3] Thus prevalence of CDI on admission should be included in future studies to account for potential differences in the prevalence of asymptomatic colonization. For example, a low prevalence of colonization on admission may explain the outlier status of the burn unit in the study by Brown et al. where, despite high rates of antibiotic use there were low rates of CDI.[2] Not only were these patients younger, they were also more likely admitted from the community without previous antibiotic or healthcare exposures, all factors that would be expected to result in a lower rate of asymptomatic colonization on admission. In contrast to the larger effect size found by Brown et al., a recent estimate in which both direct and indirect antibiotic effects were modeled, along with hospital CDI rates to control for colonization pressue, suggested a 30% decline in high-risk antibiotics would result in only a 26% decline in hospital-onset CDI.[4]

Another important area for consideration is the ward and unit population effects of different risk antibiotics. Although antibiotic exposures in the study by Brown et al. were stratified as low, medium, and high risk in the evaluation of individual patient risks, it is not clear that they were considered separately in this way in the ward and unit-based analysis.[2] Because there were only 16 wards and units and 255 new-onset cases of CDI in the study, such additional stratification may not have produced meaningful results. However, certain drugs such as broad-spectrum penicillins, while having a marked impact on the human lower intestinal microbiome, have intrinsic activity against *C. difficile*, leading to the suppression of the organism while the patient is receiving the agent.[5] Experience from England suggests there was a major national decline in CDI temporally related to a marked shift in inpatient

antibiotic prescribing away from cephalosporins and floroquinolones in favor of greater use of broad-spectrum penicillins, with no change in overall use.[6] Meanwhile there was a decline in the proportion of all cases caused by the hypervirulent, fluoroquinoline-resistant PCR ribotype 027 strain.[7] Thus future studies based upon the foundational work of Brown et al should be larger, multi-centered studies that account for CDI or colonization prevalence on admission, the virulence of major strains and their acquired resistance, and the differential effects of different antibiotic classes.

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