Clostridium difficile — Beyond the Usual Suspects
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One of the central concepts guiding efforts to prevent Clostridium difficile infection has been that symptomatic patients in hospitals are the major source of transmission. Infected patients with diarrhea shed large numbers of spores, contaminating their skin, clothing, and surrounding surfaces. The basic measures that are used to prevent transmission include placement of infected patients under contact precautions until diarrhea resolves and the disinfection of surfaces and equipment with sporicidal products such as sodium hypochlorite.

Unfortunately, these measures have often proved to be ineffective during the past decade, when infection rates have risen dramatically in association with large outbreaks of the 027/BI/NAP1 strain of C. difficile. Control of outbreaks has frequently required sequential implementation of multiple control measures, including antimicrobial interventions. Even when outbreaks subside, many hospitals continue to struggle with high endemic infection rates.

The difficulty in controlling C. difficile has raised several important questions about traditional models of transmission. First, are we missing important sources of transmission? For example, asymptomatic carriers of toxin-producing strains of C. difficile outnumber infected patients, but their role in transmission has been uncertain. Curry et al. recently examined C. difficile transmission in a hospital with well-thought-out practices for the prevention of transmission from symptomatic patients. On the basis of molecular typing, incident infections were as frequently linked to asymptomatic carriers as to symptomatic patients (30% and 29%, respectively). Second, are we missing novel routes of dissemination not addressed by current control strategies? It has been proposed, for example, that airborne dispersal of spores could contribute to transmission.

Finally, are we underestimating the proportion of cases acquired outside the hospital? No hospital is an island: increasingly, patients enter and leave hospitals colonized or infected with C. difficile. In the United States, as many as 75% of infections have their onset in long-term care facilities or the community. The administration of antimicrobial agents during a previous hospitalization is a predisposing factor in many of these cases, because antimicrobial-induced alteration of the intestinal microbiota increases susceptibility to infection for several weeks. However, the time from the acquisition of colonization to the onset of C. difficile–associated illness is short, which suggests that C. difficile is frequently acquired outside the hospital, even in cases occurring after a recent hospitalization. In addition to long-term care and outpatient health care settings, other potential reservoirs outside the hospital include colonized infants, food, and animals.

In this issue of the Journal, Eyre et al. present the results of an impressive 3.6-year study in which they used whole-genome sequencing, a highly discriminatory typing method, to study the epidemiology of C. difficile infection in Oxfordshire, United Kingdom. Of 1223 isolates sequenced, 71% were obtained from inpatients, 25% from outpatients, and 4% from patients at other hospitals. Only 35% of isolates obtained from patients with C. difficile infection were genetically linked. Moreover, only 38% and 54% of genetically linked cases shared ward-based and hospital-wide contacts, respectively. Remarkably, 45% of isolates were genetically distinct from all others, suggesting diverse sources of acquisition.

The results of this study challenge the tradition...
tional concept that symptomatic patients in hospitals account for most \textit{C. difficile} transmission and infection. However, there are some caveats. First, the findings may not apply to all settings. The study was conducted in a nonoutbreak setting in hospitals with well-established measures to limit transmission from symptomatic patients (e.g., isolation of patients with suspected \textit{C. difficile} infection, daily hypochlorite disinfection, and monitoring of compliance). In similar settings, other investigators have found that nosocomial transmission from symptomatic patients may account for a minority of cases.\textsuperscript{5,9,10} In contrast, epidemic strains with a propensity to disseminate often predominate during outbreaks.\textsuperscript{2} Second, many patients with symptomatic infection may have been missed by the relatively insensitive testing method used. Third, the study does not present evidence contradicting the prevailing concept that most hospital-onset infections occurring 3 or more days after admission are acquired in the hospital.\textsuperscript{1,4} Obtaining cultures to determine whether colonization is present on admission or acquired during hospitalization will be required to make this determination. If strains are hospital-acquired, potential reservoirs other than identified patients with symptomatic infection might include undetected symptomatic cases, asymptomatic carriers, and environmental contamination. Finally, although community sources such as food and animals must be considered, given the diversity of strains that were identified, the study by Eyre et al. does not address long-term care facilities, a major potential reservoir for \textit{C. difficile}.\textsuperscript{5}

What are the practical implications of this study for health care systems struggling to control \textit{C. difficile}? The findings will not alter recommendations that basic control measures are essential. Ineffrquent transmission from symptomatic patients in the study hospitals may in fact attest to the effectiveness of well-implemented control programs. The major implication of the study is that control of \textit{C. difficile} will require that we move beyond the usual suspects (symptomatic patients in hospitals). Although additional work is needed to identify sources of acquisition, Eyre et al. have shown the potential for highly discriminatory typing methods to transform our understanding of the transmission of \textit{C. difficile} and other health care–associated pathogens.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1310454

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**Dabigatran and Mechanical Heart Valves — Not as Easy as We Hoped**

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Warfarin is the mainstay of anticoagulation for patients with mechanical heart valves. However, warfarin has well-known limitations, including interactions with food and drugs and the requirement for lifelong monitoring of the international normalized ratio (INR).\textsuperscript{1} Variability of the INR is the strongest independent predictor of reduced survival after mechanical valve re-