Recent outbreaks of *Clostridium difficile* infection have been attributed to the emergence of an epidemic strain characterized as North American pulsed-field gel electrophoresis type 1 (NAP1) or restriction endonuclease assay group BI (1,2). Fluoroquinolone resistance is a hallmark of epidemic *C. difficile* isolates (1), and fluoroquinolone use has been associated with *C. difficile* infection (2–9). Because the C-8 methoxy fluoroquinolones gatifloxacin and moxifloxacin have enhanced anaerobic activity, they might promote *C. difficile* infection to a greater degree than ciprofloxacin and levofloxacin (10). In 3 studies, substitution of gatifloxacin or moxifloxacin for levofloxacin was associated with an increase in *C. difficile* infection (6,8,9); in 2 of the 3 studies, a formulary change back to levofloxacin was associated with reduced *C. difficile* infection (6,9). However, ciprofloxacin and levofloxacin also have been associated with *C. difficile* infection (2–5,7).

Beginning in 2002, outbreaks of *C. difficile* infection occurred in several hospitals in the Cleveland, Ohio, USA, area. In response, the Ohio Department of Health (ODH) made *C. difficile* infection a reportable disease in 2006. One objective of the current study was to examine the magnitude of the outbreaks in Cuyahoga County, which comprises Cleveland and the surrounding area, and to determine whether the outbreaks were associated with epidemic BI/NAP1 strains. A second objective was to examine whether use of gatifloxacin and/or moxifloxacin was associated with increased rates of *C. difficile* infection in healthcare facilities and to assess whether outbreaks correlated with formulary changes in fluoroquinolones.

The Study

We used the ODH website (www.odh.state.oh.us) to obtain rates (cases/10,000 patient-days) of initial *C. difficile* infections during January–December 2006 for the 22 hospitals in Cuyahoga County. All healthcare facilities in Ohio were required to submit *C. difficile* infection rates by using a standardized method of reporting. An initial case was defined as a first positive laboratory diagnostic test for *C. difficile*, pseudomembranes on endoscopy, or confirmatory histologic features from surgical or autopsy specimen. An infection that occurred >6 months after a previous infection was classified as an initial infection.

For a subset of 5 hospitals, up to 20 consecutive stool samples from individual patients with *C. difficile* infection were cultured for *C. difficile* (11). *C. difficile* isolates were tested for in vitro cytotoxicity production and moxifloxacin susceptibility and analyzed for binary toxin gene cdtB and partial deletions of the tcdC gene (11–13). Molecular typing was performed by using PCR ribotyping (11). The 5 hospitals were 1 community hospital, 3 tertiary care facilities, and 1 Veterans Affairs hospital. Three of the hospitals had experienced large outbreaks of *C. difficile* infection in 2002–2003 (i.e., their *C. difficile* incidence doubled and their peak incidence was >20 cases per 1,000 discharges); the other 2 reported an increase in the proportion of cases that were fulminant. The infection control departments of each institution provided information about *C. difficile* infection rates, fluoroquinolones on formulary, and infection control measures for *C. difficile* during January 2000–December 2006.

Rates of *C. difficile* infection for 2006 were compared among hospitals with moxifloxacin or gatifloxacin versus those with levofloxacin on formulary as primarily fluoroquinolones used to treat respiratory infections. In addition, for 2 hospitals in the molecular typing analysis that had a formulary change from 1 respiratory fluoroquinolone to another, we used Poisson analysis to compare rates of *C. difficile* infection during the 12 months before and after the formulary change, with a lag of 1 month after the change. We analyzed data using SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA) and STATA 9.1 (StataCorp, College Station, TX, USA).
For the 18 adult acute-care hospitals and 4 long-term acute-care (LTAC) facilities in Cuyahoga County, the median C. difficile infection rate in 2006 was 7.3 (range 4.2–63.1 cases/10,000 patient-days). The highest rates were observed in 2 LTAC facilities. Six facilities (3 acute-care hospitals and 3 LTACs) had higher C. difficile infection rates than did each of the 5 hospitals in the molecular typing analysis.

A total of 64 toxigenic C. difficile isolates were cultured from feces samples obtained from 5 hospitals. Features of 42 (66%) isolates were consistent with epidemic BI/NAP1 strains (range 55%–83% for each facility), including ampicillin (66%) isolates were consistent with epidemic BI/NAP1 from feces samples obtained from 5 hospitals. Features of the epidemic strain; 6 isolates with this banding pattern were confirmed as BI strains in the laboratory of D.G.

Of the 22 facilities, 8 used moxifloxacin as the primary respiratory fluoroquinolone, 13 used levofloxacin, and 1 did not have a respiratory fluoroquinolone on formulary. The C. difficile infection rate did not differ between facilities with levofloxacin (8.5 cases/10,000 patient-days, 95% confidence interval [CI] 7.8–9.3) and moxifloxacin (8.5 cases/10,000 patient-days, 95% CI 7.8–9.2) on formulary (p = 1) (Table). The facility that did not have a respiratory fluoroquinolone on formulary had a lower rate of C. difficile infection than the median rates for facilities that used levofloxacin or moxifloxacin. However, 8 facilities had lower C. difficile infection rates than did this institution.

Two of the 5 hospitals in the molecular typing analysis changed their formulary fluoroquinolones during the study period (Figure). Both hospitals made formulary changes from levofloxacin to gatifloxacin; however, the increase in C. difficile infection rates preceded the formulary change in each hospital. C. difficile infection rates did not differ significantly in the 12 months before and after the change from levofloxacin to gatifloxacin (relative risk [RR] 1.0, 95% CI 0.97–0.86; p = 0.973). For hospital 2 (Figure, panel B), a subsequent formulary change from gatifloxacin to levofloxacin was associated with a reduction in C. difficile infection (RR 0.59, 95% CI 0.51–0.70; p<0.001); an intervention to improve environmental cleaning with a 10% bleach solution occurred at the time of the formulary change.

**Conclusions**

Our findings provide further evidence that emergence of epidemic NAP1/BI strains in a geographic region may be associated with large multihospital outbreaks of C. difficile infection. Before the ODH decision to require mandatory reporting, many area hospitals were either not collecting surveillance data about C. difficile infection or were reluctant to share their rates. Therefore, we believe that mandatory public reporting of C. difficile infection rates provided a valuable tool to examine the full magnitude of the outbreaks and an incentive for hospitals with high rates to increase efforts to control infection. One area hospital recently reported that the ODH database underestimated the incidence of C. difficile infection (14), but this observation does not affect our conclusions because all facilities used the same surveillance definitions. Our findings do not support the hypothesis that use of moxifloxacin or gatifloxacin is associated with higher rates of C. difficile infection than is use of levofloxacin or ciprofloxacin.

Our analysis of formulary fluoroquinolones and C. difficile infection has several limitations. First, data on the amount of the fluoroquinolones used in the hospitals were not available. Second, analysis of hospital formularies does not account for the effects of fluoroquinolones used in long-term care facilities and among outpatients. Third, we did not assess confounding factors, such as use of other classes...
of antimicrobial drugs and differing patient populations. Finally, studies that evaluate group-level effects may not reflect the biological effects at the individual-patient level. Additional studies are needed to evaluate the risk for *C. difficile* infection associated with different fluoroquinolones.

This study was supported by an Advanced Research Career Development Award from the Department of Veterans Affairs to C.J.D. Restriction endonuclease assay typing was provided by Susan Sambol under a Department of Veterans Affairs Research Service grant to D.N.G.

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References


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