Outbreak of Clostridium difficile Infection in a Long-Term Care Facility: Association with Gatifloxacin Use

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(See the editorial commentary by Gerding on pages 646–8)

To determine the cause of an increase in the rate of Clostridium difficile–associated diarrhea (CDAD) in a long-term care facility (LTCF), we analyzed CDAD cases among LTCF patients from October 2001 through June 2002. CDAD cases were identified from review of all enzyme immunoassays positive for C. difficile toxin A. The increase coincided with a formulary change from levofloxacin to gatifloxacin. We performed a case-control study in which we randomly selected control subjects from 612 LTCF admissions during this period. Although we examined a variety of risk factors, logistic regression analysis only demonstrated associations between CDAD and use of clindamycin (P < .005) and gatifloxacin, the latter being associated with an increasing risk of CDAD with increasing duration of gatifloxacin therapy (P < .0001). We concluded that an outbreak of CDAD in an LTCF was associated with a formulary change from levofloxacin to gatifloxacin. The rate of CDAD in the LTCF decreased after a change back to levofloxacin.

Clostridium difficile–associated diarrhea (CDAD) remains a difficult challenge among institutionally acquired infections. Numerous outbreaks have been described in hospitals [1–9]. Although less common, outbreaks of CDAD have been reported in long-term care facilities (LTCF) [10–13]. The most consistently described risk factor in all settings has been exposure to antimicrobial agents. Although virtually all antimicrobial agents have been associated with C. difficile colonization, and although exposure to any agent increases the risk of CDAD, the risk with certain antimicrobial agents, such as clindamycin, appears to be higher than with others. Other previously described risk factors include gastrointestinal (GI) surgery, use of feeding tubes, receipt of chemotherapy agents, environmental exposure (e.g., being a roommate of or in the adjacent room of a patient with CDAD), and, most recently, severity of underlying illness [14]. The risk factors associated with CDAD in an LTCF may differ from those in an acute care hospital.

In October 2001, the Pharmacy and Therapeutics Committee at the Atlanta Veterans Affairs (VA) Medical Center changed the fluoroquinolone in the formulary from levofloxacin to gatifloxacin as a result of modest financial considerations. Within the following 2 months, the rates of CDAD in the VA’s LTCF began to increase. We report the results of this retrospective investigation and the prospective monitoring of the effects of switching from gatifloxacin back to levofloxacin on the rates of CDAD in the LTCF.
METHODS

The Atlanta VA Medical Center is a 173-bed acute care hospital consisting of 2 medical floors and 1 surgical floor, a medical and a surgical intensive care unit, 2 inpatient mental health floors, and a 100-bed LTCF. The LTCF consists of 2 identical floors that are separate from other patient units but attached by a connecting corridor to the acute care facilities. The LTCF’s nursing, house, and attending staff are separate from those of the acute care hospital, but the 2 facilities share use of laboratories, radiology, dietary, and pharmacy services. Approximately 50% of the LTCF admissions come from the acute care hospital. LTCF residents requiring hospitalization are transferred directly to the acute care hospital in the Atlanta VA Medical Center.

To identify cases of CDAD, all patient records in the LTCF and the acute care hospital with enzyme immunoassays positive for C. difficile toxin A (Premier C. difficile Toxin A Microwell Enzyme-Immunoassay; Meridian Bioscience) (this is noted for identification purposes only and does not denote endorsement by the US Public Health Service or the Department of Veterans Affairs) were reviewed for the period of 1 January 2001 through 30 April 2003. A case patient was a patient who had acute onset of loose bowel movements persisting for ≥2 days and who tested positive for C. difficile toxin A. The incidence density of CDAD was calculated on the basis of the number of cases per 1000 patient-days.

Because of the temporal association between gatifloxacin introduction and an increase in the number of CDAD cases in the LTCF, the records for all patients in the facility receiving fluoroquinolones were reviewed. We examined 3 periods of quinolone use in the LTCF: (1) from 1 January 2001 through 30 September 2001, when levofloxacin was the fluoroquinolone in the formulary and represented 99% of the fluoroquinolones used; (2) from 1 October 2001 through 30 June 2002, when gatifloxacin represented 98% of fluoroquinolones used; and (3) from 1 July 2002 through 31 March 2003, when levofloxacin represented 99% of fluoroquinolones used. These periods of fluoroquinolone use in the acute care hospital were identical to those in the LTCF except that the switch from gatifloxacin back to levofloxacin occurred later in the acute care hospital (on 1 November 2002).

LTCF control measures. In November 2001, hand washing and wearing of gloves and gowns for contact with patients with diarrhea were emphasized. Patients with CDAD were treated under enhanced contact precautions, to the extent that this was possible, until their diarrhea resolved. Generalized cleaning of the LTCF was performed with a hypochlorite disinfectant during the period of 9–12 June 2002 [8]. Disposable single-use thermometer probe covers have been used at the LTCF since 1995.

Case-control study. To more fully characterize the risk factors for CDAD, from 1 October 2001 through 30 June 2002 (the period of gatifloxacin use in the LTCF), we performed a case-control study. Control subjects were randomly selected from a list of 612 LTCF admissions during this period. The medical records for case and control subjects were reviewed for demographic information; patient location; comorbid conditions; Horn score (a score of 1–4 that uses physician judgment to classify a patient’s overall condition, as follows: mild, 1; moderate, 2 [i.e., more severe but uncomplicated disease, with recovery expected]; severe, 3 [major illness or complications]; and extremely severe, 4 [catastrophic illness that may lead to death]) [10]; presence of toxin; symptoms of diarrhea, as determined by physician, physician assistant, or nursing notes (nurses routinely noted the presence or absence of a bowel movement on each shift); antimicrobial exposure ≤30 days before illness or during the epidemic period (for control subjects); use of feeding tube; and a GI procedure or surgery within 60 days of illness or during admission.

Three control subjects were randomly chosen for each patient with CDAD. Four control subjects were excluded because they had diarrhea (i.e., loose bowel movements persisting for ≥2 days) but did not have a stool sample tested at the laboratory for C. difficile toxin A. Three of these 4 patients were treated empirically with metronidazole, and their symptoms resolved. Once these 4 patients were excluded, no control subject had diarrhea or a laboratory test result positive for C. difficile toxin A.

Laboratory studies. C. difficile isolates that had been obtained as part of the diagnostic evaluation were saved and typed using arbitrarily primed PCR analysis [15]. Isolates from LTCF patients were also tested for susceptibility to gatifloxacin, levofloxacin, and moxifloxacin using the Etest method (AB Biologicals). Quality-control strains included Bacteroides fragilis ATCC 25285, Bacteroides thetaiotaomicron ATCC 29741, Pseudomonas aeruginosa ATCC 27853, and Enterococcus faecalis ATCC 29212. [16]. Because there are no quality-control ranges defined for gatifloxacin and levofloxacin for anaerobic organisms, the potency of the Etest strips was monitored aerobiologically using the E. faecalis and P. aeruginosa strains. Quality-control of the Brucella blood plates and anaerobic conditions of the test were ascertained using moxifloxacin (for which a quality control range is defined) and the B. fragilis and B. thetaiotaomicron strains.

Statistical analysis. Data analysis was performed using EpiInfo 2002 (Centers for Disease Control and Prevention). Incidence density rates of CDAD were compared using the F statistic. Additional analyses, such as t test, were performed using SAS software, version 7.0 (SAS Institute). Logistic re-
gression analysis included all variables that were significantly associated with cases at the .1 level in a stepwise analysis by use of the logistic procedure in SAS software, version 7.0.

RESULTS

Descriptive epidemiology. From 1 January 2001 through 31 March 2003, a total of 37 patients in the LTCF had cases that met the CDAD case definition. Of these patients, 9 (24%) had relapses of CDAD, and 21 had CDAD during the epidemic period (defined as 1 October 2001 through 30 June 2002). The rate per 1000 patient-days increased from 0.44 during January to September 2001 to 1.32 during the epidemic period ($P < .01$) (figure 1).

Association with gatifloxacin use. The change in the CDAD rate temporally coincided with the switch from levofloxacin to gatifloxacin in the LTCF. Because of this association, we examined the risk of CDAD after fluoroquinolone exposure. From January through September 2001 (i.e., the levofloxacin period), 58 LTCF patients received levofloxacin, 10 (17%) of whom contracted CDAD. For these 10 patients, the average duration of levofloxacin therapy was 13.0 days. For the 48 patients without CDAD, the average duration of levofloxacin therapy was 10.7 days ($P > .07$, by t test). Review of data for these 10 patients with CDAD did not reveal any patients who had CDAD after 1 October 2001. In contrast, from 1 October 2001 through 30 June 2002 (i.e., the gatifloxacin period), 47 LTCF patients received gatifloxacin, 14 (30%) of whom contracted CDAD ($P < .02$, by $\chi^2$ test) (table 1). For these 14 patients with CDAD, the mean duration of gatifloxacin therapy was 13.5 days. For the 33 patients receiving gatifloxacin during this time who did not have CDAD, the mean duration of gatifloxacin therapy was 6.9 days ($P < .02$, by t test).

The remainder of the investigation focused on CDAD cases that occurred during the epidemic period. The mean age of the case patients was 75.5 years. The time to onset of CDAD from admission to the LTCF varied widely; the mean time was 193 days (range, 5–717 days). Although 9 (43%) of 21 patients whose CDAD occurred during the epidemic period died, none died within 30 days after the diagnosis of CDAD. CDAD did not cause or importantly contribute to death in any of these patients. All 21 case patients with CDAD were exposed to $\geq$1 antimicrobial within 30 days before diagnosis of CDAD (mean number of antimicrobials, 1.76). Gatifloxacin was the most commonly used antimicrobial agent (it was used by 14 [70%] of 21 patients with CDAD). Five patients were exposed to clindamycin, 4 were exposed to piperacillin-tazobactam, and 3 were exposed to parenteral vancomycin. A variety of other antimicrobial agents, including ceftriaxone, cefazolin, azithromycin, and ampicillin-sulbactam, constituted the other antimicrobial exposures; exposure to these drugs occurred in only 1 or 2 of the patients with CDAD each.

A variety of risk factors were examined in the case-control study (table 2). Although trends toward greater severity of illness (based on Horn scores), length of stay, and number of comorbidities were observed among the case patients, none were statistically significant at the .05 level. Exposures to antimicrobials—and, specifically, to gatifloxacin and clindamycin—were significantly associated with cases of CDAD. Nineteen (90%) of 21 patients with CDAD were exposed to either clindamycin or gatifloxacin in the 30 days before onset of CDAD.

Logistic regression analysis included whether a patient was in an adjacent room to a patient with active CDAD during his or her hospital stay, use of GI feeding tubes, number of antimicrobials received (30 days before the onset of CDAD or, for control patients, for the entire hospital stay), clindamycin exposure, number of days of gatifloxacin exposure, Horn score, and number of comorbidities at admission to the LTCF. Only exposure to clindamycin and the number of days of gatifloxacin remained in the model (table 3).

Change back to levofloxacin follow-up. On 1 July 2002, the fluoroquinolone in the formulary was changed back to levofloxacin, with a subsequent significant decrease in CDAD rates (figure 1). The decrease in this rate has been sustained through 31 March 2003. CDAD rates in the acute care hospital facility were also monitored (figure 2). From July 2002 through December 2003, the updated rate of CDAD in the LTCF was 0.5 cases of CDAD per 1000 patient-days, remaining lower than during the gatifloxacin period. Rates of CDAD were higher in the acute care hospital than in the LTCF but increased during the period of predominant gatifloxacin use and decreased after the change back to levofloxacin.
Table 1. Attack rate for Clostridium difficile–associated diarrhea (CDAD) among patients in a long-term care facility (LTCF) receiving fluoroquinolones.

<table>
<thead>
<tr>
<th>Period</th>
<th>Fluoroquinolone</th>
<th>No. of LTCF patients receiving fluoroquinolone therapy</th>
<th>No. of LTCF patients with CDAD</th>
<th>Attack rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Jan 2001 through 30 Sep 2001</td>
<td>Levofloxacin</td>
<td>58</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>1 Oct 2001 through 30 Jun 2002</td>
<td>Gatifloxacin</td>
<td>47</td>
<td>14</td>
<td>30a</td>
</tr>
</tbody>
</table>

a P < .02, by χ² test.

Epidemiologic typing. From 1 January 2001 through 31 October 2002, 176 C. difficile isolates were cultured from samples obtained from patients in either the acute care hospital or the LTCF. Forty-five of these isolates were available for typing. Twenty-five of 45 C. difficile isolates were type A; no other types were found in more than 2 patients. Unfortunately, only 4 isolates were recovered from patients in the LTCF, and 2 of these 4 were type A. Of the remaining locations, the proportion of isolates that were type A was approximately the same, with the exception of the surgical ward, where 5 of 5 isolates were type A. However, the number of isolates available for typing limited the analysis by ward.

Fluoroquinolone susceptibility testing of C. difficile isolates. The 45 typed C. difficile isolates for which strain types were available underwent fluoroquinolone susceptibility testing. All were resistant to levofloxacin, gatifloxacin, and moxifloxacin (MIC, >32 μg/mL), with the exception of 2 isolates. For one isolate, the MICs of gatifloxacin, levofloxacin, and moxifloxacin were 0.75, 3.0, and 0.5 μg/mL, respectively; whereas the MICs were 0.75, >32, and 0.5 μg/mL for the other isolate. Both patients from whom the susceptible isolates were obtained were from the acute care hospital, not the LTCF.

DISCUSSION

Our study suggests that the outbreak of CDAD in an LTCF was associated with a change in the predominant fluoroquinolone used from levofloxacin to gatifloxacin. The association was evident from the higher attack rate among LTCF patients receiving gatifloxacin than among those receiving levofloxacin during 2 different periods, even though the courses of levofloxacin had a slightly longer duration than did courses of gatifloxacin, and from the case-control analysis during the period when gatifloxacin was predominantly used. The association between CDAD and gatifloxacin use was especially robust considering the increasing risk of CDAD with increasing numbers of days receiving gatifloxacin among LTCF patients. The decrease in CDAD rates after the switch back to levofloxacin

Table 2. Characteristics of patients in a long-term care facility (LTCF) in a case-control study of Clostridium difficile–associated diarrhea (CDAD).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case patients (n = 21)</th>
<th>Control subjects (n = 59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>75.75</td>
<td>71.7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of LTCF stay, median days</td>
<td>38</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Roommate with CDAD</td>
<td>5 (24)</td>
<td>7 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of comorbidities</td>
<td>3.3</td>
<td>2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Horn score</td>
<td>3.08</td>
<td>2.80</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>9 (43)</td>
<td>19 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>GI procedure or surgery</td>
<td>3 (14)</td>
<td>4 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Use of feeding tube</td>
<td>3 (14)</td>
<td>3 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Any antibiotic exposure</td>
<td>21 (100)</td>
<td>32 (54)</td>
<td>.0001</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>5 (24)</td>
<td>2 (3)</td>
<td>.004</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>14 (67)</td>
<td>15 (25)</td>
<td>.0006</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>4 (19)</td>
<td>10 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>3 (14)</td>
<td>7 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of gatifloxacin therapy, mean days</td>
<td>14.6</td>
<td>7.45</td>
<td>&lt;.0002</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. NS, not significant.

a The t test was used for continuous variables with the exception of length of stay, for which the Wilcoxon rank sum test was used. The χ² test was used for noncontinuous variables.
Further supports this association, not just in the LTCF, but also in the acute care hospital.

Associations between CDAD and fluoroquinolones have been described elsewhere [17–24], although the occurrence of an outbreak in an LTCF and an association between CDAD and a specific fluoroquinolone (gatifloxacin) provide unique features to this investigation. The antimicrobial spectrum of gatifloxacin provides some possible explanation for the outbreak, because gatifloxacin has anaerobic activity that levofloxacin lacks. Antimicrobial agents with anaerobic activity seem to be more highly associated with CDAD as a result of greater disruption of colonic flora [25]. The results of the susceptibility tests suggest that *C. difficile* is usually resistant to fluoroquinolones, including the newer agents, such as gatifloxacin and moxifloxacin, a finding noted elsewhere [26].

This outbreak of CDAD adds support to the finding that antimicrobial restriction may be one of the most useful control measures for an outbreak [27]. As is often the case, infection-control policies that are well established may fail. We attempted to use a sporocidal disinfectant for the environment and emphasized hand washing and gown and glove use. It seems likely, however, that the change of fluoroquinolones was responsible for the decrease in CDAD rates, because it is unlikely that the effect of the other infection-control measures was maintained. Cohorting is a particular problem in LTCFs, because patients are often in the institution for months or even years, so considerable difficulty occurs in moving them. Although we attempted to cohort our patients, this proved difficult to maintain. We do not purport to use exposure to gatifloxacin to explain every case of CDAD, merely that the increase in the rate of CDAD was explained by a change to gatifloxacin. The finding that clindamycin was strongly associated with CDAD, even though only 5 case patients received the drug, is consistent with many reports and emphasizes the need to be extremely judicious with this drug in the LTCF.

We were fortunate that mortality did not seem to be affected by CDAD, even in this aged and frail population. However, CDAD remains a costly complication of institutionalization, with a mean cost of $3667 per case in an acute care hospital [28].

We do not consider the change from gatifloxacin to be the only reason for improvement in the CDAD rates, because other unmeasured events may have occurred, including a change in the severity of illness of patients in the LTCF. Our case-control analysis suggested a possible association between CDAD and severity of disease that was similar to findings of a recent report [14], although this was not seen in the multivariable analysis. It is possible that patients admitted to the LTCF were less severely ill after November 2002, but we have no evidence that this occurred. Severity of illness may be related to an individual’s ability to mount an antibody response to toxin A. Higher serum levels of IgG antibody against toxin A correlate with asymptomatic carriage of *C. difficile* [29, 30]. It is also possible that patients who received levofloxacin before the switch to gatifloxacin developed CDAD during the gatifloxacin period and were treated for CDAD without performance of assays for toxin. However, results of the case-control study during the gatifloxacin period suggested that it was uncommon for patients with symptoms of CDAD to be given treatment without a toxin assay being performed. Another possible reason for the observed decrease in CDAD rates may have been an ascertainment bias. We found no evidence of ascertainment bias in the numbers of toxin assays requested during these time periods, but bias remains a possibility, because it is difficult to measure clinicians’ behavior. We are also continuing to monitor the situation in the LTCF and the acute care hospital, because changes can continue to occur with this uncertain disease.

In conclusion, we demonstrated that an outbreak of CDAD in an LTCF was associated with a change in the predominant fluoroquinolone from levofloxacin to gatifloxacin, with a higher attack rate for LTCF patients receiving gatifloxacin than for those receiving levofloxacin during 2 different periods. Furthermore, we demonstrated that the risk of CDAD increased with an increase in the duration of gatifloxacin therapy among LTCF patients during the outbreak. The CDAD rate in the LTCF decreased after a change back to levofloxacin use.

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Table 3. Logistic regression analysis for a case-control study of *Clostridium difficile*-associated diarrhea among patients in a long-term care facility.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Wald χ² value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.1586</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Clindamycin exposure</td>
<td>3.2845</td>
<td>7.69</td>
<td>.005</td>
</tr>
<tr>
<td>Duration of gatifloxacin therapy</td>
<td>0.2082</td>
<td>10.99</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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Figure 2. Rate of *Clostridium difficile*-associated diarrhea at an acute care hospital. P < .002 for either period of levofloxacin use versus the second period of gatifloxacin use (July through October 2002). No other rates differed significantly when compared with the adjacent period.
Acknowledgments

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References