CONCISE COMMUNICATION

Is High Consumption of Antibiotics Associated with *Clostridium difficile* Polymerase Chain Reaction–Ribotype 027 Infections in France?

Gabriel Birgand, PharmD, MPH; Katiuska Miliani, MPH; Anne Carbonne, MD; Pascal Astagneau, MD, PhD

We compared antibiotic consumption between hospitals affected by a strain of *Clostridium difficile* designated as polymerase chain reaction–ribotype 027 (CD-027) and those unaffected during an outbreak in northern France. The mean consumption of several β-lactams, amikacin, and fluoroquinolones was high in affected hospitals ($P < .05$). However, only levofloxacin and imipenem remained associated with emerging CD-027 in the multivariate analysis, suggesting that those antibiotics should be better targeted by prevention campaigns.

Infect Control Hosp Epidemiol 2010; 31:302-305

Clostridium difficile is responsible for 15%–25% of cases of antibiotic-associated diarrhea in developed countries and most cases of pseudomembranous colitis.[1] Broad-spectrum antibiotic prescribing has been reported to be an important risk factor associated with *C. difficile* infection (CDI).[2,3] Since 2003, outbreaks of severe CDI related to a new hypervirulent strain designated as polymerase chain reaction–ribotype 027 (CD-027) have been reported in Canada and the United States.[1] This strain, characterized by a high-level resistance to fluoroquinolones and erythromycin, has changed the pattern of the disease with an increasing frequency of incidence and attributable mortality.[4,5] After the appearance of cases in the United Kingdom, Netherlands, and Belgium, France was stricken by this strain in 2006.[1] The first cases were reported by healthcare facilities (HCFs) through the national nosocomial infection mandatory notification system to the regional coordinating center for infection control and the French Institute for Public Health Surveillance on February 2, 2006.[1,6] Overall, from January 2006 through November 2007, 639 cases of CD-027 were diagnosed in 48 HCFs in northern France. To determine a potential link between the emergence of a CD-027 outbreak and prior antibiotic consumption, we conducted a study to compare the HCFs affected by CD-027 with the HCFs unaffected by CD-027 during the 2006 outbreak in northern France.

METHODS

Data were extracted from 3 sources, as follows: (1) the French antimicrobial surveillance network based on volunteer participation of HCFs in northern France (previously described[7]) provided antibiotic consumption data, (2) the national nosocomial infection mandatory notification system provided information on HCF infection status with regard to the CD-027 outbreak, and (3) the public reporting system of infection control indicators,[8] which is annually required by the Ministry of Health for all hospitals (previously described[9]), provided the composite score measuring nosocomial infection control organization, resources, and action (ICALIN) for 2005 and the overall alcohol-based hand rub consumption (ICSHA) for 2005. The latter is the percentage of target value of volume of products (in liters) per 1,000 patient-days used that year.

This study used a retrospective case-control design. Comparisons were performed between HCFs affected by CD-027 (HCF 027+) and HCFs unaffected by CD-027 (HCF 027−) (Table 1). Antibiotic consumption data were expressed in defined daily doses (DDDs)/1,000 patient-days, in accordance with the guidelines of the World Health Organization. For selected antibiotics (Table 2) as well as overall consumption, comparisons between the 2 groups of HCFs were performed using mean values and the 75th percentile (p75) distribution as a dichotomous variable ($\leqslant$p75 or >p75). Hospital characteristics, such as hospital ownership (public or private), hospital size ($\leqslant$400, 401–800, or >800 beds), proportion of beds that provide long-term care (<33% or $\geqslant$33%), and p75 of ICALIN and ICSHA score distribution, were also compared. The univariate analysis was performed using a 2-tailed Fisher exact test or Wilcoxon test. Variables with a $P \leqslant .20$ in the univariate analysis were included in a multiple logistic regression using a dichotomous variable according to the p75 distribution of antibiotic consumption. Statistical analysis was performed using STATA statistical software, version 10.0 (StataCorp).

RESULTS

Of 772 HCFs in northern France, the survey included the 102 HCFs that participated in the antimicrobial surveillance network in 2005. Of the 102 HCFs, 10 (9.8%) reported at least one severe case or outbreak of severe CDI in 2006. This accounted for 448 cases of CDI, with 331 cases of hospital-acquired CDI (73.9%) and 187 confirmed cases of CD-027 (41.7%). Overall, HCFs were predominantly public hospitals (66 [64.7%]), had 400 or fewer beds (57 [55.8%]), and had a proportion of long-term care beds greater than 33% (59 [57.8%]). The p75 of ICALIN score was 96 points, and the p75 of ICSHA ratio was 58.6%. There was no significant difference between HCF CD-027+ and HCF CD-027− with regard to those variables (Table 1). Overall antibiotic consumption was 42,639.1 DDDs/1,000 patient-days, the most highly consumed being penicillins (54.8% of the overall consumption), including coamoxiclav (31.7%), followed by fluoroquinolones (10.7%) and cephalosporins (9.8%). Overall

TABLE 1. Main Characteristics of Healthcare Facilities (HCFs) According to *Clostridium difficile* Infection Status

Characteristic	HCF CD-027+, no. (%) (n = 10)	HCF CD-027−, no. (%) (n = 92)	P [a]
Hospital ownership			
Public	7 (70)	59 (64.1)	>.99
Private	3 (30)	33 (35.9)	
Hospital size			
⩽400 beds	3 (30)	54 (58.7)	.09
401–800 beds	3 (30)	25 (27.2)	
>800 beds	4 (40)	13 (14.1)	
Proportion of beds that are long-term care			
⩽33%	5 (50)	38 (41.3)	.74
>33%	5 (50)	54 (58.7)	
2005 ICALIN score[b,c]			
⩽p75	7 (70)	75 (83.3)	.38
>p75	3 (30)	15 (16.7)	
2005 ICSHA ratio[b,d]			
⩽p75	7 (70)	68 (75.6)	.71
>p75	3 (30)	22 (24.4)	

NOTE. HCF CD-027+, HCFs affected by at least one cluster of cases of *C. difficile* polymerase chain reaction–ribotype 027 (CD-027); HCF CD-027−, HCFs unaffected by any cluster of cases of CD-027.

[a] Two-tailed Fisher exact test comparing HCF CD-027+ and HCF CD-027−.

[b] From the public reporting of infection control indicators.[8]

[c] The ICALIN score is a level performance indicator of healthcare-associated infection control. This indicator is a composite score varying from 0 to 100 points. It involves 3 main components related to organization of infection control (33 points), dedicated resources (33 points), and activities (34 points) implemented by HCFs against nosocomial infections.[9]

[d] The ICSHA is a level performance indicator on infection control. This indicator is the percentage of target value of volume of alcohol-based hand rub products (in liters) per 1,000 patient-days.[9]

antibiotic consumption was not significantly different between the 2 HCF groups (P = .23). However, mean consumption of ceftriaxone, penicillins with β-lactamase inhibitors other than coamoxiclav (piperacillin-tazobactam or ticarcillin-clavulanate), imipenem, amikacin, ofloxacine, and levofloxacin were significantly higher ($P < .05$) in HCF CD-027+ than in HCF CD-027− (Table 2). In the multivariate analysis, the logistic model included the 9 antibiotic consumption variables significant in the univariate analysis ($P \leqslant .20$) and hospital size as a hospital characteristic variable. Two antibiotics, imipenem (odds ratio [OR], 6.0; 95% CI, 1.3–27.8) and levofloxacine (OR, 6.0; 95% CI, 1.3–27.8), remained significant in the final model ($P < .05$; −2 log likelihood ratio test, P = .39) (Table 2).

DISCUSSION

Our results showed that healthcare settings affected with CD-027 epidemic strains had significantly higher prior consumption of certain antibiotics than those unaffected by the epidemic strains. In particular, we found that consumption of levofloxacin in contrast to other fluoroquinolones (ie, ofloxacin and ciprofloxacin) and consumption of imipenem were significantly higher in HCF CD-027+, compared with the corresponding consumption in HCF CD-027−. Although CDI can occur as a result of exposure to any antimicrobial, clindamycin, cephalosporins, and fluoroquinolones are the most frequently reported risk factors.[2] Rarely has imipenem been described as a risk factor for CDI. A recent retrospective case-control study showed that imipenem use within the previous 60 days was a significant predictor of CDI.[10] The CD-027 strains are characterized by in vitro resistance to the newer fluoroquinolones.[4,11] However, the role of these antimicrobial agents in the selection of *C. difficile* epidemic strains remains controversial, as reported in recent publications.[3,4,10,12] For instance, Pepin et al[3] from Quebec found that the risk of *C. difficile*–associated diarrhea tended to be lower among patients who were receiving levofloxacin than among those who were receiving ciprofloxacin. In contrast, Muto et al[12] found that the exposure to levofloxacin as well as clindamycin and ceftriaxone were independent risk factors for CDI caused by CD-027 strains. In the latter study, the outbreak occurred following the introduction of levofloxacin and a large increase in fluoroquinolone consumption. Other studies reported that new fluoroquinolones, such as gatifloxacin and moxifloxacin, were important risk factors for the emergence of CD-027 infection outbreaks.[3,4,10,13]

In our study, antibiotic consumption data were collected

TABLE 2. Antibiotic Consumption Comparisons According to *Clostridium difficile* Infection Status of Healthcare Facilities (HCFs)

	Univariate analysis					Multivariate analysis[a]	
	HCF CD-027+		HCF CD-027−				
Antibiotic	Total consumption	Mean	Total consumption	Mean	P[b]	Adjusted OR (95% CI)[c]	P
Coamoxiclav	1551.0	155.1	11962.7	130.0	.20	…	NS
Other penicillins and/or β-lactamase inhibitors[d]	69.4	6.9	329.6	3.6	.002	…	NS
Other penicillins[e]	636.1	63.6	8815.6	95.8	.42	…	NS
Cefotaxime	33.9	3.4	439.0	4.8	.99	…	NS
Ceftriaxone	226.3	22.6	799.4	8.7	<.001	…	NS
Ceftazidime	35.4	3.5	368.8	4.0	.04	…	NS
Other cephalosporins	170.2	17.0	2097.9	22.8	.29	…	NS
Imipenem	55.6	5.6	248.8	2.7	.003	6.0 (1.3–27.8)	.02
Clindamycin	8.5	0.8	141.8	1.5	.55	…	NS
Amikacin	75.7	7.6	397.8	4.3	.006	…	NS
Gentamicin	71.2	7.1	637.3	6.9	.36	…	NS
Other aminoglycosides	4.1	0.4	124.9	1.4	.54	…	NS
Ofloxacin	333.2	33.3	1976.3	21.5	.04	…	NS
Ciprofloxacin	169.6	17.0	1445.3	15.7	.25	…	NS
Levofloxacin	139.7	14.0	488.7	5.3	<.001	6.0 (1.3–27.8)	.02
Vancomycin	64.4	6.4	618.3	6.7	.11	…	NS
Metronidazole	109.9	11.0	874.6	9.7	.44	…	NS
Overall consumption	4674.3	467.4	37964.8	412.7	.24	…	NS

NOTE. HCF CD-027+, HCFs affected by at least one cluster of cases of *C. difficile* polymerase chain reaction–ribotype 027 (CD-027); HCF CD-027−, HCFs unaffected by any cluster of cases of CD-027; NS, nonsignificant ($P > .05$); OR, odds ratio; p75, 75th percentile.

[a] The OR is shown only for variables that remained significant in the final model ($P < .05$). The full model included all antibiotic variables with a $P \leqslant .20$, as well as hospital size, which had a $P = .09$ in the univariate analysis and a $P = .87$ in the multivariate analysis.

[b] Wilcoxon test.

[c] Adjusted OR obtained after dichotomization of antibiotic variables according to ⩽p75 or >p75.

[d] Piperacillin-tazobactam and ticarcillin-clavulanate.

[e] Aminopenicillins (without β-lactam inhibitor), penicillinase-resistant penicillins, piperacillin, and ticarcillin.

during the year before the outbreak. This choice aimed to evaluate prior antibiotic selective pressure that may favor emergence of CD-027 strains. However, it remains hard to determine whether a CD-027 infection outbreak could be influenced by antibiotic pressure or transmission from patient to patient related to failures in standard precautions. The CD-027 infection outbreak that occurred in northern France was mainly controlled after reinforcement of the antibiotic stewardship program in addition to the implementation of extensive hygiene measures, such as double hand hygiene (hand washing with liquid soap before using alcohol-based hand rub), dedicated equipment, cohorting units (isolation care areas with private rooms and dedicated staff personnel), and environmental cleaning with hypochlorite solutions (0.5%). In our study, we demonstrated that antibiotic consumption was associated with emerging CD-027 infection outbreaks regardless of the hospital size and of the level of performance indicators measuring infection control activity and alcohol-based hand rub consumption. These indicators are required for annual public reports in French hospitals. The lack of difference between HCF groups with regard to these characteristics suggests that cross-transmission was not the only reason for the spread of CD-027. Finally, this study supports the promotion of better antibiotic usage in healthcare settings, in parallel with hygiene precautions. Fluoroquinolones with an extended spectrum against gram-positive bacteria, such as levofloxacin, which is increasingly prescribed for respiratory tract infections, should be the primary target in programs aiming to reduce antibiotic consumption.

ACKNOWLEDGMENTS

We thank the members of the antimicrobial surveillance network in northern France and Fréderic Barbut from the national reference laboratory for *C. difficile*.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

From the Regional Coordinating Center for Nosocomial Infection Control (G.B., K.M., A.C., P.A.) and the Department of Epidemiology and Public Health, Pierre et Marie Curie University School of Medicine (P.A.), Paris, France. G. B. and K. M. contributed equally to this study.

Address reprint requests to Pascal Astagneau, MD, PhD, C-CLIN Paris

Nord, Centre des Cordeliers, Université Pierre et Marie Curie, 15 Rue de l'Ecole de Médecine, 75006 Paris, France (p.astagne@bhdc.jussieu.fr).

Received June 29, 2009; accepted September 9, 2009; electronically published January 25, 2010.

 0899-823X/2010/3103-0012$15.00. DOI: 10.1086/650758

REFERENCES

1. Kuijper EJ, Coignard B, Tull P. Emergence of *Clostridium difficile*–associated disease in North America and Europe. *Clin Microbiol Infect* 2006;12(Suppl 6):2–18.
2. Owens RC Jr, Donskey CJ, Gaynes RP, et al. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clin Infect Dis* 2008;46(Suppl 1): S19–S31.
3. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*–associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; 41:1254–1260.
4. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*–associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;353:2442–2449.
5. Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*–associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ* 2005;173:1037–1042.
6. Tachon M, Cattoen C, Blanckaert K, et al. First cluster of *C. difficile* toxinotype III, PCR-ribotype 027 associated disease in France: preliminary report. *Euro Surveill* 2006;11:E060504.
7. Miliani K, L'Heriteau F, Alfandari S, et al. Specific control measures for antibiotic prescription are related to lower consumption in hospitals: results from a French multicentre pilot study. *J Antimicrob Chemother* 2008;62:823–829.
8. Ministère de la Santé et des Sports. Tableau de Bord des Infections Nosocomiales [in French]. 2008. Available at: http://www.icalin.sante.gouv.fr/. Accessed January 13, 2010.
9. Carlet J, Astagneau P, Brun-Buisson C, et al. French national program for prevention of healthcare-associated infections and antimicrobial resistance, 1992–2008: positive trends, but perseverance needed. *Infect Control Hosp Epidemiol* 2009;30:737–745.
10. Baxter R, Ray GT, Fireman BH. Case-control study of antibiotic use and subsequent *Clostridium difficile*–associated diarrhea in hospitalized patients. *Infect Control Hosp Epidemiol* 2008;29:44–50.
11. Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet* 2005;366:1079–1084.
12. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*–associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2005;26:273–280.
13. Biller P, Shank B, Lind L, et al. Moxifloxacin therapy as a risk factor for *Clostridium difficile*–associated disease during an outbreak: attempts to control a new epidemic strain. *Infect Control Hosp Epidemiol* 2007;28: 198–201.