

Letters to the Editor

Ciprofloxacin and *Clostridium difficile*-Associated Diarrhea

To the Editor:

We believe that the study reported by Yip et al.¹ in the September 2001 issue of *Infection Control and Hospital Epidemiology* regarding exposure to ciprofloxacin as a risk factor for *Clostridium difficile*-associated diarrhea (CDAD) is flawed from both an epidemiologic and a microbiological perspective.

Several issues regarding the research methodology and statistical analysis used in this study are worthy of comment. First, the authors matched controls to cases by date of admission, ward, age, and gender. They found that they could not also match on length of stay and had to use a second control group. If the authors intended to use logistic regression to analyze the results, then why did they match on so many factors? It would have been easier to match only on date of admission and ward, and then include the remaining variables in the analysis. This would have had the added advantage of exploring interaction effects (eg, between age and antibiotic exposure). Moreover, matching on date of admission in this study may not have been to any advantage because the study period was only 3 months. The local environment was not likely to have changed significantly during this period, and it would have been acceptable to randomly select controls from this period. Finally, matching on the factors described in this study does not control for comorbidities, as stated by the authors.

The authors concluded that "... patients with CDAD were at least five times more likely to have been exposed to ciprofloxacin than control patients. ..." The results should have been interpreted as patients with CDAD were between 1.2 and 24.8 times more likely to have been exposed to ciprofloxacin for the first control group, based on univariate analysis, and between 1.01 and 88.4 times for the second control group, based on multivariate analysis. These wide confidence intervals (CIs),

although statistically significant, are of no real practical importance. Wide CIs reflect unstable odds ratio (OR) estimates that generally occur when the sample size is too small, reducing the power of the study. The lower bounds of CIs close to 1 (ie, the null value) provide evidence for lack of an effect.

When viewed in conjunction with other studies that have explored the association of ciprofloxacin with CDAD, this study adds nothing new. Shah et al.² found a statistically significant association of ciprofloxacin exposure with CDAD using patients with diarrhea not due to *C. difficile* as controls. Although they did not report the OR and CI, these could be calculated as 2.33 and 1.23 to 4.43, respectively. Ciprofloxacin exposure remained significant in their multivariate analysis, along with macrolides, cefuroxime, and lactulose. Nath et al.³ also reported a statistically significant association of ciprofloxacin in a multivariate model that also found clindamycin, ceftazidime, and cefuroxime to be independently associated with CDAD, but the CI of 1.05 to 13.79 provides little in terms of practical importance. Other studies have reported associations that have not been statistically significant. However, all had relatively small sample sizes and could have lacked power.⁴⁻⁸

Regarding the microbiology, Yip et al.¹ state, "Ciprofloxacin and other oral quinolones are active against many intestinal bacteria. ..." This is true, but ciprofloxacin (unlike the newer fluoroquinolones) is not active against the anaerobic component of the intestinal flora and it is these bacteria that comprise the "colonization resistance barrier."⁹ We previously demonstrated this in an in vitro model in which "treatment" with ciprofloxacin did not result in proliferation of *C. difficile*, whereas "treatment" with clindamycin, a known CDAD inciting agent, resulted in a significant increase in *C. difficile*.¹⁰ In addition, we investigated prospectively 213 patients receiving ciprofloxacin monotherapy and failed to show any association between CDAD and ciprofloxacin.¹⁰

Two of the references cited by Yip et al. in support of their argument^{11,12} were letters to the editor in *Lancet* in 1990. However, Yip et al.

failed to mention our letter in *Lancet* in the same year¹³ that provides plausible explanations for the observations made by Bates et al.¹¹ (prior *Salmonella* infection predisposing to *C. difficile*) and Cain and O'Connor¹² (prior co-trimoxazole therapy).

The five patients described by McFarland et al.,¹⁴ for whom ciprofloxacin was linked with CDAD, all had serious disease, with four of the five having recurrences. That in itself suggests that factors other than ciprofloxacin may have been operating in most, if not all, of these cases.

Clinical data and our own continuing experience would suggest that the rate of ciprofloxacin-induced CDAD remains extremely low. Sir Charles Gairdner Hospital has been Australia's largest user of ciprofloxacin for more than 13 years (average expenditure, \$220,000 [Australian] per year), and we have not seen a case of ciprofloxacin-induced CDAD when ciprofloxacin has been used as monotherapy. Thus, we would argue that concern about CDAD following ciprofloxacin is not warranted. However, given the wider spectrum of activity of the newer fluoroquinolones, continued surveillance is justified.

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The authors reply.

We thank Thomas et al. for their interest in our study. We agree that matching only by date of admission and ward would have been a reasonable alternative approach. We disagree with their comments about matching on date of admission. Our decision to use date of admission was based on careful consideration of circumstances in our hospital, particularly staffing shortages. This variable can readily change during a 3-month period, is potentially associated with nosocomial transmission, and, in our setting, is not easily measurable—all arguments for matching. Randomly selecting controls, as suggested by Thomas et al., may have led to a loss of precision compared with matching on length of stay. Regardless, the pertinent point is

that we obtained similar results with relatively large effect sizes using two different sets of controls. In their interpretation of confidence intervals, Thomas et al. ignore the fact that it is the point estimate of the odds ratio that is most likely to reflect the "truth." The point estimates of the odds ratios for the two sets of controls, 5.5 and 6.7, both based on multivariable analysis, obviously do not represent a "lack of effect" as suggested by Thomas et al. Their discussion about sample size and power is misinformed; these are a priori concepts that should not be used to interpret completed studies.¹ Thomas et al. cite epidemiologic studies that in fact support our findings of an association between fluoroquinolone use and *Clostridium difficile*-associated diarrhea.^{2,3} We acknowledge that the generalizability of such studies may be limited. We would suggest that Thomas et al. exert similar caution when making generalizations based on their experience in a single hospital. We agree that continued surveillance of fluoroquinolones and *Clostridium difficile*-associated diarrhea is justified.

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Transmissions From Infected Healthcare Providers to Patients Are Medical Errors

To the Editor:

Do no harm. This is a principle all medical personnel live by and

should be referred to whenever we discuss interactions between patients and healthcare providers. In the June issue of *Infection Control and Hospital Epidemiology*, there were two editorials,^{1,2} one article,³ and two letters^{4,5} regarding the transmission of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus from surgical personnel to patients. It serves our collective interest to analyze this issue through the principle stated above and its necessary practical companion, reducing medical errors. After all, isn't transmission of disease in our healthcare institutions by definition a medical error?

A critical component of accident prevention is building systems that prevent errors from occurring. What we have learned from other industries, such as the aviation sector, is that rather than focusing on the individual, a successful strategy requires standardizing procedures that everyone in the system must follow. If an individual working inside the system has the choice of whether to follow an aspect of the recommended procedures, doesn't this in effect mean that there is no system? Instead, there is individual compliance or noncompliance. Could you imagine if the same "system" existed in the airline industry? Would we accept a situation in which the pilot could choose whether to conduct inspections before takeoff? Isn't a pilot with individual choice equivalent to a surgeon who can choose whether to be vaccinated or whether to be tested for hepatitis B virus?

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