Antibiotic Stewardship and *Clostridium difficile*–Associated Disease

To the Editor—In the past 2 decades, *Clostridium difficile* has emerged as a major cause of nosocomial infection,[1,2] largely facilitated by antibiotic use, much of which is excessive and/or unnecessary.[3] We applied recently described case definitions of *C. difficile*–associated disease (CDAD)[4] to document the beneficial effects of an antibiotic stewardship program.[5]

Beginning January 1, 2001, we tracked every case of CDAD at our 550-bed teaching hospital. Despite continued emphasis on handwashing and isolation procedures, the incidence of CDAD remained constant during the period from October 2003 through August 2006 (Figure).

In September 2006, we instituted an antibiotic stewardship program, under which prescriptions for most parenteral antibiotics required approval by an infectious disease physician or clinical pharmacist. Penicillin, ampicillin, ampicillin-sulbactam, nafcillin, ceftriaxone, aztreonam, aminoglycosides, metronidazole, and oral formulations of antimicrobial agents could be ordered without approval; daytime orders for all other antibiotics were only honored if approved. Nighttime orders for formulary antibiotics were honored until 7:30 AM the following day, when the pharmacist and infectious diseases physician reviewed them, either approving the order or contacting a resident to make other recommendations. Antibiotic prophylaxis before surgery was not addressed, although continuation of such treatment after 48 hours required approval through the antibiotic stewardship program.

Beginning February 2007, we applied Centers for Disease Control and Prevention case definitions of CDAD[4] retroactively to 2003 and prospectively. CDAD was defined as a diarrheal disease (loose or watery stools generally 3 or more times per day) and/or an abdominal discomfort with a positive result of an enzyme-linked immunosorbent assay (ELISA) for *C. difficile* toxins A and B (Premier Toxins A&B EIA; Meridian Bioscience). A new case of CDAD was diagnosed if a patient met the case definition and had not had a diagnosis of this disease any time in the preceding 8 weeks. Recurrent disease was considered to be present if symptoms reappeared 2–8 weeks after the initial assay result was found to be positive for *C. difficile* toxin in a patient who had responded to therapy. A patient with continuous symptoms and repeated positive test results was considered to have a single case. The total number of cases equals the sum of new and recurrent cases.

For the 3 years preceding the introduction of the antibiotic stewardship program, the mean incidence of all cases of CDAD was 41.7 cases per month (3.3 cases per 1,000 bed-days) (Figure). Implementation of the program was followed by a decline to 22.0 cases per month (1.7 cases per 1,000 bed-days) during the ensuing 12 months, a 47.2% decrease ($P < .001$, by t test). The mean incidence of first-time CDAD, which we defined as a documented case of CDAD in a patient who had never previously had this disease, was 28.4 cases per month (2.2 cases per 1,000 bed-days) before implementation of the antibiotic stewardship program and 16.4 cases per month (1.2 cases per 1,000 bed-days) after, a 42.2% decrease ($P < .001$).

These data show that implementation of a hospital-wide

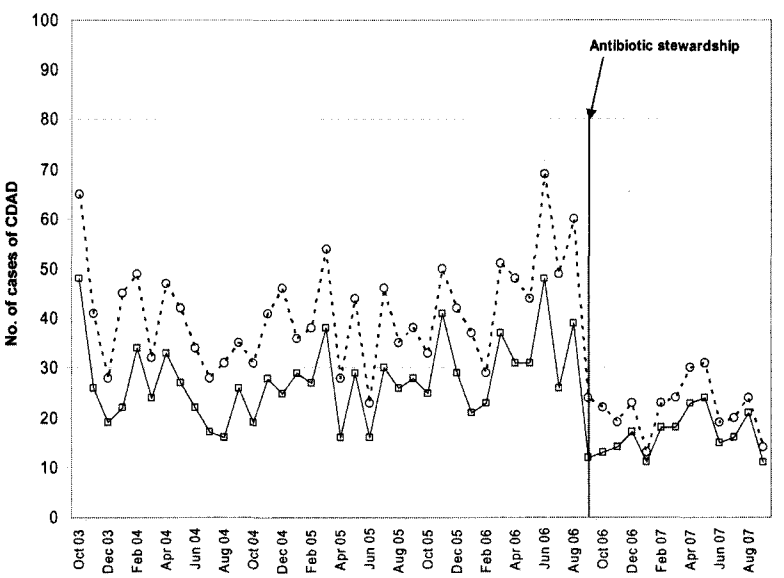

FIGURE. Incidence of *Clostridium difficile*–associated disease (CDAD), before and after implementation of the antibiotic stewardship program. *Upper dotted line,* total number of cases of CDAD, as defined in the Centers for Disease Control and Prevention criteria[4] during the years under study; *lower solid line,* number of first-time cases, as determined from electronic medical records.

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antibiotic stewardship program brought about a significant and lasting reduction in the incidence of CDAD. Other investigators have suggested this, either with control of specific antibiotics such as clindamycin, cephalosporins, or fluoroquinolones or with general measures aimed at all antibiotics.[6,7] Our results are particularly robust, meeting standardized case definitions and showing consistent findings for several years before the intervention as well as for a full year afterward. Interestingly, our antibiotic stewardship program was as successful as a recently reported "bundle" approach[8]; it is possible that implementation of both approaches might have further reduced the incidence of CDAD.

The Centers for Disease Control and Prevention case definitions introduce 2 potential sources of bias. First, some patients respond poorly to treatment[9] and continue to have intermittent symptoms. ELISA results may be only intermittently positive, and a single, poorly responding patient may meet case definitions for having several recurrent cases or new cases. Second, patients who remain free of symptoms and have negative test results for 8 weeks but again develop diarrhea and have positive ELISA results may have a recurrence of CDAD rather than a new infection; only fecal culture with molecular fingerprinting would distinguish the 2 possibilities. Our demonstration of a similar reduction in the incidence of first-time cases supports the validity of the case definitions for CDAD.

Some of the observed reduction in the incidence of CDAD may have reflected the implementation of a program to reduce the spread of methicillin-resistant *Staphylococcus aureus* (MRSA). Beginning in August 2006, our medical center took the initial steps toward an eventual hospital-wide policy of culturing samples from the nares of every patient admitted and isolating patients for whom culture yielded MRSA. These steps included hospital-wide briefings on the importance of infection control and renewed attempts to emphasize the importance of patient isolation procedures. This project began on a single 40-bed medical ward in our hospital. In the ensuing year, this effort was expanded to 3 other areas in the hospital, totaling 110 beds. Although this program has steadily heightened hospital-wide interest in infection control, it is unlikely to have accounted for the immediate decrease in new cases of CDAD. Furthermore, its expansion has led to no additional decrease in cases of MRSA infection. According to a recent report,[10] partial (as opposed to hospital-wide) implementation of a policy to control MRSA infection did not reduce its incidence. Similarly, in our hospital, the incidence of MRSA infection did not decline during the first year of the program. These observations support our conclusion that the reduction in the incidence of CDAD is largely attributable to the antibiotic stewardship program.

In summary, motivated by the ongoing epidemic of CDAD in our medical center, we instituted an antibiotic stewardship program. Utilizing data on the incidence of CDAD at our medical center for the 3 years before the implementation of antibiotic stewardship program and for 1 year after implementation, we showed that there was a 47% decrease in all cases of CDAD and a 42% decrease in new cases of CDAD.

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