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Antibiotics and *Clostridium Difficile*

It is hard to remember a time in the past decades when *Clostridium difficile* was not a scourge in our hospitals. As a house officer in the early 1960s, I recall seeing only one patient with hospital-acquired colitis, which we called staphylococcal colitis. On the basis of what in retrospect was probably a false diagnosis, we treated the infection successfully with bacitracin, which fortuitously is active against *C. difficile*.

Recognition of the current disease began in the early 1970s with a few isolated reports of a severe, and even lethal, colitis characterized by the formation of pseudomembranous plaques. Because of its frequent association with exposure to a specific drug, the condition became known as "clindamycin colitis." After the cause was identified as *C. difficile* in 1978,¹ it became apparent that the frequency of the disease was increasing. Aronsson et al. reported on a large number of cases of *C. difficile* diarrhea in Sweden during the period from 1980 to 1982.² Clindamycin and lincomycin, along with a newly implicated group, the cephalosporins, were 10 to 70 times as likely to cause this disease as were the narrow-spectrum penicillins.

By the late 1980s McFarland et al. reported that 7 percent of patients had *C. difficile* in the stool on admission and that 21 percent acquired it during hospitalization, for an overall incidence of 28 percent among hospitalized patients.³ The acquisition of this organism was not necessarily a benign event, since diarrhea developed during hospitalization in 37 percent of the patients with newly acquired *C. difficile* infection. *C. difficile* is now acknowledged to be the chief cause of nosocomial diarrhea in the United States and many countries in Europe. The organism is endemic not only in general hospitals but also in long-term-care institutions. Many observers have noted a steady increase in the number of cases over the past 15 years.

In this issue of the *Journal*, Johnson et al. describe the molecular detective work they performed to identify a clindamycin-resistant strain of *C. difficile* in outbreaks of diarrhea that occurred in four U.S. hospitals during the period from 1989 to 1992.⁴ Treatment with clindamycin had a dual effect. It selected for the clindamycin-resistant epidemic strain of *C. difficile*, and the suppressive action of the drug on the patients' bowel flora facilitated overgrowth of the organism. The strain was identified on restriction-enzyme analysis as type J9. This same strain or a closely related strain of *C. difficile* was responsible for outbreaks of diarrhea in geographically diverse hospitals in the United States and in the United Kingdom.

The findings of Johnson et al. confirm what has been known since the earliest observations about the role of clindamycin in causing *C. difficile* diarrhea. Yet, the use of

clindamycin has declined in U.S. and European hospitals over the past two decades. Indeed, the inclusion of a warning in the package insert of clindamycin greatly reduced the use of this drug in the United Kingdom. During this same period of declining clindamycin use, *C. difficile*-associated diarrhea has increased, even in hospitals in which this drug is only rarely used.

The chief risk factor for the disease is prior exposure to antibiotics. Thus, the term "antibiotic-associated *C. difficile* diarrhea" is still appropriate. A prolonged course of antibiotics or the use of two or more antibiotics in combination increases the risk of *C. difficile* diarrhea. Nevertheless, even brief exposure to a single drug for surgical prophylaxis can cause the condition. This scenario is seen with increasing frequency in surgical units.

Our antibiotic mainstays in hospitals, the cephalosporins, especially those of the second and third generations, are the leading instigators of *C. difficile* diarrhea. In a case-control study, Nelson et al. found that prior use of a second- or third-generation cephalosporin was the chief independent risk factor for *C. difficile* diarrhea (odds ratio, 8.3).⁵ Using a similar case-control design, Zimmerman showed that treatment with clindamycin (odds ratio, 3.5) and treatment with a third-generation cephalosporin (odds ratio, 3.0) were the only risk factors among 22 studied that showed an association with the disease.⁶ The use of first-generation cephalosporins was not related to *C. difficile* diarrhea in that study.

Privitera et al. administered a single prophylactic dose of either a cephalosporin or an extended-spectrum penicillin, mezlocillin, to patients undergoing elective surgery and then analyzed the stool for *C. difficile* in the postoperative period.⁷ This organism was found postoperatively in the stool of 23 percent of the patients who received the cephalosporin but in only 3 percent of those who received mezlocillin. In another study of *C. difficile* diarrhea at a large urban hospital, 85 percent of affected patients had received ceftriaxone, ceftazidime, or both in the preceding six weeks.⁸ The most commonly used antibiotic in that hospital during the study period was ticarcillin-clavulanate, but no patients who received this combination had *C. difficile* diarrhea.

Several hospitals have noted an increase in the number of cases of *C. difficile* diarrhea after antibiotic restrictions were relaxed, thereby increasing access to newer antibiotics, including third-generation cephalosporins. The few attempts to limit the use of these newer antibiotics in an effort to control *C. difficile* infections have produced some provocative results. In an elderly-care unit in the United Kingdom, McNulty et al. radically restricted access to the most commonly used antibiotic, cefuroxime, allowing instead the use of such drugs as penicillin G, trimethoprim, and gentamicin, depending on the suspected pathogen.⁹ The number of cases of *C. difficile* diarrhea fell by more than 50 percent after the change in antibiotic policy. Jones et al. also reduced the use of cefuroxime for lung infections and noted a decrease in the number of cases of *C. difficile* diarrhea.¹⁰ Quale et al. attempted to deal with a dual epidemic of vancomycin-resistant enterococcus and *C. difficile* diarrhea in their hospital by what may appear to some to be a draconian approach — namely, reducing the use of third-generation cephalosporins, vancomycin, and clindamycin, with corresponding increases in the use of piperacillin—

tazobactam and ampicillin–sulbactam.¹¹ The result was a decline in both infections; cases of *C. difficile* diarrhea, for example, declined by 60 percent.

It is not just the total use of antibiotics but the specific choice of drugs that seems to propel this modern hospital epidemic. Analysis of the available data suggests that use of second- and third-generation cephalosporins, clindamycin, ampicillin, and amoxicillin is associated with the highest risk of *C. difficile* diarrhea. Quinolones, aminoglycosides, macrolides (especially the newer agents clarithromycin and azithromycin), vancomycin, and extended-spectrum penicillins — ticarcillin, mezlocillin, and piperacillin — are associated with lower risks, and trimethoprim, tetracycline, imipenem, and meropenem seem to carry an intermediate level of risk. The literature is not definitive on the value of changing antibiotic policies, nor is there agreement on which drugs need to be restricted, since this varies depending on patterns of use. However, altering antibiotic-prescribing patterns by instituting strict control measures is worthy of consideration when standard isolation and environmental policies are unsuccessful.

When one confronts such situations as the epidemic of *C. difficile* diarrhea in our hospitals, there is a temptation to resort to various approaches that avoid the hard issues. Restricting the use of clindamycin is an obvious and relatively easy approach, since the use of this drug has largely been supplanted by other agents. Indeed, a reduction in the use of clindamycin would be expected to decrease the incidence of *C. difficile* diarrhea in hospitals such as those described by Johnson et al., in which this drug was clearly implicated in the outbreak. It is far more difficult to deal with this disease in institutions in which it is endemic despite the infrequent use of clindamycin. This is the situation today in most hospitals with many cases of *C. difficile* diarrhea. The question to be faced is whether physicians are willing to make radical changes in their antibiotic-prescribing practices, even if it means forsaking some of their favorite antibiotics. The decision, although not an easy one, is one that many physicians, hospital epidemiologists, and administrators will need to consider in the near future as the epidemic of *C. difficile* diarrhea continues to grow in our health care institutions.

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