## **Editorial**

## Clostridium difficile Nosocomial Infections -- Still Lethal and Persistent

Joseph Silva Jr, MD

Pseudomembranous colitis was recognized a hundred years ago, yet it continues to be an ongoing problem in hospitals. In the late 1970s, *Clostridium difficile* was identified as a cause of this disease in the setting of prior antibiotic use. Subsequent observations were published rapidly, describing the organism's growth characteristics, clinical epidemiology, pathophysiology, diagnosis, and treatments. Theoretically, the final chapter of its story, the control of this disease, should have been written by the early 1980s. Why then should two articles regarding its continuing clinical significance be published in the 1990s?

C difficile is the most common cause of hospitalacquired infectious diarrhea. Indeed, it is not generally appreciated that diarrhea is the fifth most common nosocomial infection, ranking just behind the wellknown quartet of urinary tract, wound, respiratory tract, and bloodstream infections. This observation is astounding in that a fairly fastidious anaerobic organism can colonize and infect so many patients. Spores are felt to play a critical role in nosocomial transmission,<sup>3</sup> because the vegetative organism readily dies via oxidation outside the warm, cozy, fertile environment of the colon, where controlled states of reduced redox potentials with many complicated foodstuffs are provided on the menu. C difficile shows a proclivity for colonizing patients in hospitals, involving up to 20% of patients hospitalized in tertiary centers. 4 However, only a minority of the colonized patients develop detectable infection. Why is this so? Many factors must be operating, and the articles in this issue<sup>5,6</sup> have

provided us insights as to the complexity of this organism's interactions with humans.

One third or more of patients in large hospitals receive an antibiotic or another agent such as cancer chemotherapy that alters colonization resistance of the gut, thus favoring growth of *C difficile*. Trouble begins when these colonizing strains are toxigenic. The organism is shed readily into the immediate environment of a patient who has C difficile-associated diarrhea (with or without colitis).<sup>7</sup> In the article by Nath et al<sup>6</sup> reported in this issue, one strain of C difficile predominantly accounted for 81% of identified cases, although six other strains were detected with lower frequency in patients with colitis. The authors used an inexpensive typing system of identifying the protein patterns of C difficile on SDSPAGE analysis (unidimensional). What are the virulence factors at play here? Both articles in this issue address the presence of the organism in the environment, although the number of environmental cultures performed were limited. Larson et al<sup>8</sup> have demonstrated that as few as one colony-forming unit of C difficile can infect a hamster given an antibiotic prior to oral inoculation (this degree of infectivity rivals Giardia and some strains of Shigella). I believe that even a few spores can infect a human at risk.

Besides antibiotic therapy, other important risk factors include: certain high-risk patients (such as those who have gastrointestinal dysautonomia, diabetes mellitus, liver or renal failure, leukemia or lymphoma); certain types of procedures (such as enemas, nasogastric tube, upper gastrointestinal tract surgery,

From the University of California, Davis, Sacramento, California.

Address reprint requests to Joseph Silva Jr, MD, University of California, Davis, Room 6312, 2315 Stockton Blvd., Sacramento, CA 95816.

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or otherwise benign devices such as electronic thermometers<sup>9</sup> or commode chairs<sup>10</sup>); certain drugs (such as laxatives and histamine inhibitors that reduce the gastric acid barrier); or certain locations in hospital units or rehabilitation hospitals.<sup>11</sup> The application of molecular biotyping (such as that used by Nath et al<sup>6</sup>) by a variety of methods indicates that hospitals or nursing homes can have "residential" *C difficile* isolates that cause endemic colitis.

Patients infected by *C difficile* during the initial 5 years of the Minneapolis VA experience observed by Olson et al<sup>5</sup> tended to be housed on the surgical services, but in later years infection occurred more predominantly on the medicinal services. This change may be attributable to major shifts in antibiotics used, related to educational interventions that the article addresses, Interestingly, the urology service had the third largest number of cases. In my experience, general surgeons and gynecologists also have many cases<sup>12</sup> and are less experienced in diagnosing *C difficile* colitis.

Accuracy of diagnosis continues to be a problem. An important message from the article by Olson et al<sup>5</sup> is that the Gram's stain of stool can be eliminated from the repertoire of routine clinical tests. In addition, the authors stress that, for all practical purposes, a culture still is the most sensitive technique for detecting colonization, reiterating that cytotoxic assays performed on fibroblasts are a fairly sensitive method. It should be noted that of their 569 stool samples that were positive for *C difficile* cytotoxin, 30 (5%) were negative by culture. Recent studies employing polymerase chain reaction analysis seem to indicate that there is a small number of patients (some very ill) whose fecal samples either can be negative for C difficile by culture yet have its cytotoxin present, or have no evidence of C difficile by either toxin or cultural analyses. 12 Similarly, Olson et al found that 38% of those who had C difficile demonstrated in their feces were negative for C difficile toxin. Related to these observations, clinicians may have to repeat some of these standard assays in patients who have persistent diarrhea. It is interesting that physicians will order sequential blood counts or liver function studies regularly but have a solitary knee-jerk response when looking for *C difficile*. Multiple assays for toxins of C difficile may be necessary, although the yield is not great.

The background rate of nosocomial diarrhea is substantial; in many such patients, a specific microbial etiology is never determined. Most patients in the Olson et al study had received multiple antibiotics, and therefore it is hard to implicate one particular agent, including the antifungal antibiotics. Endoscopy still has proven worth and should be used more

frequently in confusing cases where test results are unclear or clinical symptoms are not classic for C difficile colitis. About 15% of patients reported by Olson et al responded just to termination of the antibiotic, and this may be an important "passive" therapeutic maneuver. Response rates to oral metronidazole and vancomycin were comparable, and the Olson article contains important data related to the delivery and efficacy of vancomycin enemas or nasogastric delivery in those patients who could not take an antibiotic by mouth. The authors also point out the seeming paradox that patients receiving either intravenous metronidazole or vancomycin can experience this disease; this also has been the experience of others.

Unfortunately, C difficile will continue to plague us in the 1990s. Hospitals are "loaded" with the organism and hospitalized patients frequently become infected; yet many healthcare providers are not sufficiently familiar with the disease. More than 1.6 million tests for C difficile colitis were performed in the United States in 1991, so this is an exceedingly important infection. In contrast to other studies, Olson et al indicate that handgloving did not assist in preventing the infection. My experience and those of others in limiting hospital outbreaks is to follow strict handwashing, gowns, and gloving guidelines for hospital personnel when in contact with patients who have diarrhea and with their surrounding environment.<sup>4,13</sup> Both groups reporting in this issue have demonstrated that control of antibiotic use can influence the occurrence of *C difficile* colitis in hospitals.

Until a better understanding of virulence is gleaned from the study of subtypes of *C difficile*, *we* will continue to have problems with this organism, which has capitalized on the need for patients to receive multiple, broad-spectrum antibiotics to sustain life. Maybe the advent of a toxoid similar to that used for *Clostridium tetani* will be in our armamentatium in the next century. In the meantime, while healthcare providers will depend heavily on laboratory testing to diagnose *C difficile* colitis, a Listerian vigilance can be assisted by our suspicion for this organism in any patient who has acquired diarrhea in the hospital/nursing home environment.

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