

This Week's Citation Classic™

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Bartlett J G, Chang T W, Gurwith M, Gorbach S L & Onderdonk A B.

Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N. Engl. J. Med.* 298:531-4, 1978.

[VA Hosp.; New England Med. Ctr. Hosp.; Tufts Univ. Sch. Med., Boston, MA; and Univ. Manitoba, Winnipeg, Canada]

Stools from four patients with antibiotic-associated pseudomembranous colitis contained a cytotoxin that is neutralized by gas-gangrene antitoxin. These specimens caused colitis when injected intracecally into hamsters. The toxicity in tissue cultures and hamsters could be reproduced with broth cultures of *Clostridium difficile* strains recovered from three of the four specimens. [The SCF[®] indicates that this paper has been cited in over 280 publications since 1978.]

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"In the early 1970s, there were three interrelated observations that prompted our interest in antibiotic-associated pseudomembranous colitis (PMC). First, a prior *Citation Classic* by Francis Tedesco showed an extraordinarily high incidence of this complication among clindamycin recipients at Barnes Hospital.^{1,2} Second, *Staphylococcus aureus* was the traditionally accepted pathogen, but this organism could not be recovered from these patients. Third, multiple other antimicrobial agents caused a lethal colitis when given to hamsters, and the etiology of this lesion was also enigmatic.

"In 1975, our investigative group of 12 moved from the UCLA-Sepulveda VA Hospital program in Los Angeles to Tufts-New England Medical Center. Andy Onderdonk and I decided to take on antibiotic-induced colitis in hamsters as a major new project despite skepticism that this mechanism had anything to do with the disease in patients. Under the advice of Sherwood Gorbach, it was decided that stool cultures would be futile, since this traditional approach had failed in extensive studies, presumably reflecting the complexity of normal stool flora. The alternative study plan we used was a number of indirect tests to demonstrate a transferable agent via intracecal injections in hamsters and then to characterize the substances responsible for disease transmission. The work eventually led to the detection of *C. difficile* and its toxin.³ We collaborated with Te Wen Chang, the virologist at Tufts, who failed to find the virus he

anticipated but discovered the tissue-culture assay with clostridial antitoxin neutralization that has subsequently become the standard method used to detect *C. difficile* toxin. These studies were far less simple than they may appear. Experimental groups were labeled sequentially starting with 1HA through 1HZ, then 2HA, and so forth. The original appellation applied to the putative agent in the hamster project was 'Clostridium 17HF 1-9' indicating it was the ninth stool isolate picked from the first hamster in the 422nd experimental group!

"Once this work was completed, it was then rather easy to utilize the techniques developed in hamsters to show that the mechanism applied to patients with antibiotic-associated PMC. The major problem encountered at this juncture was simply finding appropriate patients to study, since the experience with clindamycin in Boston was far different from that reported by Tedesco. After six months, our first stool specimen was finally obtained in March 1977 from a patient with lethal PMC at our prior institution, the Sepulveda VA. Additional specimens were added by Marc Gurwith, who had the foresight to save stools during a study of antibiotic-associated diarrhea in Canada.⁴ The *Citation Classic* detailing this work in patients was rejected by the first journal we sent it to, although the editor subsequently wrote me an apology, noting that he had 'overlooked an important observation.' The *New England Journal of Medicine* also caused us considerable anxiety, since one reviewer lost the paper, causing an extraordinary delay in the review process. The fact that we had reported these data at the annual meeting of the American Society for Microbiology five months earlier threatened our pride of place in the publication scheme.

"The paper cited was one of several that identified *C. difficile* as the agent of antibiotic-associated colitis. We think it has been frequently cited because the disease was topical, it was the first to identify *C. difficile* as the responsible agent, and most importantly, it provided convincing evidence based on the Koch-Henle postulates using the hamster model. This initiated the anticipated cascade of events that have subsequently led to effective methods for both disease detection and effective therapy."⁵

1. Tedesco F J, Barton R W & Alpers D H. Clindamycin-associated colitis: a prospective study. *Ann. Intern. Med.* 81:429-33, 1974.
2. Tedesco F J. *Citation Classic*. Commentary on *Ann. Intern. Med.* 81:429-33, 1974. *Current Contents/Clinical Practice* 12(25):16, 18 June 1984.
3. Bartlett J G, Onderdonk A B, Cisneros R L & Kasper D L. Clindamycin-associated colitis due to a toxin-producing species of *Clostridium* in hamsters. *J. Infect. Dis.* 136:701-5, 1977. (Cited 105 times.)
4. Gurwith M J, Rablin H R & Love K. Diarrhea associated with clindamycin and ampicillin therapy: preliminary results of a cooperative study. *J. Infect. Dis.* 135:S104-S110, 1977. (Cited 50 times.)
5. Bartlett J G, Taylor N S, Chang T W & Dzink J A. Clinical and laboratory observations in *Clostridium difficile*-induced colitis. *Amer. J. Clin. Nutr.* 33:2521-6, 1980. (Cited 45 times.)