New Therapies for *C. difficile* in Development

BY MIRIAM E. TUCKER
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WASHINGTON — At long last, new treatments for *Clostridium difficile* appear to be on the horizon.

For the last 30 years, the treatment of a first episode of *C. difficile* infection (CDI) has involved stopping the offending antibiotics if possible—effective in 25% of patients—and treating with either oral metronidazole or oral vancomycin. "I could have given this talk in 1983," Dr. Dale N. Gerding quipped during a symposium on CDI at the jointly held annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the annual meeting of the Infectious Diseases Society of America.

Recently, vancomycin has appeared somewhat more effective than metronidazole, particularly in patients with severe disease. In one prospective, randomized, blinded trial of 150 patients with diarrhea due to CDI, response rates were similar for the 81 with mild disease (98% with vancomycin vs. 90% with metronidazole), but the difference was significant—97% with vancomycin vs. 76% for metronidazole—among the 69 patients with severe disease (Clin. Infect. Dis. 2007;45:302-7).

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In a recent observational study of 52 patients, however, most patients responded clinically to either drug, but microbiologic response appeared to be slower and less consistent with metronidazole than with vancomycin (Clin. Infect. Dis. 2008;47:56-62).

The lack of a standard definition for disease severity is a problem, and no prospective scoring system for CDI severity has been validated. Candidate scoring elements such as peripheral leukocytosis, increased serum creatinine, or low albumin aren't specific enough, while stool frequency is difficult to measure. "Who's counting after 15-20 bowel movements?" remarked Dr. Gerding, professor of medicine at Loyola University Chicago, Maywood.

Other elements, such as documented pseudomembranous colitis or abdominal CT findings, may be useful but haven't been validated. "We really need validated data for a scoring system available on the day of diagnosis, so we can look at the parameters and make a judgment or a change in initial therapy. … We'd like something simple, maybe two or three elements, to hang our hats on," he said.

But new treatment options now offer the possibility that the severity of CDI may be reduced—or the infection cleared entirely. "We're currently seeing a marked resurgence in interest in the disease and seeing a lot more research being done and new drugs under development," Dr. Gerding said.

Among those are narrow-spectrum antimicrobials that spare the normal flora. One, called OPT-80, is a poorly absorbed macrolide that is selectively active against gram-positive anaerobes. (In this case, poor absorption is desirable because it remains in the colon longer.) Phase IIa open label data in 45 patients with mild to moderate CDI showed an overall diarrhea response of 91% (41 of 45 patients) and recurrence rate of 4.9% (2 of 41). There were no treatment failures at the highest dose of 200 mg given every 12 hours.

The agent, which is made by Optimer Inc., has now completed its first phase III trial, in which the response rate was equivalent to vancomycin. The recurrence rate was reduced from 24% with vancomycin to 13.3% with OPT-80, Dr. Gerding said in an interview after the meeting.

Another poorly absorbed narrow-spectrum antimicrobial, rifaximin, already is approved on the U.S. market (Xifaxan, Salix Pharmaceuticals Inc.) for traveler's diarrhea but not for CDI. It is highly active against *C. difficile* in vitro, and data suggest it may be particularly effective as a "chaser" following vancomycin therapy for multiple relapses (Clin. Infect. Dis. 2007;44:846-8). However, resistance has become an increasing concern, Dr. Gerding noted.

Nitazoxanide (Alinia, Romark Laboratories L.C.) has broad-spectrum activity against helminthic and protozoan intestinal parasites, as well as anaerobic bacterial enteric pathogens, including *C. difficile*. It is currently approved for the treatment of diarrhea caused by *Giardia* and *Cryptosporidium* but not for CDI. In a randomized double-blind study of 110 patients with CDI, 500 mg nitazoxanide given twice daily for 7 days produced a response in 89.5% of 76 patients, compared with 82.4% of 34 who received 250 mg metronidazole four times daily for 7 days, suggesting that it was "at least as effective" as metronidazole (Clin. Infect. Dis. 2006;43:421-7).

In a small, prospective, randomized double-blind trial of 27 patients who received vancomycin 125 mg four times daily vs. 22 patients given nitazoxanide twice daily for 10 days, response rates were 77% for nitazoxanide vs. 74% for vancomycin, and recurrence rates were 5% vs. 7%, respectively. In that study, presented at the Digestive Disease Week conference in 2008, there was no stratification for severity but about 50% of the patients had leukocytosis, Dr. Gerding said.

Potential "out of the box" therapies for CDI include toxin binders, monoclonal antibodies (Mabs), vaccines, and administration of nontoxigenic *C. difficile*.

Tolevamer (Genzyme Corp.) is a high-molecular-weight polymer that binds the *C. difficile* toxins A and B, thus representing a potential nonantibiotic therapy. It failed to meet criteria for noninferiority to vancomycin in its first phase III study, presented at the 2007 ICAAC meeting. Still, the recurrence rate for tolevamer (3.4%) was significantly lower than for vancomycin (23.4%) or metronidazole (27.1%), suggesting that this agent could prevent relapse in patients who are able to stay off antibiotics, Dr. Gerding said.

Phase II data on the neutralizing monoclonal antibody to *C. difficile* toxin A, developed by Massachusetts Biologic Lab and Medarex Inc., were presented in a poster at the 2008 ICAAC/IDSA meeting. There were no differences in recurrence among 29 patients who received the agent, compared with 17 receiving placebo (17% vs. 18%), but recurrence of disease was associated with significantly lower concentrations of antitoxin B antibody, suggesting that both toxins need to be targeted.

The companies are now conducting phase II trials of antitoxin A and B human Mabs as an adjunctive treatment and for the prevention of recurrence. In one such phase II study of 200 patients treated with vancomycin or metronidazole and randomized to Mabs against toxin A and toxin B versus placebo, there was a 70% reduction in recurrence with the Mabs, Dr. Gerding said in the interview.

Also targeting the two toxins is a toxin A/B toxoid vaccine made by Acambis PLC, which has completed phase I immunogenicity and safety trials and is undergoing phase II trials for patients with recurrent CDI in the United Kingdom.

Finally, Dr. Gerding outlined his own work on toxigenic *C. difficile*, a product he is working on in collaboration with ViroPharma Inc. The idea is based on work initially done 2 decades ago, in which prior colonization of clindamycin-treated hamsters with nontoxigenic strains of *C. difficile* protected them from subsequent colonization with a toxigenic pathogenic strain (J. Med. Microbiol. 1985;19:339-50). More recent work again showed that colonization with nontoxigenic CD strains is highly effective in preventing CDI in hamsters challenged with toxigenic CD strains (J. Infect. Dis. 2002;186:1781-9).

Similarly, Dr. Gerding's work has shown that, in hamsters that have been treated for CDI with vancomycin, giving a nontoxigenic CD strain followed by a toxigenic strain protected 9 out of 10 hamsters from relapse, compared with 0 of 5 that had not been pretreated. Human trials are set to begin in early 2009. "To the extent that hamsters are like humans, we may have something going here," he said.

Dr. Gerding holds patents for the treatment and prevention of CDI licensed to ViroPharma and is a consultant for and/or holds research grants from Genzyme, Massachusetts Biological Laboratories, GOJO Industries Inc., Optimer, Salix, Merck & Co., Cepheid, Schering-Plough Corp., and ViroPharma. ■

C. difficile Often Passed to Same-Room Occupants in ICU

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WASHINGTON — The risk of a nosocomial *Clostridium difficile* infection was doubled in one intensive care unit when patients occupied rooms that were previously occupied by an infected patient.

The finding was seen in a retrospective cohort study. Records were reviewed from 1,844 patients admitted over an 18-month period to a 20-bed intensive care unit at a large tertiary care hospital in Michigan. The increased risk was noted even though the unit observed cleaning protocols, and it persisted after correcting for other risk factors associated with *C. difficile* infection (CDI), according to Dr. Megan Shaughnessy of the University of Michigan, Ann Arbor.

In the study, 47 patients had CDI prior to or at the time of ICU admission and were excluded from the analysis. Another 91 patients were not infected and were placed in rooms previously occupied by patients with CDI; 10 (11%) developed CDI. Of the other 1,679 patients, 77 (4.6%) developed CDI.

The difference was statistically significant, with a *P* value of .002. Difference in risk remained significant, with a hazard ratio of 2.35 and *P* value of .01, even after researchers controlled for other risk factors associated with CDI, including patient age, Acute Physiology and Chronic Health Evaluation (APACHE) III score, proton pump inhibitor use, and antibiotic use.

"These findings have implications for room placement and isolation, room-cleaning practices, and hospital design," Dr. Shaughnessy said at the jointly held annual Interscience Conference on Antimicrobial Agents and Chemotherapy and annual meeting of the Infectious Diseases Society of America.

Protocols for the intensive care unit dictated that bathrooms in patient rooms were cleaned daily with bleach, and that the rooms themselves were cleaned with bleach upon patient discharge. Further, infection risk didn't appear to vary depending on where in the room a patient was placed, according to Dr. Shaughnessy.

Dr. Shaughnessy stated that she had no disclosures. ■