Progress reported in tackling initial, recurrent bouts of health care-associated infection

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Surgeons are making progress toward preventing initial and recurrent episodes of clostridium difficile colitis (*C. difficile* or *C. diff*), a vicious bacterial infection that is estimated to affect about 336,000 people each year, typically patients on antibiotics. Using mouse models, researchers at the Massachusetts General Hospital (MGH), Boston, found that an oral medication may prevent *C. difficile* infections (CDI). Also, surgeons at Penn State University College of Medicine, Hershey, PA, examined human patients to detect a genetic mutation that could steer treatments to prevent repeat infections. The findings from these two separate novel studies were recently presented at the 2012 Annual American College of Surgeons Clinical Congress in Chicago.

The *C. difficile* bacteria can be spread by exposure to contaminated feces but is also naturally present in some people's large intestines. All humans all have some "bad" infective bacteria, along with trillions of good, protective bacteria. *C. difficile* is one of the former. It usually lies dormant, until a regimen of antibiotics kills off the good bacteria, allowing *C. difficile* to become active.

Symptoms of CDI include diarrhea, fever, abdominal pain and colitis (inflammation and swelling of the colon). Although it is normally treated with 10 days of another class of antibiotics, *C. difficile* infections are linked to 14,000 deaths and $1 billion in extra costs each year. "The worst case scenario is that patients need to have their colons removed,"

said Richard Hodin, MD, FACS, chief of endocrine surgery at MGH, and surgical director of the hospital's Crohn's and Colitis Center, "or they have to get an ileostomy bag," a pouch externally attached to the skin of the abdominal wall to collect intestinal waste.

Stopping *C. Difficile* Before It Starts

In addition to a mix of hostile and friendly bacteria, the colon naturally contains an enzyme in the intestinal lining called intestinal alkaline phosphate (IAP), which tends to keep these intestinal bacteria balanced. "If you're sick in the intensive care [unit], IAP levels probably go down," Dr. Hodin explained. "Then, with antibiotics, patients are more susceptible to *C. diff* infections." He was the supervising surgeon on a study that examined whether giving an oral supplement would curb the risk of CDI.

Dr. Hodin's team gave four days of antibiotic treatment to mice. One group of mice also received oral doses of purified IAP while the other group of mice, the control group, received no IAP and just received the standard antibiotic course. Mice typically don't have naturally occurring traces of *C. difficile* bacteria like humans. On day six, all the mice orally received an equal dose of *C. difficile*.

CDI is diagnosed with a clinical stool test, which detects a toxin from the bacteria. Both mice and humans are able to clear the *C. difficile* bacteria and its toxin from their bodies through bowel movements. Study results showed that the mice that received IAP had 10-fold more of the *C. difficile* bacteria in their stool, meaning the mice with IAP cleared the bacteria by day five. However, the mice without IAP still tested positive for the toxin after five days.

Standard tests to score diarrhea and colitis severity were also evaluated. After a blinded analysis, the IAP-treated mice showed more improved

diarrheal scores. The levels of IL-1 beta, a cell molecule associated with inflammation, were also 10-fold higher in mice without IAP treatment.

Dr. Hodin reported that this is the first time a study has been nationally presented on preventing CDI. The team is eager to investigate whether similar IAP treatment can prevent CDI in humans. "It's ironic that you get *C. diff* from taking antibiotics, then you treat it with antibiotics," Dr. Hodin noted. "In humans, we envision that patients on antibiotics could also be taking an oral IAP supplement to prevent a *C. difficile* infection."

Stopping *C. Difficile* Before It Comes Back

One of the significant challenges in treating CDI is its high recurrence rates, which can range from 20 to 50 percent among all *C. difficile* patients, according to David B. Stewart, MD, FACS, FASCRS, assistant professor of surgery at Penn State University College of Medicine. A gene in the *C. difficile* bacteria, known as tcdC, sends a signal for the bacteria to stop producing the toxin. But when this gene is mutated, it may promote a larger volume of *C. difficile* toxin, which may increase recurrence rates. In a separate study, Dr. Stewart examined whether a mutation in that *C. difficile* bacteria could predict recurrent infections.

Dr. Stewart and his team analyzed clinical stool samples from hospitalized *C. difficile* patients, including 38 men and 35 women ages 50 to 75, the age group most commonly diag-nosed with CDI. Dr. Stewart and his colleagues were able to isolate and sequence the tcdC gene from each patient's *C. difficile* using these stool samples. "We wanted to determine whether the gene was present in each case and whether any mutations correlated with disease recurrence rates," Dr. Stewart reported. "Accidents happen during gene replication," he continued. "Sometimes a bacteria does not produce an exact copy of a gene, which can produce mutations. Those mutations, can significantly alter how the bacteria functions, sometimes to the detriment of the

bacteria, and sometimes to its advantage."

Dr. Stewart followed the patients for several months to see who developed a recurrent *C. difficile* infection three weeks after being treated for the first episode. Infections that occurred less than three weeks from the first episode were not counted as recurrences, because these infections could have been a persistence of the first infection.

The research team found that two particular base pair changes within tcdC (called single nucleotide polymorphisms) were especially important, C184T and A117T. Mutations on those base pairs resulted in significant changes to the protein normally produced by tcdC, which may lead to higher production of the *C. difficile* toxin. The study results showed that when either of these mutations occurred, the risk of recurrent infection increased by 80 percent. "This is the first study to identify particular mutations in tcdC and to directly correlate them with recurrent *C. difficile* infection," Dr. Stewart reported.

Dr. Stewart said the results could change how *C. difficile* patients are treated: "With this kind of information, physicians may need to give patients a longer course of antibiotics to treat *C. difficile* if their form of infection has these genetic mutations."

Dr. Stewart said he hopes to continue studying whether these genetic mutations can pre- dict recurrent *C. difficile* infections. Such a prediction could have implications for the national push to cut health care costs from hospital readmissions by possibly prompting clinicians to hold off on discharging or transferring patients who are more likely to end up back in the hospi-tal because they have a higher risk of recurrent *C. difficile*. About 40 percent of the patients in Dr. Stewart's study had developed a recurrence severe enough to require hospital readmission.

"We need more information such as these findings to better tailor the

medications we prescribe for patients based on their specific infection type," he added. "That way, we're providing patient-specific, personalized medicine by treating each patient's specific type of *C. difficile*. We're not there yet in terms of a firm solution, but the present research demon-strates the feasibility of this kind of approach to personalized medicine," he concluded.

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