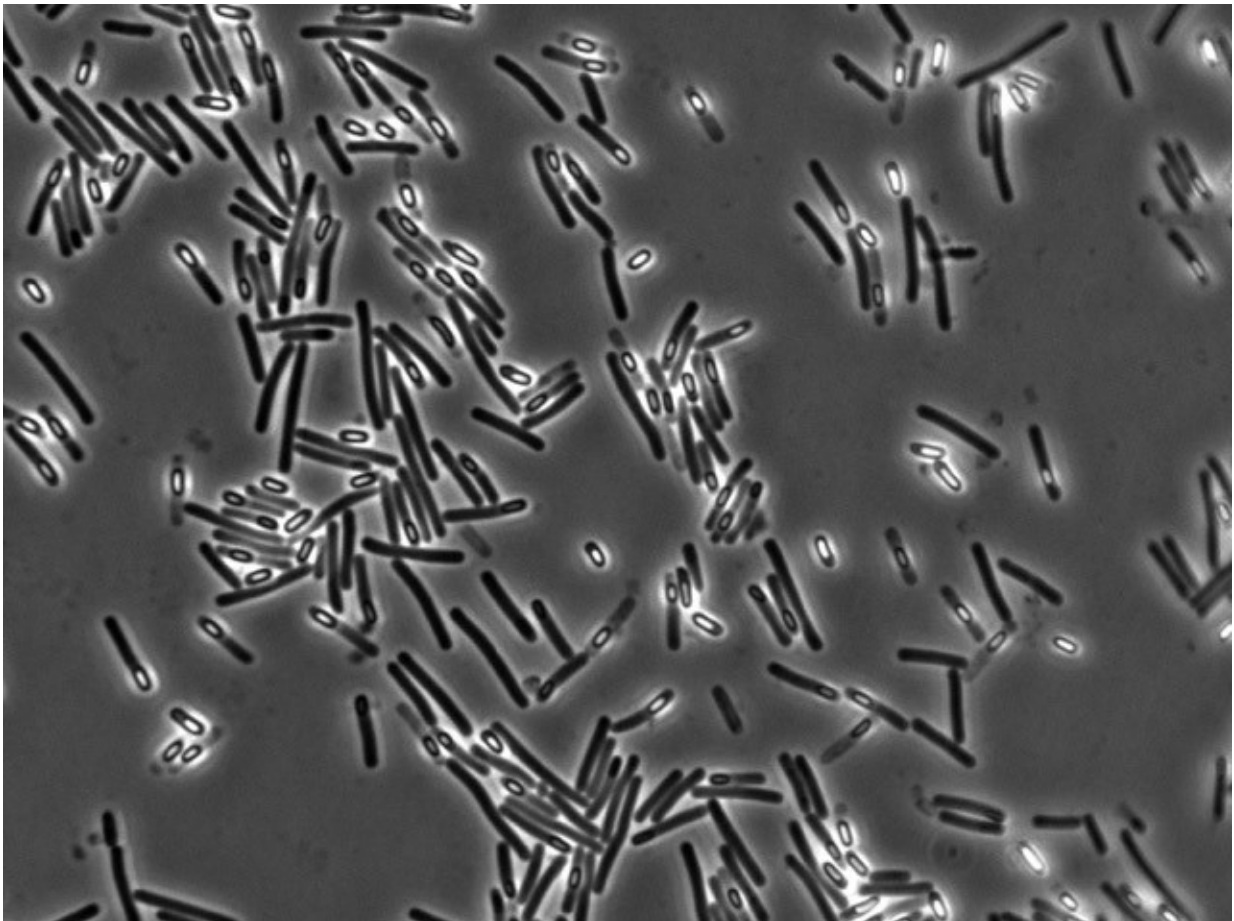


Could calcium hold the key to fighting a dangerous hospital infection?

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This image made by the research team shows *Clostridium difficile* bacteria cells in the process of forming hard-shelled spores. Such spores allow the organism to lurk in hospital and nursing home rooms and awaken only once they are in the small intestine of their next victim. The small bright particles are spores, while the long dark rod-shapes are *C. diff* bacteria cells Credit: University of Michigan - Hanna Laboratory

It lurks in hospitals and nursing homes, surviving the cleaning crew's attempt to kill it by holing up in a tiny hard shell. It preys upon patients already weak from disease or advanced age.

And when it reaches their guts, it breaks open its shell and unleashes infections that kill nearly 30,000 Americans a year, and sicken half a million more.

But, new research shows, it can't make this last, crucial move without enough of a humble nutrient: calcium. And that new knowledge about *Clostridium difficile* (a bacterium also known as "*C. diff*") may lead to better treatment for the most vulnerable patients.

The discovery, made in research laboratories at the University of Michigan Medical School and the U.S. Food and Drug Administration, is published in the online journal *PLoS Pathogens*. It helps solve a key mystery about *C. diff*: What triggers it to germinate, or break its dormancy, from its hard spore form when it reaches the gut.

Though the findings were made in mice, not humans, the researchers say the crucial role of calcium may help explain another mystery: Why some hospital patients and nursing home residents have a much higher risk of contracting *C. diff* infections and the resulting diarrhea that carries its spores out of the body.

That group includes people whose guts are flooded with extra calcium because they're taking certain medications or supplements, have low levels of Vitamin D in their blood or have gut diseases that keep them from absorbing calcium.

The new discovery shows that *C. diff* can recognize this extra calcium,

along with a substance called bile salt produced in the liver, to trigger its awakening and the breaking of its shell.

Previous research had suggested it couldn't do this without another key component, an amino acid called glycine. But the new findings show calcium and the bile salt called taurochlorate alone are enough. Mouse gut contents that were depleted of gut calcium had a 90 percent lower rate of *C. diff* spore germination.

"These spores are like armored seeds, and they can pass through the gut's acidic environment intact," says Philip Hanna, Ph.D., senior author of the new paper and a professor of microbiology and immunology at U-M. "Much of the spore's own weight is made of calcium, but we've shown that calcium from the gut can work with bile salts to trigger the enzyme needed to activate the spore and start the germination process."

Ironically, the researchers say, one way to use this new knowledge in human patients might be to add even more calcium to the system.

That could awaken all the dormant *C. diff* spores in a patient's gut at once, and make them vulnerable to antibiotics that can only kill the germinated form. That could also prevent the transmission of more spores through diarrhea to the patient's room. That could slow or stop the cycle of transmission that could threaten them or other patients in the future.

Hanna's graduate student, Travis Kochan, made a key observation that led to the discovery. He noted that the fluid "growth medium" that the researchers typically grow *C. diff* in for their studies had calcium in it. He realized this could artificially alter the results of their experiments about what caused *C. diff* spores to germinate.

So, he used a chemical to remove the calcium while leaving all the other

nutrients that keep *C. diff* growing. The result: no new spore germination happened in the calcium-free growth medium.

FDA's Center for Biologics Evaluation and Research conducted further research in laboratory dishes and in the guts of mice. FDA's Paul Carlson, Ph.D., a former U-M research fellow, and his laboratory found that *C. diff* spores that were mutated so that glycine couldn't act on them could still germinate and colonize mice. This suggested that calcium, and not glycine, was critical for this process.

Both mutant and regular forms of the bacteria could still activate an enzyme inside the *C. diff* spore that led the bacteria to start dissolving their hard shell. This released the store of calcium that the spore had been harboring inside itself, and increases the local level of the nutrient even further.

"These spores don't want to germinate in the wrong place," says Kochan, whose grandfather suffered from a severe *C. diff* infection which ultimately led to his death. "*C. diff* spores have specialized to germinate in the gut environment, especially in the environment of the small intestine, where calcium and the bile salt injection from the liver comes in."

Hanna notes that the bile salt connection to *C. diff* spore germination was first discovered at U-M in 1982 by a team led by Ken Wilson, M.D.

Calcium and the gut

Certain ailments and treatments cause defects in calcium absorption, but are also risk factors for *C. diff* infections. For example, patients with vitamin D deficiency are five times more likely to get *C. diff*.

Medications aimed at calming acid reflux - such as proton pump

inhibitors - and steroids can increase the amount of calcium in the gut. A Vitamin D deficiency can keep the body from reabsorbing calcium through the gut wall, allowing it to build up. And people with inflammatory bowel diseases such as Crohn's and colitis also have a harder time absorbing calcium from food through their gut walls. Older adults are also often counseled to take calcium supplements to compensate for lower [calcium](#) levels and protect their bones from fracturing.

Hanna cautions that the new findings should not cause any patients to stop taking their medications or doctor-recommended supplements, or to start taking new ones. But he hopes to work with clinicians at U-M and beyond to test the new knowledge in a clinical setting. Meanwhile, he and Kochan and their FDA and U-M colleagues will continue to study *C. diff* germination in mice and look for ways to block the enzymes crucial to spore germination.

More information: *PLoS Pathogens* (2017).
[journals.plos.org/plospathogen ... journal.ppat.1006443](https://journals.plos.org/plospathogen/article/journal.ppat.1006443)

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