Cluster of factors could help predict Clostridioides difficile

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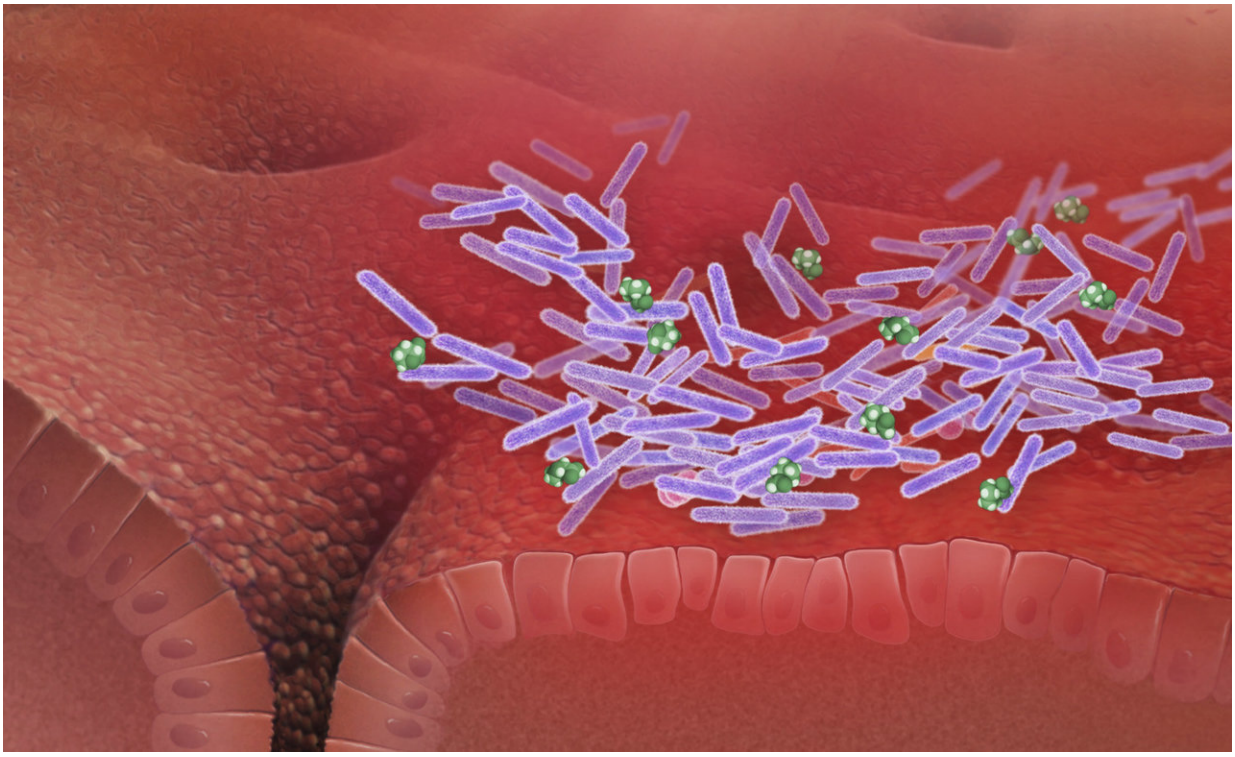

C. difficile exploits amino acid availability to thrive and cause infection in the gut. Credit: Cover art was designed by David T. Smyrk and contributed by Purna Kashyap

A cluster of factors may help predict which patients are likely to develop *Clostridioides difficile*, a potentially life-threatening disease commonly known as *C. diff*icile or *C. diff*, a new study has found.

And that could help in efforts to prevent infection, according to the researchers.

Reduced immune function, recent antibiotic use, current or recent hospitalization and prior *C. difficile* infection predicted risk of subsequent infection, opening the door to potential preventive interventions.

"This could help health care providers red-flag those patients who are at high risk of *C. diff*, and may one day lead to therapeutic or dietary tactics to lower the chances of infection," said the study's co-lead author, Vanessa Hale of The Ohio State University.

The study appears in the journal *Science Translational Medicine*.

The research included studies in both humans and mice, and involved the transplant of feces from human study participants to mice to assess differences in susceptibility to *C. diff*icile infection and molecular-level explanations for that increased risk.

"Microbes in the gut play a critical role in defending against disease, and the really exciting part of this study is that it might help us better identify the risk factors that are linked to problems in the gut and susceptibility to these dangerous infections," said Hale, an assistant professor of veterinary preventive medicine at Ohio State. The study was conducted at the Mayo Clinic, where she previously worked.

The researchers started by looking at the gut microbes of a group of 115 people who had diarrhea but who did not have *C. diff* when they first sought medical care, some of whom went on to develop a *C. diff* infection. They also analyzed the gut microbes of 118 healthy volunteers for comparison.

"About half of the diarrhea patients had gut microbial communities that looked healthy, but the guts of the other half were really intriguing—they had different microbes and very different levels of metabolites. We called this half the 'dysbiotic' - or unhealthy—group," Hale said.

"When we transplanted human stool from the dysbiotic group into mice, we discovered that these mice were more likely to become infected with *C. diff* than mice that received human stool from the healthy-looking group."

The researchers then examined potential risk factors found on the medical charts of individuals with "dysbiotic" and healthy-looking gut microbial communities and found a cluster of five factors that were associated with unhealthy communities.

"We knew that dysbiotic microbial communities put mice at higher risk of *C. diff* infection, and we wanted to see if the five factors could be used to predict *C. diff* infections in humans," Hale said.

To do this, the research team went back and looked at the medical charts of more than 17,000 previous patients who were free of *C. diff* when they initially sought care. In that larger group, there also was a clear connection between the risk factors and subsequent *C. diff* infection.

Furthermore, the researchers found higher levels of amino acids—particularly proline—in the guts of mice that received transplants from people whose gut microbiomes were unhealthy, or dysbiotic.

That was interesting, and potentially important, because *C. diff* needs amino acids like proline to proliferate and it cannot make proline on its own. That prompted the team to wonder if reducing dietary amino acids could protect against *C. diff*, Hale said.

Feeding the mice diets low in protein moderately lowered the growth of *C. diff*, providing further evidence that amino acids—including proline—play a role in risk of infection and leaving researchers curious about the potential for dietary interventions in at-risk humans, Hale said.

"It's possible that a dietary strategy could reduce *C. diff* infection in those patients who are deemed to be susceptible based on the cluster of risk factors we identified," she said, adding that more study is needed to understand that relationship.

The study also showed that prophylactic fecal transplantation from a healthy donor could protect against *C. diff* in mice that were initially prone to infection.

"The transplants were fully protective against *C. diff* infection in all of the animals we tested, which was pretty amazing," Hale said.

The U.S. Food and Drug Administration currently allows fecal transplantation for treatment of recurrent *C. diff* in individuals who do not respond to conventional therapies—primarily antibiotics. However, it is unlikely that fecal transplantation would quickly be adopted as a prevention strategy in those deemed to be at elevated risk of infection, Hale said.

More information: E.J. Battaglioli el al., "Clostridioides difficile uses amino acids associated with gut microbial dysbiosis in a subset of patients with diarrhea," *Science Translational Medicine* (2018). stm.sciencemag.org/lookup/doi/ … scitranslmed.aam7019

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