Multiple, co-existing groups of gut bacteria keep Clostridium difficile infections at bay

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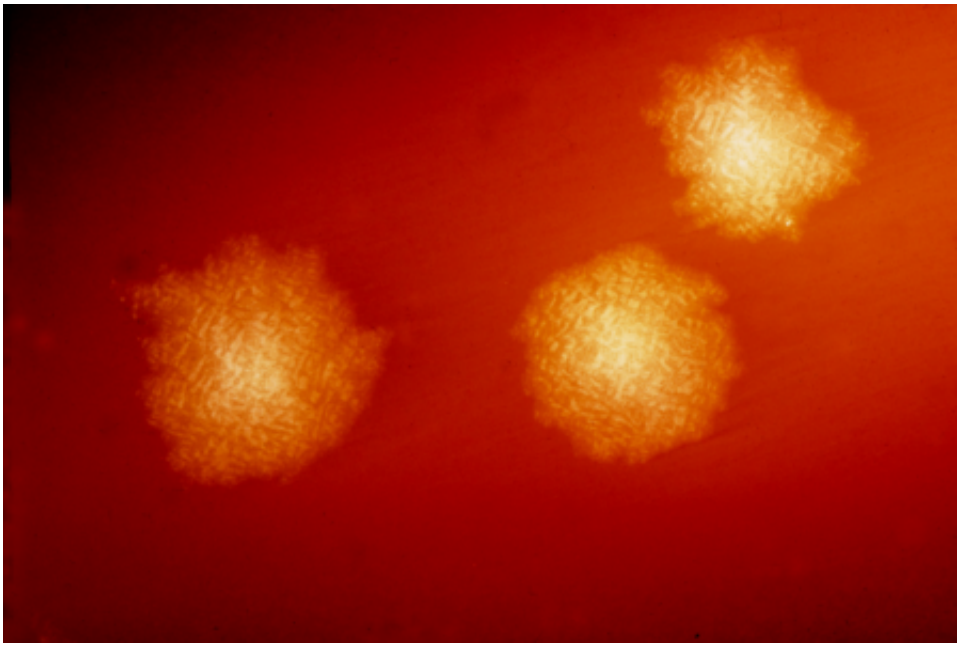

This photograph depicts Clostridium difficile colonies after 48hrs growth on a blood agar plate; Magnified 4.8X. C. difficile, an anaerobic gram-positive rod, is the most frequently identified cause of antibiotic-associated diarrhea (AAD). It accounts for approximately 15–25% of all episodes of AAD. Credit: CDC

Multiple species of bacteria working together in healthy guts are responsible for keeping out nasty bacterial invader, *Clostridium difficile*, a hospital-acquired culprit responsible for 15,000 deaths each year. The study, published this week in *mBio*, the online open-access journal of the American Society for Microbiology, could lead to tests to predict which

hospital patients are at highest risk of infection and better management of infections.

"Hospital-acquired *C. difficile* infections have bloomed as a problem in the last 10-15 years, representing $4.8 billion in added healthcare costs," says Patrick Schloss, a microbiologist at the University of Michigan in Ann Arbor who oversaw the study. "One of the biggest risk factors for someone acquiring *C. difficile* is exposure to antibiotics. That puts a huge pool of people at risk."

To mimic those patient conditions, Schloss's former graduate student, Alyxandria Schubert tested 8 antibiotics in 16 different treatment conditions to see how they altered the normal gut microbiota of mice. Then, she measured how those altered communities responded when exposed to *C. difficile*.

Not surprisingly, each treatment yielded different alterations in the communities, with different bacterial species increasing or decreasing in abundance. No single species accounted for either protection against or susceptibility to *C. difficile*.

"Mathematical modeling became really critical for the large amount of data we had," says Schloss. Previous work by the Schloss lab and others had hinted that protection against *C. difficile* colonization was likely due to multiple species within the gut microbiota. Ultimately, the team wanted to build a model that could use a mouse's starting gut bacterial community to predict that mouse's risk of infection.

To do that, the team applied a machine-learning algorithm to their entire dataset of the 16 treatment conditions and the resulting community-wide changes in bacterial species. In a sense, the algorithm acts akin to an email spam filter, says Schloss, using a 'forest' of decision trees to classify all the moving parts in a complicated data set.

The team built a mathematical model that could predict with about 90% accuracy whether a given mouse, starting with a particular gut bacterial community, would fall ill with *C. difficile*. The analysis also revealed the complex bacterial relationships that governed resistance to *C. difficile*.

Resistance was associated with members of the Porphyromonadaceae, Lachnospiraceae, *Lactobacillus*, *Alistipes*, and *Turicibacter*. Susceptibility to *C. difficile*, on the other hand, was associated with loss of these protective species and a rise in *Escherichia* or *Streptococcus*.

"Susceptibility is not all or nothing—it's extremely context dependent," says Schloss. He says that simply having a 'good' protective bacterial species present does not equal protection, nor does simply harboring one of the 'bad' bacterial species equal illness. "I think about it as a buffet, where you have to mix and match different ingredients to get resistance or sensitivity to *C. difficile*."

Having an accurate, predictive model in mice is a proof-of-principle that such a model could also work for human patients in a hospital setting. "If we could assess a patient's microbiota from a stool sample—especially if they are getting antibiotics—we could look at what bacteria are missing," says Schubert, now a postdoctoral researcher in the Schloss laboratory. "You could perhaps give patients a probiotic supplement with the goal of restoring their microbiota community structure to a healthy state."

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