C. difficile needs iron, but too much is hazardous

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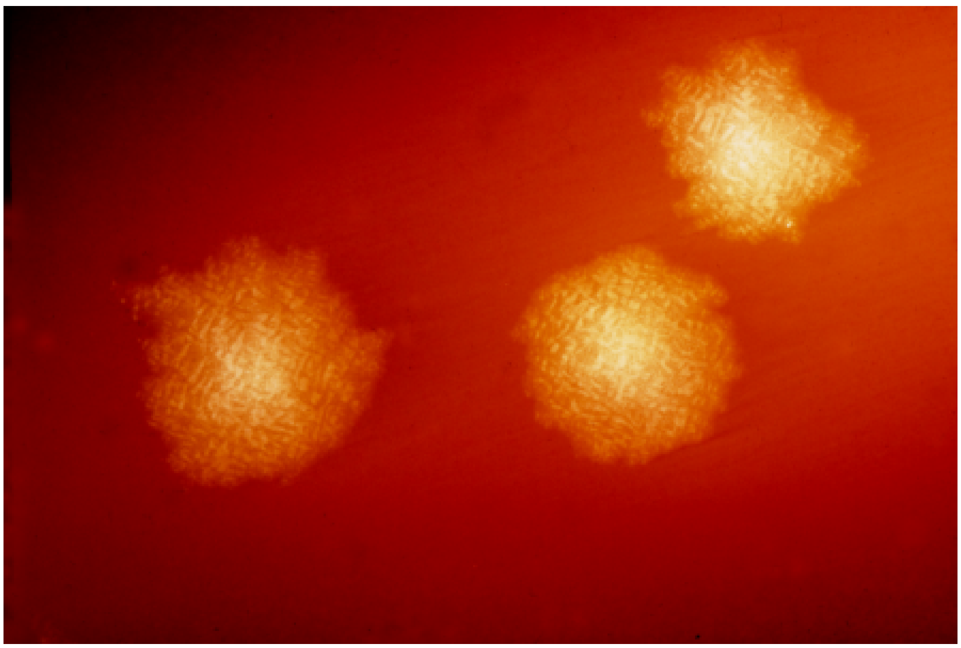

This photograph depicts Clostridium difficile colonies after 48hrs growth on a blood agar plate; Magnified 4.8X. C. difficile, an anaerobic gram-positive rod, is the most frequently identified cause of antibiotic-associated diarrhea (AAD). It accounts for approximately 15–25% of all episodes of AAD.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

Those bacteria that require iron walk a tightrope. Iron is essential for their growth, but too much iron can damage DNA and enzymes through oxidation. Therefore, bacteria have machinery to maintain their intracellular iron within a range that is healthy for them. Now Theresa D. Ho, PhD, and Craig D. Ellermeier, PhD shed new light on how the pathogen, Clostridium difficile, which is the most common cause of hospital-acquired infectious diarrhea, regulates iron. The research is published online ahead of print July 6 in the *Journal of Bacteriology*, a publication of the American Society for Microbiology.

"We hypothesized that C. difficile must tightly control the production of its iron acquisition mechanisms so that just the right amount of iron is brought into the bacteria," said Ellermeier, who is an Associate Professor in the Department of Microbiology, University of Iowa, Iowa City. They further posited that a compound called "Ferric-uptake regulator," or Fur, which is known to control intracellular iron homeostasis in many other species of bacteria, functioned similarly in C. difficile. Fur exerts this control by repressing production of the iron-acquiring proteins when iron is plentiful in the environment.

In the study, they constructed a mutant C. difficile that does not make Fur. That way, they reasoned, those genes that are normally repressed by Fur in the presence of environmental iron would be produced in large quantities by the mutant, but not by wild type C. difficile, which would help them identify the iron-importing proteins.

These experiments suggested that C. difficile has multiple systems for importing ferrous iron compounds, said Ho. C. difficile grows only under anaerobic conditions (without oxygen). "These iron oxide import systems may be more important—and thus the redundancy—in the strict anaerobe," said Ho. She explained that the forms of iron which are soluble are different under aerobic versus anaerobic conditions, and that little work on bacterial iron homeostasis has been done in strict anaerobes, such as C. difficile.

In the short term, the scientists do not foresee this research resulting in therapeutics for C. difficile, which is unfortunate, because the microbe is highly resistant to existing antibiotics, and very hard to eradicate. Ho pointed out that limiting the bacterium's growth by reducing iron availability could also affect "good" gut microbiota—possibly negatively. "But in the long term," said Ellermeier, "if iron transport is critical one could imagine the development of drugs which would inhibit iron transport in C diff.

But fecal transplant appears to be a very effective way to eradicate C. difficile. www.asm.org/index.php/asm-news … -resistant-pathogens.

C. difficile causes inflammation of the large intestine, resulting in diarrhea. The disease frequently returns after an initial case has been successfully treated. C. difficile is estimated to cause roughly half a million cases, and nearly 30,000 deaths annually. This disease is a particular scourge among elderly patients receiving hospital care.

More information: "Ferric Uptake Regulator Fur control of Putative Iron Acquisition Systems in Clostridium difficile." *J. Bacteriol.* JB.00098-15; Accepted manuscript posted online 6 July 2015, DOI: 10.1128/JB.00098-15

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