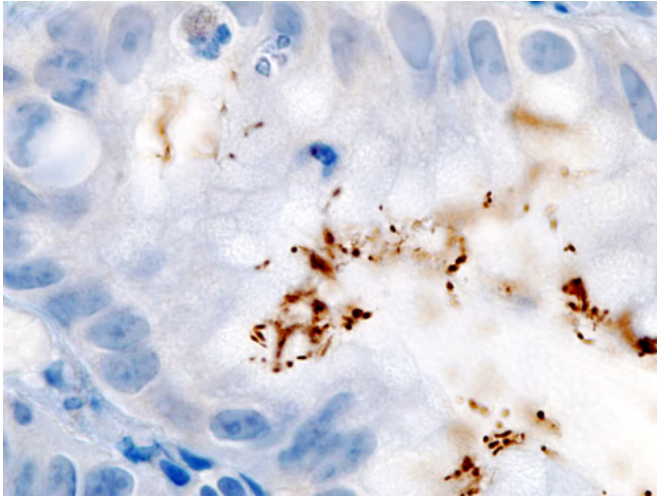


Study shows why stomach pathogen is so tough to eradicate

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Histopathology of *Helicobacter pylori* infection in a gastric foveolar pit demonstrated in endoscopic gastric biopsy. Credit: Wikipedia.

The stomach-dwelling bacteria *Helicobacter pylori* survives in the stomach—a hellish, churning vat of hydrochloric acid—by holing up inside that organ's pitlike glands and establishing squatter's rights. Once the germ has set up shop, Stanford University School of Medicine investigators have learned, even competing strains of the same species can't displace it, or even share its hideout.

The findings, to be published online May 2 in *PLoS Biology*, raise questions about the effectiveness of probiotic approaches, in which "good" germs are ingested in an effort to supplant "bad" germs. Yet the findings also hint at possibly effective ways to deal with the potentially life-threatening *H. pylori* [strains](#) now inhabiting one of every two human stomachs.

"This study changes the way we think about how microbes like *H. pylori* establish their chronic persistence in the body," said Manuel Amieva, MD,

Ph.D., associate professor of pediatrics and of microbiology and immunology, who is the study's senior author. The lead author is former graduate student Connie Fung, Ph.D.

H. pylori is the primary cause of stomach ulcers and stomach cancer. Fortunately, the great majority of infected people remain asymptomatic throughout their lives: Only 10-15% of infected people get ulcers, and only 1% get [stomach cancer](#).

Plus, there are reasons for thinking that infection by *H. pylori*, which has co-existed with humans since the earliest days of our species, may have some advantages. For instance, *H. pylori* infection is associated with lower incidences of asthma and other allergies. The combination of that upside and the low-incidence, high-impact nature of *H. pylori*'s adverse effects gives pause to medical researchers considering ways of preemptively eradicating it from all of our stomachs. It may be wiser to substitute friendlier "designer" strains.

But that won't be easy, the study showed.

Succeeding where others fail

From an ecological point of view, *H. pylori* has succeeded where practically every other bacterial pest has failed. It has evolved the capacity to persist for prolonged periods—often for a person's entire life—in the stomach, whose intense acidity, swiftly shifting chemical contents and rapid cellular turnover make it one of the harshest environments a microbe encounters.

Although *H. pylori* is susceptible to antibiotics, it's not uncommon for these drugs to fail to completely clear the stomach of the microorganism. "The re-emerging strain is invariably just the same as the one thought to have been eradicated," Amieva said, suggesting the presence of some niche where *H. pylori* can find refuge and replenish its numbers in safety. But exactly how has been unclear.

H. pylori is a corkscrew-shaped microbe equipped with a tuft of spinning, hairlike projections called flagella that enable it to swim freely in an aqueous liquid medium or to bore into viscous fluids. Microbiologists have long thought it avoids being dissolved in a sea of stomach acid by hiding out in the mucus layer that lines the stomach and protects the digestive organ from being eaten by the acid it produces.

That's part of the story. But the new study reveals a safer survival tactic for the bug: steering itself into one of the myriad pitlike glands that dot the stomach's inner surface and, afterward, fending off all comers.

In a study published in 2015, Amieva's group discovered the presence of *H. pylori* within stomach glands. But why the microbe would choose to hang out there was not obvious.

The new study, Amieva said, shows that once a particularly hardy, or lucky, individual *H. pylori* bacterium manages to colonize a gland, the resulting "founder" strain becomes extremely difficult to dislodge even by members of an essentially identical strain, for reasons that remain mysterious but may have to do with the fact that each gland has only a single, tiny entry point.

Glowing green and red

The researchers inoculated mice's stomachs with two versions of an otherwise identical *H. pylori* strain, differing only in that one group had been genetically modified so it emitted fluorescent green light when stimulated by a laser, while the other group was modified to glow red. Later, the scientists could observe the different-colored strains' success in establishing themselves within glands along the length of the mice's stomachs.

The scientists used a form of microscopy that allowed them to move their focus through successive depths of intact tissue rather than view separate thin tissue slices. They also used a technique called CLARITY that renders tissues transparent without destroying their microanatomical integrity. That combination let them visualize, in three dimensions, *H. pylori*'s

presence along the depths of the stomach glands.

Instead of mixing randomly—as one would expect if occupancy of a gland by one "color" of bugs presented no barrier to entry by the other color—the two sets of *H. pylori* occupied distinct patches of [stomach](#)-surface area, indicating an exclusive "first-come, first-served" advantage for a given gland's initial occupant and further suggesting that, having established itself within a gland, a "red" or "green" *H. pylori* strain sends forth individual progeny to adjacent glands in which they plant their flags, thrive, exclude newcomers, multiply and eventually release new single-celled troops to repeat the gland-by-gland expeditionary advance.

Precisely which tools the bacteria need to establish squatter's rights in a [gland](#) is still guesswork. But when the scientists inoculated mouse stomachs with mutant *H. pylori* lacking the functioning chemical sensor machinery that guides its swimming direction, the bugs were unable to maintain exclusive colonies in glands.

This raises the issue of how to eradicate potentially pathogenic bacterial strains ensconced in our bodies or how to replace them by others that are less pathogenic. Probiotics have not demonstrated much success in achieving that goal yet, Amieva said.

"It's not enough to find a good probiotic strain that can survive in the organ you want it to live in," he said. "You need to create space for it."

One potential approach, Amieva suggested, would be to find some way to draw the bacteria out of their protective hideouts before treating them and then replacing them with a less-virulent strain.

Provided by Stanford University Medical Center

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