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Staph 'gangs' share nutrients during infection, study finds

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Antibiotic-resistant bacteria can share resources to cause chronic infections, Vanderbilt University investigators have discovered. Like the individual members of a gang who might be relatively harmless alone, they turn deadly when they get together with their "friends."

The findings, reported Oct. 8 in *Cell Host & Microbe*, shed light on a long-standing question in infectious diseases and may inform new treatment strategies, said Eric Skaar, Ph.D., MPH, Ernest W. Goodpasture Professor of Pathology, Microbiology and Immunology.

One way that *Staphylococcus aureus* and other pathogens can become resistant to antibiotics is by changing the way they generate energy and becoming "small colony variants," which are small and weak, Skaar explained.

"The question has been: how do bacteria that are less fit and grow poorly in the laboratory cause such persistent infections in humans?"

The current studies support the notion that antibiotic-resistant staph bacteria, including methicillin-resistant (MRSA) strains, can exchange nutrients with each other and even with other bacterial species, including the "normal" microbes of the microbiome, to increase their virulence during an infection.

The findings challenge infectious disease dogma, Skaar said.

"The thinking has been that if an infection becomes resistant to antibiotics, then the resistant organisms appeared clonally, meaning they're all genetically the same."

Skaar and his colleagues wondered if perhaps instead "there are a bunch of organisms that became resistant in different ways and that can exchange the molecules they're each individually missing."

Two fellows in the lab, Neal Hammer, Ph.D., and James Cassat, M.D., Ph.D., now an assistant professor of Pediatrics at Vanderbilt, tested this hypothesis by mixing together two different small colony variant strains of staph – one that can't produce heme and the other that can't make menaquinone. They found that in culture, these strains exchanged the two metabolites and grew as if they were wild-type staph.

Next, they tested the idea in a mouse model of bone infection (osteomyelitis). Antibiotic-resistant small colony variant *S. aureus* is the cause of chronic and difficult to treat osteomyelitis and also of lung infections in patients with cystic fibrosis (CF).

The investigators demonstrated that either staph strain alone (heme- or menaquinone-deficient) caused only minimal bone infection, but mixed together, they caused a fully virulent and bone-destroying infection.

"In bone, these bacteria are trading molecules," Skaar said.

In collaboration with C. Buddy Creech, M.D., MPH, associate professor of Pediatrics, the researchers isolated samples of staph small colony variants and normal bacteria from the lungs of CF patients.

When individual CF staph small colony variants were mixed together in culture, they grew like wild-type bacteria. Likewise, co-culture of CF staph small colony variants with normal microbiome bacterial species

also enhanced the growth of staph in culture.

"The microbiome of a cystic fibrosis patient's lungs can provide nutrients to these small colony variants and revert them to wild-type behavior," Skaar said.

"Our findings show that these antibiotic-resistant infections are not what we thought they were – they're not a single strain of bacteria with a single lesion leading to the small colony variant phenotype," he said. "Instead, they're a mixed population of organisms that are sharing nutrients.

"They act like a big group of bullies until you hit them with drugs, then they stop sharing resources and are resistant. When the drugs go away, they start sharing resources again and get even tougher.

"We're now a little bit smarter about how these organisms are behaving in an infection, which I think we can use to inform new treatment approaches."

Preventing the nutrient exchange, for example, may offer a new therapeutic strategy against these antibiotic-resistant organisms, Skaar said.

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