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The Human Nose Pilots a New Antibiotic Era

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Hannah Martin Lawrenz

Researchers discovered a new antibiotic hiding in the nose microbiota that kills common sources of dangerous infections, including MRSA. Read more...

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Over the past decade, the international health community has faced rapidly diminishing supplies of effective antibiotics amidst increasing antibiotic resistance. As teams across the globe scramble to solve this dilemma, Andreas Peschel and colleagues at the University of Tübingen, Germany have located a new antibiotic hiding right under—or, more accurately, in—our noses.

A resident of the human nostril in 9% of the population, *Staphylococcus lugdunensis*, kills potentially deadly infectious agents such as methicillin-resistant *Staphylococcus aureus* (MRSA). For concerned public health officials and researchers, this finding, published in *Nature*, heralds a new era in antibiotic discovery and the international fight against mounting microbial resistance.

Staphylococcus Infections: Nothing to Sneeze At

Nasal carriers of *S. aureus* have an increased risk of developing dangerous infections, especially in hospital settings. This Gram-positive coccal bacterium resides in the noses of 20-30% of the population and causes the most life-threatening invasive infections in the northern hemisphere. Its aggressive MRSA strain is listed among the top 18 drug-resistant threats in the United States.

The origins of increasing resistance to antibiotics in bacteria such as *S. aureus* are multifactorial, and overly strong selection pressures can promote the spread of resistant bacteria. Hygiene is also a major problem. Because so many microorganisms reside in the human nose, without excellent hand hygiene, they can be easily transferred between patients in a hospital setting or from a nose to an open wound. Additional factors such as overcrowding, international travel, and abuse of antibiotics by over-prescription also influence resistance development. “At the moment, we are using too many antibiotics applied in incorrect ways—the wrong antibiotic amount, or wrong timescale,” said Peschel.

But according to Kim Lewis, director of Northeastern University’s Antimicrobial Discovery Center, who was not involved in the new study, “The primary cause of decreased antibiotic effectiveness is our inability to discover new antibiotics.”

Nosing Around the Microbiota

Bacteria living on and in the human body often compete for nutrients and space, and those that produce antibiotics nudge out their competitors more easily. Genomic analysis of the human microbiome has also identified certain genes that encode enzymes for antibiotic production, making them attractive as a source for new antibiotics.

“This is our first case of antibiotics found in human bacteria. All other antibiotics come from bacteria in the environment and such,” said Peschel. “Nobody expected these compounds to be produced in our human body.”

Although about a third of the population carries some *S. aureus* in their noses, few develop infections. Peschel’s team hypothesized that other bacteria compete locally with *S. aureus* and other pathogens, keeping them in check. To explore this idea, they tested individual candidates from the human nasal microbiota that could limit *Staphylococcus* growth, then screened

New antibiotics produced in our noses could guard against dangerous infections.

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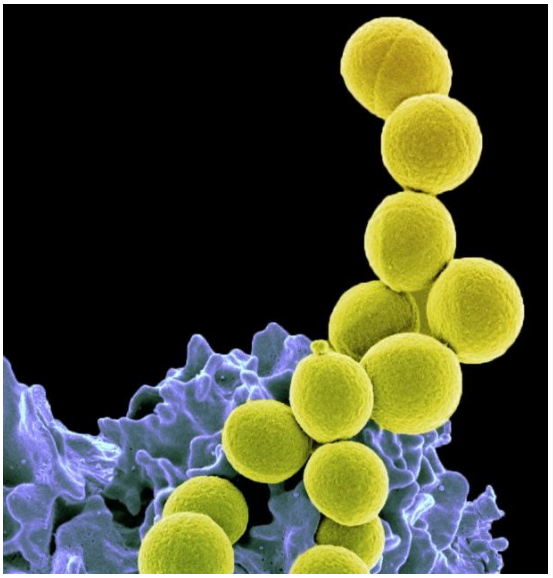
90 bacterial strains to find a local competitor. They co-cultured each of these strains in the presence of *S. aureus* to see if any competed with *S. aureus*. Only the strain *S. lugdunensis* showed strong bactericidal activity against *S. aureus*.

After identifying responsible genes through mutagenesis and systematically conducting knock outs in *S. lugdunensis*, the researchers found a single mutant strain that had lost its ability to compete with *S. aureus*. This impaired strain lacked the cyclic peptide substance that kills *S. aureus*—a new antibiotic the researchers called lugdunin.

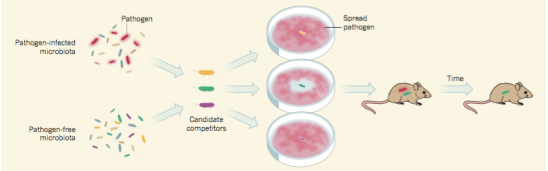
To understand lugdunin more completely, the team needed to expand the study's original scope and recruit additional expertise. "The major challenge was coordinating a very interdisciplinary topic," Peschel noted. "We're bacteriologists, but we needed help from analytical chemists and synthetic chemists who can synthesize the compound." Although this extensive collaboration created several practical challenges, Peschel said the work was "also fun—it's just fantastic to work with all these colleagues and learn from each other."

After confirming activity with natural and synthetic lugdunin, the team tested its ability to inhibit *S. aureus* growth in cell cultures, on the skin of mice, and in the noses of cotton rats. In both initial in vitro testing and later in vivo studies, lugdunin killed *S. aureus*, and also successfully thwarted the growth of several bacterial pathogens, including MRSA and *Enterococcus* strains that are resistant to vancomycin. Interestingly, these bacteria did not develop resistance to lugdunin, unlike many other antibiotic regimens.

Finally, the researchers investigated *S. lugdunensis* in humans, examining nasal swabs from 187 hospitalized patients. Individuals who carried *S. lugdunensis* in their nostrils showed a much lower *S. aureus* colonization rate than those without *S. lugdunensis.*



Methicillin-resistant S. aureus bacteria (MRSA) are ingested by a neutrophil (credit: NIAID).



The researchers tracked lugdunin's activity on the skin of mice, demonstrating its ability to kill local pathogens (5).

Lugdunin faces a long road of clinical trials before gaining approval as a new antibiotic.

Future Possibilities and Long-term Solutions

Peschel's team now plans to explore whether lugdunin or the microbes that produce it can be used to develop new therapies. "If you can make sure that an at-risk patient is colonized with *S. lugdunensis*, you may not have to prescribe an antibiotic," noted Peschel. "The bacteria is producing its own antibiotic all the time, so *S. aureus* will not have a chance to colonize these people."

Locations such as the nostrils are already accustomed to lugdunin's presence, so using this compound as an antibiotic may create minimal side effects as well. However, because the compound comes from a bacterium that could cause infection under some circumstances such as immune suppression or poor health, *S. lugdunensis* would not work as a probiotic supplement.

Initial biochemical experiments showed that *S. lugdunensis* exclusively encodes a unique combination of antibiotic biosynthesis enzymes, all with less than 35% resemblance to known enzymes, indicating a previously unknown antibiotic category. Peschel hopes that further elucidating this distinctive metabolic pathway could lead to the synthesis of a new compound and provide a model for drug development.

"We've filed a patent for lugdunin and started talking to pharmaceutical companies. We'll see if we will collaborate to evaluate the compound first in a pre-clinical setting for pharmacology, toxicology, and so on," said Peschel. "There needs to be clinical studies to show its efficacy and non-toxicity. That will take many years, of course. But, it gives us something to start from now, and that gives hope in light of the amount of antibiotic-resistant *Staphylococcus* [infections]."

"We are at the beginning of developing a concept," he concluded.

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