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Overcoming the last line of antibiotic resistance against bacterial infections

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A common type of bacteria is causing a major healthcare crisis as we inch closer towards the last line of antibiotic resistance against bacterial infections. The bacterium known as *Staphylococcus aureus* (*S. aureus*) is harboured by up to 60% of the human population and causes a variety of infections with severities ranging from mild to life threatening. While *S. aureus* is the cause of many common skin infections, it can also infect our essential organs such as the heart and lungs by travelling through our body's bloodstreams. This can lead to fatal illnesses such as septicemia, endocarditis, and necrotizing pneumonia which cause blood poisoning, heart inflammation, and lung failure respectively. Regrettably, there are currently no vaccines against *S. aureus* infections.

So how is *S. aureus* so effective at infecting us with various illnesses? A recent study published in *Frontiers in Cellular and Infection Microbiology* by a research group at Montana State University of the United States examined over 220 studies on this subject. They present a comprehensive overview of *S. aureus*' remarkable resilience against our body's immune system which protects us against foreign invaders.

"Many bacteria depend on a few key virulence factors, which are molecules that make the bacteria stronger, to cause disease. We have yet to find a key virulence factor used by *S. aureus* to initiate disease in humans," says Fermin Guerra who is the first author of this landmark study. "Gaining an understanding of how *S. aureus* initiates infection will lead to new methods to combat ailments caused by this bacterium to ultimately reduce disease and decrease dependence on antibiotics."

Neutrophils are a type of immune cells that protect us against foreign invaders such as *S. aureus*. They are an essential part of our body's immune defense system and are one of the first responders to the site of bacterial infection. Once neutrophils are recruited to the site of infection in a process called chemotaxis, neutrophils recruit other soldiers of the immune system army to kill the invader. Neutrophils can also directly kill bacteria by swallowing and digesting them. Neutrophils are very effective at eliminating most types of bacteria but the pesky *S. aureus* has developed various methods to defend against neutrophils. "The ability of neutrophils to kill *S. aureus* is crucial to infection resolution but *S. aureus* has developed mechanisms to counter neutrophils' killing mechanisms," explained Fermin.

"We sought to highlight the virulence factors used by *S. aureus* to interrupt neutrophil functions, provide an understanding of how *S. aureus* senses neutrophils, and identify novel therapeutic approaches that attack the ability of *S. aureus* to "see" its environment and sense neutrophils," summarized Fermin. The main findings of this seminal study are highlighted below.

S. aureus is equipped with the ability to sense approaching neutrophils by recognizing the molecules produced by our defenders. The bacterium releases virulence factors that slow down the migration of neutrophils which gives *S. aureus* more time to infect our bodies before neutrophils reach the site of infection. To make themselves more effective at killing bacteria, neutrophils undergo an enhancement process called priming. *S. aureus* can also release a family of molecules that impede this enhancement making neutrophils less potent.

S. aureus has also developed various methods to combat neutrophils once they are near each other. To protect itself from being eaten by neutrophils, *S. aureus* produces both physical capsules to shield themselves and releases molecules that disrupt neutrophils' recognition

of the bacterium. If a neutrophil does manage to swallow *S. aureus*, the persistent bacterium repels digestive proteins and releases molecules to degrade these proteins minimizing the effects of digestion. Furthermore, *S. aureus* can even release toxins that rupture and ultimately kill neutrophils.

An over-abundance of neutrophils at the site of bacterial infection can lead to prolonged inflammation which may lead to the thickening of our blood vessels and autoimmunity. *S. aureus* interrupts our immune system's ability to constrain the number of neutrophils at the site of infection causing prolonged inflammation in the infected region.

Evidently, *S. aureus* employs a variety of tactics to identify, defend, and even attack neutrophils.

While this study provides extensive insight into the mechanisms by which the *S. aureus* evades our immune system, the authors stressed that more studies are required to fully understand its behaviour. "We still have a long way to go to fully understand the mechanisms used by *S. aureus* to be so successful at causing infections in humans," says Fermin.

"What makes community-associated *S. aureus* strains unique (compared to healthcare-associated) in establishing infections in healthy individuals? Can we successfully develop vaccines that simultaneously target multiple virulence factors? We hope the review helps in designing future research studies tackling issues described in this review. We also hope this review sheds more light on the public health danger *S. aureus* poses especially as we reach the last lines of antibiotic defense used to treat infections," concluded Fermin.

More information: Fermin E. Guerra et al, Epic Immune Battles of History: Neutrophils vs. Staphylococcus aureus, *Frontiers in Cellular and Infection Microbiology* (2017). DOI: 10.3389/fcimb.2017.00286

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