MRSA biofilms in joint fluid make infections tough to tackle

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Physicians have long speculated at the hard-to-treat nature of joint infection. In an article published in *Journal of Infectious Diseases*, Thomas Jefferson University scientists, in collaboration with scientists at the National Institutes of Health, come one step closer to understanding why these infections are so tough to tackle. The results could help explain the joint pain caused by different infections, including Lyme disease and why they're so resistant to antibiotic treatment.

"Biofilm formation has been suspected to play a key role during septic arthritis and prosthetic joint infection." said Noreen Hickok, Ph.D., Associate Professor in the Department of Orthopedic Surgery in the Sidney Kimmel Medical College at Thomas Jefferson University. "This study could help explain why these infections have been so difficult to treat and point to therapeutic approaches that could make antibiotics more effective."

Hickok and Michael Otto, Ph.D., a Senior Investigator with the Laboratory of Human Bacterial Pathogenesis National Institute for Allergies and Infectious Diseases, National Institutes of Health, served as co-senior investigators on the study.

"Our goal was to determine why Staphylococcus aureus, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), infections of the joint tend to be relatively unresponsive to standard antibiotic treatment," offered Sana Dastgheyb, lead author on the study and student at Jefferson's Graduate School of Biomedical Sciences.

Although many researchers study bacterial growth in standard growth medium, Hickok, Otto, and their teams wanted to know whether the bacteria behaved differently in the liquid that surrounds the joints – the so-called synovial fluid. They grew up several strains of MRSA in human synovial fluid, blood, and typical bacterial growth medium.

The researchers found that the bacteria begin to grow as clumps in the synovial fluid, and that these clumps share many of the same properties as biofilms. For example, the clumped bacteria embed themselves in a protective mesh of proteins that resist the penetration of antibiotics. They also found that the bacteria slow their growth, making them even less susceptible to antibiotics, which are designed to target rapidly growing cells like bacteria.

The collaborators showed that they could inhibit the formation of these biofilm clumps that they called "bio-floaters" by pre-treating the synovial fluid with a plasmin enzyme that degraded the protein matrix. With this pre-treatment, the research team reduced the formation of bio-floater clumps and increased the bacterial susceptibility to antibiotics.

"The study also helps explain why joint infections are so difficult to diagnose, even when there are overt signs of infection," said Dr. Hickok. Current tests for bacterial growth cannot differentiate a single bacterium from a bio-floater clump containing millions of cells, leading to an underestimate of the infection or a lack of detection altogether.

"This study strikes at the heart of one of the most pertinent questions in medicine, namely how the medical community can use antibiotics in the most effective manner to prevent infections." said Javad Parvizi, M.D., the James Edwards Professor of Orthopaedic Surgery in the Sidney Kimmel Medical College at Thomas Jefferson University, Director of Clinical Research at The Rothman Institute, and an author on the study. "Dr. Hickok and her team, by conducting this groundbreaking research,

have enhanced our understanding of this phenomenon and opened our eyes to a very novel concept."

Although the pre-treatment appeared to stall growth in the lab, more research is needed before the results can be translated to patient care.

More information: Sana Dastgheyb, Javad Parvizi, Irving M. Shapiro, Noreen J. Hickok, and Michael Otto. Biofilms cause recalcitrance of staphylococcal joint infection to antibiotic treatment *J Infect Dis*. first published online September 11, 2014 DOI: 10.1093/infdis/jiu514

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