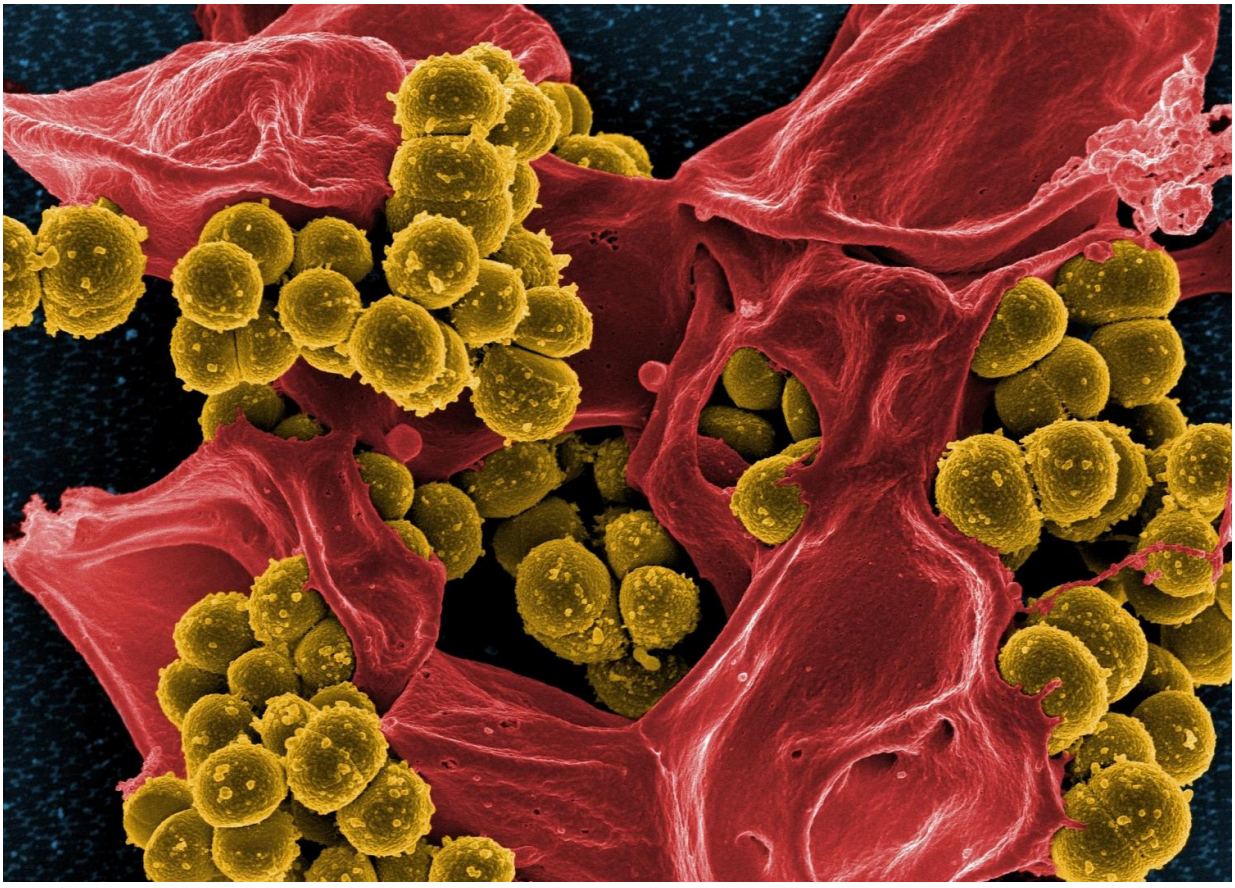
Researchers discover why sepsis from a staph infection causes organ failure

July 26 2018



Credit: CC0 Public Domain

For patients diagnosed with a *Staphylococcus aureus* infection, often referred to as a staph or MRSA infection, every minute counts. The

bacteria create havoc in the body. The immune system goes into overdrive. The heightened immune response can lead to sepsis, which kills 30 to 50 per cent of the people who develop it. In Canada, sepsis is the 12th leading cause of death.

Scientists have known for some time that one of the reasons a staph infection is so deadly is that the bacteria send out a toxin, known as Alpha Toxin (AT), which quickly worsens sepsis. University of Calgary scientists at the Cumming School of Medicine's (CSM) Snyder Institute for Chronic Diseases have discovered the most important target of the toxin and how to neutralize the danger.

"For years, we've been looking at the effects of the toxin on cells inside a test tube, but we really didn't know what was happening inside the body at the height of an infection," says Dr. Bas Surewaard, Ph.D., a postdoc in the Department of Physiology & Pharmacology and first author of the study.

Using a process that allows scientists to see what's happening inside living animals, called intravital microscopy, researchers discovered that the toxin causes platelets to respond abnormally in mice. Platelets' primary role is to help stop bleeding in mammals after injury. What's relatively unknown is that platelets also play a role in the body's defenses against bacteria. Normally, platelets coat bacteria to prevent the spread of a microbe throughout the patient. However, during sepsis caused by staph infection, as the amount of toxin in the bloodstream increases, the platelets aggregate to form clumps. Those clumps deposit in the liver and kidneys, causing serious damage and eventually organ failure.

"Once you understand exactly how an infection is impacting the body, you can target treatments to mitigate the infection so that the body can begin to heal," says Dr. Paul Kubes, Ph.D., professor in the Department of Physiology & Pharmacology and director of the Snyder Institute. "We

knew clots were forming in the organs during sepsis from staph infection. Now we know where and why these clots are forming."

Next, the team wanted to know whether an antibody that targets the toxin could be effective in preventing platelets from clumping. The researchers started working with MedImmune. The drug company is conducting a phase ll clinical trial where an Alpha Toxin antibody that they have developed is given to intensive care unit patients prone to develop pneumonia caused by staph due to long-term use of a ventilator. Early indications are the antibody is effective in preventing lung damage.

"When we introduced the antibody to the bloodstream of the mice during sepsis, we saw an immediate reduction in the amount of clotting," says Surewaard. "A single dose of the antibody reduced liver damage by 50 per cent. By knocking out the toxin, the platelets could begin flowing in the blood stream again."

The findings, published in *Cell Host & Microbe*, help explain why some people who are taking antibiotics to kill staph infection still die from sepsis, because the antibiotics do not neutralize the toxin.

"Knowing how the toxin created by staph target platelets, we can now start looking at other bacteria that cause sepsis to see whether we can uncover a similar pattern and find antibodies that can be effective in those cases," says Kubes.

More information: Bas G.J. Surewaard et al, α-Toxin Induces Platelet Aggregation and Liver Injury during Staphylococcus aureus Sepsis, *Cell Host & Microbe* (2018). DOI: 10.1016/j.chom.2018.06.017

Provided by University of Calgary