Battling bacteria in the blood: Researchers tackle deadly infections

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It's a leading cause of death, but no one knows for sure how and why it happens. It's a major source of health care costs, adding days or weeks to the hospital stays and lost work time of millions of people. But no one fully understands how best to fight it.

"It" is bacterial infection in the blood, also called bacteremia, and it's a major part of the very serious illness called sepsis.

It's an infection that will turn deadly in some people, especially cancer patients and others with weak immune systems — while being easily treated in others. It doesn't get much public attention, although it affects ten times more Americans than breast cancer. Hospitals struggle mightily, but often futilely, to prevent and treat it every day.

Now, new research by a University of Michigan team and their colleagues is tackling the problem at its most basic level, in hopes of finding new and more effective ways to treat bacteremia and sepsis.

In a research paper published in the November issue of the journal *Shock*, and recent papers in the journals Bulletin of Mathematical Biology and Academic Emergency Medicine, the team describes new computer-based models of bloodstream infection that may help guide the development of new treatments.

The models use complex mathematical techniques, but have been validated by laboratory experiments in mice and in engineered

bloodstream models.

The new findings give more information than ever before about how bacteria act within the blood vessels of the body, and how they might be filtered out of the blood and into organs where the immune system can attack and kill them.

Now, this model of how bacteremia occurs in "real world" of the fast-moving bloodstream – rather than a placid Petri dish or test tube – can be put to work to study how best to combat or prevent bacteria in the blood.

John Younger, M.D., M.S., an associate professor of emergency medicine at the U-M Medical School, leads the team, which includes members with training in medicine, mathematics, and chemical engineering. He says the team's model reveals that a bacterial bloodstream infection can be thought of a high-speed police chase in heavy traffic.

"The bacteria are each a micron across – a thousandth of a millimeter – and they're traveling at the same fast speeds – up to three feet per second -- as other cells in the bloodstream, like red and white blood cells and platelets," he explains. "The white blood cells, which are the police of the body, are stuck in the same flow and can't 'change lanes' in the fast-moving traffic to capture and kill them."

That means the bacteria have to stick to the wall of a blood vessel before they can get caught, he says. And they're most likely to do that in the small blood vessels, or capillaries, within our organs or extremities.

Antibiotic drugs have been the standard treatment for these conditions since the drugs were developed in the mid-20th century. But because common bacteria have evolved to evade those drugs, antibiotics are

becoming less and less effective against bloodstream infections.

Better treatment for bacteremia and sepsis, then, might include strategies that can help the body filter bacteria out of the bloodstream and into these areas.

In the paper published in *Shock*, Younger and his team describe their new model of bacterial infection of the blood and organs, which they validated through experiments in mice.

The model combines the physiology of a blood vessel, the fluid dynamics of blood, and math-based models of how bacteria multiply and move between the bloodstream and organs. It also allows the researchers to better understand different conditions – including a low-immunity state such as what a cancer patient might experience, and a higher-than-usual blood flow rate that is often seen in patients who are fighting off a severe bloodstream infection.

"Bloodstream infections are infections that typically begin in a local part of the body, say in the bladder or the lung or the skin. But then the bacteria that cause these infections manage to break free from the usual local defenses and make it into the bloodstream, giving them an opportunity to go essentially anywhere they want," Younger explains. "Once in the bloodstream they can travel to distant organs; they can travel to the lung; they can travel to the heart. They're basically 'horses out of the barn'."

While creating the model, the researchers tested it by seeing how well it matched real-life mouse infections. Using bacteria that had been modified to give off a weak light signal that can be detected from outside the body, and other bacteria that could be detected through blood tests, they could see where the bacteria concentrated in the body during different stages of the infection, and how quickly they were killed and

cleared from the body.

The liver, lung and spleen had the highest concentrations, and the lung appeared to have the most effective bacteria-killing system.

Some of the mice were given a chemotherapy drug that is often used in cancer patients – one that kills white blood cells. Cancer patients and intensive-care unit patients are especially prone to bloodstream infections not only because of their weakened immune systems, but also because they often have long-term intravenous catheters that allow medicines to be given directly into the bloodstream.

While this helps patients avoid repeated intravenous needles, it also gives bacteria an easy pathway straight into the blood.

Indeed, the mice that received the chemo drug and an injection of bacteria all died of an out-of-control bacterial infection, while mice that didn't receive the drug were able to clear the infection from their bloodstream. The model successfully showed the same outcome.

An important part of bloodstream infections associated with catheters is the clumping-together of bacteria on surfaces – which is also seen in urinary catheters that cause many thousands of infections each year. But clumping that occurs within the bloodstream itself is also important since it may help bacteria become more vulnerable to immune system response.

The paper in the *Bulletin of Mathematical Biology* describes a model of this process -- known as flocculation – and sets the stage for further study of treatments that might accelerate clumping or make the clumps more stable. That, in turn, might help the body fight off infection more effectively.

Younger and his team have more research to do before their models yield results that might affect human treatment. But already, they are seeing the potential for how to improve the models and use them to simulate different aspects of human bacteremia and sepsis.

"We're trying to understand the rules for how bacteria traffic in the bloodstream -- and if you understand the timing of those events you might be able to better understand how best to detect the bloodstream infection when it's present," he says. "We're also working on ways to fundamentally change the rules of engagement between the bacteria and the host. There are mechanical features at play in terms of getting these bacteria in flowing blood out. If we can change the mechanics of that interaction, then we can potentially have a therapy that the bacteria don't really have an opportunity to defend against or develop resistance against. And that could be a useful therapy."

Source: University of Michigan

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