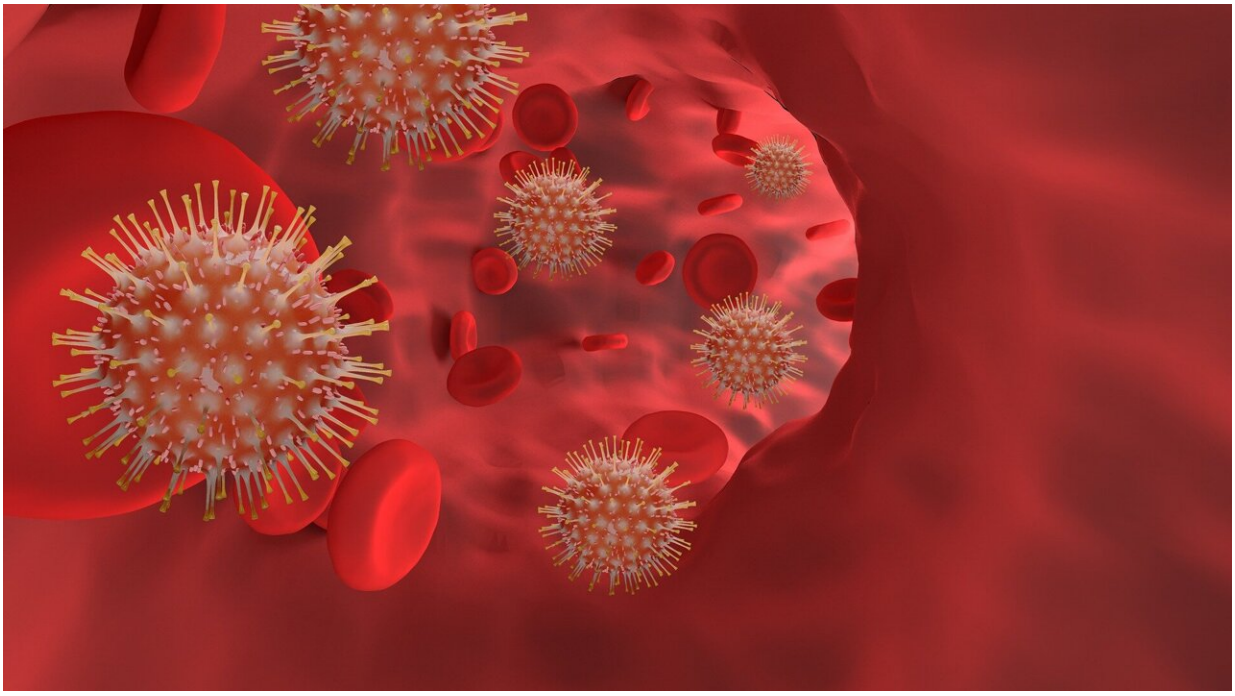
Deadly sepsis and antibiotic-resistant bacteria are in Europe's crosshairs

November 17 2023, by Michael Allen



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EU researchers are looking for new ways to tackle bloodstream infections that kill millions of people worldwide every year.

Professor Evangelos Giamarellos-Bourboulis has spent the past 18 years investigating a new way to treat sepsis—a medical condition that kills an estimated 11 million people worldwide every year. That's almost a fifth

of all global deaths.

Now Giamarellos-Bourboulis, an infectious-diseases expert at Attikon University Hospital in the Greek capital Athens, may be closer to a breakthrough as part of a research project.

Urgent action

Sepsis is an extreme immune response to an infection, usually a bacterial one. It is triggered when an infection starts in one organ and spreads across the whole body. Without speedy diagnosis and medical treatment, sepsis can rapidly lead to tissue damage, organ failure and death.

Giamarellos-Bourboulis, who is chair of the European Sepsis Alliance, has focused his research on how to trigger the body into carrying out its own immune-system repairs, allowing it to fight off the infection—an approach called immunotherapy.

"If immune function is restored to normal, then it is anticipated that the spreading of the infection will stop," he said.

The EU project on which Giamarellos-Bourboulis works is trialing sepsis immunotherapy on people and is due to end in December 2023 after four years. Called ImmunoSep, the project is coordinated by Professor Mihai G. Netea from Radboud University Nijmegen in the Netherlands and also brings together experts from France, Germany, Italy, Romania and Switzerland.

The trial is blind, meaning the people taking part are unaware what treatment they're getting and the researchers have no knowledge of the results until the end.

As he anticipates the trial outcome, Giamarellos-Bourboulis cited the

urgency of tackling sepsis by comparing it with the COVID-19 pandemic that struck in late 2019.

Globally, 7 million people have died from COVID-19 over the past four years, according to the World Health Organization (WHO). In that time, around 40 million people will have died from sepsis, based on the WHO's estimate and published evidence.

"Everyone speaks about COVID-19, no one speaks about sepsis," Giamarellos-Bourboulis said. "The true pandemic is sepsis."

Immune responses

While antibiotics are so far the only effective way of treating sepsis, improvements in diagnosis and wider options for treatment are needed to reduce deaths.

Sepsis is both driven by and causes changes in the patient's immune system.

"This change in immune function is not the same in each patient," Giamarellos-Bourboulis said.

Immune responses are generally one of two kinds: a hyper one, where the immune system goes into overdrive and causes a lot of damage, or immunoparalysis, in which the system becomes overwhelmed and stops working.

Since 2006, Giamarellos-Bourboulis and his colleagues have run multiple studies in Greece and the Netherlands involving patients with sepsis and healthy volunteers.

The team has pinpointed tests to distinguish between a hyper-immune

response and immunoparalysis. It has also looked at possible treatments to restore immune function in both cases.

The ImmunoSep trial aims to apply these tests and treatments to 280 patients with sepsis. Results are expected in spring 2024.

The medications being tested by ImmunoSep are already in use for other conditions.

For instance, the team hopes that a drug known as recombinant human interferon gamma, which is used to treat some rare diseases of the immune system, may restore it in patients with immunoparalysis.

If the treatments prove successful, Giamarellos-Bourboulis intends to work with the European Medicines Agency to win regulatory approval for them to be used for patients with sepsis.

Even if the treatments prove unsuccessful, he will press on with the knowledge gained from the trial.

"If none of the drugs work, we will analyze the data to see why so that adjustments can be made," Giamarellos-Bourboulis said.

Antibiotic resistance

A significant hurdle in treating sepsis is antimicrobial resistance, also known as AMR, which is the increasing ability of pathogens to resist antimicrobial treatment.

Giamarellos-Bourboulis said his biggest concern is that immunotherapy may fail to work in patients with AMR infections.

"If we don't reverse resistance to antibiotics, or we don't find new

antibiotics, the number of deaths in the years to come will be frightening," he said.

In 2019, the WHO declared AMR one of the top 10 public health threats . In the EU, AMR is responsible for more than 35,000 deaths a year.

To help address this threat, a pan-European clinical research network for infectious diseases was created. Called Ecraid, it is the first network of its kind in Europe.

AMR plays a big role in the work of Giamarellos-Bourboulis.

"We anticipate that 50% of sepsis cases are due to resistant bacteria," he said.

Widening options

Around 70 potential new antibacterial treatments are currently under development, with most of these acting in similar ways to current antibiotics, according to the WHO.

On average, AMR is reported in new antibacterial agents two to three years after the agents become available.

Powerful broad-spectrum antibiotics can treat a range of infections and are useful when doctors don't know exactly what they're dealing with. But these drugs also help drive antibiotic resistance.

This dilemma has preoccupied Grzegorz Gonciarz, chief operating officer of Resistell, a Swiss medical-technology company.

"The clinical problem we are addressing is the speed of diagnostics for patients with bloodstream infections," Gonciarz said.

Resistell aimed to develop a rapid-testing platform for getting the right treatment to patients fast. The project, called RAPID-SEP-AST, ran for two years through July 2022.

Current tests take around two days or longer to identify the best antibiotic to combat an infection. While waiting for these results, doctors usually start treatment with broad-spectrum antibiotics.

RAPID-SEP-AST's goal was to develop the world's fastest antibiotic susceptibility testing platform. That would enable speedy identification of the best antibiotic to treat the infection.

Final results from the project will be announced in the coming months, but the device appears to be able to identify the most effective antibiotic treatment for a bacterial sepsis infection in about two hours, according to Gonciarz.

Vibrating bacteria

What's different about Resistell's test is the way it measures how effective different antibiotics are at knocking bacteria on the head.

Called antibiotic susceptibility, it is usually tested by growing bacteria in a petri dish or other more automated systems with different antibiotics and seeing which ones best inhibit their growth.

Resistell's technology takes a different path. It does away with the need to grow bacteria and instead measures their vibrations.

When exposed to effective antibiotics, bacteria are killed and their vibrations lessen. The test uses algorithms developed with machine learning to measure these bacterial vibrations and tell which antibiotics work and which don't.

Resistell is now working to make the technology more automated and explore applications beyond sepsis such as tuberculosis and urinary tract infections.

More information:

- ImmunoSep
- RAPID-SEP-AST

Provided by Horizon: The EU Research & Innovation Magazine