HEALTH

Against antibiotic resistance, bacteria-eating viruses

The WHO calls it a silent pandemic. Antibiotic resistance or antimicrobial resistance is one of the major global public health threats. With consumption on the rise, France appears to be a bad student. In Lyon, a hospital is working on a natural treatment, phage therapy.

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At the Croix-Rousse hospital, in Lyon, on February 29, 2024. Professor Tristan Ferry examines the scar of Alexandre Vuitton, a patient he is following for an osteoarticular infection on the knee prosthesis. • BASTIEN DOUDAINE / HANS LUCAS, FOR LIFE

Installed in his hospital bed, Alexandre Vuitton patiently waits for someone to come pick him up. *"You're well-versed, no need to explain*

yourself anymore? » asks Koudedia, the nurse who welcomes him, kindly. For the third Thursday in a row, this 51-year-old patient travels from his home in Jura to the Croix-Rousse hospital, on the heights of Lyon, to receive his last injection of bacteriophages into his knee: these viruses, which do not only attack bacteria, could overcome the staphylococcus aureus which has developed around the prosthesis he has worn in his leg since he was 24. At the end of 2022, he had been living in Vietnam for 12 years when a violent infection brought him *"close to death"*: urgently repatriated, he underwent washings and antibiotic treatments for months. But *"one year to the day after the first attack"*, the infection returned. It is in this context that Professor Tristan Ferry, infectious disease specialist and coordinator of the Reference Center for Osteoarticular Infections (CrioaC), suggested that he try this treatment called "phage therapy".

"Slow speed tsunami"

In this renowned department where the most delicate cases flock, Professor Ferry has seen an increase in complex infections involving bacteria that are multi-resistant to antibiotics, like that of Alexandre, over the past 10 years. *"In hospitalization, that's half of our patients.* » If antibiotic resistance has stopped making the headlines in recent years, it is taken more seriously here than ever. Above the infectious disease specialist's office, a poster of the Kanagawa wave symbolizes this "slow-speed tsunami", which he also describes as a "silent plural pandemic": *"plural because the bacteria involved are numerous, silent because they manifest themselves through various illnesses."* According to the WHO, it will cause more deaths than cancer in 2050.

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Coming from the East under *"the effect of globalization and travel"*, this scourge has developed through self-medication or excessive prescriptions of antibiotics in certain countries, leading the bacteria to adapt. In France, this resistance to antibiotics has increased with

the aging of the population, which brings with it the progression of implants (prostheses, heart valves, etc.). The latter, explains Professor Ferry, *" help prolong and improve life but open the way, mechanically, to more numerous infections that are difficult to treat".* Like that of MB: visiting the day hospital this Thursday, this 76-year-old patient developed a pseudomonas infection on a prosthesis placed in 2021 for osteoarthritis. But even new antibiotics fail to stop it.

Phages, a "natural" response

Faced with these dramatic situations, the Croix-Rousse hospital became one of the world pioneers in phage therapy in 2015. This last-chance treatment to *"eliminate or at least contain the infection"* is not new: in 1917, the French biologist Félix d'Hérelle discovered the ability of these viruses present in the environment to "eat" bacteria. *"These phages, called lytic, recognize certain bacteria, introduce their genetic heritage, multiply and produce an enzyme, lysine, which causes the bacteria to explode. The hundreds of new phages released will then infect neighboring bacteria,"* explains the infectious disease specialist. Predating antibiotics, phage therapy was quickly eclipsed in Western Europe by the discovery, in 1928, of penicillin. However, it survives in the USSR – history says that it saved Soviet troops from cholera during the Battle of Stalingrad.

If Professor Ferry is so interested in it, it is because it is based on *"the properties of nature by reproducing what happens there".* The argument speaks to Mr. B., a former farmer. *"You understood that this was a natural process, didn't you?" »* asks the doctor. *"Yes, the bugs that eat bacteria! »,* smiles the patient. A few weeks ago, he received intravenous phage injections for 6 days. However, few patients benefit from it because, in the absence of a clinical trial at this stage, phage therapy remains prohibited in France and reserved for cases of therapeutic impasse, when *"the vital or functional prognosis is engaged".* Mr. Vuitton, who walks with a crutch, risks amputation. *"I have three young children, I would like to enjoy nature with them again. »*

Each request is therefore studied during a weekly meeting of the team, which reflects on the best treatment plan for the patient. When using phages, three procedures are possible, within a precise framework controlled by the National Agency for the Safety of Medicines and Health Products (ANSM). If most cases concern osteoarticular infections, a specialty of the center, *“we also treat endocarditis or pulmonary infections”,* specifies Professor Ferry who has already treated 65 patients at the Croix-Rousse hospital – and supported around twenty others remotely in France.

Still empirical

In France, only one manufacturer, Phaxiam, produces these phages, the development of which is long and costly: *"As they are found in nature, by harvesting water in the sewers, it is not patentable: only the method purification is,”* continues Tristan Ferry. The company currently produces 6 phages – provided free of charge or reimbursed depending on the case – but which do not cover all needs: the hospital sometimes has to request other strains from Belgium or the United States.

Once delivered, the phages are prepared on the big day in a clean, germ-free room. This morning, Dr. Thomas Briot mixed two 1 mL vials of phages, diluted in sodium chloride, in the syringe intended for Alexandre Vuitton. An hour later, in the x-ray room, the patient receives his dose. The operation, which Dr. Miailhes, radiologist, performs under ultrasound, lasts only a few minutes: a puncture to analyze the joint fluid in his knee, then the injection. In terms of side effects, the main risk identified at this stage is a high fever if bacteria debris remains in poorly purified phages.

During 2022, 70% of patients treated at Croix-Rousse hospital as part of rescue treatment with phage therapy saw their condition improve. For Alexandre Vuitton, a first assessment is planned for the end of March. *"We first rely on clinical signs to judge the effects. »* MB will return in two weeks: *"The scar is beautiful but microscopically on the bone we don't yet know if our little animals have done their job. »,* adds the doctor gently. Unlike traditional drugs, *"whose presence in the body decreases over time, phage therapy is based on self-replication: we do not know the fate of the phage in the body,"* continues Dr Briot.

The causes of the failures encountered remain difficult to understand because a number of parameters come into play: the method of administration (intravenous, aerosol, gel), its dosage, the antibiotics associated or not, etc. The team is also studying the presence in certain patients of an immune reaction that attacks viruses. *"We manage to justify this treatment with our expertise and the experience acquired over all our years, by prioritizing the well-being of patients... Everything is still empirical! »,* concludes Tristan Ferry with a smile.