Combatting antibiotic resistance in a clever way

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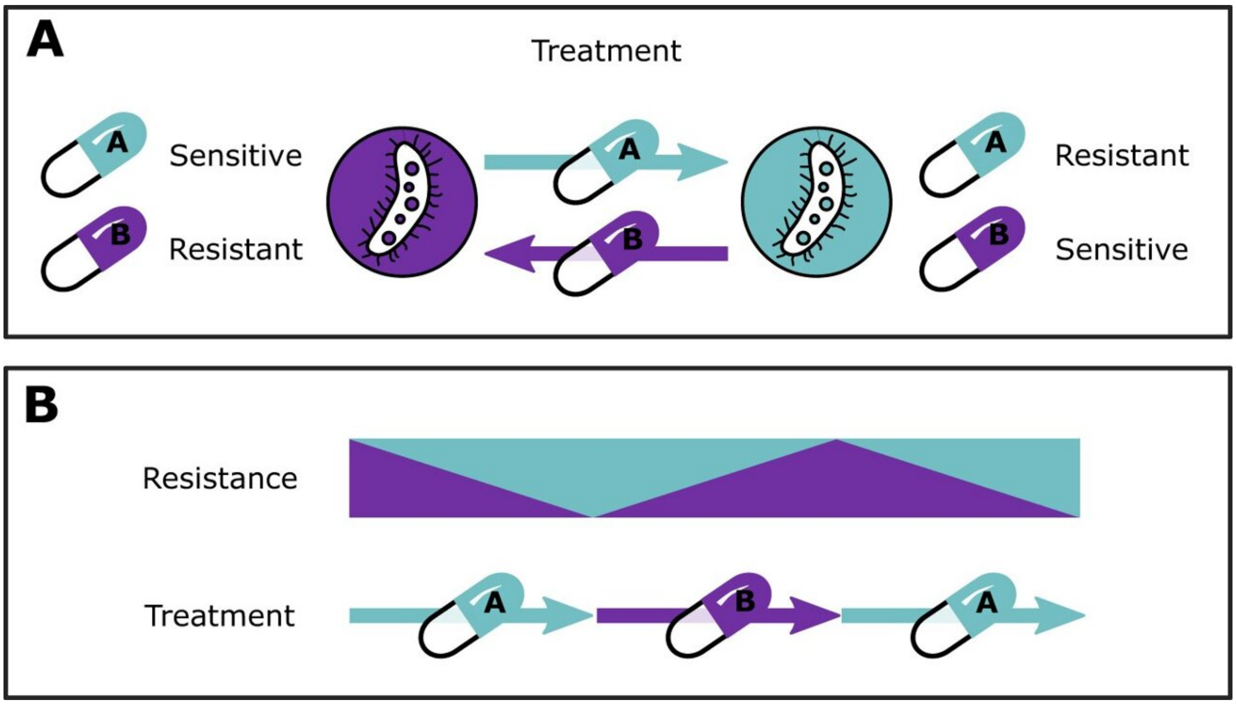

Fig. 1: Concept of collateral sensitivity (CS)-based treatments using two hypothetical drugs, antibiotic A and B, based on Pál et al. (A) Reciprocal CS relationship between antibiotic A and B. (B) Theoretical cycling regimen exploiting CS between antibiotic A and B to suppress resistance. Credit: DOI: 10.1038/s41467-021-25927-3

When you become very good at one thing, that sometimes comes at the expense of something else. Such trade-offs also apply to bacteria. When becoming more resistant to one antibiotic, bacteria can sometimes become more sensitive to another. Linda Aulin, Ph.D. candidate in the pharmacology group of Coen van Hasselt now try to figure out how we can use this phenomenon to combat the emergence of antibiotic resistance in patients. Their publication appears in *Nature Communications*.

Already many years ago, scientists discovered that, in bacteria, increased resistance to one antibiotic sometimes leads to an increased sensitivity to a second antibiotic. This phenomenon is called collateral sensitivity (CS). Sometimes, being good at one thing, comes at the expense of something else," says Van Hasselt.

Several publications have proposed the idea that the principle of CS can be used to design treatment to prevent the emergence of antibiotic resistance in patients. Van Hasselt: "We wanted to understand how we could achieve this. How do you design a dosing schedule that optimally uses this principle? What amount of drugs do you give, how do you combine those different antibiotics? And what factors do we need to consider when designing such treatments? There was no clear answer yet to those questions."

Infecting a virtual patient

In order to design a safe and effective CS treatment, it is important to understand how properties of different bacteria and antibiotics contribute to the eventual treatment outcome. "Previous research has been primarily done in lab conditions," says Van Hasselt. "These results however, cannot be directly translated into a treatment for a real patient. The circumstances are too different."

Testing many different dosing schedules in patients is not ethical or practically possible. "Besides, it would not allow us to understand in detail how those different factors contribute to the treatment," says Aulin. "That's why we created a special computer model that mimics a bacterial infection in a virtual patient. This model allows us to play around with different factors and find the specific factors that will impact treatment outcomes."

Many factors play a part

"We found that several properties of both bacteria but also the type of antibiotic, determine how to best design a CS treatment," says Aulin. "For example how fast certain bacteria can grow or how fast they develop mutations. Those factors determine how quickly they evolve and develop resistance." Furthermore, different drugs affect bacteria in different ways, she explains. "Some antibiotics kill the bacteria, some only inhibit their growth. Some antibiotics need a certain amount of time to work, while others more rely on a certain concentration."

More opportunities for treatment

Besides learning more about different bacteria and drug-related factors, Aulin also found that effective treatments can be based on either a one or two-directional CS relationship. "Most CS relationships only work in one way: higher resistance to one antibiotic increases the sensitivity to a second antibiotic, but not the other way around. In some cases, CS relationships work both ways, so decreased sensitivity to either of the antibiotics results in a higher sensitivity to the other." Scientists previously thought that only reciprocal relationships would be useful, but Aulin proofed them wrong. "We found that one-direction relationships can be useful as well! That's good news because these CS relationships are way more common. So this gives us way more options to design new treatments!"

Specific treatments for chronic infections

Now we generally know how to design a CS-based treatment, the next step is to transform it into a real treatment for patients," says Van Hasselt. "We expect that CS-based treatments could be very important for patients with chronic infection. Because they are often treated with antibiotics for a long period, so resistance has a higher chance to develop. Using our model we are now going to explore and develop specific treatments strategies for this type of infections. This way, we can hopefully prevent the emergence of antibiotic resistance and treatment failure in patients," van Hasselt concludes.

More information: Linda B. S. Aulin et al, Design principles of collateral sensitivity-based dosing strategies, *Nature Communications* (2021). DOI: 10.1038/s41467-021-25927-3

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