Can antivirulence drugs stop infections without causing resistance?

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Antivirulence drugs disarm pathogens rather than kill them, and although they could be effective in theory, antivirulence drugs have never been tested in humans. A new study to be published in the online journal *mBio* on Tuesday, October 18 reveals these drugs have the potential to fight infection while avoiding the pitfalls of drug resistance.

Traditional antibiotics aim to kill or stop the growth of pathogens, but antivirulence drugs prevent disease by neutralizing virulence factors, the specific proteins or toxins that a pathogen uses to establish an infection. Scientists have long thought such a strategy could prevent pathogens from developing drug resistance, since antivirulence drugs don't kill the pathogens that are susceptible and leave a wide opening for the few resistant organisms that may be left. Thus, in theory, antivirulence drugs don't offer much benefit to the pathogens that get around the drug. However, these ideas have never been tested.

The study coming out this week provides evidence that antivirulence drugs have the potential to suppress resistance if they are applied in the right way. Brett Mellbye and Martin Schuster from Oregon State University carried out laboratory simulations to determine the effect antivirulence drug-resistant strains could have on therapy. They found that in pathogens that rely on cell-to-cell communication and cooperation, resistant strains will not overtake sensitive strains, allowing antivirulence therapies that target social interactions to work even when resistance arises.

"It's a very important demonstration of the principle that social effects can slow or even halt the spread of resistance to antivirulence drugs," says Sam Brown, of Edinburgh University, Invited Editor on the study. "Their results align with our understanding of social evolution."

Mellbye and Schuster created a microcosm that simulates an infection, says Brown, and they used bacteria that employ quorum sensing, a form of communication that enables the bacteria to time their attack for greatest effect. Quorum sensing is an important target for antivirulence drugs because many bacterial pathogens, including the lung pathogen Pseudomonas aeruginosa, employ quorum sensing to control the manufacture of their virulence factors.

To circumvent the problem of creating a strain that is resistant to an antivirulence drug, Brown says, the authors used surrogates. "It's kind of a role-playing exercise," to test their ideas, he says. "They used bacteria that behave as we expect drug-resistant bacteria might behave." "Sensitive" mimics are bacteria that lack the ability to communicate and cooperate. "Resistant" mimics are actually run-of-the-mill bacteria that retain the ability to "talk" amongst themselves.

The researchers pitted resistant mimics against sensitive mimics to test whether resistant strains can proliferate in an infection. The results showed that sensitive mimics cheat to get ahead: they exploit the resources that the resistant bacteria provide through quorum sensing. This delays the growth of all the bacteria, suggesting that resistance to an antivirulence drug that targets quorum sensing would not spread. The authors say this highlights the potential of antivirulence strategies that target cooperative behaviors and shared virulence factors.

Brown is optimistic but circumspect about the findings. "These results could very well stand, but in the the real world resistance could still emerge and we need to be cautious."

"I think these drugs are promising, even if we do anticipate resistance, because they can slow the rate of resistance evolution, much slower than the rate of resistance evolution to traditional antibiotics," says Brown.

More information: www.mbio.asm.org/

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