Alternating antibiotics render resistant bacteria beatable

April 8 2015

Given the alarming rise of antibiotic-resistant bacteria, and the long lead-in time for developing novel drugs, the discovery of new ways to use the antibiotics already available and approved for use in humans is paramount. It is generally believed that to eliminate a bacterial infection before the onset of drug resistance one must treat with large doses of antibiotics, but recent research has indicated that this type of treatment might actually be driving the emergence of drug-resistant pathogens.

New research publishing April 8th in the Open Access journal *PLOS Biology* from Ayari Fuentes-Hernandez, Jessica Plucain, Robert Beardmore and colleagues, demonstrates that drug treatments with two antibiotics can be designed to kill bacteria at dosages that - when the drugs are administered alone or in combination - cause rapid development of drug resistance and sustained bacterial growth. These treatments, called "sequential treatments," use alternating low doses of two antibiotics. The researchers used a test-tube model of a bacterial infection to show that, even in bacteria that contain drug resistance genes, sequential treatments could kill the bacteria, while high doses of single drugs or mixtures of two drugs failed to do so.

"Our study finds a complex relationship between dose, bacterial population densities and drug resistance," says the paper's lead author Dr. Robert Beardmore (whose research group is based at the University of Exeter). "As we demonstrate, it is possible to reduce bacterial load to zero at dosages that are usually said to be sub lethal and, therefore, are assumed to select for increased drug resistance."

Interestingly, the researchers found by comparing the genetic changes occurring during single-drug versus sequential treatments that both treatments promoted the emergence of known drug-resistance mutations.

Therefore, the success of sequential treatments was not through averting or suppressing drug resistance. Instead, they hypothesize that the evolutionary response to sequential drug treatment leads to a state where one drug sensitizes the bacteria to the second drug.

"Research has concentrated for decades on synergistic drug cocktails. We believe 'sequential synergies' might be just as potent if we look for them, this research will therefore be of interest to the pharma and dwindling antibiotic discovery communities," says Dr. Beardmore. While bacteria are masters at adapting to antibiotic challenge, this research suggests that there is a way to use this adaptation against them. The fluctuating environments created by well-designed sequential treatments can sensitize bacteria and render them susceptible to concentrations of antibiotics that would normally induce drug resistance and continued existence.

Unfortunately, not all sequential treatments are equally efficacious. Extensive further work will be needed before sequential treatments make it in to the clinic, but this study demonstrates that they can be effective even when using drug doses below their maximal potency. According to Dr. Beardmore, "One outcome of this highly surprising result will be to set in motion a series of studies to determine ways of using antibiotics not only in combination, but sequentially and with the potential for lower dosages than is currently thought possible."

More information: Fuentes-Hernandez A, Plucain J, Gori F, Pena-Miller R, Reding C, Jansen G, et al. (2015) Using a Sequential Regimen to Eliminate Bacteria at Sublethal Antibiotic Dosages. *PLoS Biol* 13(4): e1002104. DOI: 10.1371/journal.pbio.1002104