Why hospital antibiotic management strategies do little to curb resistance

January 17 2017

With an alarming growth in antibiotic resistance and doctors increasingly having to resort to last-chance antibiotics to save patients, is there a better way for hospitals to manage antibiotic treatment regimens?

A generation ago, two antibiotic strategies known as cycling and mixing were employed to outwit bacteria. Cycling is like antibiotic crop rotation where certain classes of antibiotics are withdrawn for a period of time. Doctors thought this would combat resistance because bacterial pathogens would lose their abilities to resist treatment because of the costs associated with a drug-resistant lifestyle. The mixing strategy, with its roots in computer predictions and epidemiological models of the time, was thought to reduce drug resistance because the random assignment of antibiotics to patients, within the appropriate class, would give bacteria the fastest possible moving target.

In reality neither strategy works, according to the analysis performed in a new study published in the advanced online edition of *Molecular Biology and Evolution*. This theoretical work, by mathematicians Robert Beardmore, Rafael Pena-Miller, Fabio Gori and clinician Jon Iredell, may help explain why recent clinical trials like the Saturn project—explicitly designed to resolved the ongoing issue of high controversy (antibiotic cycling vs mixing)—may not work. In the Saturn project, the researchers concluded that there were no statistically significant differences in the prevalence of antibiotic resistance during mixing and cycling interventions.

The team have shown that "determining whether cycling or mixing selects best against drug resistant pathogens is not possible, even in standardized questions using mathematical models, let alone in the clinic," according to lead author Robert Beardmore.

Instead, in the MBE study, the international team of clinical scientists and mathematicians recommends other strategies, like "reactive cycling" which they have shown outperforms cycling and mixing in all the computational models they tested.

Their results could have profound implications for future clinical trials. "Mathematically speaking, it was very clear early in this study that antibiotic mixing was not the optimal way of allocating antibiotic to patients yet this is what some clinicians have come believe," said Prof. Beardmore. "But communicating this was difficult, given the complexity of the mathematical ideas. In the end, the real mathematical optimum is little more than common sense: get the right drugs to the right patients as soon a possible."

Dr. Gori added, "Prior studies did not see this due to their over-reliance on computer simulations that didn't paint a full picture of the antibiotic optimization problem. When we used an analysis technique developed during the space race era developed to solve optimization problems, some new solutions dropped out of that analysis."

They recommend that individualized treatments, both pathogen-specific and patient-specific, may be a necessity to properly optimize antibiotic use. By using computer models to study different personalized medicine scenarios they advocate for the use of devices that target infections based on rapid diagnoses of the pathogen responsible for the infection from molecular signatures or blood cultures."

"It is clear that information-rich, personalized protocols can outperform antibiotic cycling and mixing in mathematical models but even this conclusion can depend on nuanced model circumstances," said co-author Pena-Miller.

"For example, in the doomsday scenario that multi-drug resistance is endemic and present in every infection before the patient begins treatment, it matters little which treatment patients are given. But before that stark situation arises, targeting appropriate treatment at as many individuals as possible outperforms both mixing and cycling."

"Personalised medicine is rapidly becoming a reality with dramatic increases in the availability of clinical testing at the point of care," added Prof. Iredell, "Antibiotic use in severe infection remains one of the most powerful interventions in medicine, and intelligent use of antibiotics is essential to optimize immediate patient outcomes and to preserve long-term benefits."

Provided by Oxford University Press