

## Development of tolerance affects antibiotic drug response

Professor Mark Wilcox, reviewing Liu J, *et al. Science* 2020; **367**: 200–4.

*Bacterial tolerance promotes the evolution of resistance under combination antibiotic treatment*

Antibiotic resistance is a considerable problem worldwide, accounting for 35,000 deaths per year in the USA alone (1). Before developing resistance, bacteria often develop increased antimicrobial tolerance that enables them to survive under treatment without necessarily developing resistance. Combinations of antibiotic drugs are often used in an effort to prevent the development of resistance, albeit without a strong evidence base; it is unclear whether such use avoids the emergence of tolerance.

In order to understand whether evolving tolerance prior to resistance development occurs in clinical bacterial isolates, Liu and colleagues examined sequential *Staphylococcus aureus* isolates obtained from patients during treatment with different combinations of vancomycin, daptomycin and rifampin (2). Two adult patients were identified with methicillin-resistant *S. aureus* blood stream infections persisting for at least 2 weeks despite antibiotic treatment who were admitted to hospital between 2017 and 2018. With further antibiotic exposure, including combinations, rapid emergence of tolerance mutations was detected, followed by the emergence of resistance.

Although combination antibiotics delayed the emergence of tolerance, once this was established, the benefits of combination antibiotic treatment in preventing resistance disappeared. The study found that tolerance to daptomycin consistently occurred before the development of resistance to rifampin. However, mutants that were fully rifampin resistant underwent enhanced killing by daptomycin as suppression of bacterial growth under rifampin had been removed. Nevertheless, once tolerance was established, the selective pressure against resistance development was lost. Worryingly, the authors found that this effect was general to other bacteria, such as *Escherichia coli*, and also applies to other antibiotic combination therapies – a finding that could have important implications for assessing the development of resistance in patients treated with combination therapies.

### **Comment**

While combined antibiotic therapy is often used to improve efficacy, this study highlights the limitations of this approach with regard to bacterial tolerance. Currently, antimicrobial resistance is determined through susceptibility testing that establishes the minimal inhibitory concentration, a process that is unable to identify antimicrobial tolerance. There is, therefore, a need to develop diagnostic methods that enable the emergence of tolerance to be detected, and also to identify antimicrobials that can retain their potency in the presence of antibiotic-tolerant bacteria. Such information is vital to allow clinicians to make informed decisions regarding the use of antibiotic drug combinations.

### **References**

1. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>. Accessed 20 October 2020.
2. Liu J, Gefen O, Ronin I, *et al*. Effect of tolerance on the evolution of antibiotic resistance under drug combinations. *Science* 2020; **367**: 200–4.