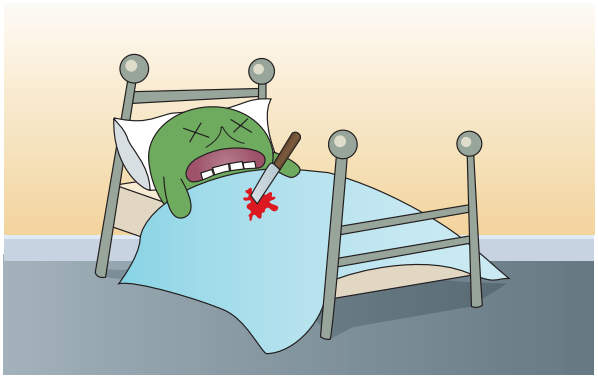
ANTIMICROBIALS

Killing persisters while they sleep

“it may be possible to eradicate bacterial persisters in a clinical setting by stimulating their underlying metabolic activity concurrently with antibiotic treatment.”

Bacterial persisters are a subpopulation of dormant cells that have been implicated in a range of chronic and recurrent infections through their ability to survive antibiotic treatments. Although most cellular processes are completely shut down in persisters, translation still occurs, albeit at a reduced rate, making the use of aminoglycoside antibiotics (which target the ribosome) an attractive option. However, aminoglycosides have only weak activity against this subpopulation of cells. Writing in *Nature*, Collins and colleagues now show that the addition of certain metabolites can enhance the killing of both Gram-negative and Gram-positive persisters by aminoglycosides.



Aminoglycoside uptake into the bacterium is energy dependent, leading the authors to investigate whether metabolic stimulation enhances the killing of persister cells by increasing the uptake of these antibiotics. They found that the addition of glucose, mannitol, fructose or pyruvate increased the killing of isolated *Escherichia coli* persisters by gentamicin, kanamycin and streptomycin by more than three orders of magnitude. The effect was specific to aminoglycosides, as none of the metabolites that were screened enhanced killing by either quinolones or β-lactam antibiotics, which target DNA replication and cell division, respectively. The authors observed that the addition of these metabolites enhanced gentamicin uptake and that killing was reduced by blocking this uptake using the proton-motive force inhibitor carbonyl cyanide *m*-chlorophenyl hydrazone (CCCP).

In an *E. coli* biofilm model, the authors found that the addition of mannitol enhanced gentamicin killing of persister cells by more than two orders of magnitude. Similarly, in mice that were implanted with catheters which had been colonized by a uropathogenic *E. coli* strain, administration of mannitol together with gentamicin reduced the viability of biofilm bacteria on the catheter by more than an order of magnitude. Finally, the authors tested whether metabolite addition enhanced aminoglycoside killing of Gram-positive bacteria; whereas mannitol, glucose and pyruvate had no effect, the addition of fructose enhanced killing of *Staphylococcus aureus* persisters by more than two orders of magnitude.

These findings indicate that it may be possible to eradicate bacterial persisters in a clinical setting by stimulating their underlying metabolic activity concurrently with antibiotic treatment.

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ORIGINAL RESEARCH PAPER Allison, K. R., Brynildsen, M. P. & Collins, J. J. Metabolite-enabled eradication of bacterial persisters by aminoglycosides. *Nature* **473**, 216–220 (2011)