Targeted antibiotic treatments–What's on the horizon?

Streptococcus ("strep") is always circulating in the population, but becomes more pervasive this time of year with school back in session and dropping temperatures herding people indoors, confined together in smaller spaces. Antibiotic prescriptions tend to rise concomitantly. Over the past few decades, this seasonal rise in antibiotic use has caused significant problems. Group-A *Streptococcus* (GAS), for example, is relatively easy to transfer and there are many people in the population who are considered carriers.

The gold-standard for treating *Streptococcus*, amoxicillin, is used to combat sore throats caused by strep, as well as other bugs, unless patients are allergic to it. In many cases, such as being strep A-negative (*i.e*., group-A strep not present) with a sore throat, which may be caused by *Rhinovirus* or a different viral or bacterial infection, antibiotics given to address the patient would be totally ineffective, and potentially even harmful. And herein lies the problem.

Natural selection

All of the creatures on the planet, including the organisms residing on and within our body, have been selected for by evolutionary mechanics and genetic fitness. Different social groups of humans have their own co-strains of skin and salivary flora because they are co-located; people who spend lots of time in the same space at home or in offices tend to begin to share and develop particular microflora. In the same way, pathogenic microbes are selected for–or against–based on their survival needs and environmental conditions.

For decades we have been creating antibiotic resistant microbes by our overuse of antibiotics. How often have I heard "I've had a cough since yesterday, can I have a Z-pack?" This is bad public education on our end. These treatments aren't candy. Azithromycin is prescribed over 40 million times each year, and its particular class of bacteriostatic antibiotic (macrolides) has a significant list of side effects, including newly-surfacing correlations with heart problems due to being proarrhythmic.

We've now very effectively selected for extremely virulent strains of *Clostridium difficile* (known in the jargon as *C. diff*), which causes diarrhea so intense it can be fatal, as well as *klebselli*a, carbapenem-resistant *Enterobacteriaceae* (CRE) like Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP), and others. It was not too long ago that drug-resistant *C. diff* infections were limited to hospital stays, but now they are being encountered in the wild (to you and me that's the mall, post office, gas station, etc.).

It is extremely concerning that our innate immunity to environmental pathogens is disrupted by taking antibiotics which can leave us more susceptible to being colonized by *C. difficile* (or other microbes). A *C. difficile* infection can lead to several months of negative repercussions including repeat occurrences of symptoms, continued exposure to different antibiotics to address the new infection, and so on. Inpatient only cases of disease result in 14,000 deaths per year in the U.S. alone. That's on the order of the mortality rate of seasonal influenza (*c.* 3,000-49,000) and we hear an awful lot about vaccination for that every year. Not so much about *C. diff*.

Although *some* awareness is building about the overuse of antibiotics in some circles, there are still regions where antibiotics like amoxicillin are available over-the-counter. Somewhere, even though he actually never said those words in his oath, Hippocrates must be thinking "do no harm."

What's Next?

In a society where we like our reactivity more than our proactivity–treatment rather than prevention–how can we educate and incentivize the public to make wiser choices? What else is on the horizon for next-generation treatments? Just published in *Nature Biotechnology* is a novel research study on the use of a bacterial enzyme (RNA-guided nuclease), Cas9, which was used to target bacterial genes that cause virulence–those factors that cause an organism (*e.g.,* the bacteria) to be infective. The new methodology allowed for hyperspecific targeting of parts of the bacteria or its genome. It could thus be harnessed to combat only select bacteria residing within us, in contrast to contemporary antibiotics which ablate every species they encounter.

David Bikard, one of the researchers, observed, "we selected guide sequences that enabled us to selectively kill a particular strain of microbe from within a mixed population." Thus future development of this idea could lead to targeted antibiotics which don't disrupt the normal healthy flora of the microbiome and would thus be less likely to lead to secondary infections such as *C. diff*.

Therapeutic potential

It's likely that widespread consumer availability of such treatments would not occur for at least the next decade or two, because the concept was demonstrated using bacteriophages (a particular type of virus) to deliver the nuclease into the target cells and this is impractical for human use.

Incredibly, the researchers also expanded the scope of the research a bit to target the genes for antibiotic resistance in a particular bacterial strain. They used the same nuclease (Cas9) to eliminate the antibiotic-resistant genes from the potentially-deadly multi-drug resistant *staphylococcus aureus* (MRSA), rendering it susceptible to tetracycline. Also being tested are microbe treatments (purposely inoculating patients with certain microbes for a therapeutic effect), which have their own–and different–set of regulatory hurdles to clear before they would be fit for human use and available by prescription.

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