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Pharmacology Consult
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Pseudouridimycin

Light in the Darkness of Antimicrobial Resistance

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One touch of nature makes the whole world kin…. (William Shakespeare)
https://www.brainyquote.com/quotes/william:shakespeare_106907

THE PROBLEM

Antimicrobial resistance (AMR) is an expanding worldwide threat associated with prolonged illness, disability, and death. Also at an increased risk are outcomes for surgery and cancer chemotherapy from infections caused by bacteria, viruses, fungi, and parasites. Consider the 480 000 persons who will develop multidrug-resistant tuberculosis this year and the rise of multidrug-resistant human immunodeficiency virus (AIDS) and malaria. As AMR increases, so goes rising healthcare cost related to lengthy illness trajectories, which require much more expensive drug therapy.[1,2]

A natural genetic process, AMR occurs over time. This process is accelerated with the misuse and overuse of antibiotics in humans and animals for viral infections and in animals to promote growth or prevent disease. Nearly half of all antibiotics prescribed are not indicated or effective as prescribed. Resistant microbes are found in humans, animals, food, and the environment and are spread via person to person, person and animal, food of animal origin, poor infection control practices, and unsanitary conditions. Antibiotic resistance is present in every country of the world.[1,2]

The Centers for Disease Control and Prevention estimates that, each year in the United States, more than 2 million persons experience an antibiotic-resistant infection and 23 000 die as a direct result of the resistance. Add to this number 250 000 *Clostridium difficile* infections directly related to antibiotic use and AMR, which contributes to an additional 14 000 deaths a year. What is unsettling is that these Centers for Disease Control and Prevention figures are likely lower than the actual number of infections. Finally, consider that antibiotics are responsible for 1 in 5 visits to the emergency room for treatment of an adverse event.[2]

Gram-negative pathogens are of concern because many have become resistant to nearly all available drugs along with a few gram-positive infections (eg, *Staphylococcus* and *Enterococcus*). At this time, in the healthcare setting, the most dangerous gram-negative infections are Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter*.[2]

THE SCIENCE

Almost all of antibiotics have been discovered in soil—remnants of the battles between bacteria to thrive and survive. For decades, the earth under our feet has been all but ignored for antibiotic development based on the belief that there were no further cures to discover. That is until now.[3]

A team of scientists from Rutgers University, University of Milan, and University of Bonn, together with 3 Italian biotechnology companies led by Richard Ebright and Stefano Donadio, have discovered nucleoside analogue called *pseudouridimycin* (PUM). Through the screening of 3000 actinobacterial and fungal culture extracts for selective inhibition of bacterial RNA polymerase (RNAP), a powerful new weapon against many infections may have been found.[3,4]

Inhibition of RNAP is the standard pathway for antituberculosis therapy and for 4 current classes of broad-spectrum antibiotics because prevention of RNA synthesis results in bacterial cell death.[3] Rifamycin, which inhibits RNAP, is useful for gram-positive and gram-negative infections and a first-line antituberculosis therapy. However, resistance has developed, a significant threat to public health particularly for persons with rifamycin-resistant tuberculosis. What is needed now is an antibiotic that can inhibit RNAP such as rifamycin without AMR and shared cross-resistance.[5]

Pseudouridimycin is different because it selectively inhibits bacterial RNAP necessary for conversion of DNA into RNA in vitro and acts against gram-positive and gram-negative bacteria across a broad spectrum of drug-sensitive and drug-resistant bacteria. Early evidence suggests that

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The author reports no conflicts of interest.

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DOI: 10.1097/NUR.0000000000000367

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PUM inhibits RNAP through a binding site and processes different from previous agents and with very low rates of AMR. Early testing has revealed in vitro activity against 18 gram-positive and 2 gram-negative infections, predominately streptococcus and staphylococcus.[6,7]

THE FUTURE

New antibiotics will probably continue to emerge using small molecule inhibitors of bacterial RNAP via genetic, biochemical, biophysical, and crystallographic pathways, as well as new binding platforms to inhibit RNAP. The hope is for new weapons for a broad spectrum of pathogens including methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Clostridium difficile*, *Mycobacterium tuberculosis*, *Bacillus anthracis*, *Francisella tularensis*, *Burkholderia mallei*, and *Burkholderia pseudomallei* without cross-resistance with current antibiotics.[7,8] Considering how nucleoside analog inhibitors have changed the treatment of human immunodeficiency virus/AIDS and hepatitis C, it seems very possible to have a broad-spectrum antibiotic for multiple pathogens as well as multidrug-resistant strains without residual survivors.[6,9] Human clinical trials are predicted to begin within 3 years and may become part of the antibiotic formulary in a decade.[3]

While the testing of PUM continues, due diligence is needed now. Currently, national and state capacity to identify and act on emerging AMR threats is weak. Furthermore, international surveillance of AMR is poor. Thus, accurate evidence regarding the incidence, prevalence, mortality, and costs for AMR is not available. Nor is there a benchmark for antibiotic use in healthcare or agriculture.[2] Nursing and medicine need to come forward regarding this issue.

Use of advanced technologies such as advanced molecular detection could significantly help in identifying AMR earlier than later. Although education regarding antibiotic stewardship has begun, programs are not widely used or adhered to.[2] Clinical nurse specialist practice could certainly move stewardship forward in all clinical settings and change the healthcare culture regarding antibiotics. Finally, the discovery of PUM has demonstrated that the conventional microbial screening of the past is still possible for future antibiotic development.[10] This is a comforting thought considering the rise of AMR that a cure is still possible; humans have not exhausted the treasures of healing from nature.

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