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Perspective

Confronting Accelerating Global Antimicrobial Resistance and the Associated Increase in Deaths

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Abstract: Although advances in contemporary medical care have broadened access to healthcare and extended the human life span, deaths resulting from antimicrobial-resistant pathogens continue to increase. This minireview summarizes the evidence that AI and machine learning, coupled with precision medicine and alternative therapies, such as repurposing non-antibiotic drugs and the use of bacteriophages, has promise to halt this advance.

Keywords: antimicrobial resistance; artificial intelligence; global mortality; bacteriophage therapy; antimicrobials with unique mechanisms of action

1. Introduction

Three themes in contemporary medicine have come together to extend the human life span, decrease pain and suffering, and permit accessibility to healthcare. They are artificial intelligence (AI), precision medicine, and equality and diversity in access to healthcare. Clearly, in future years, AI will have the overarching priority compared to the other two components. This minireview will address the first two initiatives.

Although all three components have been operative for some time, the number of deaths associated with resistance to antimicrobial agents remains unchecked [1]. In 2019, estimates attributed 1.27 million deaths due to antimicrobial resistance (AMR) and 10 million deaths by 2050 [2,3]. Clearly AMR poses a global health threat, and the development of new antimicrobial agents has not kept pace to meet the challenge. When Alexander Fleming accepted the Nobel Prize in 1945 for the discovery of penicillin, he remarked in his acceptance speech that "it is not difficult to make microbes resistant to penicillin in the laboratory and the same has happened in the body". Soon after, that resistance was recognized in the clinical setting. It was another Nobel Laureate, Jacques Monod, who won the prize for elucidating the nature of the lac operon in *E. coli* who stated in a talk I attended at Columbia University in New York, "it is the dream of every bacterium to become two". It is that driving force inherent in microbial DNA genome replication that leads to propagating resistance.

In an introductory chapter to Antibiotics in Laboratory Medicine [4], authors Amsterdam and Stratton underscored that the concept of antibiotic resistance is not a contemporary phenomenon as some might believe. Genomic evidence has traced resistance to β-lactam, tetracycline, and glycopeptide antibiotics in 30,000-year-old Beningian permafrost sediments in Alaska [5]. Clearly, although resistance genes are ancient, the inappropriate recent use of antimicrobials in medicine, livestock breeding, and agriculture have increased the emergence of AMR.

In the work referred to earlier, Amsterdam and Stratton addressed the "constricted antibiotic pipeline" [4]. From 2014 to 2021, only 16 FDA-approved antibiotics were developed. Only two, raborbactam and lefamulin, have new mechanisms of action (MOA) [6]. The remainder are in the known classes of fluoroquinolones, β-lactams/β lactamase inhibitors, glycopeptides, tetracyclines, oxazolodines, and aminoglycosides, nitroimidazoles and triazoles, and siderophore β-lactams. According to the World Health Organization's (WHO)

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annual report [7] on the pipeline of drugs, there has been an interest leading to an increase in the expansion of biologicals, i.e., monoclonal antibodies, phage enolysins, and polyclonal antibodies to name a few in development to augment the paucity of antimicrobial agents.

2. New Targets and MOAs

The WHO has encouraged the development of new avenues to address AMR; Table 1 summarizes several of these initiatives, beginning with AI. As others and I have indicated, AI will increasingly be utilized to discover new antimicrobials with unique MOAs [8,9]. Augmented by machine learning and its constituent, deep learning, AI represents a dominant tool to limit AMR by forecasting new antibiotic structures and recognizing AMR bacteria.

Table 1. Contemporary Advances in Limiting Antimicrobial Resistance.

Advance	Description	References
AI/ML	• Forecasting new antibiotic structures • Recognizing AMR bacteria	[6] [8]
Antimicrobials with unique MOAs	• SOS inhibitor OXF-O77 • Lolamycin • Cresomycin	[9] [10] [11]
Antibacterial viruses	• Repurposing bacteriophages to address AMR	[12]
ML	• Non-antibiotic medications, e.g., cancer, diabetes, and depression therapies	[13,14]

Key: AI—artificial intelligence; AMR—antimicrobial resistance; ML—machine learning; MOA—mechanism of action; SOS—"save our soul" bacterial response.

Recent reports present findings that propose alternative approaches. Bradbury et. al. [9] formulated a compound that suppresses the evolution of AMR in bacteria and can render resistant bacteria more susceptible to treatment. The finding relates to the development of resistance to quinolone antimicrobials. Quinolones' MOA is to impair bacterial DNA, resulting in cell death. However, this process can initiate a bacterial recovery process referred to as the "SOS response" which repairs the damaged DNA and can lead to an increased rate of resistance to the administered antimicrobial agent. By restructuring a group of molecules known to increase the susceptibility of methicillin-resistant bacteria, Bradbury and coworkers have developed the most effective SOS inhibitor molecule which they have referred to as OXF-077 [9].

Another recently developed antimicrobial agent has a unique MOA. The antibiotic, lolamycin, is capable of inhibiting drug-resistant bacteria associated with cases of sepsis and pneumonia and was effective in containing secondary infections of *Clostridium difficile* [10]. It has also demonstrated effective in vitro action against 130 multi-drug-resistant strains. The target of lolamycin is the Lol system, which is comprised of five different proteins. Apart from its effectiveness against a wide array of clinical isolates, it demonstrates the sparing of the gut microbiome, preventing superinfection with *Clostridium difficile*. The capability of lolamycin in preventing secondary infections with the anaerobe is of no small consequence as *C. difficile* causes 500,000 infections and 30,000 deaths annually with a 35% recurrence rate in the USA [10].

Parallel with the knowledge of the reservoir of ancient resistance genes in bacteria, Wu et al., using machine learning and computational biology, surveyed and widely expanded our knowledge regarding natural product families that have gradually developed over time as antimicrobial agents. Toward this end, they synthesized the natural antimicrobial agent, cresomycin, with effectiveness against a wide array of multidrug-resistant Gram-positive and Gram-negative bacteria [11].

In order to develop any new drug with the aspiration for it to be successful in human trials, it is necessary to obtain FDA approval. There is an ongoing imperative to develop new

drugs and AI will clearly lead that direction. Bacteriophages, "bacteria-killing viruses", offer an alternative to chemical antimicrobial agents. Although bacteriophage therapy presents an interesting alternative and addition to the armamentarium of antimicrobial therapy, it is not without some drawbacks. The capability of bacteriophages to kill and clear a turbid broth suspension in the laboratory is enlightening. In reality, bacteria can also rapidly become resistant to phages by several different mechanisms. One of the mechanisms includes modifications in the receptors to which the phage attaches or the evolution of adaptive immunity which interferes with CRISPR sequences [12]. Clearly, the mechanisms of bacterial resistance to phages differs substantially from those of antimicrobial agents; however, the overall solution would be similar to the use of multiantibiotic regimens or treatment with "phage cocktails".

Precision medicine incorporates several aspects of the patient's health status and the nature and source of the infecting microbe. In an earlier publication, Amsterdam referenced this practice as part of an antibiotic stewardship, incorporating an individual's health status and predicted or anticipated response to antibiotic treatment [8]. Further advances in the utilization of precision medicine will be key in thwarting AMR.

In parallel with the search for new drugs, AI has been and should be continually used for drug repurposing applications. Significant inroads and advances have been made against pandemics and AMR with the assistance of AI. In this effort, 4707 compounds encompassing 3422 marketed drugs were collected in an online Drug Repurposing Hub [13]. Machine learning has been used to identify new targets and antibacterial activity of non-antibiotics. The source of the non-antibiotics are cancer, diabetes, and depression medications [14]. It remains to be evidenced how applicable and effective these drugs will be in combating resistant organisms in the challenges we face in curing human disease.

I am suggesting here that the AI tool be used by a healthcare organization, medical specialty, or individual practitioner to administer the "right" antimicrobial agent at the "right" time for the "right" duration of time for the "right" patient in accordance with the Institute of Medicine's principles for optimal healthcare [15]. The misuse of antibiotics in developing countries due to inappropriate testing and/or unregulated accessibility can be reduced if AI practices are implemented by national and/or professional groups. Whenever AI is used to select an antibiotic to treat a patient, a statement should be added to the record that the physician implemented the AI algorithms in decision-making.

AI should also be vigorously explored to discover new antibiotics. Recognizing that antibiotic development is slow, prone to failure, and expensive, a limited number of new drugs have been developed in the past decade. Therefore, it would seem wise to investigate alternatives. AI enables the opportunity to potentially discover small molecule antibiotics, antimicrobial peptides, and/or computer-assisted drug design to overcome these barriers.

Moreover, we should anticipate that AI discovery will encompass drugs of a unique design that are bactericidal, possess a wider spectrum of activity with diminished potential for resistance, and reduced activity against normal gut microflora. Defining and determining the antimicrobial arsenal in hospital healthcare system formularies and clinics is a forward-thinking approach to meet resistance concerns now and in the future.

3. Conclusions

It is anticipated that the varied alternative therapies reviewed above will quell the advancing pace of AMR. It is up to the combined efforts of scientists and clinical practitioners worldwide to utilize these innovations to prevent disease and death in the populace due to resistance by the microbial pathogens.

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