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Research Article

Antimicrobial Discovery, Resistance and Death: The Role of AI in Expanding the Antibiotic Pipeline

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Abstract

As the number of deaths associated with antimicrobial resistance continues to increase, efforts to identify new sources of effective antimicrobial agents and methods of mitigating resistance are ongoing. These include the application of Artificial Intelligence, the discovery of repurposed drugs, immunological approaches and the exploration of heretofore unexplored natural sources like, extremophiles, plants, repurposing non-antimicrobial medicines, and exploring marine microorganisms. Mitigation of antimicrobial resistance does not solely depend on the discovery of new compounds with unique modes of action but is heavily reliant on the appropriate use of antimicrobial agents by qualified medical practitioners.

Keywords: Antimicrobial resistance, Mechanism of action, Artificial intelligence, Repurposed pharmacologic agents

Abbreviations: Spp: Species, MRSA: Methicillin Resistant *Staphylococcus aureus,* ESBL: Extended Spectrum B Lactamase, PBP: Penicillin Binding Protein, DNA: Deoxyribonucleic Acid, *E. coli*: Escherichia coli, N. Gonorrhoea: *Neisseriae gonorrhoea*

Introduction

The ongoing concern for antimicrobial resistance and increased human mortality continues to pervade modern medicine [1]. In 2019, the World Health Organization estimated that there were 1.3 million deaths annually worldwide due to antimicrobial resistance [2]. In his summary report on the future impact of antimicrobial resistance, O'Neill wrote: "the magnitude of the problem is … estimated that by 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output are at risk due to the rise of drug-resistant infections" [3]. To prevent the development of resistance and hence the death of their patients from microbial diseases, infectious disease physicians follow the operational maxim of HIV physicians: "hit 'em hard, hit 'em fast" [4]. Interestingly, this approach has now been adapted by oncologists [5] and rheumatologists' battle against inflammation in early disease who now also follow the same concept [6].

Addressing Antimicrobial Resistance

To be able to prevent worldwide death due to antimicrobial resistance, and to also continue to tackle complex infections in HIV patients, and in high-risk oncology and rheumatology patients (due to modern therapies for these disorders), effective antimicrobial agents that address resistance concerns must continue to be identified. However, the Golden Age of antibiotic discovery when "the antibiotic pipeline" was at its peak – became constricted by 2015 [7]. Before then, in the prior century, most generations of antibiotics were from products of bacteria and fungi. Unique sources

of antimicrobials must be identified as they had been in the past. For example, following the serendipitous discovery by Alexander Flemingin 1928 of the antibacterial activity of *Penicillium notatum* against several species of bacteria, bacteriologists sought other effective compounds from soil. In fact, many of the antimicrobials in use today were initially discovered in soil during the Golden Age of antibiotic discovery referred to above. In some cases, it was assumed the soil was the "front lawn" of a major US pharmaceutical company; case in point: Terramycin derived from the actinomycete, *Streptomyces remous,* was isolated from the lawn at a Pfizer facility. Following the global concerns raised in the prior decade, in 2024 the United Nations General Assembly declared antibiotic resistance to be "one of the most urgent global health threats" [8]. Butler et al [9] documented that as of 2022, multiple new antibiotics were approved, most by the US Food and Drug Administration (FDA). Only two, vaborbactam and lefamulin, have distinct mechanisms of action (MOAs). Newer antimicrobial agents approved by the FDA in recent years may or may not have novel MOAs but are agents modified to be successfully directed at Gram-negative bacterial resistance mechanisms. An abbreviated list of such antimicrobials is summarized in the Table 1.

Table 1: Recent Antimicrobial agents approved by the Food and Drug Administration.

Agent	Target (s)	Comments
Sulbactam/durlobactam	Acinetobacter baumanni	β-lactam & novel diazobicyclooctane β-lactamase inhibitor
Rezafungin	Candida spp	Echinocardin glucan synthesis inhibitor
Ceftobiprole	MRSA, S. pneumoniae, Gram-negatives	Advanced cephalosporin (PBP binding)
Pivmecillinam	Enterobacteriaceae (E. Coli, Proteus)	Extended-spectrum penicillin (PBP)
Sulopenem etzadroxil + Probenecid	ESBL-producing Enterobacteriaceae	Oral penem (β-lactam) & renal excretion Inhibitor
Gepotidacin	E. coli, Enterococcus, N. gonorrheae	First in-class triazaacenepthylene DNA gyrase/topoisomerase inhibitor
Zoliflodacin	N. gonorrheae	Topoisomerase inhibitor

New MOAs

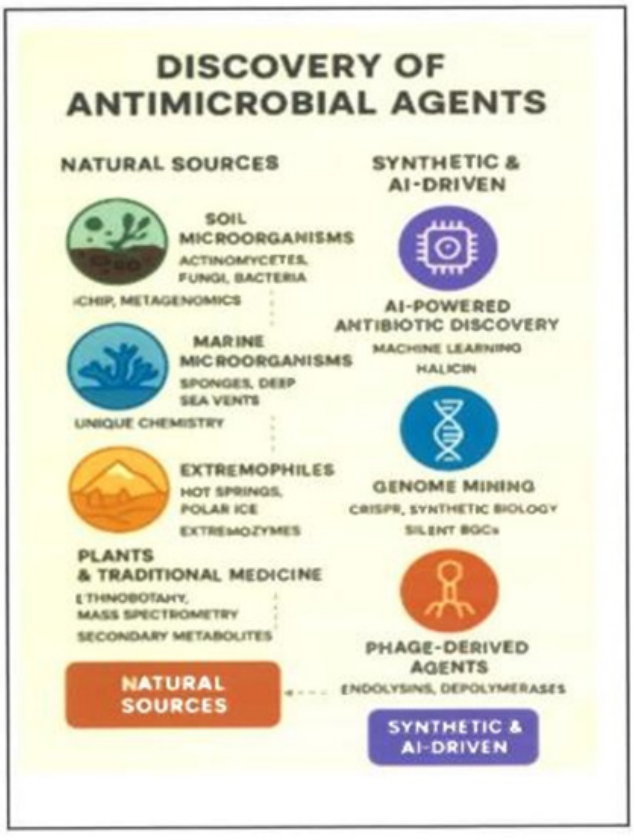

Figure 1: Discovery of A antimicrobial Agents (Figure generated by Chat GPT August 30, 2025).

Identification of previously unknown biological mechanisms that demonstrate antimicrobial effects are currently the focus of researchers around the world. The Figure summarizes key avenues of development. Recent discoveries by Tang et al [10], showed that antibodies recognizing sugars on bacterial cells can clear an otherwise potentially lethal bacterial infection in mice. Targeting these distinctive bacterial sugar(s) signals the immune system to destroy the pathogen. Two unusual sources of antimicrobial activity have recently come to light. In one, the origin is from a novel sulphur-based polymer which surpasses previous limitations of this chemical moiety and demonstrates great potency against a wide variety of bacterial and fungal pathogens [11]. A second is derived from a known non-antimicrobial source, a common blood pressure medication, the drug, candesartan cilexitil. This latter compound has been shown to be effective against methicillin-resistant *Staphylococcus aureus* (MRSA). It downregulates acterial virulence genes and works synergistically with other antibiotics to block antimicrobial resistance. The MOA of this compound is to penetrate and then disrupt the MRSA cell membrane [12] (Figure 1).

Incorporation of Innovative Technology

Other novel approaches include the concept of vaccination against anti-microbial-resistant strains of bacteria. Unlike antibiotic development, vaccines can and have been developed in rapid time. In the case of the COVID-19 vaccine, it took only 326 days to market a vaccine after the disclosure of the virus's genetic sequence [13]. Bergstrom et al [14] proposed using the mRNA approach for antimicrobials against resistant bacterial species. However, it would be onerous to conceive of the synthesis and manufacture of mRNA vaccines for all known bacterial pathogens. It might be advisable and manageable to use this approach to limit the number of the most egregious species.

Identification of New Sources of Antimicrobials

To further improve the discovery and development of unique antimicrobial agents, Artificial Intelligence (AI) has been utilized, but the results have been limited thus far. AI can considerably accelerate the discovery of novel antibiotics and antimicrobial agents thereby facilitating clinical decision making for advanced patient care. AI allows researchers to identify agents with unique MOAs and diminished toxicity which makes clinical testing safer, more rapid and efficient. Additionally, by using AI, scientists can more quickly identify alternative treatments/medicines which can be made available to larger populations. Recently, using AI tools, new agents have also been uncovered with unique origins and MOAs. The initial application of AI in the search for new antimicrobial agents, perhaps with distinct MOAs came from exploration of actinomyces chemistry [15]. Antimicrobials have also been discovered from snake venoms and from compounds from the third branch of life besides bacteria and eukaryotes, the archeaea, some of which thrive in hot springs such as in Yellowstone National Park in the United States [16].

Science must confront the issues of the availability of antimicrobial agents for the patient population, the appropriate utilization of antimicrobial agents by qualified medical experts, and the discovery of novel compounds with unique MOAs. Overarching these individual discoveries are the changes that FDA will be adopting to reinforce the expansion of the antibiotic pipeline as well as that of other drugs allowing trials to bypass animal toxicity studies, thus bringing new drugs to market more quickly [17]. These adaptations are crucial to reduce human mortality due to antimicrobial resistance and more rapidly allow incorporation of discoveries such as AI driven innovation in antimicrobial development.

Future Directions

The ongoing commitment of medical experts to treat with the "right" drug as well as curtailing the unnecessary acquisition of antimicrobial drugs by the lay public is essential. Newly anticipated changes by regulatory agencies like the FDA to bypass animal toxicity studies will allow bringing new drugs to market more quickly and thus reduce human mortality. Many anticipated solutions going forward will include the application of AI for the discovery of novel, effective agents with unique MOAs.

Acknowledgements

None.

Conflicts of Interest

None.

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