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DEVELOPING NEW ANTIBIOTICS: THE CRYING NEED OF THE TIME – A SYSTEMATIC REVIEW

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Abstract

Background: Antibiotic resistance (ABR) has reached a critical level. In the near future, even the "last resort" antibiotics are likely to become ineffective against serious multidrug resistant (MDR) infections, resulting in massive morbidity and mortality.

Objective: Developing a state-of-the-art update on the current situation with regard to ABR, impact of the ongoing COVID-19 pandemic on it, the preventive and control measures in progress and the solution with special reference to developing new antibiotics from new classes.

Design: A review of the English medical literature with inputs from authors' own experience.

Salient Points: The growing challenge of ABR infectious diseases has further worsened since the onset of the ongoing pandemic of COVID-19. We are now fast heading towards a situation when even the "last resort" antibiotics are likely to become ineffective against the serious bateral infections. Unfortunately, researchers and innovators are still not able to develop new antibiotics from new classes. This failure is further fueling the impact of ABR crisis and posing a serious threat to our ability to successfully treat serious bacterial infections. The so-called "alternative approaches" comprising nonconventional strategies aimed at tackling MDR bugs, though in progress, are likely to provide just adjuvants rather than real substitutes for antibiotics. The hindrances in Research and Development (R&D) of new antibiotics must be handled as a top priority, clearing the way for developing newer antibiotics, not from existing classes but from brand new classes.

Conclusion: The roadblocks in the endeavors aimed at developing new antibiotics from new classes need to be addressed as a top priority.

Keywords: Adjuvant therapy; Antibiotics; Antibiotic resistance (ABR); New antibiotics; Multidrug resistance (MDR).

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Introduction

Antibiotic resistance (ABR), defined as the ability of the bacterial pathogens to render the antibiotics ineffective against them, has assumed a critical proportion (1). Over and above, this being a natural phenomenon, irrational use of antibiotics accelerates it (2,3). The growing multidrug resistance (MDR), may become extensive drug resistance (XDR) or even pan-drug resistance (PDR) in some cases. Currently, hundreds of thousands of lives are being lost year after year on account of serious infections that can no longer be treated with the existing antibiotics. The willy-nilly lowering of the guards in relation to the silent pandemic of ABR in the wake of attention taken away by the issues pertaining to the COVID-19 pandemic, especially upswing in antibiotic misuse (3), has further worsened the ABR situation. Seemingly, the "flashpoint" is not too far when we are left with by and large no effective antibiotic for serious bacterial infections unless absolutely new antibiotics from new classes on ongoing basis are developed.

This systematic review sheds light on the current issues related to the misuse of antibiotics, particularly exacerbated during the ongoing COVID-19 pandemic. This misuse further exacerbates the threat of antibiotic resistance (ABR) and serves as an example of the need to develop new antibiotics from novel classes on a regular basis.

Antibiotics: Importance in Therapeutics

Ever since the discovery of penicillin in 1928 by Sir Alexander Fleming (4), antibiotics have been playing a crucial role in transforming and revolutionizing the practice of medical therapeutics. The once fatal infections became by and large treatable. Moreover, cancer chemotherapy and organ transplants became a reality. Consequent upon that, both morbidity and mortality got considerably reduced. Over the decades, antibiotics have remained the primary treatment for potentially fatal bacterial infections. Thus, antibiotics have prevented millions of deaths in all these decades.

Antibiotics: Irrational Use

Unfortunately, over the past few decades, the use of antibiotics has assumed the shape of "misuse", "overuse" irrational use" and even "abuse" globally in a big way. According to the estimates by the Center for Disease Control and Prevention (CDC), some 20-50% of all antibiotics prescribed in acute care hospitals in the United States are either "unnecessary" or "suboptimal" (5). In the resource-limited countries (RLCs), the magnitude of the misuse of antibiotics is yet more overwhelming (3). During the current COVID-19 pandemic, the antibiotic overuse has zoomed considerably (3).

Adverse Impacts of Antibiotic Irrational Use

All drugs are likely to cause some adverse drug reactions (ADRs) that may be just mild or moderate. In a relatively small proportion of cases, even severe ADRs may occur. So do the antibiotics.

More importantly, the irrational use of antibiotics has also contributed to the development of ABR, a serious threat to public health globally (1). The health of patients who are not even exposed to them may also be negatively impacted. How? This is through the transmission of resistant bugs. This impact of ABR is most severe in resource-limited settings, more so among the newborns, young children and the elderly subjects. Around one-third newborns with sepsis succumb to bacterial infections that are resistant to multiple first-line antibiotics (6).

The high prescription rates and overuse of antibiotics have led to resistance that has created a global health emergency and kills at least 700,000 people a year. If no action is taken, it is predicted to increase to 10 million deaths per year by the year 2050.

Antibiotic Resistance: Preventive and Control Endeavors

The WHO and its partner agencies continue to be engaged in formulating strategies to prevent and control ABR. Every year WHO along with Food and Agriculture Organization of United Nations (FAO) and World Organization for Animal Health (OIE) - collectively called "Antimicrobial Resistance Tripartite Organizations (AMRTO) - observe globally

"*Antimicrobial Resistance Awareness Week"* from 18-24 November. Its overarching slogan continues to be 'Antimicrobials: Handle with Care'. The 2021-year theme is: 'Spread Awareness, Stop Resistance'.

Then, there is *Antimicrobial Stewardship Program* (7, 8). This is a healthcare-system-wide approach aimed at safeguarding the future effectiveness of antibiotics with focus on antibiotic prudency (9).

WHO's Global Action Plan on AMR, aimed at promotion and monitoring of the judicious use of antibiotics (3), is a mega program that motivates all member countries to fight this malady in a systematized manner. Many countries, including India, have formulated their own strategies inspired by the WHO guidelines (3).

All these endeavors have met with only limited success. Result: antibiotic irrational use continues to have a field day, thereby escalating the magnitude of ABR (10). The current COVID-19 pandemic with massive overuse of antibiotics (usually without any justification) has turned out to be a fuel to fury and has added up to the sordid situation**.**

The Sordid State

Let's concede that, despite the laudable remedial endeavors of the WHO and its affiliate agencies as well as governments of various countries, the AMR crisis is likely to stay put as a silent pandemic, posing a tough challenge to modern pharmacotherapeutics in a considerable measure. The fresh resistance is very likely to continue to emerge and proliferate at new sites.

The currently available antibiotics have either already become ineffective or shall become ineffective in the next some years. The so-called "alternative medications" have not yet been researched to the extent of their acceptable applicability in practice. Under the circumstances, in the foreseeable future we shall be left with hardly any antibiotic that is effective against serious infections.

The matter of concern is that the clinical pipeline along with recently approved antibiotics are incapable of tackling the challenge of increasing emergence and spread of antibiotic resistance. This is likely to lead to emergence of new infectious diseases and re-emergence of those either eradicated or close to eradication. Admittedly, until and unless this trend is brought under control, antibacterial agents are bound to become obsolete, turning common infections into deadly weapons.

Alternative Medications to Antibiotics: Are They the Answer?

The deteriorating situation with regard to ABR has led to exploration of innovative approaches to treat bacterial infections (11,12). Frequently-consumed food items such as garlic, ginger, onion, honey and clove traditionally claim to have some antibacterial activity. But, so far, these lack stringent scientific evaluation (11).

The WHO (13) has taken cognizance of 27 non-traditional antibacterial agents in the pipeline such as antibodies, immunothereutics, bacteriophages, antibacterial peptides, fecal microbiota transplant, probiotics & oligonucleotides. Evaluation of therapies that support the patient's immune response and diminish the toxic effect of the invading pathogen is also under the radar.

Table 1 presents the salient features of the leading so-called "alternative medications".

Broadly speaking, their role appears to be, at best, "supportive, complementary or adjuvant". So far, hardly any of them has convincingly stood the test of time as an independent and acceptable alternative to antibiotics.

Table 1: The so-called "alternative medications" for antibiotics

Antibodies	Known ever since the preantibiotic times**,** pathogen-specific antibodies (passive immunization), administered before or after exposure to the pathogens, may well be an effective therapy. Despite the fact that these are virtually abandoned over the past 8-9 decades, now that the available antibiotics are becoming ineffective, it is beginning to gain attention as an alternative to chemical/conventional antibiotics.
Immunotherapeutics	Immunotherapy involves molecules that boost the host immune system to generally prevent disease in the course of infection-prone times.
Bacteriophage (Phage) therapy	Bacteriophages are viruses that infect bacteria, which potentially could be utilized for therapeutic purposes. Bacteriophage (also termed "phage") therapy has been ranking amongst the most actively researched alternatives to antibiotics. However, there are many hurdles that need to be circumvented before these or other alternatives could substitute antibiotics, or even reach the market.
Probiotics (also prebiotics and synbiotics)	They are good bacteria that are supposed to modulate the gut microbial community toward health. However, few reports indicate lack of dependable efficacy. Clearly, more work is required to demonstrate their role as an alternative to antibiotics.
Fecal microbiota transplant	Fecal microbiota transplant therapy is an effective option for therapy of recurrent or persistent infection with *Clostridium difficile*. Currently, its use in other indications needs to be a part of clinical trials.
Antimicrobial Peptides	Plants and animals produce substances known as antimicrobial peptides as a defense against intruding pathogens. The utility of antimicrobial peptides in human medicine is being evaluated**.** Antimicrobial peptides/ proteins (AMPs) have broad activity to directly kill pathogens.
Oligonucleotides	This therapy is in the process of research trials as a new approach for the treatment of MDR pathogens. Recently, there is research evidence of powerful antimicrobial activity of this lipid oligonucleotide (LON) on the ß-lactamase activity in clinical and laboratory studies. The self-delivery of oligonucleotide sequences via lipid conjugation may be extended to several antibiotics, opening-up novel ways to tackle the nasty problem of ABR.

The Way Forward: Developing New Antibiotics

Under the existing circumstances, discovering new antibiotics that are effective against the MDR pathogens is, therefore, mandatory for saving lives. Table 2 list the antibiotic-resistant "priority pathogens " – a catalogue of 12 families of pathogenic bacteria (14).

Table 2: WHO priority pathogens that pose the greatest threat to human health for research and development of new antibiotics (14)

Priority 1: CRITICAL • *Acinetobacter baumannii*, carbapenem-resistant4 • *Pseudomonas aeruginosa*, carbapenem-resistant • *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
Priority 2: HIGH • *Enterococcus faecium*, vancomycin-resistant • *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant • *Helicobacter pylori*, clarithromycin-resistant • *Campylobacter* spp., fluoroquinolone-resistant • *Salmonellae*, fluoroquinolone-resistant • *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: MEDIUM • *Streptococcus pneumoniae*, penicillin-non-susceptible • *Haemophilus influenzae*, ampicillin-resistant • *Shigella* spp, fluoroquinolone-resistant

To make sure that the supply of new antibiotics keeps pace with these evolving pathogens, it is necessary to have a robust pipeline of new molecules from new classes as well as innovative pathways. Development of an antibiotic involves several stages as shown in Table 3 (15).

Table 3: Stages of antibiotic research and development

Stage 1 Identifying the Source	Fundamental research to identify organisms that produce antibiotic substances , including Komodo dragon blood, ants or inside the human nose, ensuring that the identified sources are not toxic. This may involve testing hundreds and thousands of possibilities.
Stage 2 Three phases of Clinical Trials	The new drugs are tested to see if they're safe and effective in people. Three faced Clinical trials are yet more expensive & cumbersome. Only large pharmaceutical houses are capable of providing huge resources, infrastructure & skills.
Stage 3 Final phase of Trial	The final phase of trials and the trials needed after an initial product launch can account for more than 80% of the total R&D expenditure on a new drug.
Stage 4 Registration	Once a new antibiotic established its effectiveness and safety, it needs to be registered with a government drugs regulatory agency. Only thereafter, it becomes eligible for marketing and legally prescribed in a Country. The whole procedure is slow and full of regulatory hurdles.
Stage 5 Marketing	Marketing per se consumes lot of money. It is very cumbersome to convince the health systems to use new antibiotics and, at the same time, emphasize their sparing use in order to limit the development of resistance.

Hinderances in Developing New Antibiotics

Discovering (via researching and developing) and marketing new antibiotics is a tough, cumbersome, time-consuming and exorbitantly expensive field with many bottlenecks (16, 17). Understandably, the hinderances in research and development of new antibiotics have got to be overcome to save human lives and livestock. Table 4 lists the important hurdles that render

it a formidable exercise. Notwithstanding all these challenges, the research and development efforts may finally end.

Table 4: Hindrances and hurdles in research and development of new antibiotics from new classes

S. No.	Hinderance/Hurdle
1	Reluctance of the big pharma companies to invest in the field on account of limited incentives and returns, uncertainty of approval and inability to recover the huge monetary and technical expenditure.
2	Exorbitant expenditure to the extent of one billion US dollars for a single new antibiotic.
3	Time consuming exercise: Around 10-15 years are needed to research and develop a new antibiotic.
4	Extraordinarily high-level research

Clearly, discovering and developing an antibiotic need herculean effort. Not just that. It may also be very tough to get doctors and health systems to use new antibiotics. And, as the last line of treatment against certain serious infections, antibiotics need to be used sparingly to safeguard against the development of ABR.

According to the WHO (18) none of the 43 antibiotics that are currently in clinical development sufficiently address problem of AMR in relation to dangerous bacteria. Almost all new antibiotics that have been brought to market in recent decades are variations of antibiotic drugs classes that had been discovered by 1980s. According to 2020 WHO documentation, a near static pipeline with only few antibiotics being approved by regulatory agencies in the recent years. Most of these agents in development offer limited clinical benefit over existing treatments, with 82% of the recently approved antibiotics being derivatives of existing antibiotic classes with well-established drug-resistance. Therefore, rapid emergence of drug-resistance to these new agents is expected.

An overwhelming chunk of the antimicrobials in development offer limited clinical benefit over existing antimicrobials. In actuality, about 82% of the recently approved antibiotics are derivatives of existing antibiotic classes that are known to have established drug-resistance. It is but natural to anticipate rapid emergence of drug-resistance to these so-called “new antibiotics”.

Understandably, there is a growing need for developing newer antimicrobials, particularly the antibiotics against MDR Gram-negative bacteria in hospitals and against community-acquired microbes such as causing tuberculosis, gonorrhoea and urinary tract infections. What is noteworthy, the new antibiotics must not be been from the same classes as are already in the domain of ABR.

Ongoing Endeavors

In order to accelerate research and development of new age antibiotics, the WHO and the Drugs for Neglected Diseases Initiative (DNDi) have established the Global Antibiotic Research and Development Partnership (GARDP), a non-profit organization (19). The strategy of the GARDP is to deliver five new antibiotics by 2025. The GARDP is working in collaboration with over 50 public and private sector partners in 20 countries. Over and above new antibiotics, it is supposed to develop and ensure sustainable access to treatments, promoting responsible use and affordability to the needy.

Another important new initiative is the Antimicrobial Resistant Action Fund (AMRAF) that strives to strengthen and boost antibiotic development through global pooled funding (20). AMRAF was set up by a coalition of pharmaceutical companies, philanthropies, European Investment Bank. Supported by the WHO, the Fund aims at ensuring that the most innovative and promising products receive the required funding and that a sustainable pipeline of new antibiotics to fight superbugs.

New Approaches

In run-up to discovery of new antibiotics, recently the researchers from the Children's Hospital of Philadelphia (21) have reported development of a novel method for producing effective antibiotics to overcome issues of ABR. The approach comprises targeting bacteria with an antibiotic that is masked by a pro-drug which the bacteria would themselves remove.

Summary and Conclusion

Currently, we are on the verge of exhausting even the "last resort" antibiotics that are effective against the growing challenge of ABR infectious diseases. This threat has hiked during the uncontrolled pandemic of COVID-19. However, the researchers and innovators are still persistently unsuccessful in developing desperately needed new antibiotics from new classes. This failure is further fueling the impact of ABR and threatening our ability to successfully treat lethal bacterial infections. The hindrances in this endeavor must be tackled as a top priority, clearing the way for developing new antibiotics, not from existing classes but from brand new classes. Hopefully, enough "political will" shall see us through this colossal though silent crisis of ABR with discovery of new antibiotics from novel classes.

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Conflict of Interest

None

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