Novel Strategies to Combat Antimicrobial Resistance

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Abstract

Infectious diseases form the major health-care burden for the developing world and antimicrobials prove to be the magical drugs to combat this. The discovery of antimicrobial agents was boon for the global health-care system and the wonderful cure by antimicrobials shifted the disease trends from infectious to life-style diseases in the developed world. Sudden appearance of the antimicrobial resistance hampered the whole success; and this situation is further complicated by the dry pipeline of antimicrobial development. Now, this is heading the world towards the “pre-antibiotic” era. The development of new antimicrobials is not able to match pace with the speedily growing antimicrobial resistance. Development of new active pharmaceutical principles is a difficult and costly practice. The other approach to achieve the same is by rejuvenating the existing antimicrobials. These contemporary novel approaches include bacteriophage therapy, fecal microbiota transplantation, antimicrobial peptides, combination drug therapy and antimicrobial adjuvants to combat antimicrobial resistance forms the main stay of discussion of this article.

e) Antimicrobial peptides

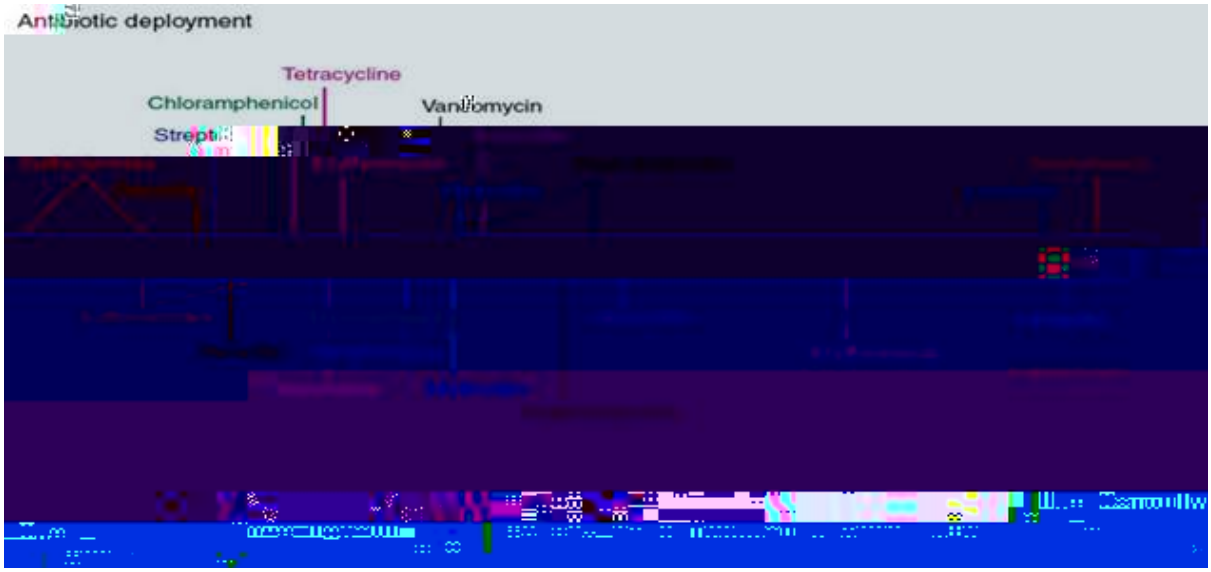

Figure 1: The time difference from manufacturing and marketing of an antimicrobial to development of resistance is decreasing significantly, driving away the pharmaceutical industry from further research and development

infections. Bacteriophage is a virus that infects and replicates within a bacterium. Ħese are composed of proteins that encapsulate a DNA or RNA genome and replicate within the bacterium following the injection of their genome into its cytoplasm. Ħis property can be used to kill the bacteriophage occupied bacterial cells, forming the principle of this therapy. Originally, developed by Frederick Twort and Felix d'Hérelle in 1915 and 1917, phage therapy was immediately recognized as an important tool for treating bacterial infections [13]. In 1896, the British bacteriologist Ernest Hankin reported antibacterial activity against *Vibrio cholerae*, which he observed in the Ganges and Jumna rivers in India. He suggested that an unidentiÎed substance was responsible for this phenomenon and for limiting the spread of cholera epidemics [14]. Ħis unidentiÎed substance is now recognized as Bacteriophage. Much of the knowledge about this therapy remained hidden from the world, possibly due to publishing of scientiÎc literature in non-english journals.

Ħese bacteriophages have a high speciÎcity in killing particular bacteria, leaving the other useful bacteria unharmed. Ħis property is especially useful while killing the pathogens, without altering gut Îora. Antibiotics being non-speciÎc in their action destroy commensals in gut as commonly seen with Îuoroquinolone, leading to super-infections with *Clostridium diffcile* [15].

Ħere are several advantages seen with bacteriophage therapy over antibiotics. Small doses of bacteriophages are required to treat bacterial infections as they self-replicate *in vivo*. Ħis also provides an additional advantage of being less immunogenic as less dose of foreign substance is administered in the body. Ħe concept of sub-lethal dose, as seen with antimicrobials holds no place in bacteriophage therapy as single bacteriophage is suffcient to kill single bacterium. As phages also continue to participate in evolution, they keep on adapting themselves at-par with the mutational changes occurring in bacteria, leaving less chances of development of resistant bacteria [16]. Bacteriophage therapy also has high therapeutic index. Being speciÎc to bacterial species, development of cross-resistance is infrequent.

Ħere are certain limitations to this therapy, not enough to limit their applications. Being highly speciÎc for bacteria, in case of mixed bacterial infections (as commonly observed in clinical practice), we

Antimicrobial Adjuvants

The discovery of new and effective antimicrobials is the ideal approach to combat the issue of antimicrobial resistance. It seems a fair solution for the deficiencies in the existing antimicrobials for resistance-development point of view. But the development and marketing approval of these drugs by US-FDA had not matched the pace of development of antimicrobial resistance. So, the best practical

antimicrobial resistance. To conclude, we feel that rejuvenating the already existing antimicrobials is more practical and better approach than to look for newer molecules from the beginning. The various modalities listed above seem to be quite promising, although more research into these is need of the hour. The combination therapy helps in overcoming the vulnerabilities of the existing antimicrobials by supplementing them with the missing links in their natural lytic pathway. Bacteriophage therapy is conÎned only to certain parts of the globe, this need to be highlighted to the entire scientiÎc community for better understanding and newer applications. Fecal microbiota transplantation is a recently employed approach promoting the growth of commensals to outnumber the pathogenic resistant bacteria. Certain newer potential application to this approach is under research. Antibiotic adjuvants act like combination therapy, but they target more metabolic and other pathways vital in the survival of microbes and works by boosting the action of antimicrobials, even for the molecules with zero intrinsic antimicrobial activity. Antimicrobial peptides are ultra-fast acting broad spectrum proteins which mimic the natural innate immune system for clearing microbes. This

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