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Review Article

Effectiveness of Antibiotics: Anti-Bacterial Activity or Microbial Drug Resistance?

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Antibiotics, both broad- and narrow spectrum, are widely used for treatment of specific infection by a consortium of microorganisms or by a single pathogen, respectively. Oral or intravenous, or even topical administration of different categories of antibiotics in various forms is a common practice round the globe. Yet for the recent years a major public health issue has been raised by the emergence of the drug-resistance microorganisms. A number of researches focused on the issue of the ineffectiveness of antibiotics as well as regarding the evolution of the drug-resistance genes within the pathogenic microorganisms. Isolation of the drug-resistant microorganisms including the multi-drug resistant (MDR) and the extensively drug resistant (XDR) bacteria from a range of patients with microbiological infections has been seriously challenging the disease mitigation approaches. Besides, the dominance of the methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Staphylococcus aureus* (VRSA), etc. are quite frequent as evident from different case studies. Current review focused on the origin and evolution of such drug-resistance incidences, and the promising remedies over the problems of drug-resistance.

Keywords: Antibiotics, Drug-resistance, Public health

Introduction

Antibiotic, for example, penicillin, cephalosporin, streptomycin, tetracycline, gentamicin, griseofulvin, etc. is well defined by Huggo and Russell as the substance produced by a microorganism (mostly *Streptomyces* species, *Penicillium* spp., *Bacillus*, *Micromonospora purpurea*; *Pseudomonas acidophila* or *Gluconobacter*, etc.), or as an analogous material resulting from chemical synthesis (like chloramphenicol, sulphonamides, diaminopyrimidine derivatives, trimoxazole, ntrofuran compounds, quinolones, imidazole derivatives, etc.), which can inhibit the growth of other microorganisms in low concentrations[1]. Eventually, to combat the bacterial and the fungal infection, a range of different categories of antibiotics (including the anti-bacterial antibiotics like the b-lactam antibiotics, tetracycline group, rifamycins, aminoglycoside-aminocyclitol antibiotics, macrolides, polypeptide antibiotics, glycopeptide antibiotics like vancomycin; or the anti-fungal antibiotics like griseofulvin, polyenes, etc.) has long been practiced as per the physicians' prescriptions marinating the defined forms of administration and dosage[1]. While the liquid forms of antibiotics (i.e., the antibiotic solutions or suspensions) are usually suggested for the pediatric usage, the granular antibiotics are widely taken by the adults following the appropriate drug concentrations as well as the correct dose of administration to get rid of the microbial infection[2]. The industrial manufacturing of antibiotics is of significant importance in order to maintain the quality of the active ingredients of the antibiotics and additionally, it's really important to set the excipients at appropriate concentrations as per the recommendations and guidelines set by the British Pharmacopoeia (BP) or the European Pharmacopoeia (EP), or the United States Pharmacopoeia (USP)[3]. Moreover, as per the guidelines set by the Food and Drug Administration (FDA) as well as by the standard operating procedures (SOPs) set by the pharmaceutical manufacturing and packaging regulatory guidelines (usually guided both by the FDA and the Pharmacopoeia), the total quality management (TQM) is emphasized through the implementation of the good manufacturing practice (GMP) starting from the raw materials ending up to the finished products ready for distribution into the market for sales[3-5].

The mechanism of different groups of antibiotics against bacteria principally relies on different components of the bacterial cells as the set target sties of specific antibiotic[1,6]. For example, the cell wall of bacteria is commonly known to be prone to attack by the b-lactams, glycopeptides, and cycloserines (isoniazid, ethambutol, etc.). The cell membrane is usually attacked by the polymyxins like polyenes, imidazoles, etc. Ribosome serves as the target site for aminoglycosides, tetracyclines, chloramphenicol, macrolides, fusidic acid, etc. The bacterial chromosome acts as the target site for fluoroquinolones, rifampicin, nitrofurans, etc[1]. However, the onset of microbial drug resistance (MDR) is has been a burning clinical issue since long especially revealed through the multi-drug resistance (MDR) or the extensively drug-resistance (XDR) phenomena whereby a

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single microorganism becomes resistant against several types of antibiotics[6-12]. The frequency of the methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), vancomycin-resistant *Enterococcus* (VRE) species, penicillin-resistant *Streptococcus pneumonia*, glycopeptide intermediate sensitivity *S. aureus* (GISA), the extended-spectrum ²-lactamase (ESBL) producing bacteria is also increasing[1,7-13].

Therefore, a number of antibiotics are now appearing ineffective against various pathogenic microorganisms which in turn are increasing the fatality and morbidity around the world especially within the undeveloped or developing countries where the appropriate legislations about the usage of antibiotics are unfortunately lacking[14]. Furthermore, the increasing tendency of the antibiotic resistance certainly sheds light on specific resistance determinants as well as on the drug-resistant microorganisms which are concomitantly spreading both locally and globally, possibly due to the pervasive use of the same antibiotics for human, animal, and in the agricultural sectors[15]. Along these lines, the present review discussed the aspects of the microbial drug-resistance phenomenon against the antibiotics including the causes and effects, and also suggested some possible steps towards minimizing such resistance.

Antibiotic Resistance: Origin and Evolution

Initially, around 40 years ago, the origins of antibiotic resistance genes were blurred[1]. However, the basic mechanisms of resistance against antibiotics was characterized by the inactivation of the drug, alteration of the target, reduced cellular uptake, and the increased efflux[1]. Afterwards the reasoning behind such resistance were unraveled through the findings of the horizontal acquirement of genes imparting drug-resistance into the bacterial cells; or by the mobilization via insertion sequences, transposons and the conjugative plasmids, by the homologous recombination of the foreign DNA into the chromosomal DNA; or by mutations in the different loci of chromosome[1,16-17]. It is to be pondered that the antibiotic itself may play a role as the selective marker and secondly the resistance gene acts as the vehicle of resistance; and the resultant impact over time and antibiotic concentration is noticed as the resistance of microorganisms against different antibiotics[15]. In a nearly similar way to Hugo and Russell's work[1], recently Munita and Arias categorically reported the antibiotic resistance mechanisms again focusing on the modifications of the antibiotic, making the antibiotic excluded by diminishing penetration into the microbial cells, altering the target sites, and certainly by acquiring the adaptation and survival capacity in presence of antibiotic[17].

Resistance to ²-lactam antibiotics primarily accounts for the presence of ²-lactamase, mutation in the penicillin binding protein (PBS); mutation of the ²-lactam targets and due to the overexpression of efflux pumps[1,18]. Although known, yet it's to ponder that resistance was also noticed to be imparted by plasmids encoding the extended-spectrum b-lactamases (ESBLs) [1]. Moreover, it should recalled while studying the evolution of the drug-resistance phenomenon that at the early 1950s, the possession of plasmid encoded b-lactamases had stopped the anti-bacterial activity of penicillin for the treatment of *Staphylococcus aureus* infections which led the then scientists to discover the b-lactamase-stable methicillin (in 1959)[1]. Ironically within a year, the methicillin-resistant *S. aureus* (MRSA) strains evolved; and then vancomycin (the glycopeptide antibiotic) was launched[1]. With a great surprise the resistance even to this antibiotic was noted in 1988 through the identification of the vancomycin-resistant enterococci (VRE)[1].

Microbial resistance against the aminoglycoside antibiotics (streptomycin, kanamycin, gentamicin, tobramycin, apramycin and amikacin) has been reported to be imparted by the enzymatic modification; through increased efflux; and by modifications of the 30S ribosomal subunit[1,19]. Another aspect of antibiotic resistance is seen through the colistin-resistant and carbapenemases-producing *Klebsiella pneumoniae*[20-21]. Indeed the carbapenemases-producing *K. pneumoniae* became rebellious candidate for the antimicrobial treatment of the hospitalized patients[21]. Resistance against chlortetracycline and oxytetracycline is relatively modern[1]. *Shigella flexneri*, ESBL-producing *Escherichia coli* (MRSA), *Streptococcus pneumoniae, Klebsiella* species and *Salmonella enterica* serovar *typhimurium* isolates have been commonly noticed to be resistant against tetracycline[1,22].

Tetracycline resistance mechanisms have been unraveled through the efflux mechanism, protection of bacterial ribosomes, and finally the inactivation of the antibiotic by defined enzymes[22]. The MDR *M. tuberculosis* and the efflux-mediated resistance has been identified in case of the fluoroquinolone antibiotics[1]. Resistance to macrolide, lincosamide and streptogramin (MLS) antibiotics have been studied for long while[1]. Fluoroquinolone resistance has been reported to be conferred through a single point mutation wihin the *gyrA* gene whose product is known to be involved in the DNA supercoiling[23]. This type of resistance is environmentally significant since the accumulation of fluoroquinolone resistance has been evidently shown the formation of biofilm as well as to confer pathogenicity to *Campylobacter jejuni*[23]. Mechanisms of chloramphenicol resistance has long been known to be mediated by the outer membrane permeability and active efflux in Gram-negartive bacteria; and the resistance is principally conferred by the enzyme acetyltransferase in case of the Gram positive bacterium *Staphylococcus epidermidis*[1,24].

Resistance against trimethoprim (TMP) can be caused by the cell wall impermeability (in *Klebsiella pneumoniae* and *Serratia marcescens*), alternative metabolic pathways, overproduction of host dihydrofolate reductase (DHFR) and by the mutation in the structural gene for DHFR or by the acquisition of the *dfr* gene encoding a resistant form (i.e., the alternative DHFR of type I, II or V) as seen in the Enterobacteriaceae[1,25]. Polymyxin B and

colistin are now a days regarded as the last-resort treatment option because of the abnormal elevation of the MDR Gram-negative bacteria and the carbapenem resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Escherichia coli* [26]. However, there are reports regarding the dominance of the naturally polymyxin-resistant bacteria including *Proteus*, *Providencia, Morganella*, and *Serratia*[26]. Earlier it was noted the addition of a 4-amino-4-deoxy-L-arabinose (L-Ara4N) moiety to the phosphate groups on the lipid A component of Gram-negative lipopolysaccharide (LPS) conferred the microbial resistance against polymyxin[1]. Resistance against the common drugs; i.e., rifampicin (RIF) and isoniazid (INH), used for the treatment of tuberculosis and the dominance of both MDR- and XDR-tuberculin bacilli have been demonstrated through various studies[7-9].

Possible Remedies for Minimization of Antibiotic Resistance

Microbial drug resistance is certainly one of the most dreadful public health issue for the current time when lots of emerging diseases are being disseminated throughout the world[14-15,17-19]. In the environment there may be an interesting framework consisting of both antibiotic-susceptible and the antibiotic-resistant bacteria which in turn may raise a competition; among which the growth of the antibiotic-resistant strains may be enhanced through the excessive usage of antibiotics[15]. In order to restore the efficacy of the antibiotics to their earlier forms as well as to achieve the efficacy of the new antibiotic molecules, a precise rationale of antibiotic usage has to be kept which in turn would esteem the antibiotic sensitive bacteria[15]. Besides treatment/ chemotherapeutic purpose, the unreasonable use of antibiotics in agriculture should be minimized since the over dosage of antibiotics have been correlated with the dominance of an array of pathogenic drug-resistant microorganisms[18]. A recent interesting aspect on controlling the antibiotic exposure with a motive to minimize the drug-resistance phenomenon has been seen through the suggestion of generating the evidence based policies by using mathematical models which can play as the key drivers of the drug-resistance transmission dynamics in a complicated infection[27]. Such modelling also focuses on the evolutionary processes of the microbial drug resistance. Of course the challenges associated with measuring the antibiotic resistance evolution using such mathematical models needs to be further chalked out, together with translating the mathematical modelling evidence into policy[27].

Laboratory research based on the random examination of anti-bacterial activities of different antibiotics can be exercised as a collaborative means with either the industrial manufacturing and packaging pharmaceutical companies or the diagnostic centers[6]. Community base remedies about the misuse of antibiotics can be implemented like putting the restrictions in the selling of antibiotics without physicians' prescriptions. Antibiotics should not be advised by any physician at the very beginning of any suspected infection; rather the diagnosis needs to be conducted first. No antibiotics should be suggested for simple cold, cough, sneezing, etc. Without the evidence of bacterial infection, no antibiotics should be routinely prescribed for sore throat or the acute otitis media and sinusitis. Besides, in hospitals, physicians need to be very careful about the routine use of antibiotics for surgical prophylaxis which should be actually minimal[28].

Indeed the presence of an antibiotic is thought to be a selection marker for a high frequency of microorganisms resistant to that specific antibiotic since resistance to any antibiotic treatment actually imparts the microbial strains a benefit compared to the antibiotic susceptible strains[27,29]. This leads to a bit strange situation that the drug-resistant bacteria may possess lower survival capacity within the host in absence of antibiotics[27,30]. Lack of understanding of such selection pressure for the antibiotic resistance is a major challenge to resolve the problem of the microbial drug resistance. Physicians should rethink on such facts to actually find out the root causes for the antibiotic resistance; and should focus more on the drug-resistance resulting from the case studies and diagnostic tests.

Conclusion

Microbial drug-resistance is a major public health throughout the world; and it's one of the greatest threats to the success of the modern Medical Science. The dominance of the MDR or XDR bacteria within the environment as well as the transmission of the drug resistance genes in certain ecological niches is gradually increasing. In addition, the intense genetic agility of microorganisms especially of the pathogenic ones that activate defined responses in course of mutational tolerances, or the amendment of gene expression imparting the resistance to multiple antibiotics. Eventually, such a situation brings failure in the chemotherapy or in the treatment of any specific disease. Therefore, perceptive knowledge on the genetic makeup of the associated factors is of significance to devise strategies to diminish or decrease the emergence and subsequent stretching of such drug-resistance.

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