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RESEARCH ARTICLE

ANTIBIOTIC RESISTANCE IN BACTERIA-A MENACE

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ABSTRACT

Antibiotic resistance in microorganisms has become a critical health issue and has evolved to become a worldwide health threat. Over a decade, the resistance level of bacteria has increased many folds due to various factors, accounting to the added pressure on the environmental pollutions. When bacteria become resistant to an antibiotic, that medicine becomes less effective. Medical treatment of people infected with drug-resistant organisms can become more complicated, leading to longer hospital stays, increased health care costs, and in extreme cases, to untreatable infections. Prevention of antibiotic drug resistance can be achieved by rational uses according to the instructions of medical practitioners, by educating mass publics and health care workers, also by using combined therapy, alternative treatments or search for new resources.This review focuses on the history of development of antibiotics, the broad mechanism of antibiotic resistance and enlists some of the factors which contribute to the resistance and alternative ways to overcome resistances.

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INTRODUCTION

The concept of using antimicrobial agents is in practice in some other form from ancient time itself. The Egyptians were used microbicidal agents for mummification. The use of natural spices as food preservatives was there since ancient period.Some natural agents like honey, citrus food were used in wound dressing and in hospital practice (Forrest, 1982). The Chinese were aware 2500 years ago of using moldy curd of soybean for wound healing and other external infections (Weinstein, 1975).In ancient India Charka and Susruta used several herbal products for therapeutic purposes. The Modern Antibiotic Era was associated with Paul Ehrlich's idea of Magic Bullet as aniline and other synthetic dyes which used to stain specifically disease causing microbes but not host cells. With this idea he started screening a large number of chemicals to control the disease Syphilis causing pathogen *Treponemapalladium* (Williams, 2009) and in 1904 synthesized a large number of chemicals derived from a drug Atoxyl and tested them in syphilis infected rabbit.In 1909 first antimicrobial chemical compound called Salvarsanwas marketed which was a great success as antisyphiliticdrug. Along with more soluble and less toxic Neosalvarsan was used as a promising drug to treat syphilis (Goodman *et al.,* 1941).

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During the earlier days of antibiotics research, this approach led to the discovery of sulpha drugs, namely sulfonamido chrysoidine (Prontosil), which was synthesized by Bayer chemists Josef Klarer and Fritz Mietzsch and tested by Gerhard Domagk for antibacterial activity in a number of diseases (Bosch and Rosich, 2008). Prontosil, however, appeared to be a precursor to the active drug, and the active part of it, sulphanilamide, was thus not patentable as it had already been in use in the dye industry for some years. As sulphanilamide was cheap to produce and off-patent and the Sulphanilamide moiety were easy to modify therefore many companies started synthesizing a large number of such chemicals. The Golden Era of Antibiotic began with discovery of Penicillin from the mold Penicillium by Alexander Fleming. For 12 years after his initial observation, A. Fleming could not purify the penicillin and he finally abandoned the idea in 1940, but, fortunately, in the same year an Oxford team led by Howard Florey and Ernest Chain published a paper describing the purification of penicillin quantities sufficient for clinical testing (Florey, 1945).Their protocol eventually led to penicillin mass production and distribution in 1945. The period between the 1950s and 1970s was indeed the golden era of discovery of novel antibiotics classes, with no new classes discovered since then. Therefore, with the decline of the discovery rate, the mainstream approach for the development of new drugs to combat emerging and re-emerging resistance

of pathogens to antibiotics has been the modification of existing antibiotics (Van Epps, 2006).

Definition

Antibiotics can be defined as the variety of biochemical substances produced by one type of microorganism but that controls the growth of or kills other type of microorganisms. Normally various bacteria, actinomyces are the producers of antibiotics.

Classifications

A common scheme of classifications (Pelczar *et al.,* 1999) for antibiotics is drawn below: Antibiotics can also be classified based on theirphysico chemical structure. A similar level of effectiveness, toxicity and side-effects is rendered by the antibiotics of same structural group. Route of administration of antibiotics may be oral or injectable. Broad spectrum antibiotics are effective against a broad range of microorganisms in comparison to narrow spectrum antibiotics. Based on types of activity antibiotics divided into bactericidal antibiotics kill the bacteria and bacteriostatic antibiotics stop the growth of bacteria. A large number of semi synthetic and synthetic antibiotics are being used in market to combat various diseases. Antibiotics have transformed health care since they were introduced in the 1940s and have been widely used to fight infections.

Antibiotic Resistance

The resistance of bacteria to antibiotics and similar drugs called antimicrobials is considered a major public health threat around the world (Pearson and Carol, 2007). Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections. Antibiotic resistance in microorganisms, especially in bacterial species, has become an eminent and serious concern in the field of healthcare and medicine (Larson, 2007). Antibiotic resistant bacteria have been found in the initial stages of antibiotic use, but over the time, they have become resistant to more than one antibiotic, termed as multidrug resistant organisms (also called "superbugs").It has been observed that very high rates of resistance are growing among common health-care associated and community-acquired infections (Urinary tract infection, Pneumonia). Fleming was also among the first who cautioned about the potential resistance to penicillin if used too little or for a too short period during treatment. When bacteria become resistant to an antibiotic, that medicine becomes less effective. Medical treatment of people infected with these drug-resistant organisms can become more complicated, leading to longer hospital stays, increased health care costs, and in extreme cases to untreatable infections and life threats (Cassir *et al.,* 2014).

Mechanism of antibiotic resistance

The appearance of antibiotic resistance has been regarded as an inevitable genetic response to the selection pressure imposed by antimicrobial therapy. The microorganisms have a great ability to adapt or resist to a new environment contain antibiotics. So far many experiments and results showed that antibiotic resistance may be Intrinsic or Acquired (D'Costa *et al.,* 2011). The microorganisms which were resistant at the time of treatment represents natural or intrinsic or de novo resistance whereas initially sensitive pathogens became drug resistant after treatment represents acquired resistance. Intrinsic resistance are chromosomally encoded and acquired resistance results from a mutation in the existing DNA of an organism or acquisition of resistant gene through the process of transformation, transduction, and conjugation or through transposons. There is an evidence that naturally occurring antibiotic resistance is common (Aminov and Mackie, 2007). The genes that confer this resistance are known as the environmental resistome (McNulty *et al.,* 2007) .These genes may be transferred from non-disease-causing bacteria to those that do cause disease, leading to clinically significant antibiotic resistance (Levy and Stuart, 2002). In 1952, an experiment conducted by Joshua and Esther Lederberg showed that penicillin-resistant bacteria existed before penicillin treatment (Pollock, 1967). While experimenting at the University of Wisconsin-Madison, Joshua Lederberg and his graduate student Norton Zinder also demonstrated pre-existent bacterial resistance to streptomycin also (Ochiai, 1959).

Molecular mechanism of resistance

The mechanisms of antibiotic resistance can be classified as a target related. Targets can be:

- protected by modification (mutations making it insensitive to antibiotic action such as mutations in RNA polymerase conferring resistant to rifampin;
- modified by an enzyme (such as methylation of an adenine residue in 23S rRNA making it insensitive to macrolides);
- replaced (for example, ribosomal protection proteins conferring resistance to tetracycline); and
- protected at cellular or population levels (formation of a protective barrier by secretion, for example, of large amounts of exopolysaccharides). The resistance can be defence related. The defence can bemodified so the efficiency is lost, as in the case of acetylation of aminoglycosides, destroyed (as the β-lactam antibiotics by the action of β-lactamases), and pumped out from the cell as in efflux pump mechanisms of resistance (Li *et al.,*2009).Pathogens show inherent resistance to antimicrobial agents through a variety of mechanisms of decreased permeability of the outer membrane, efflux systems which actively pump antibiotics out of the cell, and production of antibiotic-inactivating enzymes and finally alteration of target sites (Aminov and Mackie, 2007).

Decreased Permeability

The outer membrane of Gram-negative bacteria is a barrier which prevents large hydrophilic molecules to pass through it. Amino glycosides and colistin interact with lipopolysaccharideschanging the permeability of the membrane in order to pass whereas beta-lactams andquinolones need to diffuse through certain porin channels. The pathogens impede the entry of hydrophobic antibiotics like naficillin or erythromycin. Bacteria produce two major classes of porins: general; which allow almost any hydrophilic molecule to pass (Fluit *et al.,* 2001) and specific; which have

binding sites for certain molecules, allowing themto be oriented and pass in the most energy-efficient way (Quintiliani and Courvalin, 1995).Most bacteria possess lots of general porins and relatively few specific ones. Loss of porins leads to increased resistance to betalactams.

Efflux System

Bacteria express several efflux pumps that expel drugs together with other substances out of the bacterial cell. These pumps consist of three proteins a protein transporter of the cytoplasmic membrane that uses energy in the form of proton motive force, a periplasmic connective protein, and an outer membrane porin. Most antibiotics except polymyxins are pumped out (Hooper, 1999) by these efflux systems. Therefore their first two components are named multidrug efflux (Mex) along with a letter (MexA and MexB). The outer membrane porin is called Opr along with a letter (OprM) (Akama, 2004).For example MexAB-OprM resistance works against fluoroquinolones, amino glycosides, β-Lactams (preferablymeropenem, ticarcillin), tetracycline, tigecycline and chloramphenicol where as Mex CD-Opr Jpreventsfluoroquinolones, β-Lactams (preferably Meropenem, Ticarcillin), tetracycline, tigecycline, chloramphenicol, erythromycin and roxythromycin. MexEF-OprNresistsfluoroquinolones, β-Lactams (preferably meropenem, ticarcillin), tetracycline, and tigecycline and chloramphenicol. MexXY-OprMinduces resistance against fluoroquinolones, aminoglycosides, β-Lactams (preferably Meropenem, Ticarcillin, and Cefepime), tetracycline, and tigecycline and chloramphenicol. AmrAB-OprA system shows resistance towards amino glycosides.

Altered target sites

Natural variations or acquired changes in the target sites of antimicrobials that prevent drug binding or action is a common mechanism of resistance. Target site changes often result from spontaneous mutation of a bacterial gene on the chromosome and selection in the presence of the antimicrobial (Lambert, 2005).The use of methicillin and beta-lactams against Staphylococci do not adequately bind beta-lactams to inhibit cell wall synthesis. vancomycinused against Enterococci causes alteration in cell wall precursor components to decrease binding of vancomycin. Modification of ribosomal proteins or of 16SrRNA was occurred in Mycobacterium spp. against streptomycin. Mutations occurred in RNA polymerase resulting in resistance to the rifamycins whereas mutations will cause in DNA gyrase resulting in resistance to quinolones.

Production of antibiotic inactivating enzymes

Enzymatic inactivation either by hydrolysis or by modification (group transfer andredox mechanisms) is a major mechanism of resistance to natural antibiotics in pathogenic bacteria (Davies, 1994). The resistant isolates in most cases inherit the antibiotic resistance genes on resistance (R) plasmids. These resistance determinants are most probably acquired by pathogenic bacteria from a pool of resistance genes in other microbial genera, including antibiotic producing organisms. No enzymes that hydrolyse or modify manmade antimicrobials have been found. Furthermore, antibiotic inactivation mechanisms share many similarities with well-characterized enzymatic reactions and resistance proteins show homologies to known metabolic and signaling enzymes with no antibiotic resistance activity. Therefore these may be the original sources of resistance. Either hydrolysis or group transfer reactions; or alternatively oxidation or reduction reactions can cause inactivation mechanism. Many antibiotics possess hydrolytically susceptible chemical bonds (e.g. estersandamides) whose integrity is central to biological activity. When these vulnerable bonds are cleaved, the antibiotic activity is destroyed. The most diverse and largest family of resistance enzymes is the group transferases. Those enzymes covalently modify antibiotics leading to structural alterations that impair target binding. Chemical strategies include *O*-acylation and *N*-acylation, *O*-phosphorylation, *O*-nucleotidylation, *O*-ribosylation,*O*-glycosylation and thioltransfer. The oxidation or reduction of antibiotics has not been frequently exploitedby pathogenic bacteria. Lyases are enzymes that cleave C-C, C-O, C-N and C-S bonds by non-hydrolytic or non-oxidative routes. These reactions frequently result in double bond formation or ring closure .The most common resistant enzyme is beta-lactamase which destroys beta-lactam containing antibiotics. There are several classes of these enzymes are identified (Fisher, 2005).Class A:Plasmid mediatedserine residue at the active site preferentially hydrolyzepenicillin.ClassB:ChromosomalMetalloenzymes;Hydrolyzecarbapenems, penicillin and cephalosporin ClassC: Chromosomal Amp C ,mainly active against cephalosporin Class D: Plasmid mediated Oxacillinhydrolyzing enzymes Carbapenemasescanhydrolyzepenicillin, cephalosporin, monobactams and carbapenems. Groups Metalloblactamases (MBLs) confer a high level of resistance against*Pseudomonas, Acinetobacter, Enterobacter.*ESBL (Extended Spectrum Beta-Lactamase) mediated Resistancecontain a number of mutations that allow them to hydrolyze expanded spectrumBetalactam antibioticderived from older antibiotic hydrolyzing Betalactamase enzymes (TEM1,TEM2,SHV1).A single amino acid substitution can give rise to new ESBLs.

Prevention of resistance

The main problem is that after a new antibiotic is introduced, resistance to it will, sooner or later, arise. A significant factor to consider apparently is the use of antibiotics by humans. Implementation of a screening program of antibiotic resistance would be of great value in forecasting future changes in resistance pathogens (Mouton, 1999). Moreover the level of antibiotic-resistant infections strongly correlates with the level of antibiotic consumption. There may be requests from patients to prescribe antibiotics when there is no need for them, as in the case of viral infections, and which should be explained to them (Soothill *et al.,* 2013). Antibiotic therapy is widely used for veterinary treatment. The agricultural use of antibiotics, however, is not limited exclusively to this use. Antibiotics are also used for the growth promotional and prophylactic purposes in food animals, as well as for a broader and less-targeted treatment in aquaculture and horticulture. Although there are some potential alternatives to antibiotic treatment such as passive immunization (Levin and Bull, 2004) or phage therapy, the mainstream approach relies on the discovery and development of newer, more efficient antibiotics. A combination of antimicrobial photodynamic therapy with various antimicrobial and antibiofilm approaches to obtain a synergistic effect to permit efficient microbial

growth control at low photosensitizer doses. PDT (Photo dynamic therapy) has gained clinical acceptance, and many clinical trials are being conducted, while APDT (Antimicrobial PDT) is in its infancy. As antibiotic therapies become less effective because of increasing microbial resistance to antibiotics, alternative methods such as APDT for fighting infectious diseases are urgently needed.

Conclusions

The current state in the field of antimicrobials, resistance, and chemotherapy is certainly not limited to clinical microbiology as it was in the early years of the antibiotic era. Thus, it is not a single grand challenge; it is rather a complex problem requiring concerted efforts of microbiologists, ecologists, health care specialists, educationalists, policy makers, legislative bodies, agricultural and pharmaceutical industry workers, and the public to deal with. In fact, this should be of everyone's concern, because, in the end, there is always a probability for any of us at some stage to get infected with a pathogen that is resistant to antibiotic treatment. Moreover, even the behavioural patterns, such as hygienic habits or compliance with antibiotic treatment regimens, may have consequences that are not limited only to individual health issues but, on a larger scale, contribute to the interaction with the resistomes around us. This overview has given insight in the many therapeutic possibilities that exist for treatment of bacterial infections and in the continuous battle between resistance development and overriding mechanisms. Therefore, to prevent the emergence and dissemination of resistant bacteria, continuing efforts to develop new antibacterial agents are warranted. Although this is not an easy assignment, there is still hope and many new avenues are being explored. There is an urgent need for an alternative therapy which could be cocktail of drugs or alternative medicines itself.

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