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Review Article

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A Dumpy Review on Antimicrobial Resistance

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Abstract The discovery and introduction of antimicrobials to clinical medicine was one of the furthermost medical achievements of the 20th century that revolutionized the treatment of bacterial infections. However, the continuing appearance of populations of antimicrobial-resistant pathogenic bacteria resulting from use, misuse, and abuse of antimicrobials has today become a major global health worry. Antimicrobial resistance (AMR) genes have been suggested to originate from bacteria, as clinically important resistance genes have been detected on the chromosome of bacteria. As only a few new antimicrobials have been developed in the last decade, the further evolution of resistance creates a serious menace to public health. Urgent measures are essential not only to reduce the use of antimicrobials for prophylactic and therapeutic purposes but also to look for option strategies for the control of bacterial infections. This review look at the global depiction of antimicrobial resistance, factors that favor its increase, strategies, and limitations for its control and the need for continuous training of all stake-holders i.e., medical, veterinary, public health, and other relevant professionals as well as human consumers, in the suitable use of antimicrobial drugs.

Keywords Human medicine, mechanisms, resistance genes

Background

Antibiotics are low-molecular-weight compound, whether it is a microbial or other living organism's metabolite or synthetic compound, which at low concentrations will kill or inhibit the growth of other microorganisms [1].

Antibiotic agents affect the growth of bacteria in two general ways. Those that kill bacterial cells outright are known as bacteriocidal. Bacteriocidal antibiotics generally bind tightly to their cellular targets and are not removed by dilution [2-3]. Antibiotics that do not kill, but inhibit growth are known as bacteriostatic. Bacteriostatic antibiotics are frequently inhibitors of protein synthesis and act by binding to ribosomes. The binding is not tight, and when the concentration of the antibiotic is lowered, it becomes free from the ribosome and growth is resumed [2].

An antibiotic that kills or inhibits the growth of many types of bacteria is called a broad-spectrum antibiotic [3]. A broad-spectrum antibiotic will generally find wider medical usage than a narrow-spectrum antibiotic, which is one that acts only on a single group of organisms. Narrow-spectrum antibiotics may be quite useful, however, for control of bacteria that fail to respond to other antibiotics. Some antibiotics have an extremely narrow range of action, being effective for only one or two bacterial species [1,3].

Discovery of antibiotics

It wasn't until the second half of the 19th Century that Robert Koch observed and first reported in 1877 that some microorganisms could destroy others, a phenomenon confirmed by Louis Pasteur and believed might be utilized in medicine[4]. By the end of that century, the German bacteriologist Paul Ehrlich, often called the "father" of scientific antibacterial chemotherapy, had begun his quest to systematically seek out new,

antimicrobial compounds [5]. In 1909, Paul Ehrlich discovered the first chemical "cure" for a disease, the arsenical compound, arsphenimine (marketed as Salvarsan), that was selectively toxic for *Treponema pallidum* [6]. The medical profession dubbed this compound "the magic bullet" because it killed the specific "germs" that caused syphilis. It was in early September of 1928 that Alexander Fleming, returning from holiday to his laboratory at St. Mary's Hospital in London, made his famous observation on an old uncovered culture plate of bacteria [7]. Along with the "expected" staphylococci on the petri plate, he noticed a blue-green mold and "something" in the mold was attacking the bacteria. He identified the mold as *Penicillium notatum*, cultured it in nutrient broth, filtered it, and discovered in the filtrate a substance that ravaged bacteria, this discovery was as named penicillin [7]. Fleming was unable to purify the penicillin himself and was also unable to arouse much interest in his discovery. It took the economic and political (as well as medical) pressures of disease-ridden soldiers and civilians of World War II to awaken pharmaceutical company's interest in penicillin. The British pathologist/bacteriologist Howard Florey and German chemist Ernst Chain extracted the first "real" sample of penicillin in the spring of 1942, which was a million times more powerful than Fleming's original filtrate. Penicillin became the starting point for modern antibiotic therapy.

Close on the heels of Alexander Fleming's discovery, and inspired by it, came the investigations of Selman Waksman into the antimicrobial substances produced by the soil-borne fungi and microorganisms that destroy or slow the growth of other microbes. In 1940, he initiated a systematic search for non-toxic antibiotics produced by soil microorganisms, particularly the actinomycetes [8]. By the middle of the 1950s, representatives of most of the major families of antibiotics, including chloramphenicol, tetracyclines, and macrolides, had been discovered [9].

Bacterial species vary tremendously in their susceptibility to an antibiotic. The term antibiotic resistance is often used in a general sense to signify the lack of effect of an antibiotic agent on a bacterial cell. A commonly accepted definition states that a bacterial strain derived from a species that is susceptible to an antibiotic is said to be resistant when it is inhibited by the minimal concentration of the antibiotic that inhibits the growth of typical strains of that species [10].

Development of Resistance

Indeed, the discovery of these first "wonder drugs" was declared by some in the medical establishment to herald the end of bacterial infection and disease as a threat to public health. No longer would tuberculosis, dysentery, pneumonia, and other killers take their enormous toll on mankind and its social systems (or so it was thought). The initial success of antibiotics during the 1960s and 1970s in "conquering" many bacterial infections led to the opinion by many that infectious diseases had lost their threat.

However, with the benefit of more than half a century's worth of hindsight, we are now able to take a more dispassionate, and perhaps objective, view of the benefits and limitations of antibiotic therapy. What the past fifty years has shown us and what scientific research in fields such as bacterial genetics and microbial ecology continue to reveal are two main things. First, that microbes display a truly amazing versatility in terms of their ability to avoid, withstand or repel the antibiotic onslaught [11-13]. Secondly, it is often the use of antibiotics that disturbs the delicate bacterial ecology within the body of both humans as well as animals, allowing the proliferation of resistant species, and sometimes initiating new infections that are worse than the one originally treated [14]. The historical cycle that we have witnessed over and over in the last fifty years is that drugs were discovered, diseases (supposedly) were conquered, and more drugs were discovered in an inexhaustible go-around. Old disease "scourges" of both humans and animals, re-emerged as significant problems of the 1980's. Antibiotic drug resistance allowed diseases such as cholera, bacterial meningitis, tuberculosis, pneumonia, and even plague to spring back with a renewed vengeance [12, 15-17].

Antibiotic Resistance is a complex and multifaceted problem and many factors lead to the development of resistance such as:

- Bacterial population density in health care facilities, which allow transfer of bacteria within a community and enables resistance to emerge.
- Inadequate adherence to proven hospital hygiene measures;

- An increasing number of high risk populations, including chemotherapy, dialysis, and transplant patients as well as those in long-term care facilities;
- Overuse of antibiotics in agriculture;
- Global travel and trade, which can lead to transfer of resistant infections and resistance genes;
- Poor sanitation in certain areas, which can contaminate water systems and spread resistant bacteria in sewage;
- Inappropriate use of antibiotics in human medicine (e.g. for viral infections);
- Overprescribing of broad-spectrum drugs, which can exert selective pressure on commensal bacteria and predispose to secondary infection and
- Lack of rapid diagnostics to help guide appropriate use of antibiotics.

The Evolution of Antibiotic Resistance

The ability of bacteria to evolve in response to pressure from antibiotics has been recognized since the discovery of penicillin [18]. In less than a century, a complex array of factors has led to the emergence of bacteria that no longer respond to any approved antibiotics. Numerous recent calls to action (CDC, 2013) have highlighted the urgent need to respond to this growing global health threat with improved surveillance and infection control, more judicious use of antibiotics, new prevention measures, and new therapeutic strategies to combat resistant bacteria.

Bacteria can acquire resistance through mutation or through horizontal transfer of genetic information. Resistant members of a population that are exposed to the selective pressure of antibacterial drugs will be amplified, which can ultimately result in treatment failures in the clinic. Resistance genes are ancient (even pre-dating human beings) and ubiquitous [19] and some of the most worrisome resistance genes have been found in diverse environmental samples, including drinking water [20]. Furthermore, many bacterial species harboring resistance genes can colonize the human gut, skin, and other niches, where they serve as a ready source of infection when host defenses are breached. These bacteria can also serve as a source of Antibiotic Resistance genes for transfer to other bacteria, facilitating the interspecies spread of resistance.

The Antimicrobial Resistance Gene Pool

AMR genes can be differentiated depending on the genetic event that is required for acquiring an AMR phenotype. These include genes that are acquired by horizontal gene transfer and genes that are present in the bacterial genome and that can encode AMR following gene mutations or activation [21].

AMR features evolve as a consequence of permanent exchange of and ever new recombinations of genes, genetic platforms, and genetic vectors. Many of these genes are not primarily resistance genes, but belong to the hidden resistome, the set of genes able to be converted into AMR genes [22]. As evidenced by our discussion above, microbial organisms harboring these genes are present naturally in all kinds of environments, but also released into water and soil from organisms, including humans, where they evolve or increase in abundance under direct selection from exposure to antimicrobials. At the same time, antimicrobials (often at low concentrations), disinfectants, and heavy metals are disseminated into the water as well, and may act as selective factors fostering the evolution of new AMR features [23-25]. The rate of degradation of antimicrobials in the environment varies and is dependent on a range of environmental conditions, for example: temperature, available oxygen, pH, presence of alternative sources of organic and inorganic discharges.

Mechanisms of Antibiotic Resistance

Bacteria exploit a variety of mechanisms to combat antibiotics [26]. These strategies include limiting the intracellular concentrations of the antibiotic by decreased influx or increased efflux of the drug, modification or neutralization of the antibiotic by enzymes that reversibly or irreversibly inactivate the drug, alteration of the "target" of the antibiotic so that the drug no longer interferes with it, and elimination of the target altogether by the utilization of different metabolic pathways. Bacteria may use or combine multiple mechanisms against a single agent or class of agents or a single change may result in development of resistance to several different agents [27].

Decreased Uptake/Reduced Permeability of the Cell

Permeability barriers are an important component of the intrinsic resistance of many organisms. The outer membrane contains porin proteins, which form channels that allow the exchange of nutrients and other substances, including antibiotics, between the extracellular environment and the periplasmic space [28-29]. Changes in the cell envelope, including loss of outer membrane porins or alterations of the lipopolysaccharide (LPS) layer, can be partially responsible for decreased susceptibility to a wide range of antibiotics [30-31].

Active Efflux

Besides preventing an antibiotic from entering the cell by the elimination or modification of entry ports, some bacteria are able to protect sensitive targets and become resistant to antibiotics by manufacturing "pumps" that export the drug out as fast as it enters. This mechanism has been characterized in both bacterial strains that produce antibiotics and in clinical isolates, as well. Efflux is due to the presence of specialized membrane proteins, which fall into one of two basic "mechanistic" classes. One group resembles the multiple drug resistance (MDR) determinants found in tumor cell lines resistant to methotrexate and similar anticancer agents [32].

Modification/Inactivation of the Antibiotic

Although the above two mechanisms prevent the antibiotic from accumulating in the desired compartment, they leave the antibiotic unchanged. Another strategy of resistance is the destruction or inactivation of the chemical "warhead" of the antibiotic. The resistant bacteria produce an enzyme that is capable of either degrading the antibiotic or chemically modifying it into an inactive form. Antibiotics can be inactivated either by enzymatic cleavage or by chemical modification such that they no longer interact with the target site or are no longer taken up by the bacteria [33]. Inactivating enzymes remain the predominant mechanism of resistance to several major classes of antibiotics, with chemical modification conferring clinical resistance to the aminoglycoside antibiotics, chloramphenicol, penicillins, cephalosporins, and other β-lactam antibiotics [33-34].

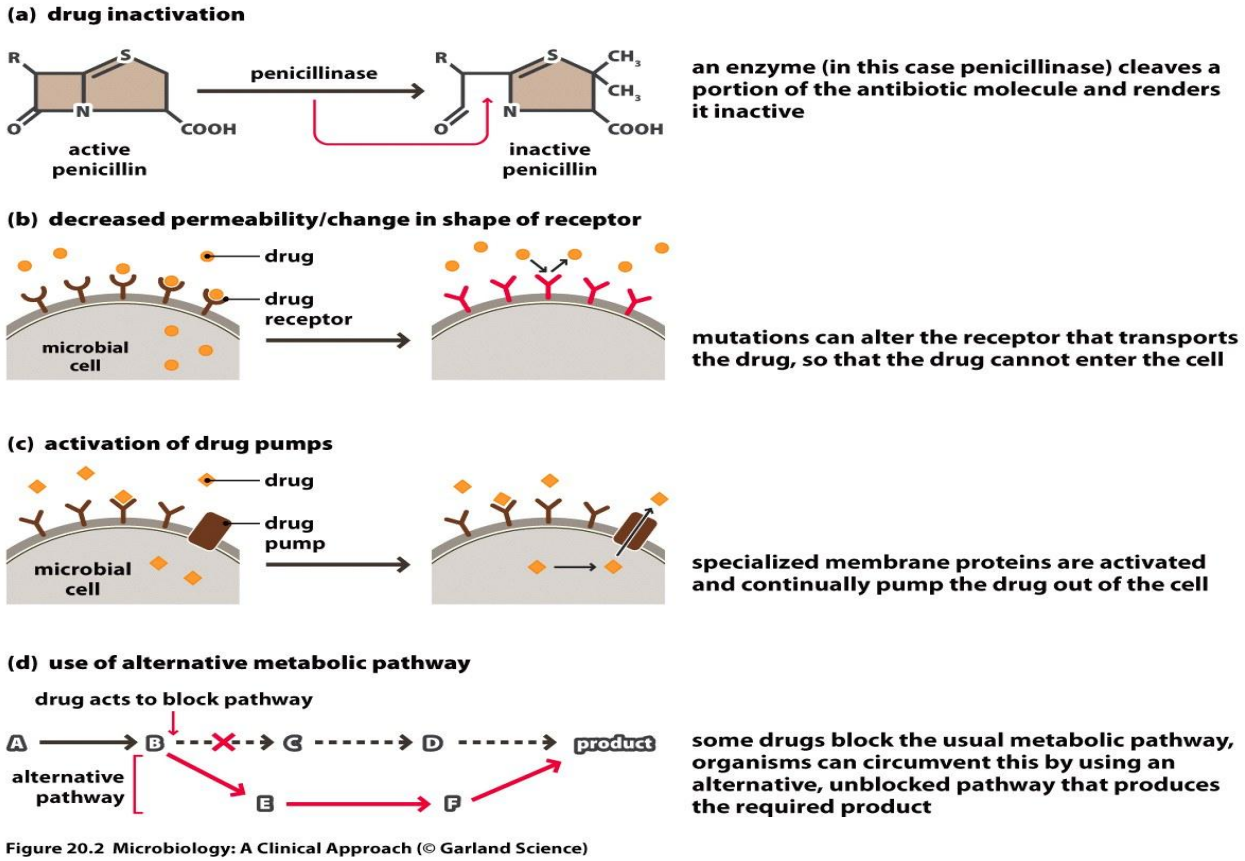

Figure 1: Diagram illustrating the mechanisms for acquiring resistance

Alteration of the target

Another resistance strategy focuses not on removal or destruction of the antibiotic, but on a "reprogramming" or camouflaging of the normal target to the antibiotic in the bacteria. Many antibiotics act by inactivating a target protein that can generically be called a "receptor". Resistant bacteria, sometimes by as little as a single mutational event in the primary target, develop a target protein that will not bind the antibiotic, or less often, a target that retains its function even after formation of the target-antibiotic complex. There is a wide array of different types of target modifications used by bacteria to develop resistance to a variety of antibiotics. For example, the ribosome of *Staphylococcus aureus* can become insensitive to the antibiotic erythromycin following specific enzymatic modifications in the rRNA [35].

Elimination of the target/Bypass Pathways

Some bacteria have gone beyond simple target modification and have acquired novel systems in which the need for the target has been eliminated by creation of new metabolic pathways to bypass the primary target. Resistant bacteria protect themselves from the antibiotic by the production of an alternative target (usually an enzyme) that is resistant to inhibition by the antibiotic, while continuing to produce the original sensitive target; the alternative enzyme "bypasses" the effect of the antibiotic. The most well documented examples of this mechanism are the alternative penicillin binding protein (PBP2a) in methicillin resistant *Staphylococcus aureus* (MRSA), resistance to the glycopeptides in enterococci, and the major means of acquired resistance to the folate antagonists [36-37].

Superbugs and super resistance

Many of the bacterial pathogens associated with epidemics of human disease have evolved into multidrug-resistant (MDR) forms subsequent to antibiotic use. Currently, the most notorious superbug is the Gram-positive organism *Staphylococcus aureus*. Whether it is the most serious superbug can be debated, since one wonders to what extent its bad reputation is due to its extensive press coverage. Following the discovery of penicillin, it seemed that *Staphylococcus aureus* infections were controllable; however, the respite from resistance was short-lived. The landmark discovery and introduction of methicillin (the first designer anti resistance antibiotic) in 1959 were thought to be a sure defense against the penicillinases, but the appearance of methicillin-resistant *Staphylococcus aureus* (MRSA) within just 3 years led inexorably to other multiantibiotic-resistant variants, and the acronym now denotes multidrug-resistant *Staphylococcus aureus*. Relatively, MRSA has moved outside the hospital and become a major community-acquired (CA) pathogen, with enhanced virulence and transmission characteristics. CA-MRSA has most of the properties of MRSA, albeit with different mec gene clusters and has acquired new pathogenicity genes, such as the gene encoding the cytotoxic Panton-Valentine leukocidin. These are regulated by defined signaling systems [38].

A long-recognized hospital denizen, the toxin-producing anaerobe *Clostridium difficile*, is increasingly found as the cause of severe intestinal infections; recently, hypervirulent toxin producing strains have been recognized [39]. Being a Gram-positive spore former, it is a hardy organism and is readily transmitted by hospital personnel, on equipment, and as aerosols. Its renewed prominence is considered the result of extensive hospital use of antibiotics such as expanded-spectrum cephalosporins, the newer penicillins, and fluoroquinolones that cause significant depletion of the Gram-negative intestinal microflora, thus enhancing *Clostridium difficile* colonization. In other words, these infections are the direct result of antibiotic use.

Conclusion

The problem of AMR is widespread all over the world, therefore it is not eradicable, but can be managed. Concerted efforts between Medical Laboratory Scientists, Medical Doctors, Dentists, Veterinarians, funders, industry, regulators, and multi-disciplinary approaches are needed to track resistance. Furthermore, global monitoring of the antimicrobial drug consumption in human and veterinary medicine and AMR, is an essential part of an overall strategy to inform, educate and get commitment of all parties, including farmers and patients All these are important measures for the efficient future use of antimicrobials in medicine. All members of society should be conscious of their role and take on responsibility for maintaining the effectiveness of current

and future antimicrobials. We believe that future interventions can be successful in minimizing this problem. Future research should focus on finding unknown routes of transfer of AMR between microbiotas of relevance to the food chain and to all microbiotas of importance for bacterial pathogens when they acquire antibiotic resistance genes laterally.

References

[1]. O'Grady, F., Lambert, H.P., Finch R.G., and Greenwood, D. (1997). Antibiotic and Chemotherapy: Anti-infective Agents and Their Use in Therapy. *Churchhill Livingstone, New York.*40:987.

[2]. Lancini, G., Parenti F, and Gualberto, G. (1995). Antibiotics: a multidisciplinary approach. *Plenum Press, New York*

[3]. Madigan, M., Martinko, J.M., and Parker, J. (1999). Brock's Biology of Microorganisms. *Prentice Hall, Upper Saddle River, N.J.*5:3-12

[4]. Pasteur, L. (1880). Compt. Rend. *Acad*. d. sc. *Paris*: 86:455,697.

[5]. Himmelweit, F. (1960). The Collected Papers Paul Ehrlich.*Pergamon Press, New York. 6*:20-28

[6]. Ehrlich, P. and Hata, S. (1910). Die experimentelle chemotherapie der Spirillosen., Berlin.

[7]. Fleming A (1929). On antimicrobial activity of Penicillium cultures. *Br. J.Exper.Path*.10:226.

[8]. Waksman, S.A., and Woodruff, H.B. (1942). Streptothricin, a new selective bacteriostatic and bactericidal agent, particularly active against gram negative bacteria. *Proc. Soc. Exper. Biol. Med*. 49:207-210.

[9]. Glasby J (1992). Encyclopedia of Antibiotics 3rd Edition. *Wiley and Sons, Chichester N.Y.*7:320-322.

[10]. Greenwood, D. (1995). Historical introductionin*Greenwood D, ed. Antimicrobial Chemotherapy. Oxford University Press*, New York. Pp. 1-10.

[11]. Jacoby, G.A., and Archer, G.L. (1991). New mechanisms of bacterial resistance to antimicrobial agents.*New Engl. J. Med*. 324:601-612.

[12]. Neu, H.C. (1992). The crisis in antibiotic resistance. *Science* 257:1064-1073.

[13]. Courvalin, P. (1996). Evasion of antibiotic action by bacteria. *J. Antimicrob. Chemother*. 37:855-869.

[14]. Levy, S.B. (1997). Antibiotic resistance: an ecological perspective. In Chadwick D. J. and Goode J, eds. Antibiotic resistance: origins, evolution and spread. *Wiley, Chichester, West Sussex.* 1-14.

[15]. Caputo, G.M., Applebaum P.C and Liu, H.H. (1993). Infections due to penicillin resistant pneumococci: Clinical, epidemiologic, and microbiologic features. *Arch. Intern. Med*. 153:1301-1310.

[16]. Fraimow, H.S and Abrutyn, E. (1995). Pathogens resistant to antimicrobial agents: epidemiology, molecular mechanisms, and clinical management. *Infect. Dis. Clin. North Am* 9:497-530.

[17]. Doern, G.V.,Brueggemann, A., Holley H.P,J and Rauch, A.M. (1996). Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994-1995: results of a 30-center national surveillance study. *Antimicrob. Agents Chemother*. 40:291-221

[18]. Flemming A. Nobel Lecture: Penicillin. Available at:http://www.nobelprize.org/nobelprizes/medicine/laureates/1945/flemingspeech.html.

[19]. D'Costa, V.M., King C. E. and Kalan L. (2011). Antibiotic resistance is ancient. *Nature.* 22; 477 (7365): 457461

[20]. Walsh, C.T., Fisher, S.L., Park, I.S., Prahalad, M., and Wu, Z. (1996). Bacterial resistance to vancomycin: five genes and one missing hydrogen bond tell the story. *Chem. Biol*. 3:21-8.

[21]. Olliver, A., Vallê, M., Chaslus-Dancla, E., and Cloeckaert, A. (2005). Overexpression of the multidrug efflux operon acrEF by insertional activation with IS1 or IS10 elements in *Salmonella enterica* Serovar *Typhimurium* DT204 acrB mutants selected with fluoroquinolones. *Antimicrob. Agents Chemother*. 49, 289–301.

[22]. Baquero, F., Alvarez-Ortega, C., and Martinez, J. L (2009). Ecology and evolution of antibiotic resistance. *Environ. Microbiol. Rep*. 1, 469–476

[23]. Cantas, L., Le Roux, F., Mazel, D., and Sørum, H. (2012a). *Impact of Antibiotics on the Expression of the tra Genes and on the Host Innate Immune Gene Activity during SXT Element Bearing Aeromonas salmonicida Infection in Atlantic Salmon (Salmo salar L.)*. PSN-ICAAC12PS1-B-1330. San Francisco, CA.

[24]. Cantas, L., Torp, J. R., Alestrøm, P., and Sørum, H. (2012b). Cultureable gut microbiota diversity in zebrafish. *Zebrafish* 9, 26–37.

[25]. Cantas, L., Midtlyng, P. J., and Sørum, H. (2012c). Impact of antibiotic treatments on the expression of the R plasmid tra genes and on the host innate immune activity during pRAS1 bearing *Aeromonas hydrophila* infection in zebrafish (*Danio rerio*). *BMC Microbiol*. 12:37. doi: 10.1186/1471-2180-12-37.

[26]. Alekshun, M.N and Levy S.B. (2007). Molecular mechanisms of antibacterial multidrug resistance. Cell 128:1037–1050.

[27]. Allen, H.K., Donato, J., Wang, H.H., Cloud-Hansen, K.A., Davies, J.E and Handelsman, J. (2010). Call of the wild: antibiotic resistance genes in natural environments. *Nat. Rev. Microbiol.* 8:251–259.

[28]. Yoshimura, F., Zalman, L.S., and Nikaido, H.L. (1983). Purification and properties of *Pseudomonas aeruginosa*. *J. Biol. Chem.* 258:2308-2314.

[29]. Nikaido, H. (1988). Bacterial resistance to antibiotics as a function of outer membrane permeability. *J. Antimicrob. Chemother*.22 (Suppl. A):17-22.

[30]. Cohen, S.P., Hooper, D.C., Wolfson J. S., Souza, K. S., McMurry, L. M. and Levy, S. B.(1988). Endogenous active efflux of norfloxacin in susceptible *Escherichia coli*. *Antimicrob Agents and Chemother*. 32:1187-1191.

[31]. Rajyaguru, J.M., and Muszynski, M.J. (1997). Association of resistance to trimethoprim/ sulphamethoxazole, chloramphenicol, and quinolones with changes in major outer membrane proteins and lipopolysaccharide in Burkholderiacepacia. *J. Antimicrob. Chemother*. 40:803-809.

[32]. Guilfoile, P.G., and Hutchinson, C.R. (1991). A bacterial analog of the MDR gene of mammalian tumor cells is present in *Streptomyces peucetius*, the producer of daunorubicin and doxorubicin. *Proc. Natl. Acad. Sci.* USA 88:8553-8557.

[33]. Pratt, W., Band, Taylor, P. (1990). Principles of Drug Action: the Basis of Pharmacology. *Churchill-Livingstone, Inc., New York.*20:200,212.

[34]. Brody, T.M., Larner J., Minnerman, K.P and Neu, H.C. (1994). Human pharmacology. *Mosby-Year Book, Inc., St. Louis, Missouri*. 9:300-311.

[35]. Davies, J. (1992). Another look at antibiotic resistance. *J. Gen. Microbiol*. 138:1553-1559.

[36]. Michel, M., and Gutmann, L. (1997). Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: therapeutic realities and possibilities. *Lancet* 349:1901-1906.

[37]. Higashi, Y., Wakabayashi, A., Matsumoto, A., Watanabe, Y. and Ohno, A. (1999). Role of inhibition of penicillin binding proteins and cell wall cross-linking by beta-lactam antibiotics in low- and high-level methicillin resistance of *Staphylococcus aureus*. *Chemotherapy* 45:37-47.

[38]. NovickR, P., and Geisinger, E. (2008). Quorum sensing in staphylococci. *Annu. Rev. Genet.* 42:541–564.

[39]. Kelly C. P., and LaMont, J.T. (2008). *Clostridium difficile*-–more difficult than ever. *N. Engl. J. Med*. 359:1932–1940.