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Review

Microbial resistance to antibiotics

IBEZIM EMMANUEL CHINEDUM

Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.
E-mail: ecibezim@yahoo.com, Tel: 08043180627.

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Organisms that are normally sensitive to the action of an antibiotic may sometimes develop resistance or insensitivity to it. This, they may do through destroying the antibiotic or by retaining their growth even in the presence of the drug. Microbial resistance to antibiotics is now widespread and poses a serious clinical threat. Microorganisms develop resistance to antibiotics by any of the following mechanisms: selection, mutation, phage transduction, and transference while microbial resistance can either be inherent in the organism or acquired through the environment. Factors that have led to the continued occurrence of bacterial resistance to antimicrobial agents include: over prescription of antibiotics, use of under dose, prescribers' irrational attitudes, patients' demands, inappropriate advertisements and use of antibiotics in agriculture. Microbial resistance to antibiotics can thus be minimized through proper enlightenment, more rational antibiotic selection during treatment and proper legislation.

Key words: Microorganisms, resistance, antibiotics, sensitivity.

INTRODUCTION

Antibiotics are organic substances produced by microorganisms and capable at low concentration of inhibiting the growth of, or destroying another microorganism (Ibezim, 2005). These drugs have been isolated from numerous sources but principally from bacteria (tetracyclines, bacitracin, polymyxin, chloramphenicol, streptomycin) and fungi (cephalosporins, penicillins). Penicillin was the first antibiotic discovered by Sir Alexander Flemming in 1928. With industrialization however, came the revolutionary development of many more antibiotics. Since then, the use of antibiotics has steadily increased both in human treatment and animal disease management (McKeon, et al, 1995).

Soon after the introduction of the penicillins into clinical practice, the fact that the development of antibiotic resistance would be a problem became apparent. The increased use of antibiotics in man and animals and the extension of uses to areas other than prophylaxis and treatment of diseases have helped to create serious problems. Bacterial resistance to antibiotics has thus been recognised since the first drugs were introduced for clinical use.

Bacterial resistance to antibiotics refers to the insensitivity of bacteria to the antimicrobial actions of a given antibiotic. The organism in question may develop the ability to destroy the antibiotic or to grow in its presence. Example of the former type are penicillin-inactivating staphylococci and chloramphenicol-acetylating staphylococci (British Pharmaceutical Codex, 1979).

Sulphonamides were introduced in 1935 and about ten years later, 20% of clinical isolates of *Neisseria gonorrhoea* had become resistant to them. Resistance to penicillin in some strains of *Staphylococcus* was recognized almost immediately after introduction of the drugs. Resistance to penicillin today occurs in as many as 80% of all strains of *Staphylococcus aureus* (Bryan, 1989). More and more strains of organisms have become resistant to the available antibiotics.

In the late 1940s and early 1950s, the discovery and introduction of streptomycin, tetracycline and chloramphenicol made the age of antibiotic chemotherapy come into full being. These antibiotics were effective against Gram positive and Gram-negative bacteria, tuberculosis bacilli and intracellular parasites. By 1953 however, during a Shigella outbreak in Japan, a strain of the dysentery bacillus was isolated which had multiple resistance exhibiting resistance to chloramphenicol, streptomycin, sulphonamides and tetracyclines. There was evidence to support the fact that the bacteria could pass genes for multiple drug resistance between strains and even between species. It was also apparent that *Mycobacterium tuberculosis* was capable of rapid development of resistance to streptomy-

cin, which has become a main stay in tuberculosis therapy.

It is noteworthy that antibiotic resistance can be single or multiple. Multidrug resistant tuberculosis is no longer confined to any one country or to those co-infected with Human Immune Deficiency Virus (HIV), but has appeared in locations as diverse as Africa, Asia and Eastern Europe, among health care workers and in the general population (Essential Drug Monitor, 2000).

An increased incidence of resistant organisms in a population exposed to an agent that affects growth and reproduction can be attributed to the survival and proliferation of a small fraction of the original population. The resistant survivors are genetically, structurally, behaviourally and physiologically different from the majority. When antibiotics are introduced, they will surely have this effect because by creating a hostile environment for susceptible pathogen population, they encourage the selective survival and multiplication of forms against which the antibiotics has little or no effect. This caused serious concern because it seemed possible that each new antibiotic will loose its usefulness as pathogenic organisms become resistant to them. This necessitated the research into the mode of action of antibiotics and the mechanisms by which their effects are circumvented by resistant organisms.

Most of the microorganisms producing antibiotics are resistant to the action of their own antibiotics. Although they are affected by other antibiotics, their antibiotics are effective against closely related strains. It was stipulated that these antibiotics afford them some nutritional advantage in their habitat by inhibiting or antagonizing other organism or they act as some sort of hormone or signal molecule associated with sporulation, dormancy or germination. The maintenance of a substantial component of the bacterial genome devoted solely to synthesis of antibiotics leads to the conclusion that the process or molecule is very important if not essential to the survival of these organisms in their natural habitat, because antibiotics are rather large, complicated organic molecules and may require as many as 30 separate enzymatic steps to synthesize.

Bacteria may be inherently or naturally resistant to an antibiotic when inherent properties of the bacterium are responsible for preventing antibiotic action (Godfrey et al., 1984). Inherent resistance is therefore that, possessed inherently by bacteria. For example, some bacteria are more resistant to certain antibiotics than others. For instance, Gram-negative bacteria are inherently resistant to a number of antibiotics such as vancomycin and fusidic acid, which are highly effective against Gram-positive organisms like streptococci and staphylococci (Franklin, 1992). Within the Gram-negative group, *Pseudomonas aeruginosa* presents especially intractable chemotherapeutic problem as it has unusually high intrinsic resistance to many antibiotics. This inherent resistance seems to be associated with the permeability of the complex outer layers of the cell envelope to some drugs, which prevents the attainment of an inhibitory concentration within the cell. The non-specific resistance of Gram-negative bacteria is recognized as a limitation in the treatment of infections of these organisms. However, the general pattern of resistance is well known and stable, so that drugs are prescribed of which the infecting organism are not inherently resistant (Franklin, 1992).

The ability of Gram-negative bacteria to be resistant to antibiotics active against most Gram-positives is associated with the outer cell layer like the outer membrane, which is absent in Gram-positive organisms. This outer membrane establishes a permeability barrier against antibiotics. An organism may lack the transport system for the antibiotics or lack the target sites or the reaction that is targeted by the antibiotics.

Bacteria can develop resistance to antibiotics usually but not always after exposure to the antibiotics. This type of resistance results from changes in the bacterial genome. In bacteria, acquired resistance is driven by two genetic processes, which are mutation and selection that is sometimes referred to as vertical evolution and exchange of genes between strains and species also called horizontal evolution. In other words, acquired immunity is a type of immunity acquired by the microorganisms in response to environmental and other changes. For instance, when a new antibiotic is introduced into clinical practice, for treating infections resulting from bacteria not inherently resistant to it, the drug would be quite effective. After some time however, treatment failures may result with the same drug on the same infection due to this newly acquired resistance of the drug by the infecting organism. The time before emergence of the resistance and the rate of emergence may not be predictable. Resistance of *Staphylococci,* for instance, to neomycin did not appear until after nine years of its introduction (Franklin, 1992).

Natural resistance is always chromosomally mediated while acquired resistance may be by mutations in the chromosome or acquisition of gene coding for resistance from an external source usually through a plasmid or transpon. Acquired and natural resistances are clinically important and can cause treatment failure. Acquired resistance is however, the major threat in the spread of antibiotic resistance (Russel, 1996).

Bacteria are able to exchange genes in nature by three processes – conjugation, transduction and transformation. Conjugation involves cell-to-cell contact as DNA crosses a sex pillus from donor to recipient. Plasmids that can mediate their own transfer are called conjugative plasmids. Gram positive and Gram-negative bacteria can conjugate. During transduction, a virus transfers the gene between mating bacteria. DNA is acquired directly from the environment having been released from another cell during transformation. The numbers of bacteria that can undergo transformation are limited e.g. *Neisseria gonorrhoea* can naturally acquire

DNA from their own species, so are selective in their acquisition of DNA from the environment (Scholer et al., 1984).

Genetic recombination can follow the transfer of DNA from one cell to another leading to the rates of adaptation and evolution that can be observed in the bacteria. For these reasons, bacterial resistance to the antibiotic environment seems to take place very rapidly in evolutionary time.

Treatment failure in bacterial infectious diseases is commonly caused by bacterial resistance (Tenover et al., 1996a, b). Obviously, if a pathogen is able to develop or acquire resistance to an antibiotic, then that substance becomes useless in the treatment of infectious diseases caused by that pathogen unless the resistance can somehow be overcome with secondary measures. An antibiotic resistant bacterial infection leads to the use of more expensive and often more toxic drugs. So as pathogens develop resistance, we must find different antibiotics to fill the place of the old ones in treatment regimes. Natural penicillins, for instance, have become useless against staphylococci and must be replaced by other antibiotics (Sabath, 1982).

Tetracycline has been so widely used and misused for decades and has become worthless for many of the infections that once designated it as a 'wonder drug'. The emergence of vancomycin resistant enterococci (VRE) has caused great concern because vancomycin is often the only effective antibiotic against methicillin resistant *Staphylococcus aureus* (MRSA) strains. So when methicillin resistant *S. aureus* acquires resistance to vancomycin, it will leave us with serious pathogens untreatable with any existing antibiotics. In no distant time, resistance of methicillin resistant *S. aureus* to vancomycin will be clinically possible because the transfer of vancomycin resistance from VRE to methicillin resistant *S. aureus* has been demonstrated in the laboratory (Saravolatz, 1982). There is also a problem in finding new antibiotics to fight new diseases. In the past two decades, many new bacterial infections have been discovered – Lyme disease, toxic shock syndrome, Legionnaires disease, gastric ulcers and 'skin eating' streptococci infections.

MECHANISMS OF BACTERIAL RESISTANCE TO ANTIBIOTICS

Bacterial cells may develop resistance to given antibiotics by any of the following mechanisms:

Selection

Resistant organisms may become apparent as a result of the destruction of sensitive strains by the antibiotic, allowing naturally resistant strains to colonise the patient. For example, penicillin therapy destroys much of the normal mouth flora and the mouth becomes colonized by penicillin-resistant organisms previously present in small numbers.

Mutation

A genetic mutation may occur during treatment and becomes apparent when the sensitive organisms are destroyed. Mutation occurs more readily with some antimicrobial agents than with others, and especially with streptomycin, rifampicin, and nalidixic acid.

Phage transduction

Certain organisms may acquire resistance as a result of the activity of phages (bacterial viruses) which incorporate a resistance present in one organism and when released carry the resistance over to an organism which was originally sensitive.

Transference

Resistance may be transferred from one bacterial genus to another as a result of an exchange of extra-chromosomal genetic particles (plasmids) during conjugation. This process occurs in many bacterial genera including most Gram-negative bacilli. It is most readily demonstrated among the Enterobacteriaceae. Resistance to a number of drugs including aminoglycosides, cephalosporins, chloramphenicol, fusidic acid, penicillins, and tetracyclines can be transmitted in this way. Resistance to several antibiotics may be transferred at one time. Resistance to other antibacterial agents such as sulphonamides and trimethoprim may also arise by transference.

FACTORS THAT PROMOTE MICROBIAL RESISTANCE TO ANTIBIOTICS

When antibiotics are underused, overused or misused, the process of antibiotic resistance is increased (Williams, 2000). The indiscriminate use of antibiotics, which promotes antibiotic resistance, results from patients' demand, prescribers, drug advertisement, dispensing doctors and antibiotic use in agriculture.

Patients' demand

Doctors and prescribers are influenced greatly by patients' demand even if they are sure of their diagnosis. Because patients prefer allopathic medicines, many trad-

itional doctors/practitioners are prescribing allopathic medicine instead of herbal medicines. To avoid being labeled difficult, 60% of health workers in Tanzania for instance, admitted to prescribing inappropriate drugs especially those demanded by socially influential patients (Muyika et al., 1991). A study in India revealed that many Indians believed in the efficacy of tonics and would not return to a doctor unless a tonic is prescribed as they wish. The doctors prescribe tonics to patients even when they are ineffective because their livelihood depends on the number of patients that attend their clinics (Council of European Community, 1980).

Prescribers

Prescribers have different variations in the prescribing of antibiotics and other drugs. It has been shown that 30 to 60% of patients receive twice or more of what is perhaps needed. Incorrect dosage or inappropriate prescription makes misuse of antibiotics common. In India, a study showed that over 90% of prescriptions do not have dose specifications (Uppal et al., 1993). Inappropriate prescription of antibiotics has been reported to occur for viral respiratory tract infections in 97% of cases in China (Hui et al., 1997), and 81% of cases in Ghana (Bosu et al., 1997). In Pakistan, there have been reports of inappropriate use of antibiotics for childhood diarrhoea where private medical practitioners were reported to prescribe significantly more antibiotics in 41% of paediatric cases than paediatricians in 36% of paediatric cases in the public hospitals (Nizami et al., 1996).

Providers prescribe antibiotics too often and unnecessarily because of patients' demand, lack of adequate knowledge or information concerning the drugs leading to uncertainty about the choice of drug.

Drug advertisement

The pharmaceutical companies aid in promoting bacterial resistance to currently available antibiotics. According to an advert by a company, Ciprofloxacin is the appropriate drug of choice for a patient at risk. There was then a question in the advert: 'For whom?' This was answered by a small asterisk on the word 'risk' showed at the bottom of the page. For who the drug was appropriate, was answered in small type and they stated that it should be used in challenging respiratory tract infections. The term 'challenging' was never explained nor defined. This company ironically, claimed in the same advert to support the appropriate use of antibiotics (Lexchin, 2000).

Adverts that do not clearly explain the use of drugs, for whom and other needed information or that gives them in very small prints that they are not noticeable, do not support the appropriate use of drugs. In the advert described above, the message to doctors is that they should freely use it as a first line agent whenever they are challenged with their patients' ailment or when they feel that something strange is going on. Ciprofloxacin is a first drug choice for some ailments but not for most respiratory tract infections. The use of ciprofloxacin has been restricted in these situations by the Australian Schedule of Pharmaceutical Benefits and also in some Canadian provinces (Lexchin, 2000). The potentials for drug interactions with the antacids and theophylline, the potential of developing bacterial resistance during treatment and the risk of toxicity especially in elderly patients who have decreased level of renal functions, are drawbacks to the use of these drugs in therapy. The fluoroquinolones are known to cause erosion of cartilages in the joint of immature animals. Therefore, they are contraindicated in the treatment of children. What this advert did, was to promote a drug as the first drug of choice, which should be reserved. They also promoted inappropriate use of the antibiotic that has the potential of leading to antibiotic resistance.

An advertisement in the Philippines in 1994 and 1995 promoted the use of clindamycin for upper respiratory tract infections and lincomycin for pharyngitis/tonsillitis. The most likely causative agent of these diseases is viral infections that cannot be treated with antibiotics. This is a clear case of antibiotics being advertised for conditions that do not require them. In 1996, researchers presented a group of primary care doctors with three cases, two of which involved infectious diseases and they asked them to choose between four treatment options of equal efficacy but they had wide varying costs. The results showed that the more credibility that the doctors attached to the information from the sales representatives, the higher the doctors' cost of prescription (Caudill et al., 1996). In many cases of inappropriate use of antibiotics, the doctor lack sources of objective information about the antibiotics. They are totally reliant on promotional materials from the companies with all the biases that they contain. In a peripheral health care in Sri Lanka in the mid 1980s, where multiple antibiotic therapies, polypharmacies and the use of mixtures of unproven efficacy were common, the physicians depended totally and were positively confident on the information from pharmaceutical companies (Tomson et al., 1990).

Dispensing prescribers

Many doctors and prescribers make a living from selling drugs and not necessarily from consultations. Many such doctors that earn money from dispensing drugs tend to prescribe more than those that do not. A study in Zimbabwe, for instance, showed that such doctors prescribed antibiotics to 58% of their patients while the non-dispensing prescribers, prescribed same antibiotics to 48% of their patients (Trap et al., 2000; Unpublished

Study). Following the socialist reforms of China in the late 70s, sale of drugs became a significant source of income, forming part of the salaries of many health workers and prescribers. Subsequently, more polypharmacies were observed and cost of prescriptions increased by two to six times (Sha-Kang et al., 1998). Because these dispensing prescribers earn more money through selling high cost drugs such as the antibiotics, they tend to over-prescribe them. However, most patients are not able to afford these drugs; hence they end up not completing the required dosage, creating room for development of resistance.

Use of antibiotics in agriculture

Some antibiotics used in treatment of human infections, especially the enterococcal and staphylococcal types, are equally employed in similar infections occurring in plants and animals. The use of penicillin and tetracyclines in animal feeds increases the number of resistant organisms within the animal bowel and the existence of such organisms appear to increase the proportion of resistant organisms in man. The use of antibiotics in animal feeds was restricted in the United Kingdom following the adoption of recommendations of the report of the Swann Committee (1969). Some of the newly emerging resistant strains of bacteria found in animals can be transmitted to humans through direct contact with the animals in question or food/materials from them. Resistance to salmonella and enterococcus has been attributed to the use of some antibiotics in agriculture. Some of the factors responsible for development of resistance to antibiotics by animals include use of sub-therapeutic doses as growth promoters, inefficient regulatory mechanisms, poor training of personnels and predominance of empirical treatments due to limited diagnostic tools. The use of vancomycin in agriculture has been implicated in the development of vancomycin-resistant strains of enterococcus and staphylococcus in many countries (Stor, 2000).

MEASURES TO MINIMISE DRUG RESISTANCE

The more frequently an antibiotic is used, the greater the prevalence of bacteria resistant to that agent. For example, neomycin-resistant staphylococci appear when neomycin sprays or powders are widely used. The resistant organisms decrease in numbers when the use of the antibiotic is curtailed. When a resistance factor carrying resistance to several agents, for example ampicillin, carbenicillin, streptomycin, and tetracycline, is present in a hospital unit the resistant organisms may not disappear until the use of all these agents is stopped. Antibiotics should therefore not be used unless specifically indicated.

Since much antibiotic therapy is given in the absence of bacteriological studies in the individual patient, the current antibiotic sensitivity patterns of common organism can provide a guide to the most suitable agent. Early treatment should be based on antibiotics that are most likely to succeed in a particular case, and should be modified as necessary when the results of sensitivity tests are available. This is particularly important in hospitals where the majority of resistant bacteria are found. The pattern of resistance found among hospital organisms should influence the choice of antibacterials in general use. Periodic revision of prescribing policies is essential in limiting the spread of resistant organisms. In long-term therapy, as in tuberculosis, two or more antibiotics or chemotherapeutic agents of different types should be given at the same time to delay the development of resistance.

REFERENCES

Bosu WK, Afori-Adjei D (1997). Survey of antibiotics prescribing patterns in government health facilities of the Wassa West District of Ghana, E. Afr. Med. J. 74: 138-142.

British Pharmaceutical Codex (1979) 11th Edition, The Pharmaceutical Press, London. p 791.

Bryan LE (Ed) (1989). Microbial Resistance to Drugs. In: Handbook of Experimental Pharmacology, Vol. 91, Springer-Verlag, New York.

Caudill TS, Johnson MS, Rich EC, McKinney WP (1996). Physicians, Pharmaceutical Sales Representatives and the cost of prescribing, Arch. Fam. Med. 5: 201-206.

Council of European Community (1980).

Editorial (2000). Antimicrobial Resistance: A global threat, *Essential* Drug Monitor, Vols. 28 & 29. p.1.

Franklin TJ (1992). Bacterial resistance to Antibiotics. In: Pharmaceutical Microbiology, Hugo WR, Russell AD (eds), Blackwell Sci. Oxford, pp. 208-230.

Godfrey AJ, Bryan LE (1984). Intrinsic resistance and whole cell factors contributing to antibiotic resistance. In: Antimicrobial Drug Resistance (Ed. L. E. Bryan) Academic Press, New York. pp.???

Hui L, Li XS, Zong XJ, Dai YH, Foy HM (1997). Patterns and determinants of use of antibiotics for acute respiratory tract infection in children in China, Paediatr. Infect. Dis. J. 16: 560-564.

Ibezim EC (2005). Dictionary of Pharmacy, Nezim Pub., Nsukka. p. 17.

Lexchin J (2000). Promoting resistance? *Essential Drug Monitor,* Vols. 28 &29. p. 11.

McKeon DM, Calabrese JP, Bissonnettes GK (1995). Antibiotic resistant Gram-negative bacteria in rural groundwater supplies. Water Resour. 29: 1902-1908.

Muyika KS, Killewo JZJ (1991). Irrational Drug use in Tanzania, Health Policy and Planning 6: 180-184.

Nizami S, Khan I, Bhutta Z (1996). Drug prescribing practices of general practitioners and paediatricians for childhood diarrhoea in Karachi Pakistan, Soc. Sci. Med. 42: 1133-1139.

Report of Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine (1969). Cmnd. 4190, HM Stationery Office.

Sabath, LD, (1982). Mechanism of resistance to Beta lactam antibiotics in strains of *Staphylococcus aureus* Ann. Int. Med. 97: 339-341.

Scholer HJ, Polak A (1984). Antimicrobial Drug Resistance, Academic Press, Inc., London.

Tenover FC, Hughes JM (1996a). The challenges of emerging infectious diseases. Development and spread of methicillin resistant bacterial pathogens, J. Am. Med. Assoc. 275: 300-304.

Tenover FC, McGowon JE Jr (1996b). Reasons for the emergence of

antibiotic resistance., Am. J. Med. Sci. 311: 9-16.
Tomson G, Augunawella I (1990). Patients, Doctors and their Drugs: a study of four levels of health care in an area in Sri Lanka, Eur. J. Clin. Pharmacol. 39: 403-467.
Uppal R, Sarkar U, Giriyappanavar CR, Kacker V (1993). Antimicrobial drug use in Primary Health Care, J. Clin. Epidermiol, 46: 671-673.
Williams R (2000). Antimicrobial resistance: a global threat. Essential Drug Monitor, Vol. 28 and 29. p.1.