Possible Alternatives to Reduce Antibiotic Resistance

SO Ogbodo1, AC Okeke2, CDC Ugwuoru3, EF Chukwurah4

1Dept. of Medical Laboratory Sciences, College of Health Sciences, Ebonyi State University, PMB 053, Abakaliki, Nigeria.
2Dept. of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, Nnamdi Azikiwe University, Nnewi Campus, Nigeria.
3Dept. of Medical Microbiology, College of Health Sciences, Ebonyi State University, PMB 053, Abakaliki, Nigeria.
4Dept. of Haematology/Immunology, College of Health Sciences, Ebonyi State University, PMB 053, Abakaliki, Nigeria.

*Correspondence to: SO Ogbodo, osylver1@yahoo.com

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Abstract

From the early time of discovery of antibiotics, the problem of resistance by microorganisms has been there. This problem has always been temporarily solved by systematic or accidental discovery of new drugs, either of the same class but with different side chains from the existing one or of another class altogether, thus helping to switch from the first-line drug to second-line or even third-line drug. These second- and third-line drugs are usually more expensive and sometimes more toxic than the first-line drugs. However, in many cases, no sooner had this drug been introduced that resistance to it by one microorganism or the other is noticed. Hitherto, the practice of mass-producing already existing cum resisted drugs by many pharmaceutical industries with different brand names and, often lower concentrations of the active molecules, is worsening the situation. It seems that this scenario will continue ad infinitum if alternative strategy is not employed. We reasoned that alternative solution to this will be the use of non-antibiotics with antimicrobial activities, especially those employing competitive displacement or improvement in immune functions as their modes of action. We reviewed different options for this, using published journal articles, fact sheets, and unpublished and personal communications.

Keywords: Antibiotics; resistance; prevention; alternatives.

1. Introduction

Antibiotic resistance, which is a type of drug resistance, is a situation where a microorganism has developed or acquired the ability to survive the presence of an antibiotic. This resistance can be acquired through horizontal gene transfer, unlinked point mutation in the pathogen genome or chromosomal aberration and subsequent replication. When bacteria are exposed to this environmental pressure, those that can mutate to survive will live on to reproduce and pass on or transfer this trait to their offspring, resulting in full resistant colony. Genes transfer between bacteria can be by conjugation, transduction, or transformation, allowing a gene for antibiotic resistance which had evolved via natural selection to be shared [1]. Many antibiotic resistance genes are known to reside on plasmids, which facilitate their transfer. In some cases, a bacterium may carry several of such genes resulting to multi-resistant strain called super-bug.

The widespread use of antibiotics both within and outside medicine is playing a significant role in the emergence of resistant bacteria [2], implying that resistance cannot be acquired only by long or wrong use by patient. Other practices contributing towards resistance include poor hand hygiene by hospital staff [3] and household use of antibacterial in soaps and other products. Although the later is not clearly contributing to resistance, it should not be encouraged since it is not effective at infection control [4]. Probably the worst culprit in this regard is the hitherto unwholesome practices in the pharmaceutical manufacturing industries which contribute significantly towards creation of antibiotic resistant strains [5]. This is mainly seen in cases where certain antibiotic formulations are produced by many pharmaceutical companies under different brand names and with varying

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concentrations of the active ingredients – definitely lower than the original formulations. In this case, if the clinician starts with a brand of lower concentration, the optimum concentration needed to initiate antibiosis cannot be achieve; instead the microorganism capitalizes on the opportunity to develop resistance against that particular antibiotic and probably other related substances.

In human medicine, the major problem of the emergence of resistant bacteria is due to misuse and overuse of antibiotics by doctors as well as patients [6]. In some developing countries, many doctors treat many infections (especially UTI and RTI) for long before requesting for laboratory investigations, that is, when the patient fails to respond well to initial treatment. Such practice is usually due to lack of good laboratory facilities in the environment or under-use of the laboratory or outright disregard for laboratory diagnosis by clinicians. Actually, there is strong positive correlation between the duration of exposure to antibiotics and the risk of the development of resistance; therefore, this initial treatment will have two obvious effects – one, it will basically and fundamentally change the antibiogram of the organism and two, it will cause wide spread resistance to the available antibiotics (especially of the same class) within the environment, thus creating super-bugs. Again, the volume of antibiotics prescribed, rather than compliance, is another major factor in increasing rates of bacterial resistance [7]. Thus a single or suboptimal dose of antibiotics will lead to a greater risk of resistant microorganisms to that antibiotic in the patient [8]. In some countries, especially developing countries; antibiotics are sold over the counter without prescription. Therefore, the practice of buying over the counter (which is usually one or two doses and therefore suboptimal) without prescription, inappropriate prescription and treatment before laboratory investigations (without known sensitivity pattern) are great risk in developing resistance to that antibiotic, especially when taken for long. In particular, inappropriate prescription of antibiotics has been attributed to a number of causes. These include (1) some people insist on antibiotics and their physicians simply prescribe them because they do not have the time or feel it is not necessary to explain why antibiotics are not necessary [1], (2) some physicians do not know the appropriate time to prescribe antibiotics or else are overly cautious for medico-legal reasons [9], (3) some people believe that antibiotics are effective for the common cold [10], which is not the case, (4) many people do not finish a course of antibiotics primarily due to the fact that they feel better [11], (5) antibiotics to be taken many times a day are less complied with than once daily antibiotics [12], and (6) use of suboptimum antibiotic concentrations in critically ill patients[13], giving the microorganism the opportunity to develop resistance. Therefore, it is worthy to note that in antibiotic therapy, taking doses less than those recommended increases rates of resistance, while shortening the course of antibiotics may actually decrease rates of resistance [7; 14].

In veterinary medicine, drugs are used in one way or the other on animals that are consumed by human beings. As a matter of need, antibiotics are often used in animals and also in other industries, which at least in the case of agricultural use, lead to the spread of resistant strains to human populations. A good example of this is the process of addition of antibiotics to the feeds of livestock [15; 16]. For instance, in 2001, the Union of Concerned Scientists estimated that greater than 70% of the antibiotics used in the US are given to food animals (e.g. chickens, pigs and cattle) in the absence of disease. The drugs used in these animals can affect the safety of their products and thus be the source of super-bugs. Such super-bugs can be transmitted to humans through consumption of the products or close/direct contact with the animals or through the environment. For this, WHO has advised that the use of antibiotics as growth promoters in animal feeds should be prohibited, even in the absence of risk assessment; this became effective in European feeds in 2006 [17]. This measure seems to have lowered the prevalence of antimicrobial resistance in animal bacterial populations in Scandinavia [18]. In US, this advise has not actually been fully implemented [16; 19], but at least it has led to the establishment of small antibiotic-free market for animal feeds.

2. Mechanisms of development

The action of antibiotics against bacteria is an environmental pressure/stress. The mechanisms by which a microorganism develops resistance against an antibiotic are not yet fully elucidated. The few known mechanisms include:

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1. Drug inactivation or modification: Some microorganisms like the β-lactamases-producing bacteria are capable of enzymatically inactivating drugs. This is seen in enzymatic inactivation of Penicillin G in some penicillin-resistant bacteria including some strains of *Staphylococcus aureus*.

2. Alteration in binding sites: Some antibiotics have binding proteins on the cell walls of sensitive microorganism e.g. penicillin-binding protein. Alterations in such proteins will bring about development of resistance against such microorganisms. Examples are the binding target site of penicillin in methicillin-resistant *Staphylococcus aureus* (MRSA) and other penicillin-resistant bacteria, and mutations at key sites in DNA gyrase or Topoisomerase that decreases affinity of cell wall to quinolones, thus decreasing the drug’s effectiveness [20].

3. Alteration of metabolic pathway: Some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides. Instead, like mammalian cells, they turn to utilizing preformed folic acid. This makes it easy for such microorganisms to develop resistance.

4. Reduced drug accumulation: Decrease in drug permeability and/or increase in active efflux (pumping out) of the drugs across the cell surface causes development of resistance [21]. This is seen in development of resistance against fluoroquinolone where efflux pumps can act to decrease intracellular quinolone concentration [22].

3. Frequently encountered microorganisms

One of the first and major resistant pathogens is *Staphylococcus aureus*. This bacterium is commonly found as commensals on the mucous membranes and the human skin of about one third of any population [1]. It was one of the earlier bacteria in which penicillin resistance was found. It now appears to be endemic in many urban regions [23]. Streptococcal organisms are another major culprit. Though all strains have remained relatively and uniformly sensitive to penicillin [24], there have been increasing incidence of their resistance to other antibiotics, including resistance of *Streptococcus pneumoniae* (responsible for pneumonia, bacteremia, otitis media, meningitis, sinusitis, peritonitis and arthritis) to penicillin and other beta-lactams. By 1993, *Escherichia coli* were found to be resistant to five fluoroquinolone variants. Also, *Mycobacterium tuberculosis* is now commonly resistant to isoniazid and rifampicin and sometimes universally resistant to the common treatments. Personal practice has demonstrated increasing resistance of *Salmonella* species to fluoroquinolones and even other treatment plans, making the treatment of typhoid/enteric fever difficult [unpublished]. *Pseudomonas aeruginosa* is a highly prevalent opportunistic pathogen, but with low antibiotic susceptibility [25]. Besides intrinsic resistance, *P. aeruginosa* easily develop acquired resistance either by mutation in chromosomally-encoded genes, or by the horizontal gene transfer of antibiotic resistance determinants. Hyper-mutation favours the selection of mutation-driven antibiotic resistance in *P. aeruginosa* strains producing chronic infections.

4. Possible solutions

4.1. Rational use of antibiotics

*Clostridium difficile* infection is a leading cause of nosocomial diarrhea in the US [26] and a major cause of death worldwide [27]. Infection by this multi-resistant microorganism has been associated with use of fluoroquinolones. Presently, the rate of prescription of fluoroquinolones (Ofloxacin, Ciprofloxacin, Perfl oxacin and now Levofoxacin) in Nigeria is very high, especially in treatment of UTI/STDs, RTI and enteric fever. Even when proper laboratory procedures are taken, most isolates show wide resistance to many older drugs like penicillins and erythromycins, with exception of fluoroquinolones, probably due to over exposure to the older drugs. Therefore, the use of this class of antibiotic, especially without laboratory diagnosis, needs to be reviewed to checkmate the development of such wide resistance. This is because it is expected that rational use of antibiotics can reduce the chances of development of opportunistic infection by antibiotic-resistant bacteria. Before now, research efforts were to provide new drugs (of the same or different class) in time to treat bacteria that became resistant to older antibiotics. This rarely is the case now, because of marked decrease in research and development efforts of pharmaceutical industries, and alarming increase in number of resistant bacteria. Many pharmaceutical industries

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are presently interested in mass-producing already existing drugs with different brand names and even lower qualities "to survive". The proliferation of many "old" drugs with lower qualities, in addition to sale of expired ones, has been the major headache of drug law enforcement agencies in many developing countries of the world. Since this mass-production of low quality drugs provides immediate financial success for the industries, little efforts have been made towards discovery of new drugs. Credit has to be given to those few pharmaceutical industries that are still involved in research and development of new antibiotics. Such industries need encouragement in form of financial and logistic supports from renowned international health organizations, including WHO, to enable them thrive. Also, there is clinical evidence that topical dermatological preparations may be effective in preventing transmission of community-acquired resistance [28]. This has to be well investigated and practiced to help in prevention of creating super-bugs in the environment.

4.2. Possible alternatives to antibiotics

The problems caused by antibiotic resistance demand that renewed and concerted efforts be made to search for antimicrobial agents that will be effective against pathogenic microorganisms without any fear of development of resistance. Some of these alternatives that need to be tried include vaccines, phage therapy, probiotics, immune-boosting trace elements and some bioactive phytochemicals.

4.3. Vaccines

The use of vaccines is another possible way of reducing antibiotic resistance. Vaccines act by enhancing the body's natural defenses, while antibiotics operate separately from the body's normal defenses [1]; therefore, it is expected that vaccines cannot suffer the same fate as antibiotics. The only pitfall here is that new strains may evolve that can escape immunity induced by vaccines from the prevailing strain. Hence, though theoretically promising, anti-staphylococcal vaccines have shown limited efficacy, because of immunological variation between Staphylococcus species, and the limited duration of effectiveness of the antibodies produced.

4.4. Phage therapy

Phage therapy has been extensively researched and utilized as a therapeutic agent for over 60 years, especially in Russia, as an alternative that might help solve the problem of resistance. It was also widely used in US until the discovery of antibiotics in the early 1940s [1; 29-31]. Apart from the few drawbacks, its advantages (in terms of control of resistance) have made it almost imperative to look very closely at again for improvement on its use for utmost gain for therapy. Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections. It can be of immense help in control of antibiotic resistance. Bacteriophages invade bacterial cells and, in the case of lytic phages, disrupt bacterial metabolism and cause the bacterium to lyse. From different studies, phage therapy has proved to be an important alternative to antibiotics for treating multi-drug resistant pathogens [32].

4.5. Probiotics

Probiotics are technologically modified extract from life microbes that can be used to fight against other bacteria/pathogens, that is, they show some forms of antimicrobial activities against other pathogens, in addition to other health benefits. Probiotics from life microbes have shown effectiveness in mitigating the effects of stress [33]. They are produced by patho-biotechnology using stress survival technique that has not gained wide usage. The mechanism by which probiotics fight against pathogens is not yet well understood. However, few possible mechanisms can be deduced: (1) they may exclude pathogens from the host by competing for nutrients, (2) some may produce chemicals against the pathogens, (3) some may mimic the oligosaccharide receptors of the host cells used by pathogens to enter the cells, and (4) some may block the ligand-receptor contact, which helps in host-pathogen interaction. When taken orally, probiotics can neutralize toxins and interfere with gut pathogens and finally wipe out the infection from the gut region [34]. From the foregoing, probiotic does not seem to be subject to resistance by microorganisms.
4.6. Trace elements

The principal immune-boosting trace elements are selenium and zinc. Selenium has a wide range of effects, affecting oxidative stress, DNA methylation, DNA repair, inflammation, apoptosis, cell proliferation, carcinogen metabolism, hormone production, angiogenesis and immune function [35]. Its importance increases in all ages [36]. Pathologically, selenium-containing enzymes - glutathione peroxidase and thioredoxin reductase, protect neutrophils, macrophages and other tissues from free radicals intended to destroy pathogens in the fight against inflammation [37]. Hence, neutrophils with reduced glutathione peroxidase activity due to selenium deficiency were found to be unable to defend themselves against free radicals they release onto pathogens [38; 39]. Selenium compounds have also been found to block DNA transcription factors that would have otherwise worsened inflammatory response [40]. Selenium does not protect the body against sepsis by boosting the immune system only but also by acting directly against bacterial lipopolysaccharide (LPS) - a large molecule that contributes significantly to endotoxic shock [41]. This is in addition to blockage of transcription factors that would have worsened inflammatory response [40]. On the other hand, zinc is needed for a healthy immune system as it is involved in immune cell (T-cell) production in the thymus gland. In fact, zinc is a component of thymic hormone which controls and facilitates the maturation of lymphocytes [42]. It also plays a role in cell division and DNA replication, thereby aiding in the production of immune system cells. Zinc is also important in the production of prostaglandins (PGs) [43], PGs are vital to numerous functions of the body including among others, function of the immune system, expression and control of inflammation, skin and wound healing and functions of the heart and cardiovascular system. The use of these trace elements to boost immune system may be a veritable tool in the fight against antibiotic resistance.

4.7. Phytochemicals

Phytochemicals are plant chemicals that are neither vitamins nor minerals, yet, they have health-enhancing effects. They help to protect the body against many disease conditions including cancer, cardiovascular diseases and dementia, and aid in the prevention of cataracts and macular degeneration. Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins. Many of the herbs and spices used by humans to season food yield useful medicinal compounds including those having antibacterial activity [44; 45] and those with antioxidant activities. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores; therefore they can be of immense benefit to consumers.

Traditional healers have long used plants and plant products to prevent or cure infectious conditions. Many of these plants have been investigated scientifically for antimicrobial activities and a large number of plant products have been shown to inhibit growth of pathogenic bacteria [1]. A number of these agents appear to have structures and modes of action that are distinct from those of the antibiotics in current use, suggesting that cross-resistance with agents already in use may be minimal. Since 1980s, public health recommendations have emphasized the health benefits associated with the consumption of fresh fruits and vegetables [46]. Epidemiological and animal studies linking the consumption of plant foods with major reduction in the incidence of lung cancer and other malignancies give ample support for this recommendation [47]. This is also supported by the finding that people who consume more vegetables and fruits show significantly superior health compared to those eating the least. However, it has also been reported that genetically susceptible individuals who are environmentally and/or occupationally exposed to mutagens and carcinogens known to be metabolized by phase-1-bioactivating enzymes, have great tendency to easily generate oxidative stress through boost in these phase-1 enzymes [48]. Therefore, it is not advisable to simplistically reproduce the benefits of a variety of plant-derived materials containing thousands of substances in a natural matrix, since it will encourage extensive consumption of a single type of plant or mass administration of specific isolated phytochemicals [48-50]. This is the main area of disagreement between orthodox medicine and herbal medicine. Personal observations have shown that these herbal preparations work very well, but sometimes show some unpalatable reactions, probably due to oxidative stress. Therefore, encouraging the use of phytochemicals should include extensive research and purification of such antibacterial agents so found. The expectation is that since most of these chemicals function by boosting the immune system to achieve antibiosis, the possibility of development of resistance is minimal.
References


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