An Updates on Antibiotic Resistance

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Abstract

Antibiotics are immense weapon that fight microbes. For decades, several varieties of antibiotics have not only been used for clinical purposes but practiced across other industries like agriculture and animal husbandry. The regular practice in antibacterial drug development has been to rapidly make an effort to find ever-more stable and broad-spectrum alternative for a particular antibiotic, once a drug resistance for that antibiotic is detected. We are now facing bacterial resistance toward our clinically relevant antibiotics of such a magnitude that the conversation for antimicrobial drug development ought to include effective new antibiotics with alternative mechanisms of action. Microbial resistance to antibiotics is a world-wide problem in human and veterinary medicine. It is generally accepted that the main risk factor for the increase in the antibiotic resistance is an extensive use of antibiotics. This has lead to the emergence and dissemination of resistant bacteria and resistance genes in animals and humans. The aim of this review is to explore the origin, development, and the current state of antibiotic resistance, regulation, and challenges by examining available literature. We found that antibiotic resistance is increasing at an alarming rate. A growing list of infections i.e., pneumonia, tuberculosis, and gonorrhea are becoming harder and at times impossible to treat while antibiotics are becoming less effective. Antibiotic-resistant infections correlate with the level of antibiotic consumption. Non-judicial use of antibiotics is mostly responsible for making the microbes resistant. The antibiotic treatment repertoire for existing or emerging hard-to-treat multidrug-resistant bacterial infections is limited, resulting in high morbidity and mortality report. This review article reiterates the optimal use of antimicrobial medicines in human and animal health to reduce antibiotic resistance. Evidence from the literature suggests that the knowledge regarding antibiotic resistance in the population is still scarce. Therefore, the need of educating patients and the public is essential to fight against the antimicrobial resistance battle. A primary characteristic of antibiotics is that they lose their effectiveness over time. In the last twenty years, the number of antibiotic classes and analogues in development has not kept pace with antibiotic resistance. Appropriate use of existing classes of antibiotics could improve the lifespan of these drugs. The side effects of antibiotic resistance include reduced patient outcomes and increasingly potent disease states. New government task forces have been developed to increase the level of research and federal involvement into this growing public health problem.

Keywords: Antibiotics; Antibiotic resistance; Treatment; Bacterial infections

Introduction

In the golden age of the discovery of antibiotics, innumerable lives were saved. These highly potent "miracle" drugs are no longer as effective as they were a half a century ago [1]. The successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. This is true for agents used in the treatment of bacterial, fungal, parasitic, and viral infections and for treatment of chronic diseases such as cancer and diabetes; it applies to ailments caused or suffered by any living organisms, including humans, animals, fish, plants, insects, etc. Antibiotics have revolutionized medicine in many respects, and countless lives have been saved; their discovery was a turning point in human history.

Regrettably, the use of these wonder drugs has been accompanied by the rapid appearance of resistant strains. Medical pundits are now warning of a return to the pre antibiotic era; a recent database lists the existence of more than 20,000 potential resistance genes (r genes) of nearly 400 different types, predicted in the main from available bacterial genome sequences. Fortunately, the number existing as functional resistance determinants in pathogens is much smaller [2]. Nearly all classes of antibiotics has had bacterium develop resistance [3]. Antibiotic resistance takes place when bacteria or other microbes have the capability to oppose the effects of an antibiotic. These bacteria or microbes transform and diminish the overall efficiency of drugs or the chemicals in the drug itself [4]. The expenditure of antibiotic resistance to the United States health

system alone is larger than $20 billion a year [5]. Further, microbes can build up resistance to drugs, such as diverse classes of antibiotic resistance. Numerous scientists and healthcare providers, as well as policymakers, consider that the resistance levels of microbes to antibiotics has currently put patients in threat [6]. Predominantly, Gram-negative rods such as Escherichia coli, for example, have developed into resistant to almost all existing antibiotics. This resistance has freshly led to a extensive outbreak in Europe [7]. But this resistance is not just restricted to Europe or the United States. Latest reports have shown that antibiotic resistance is a Universal threat [8]. Antimicrobial resistance (AMR) creates a severe global threat of growing alarm to human, animal, and environment health. This is due to the emergence, spread, and persistence of multidrug-resistant (MDR) bacteria or "superbugs" [1]. MDR bacteria exist across the animal, human, and environment triangle or niche and there is interlinked distribution of these pathogens in this chord. The plausible causes of "the global resistome" or AMR comprise disproportionate use of antibiotics in animals (food, pets, aquatic) and humans, antibiotics sold over-the-counter, amplified international travel, deprived sanitation/hygiene, and discharge of nonmetabolized antibiotics or their remainders into the environment through manure/feces. These aspects add to genetic selection force for the emergence of MDR bacterial diseases in the population. In recent times, the global use of antimicrobials in livestock has designated the hotspots of antibiotics utilize across the continents that will have financial and public health impacts in the time to come. In food animals, antibiotics are usually used in cattle, chicken, and pigs and it is projected that in 2030 such use will augment up to 67% in the most populated countries of the globe [9].

The successful use of an antimicrobial agent is undermined owing to the potential tolerance or resistance developed from the very initial time this compound is used. This is true for antimicrobial agents used to treat bacterial, viral, fungal, and parasitic infections. Several physiological and biochemical mechanisms may steer this developing resistance. The intricacy of all the mechanisms associated with the emergence and distribution of the resistance should not be overplayed. Furthermore, lack of elementary data on these specific subjects is a vital concern, which has caused a lack of noteworthy successes from being made to handle the development of resistance. Universally, various institutes and groups have recognized this grave global public health problem. Many proposals and resolutions have been proposed, several reports have also been written, but so far little progress has been made. Unfortunately, the increase in antibiotic resistance is a persistent issue [10].

Antibiotic History

We frequently connect the commencement of the modern "antibiotic era" with the names of Paul Ehrlich and Alexander Fleming. Ehrlich's idea of a "magic bullet" that selectively targets only disease-causing microbes and not the host was based on an observation that aniline and other synthetic dyes, which first turned into accessible at that time, could stain specific microbes but not others. Ehrlich argued that chemical compounds could be synthesized that would "be able to exert their complete

action entirely on the parasite docked within the organism." This thought led him to initiate a large-scale and systematic screening program (as we would call it today) in 1904 to find a drug against syphilis, a disease that was endemic and almost incurable at that time. This sexually transmitted disease, caused by the spirochete *Treponema Palladium*, was usually treated with inorganic mercury salts but the treatment had severe side effects and poor efficacy. In his laboratory, together with chemist Alfred Bertheim and bacteriologist Sahachiro Hata, they synthesized hundreds of organ arsenic derivatives of a highly toxic drug Atoxyl and tested them in syphilis-infected rabbits. In 1909 they came across the sixth compound in the 600th series tested, thus numbered 606, which cured syphilis-infected rabbits and showed significant promise for the treatment of patients with this venereal disease in limited trials on humans [11]. Despite the tedious injection procedure and side effects, the drug, marketed by Hoechst under the name Salvarsan, was a great success and, together with a more soluble and less toxic Neosalvarsan, enjoyed the status of the most frequently prescribed drug until its replacement by penicillin in the 1940s [12]. Amazingly, the mode of action of this 100-year-old drug is still unknown, and the controversy about its chemical structure has been solved only recently [13].

Antibiotic resistance was reported to occur when a drug loses its ability to inhibit bacterial growth effectively. Bacteria become 'resistant' and continue to multiply in the presence of therapeutic levels of the antibiotics [14]. Bacterias, when replicates yet in the existence of the antibiotics, are called resistant bacterias. Antibiotics are generally efficient against them, except when the microbes become less sensitive or resistant, it requires a higher than the normal concentration of the same drug to have an effect. The emergence of antimicrobial resistance was observed shortly after the preamble of new antimicrobial compounds [15]. Antibiotic resistance can occur as a natural selection process where nature empowers all bacteria with some degree of low-level resistance [16]. For example, one study confirmed that sulfamethoxazole and trimethoprim (TMP-SMZ), ampicillin and tetracycline that were normally used in yester years, but currently have no longer function in treating non-cholera diarrhea disease in Thailand [17]. At the same time, an another study conducted in Bangladesh showed the effectiveness of the similar drugs in treat them effectively [18]. In fact, resistance was documented even before the beginning of the usage of the antibiotics in fighting the infection [19]. Non-judicial use of antibiotic is responsible for making microbes resistant. Since the introduction of sulfonamides in 1937, the development of specific mechanisms of resistance had provoked their therapeutic use. However, sulfonamide resistance was reported in the 1930s, which reveals the same mechanism of resistance that still operates even now, more than 80 years later [20]. Within six years of the production of the aminoglycosides, aminoglycoside-resistant strains of Staphylococcus aureus was developed [21]. Introduced in 1961, Methicillin was the first of the semisynthetic penicillinase-resistant penicillin to target strains of penicillinase-producing Staphylococcus aureus. However, resistance to methicillin was reported soon after its initiation [22]. Further, although fluoroquinolones were introduced for the treatment of

Gram-negative bacterial diseases in the 1980s, fluoroquinolones resistance later revealed that these drugs were also used to treat Gram-positive infections [23]. Quinolone resistance emerged as a stepwise attainment of chromosomal mutations, particularly amongthe methicillin-resistant strains. Most recently, the clinical isolates of Vancomycin resistant Staphylococcus aureus (VRSA) were found in 2002, after 44 years of Vancomycin introduction to the market [24]. Antibiotics used in agriculture are often the same or similar to antibiotic compounds used clinically [25], this over-usage could also invite drug resistance. The food chain can be considered the main route of transmission of antibiotic-resistant bacteria between animal and human populations [26]. In some developed countries, animals receive antibiotics in their food, water, or parenterally which may be responsible for carrying microbe resistance to that specific antibiotic [25]. For example, the use of antibiotics in cattle feed as growth promoters increase antibiotic resistance [27]. Recent evidence suggests that poultry or pork might be a possible source of quinolone resistant-Escherichia coli in the rural villages in Barcelona, where one fourth of children were found to be fecal carriers of these organisms. However, these kids were never exposed to quinolones [28].

The Worldwide Economic Reflection of Antibiotic Resistance

An estimation of the exact economic impact of resistant bacterial infections is still a huge global challenge. In this matter, measuring the disease distribution associated with antibiotic resistance is a key prerequisite. Antibiotic resistance is a substantial economic burden to the whole world. In the USA alone, antibiotic-resistant pathogen-associated hospital acquired infections (HAIs) cause 99,000 deaths annually. In 2006, about 50,000 Americans died due to two common HAIs, namely pneumonia and sepsis, costing about $8 billion to the US economy [29]. Patients with antibiotic-resistant bacterial infections need to stay in the hospital for at least 13 days, adding an additional 8 million hospital days annually. Costs of up to $29,000 per patient treated with an antibiotic-resistant bacterial infection have been reported. In total, economic losses of about $20 billion have been recorded in the US, while losses of about $35 billion annually have also been recorded in terms of lost productivity due to antibiotic resistance in health care systems [30]. According to the analysts of Research and Development Corporation, a US nonprofit global organization, a worst-case scenario may evolve in the coming future where the world might be left without any potent antimicrobial agent to treat bacterial infections. In this situation, the global economic burden would be about $120 trillion ($3 trillion per annum), which is approximately equal to the total existing annual budget of the US health care. In general, the world population would be hugely affected: as of the year 2050, about 444 million people would succumb to infections and birthrates would rapidly decline in this scenario [31,32]. These losses are calamitous, but due to data constraints like the inclusion of overall conditions and diseases susceptible to resistance these figures represent incomplete images of the economic costs of antibiotic resistance. Another very significant trait of AMR that was absent in the investigation is the use of antibiotics in livestock and food industry. It is an active participant in the increasing AMR and possibly brings its own expected economic losses. A malpractice of the use of antimicrobials as growth promoters is also found in many developing countries. Since 2006, this practice has been banned in the European Union [33,34]. Current estimates of resistance-related costs have limited scope and do not consider the broader social values of antibiotics. These are predisposing factors which steer inaccuracy in the estimation of the actual economic burden that the world is facing due to this issue. To get the precise estimation of the economic ramifications caused, prospective studies should employ macroeconomic methods, which consider all the effects of escalating antibiotic resistance especially the reduction in effectiveness of various antibiotics in modernized medicine. Until we address these issues, the exact estimate of the global economic burden of antibiotic resistance may not be fully calculated [31,35].

Use and Abuse of Antibiotics

India's health ministry has commenced a movement aimed at stopping the misuse of antibiotics. Introduced at the inaugural session of a three day international conference on antimicrobial resistance in New Delhi, the campaign highlighted the importance of taking antibiotics only when prescribed by a doctor, and the need to finish the course. The Medicines with the Red Line public awareness campaign had several key messages: learn how to identify prescription drugs; curb self-medication; and become more aware of the dangers of misusing antibiotics. The packaging of all prescription only drugs is now being marked with a red line. Some medicines-including antibiotics-already have the red line, but patients are often unaware of its meaning. A report published in 20151 found that India consumed more antibiotics than any other country (13 billion standard units in 2010), and from 2000 to 2010 antibiotic use increased by 66%. In per capita terms, however, the United States had the highest global consumption, with 22 units for each person in 2010, whereas the number is 11 in India and seven in China. Speaking at the conference, Health Minister J P Nadda said, "India is committed to combating antimicrobial resistance." He added, "A collective action is required by all stakeholders within a country and by all countries within a region. India would be very happy to work with other member states towards this common goal." The government initiative has had support from a range of stakeholders including the Organization of Pharmaceutical Producers of India. Soumya Swaminathan, Director General of the Indian Council of Medical Research, said, "Community based surveillance will play a major role in finding solutions to anti-TB drug resistance and other viral diseases. There is a need to study how resistance spreads and to find the drivers for antimicrobial resistance." In 2011 various countries in the region adopted the Jaipur declaration on antimicrobial resistance, which required national action plans to tackle antibiotic resistance. In May 2015 the World Health Assembly adopted a resolution to endorse a global action plan on antimicrobial resistance. The plan set out five objectives: to improve awareness and understanding of antimicrobial resistance; to strengthen surveillance and research; to reduce the incidence of infection; to optimize the use of antimicrobials; and to ensure sustainable investment in countering antimicrobial resistance [36].

How to Control or Reduce Antibiotic Resistance Development

Antimicrobial drugs such as antibiotics are a unique class of drugs that does not directly target human biochemical processes but instead affect the growth of invading pathogens and commensal microbiota. Bacteria can easily adapt to their environmental changes and decrease their susceptibility to antibiotics by several mechanisms, including mutation and horizontal gene transfer within and between species [37]. Therefore, new weapons are always indispensable for combating bacterial infections. Nevertheless, most of the antibiotic classes being used today were discovered during the period 1930-1960. Besides, during the past 30 years, only two new systemic classes of antibiotics (oxazolidinones in 2000 and cyclic lipopeptides in 2003) and two topical classes (pseudomonic acids in 1985 and pleuromutilins in 2007) were introduced in the market [38,39]. Even so, neither of these new systemic classes can effectively act against Gram-negative bacteria, in which MDR is an acute problem and the treatment options are limited [40-43]. Unlike Gram-positive bacteria, Gram-negative bacteria have an additional outer membrane comprised of lipopolysaccharide (LPS), which offers an additional barrier to block the invasion of antibiotics [44].

Conclusion

Antibiotic resistant is one of the most urgent public health crises and also enforces a significant monetary burden on world financial system. This small review established the account of antibiotic resistant, side effects and the efforts for innovative antibiotics expansion in pharmaceutical companies and strategy makers. Sluggishing the escalation of antibiotic resistance will require a joint effort of several education and research programs. Reducing antibiotic utilize in agriculture, particularly in food animals, is also vital. The dilemma of antibiotic resistance in human medicine cannot be resolve except the inflow of resistance genes into human microbiome, through food ingestion or get in touch with the environment, is restricted. Recent efforts by diverse groups including scientists, medical doctors, and even in some cases politicians, have shed flush on this dilemma, however. The endorsement of five new classes of antibiotics as the turn of the century to fight the developing resistant gram-positive patho¬gens of the 1990s was a rapidity in the right path. Progress in scientific technology have offered the tools necessary for the discovery of novel antibiotic classes and the development of already recognized ones to battle the largely unimpeded rise of resistant gram-negative pathogens. To make stronger the immune system and encourage the increase of food animals, a range of techniques, including best practice of obtainable vaccines, enhanced hygiene, by health-improving enzymes, probiotics, prebiotics, and acids, and exploiting bacteriocins, antimicrobial peptides, and bacteriophages, as substitutes for antibiotics, should be given due contemplation. For medical personnel, we advocate educational programs such as the antimicrobial stewardship programs, to restrain the surplus and overprescribing of antibiotics. Inappropriate use of antibiotics is one of the major reasons, which may be linked with the healthcare society. The collaboration of governments, public health organizations, and health care workers is desired.

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