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Global status of antibiotic resistance and management

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Abstract. The greatest achievement of the 20th century is the invention and use of antibiotics. However, the abuse use of antibiotics caused by poor regulation has become an urgent issue worldwide, and has risen to be a threat to the global public health, bringing a great financial burden on society. From the perspective of the world, the United States has a long history of development in the discovery, application and regulatory process of antibiotics, forming sufficient cognition and relatively perfect countermeasures. Although the European Union and its member states started the measures to curb antibiotic resistance late, they also caught up and gradually established a complete monitoring system. As the largest developing country, China still has a lot to work on, especially the construction of basic medical facilities and systems. It can be seen that the importance of antibiotics use and management have become a global consensus. This article elaborated and focus the current situation of antibiotic resistance in the United States, the European Union and China as well as the corresponding countermeasures taken by each country. Countries should collaborate together and establish a global system to monitor the use of antibiotics in order to control antibiotic resistance.

Keywords: antibiotic resistance, global health, management strategies.

1. Introduction

Since the discovery of penicillin by British scientist Fleming in 1928, a great revolution has been set off in the history of medicine [1]. After that, scientists have found many drugs that can control microbial infections, such as bacteria and collectively called them antibiotics. Antibiotics are secondary metabolites created in the course of life by microbes, higher animals, and plants that have anti-pathogen or other properties. It has the potential to disrupt the development of other cell processes. They are toxic to bacteria by inhibiting the synthesis of functional components, such as cell walls, membranes, nucleic acids or proteins. Benefiting from the powerful ability of antibiotics to kill bacteria, countless lives have been saved.

However, because of the overuse or misuse of antibiotics in health care and animal health, microorganisms become resistant to antibiotics to which they are sensitive, and thus become less sensitive to drugs, a phenomenon known as antibiotic resistance. Antibiotic resistance is currently a major global health threat. Worldwide, it is estimated that at least 2,868,700 bacterial and fungal infections caused by antibiotic resistance occur each year, mostly in developing countries, resulting in 35,900 deaths [2]. And because reporting and monitoring systems in developing countries are inadequate, this figure is likely to be an underestimate. Therefore, it is necessary to attach importance to and increase the development of new antibiotics. The formation of drug resistance is a natural

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process that occurs sooner or later for each drug, as well as the formation of defense mechanisms from the survival of pathogenic microorganisms. Human activities, attitudes, and policy failures, on the other hand, have considerably expedited this natural process, resulting in the current worldwide drug resistance epidemic in various regions of the world. The key to the problem of rising resistance is the rapidly growing global demand for antibiotics, and the overuse of antibiotics leads directly to greater resistance. In addition, a lack of corporate investment in research and development of new antibiotics and a lack of government regulation and policy containment of antibiotic resistance also play a part in the difficulty of tackling antibiotic resistance. This paper overviews the current situation of antibiotic infection worldwide, and the countermeasures of antibiotic resistance taken by relevant international organizations, governments, enterprises and the public.

2. Summary of antibiotic resistance

Since the 1940s, antibiotics have been widely used because of their important medical and agriculture application. However, the irrational use and abuse of antibiotics have resulted in the rapid and widespread development of bacterial resistance and the widespread spread of drug-resistant bacteria. Along the way, American perceptions of antibiotics have changed accordingly. Originally thought of as wonder drugs in the antithesis of pathogenic bacteria [3], antibiotics have been integrated into a web of universal associations with bacteria, animals, humans and the environment. The dividing line is roughly the 1970s, American scientist Stuart B. Levy proved through experiments that drug-resistant plasmid can be transferred from animals to the human body [4]. This discovery has attracted attention from the government of the United States. Awareness and calls to limit the use of antibiotics have also been echoed to some extent at the federal level. Since the 1970s, the US federal government has tended to better protect the effectiveness of antibiotics through strict regulation, and the US Food and Drug Administration has also started to explicitly advocate prudent use of antibiotics [5,6]. In the case of the United States, there are two positive aspects to protecting the effectiveness of antibiotics: first, the recognition that humans, animals, bacteria and the environment are closely linked, and second, the recognition that bacteria also follow natural laws and co-evolve with humans and animals. The emergence of these related cognition means that people are gradually abandoning the binary opposition of antibiotics and pathogenic bacteria and adopting a comprehensive perspective to understand the relationship between them. In the early 2000s, the concept of "One health" emerged from practices related to tackling bacterial resistance. At present, the World Health Organization (WHO) has repeatedly issued warnings in public publications about the spread of drug-resistant bacteria around the world, calling for global action to integrate active prevention and "one health" into action programs [7,8]. A comprehensive view of antibiotics from a "one health" perspective may lead to more effective antibiotic regulatory policies that are better for the environment on which we live.

2.1. Antibiotic resistance in the United States

Although the United States has the strictest drug administration in the world, it also suffers from the abuse of antibiotics. According to the center for disease control and prevention (CDC)'s 2019 report, there are more than 2.8 million drug-resistant infections each year, and more than 35,000 people died from antibiotic resistance every year. According to a cross-sectional study from Kao-Ping Chua et al., one in seven patients experienced at least one inappropriate antibiotic prescription annually. The results showed that more than 15 million antibiotics were prescribed in outpatient clinics in 2016, with azithromycin (19%) and amoxicillin (18%) being the most common prescriptions. Despite the large number of prescriptions, only 12.8 percent of antibiotics are rationally used [9]. In addition, there are non-hospital challenges from healthcare and community. In healthcare, bacterial transmission in non-hospital settings (such as long-term care facilities), the CDC's recommendations were inconsistently implemented in some areas (such as contact precautions). All of these health care-related factors contribute to the emergence of antibiotic resistance, and community challenges cannot be ignored. For example, poor sanitation, the spread of drug resistance in the food supply, inadequate supplies of

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vaccines to prevent infection and resistance, and a lack of understanding of the conditions under which antibiotics are used in environments such as farms and fields [2].

In 2013, a report from CDC had a wake-up call for the U.S. government to take action and invest more in the fight against antibiotic resistance. Specific measures are as follows: first, in terms of tracking data, researchers tracked resistance through a network of national laboratories and analyzed the data to provide tracking reports and guidance on the use of resistant antibiotics for healthcare providers. Second, on antibiotic use, the U.S. government works with hospitals and food partners to provide the rationale and tools for implementing antibiotic management programs and ensuring optimal use of veterinary antibiotics in food. Next, in environment and health cooperation, it will help reduce the need for antibiotics by establishing pilot data-driven solutions to guide long-term public health interventions, promote improved global sanitation and access to safe drinking water. The last is to invest millions of dollars in vaccine and drug development to support basic research, raise awareness of drug resistance, and identify new treatments to prevent infection. On the basis of these measures, the United States collects information on the emergence, threat and trend change of antimicrobial agents over time through the National Antimicrobial Resistance Monitoring System (NARMS) established as early as 1996, provides annual NARMS summary report, and regularly holds public meetings to report the monitoring results, providing a platform for other antimicrobial resistance research. Through the relentless efforts of the US government, deaths due to antibiotic resistance were reduced by 18% overall and deaths due to antibiotic resistance in hospitals by 28% from 2013 to 2019 [2]. In the US, there are four aspects worth learning. Firstly, infection prevention is the most fundamental way to reduce the use of antibiotics, so as to prevent the further spread of drug resistance; secondly, data on drug resistance and risk factors should be collected; in addition, antibiotic prescription and management should be improved; finally, Because antibiotic resistance cannot be truly eradicated, it is important to actively develop new antibiotics.

2.2. Antibiotic resistance in European Union

A report by the European Centre for Disease Prevention and Control (ECDC), which looked at deaths from 2016 to 2020, found that up to 35,000 people in the European Union (EU) die each year from complications caused by antibiotic resistance, accounting for around 100 deaths a day and making it more deadly than flu, tuberculosis and HIV combined. In addition, according to the latest data released by the EU in 2016, sulfonamides and tetracycline have developed high resistance to human Escherichia coli, with resistance rates of 34.6% and 29.2% respectively [10]. The growing resistance of bacteria to multiple drugs has led to an increasing number of drug failures to treat diseases. According to the report, Salmonella and Escherichia coli isolated from broilers, turkeys and meat showed extremely high resistance to ampicillin, tetracycline and sulfonamides, but still showed high sensitivity to the third generation cephalosporins. Moreover, Salmonella and Escherichia coli also maintained a low level of resistance to colistin [11].

Antibiotic resistance also varies by region in Europe, with scientists detecting higher rates in the southern and eastern parts of the continent. Rates of bacterial resistance were highest in Mediterranean countries and lowest in Scandinavia. It is also worth noting that although antibiotic resistance infection and death rates are on the rise in Europe, there was a significant decline between 2020 and 2021, due to the COVID-19 pandemic that year leading to a reduction in community antibiotic use, resulting in the postponement of many operations. Reports of health care-associated infections have also decreased as a result. Despite the overall decline, there was still an increase in infections caused by carbapenem resistant acinetobacter in the first year of the COVID-19 pandemic, and resistance to this pathogen is likely to continue to grow beyond 2023.

As a relatively authoritative region in the world for monitoring antibiotic resistance, the EU is often used as an important reference for other regions to develop drug resistance monitoring programs. As a political and economic community, the EU has adopted a strict legal system to restrain its member states, introduced a series of policy measures on antibiotic prescription regulation, rational drug use in animal husbandry, publicity and education, and formulated a five-year action plan on antibiotic

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resistance, pushing and guiding member states to address the growing bacterial resistance threat. In the aspect of prescription management of antibiotics, the EU has issued the guidelines for new antibacterial drug instructions, standardizing the instructions for doctors and patients, and stipulating that patients must buy antibiotics by prescription. In terms of promoting the rational use of antibiotics in animal husbandry, the EU decided to reduce the financial subsidies for antibiotics and regulate the use of antibiotics by economic means in order to avoid bacterial resistance caused by the large intake of meat containing antibiotics by humans. In terms of antimicrobial resistance publicity and education, the EU provides financial assistance for antibiotic publicity and education activities, such as "European Antibiotic Awareness Day" to popularize knowledge of rational drug use. In 2011, the EU announced a five-year action plan on antibiotic resistance with seven priority areas for action and 12 specific measures. The action plan provides governance ideas and measures for member states. In terms of specific measures taken by individual countries in the EU, the Swedish Antimicrobial Steering Group formulated clinical medication guidelines according to the risk of bacterial infection and the development trend of drug resistance, requiring no more than 250 prescriptions per 1,000 inhabitants per year. At the same time, a press conference was held every year to publicize the sales volume of antibiotics and the trend of bacterial drug resistance. As for the UK, the government made reducing Healthcare Associated Infections (HCAIs) a priority in controlling antibiotic resistance in the early 2000s [12]. In 2003, the UK Department of Health launched the Hospital Pharmacy Program to provide education and training on antibiotic use for health care staff [13]. In 2007, the UK established the Advisory Committee on Antibiotic Resistance and HealthCare Associated Infection (ARHAI) to provide professional consultation channels for addressing the problem of antibiotic resistance [14]. In Germany, the government has established nosocomial infection surveillance system to monitor and analyze items such as methicillin-resistant Staphylococcus aureus (MRSA) and postoperative wound infections using standardized survey methods and indicators. In France, the National Health Agency for Food, Environment and Labour assesses the risk of antibiotic resistance in animal husbandry and household pet health by monitoring the use of antibiotics in animals, and an annual public awareness campaign on antibiotics has been held in France since 2002.

2.3. Antibiotic resistance in China

China has become a major producer and user of antibiotics because of their widespread use in health care and agricultural breeding. However, due to insufficient research and development capacity of new antibiotics, unreasonable application of antibiotics in aquaculture, substandard waste discharge of pharmaceutical enterprises, irrational drug use by the masses and other unreasonable factors, the problem of antibiotic resistance in China is becoming more and more serious. As early as 2017, China was able to produce 210,000 tons of antibiotics every year, of which 30,000 tons were exported and the rest were sold by China itself, with per capita consumption of 138 grams, 10 times that of the United States. According to the bacterial resistance monitoring report in China in 2020, Gram-positive bacteria need to be concerned about drug-resistant bacteria are methicillin-resistant and vancomycin resistant, while Gram-negative bacteria need to be concerned about drug-resistant bacteria are third-generation cephalosporin resistant or carbapenem resistant, especially carbapenem resistant bacteria are difficult to treat clinically and have a high mortality. According to the detection of carbapenem resistant strains in all provinces and cities in China in 2020, the national average resistance rate of Escherichia coli to carbapenems was 1.6%, among which Beijing was the highest (3.1%) and Xizang was the lowest (0.2%). The national average resistance rate of Klebsiella pneumoniae to carbapenems was 10.9%, among which Henan was the highest (30.2%), and Xizang was still the lowest (0.2%). The detection rate of carbapenem-resistant Klebsiella pneumoniae has been increasing, which will bring great clinical and laboratory challenges. The abuse of antibiotics not only leads to the waste of drugs and the increase of medical expenses, but also leads to the emergence of more and more drug-resistant bacteria. The most compelling example is that over the past few decades, new drugs on the market seem to last for less and less time. Antibiotics marketed in the 1960s were used for more than ten years on average before iteration, while new antibiotics marketed after the 1990s often lasted less than two

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years, requiring the development of new and stronger antibiotics. Even vancomycin, which was regarded as the "last line of defense against drug-resistant strains" in the international pharmaceutical community in the late 1990s, has now given rise to drug-resistant strains.

Like most developing countries in the world, limited technical capabilities and experimental conditions make it particularly difficult to analyze experimental samples of drug-resistant bacteria, resulting in a lack of monitoring capacity of bacterial resistance in China. Moreover, it is difficult to ensure a regular course of treatment in the course of antibiotic use, which is also the main cause of antibiotic resistance. Combined with China's national conditions, China needs to make efforts in the following three directions in the future. First, it needs to strengthen the strict control of clinical application of antibiotics, timely improve the laboratory detection methods and drug sensitivity experiments of drug-resistant bacteria, and provide guidance for clinical solutions to problems related to drug resistance mechanism. Secondly, it is necessary to strengthen the basic medical hardware facilities and information facilities, and establish a complete bacterial drug resistance clinical application monitoring information system. Finally, it is necessary to strengthen publicity, improve the awareness of the strict use of antibiotics in the whole society, and cooperate with multiple parties to carry out epidemiological investigation and research of drug-resistant strains, so as to pay special attention to drug-resistant bacteria.

3. Conclusion

The emergence of drug resistance on Earth as a dynamically balanced ecosystem clearly demonstrates the importance of the interaction between humans, animals and the natural environment. Fortunately, people in all countries are increasingly aware of the mechanisms of antibiotic resistance and are taking proactive measures to use antibiotics scientifically and rationally. It is believed that in the future, with the concerted efforts of doctors, pharmaceutical companies and the public around the world, more nationally appropriate solutions to antibiotic resistance will be developed.

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