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Analysis of Resistance of Mycobacterium Tuberculosis to Different Anti-Tuberculosis Drugs

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Abstract: Tuberculosis has been one of the main infectious diseases in the world since ancient times. In the 19th century, Koho, a German scientist, isolated a then-new bacterium, mycobacterium tuberculosis, from the tissues of dead patients. Since then, the mystery of tuberculosis has been revealed. Then bacteriologists Callander and Ceran successfully developed a live attenuated vaccine that effectively prevented the onset of tuberculosis after vaccination, setting a precedent for active immunization against tuberculosis. At the beginning of the 20th century, streptomycin was first used in the treatment of tuberculosis, and a good curative effect was obtained. From then on, a new era of tuberculosis drug chemotherapy was entered. At present, taking rifampicin, isoniazid and other chemotherapy drugs is still the most common clinical first-line anti-tuberculosis treatment. However, factors such as irregular medication, drug abuse and serious adverse drug reactions greatly increase the likelihood of drug-resistance of mycobacterium tuberculosis. This paper analyzed the types of anti-tuberculosis drugs for patients with drug resistance in XXX region in 2018-2019, and looked forward to the development trend, so as to provide a basis for the subsequent clinical selection of drugs and the formulation of rational chemotherapy regiments for drug-resistant tuberculosis.

Keywords: Mycobacterium tuberculosis; Drug resistance; Anti-tuberculosis drugs

1. Introduction

Mycobacterium tuberculosis, commonly referred to as tubercle bacillus, is the main pathogenic bacterium. According to the latest survey report, there were 10.3 million new tuberculosis patients and 1.6 million deaths worldwide in 2017, among which China ranked third in the world in the number of new tuberculosis cases [1]. The emergence of drug-resistant tuberculosis bacilli is the root cause of the large number of deaths. According to relevant literatures, the drug resistance rate of first-line anti-tuberculosis drugs in the world has reached 35.6%, the drug resistance rate of PDR-TB has reached 32.1%, and the drug resistance rate of MDR-TB has reached 10.5%. The treatment cycle is long, the curative effect is poor, the cure rate is low, and the mortality rate is high, and because of its strong ability of transmission, mycobacterium tuberculosis has seriously endangered the life and health of the world's people, has been a worldwide medical problem.

2. Current Situation of Tuberculosis Epidemic and Mechanism of Drug Resistance

2.1. Prevalence situation of tuberculosis in china

There is a regional imbalance of tuberculosis endemicin the areas of China. For example, the prevalence of active tuberculosis in the eastern, central and western regions was 271/105, 443/105 and 635/105respectively. This geographically distributed difference in prevalence may be due to the adaptation of mycobacterium tuberculosis to the regional environment. At the same time, the long-term relationship between the host and the pathogenic bacteria may also cause the change of genetic adaptability, leading to the strain of a specific lineage can adapt to a specific host population. The characteristics and genotypes of the strains in different regions may differ, and the different genotypes may lead to differences in the molecular characteristics and pathogenicity of tuberculosis.

2.2. Prevalence situation of tuberculosis in foreign countries

It is estimated that there were 10.3 million new tuberculosis cases worldwide in 2017, including 5.1 million men, 3.2 million women and 1 million children. Typically, 90% of tuberculosis patients are adults (aged ≥ 16 years) and 10% are also HIV-positive (73% in Africa). Two-thirds of tuberculosis patients come from eight countries: India (26%), China (8%), Indonesia (9%), the Philippines (7%), Pakistan (6%), Nigeria (6%), Bangladesh (3%) and South Africa (3%) [2]. It is mainly distributed in some developing countries, which generally have a large population base, and some countries are limited by medical and health conditions. A series of breakthroughs on tu-

berculosis disease treatment and control has brought hope to the success of eliminating tuberculosis, however, the emergence of new challengessuch asthe variation of mycobacterium tuberculosis, the popularity of drug-resistant tuberculosis and tuberculosis co-infection with other disease led to the resurgence of tuberculosis outbreak trends, today's global tuberculosis situation is still grim, especially the developing countries thatshould pay enough attention to the disease.

2.3. Molecular basis of drug resistance of mycobacterium tuberculosis

The spread of drug-resistant tuberculosis (DR-TB) makes the epidemic situation of this disease more severe and seriously endangers the development of national health undertakings and the health level of citizens. In recent years, there have been many studies on the mechanism of drug-resistant tuberculosis, among which the most accepted theories are mainly caused by efflux pump and molecular level mutation.

Mycobacterium tuberculosis drug efflux pump, mainly regulated by Rv1410c, Rv1819c, Rv0783c genes, these genes coding efflux protein expressed, which can speed up the rate of drug transport, lead to substantial reduction of intracellular drug concentration, causing the drug cannot play their curative effect, so it can assist mycobacterium tuberculosisto resist one or more drugs[3]. On the other hand, recent studies have revealed some common gene mutations associated with drug resistance, such as rifampicin resistance, which is highly correlated with rpoB gene mutation. Mutations in katG and inhA genes are common in isoniazid resistant strains. If mutations occur at the katG315 site, the ability of peroxidase of the strain to activate INH will be greatly weakened, so that the mutants can not only maintain peroxidase toxicity, but also resist the bactericidal action of drugs. The mutation of emb gene may be related to the drug resistance of EMB, and may also lead to the increase of the probability of M/XDR occurrence.

2.4. Clinical causes of drug resistance of mycobacterium tuberculosis

In clinical practice, unreasonable treatment is one of the most direct factors of drug-resistant tuberculosis. The common situation is: when using the combination of drugs, the choice of drugs is not reasonable, inappropriate; Patients have deviationwhen use the drug dose, the use of drug dose is insufficient, or patients use the drug in an incorrect way; When a combination of multiple drugs is used, if one drug is interrupted or insufficientduring the course of treatment; Early treatment failure with other diseases or improper treatment with recurrent diseases; Patients or doctors have less awareness or pay no enough attention to tuberculosis, resulting inthe treatmentof anti-tuberculosis is not standard, procedures are not reasonable, the process of chemotherapy did not complete according to the provisions, etc. At the same time, the side effects of anti-tb drugs are very huge, such as severe liver and kidney damage, allergic reactions, gastrointestinal reactions, all will affect the use of anti-tb drugs. Some common situations are not in-time or delayed diagnosis of tuberculosis patients, exacerbating the patient's condition, increasing the difficulty of treatmentand MDR-TB cases.

Environmental factors are also one of reasons to blame. In China, there are more than 200 million farmers entering the city. The reason for this phenomenon lies in the heavy workload of migrant workers, poor living environment, low economic income, lack of timely medical services, non-standard treatment, and lack of effective tuberculosis control and management measures. Most tuberculosis patients with HIV are MDR-TB, which makes treatment more difficult and increases mortality. In recent years, the number of diseases requiring treatment with immunosuppressive drugs, such as organ transplantation, stem cell transplantation, autoimmune diseases and so on, has greatly increased, which has given the chance to fighting against tuberculosis.

3. Drug Resistance of Mycobacterium Tuberculosis in China

According to the different drug sensitivity results of mycobacterium tuberculosis, the drug resistance types of aggregate bacilli can be mainly divided into the following categories :(1) SDR is positive for the drug sensitivity test of any first-line anti-tb drugs; (2) MDR means that the drug sensitivity test results of INH and RFP are positive for the first-line drugs at least. (3) XDR means that the drug sensitivity test results are positive for at least one or two first-line and second-line anti-tb drugs.

To sum upmanydomestic articles on drug resistance analysisof mycobacterium tuberculosis, a total of 3536 strains of sources of different strains of mycobacterium tuberculosis patients, there 1917 strains are resistant to at least one first-line drug, accounting for 54.21% of the total number of strains, among which are428 single drug-resistant strains, accounting for 12.11% of the total number of strains, 394 strains of multi-drug resistant strains, accounted for 11.13%, as shown inTable 1.

Table 1. First-line drug resistance (n=3536)

Type	Number of strains (n)	Ratio (%)
All sensitive	1497	42.33
Single drug resistance (SDR)	428	12.11
Poly drug resistance（PDR）	394	11.13
Multidrug resistance（MDR）	1102	31.16
Resistant to at least one drug	1917	54.21
Resistant to 4 drugs	618	17.49

Among the 1672 strains that are resistant to at least one first-line drug, 105 were INH resistant, 91 were RFP resistant, 93 were SM resistant, and 65 were EMB resistant, indicating that the rate of INH resistance ishighest, which is 77.14%, followed by SM (69.29%) >RFP (66.43%) >EMB (50.00%), as shown in Table 2.

Table 2. Details of first-line drug sensitivity results (n=1672)

Drug	Number of drug-resistant strains	Ratio of drug resistance（%）
RFP	1094	65.44
INH	1288	77.01
SM	1142	68.29
EMB	808	48.30

A total of 249 strains of mycobacterium tuberculosis from multiple articles were tested for drug sensitivity to second-line drugs ofloxacin (OF) and kanamycin (KM). It was found that a total of 29 strains (13.33% of the total number of strains) were resistant to the drug OF, and 8 strains (3.67% of the total number of strains) were resistant to the drug KM. Are shown in table 3.

Table 3 Details of susceptibility results of second-line drugs (n=2603)

Drug	Number of drug-resistant strains	Ratio of drug resistance（%）
OF	347	13.33
KM	96	3.67

A total of 511 strains of mycobacterium tuberculosis from multiple articles were tested for polydrug resistance and multidrug resistance, and it was found that multidrug resistance was more prominent than polydrug resistance. The results are shown in the following table 4.

Table 4. details of poly-drug resistance and multi-drug resistance results

Drug	Number of drug-resistant strains	Ratio of drug resistance（%）
Poly drug resistance (PDR)	0	0
H+E	2	0.4
H+S	16	3.2
R+S	18	3.6
E+S	20	2.0
Multidrug resistance (MDR)		
H+R+E	13	2.3
H+R+S	36	7.1
H+R+E+S	44	8.6

4. Differences in Drug Resistance of Mycobacterium Tuberculosis in Different Regions of China

According to the national tuberculosis survey conducted in China, the prevalence of drug-resistant tuberculosis is severe in most regions of China. About one-third of new tuberculosis patients and half of treated tuberculosis patients were infected with drug-resistant mycobacterium tuberculosis, of which 5.7% were new multidrug-resistant bacteria (MDR) patients. Based on estimates of MDR-TB in different countries, China has the highest number of MDR-TB cases each year, with almost all cases being twice the average, and the situation is likely to get worse in the future. The 2014 survey showed that in addition to tuberculosis patients with MDR, 11% of new cases and 16% of previously treated patients were positive for INH or RFP susceptibility tests, and that these patients could easily progress to multidrug-resistant mycobacterium tuberculosis (MDRTB).

According to relevant literature [4], the total drug resistance rate (55.22%) and multi-drug resistance rate (30.63%) of mycobacterium tuberculosis were the highest in Qinghai province, which was significantly higher than that in other provinces and cities reported previously, such as Beijing, where the total drug resistance rate was 21.1% and the multi-drug resistance rate was 3.4%. resistant rate of Hanan city in Heilongjiangwas 33.5%, multi-drug resistant rate was 13.9%, the total resistance rate of Dali in Yunnan province area was 25.3%, of which the multi-drugresistant rate was 6.8%, Dongguan city, Guangdong province, total resistant rate was 17.3%, multi-drugresistant rate was 7.8%, Ningbo city, Zhejiang province, the total resistance was 21.2%, the multi-drugresistant rate was 3.8%, total resistant rate of Yantai city in Shandong province was 31.3%, and multi-drug resistant rate was 5.5%. At the same time, the order of tuberculosis resistance in different regions is different from that in other regions, and the types of resistance are also very different. According to a study in Shandong province, SM-resistance in Shandong province has the highest drug resistance rate, followed by INH, while EMB has the lowest drug resistance rate. The order of Tuberculosis resistance in Qinghai province was INH >SM > RFP. All the above results indicate that the tuberculosis bacteria in different regions may have their own regional characteristics and different drug resistance spectrum characteristics. Therefore, it is impossible to generalize the situation of tuberculosis resistance in different regions of China. Appropriate preventive and therapeutic measures should be taken according to the prevalence of tuberculosis in the region.

5. Discussion

Since the emergence of mycobacterium tuberculosis in human history, it has made an indelible impact on human beings. From BCG vaccine at the beginning to streptomycin discovered later, human beings have gradually gained the upper hand in this battle. However, due to the

overuse of antibiotics and the neglect of patients, due to the huge immune pressure, the evolution of bacteria has accelerated, and the emergence of mycobacterium tuberculosis poses a new challenge to the treatment of tuberculosis.

Despite the current state of drug-resistant tuberculosis is not optimistic, there is still lack of effective means of drug-resistant mycobacterium tuberculosis treatment, but the new diagnosis and treatment technology constantly emerging, new anti-tb drugs arecontinuously developed, new diagnostic and treatment strategies have pointed out the directionfor the diagnosis and treatment of drug for us, which isthe most direct way to solve resistance mycobacterium tuberculosis. At the same time, the order of drug resistance of mycobacterium tuberculosis in different regions is also very different. Drug sensitivity test is indispensable in the treatment. It should not give drugs directly according to experience, and the problem of single usage and intermittent usage of drugs should be solved, we should make clear about the most sensitive drugs and use them in shuttle way.

The differences in drug resistance of mycobacterium tuberculosis in different regions are partly related to the local climate and partly to the economic level of the region. In recent years, due to reckless patient who pay not enough attention, and discontinuous treatment that cause recurrent, taking temporary solution but not effect a permanent cure, it needs to do a one-time and short-time cure, the longer the treatment time, the greater the probability of mycobacterium tuberculosis appear, harder it is for follow-up treatment, in addition to better treatment and drugs, strengthen tuberculosis knowledge propaganda, doing personal hygiene well to prevent, improving the regional public health facilities and group consciousness of epidemic prevention, raisingpeoples' attention on the tuberculosis.

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