

Overview and New Approach to an Old Disease: Tuberculosis

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Abstract: Tuberculosis (TB) is an infection of the lungs and respiratory system, which is the organ system that allows us to breathe. TB is caused by a bacterium called *Mycobacterium tuberculosis*. It spreads from person to person when an infected person coughs, sneezes, laughs, or spits. Tiny droplets of fluid from the lungs are carried in the air and can be Excluding HIV/AIDS, Tuberculosis (TB) is responsible for more deaths worldwide than any other infectious agent, with approximately 1.4 million global mortalities in 2011 (WHO, 2012). Although TB mortality rate declined by 41% between 1995 and 2011 and a decline in the number of individuals becoming ill due to the infection has been seen (WHO, 2012), TB continues to be a huge health problem globally - not only because of the increasing number of patients which are co-infected with HIV/AIDS but also because of the rising number of cases of antibiotic resistant TB infections. The current recommended treatment course for TB is a six month regimen of antibiotics, commonly involving isoniazid and rifampicin (WHO, 2009). There are a number of second line drugs, including fluoroquinolones, also available. A combination of drugs is used in order to reduce the risk of antibiotic resistance.

Keywords- Tuberculosis, Antibiotic, *Mycobacterium tuberculosis*, isoniazid and rifampicin, fluoroquinolones

1. HISTORY OF TUBERCULOSIS [1, 2]

Consumption, phthisis, scrofula, Pott's disease, and the White Plague are all terms used to refer to tuberculosis throughout history. It is generally accepted that *Mycobacterium tuberculosis* originated from other, more primitive organisms of the same genus *Mycobacterium*. In 2014, results of a new DNA study of a tuberculosis genome reconstructed from remains in southern Peru suggest that human tuberculosis is less than 6,000 years old. Even if researchers theorize that humans first acquired it in Africa about 5,000 years ago, there is evidence that the first tuberculosis infection happened about 9,000 years ago. It spread to other humans along trade routes. It also spread to domesticated animals in Africa, such as goats and cows. Seals and sea lions that bred on African beaches are believed to have acquired the disease and carried it across the Atlantic to South America. Hunters would have been the first humans to contract the disease there.

1.1 ORIGIN [3, 4]

Scientific work investigating the evolutionary origins of the *Mycobacterium tuberculosis* complex has concluded that the most recent common ancestor of the complex was a human-specific pathogen, which underwent a population bottleneck. Analysis of mycobacterial interspersed repetitive units has allowed dating of the bottleneck to approximately 40,000 years ago, which corresponds to the period subsequent to the expansion of *Homo sapiens sapiens* out of Africa. This analysis of mycobacterial interspersed repetitive units also dated the *Mycobacterium bovis* lineage as dispersing approximately 6,000 years ago, which may be linked to animal domestication and early farming. Human bones from the Neolithic show a presence of the bacteria. There has also been a claim of evidence of lesions characteristic of tuberculosis in a 500,000 years old *Homo erectus* fossil, although this finding is controversial.

Results of a genome study reported in 2014 suggest that tuberculosis is newer than previously thought. Scientists were able to recreate the genome of the bacteria from remains of 1,000-year-old skeletons in southern Peru. In dating the DNA, they found it was less than 6,000 years old. They also found it related most closely to a tuberculosis strain in seals, and have theorized that these animals were the mode of transmission from Africa to South America. The team from University of Tübingen believes that humans acquired the disease in Africa about 5,000 years ago. Their domesticated animals, such as goats and cows, contracted it from them. Seals acquired it when coming up on African beaches for breeding, and carried it across the Atlantic. In addition, TB spread via humans on the trade routes of the Old World. Other researchers have argued there is other evidence that suggests the tuberculosis bacteria is older than 6,000 years. This TB strain found in Peru is different from that prevalent today in the Americas, which is more closely related to a later Eurasian strain likely brought by European colonists. However, this result is criticised by other experts from the field, for instance because there is evidence of the presence of *Mycobacterium tuberculosis* in 9000 year old skeletal remains.

2. MECHANISM

2.1 Transmission [5, 6]

People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis may infect 10–15 (or more) other people per year. Transmission should occur from only people with active TB – those with latent infection are not thought to be contagious. The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets

expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the *M. tuberculosis* strain, the level of immunity in the uninfected person, and others. The cascade of person-to-person spread can be circumvented by segregating those with active ("overt") TB and putting them on anti-TB drug regimens. After about two weeks of effective treatment, subjects with non-resistant active infections generally do not remain contagious to others. If someone does become infected, it typically takes three to four weeks before the newly infected person becomes infectious enough to transmit the disease to others.

2.3 Pathogenesis [7, 8]

TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within endosomes of alveolar macrophages. Macrophages identify the bacterium as foreign and attempt to eliminate it by phagocytosis. During this process, the bacterium is enveloped by the macrophage and stored temporarily in a membrane-bound vesicle called a phagosome. The phagosome then combines with a lysosome to create a phagolysosome. In the phagolysosome, the cell attempts to use reactive oxygen species and acid to kill the bacterium. However, *M. tuberculosis* has a thick, waxy mycolic acid capsule that protects it from these toxic substances. *M. tuberculosis* is able to reproduce inside the macrophage and will eventually kill the immune cell.

3. SYMPTOMS [9, 10]

Although your body may harbor the bacteria that cause tuberculosis, your immune system usually can prevent you from becoming sick. For this reason, doctors make a distinction between:

Latent TB - In this condition, you have a TB infection, but the bacteria remain in your body in an inactive state and cause no symptoms. Latent TB, also called inactive TB or TB infection, isn't contagious. It can turn into active TB, so treatment is important for the person with latent TB and to help control the spread of TB. An estimated 2 billion people have latent TB.

Active TB - This condition makes you sick and can spread to others. It can occur in the first few weeks after infection with the TB bacteria, or it might occur years later.

Signs and symptoms of active TB include:

- Coughing that lasts three or more weeks
- Coughing up blood
- Chest pain or pain with breathing or coughing
- Unintentional weight loss
- Fatigue
- Night sweats
- Chills
- Loss of appetite

Tuberculosis can also affect other parts of your body, including your kidneys, spine or brain. When TB occurs outside your lungs, signs and symptoms vary according to the organs involved. For example, tuberculosis of the spine may give you back pain.

4. CAUSES [11, 12]

Tuberculosis is caused by bacteria that spread from person to person through microscopic droplets released into the air. This can happen when someone with the untreated, active form of tuberculosis coughs, speaks, sneezes, spits, laughs or sings. Although tuberculosis is contagious, it's not easy to catch. You're much more likely to get tuberculosis from someone you live with or work with than from a stranger. Most people with active TB who've had appropriate drug treatment for at least two weeks are no longer contagious.

HIV and TB - Since the 1980s, the number of cases of tuberculosis has increased dramatically because of the spread of HIV, the virus that causes AIDS. Infection with HIV suppresses the immune system, making it difficult for the body to control TB bacteria. As a result, people with HIV are many times more likely to get TB and to progress from latent to active disease than are people who aren't HIV positive.

Drug-resistant TB - Another reason tuberculosis remains a major killer is the increase in drug-resistant strains of the bacterium. Since the first antibiotics were used to fight tuberculosis more than 60 years ago, some TB germs have developed the ability to survive, and that ability gets passed on to their descendants.

Drug-resistant strains of tuberculosis emerge when an antibiotic fails to kill all of the bacteria it targets. The surviving bacteria become resistant to that particular drug and frequently other antibiotics as well. Some TB bacteria have developed resistance to the most commonly used treatments, such as isoniazid and rifampin. Some strains of TB have also developed resistance to drugs less commonly used in TB treatment, such as the antibiotics known as fluoroquinolones, and injectable medications including amikacin, kanamycin and capreomycin. These medications are often used to treat infections that are resistant to the more commonly used drugs.

Since antibiotics began to be used to fight TB, some strains have become resistant to drugs. Multidrug-resistant TB (MDR-TB) arises when an antibiotic fails to kill all of the bacteria, with the surviving bacteria developing resistance to that antibiotic and often others at the same time.

MDR-TB is treatable and curable only with the use of very specific anti-TB drugs, which are often limited or not readily available. In 2012, around 450,000 people developed MDR-TB.

Tobacco use has also been found to increase the risk of developing active TB. Over 20 percent of TB cases worldwide are related to smoking. TB is spread from person to person through the air. The dots in the air represent droplet nuclei containing tubercle bacilli.

5. Risk factors:

Anyone can get tuberculosis, but certain factors can increase your risk of the disease. These factors include:

Weakened immune system

A healthy immune system often successfully fights TB bacteria, but your body can't mount an effective defence if your resistance is low. A number of diseases and medications can weaken your immune system, including:

HIV/AIDS

Diabetes

Severe kidney disease

Certain cancers

Cancer treatment, such as chemotherapy

Drugs to prevent rejection of transplanted organs

Some drugs used to treat rheumatoid arthritis, Crohn's disease and psoriasis

Malnutrition

Very young or advanced age

● **Travelling or living in certain areas**

The risk of contracting tuberculosis is higher for people who live in or travel to countries that have high rates of tuberculosis and drug-resistant tuberculosis, including:

Africa

Eastern Europe

Asia

● **Poverty and substance abuse**

Lack of medical care; If you receive a low or fixed income, live in a remote area, have recently immigrated to the United States, or are homeless, you may lack access to the medical care needed to diagnose and treat TB.

Substance abuse; IV drug use or alcohol abuse weakens your immune system and makes you more vulnerable to tuberculosis.

Tobacco use; Using tobacco greatly increases the risk of getting TB and dying of it.

● **Complications**

Without treatment, tuberculosis can be fatal. Untreated active disease typically affects your lungs, but it can spread to other parts of your body through your bloodstream. Examples of tuberculosis complications include:

Spinal pain-Back pain and stiffness are common complications of tuberculosis. Swelling of the membranes that cover your brain (meningitis) -This can cause a lasting or intermittent headache that occurs for weeks. Mental changes also are possible. Liver or kidney problems-Your liver and kidneys help filter waste and impurities from your bloodstream. These functions become impaired if the liver or kidneys are affected by tuberculosis. Heart disorders-Rarely, tuberculosis can infect the tissues that surround your heart, causing inflammation and fluid collections that may interfere with your heart's ability to pump effectively. This condition, called cardiac tamponade, can be fatal.

Risk of Developing TB Disease over a Lifetime

Without treatment, approximately 5% of persons who have been infected with *M. tuberculosis* will develop disease in the first year or 2 after infection, and another 5% will develop disease sometime later in life. Thus, without treatment, approximately 10% of persons with normal immune systems who are infected with *M. tuberculosis* will develop TB disease at some point in their lives.

TB disease can occur in pulmonary and extra pulmonary sites.

Pulmonary

TB disease most commonly affects the lungs; this is referred to as pulmonary TB. In 2011, 67% of TB cases in the United States were exclusively pulmonary. Patients with pulmonary TB usually have a cough and an abnormal chest radiograph, and may be infectious

Extra pulmonary

Extra pulmonary TB disease occurs in places other than the lungs, including the larynx, the lymph nodes, the pleura, the brain, the kidneys, or the bones and joints. In HIV-infected persons, extra pulmonary TB disease is often accompanied by pulmonary TB. Persons with extra pulmonary TB disease usually are not infectious unless they have

1) Pulmonary extra pulmonary disease;

2) Extra pulmonary disease located in the oral cavity or the larynx; or

3) Extra pulmonary disease that includes an open abscess or lesion in which the concentration of organisms is high, especially if drainage from the abscess or lesion is extensive, or if drainage fluid is aerosolized. Miliary TB. Miliary TB occurs when tubercle bacilli enter the bloodstream and disseminate to all parts of the body, where they grow and cause disease in multiple sites. This condition is rare but serious. "Miliary" refers to the radiograph appearance of millet seeds scattered throughout the lung. It is most common in infants and children younger than 5 years of age, and in severely immunocompromised persons. Miliary TB may be detected in an individual organ, including the brain; in several organs; or throughout the whole body. Central Nervous System when TB occurs in the tissue surrounding the brain or spinal cord, it is called tuberculous meningitis. Tuberculous meningitis is often seen at the base of the brain on imaging studies. Symptoms include headache, decreased level of consciousness, and neck stiffness.

6. DIAGNOSIS [13, 14]

During the physical exam, your doctor will check your lymph nodes for swelling and use a stethoscope to listen carefully to the sounds your lungs make while you breathe.

The most commonly used diagnostic tool for tuberculosis is a simple skin test, though blood tests are becoming more commonplace. A small amount of a substance called PPD tuberculin is injected just below the skin of your inside forearm. You should feel only a slight needle prick.

Within 48 to 72 hours, a health care professional will check your arm for swelling at the injection site. A hard, raised red bump means you're likely to have TB infection. The size of the bump determines whether the test results are significant.

Medical history

The medical history includes obtaining the symptoms of pulmonary TB: productive, prolonged cough of three or more weeks, chest pain, and hemoptysis. Systemic symptoms include low grade remittent fever, chills, night sweats, appetite loss, weight loss, easy fatigability, and production of sputum that starts out mucoid but changes to purulent. Tuberculosis should be suspected when a pneumonia-like illness has persisted longer than three weeks, or when a respiratory illness in an otherwise healthy individual does not respond to regular antibiotics.

Physical examination

A physical examination is done to assess the patient's general health. It cannot be used to confirm or rule out TB. However, certain findings are suggestive of TB. For example, blood in the sputum, significant weight loss and drenching night sweats may be due to TB.

Microbiological studies

Lab Findings

A definitive diagnosis of tuberculosis can only be made by culturing *Mycobacterium tuberculosis* organisms from a specimen taken from the patient (most often sputum, but may also include pus, CSF, biopsied tissue, etc.).[1] A diagnosis made other than by culture may only be classified as "probable" or "presumed". For a diagnosis negating the possibility of tuberculosis infection, most protocols require that two separate cultures both test negative.[1] cessary, including tissue biopsy during mediastinoscopy or thoracoscopy.

PCR

Other mycobacteria are also acid-fast. If the smear is positive, PCR or gene probe tests can distinguish *M. tuberculosis* from other mycobacteria. Even if sputum smear is negative, tuberculosis must be considered and is only excluded after negative cultures.

Immunological test

Antibodies from Lymphocyte Secretion or Antibody in Lymphocyte Supernatant or ALS Assay is an immunological assay to detect active diseases like tuberculosis, cholera, typhoid etc. Recently, ALS assay nods the scientific community as it is rapidly used for diagnosis of tuberculosis. The principle is based on the secretion of antibody from in vivo activated plasma B cells found in blood circulation for a short period of time in response to TB-antigens during active TB infection rather than latent TB infection.

Transdermal Patch

A similar approach to the ALS assay. The transdermal patch is a suggested method of detecting active *M.tuberculosis* circulating within blood vessels of patient. This skin patch contains antibodies recognizing the secreted bacterial protein MPB-64 passing through the blood capillaries of the skin creating an immunological response. If the patch detects this secreted bacterial protein, the surrounding skin will redden.

Tuberculin skin test

Two tests are available: the Mantoux and Heaf tests.

Mantoux skin test

If a person has had a history of a positive tuberculin skin test, another skin test is not needed.

BCG vaccine and tuberculin skin test

There is disagreement on the use of the Mantoux test on people who have been immunized with BCG. The US recommendation is that in administering and interpreting the Mantoux test, previous BCG vaccination should be ignored; the UK recommendation is that interferon- γ tests should be used to help interpret positive tuberculin tests, also, the UK does not recommend serial tuberculin skin testing in people who have had BCG (a key part of the US strategy). In their guidelines on the use of QuantiFERON Gold the US Centers for Disease Control and Prevention state that whereas Quantiferon Gold is not affected by BCG inoculation tuberculin tests can be affected.[10]Interferon- γ release assay Interferon- γ (interferon-gamma) release assays (IGRAs) are relatively new tests for tuberculosis. IGRAs are based on the ability of the *Mycobacterium tuberculosis* antigens for early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) to stimulate host production of interferon-gamma.

7. TREATMENT [13, 14]

Most common TB drugs

If you have latent tuberculosis, you may need to take just one type of TB drug. Active tuberculosis, particularly if it's a drug-resistant strain, will require several drugs at once The most common medications used to treat tuberculosis include:

- Isoniazid
- Rifampin (Rifadin, Rimactane)
- Ethambutol (Myambutol)
- Pyrazinamide

If you have drug-resistant TB, a combination of antibiotics called fluoroquinolones and injectable medications, such as amikacin, kanamycin or capreomycin, are generally used for 20 to 30 months. Some types of TB are developing resistance to these medications as well.

A number of new drugs are being looked at as add-on therapy to the current drug-resistant combination treatment, including:

- Bedaquiline
- Linezolid

Medication side effects

Serious side effects of TB drugs aren't common but can be dangerous when they do occur. All tuberculosis medications can be highly toxic to your liver. When taking these medications, call your doctor immediately if you experience any of the following:

- Nausea or vomiting
- Loss of appetite
- A yellow color to your skin (jaundice)
- Dark urine
- A fever that lasts three or more days and has no obvious cause

Completing treatment is essential

After a few weeks, you won't be contagious and you may start to feel better. It might be tempting to stop taking your TB drugs. But it is crucial that you finish the full course of therapy and take the medications exactly as prescribed by your doctor. Stopping treatment too soon or skipping doses can allow the bacteria that are still alive to become resistant to those drugs, leading to TB that is much more dangerous and difficult to treat.

TB treatment – Curing TB, failure, relapse & recurrence

TB treatment

The main aim of TB treatment is to cure the patient. Other aims are to prevent the spread of TB, and to prevent the development of drug resistant TB.

Curing TB

TB treatment can cure most people who have TB, using a combination of the different drugs available for TB treatment. Now that drugs are available surgery is not often used as treatment for TB.

Killing the TB bacteria

The TB drugs that are taken for the treatment of TB, have the aim of killing all the TB bacteria in the person's body. This means that the person is cured of TB. However, TB bacteria die very slowly, and so the drugs have to be taken for quite a few months. All the drugs must be taken for the entire period of TB treatment. If only one or two TB drugs are taken then the bacteria may not all be killed. They may then become resistant to the TB drugs which then don't work. If the person becomes sick again then different TB drugs may be needed.

General principles of drug treatment of pulmonary TB

Some general principles of pulmonary TB drug treatment (sometimes referred to as TB chemotherapy) are:

- Drug treatment is the only effective treatment for TB;
- Single drug treatment for active TB is associated with a substantial relapse rate. A patient is said to have a relapse if they improve whilst taking TB treatment but become ill again after they have finished their treatment. Single drug treatment is also associated with the development of bacteria that are resistant to the drug;
- Patients with active TB disease should receive at least three drugs as their initial TB drug treatment. Fewer than three drugs can result in the development of resistance;
- Never add a single TB drug to a failing regimen, a regimen simply means the course of treatment, in this instance the combination of TB drugs;
- Compliance with TB treatment is the responsibility of the treating physician as well as the patient.

TB drug treatment is sometimes referred to as antitubercular treatment or ATT.

First line drugs for TB treatment

❖ The first line drugs:

- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol

TB drugs that generally have the greatest bactericidal activity when used for TB treatment. The amount of drug that a TB patient needs to take depends on the patient's weight.

TB treatment for new patients

New patients are those who have not had TB treatment before, or they have received less than one month of anti TB drugs. New patients are presumed to have drug susceptible TB (i.e. TB which is not drug resistant) unless:

1. There is a high level of isoniazid resistance locally in new TB patients, or
 2. The patient has developed active TB disease after known contact with a patient who is documented as having drug resistant TB.
- For new patients with presumed drug susceptible pulmonary TB, the World Health Organisation (WHO) recommends that they should have six months of TB treatment. This consists of a two month intensive TB treatment phase followed by a four month continuation phase.

For the two month intensive TB treatment phase they should receive:

- Isoniazid
- Plus rifampicin
- Plus pyrazinamide
- Plus ethambutol followed by
- Plus rifampicin for the continuation TB treatment phase.

It is recommended that patients take the TB drugs every day for the six months. Although taking the drugs three times a week is possible in some circumstances, it is essential that all the recommended TB drugs are taken. If only one or two drugs are taken, then the TB treatment probably won't work, because the TB bacteria that the patient has develops resistance to the drugs. Not only is

the patient then still ill, but to be cured they then have to take drugs for the treatment of drug resistant TB. These drugs are more expensive and have more side effects.

TB treatment for other patients

A patient may not qualify for treatment as a new patient, for example because they have had TB treatment before. Then they probably need to take a different and longer course of drug treatment. If they just have the same course of TB drug treatment again, they will probably not be cured. The drug regimen or plan will need to be worked out in the same way as a TB treatment regimen or plan is worked out for a patient who needs treatment for drug resistant TB.

TB treatment failure [16]

It is often suggested that TB treatment fails because a patient doesn't take their TB drugs correctly. However there can be a number of different reasons for TB treatment failure. It is certainly true that if a patient doesn't take their TB drug treatment properly that this can lead to the development of drug resistant TB. However the patient may already have drug resistant TB. If they already have drug resistant TB, then treatment that someone is provided with may result in treatment failure even if the treatment is taken correctly.

Doctors – as a cause of TB drug treatment failure:

Inappropriate guidelines,

Non compliance with guidelines, Absence of guidelines.

• Drugs – as a cause of inadequate TB treatment:

• Poor quality,

• Irregular supply,

• Wrong delivery (dose/combination),

• Drugs are unsuitable due to drug resistance. Patients – as a cause of TB drug treatment failure:

• Lack of information,

• Lack of money for treatment and/or transport, Actual or presumed side effects,

• Lack of commitment to a long course of drugs, Malabsorption, Social barriers.

8. NEW APPROACH TO AN OLD DISEASE [17]

Recent developments show how genetic insight can help to combat the 'forgotten plague' that continues to kill Tuberculosis (TB), once such a deadly foe that it has been referred to as 'Captain of all these men of death', has been less of a problem in the UK in the last fifty years due to a combination of factors - better housing and living conditions and, of course, effective antibiotics. Even so, TB never really went away, remaining a major public health issue around much of the world and in recent years, the threat it poses to the UK population has been increasing.

Hard to treat - a modern and deadly problem

The disease is caused by the relatively slow growing *Mycobacterium tuberculosis*, and has never been easy to cure, requiring treatment over many months, sometimes years, to eliminate the infection. Poor compliance with drug treatment schedules has helped to drive the emergence of mycobacterial strains resistant to traditional drugs, which has gradually progressed to the development first of multi-drug resistant (MDR), then extensively drug resistant (XDR) strains, and finally even to effectively untreatable varieties. Since there is also no vaccine available, the spread of drug resistance means that TB is rapidly regaining prominence among threats to public health.

Linezolid in the Treatment of Multidrug-Resistant Tuberculosis.

Linezolid is a new antibiotic with activity against *Mycobacterium tuberculosis* in vitro and in animal studies. Several small case series suggest that linezolid is poorly tolerated because of the side effects of anemia/thrombocytopenia and peripheral neuropathy. To characterize our clinical experience with linezolid, the California Department of Public Health Tuberculosis Control Branch's Multidrug-Resistant Tuberculosis (MDRTB) Service reviewed cases in which the MDR-TB treatment regimens included linezolid therapy.

9. CONCLUSION

Tuberculosis is probably one of the greatest killers of all time, over the centuries taking more than 1 billion lives and up to 2 million people every year (i.e., one life every 15 seconds, as opposed to a life lost in an accident every 50 seconds). Every year, TB infects up to 100 million people worldwide, and up to 8 million develop active disease. If the tuberculosis is not treated, every source case infects, on average, 10 to 15 other persons each year. TB can be considered a social disease, disrupting families emotionally, educationally, and economically. Furthermore, only about 20% of worldwide TB cases are detected and treated successfully.

DOT strategy implemented by the World Health Organization (WHO) is probably one of the most cost-effective of all health interventions. Achievement of global targets of 70% detection and 85% cure rates would reduce incidence and mortality by 10%. The United States and several other low-incidence countries have embarked on plans to eliminate tuberculosis completely. Important elements in an elimination strategy would be to identify and treat effectively LTBI persons at risk of developing active disease, and to ensure provision of inexpensive and efficacious drugs to countries that cannot afford them. However, even though a constellation of drugs, molecular tools, and public health strategies are on the horizon, newer diagnostic tools, a better vaccine, and novel therapeutic agents are urgently needed to fight this condition more effectively.

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