**Tuberculosis Infection**

**Introduction**

Before the COVID-19 virus spread worldwide and became a pandemic in the spring of 2020, the deadliest disease on planet Earth was Tuberculosis (TB). By the end of 2022, around 10.6 million people worldwide fell ill with TB in the calendar year, and 1.3 million died. Unlike viruses such as COVID-19 and HIV, which are relatively new, the bacterium *Mycobacterium tuberculosis*, the causative agent of the tuberculosis infection, has been on Earth for possibly 3 million years, and is still a massive health crisis to this day. In the present, along with many other bacterial infections, antibiotic resistance has negatively impacted the progression of resolving the TB epidemic, leading to the birth of multidrug-resistant TB (MDR-TB). This has led to researchers attempting to find new antibiotics to treat certain TB infections, and the United Nations hopes to end the TB epidemic by 2030.

**History of Tuberculosis**

Tuberculosis has been infecting and killing humans for thousands of years and is considered one of the oldest diseases on Earth. The first written documentation of the disease originates in the 3rd millennium BCE in China, described as a “wasting disease” in the *Huang Ti Nei-Ching*, one of the earliest known medical works in the world. About 1,000 years later, a Babylonian king described a “chronic lung disease” on a stone pillar.

It was in ancient Greece when the disease was first given its first few names. In his epic poem *The Odyssey*, written in the 8th century BCE, Homer writes about a “grievous consumption which took the soul from the body and caused a person to ‘lie in sickness… a long time wasting away.’” This is another circumstance in which a disease is correlated with a person “wasting,” this time in a completely different area of the world. It is from this epic where, a few hundred years later, Hippocrates gives the disease the name “consumption.” He also names it “phthisis” after the Greek word *phthiein,* which means “to waste away.” He describes the disease affecting Greece in *Of The Epidemics* Book 1:

Early in the beginning of spring, and through the summer, and towards winter, many of those who had been long gradually declining, took to bed with symptoms of phthisis; …. Many, and, in fact, most of them died, and of those confined to bed, I do not know of a single individual survived for any considerable time, …. Consumption was the most considerable of the diseases which then prevailed, and the only one which proved fatal to many persons.  Most of them were affected by these diseases in the following manner; fevers accompanied with rigors, … constant sweats, … extremities very cold, and warmed with difficulty; bowels disordered, with bilious, scanty, unmixed, thin, pungent, and frequent dejections.  The urine was thin, colourless, unconcocted, or thick, with a deficient sediment.  Sputa small, dense, concocted, but brought up rarely and with difficulty; and in those who encountered the most violent symptoms there was no concoction at all, but they continued throughout spitting crude matters (Hippocrates, *Of the Epidemics* Book 1)

In the 2nd century CE, Aretaeus of Cappadocia described the symptoms of phthisis including the coughing up of blood from a supposed abscess in the lung, and a Greek physician named Claudius Galen of Pergamum also described this symptom, along with having a fever and sweating. Galen also found nodes, which would later be called tubercles, in the lungs.

During Hippocrates’ time, a common treatment for phthisis was milk consumption. Hippocrates recommended donkey milk, while, a few centuries later, Galen and other physicians suggested human breast milk instead. Galen also recommended patients consume wolf livers and elephant urine, as well as sending patients on voyages across the sea of Egypt and Libya, where they supposedly had more “gentle favorable winds.”

The first detailed description of consumption that more accurately describes modern knowledge of the infection came many centuries later from French physician René Theophile Hyacinthe Laennec, best known for inventing the stethoscope in 1816. Laennec used his revolutionary tool to listen to sounds lungs made when infected with consumption. The symptoms he confirmed were the presence of consolidation (airways filled with fluid or solid material), pleurisy (inflammation of tissues separating the lungs from the chest wall), and pulmonary cavitation (presence of a nodule in a consolidated area). Laennec also performed dissections on deceased patients and found tubercles inside and outside the pulmonary space, describing them as either “miliary” (millet seed-like) in early stages, or “caseous” (cheese-like) in later stages. He also noted the tubercles’ breakdown into pus and formation into cavities. He also found phthitic tubercules in other organs like the intestines, liver, and meninges, suggesting the same infection can affect organs other than the lungs.

In the late 18th and early 19th centuries, consumption became known as the “white plague,” which describes the pale pallor those infected get. It was during this period when consumption had become an epidemic in Europe, with mortality rates between 800-1,000 people per year. Physicians began to believe that the disease was infectious and not a result of genetics or cancer like previously speculated. The disease was romanticized by famous writers such as John Keats, Emily Brontë, and Edgar Allan Poe, who typically saw a dark beauty in the melancholy.

In 1834, a German physician named Johann Lukas Schönlein coined the term “tuberculosis” to describe a disease that causes tubercles but did not use it to describe what was known as phthisis and scrofula (what is now known as tuberculosis in the lymph nodes). It later took over phthisis as a term, but consumption remained a common term.

The most important event in the history of this disease occurred in 1882 when Dr. Robert Koch announced his discovery of Tubercle Bacillus, which later became known as *Mycobacterium tuberculosis*, the bacterium responsible for all these infections that caused tubercles in different organs, especially the lungs. Koch is also responsible for the discoveries of other major bacterial pathogens that cause the diseases/symptoms anthrax, suppuration, and cholera. Koch’s discovery was the catalyst for a wide range of research into the bacterium, leading to the creation of more effective treatments, and eventually of the antibiotics that are used today.

**What is *Mycobacterium tuberculosis*?**

There are mainly three types of organisms that cause infectious diseases in humans: viruses, bacteria, and fungi. *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis infection, is a bacterium. All bacteria are prokaryotic organisms. Prokaryotic cells are very different in structure than eukaryotic cells, which are the kind of cells that make up humans (which is why humans are considered eukaryotes, and bacteria prokaryotes). Prokaryotes are always unicellular, which means the entire organism is made of a single cell. They do not have a nucleus to house their DNA, which means the strands of genetic code are free-floating in the cytoplasm. Prokaryotic cells also lack many of the organelles that eukaryotic cells have. On the other hand, prokaryotic cells have an extra layer surrounding the cell known as the cell wall along with a cell membrane, while eukaryotic cells only have a membrane.

Bacteria are also incredibly different from viruses, which are also extremely common causative agents of disease. Viruses do not fit into any of the three domains of life (prokaryotes, eukaryotes, and archaea), but are still microbes that contain genetic information such as DNA and can infect a host like some bacteria. Unlike viruses, bacteria can reproduce on their own without the help of other cells, which is how they can survive outside of a host and sometimes are not pathogenic (disease-causing).

*Mycobacterium tuberculosis* is considered a Gram-indeterminate bacteria but is in many ways like Gram-positive bacteria. This means that a Mtb cell only has one membrane layer but has a thick protective peptidoglycan layer made of sugars and amino acids (the building blocks of proteins). Mtb also has a unique outer cell wall that has mycolic acid (long-chain fatty acids). Because of this, Mtb can live inside specific immune cells known as phagosomes without being broken down. Mtb is an obligate pathogen, meaning it can only live and reproduce inside a human host, even if it is not actively making its host ill.

**Latent vs Active TB**

*Mycobacterium tuberculosis* can exist in the human body in two ways: latently, where the bacteria does not make the host ill, and actively, where the host is symptomatic. In a latent infection, the bacteria are not killed, but surrounded and encased by a cluster of white blood cells called a granuloma. A granuloma can occur anywhere in the body but is most common in the lungs. The pathogen can survive for years, sometimes even decades, inside a granuloma, and the TB infection remains latent. The host will not be symptomatic and cannot spread the disease to others.

On the other hand, an active TB infection is the exact opposite. A patient’s infection may be active from the start, or it may start latent. In the latter case, the granuloma breaks open and the bacteria can reproduce and spread as intended. It is in this case that the host becomes symptomatic and can spread the disease to those around them through infectious aerosols by coughing, speaking, or singing. The bacterium typically travels through the respiratory tract and makes a home in the lungs, but it can travel through the bloodstream and infect other organs, including the kidneys or spine.

**Vaccine, Symptoms, and Testing**

There is one vaccine available to prevent getting infected with Mtb. It is called the Bacille Calmette-Guerin (BCG) vaccine. It is not widely used in the United States and is more common in countries in Asia, South America, and Europe, where TB is much more common. It is administered at birth, and some countries require boost BCG shots anywhere from 6-15 years later. The BCG vaccine is not 100% effective, meaning someone who gets the vaccine still has a chance of getting infected with Mtb. If infected, there is a plethora of symptoms a patient may endure.

The most common symptoms of an active pulmonary tuberculosis infection include:

* Consistent bad cough that lasts three weeks or longer
* Chest pains
* Coughing up blood and/or sputum
* Weakness/fatigue
* Weight loss
* Loss of appetite
* Fever/chills
* Night sweats

If someone is experiencing a culmination of these symptoms, they may get tested to see if they have TB. Two types of tests can diagnose TB. The first is the skin test, also called the Mantoux tuberculin skin test (TST). This specific test requires two visits with a healthcare provider: the first is to administer the test, and the second is for the provider to read it. Administration involves a little bit of fluid called tuberculin into the skin on the forearm. The patient will then go back home and return to the clinic 48-72 hours later so the healthcare provider can read the test. A positive TB test, meaning the patient does have tuberculosis, is indicated by a reaction on the arm. This is usually a raised part of the skin. A negative test shows no reaction to the test, and the patient does not have TB. This test is recommended for children under the age of five.

The second test is the blood test. There are two U.S. Food and Drug Administration (FDA) approved tests: the QFT-Plus test and the T-Spot test. Either can be done and have the same effectiveness. A healthcare provider will draw a patient’s blood and send it to a lab for analysis. A positive blood test means that the lab analysis found traces of Mtb in the blood and further testing needs to be done to see if it is a latent or active infection. A negative test means no traces of Mtb is in the blood sample and the patient does not have TB. This test is recommended for those who have received the BCG vaccine or cannot return for a second appointment for the TST.

In the unfortunate event that either the TST or one of the blood tests comes out positive for TB, then the patient must be put on one of the many treatment regimens to fight the bacteria infecting their body.

**Treatments**

Treatment for tuberculosis is different depending on whether a patient has the latent or active form of the infection and can differ within those parameters. Three antibiotics are used when treating latent TB: isoniazid, rifapentine, and rifampin. These medications can be taken separately or with one another and can be done with different treatment regimens. There are few short-course treatments, which involve one or more of these antibiotics and last 3-4 months. These typically have a higher completion rate, and thus have greater effectiveness. If one of these short-term treatments is not feasible, then there are two longer regimens that last 6-9 months.

When it comes to treating active TB, three regimens can be used. There is a 4-month treatment using four different antibiotics, known as the 4-month Rifapentine-moxifloxacin regimen. There are 2 RIPE regimens, that last either 6 or 9 months, using two of the same antibiotics as the 4-month plan and two different ones. The 4-month treatment is recommended for patients who are 12 years or older or have HIV receiving antiretroviral treatment (ART). The 6-month RIPE treatment is the most common regimen and can be used in most patients. The 9-month RIPE treatment is helpful for those with HIV who are not undergoing ART.

While there are already many different regimens that can be followed depending on the form of a regular TB infection, these treatments do not account for strains of Mtb that are resistant to one or more of these commonplace antibiotics.

**Antibiotic Resistance**

Due to the overuse of antibiotics in the past few decades, many bacteria that cause diseases have developed strains that have genetic mutations that make them resistant to certain antibiotics, specifically the ones typically used to treat them. This is the exact case with tuberculosis. These strains spread the same way as regular Mtb but are much harder to treat. The most common resistant strain, known as MDR-TB, is resistant to both isoniazid and rifampin, which are typically the most effective antibiotics against TB.

It is very complicated to treat MDR-TB. Fluoroquinolones, a class type of antibiotics, are commonly used in many regimens to fight MDR-TB. Specific antibiotics include levofloxacin and moxifloxacin. In total, there are 20 second-line antibiotics can be used when the strain infecting the patient is resistant to a certain antibiotic used in a typical treatment regimen. The timeline can last around 18 months, which is twice as long as the longest treatment for regular active TB. Because of this, some patients may find it harder to follow these regimens and not complete them, not fully overcoming the infection and continuing to spread the most deadly bacterium in the world.

**Conclusion**

Out of all the hundreds of known human diseases, tuberculosis is one of the oldest and is continually one of the deadliest. It has been known by many names and was once thought to be many different diseases, not one that can affect multiple organ systems. It is still a massive public health crisis in many countries around the world, and some which it is becoming increasingly difficult to treat, due to antibiotic resistance and issues with patients keeping up with their long treatment plans. There are many efforts across the planet to find new and improved antibiotics to treat this infection, with hopes to curve the increasing number of annual diagnoses by the start of the next decade. Whether this does happen or not, the efforts are still massively important and will someday hopefully lead to the end of tuberculosis’ 3-million-year reign on Earth.

**Resources**

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