History of Tuberculosis and Treatment

Tuberculosis (TB) is caused by a gram positive, acid-fast bacillus organism called *Mycobacterium tuberculosis*. TB can be found in organs such as the kidneys, spine, and liver, but the majority of cases are found in the lungs (Skolnik, 2015). The first cases of TB were seen in the bones of mummies dating back as far as 3500 BC. (Zink, et al., 2007).

TB is also known as the consumption disease, wasting disease, and the white plague. The number of cases was highest in the 18th century in Europe, causing an estimated 90,000 per 100,000 deaths (Schwartz, 2009). In English and British literature courses, you may have remembered hearing about TB in literature such as Edgar Allan Poe or Emily Bronte in the 18th century. TB has been depicted in art and in movies as the “coughing up of blood” disease. In early years, since there were no medications to treat TB, individuals were placed in isolation in sanitoriums for rest and forced good nutrition (Schwartz, 2009).

The first drug used to treat TB was Isoniazid, which was developed in 1952, followed by Pyrazinamide (1952), Ethambutol (1961) and Rifampin (1966) (NIAID, 2016). TB has been around for centuries, yet so few strides in medications have been made in treating this preventable disease.

Tuberculosis Today

As of 2014, there have been 9 million new cases of TB reported worldwide, 1.5 million deaths, and 13% new cases of TB as co-infection with Human immunodeficiency virus (HIV). Of the 9 million new cases of TB reported, an estimated 40% were reported among women and 60% among men (World Health Organization, 2014a). 80,000 deaths were reported among children in 2014 (World Health Organization, 2014a). Asia has the highest incidence (new cases reported) of TB at 56%, followed by Africa at 25% (World Health Organization, 2014a). The highest number of deaths from TB annually occurs in Africa as does the highest number of individuals with HIV co-infection (4 of 5 individuals). (World Health Organization, 2014a). In the United States, 9,412 cases of TB were reported in 2014. (Scott, et. al, 2015).
A breakdown of TB incidence across the United States revealed a higher incidence of TB in the larger, more crowded states, such as California, Florida, New York, and Texas. TB in the United States is reported more frequently among non-U.S. born individuals, which would account for the higher rates in the border states of California, Florida, New York and Texas (Scott, et. al, 2015).

**Multidrug-Resistant Tuberculosis**

Sometimes TB becomes multidrug-resistant TB (MDR-TB), which means the bacteria cannot be treated by several different drugs. In MDR-TB, the bacteria are resistant to Isoniazid (INH) and Rifampin, which are the two strongest anti-TB drugs. The most common reason for developing MDR-TB is non-compliance with medication regimen (World Health Organization, 2014b). In addition, MDR-TB can occur if a prescriber does not prescribe the correct dose, appropriate medication, or length of therapy. Approximately 5% of new cases of TB world-wide annually are considered to be multidrug-resistant (World Health Organization, 2014a). Twenty percent of these individuals have received prior treatment for TB (World Health Organization, 2014a). India and China have the highest rate of multidrug-resistant TB due to lack of access to treatment, poor quality of drugs, and lack of knowledge among prescribers (World Health Organization, 2014a).

**Extreme Drug-Resistant Tuberculosis**

Extreme drug-resistant TB (XDR-TB), or extensively drug-resistant tuberculosis, is more severe than MDR-TB. An individual is considered to have XDR-TB if they are unsuccessfully treated by a fluoroquinolone [levofloxacin (Levaquin)] and one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin) (World Health Organization, 2014b). These individuals are also resistant to the first-line drugs that a patient with MDR-TB is resistant to, Isoniazid and Rifampin (World Health Organization, 2014b). In developing countries, it is difficult to know how many individuals truly have MDR-TB or XDR-TB due to low quality labs with minimal resources. In order to diagnose MDR-TB or XDR-TB, a drug susceptibility test (DST) is performed on an isolated sputum specimen to determine if the mycobacterium tuberculosis growing is resistant to particular drugs (World Health Organization, 2014b).

**Total Drug-Resistant Tuberculosis**

Total drug-resistant TB is just as it sounds. There are currently no first- or second-line drugs that can treat this resistant strain of TB (Dalton, et. al 2012). Total drug-resistant TB was thought to be seen first in Italy around 2007. There are now cases in India, and a potential outbreak in Africa. The World Health Organization (WHO) does not recognize the actual definition of Total Drug Resistance because it meets
the same criteria as XDR-TB and does not meet testing criteria for TDR-TB; however, there are documented cases worldwide of TB that has not responded to any treatment (Dalton, et. al 2012).

Latent Versus Active Tuberculosis

Latent TB is described as when a person has the disease, but the microorganisms are dormant, or “sleeping,” within the lungs. Only 5-10% of persons with latent TB will develop active TB, and half of these individuals will progress to active TB within two years (Centers for Disease Control and Prevention, 2014a). People with latent TB still need to take medication in order to kill the TB causing bacteria. Persons with latent TB are not able to spread the disease to others because the disease is dormant. If a person with latent TB contracts HIV or any other illness weakening the immune system, it is likely the “sleeping disease” will awaken.

Pathophysiology

TB occurs when the bacteria Mycobacterium tuberculosis enters the lungs initially. The inhaled particles then lodge in the bronchioles and alveoli where they replicate and spread to other parts of the lungs and body via the lymphatic system (Herchline, 2014). In latent TB, these organisms remain inactive. If the patient develops a weakened immune system, has not received treatment for latent TB, or these organisms reactivate on their own, the latent TB has now become active disease. This disease can now be spread to other individuals.

Transmission

The most common way TB is spread is through the air. If a person coughs, sneezes, talks, or laughs the bacteria can transfer to that person via droplet nuclei, which are microscopic particles. These particles can remain in the air for hours, which can increase the risk a person has for acquiring the disease (Centers for Disease Control and Prevention, 2016a). Although a person can inhale particles and become infected with TB, the bacteria are usually dormant, or latent, and the person is not contagious. This is why treatment is essential, so the bacteria don’t “wake up” and turn into active TB disease. It is rare for an individual to contract TB from a child under the age of 10. There are some additional factors associated with transmission. The number of organisms expelled into the air can have an impact on transmission. Did the person expel 5 or 5 million organisms when they coughed? The concentration of organisms is important to consider. Was the contagious person housed with ten other individuals in a 300 square foot house? Other important factors to consider are the length of time a person was exposed and how their immune system is functioning. If the person was only exposed for 2 minutes and
has a 100% functioning immune system, they are more likely to not contract the disease versus someone with HIV exposed for a few hours.

Envision this: John Doe boards a full flight from Dallas to Mexico to assist with a medical mission trip. He has undiagnosed active TB. He coughs, leaving these contagious particles in the air on the airplane throughout the flight. While in Mexico, he is housed in crowded conditions with many people, speaking to many individuals, laughing, and coughing, expelling these particles into the air. Let’s say 200 of the 5,000 people he comes into contact with in Mexico end up inhaling these infected particles. Five days later, John boards a full flight to New York, again exposing many people to TB. He spends three days in New York, walking the crowded streets, talking and coughing, again exposing many individuals to TB. Let’s say 400 of 20,000 people have inhaled the particles. John Doe then boards a full flight to Japan where he attends a conference in a small space of 3,000 individuals, exposing all these individuals to TB. Each time an exposed person gets off the plane, switches planes, and goes back home to their state or country, that person, if infected, will expose many other individuals to TB. This goes back to the statement that disease knows no boundaries. This is now a pandemic (it already was, but that would still be pretty bad).

**Prevention of Transmission**

As healthcare providers, we all come into contact with individuals who have TB, so we are all at risk for contracting the disease. There is a vaccine to prevent TB transmission called Bacille Calmette-Guérin (BCG). Although this vaccine can be used for any individual, it is primarily used in developing countries to protect children against TB. BCG vaccine is not used without weighing risk versus benefit, because it has been found that this vaccine may be associated with developing TB in individuals with weakened immune systems (Ancelet, Aldwell, Rich, and Kirman, 2012). The BCG vaccine is very rarely used in the United States, primarily because it can cause a false positive result on a Tuberculin Skin Test (TST), thus making it more difficult to screen for TB.

As with any disease, educating individuals on preventive measures is essential. Covering the mouth when coughing, laughing or sneezing, or wearing a mask is an effective way to prevent transmission of TB. If more people utilized these preventive measures, there would be fewer new cases of TB and fewer deaths.

Prevention is crucial for a disease as contagious as tuberculosis. Early detection allows a person to be treated quickly and will prevent many new infections. People at high risk for TB should have annual testing, such as a Tuberculin Skin Test (TST). Starting treatment with latent TB will prevent the disease from becoming active (Mayo Clinic, n.d.). Keeping your immune system healthy by eating properly and
getting plenty of sleep also aids in preventing disease. Most importantly, finishing the entire course of treatment will kill all the bacteria instead of just creating MDR-TB, which can be spread. A person can prevent the spread of the disease by not going out until after the first few weeks of treatment (Mayo Clinic, n.d.).

Clinical Manifestations

*Latent*

Signs and symptoms of latent TB are similar to those of any other latent disease. When the disease is inactive or just “sitting in the lungs” the individual typically does not exhibit any signs or symptoms of the disease. Individuals with latent TB cannot spread the disease to others but are at likely to develop active TB themselves.

*Active*

You are likely familiar with the many signs and symptoms of active TB. These include night sweats, fever, fatigue, chills, anorexia, unexplained weight loss (weight loss without dieting), productive cough, and hemoptysis (bloody cough). Some patients may not go to the healthcare provider because they fear they may have HIV or cancer. People with active TB are capable of spreading the disease to others.

Risk Factors for Tuberculosis

The immune-compromised individual is the group at highest risk for contracting TB, which is why co-infection with HIV is common. The HIV positive person's immune system is at minimal function and susceptible to infection.

You probably know that living in crowded conditions places a person at high risk for TB. This includes individuals living in homeless shelters, prisons, refugee camps, and areas of developing countries where overcrowding is a problem. Additional risk factors include smoking, drinking alcohol, and diabetes (Skolnik, 2015).

Citizens of the developing world are at higher risk than those living in developed countries (Gupta et. al., 2009). One reason for this is that vaccinations and treatment options are limited, largely in part due to lack of funding, in the developing world. People living in developing countries are also more likely to be undernourished, which increases risk for contracting TB. Undernourished people have a weaker immune system, thus making it easier to contract a disease (Gupta, et. al, 2009).

According to Robert Tauxe of the CDC (2015), drinking raw milk or unpasteurized milk places an individual at higher risk for contracting TB. This is because bovines can be infected with mycobacterium...
tuberculosis, and when milk is not heated to kill germs (pasteurization process), the bacteria can be transmitted to humans.

Healthcare workers are at high risk for contracting TB because we are in close contact with infected individuals. A scenario I often think of that occurred on more than one occasion. Doesn’t it always make your day to find out that there is an admission, and the nurse has not received a report on them from another facility? The patient gets situated in a semi-private room after having been transported up and down hallways. The nurse at the transferring facility finally calls in the report. You learn that the patient has a positive tuberculin skin test with weight loss and hemoptysis, and you and many others have now been officially exposed to TB.

Diagnosis

_Tuberculin Skin Test (TST)_

There are several methods you might see used to diagnose TB, but we will discuss the most commonly used. One test used in many settings is a TB skin test (TST), or Mantoux test. It is administered with a very small amount (0.1mL) of purified protein derivative (PPD) injected just beneath the skin (intradermal). Within 48-72 hours, the person injected with tuberculin returns to the clinic and the healthcare provider looks at the site the tuberculin was injected for induration (raised, palpable area or edema) (Centers for Disease Control and Prevention, 2012b). There are pros and cons about using the PPD skin test. Some pros include that it is inexpensive and easily available. The downfalls of using PPD as a diagnostic tool include the individual may not return to have the test read, the individual “reading” the test may be untrained or have a different interpretation of what “induration” may be, and if a person has had the BCG vaccine, they may react positively to a skin test. It takes a person 2 to 12 weeks to actually contract the disease and show a reaction on a Tuberculin Skin Test (TST), unless they are immunocompromised, in which case they may test positive earlier (Centers for Disease Control and Prevention, 2012b).

_Interferon-Gamma Release Assay (IGRA) Blood Test_

Another method of diagnosis is blood testing. There are two types of Interferon-Gamma Release Assay (IGRA) approved for use in the United States. The QuantiFERON-TB Gold In-Tube Test (QFT-GIT) and the T-Spot TB Test (T-Spot) are IGRA that mix antigens and controls with fresh blood samples (Centers for Disease Control and Prevention, 2012a). Both tests measure the amount of interferon-gamma (IFN-g) released when an individual’s white blood cells interact with an antigen that is derived from mycobacterium tuberculosis. Advantages to IGRA testing is that the patient only comes to the clinic once, results are ready within 24 hours, and individuals that have had the BCG vaccine do not show a
false positive result. Disadvantages include cost (IGRAs are expensive), blood must be tested within an 8 to 30 hour window while the white blood cells are still viable, and they are not useful on children below age 5 or immunocompromised individuals (Centers for Disease Control and Prevention, 2012a).

**Acid Fast Bacillus (AFB) Smear**

A sputum culture, called an Acid Fast Bacillus (AFB) Smear is used to determine if the person has active TB infection. The culture determines if the infection is confined to the lungs or if it has spread to other organs, and will also determine which antimicrobial agents are best suited to effectively treat the disease (Centers for Disease Control and Prevention, 2013). An AFB can also be used to diagnose MDR-TB or XDR-TB. In order to collect the specimen, a 20mL container should be used. The specimen should be collected in the morning after the individual has rinsed their mouth. At least 5mL of sputum needs to be collected. It is important to instruct the patient to cough deeply, expelling mucus instead of saliva. The sputum should be collected on three consecutive days, rather than on the same day (Centers for Disease Control and Prevention, 2013). One thing to keep in mind: you don’t want to leave the sputum container with the patient and instruct them to work on a sample all day. I have seen this so many times in the hospital setting: a sputum container is left with the patient, and they are told to “work on it” until they meet the 5mL mark. When the container is removed from the room, there is 5mL of a sputum/saliva mixture from five days-worth of collection. This would not yield a very accurate result.

**Chest X-Ray**

A chest x-ray is not necessarily used to diagnose TB. If a person has a positive TST, a chest x-ray is often ordered to determine if a mass is present. If a mass is present, this is often followed by a bronchoscopy with biopsy to determine if the mass is cancer, TB, or another organism.

**Treatment for Latent TB**

Very rarely is only one drug used to treat TB, but it is common in patients with latent TB. Isoniazid can be prescribed daily or twice weekly for 6 or 9 months. Rifampin is also administered as a single-drug therapy daily for 3 or 4 months (World Health Organization, 2015a). Even with single-drug therapy, direct observation therapy (DOT) is recommended to ensure the patient is taking the medication as prescribed. DOT means that to ensure compliance and prevention of MDR-TB, a healthcare provider observes the individual taking each dose of the medication to confirm that the entire course of treatment is completed.

A 12-dose regimen of isoniazid and rifampin given weekly for 12 weeks is a proven effective choice for certain individuals (World Health Organization, 2015a). According to the CDC (2016b), a recent study
determined that this dosing was just as effective as a daily or twice weekly regimen for 4-6 months, as long as it was administered via DOT.

**Treatment for Active TB Disease**

First-line drugs used to treat active TB disease can include isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. Streptomycin is an injectable group two drug, but is considered first-line therapy for TB. If a patient has not received anti-tuberculosis drugs before, such as for treatment of latent TB, then shorter therapy can be prescribed. WHO recommends two months of intensive therapy, which includes isoniazid, rifampin, pyrazinamide, and ethambutol together, followed by four months of isoniazid and rifampin (World Health Organization, 2010). It is recommended these drugs be taken on a daily basis unless kidney or liver function tests require the drugs to be on a schedule of three times weekly (World Health Organization, 2010). The prescribed drugs should be taken all together, at the same time, under DOT. If the patient does not take the medication regimen as prescribed, they may develop MDR-TB, which is much more difficult to treat.

**MDR-TB therapy**

Patients with MDR-TB are resistant to isoniazid and rifampin, which are two drugs of choice from first-line category used to treat TB. Many times, the patient is resistant to all first-line drugs. A culture will determine which drugs the patient is resistant to, which will guide the prescriber in selecting the appropriate medication. Second-line parenteral drugs used to treat TB include kanamycin, amikacin, and capreomycin. Fluroquinolones, which are also used to treat MDR-TB include levofloxacin, moxifloxacin, gatifloxacin, and ofloxacin. Drugs used to treat MDR-TB from the second-line bacteriostatic category include ethionamide, prothionamide, cycloserine, terizidone, and p-amniosalicylic acid (World Health Organization, 2014b). Clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, clarithromycin, and imipenem are listed as group 5 drugs used to effectively treat MDR-TB. Group 5 drugs are not commonly used, but are thought to possibly decrease the length of treatment for MDR-TB (Dooley, et. al, 2012).

WHO recommends a medication regimen which includes four second-line anti-tuberculosis drugs (discussed in the above paragraph) and pyrazinamide (unless resistance is confirmed). The preferred regimen is pyrazinamide, a fluroquinolone, a parenteral agent, ethionamide, and cycloserine. A drug from the group 5 category can be used if the individual has severe TB disease, or if a fourth drug is needed for the standard regimen (World Health Organization, 2014b). The recommended regimen for individuals with MDR-TB are dependent on HIV status, if the patient is pregnant or breast feeding, and if the individual is a child. It is believed that treatment less than eight months is not as effective in treating MDR-TB (Fortun, et al., 2007). WHO recommends an intensive treatment period of six months, followed
by a minimum treatment length of four to 18 months past culture conversion. As with any disease, duration and medications prescribed depend on your client’s history and disease process. Culture conversion occurs when a sputum culture converts from positive to negative, determining treatment was effective.

**XDR-TB Therapy**

If a client is resistant to all first-line drugs and most or all of the second-line drugs, then options are very limited. The prescriber may use antibiotics from the group 5 category if the client is not resistant to those as well (World Health Organization, 2014b). The medication regimen is then comprised of medications to which the client’s infection has been shown to be sensitive. The mortality rate is very high among individuals with XDR-TB, especially individuals with HIV co-infection (World Health Organization, 2015b). Sirturo®, also known as bedaquiline, is a drug that was recently approved by the FDA for last-resort combination therapy of MDR/XDR-TB. This drug should be used as a last alternative because it has severe side effects, including dysfunction of the heart’s electrical system, leading to death (World Health Organization, 2014b).

**Noncompliance**

The most common cause of non-compliance is multidrug therapy. Individuals may grow tired of taking multiple drugs several times per day for several months and quit taking them because they feel better. These regimens are also conducive to patients forgetting to take their medications. When a person stops taking these drugs, the bacteria is still in their lungs developing multidrug resistance (MDR-TB), and the disease becomes more difficult and more expensive to treat (Centers for Disease Control and Prevention, 2016b). Individuals with a co-infection of HIV are less likely to comply with treatment because of the daily doses of multiple medications (Janakan and Seneviratne, 2009).

Another reason for non-compliance is something I am sure you have all encountered among your patients: lack of insurance or funding. If individuals cannot afford the medication, they may be too ashamed to ask for assistance and just not refill their medications.

Other factors contributing to non-compliance includes being of male gender, living alone, and experiencing side effects of the medication (Janakan and Seneviratne, 2009).
Interventions for Patients with TB

It is important to ask your clients if they have HIV/AIDS infection in order to determine risk of TB. You should also determine what medications they currently take, including vitamins or herbal remedies. There are many drug-drug interactions with drugs used to treat TB and other medications.

When caring for a TB-positive patient in the hospital setting, as you know, it is important to place the client in respiratory isolation to protect other clients. This means the patient will be in a private room and have a negative air pressure machine in the room. The purpose of a negative air pressure machine is to keep air from flowing through the duct work into other patient rooms. Most negative air pressure machines filter the air prior to expelling it outside.

All healthcare providers should wear a TB mask with at least an N95 respirator that has been fit tested. The N95 respirator has a filter that filters 95% of air particles prior to the wearer breathing it in (Centers for Disease Control and Prevention, 2014b). It is important the wearer has had a fit test to ensure appropriate size so that air particles infected with TB do not sneak in through gaps in the mask. If you are transporting a client outside of their room, you need to place a mask on the infected individual.

Education begins the first day you meet the client, whether it be in a hospital setting, clinical setting, or in a hut in a developing country. You will need to educate the patient on methods to prevent TB, such as covering a cough, avoiding crowds if possible (or wearing a mask if they will be among crowds), and the importance of compliance with the prescribed TB treatment regimen. The patient needs to understand every side effect of each drug. For example, the patient will need to know that rifampin will turn urine, sweat, tears, and contact lenses orange so they do not panic when they first notice these changes.

Education is the key to prevention.

Global Partnerships to Stop TB

There are a variety of organizations who share a common goal of reducing the cases of, and eventually eliminating TB worldwide. The Bill and Melinda Gates Foundation was developed to provide grants to fund research which will develop vaccines, new drugs, and better diagnostics for TB and other “neglected” diseases worldwide (Bill and Melinda Gates Foundation, 2015).

Stop TB Partnership was initially established in 2001 under the WHO umbrella. Their vision is a world free of TB by eradicating TB through the development of new drugs, vaccines, and stronger anti-TB programs in developing countries (STOP TB Partnership, 2016). Stop TB ensures that every high risk individual has access to TB testing worldwide and that every individual has access to TB treatment through funding and allocation of human resources (Stop TB Partnership, 2016).
The United Nations (UN) was developed in 1945 and has a membership of many countries world-wide. The UN works to ensure that human rights are protected and to improve lives of those less fortunate. The millennium development goals were developed by the UN in hopes to eradicate multiple diseases, such as TB and Malaria, and to improve poor conditions in developing countries (United Nations, n.d.).

WHO falls under the UN umbrella as the public health sector. WHO provides leadership and guidance to countries in developing global policy, current evidence-based practice, and support for member countries. WHO also provides the appropriate resources to aid countries worldwide in eliminating TB (World Health Organization, 2016).

The TB Alliance is a non-profit organization focused on developing new drugs to fight TB in a shorter time for less money. The TB Alliance works with global, regional, and national stakeholders to develop drugs that have an ability to be used globally (The TB Alliance, 2016). Current treatment for TB requires many pills, several times per day, which raises the incidence of non-compliance. The TB Alliance strives to create new treatments, such as a one drug equivalent of a typical “three drugs four times daily” regimen (The TB Alliance, 2016). The TB Alliance is also a member of Stop TB, created by WHO, therefore, they are committed in providing treatment that is easily accessible by all individuals worldwide (The TB Alliance, 2016).

CDC Division of Tuberculosis Elimination (DTBE) has developed policy for reducing the threat of TB globally. CDC is an essential partner in eliminating the threat of TB on a global basis and focuses on keeping the world informed of outbreaks of infectious disease, current evidence-based recommendations for treatment, diagnosis, and care for clients with TB.

Conclusion

TB is a global health problem that is receiving attention from a number of powerful agencies with the goal to eradicate the disease. Until that time, healthcare professionals will continue to play a pivotal role in the prevention, screening, diagnosis and treatment of patients with the disease. Awareness and patient education is the key to reduce transmissions and improve health globally.