Advanced Concepts in Pediatric TB: Introduction

Welcome to the first of eight sessions on Advanced Concepts in Pediatric Tuberculosis sponsored by the Southeastern National TB Center. Today we present the introduction "Mycobacteriology, Pathogenesis and Epidemiology of Pediatric TB."

Today's presenter is Dr. Ana Alvarez. Dr. Alvarez is a graduate of the School of Medicine Universidad de Panama. She did her residency training in pediatrics at Metro Health Medical Center, and her fellowship in pediatric infectious disease at Rainbow Babies and Children's Hospital Case Western Reserve University, both in Cleveland, Ohio. Since 2005, she has been the pediatric consultant for the Southeastern National TB Center and faculty of the Comprehensive Clinical TB course, sponsored by the SNTC.

In 2013 she was appointed by the Secretary of Health and Human Services to the Advisory Council on the Elimination of Tuberculosis of the CDC. Dr. Alvarez is currently an associate professor at the University of Florida, College of Medicine in Jacksonville, Florida, in the division of Pediatric Infectious Disease and Immunology. It's my pleasure to turn this call over to Dr. Alvarez. Ana?

Yes, I'm here. Thank you, Donna -- Karen. All right, let's go ahead and start. Welcome everybody. We'll start with the objectives. So my goal is that by the end of this presentation you will be able to recognize the epidemiology of tuberculosis in the United States and in the world; identify some of the typical microbiologic characteristics of mycobacterium tuberculosis, describe the pathogenesis of TB; and recognize the risk factors for tuberculosis infection and disease.

I'd like to start with a case to illustrate several points. So this is a six-year-old Boznian male who presented to our local emergency department with a one-week history of fever and occasional vomiting. He had no history of cough, difficulty breathing, or weight loss.

His social history was relevant because he and his parents and a younger sibling had immigrated to the United States from Bosnia about six months before he presented to the emergency room. At that time, they had gone through the refugee clinic, and all of them had been screened for TB via PPDs. Both the parents were tested positive but had negative chest x-rays, and they elected not to take medicines that were offered. Both children at the time were negative, the patient and the other sibling.

In the ED, his temperature was 100.3, but he was not in any respiratory distress. He was awake, alert. His exam was remarkable for decreased breath sounds in the right lung field, but the rest of his exam was within normal limits. So based on this, the ED performed a chest x-ray. As you can see in this x-ray, two-thirds of the right lung are actually affected. You can see this. There is pleural thickening, so you can see that there is a pleural effusion there, probably a large one. We can't really see how much of the lung parenchyma is involved, but presumably some is. It's hard to define what is what in here. He also had a lateral decubitus x-ray to see if there was layering of the fluid, and that and there was no layering.

So he was admitted to the hospital, and he was started on IV antibiotics. Initially he was started on Ceftriaxone, and then the next day they added Vancomycin. After three days of IV antibiotics, he continued to have fever daily, and very high spikes, but without any changes in his respiratory status. At that point, TB was consulted.

So these are the questions that I want you to think about, and we will come back to those at the end of the presentation. So at this point, think about what is your differential diagnosis? Would you do any further evaluation? Do you want to repeat the PPD? What would be the best, to send for cultures and what other tests you could do to try to decide what this patient has? We will go back to those at the end.

Let's jump to review the epidemiology of TB. First, in the world, tuberculosis is the second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. It is estimated that there are 1.7 billion persons infected with TB worldwide. This is approximately one-third of the world's population that has this infection. In 2012, there were 8.6 million cases of TB, and 1.3 million deaths due to TB in the world. Over 95% of the TB deaths occur in low- and middle-income countries. About 80% of the reported cases of TB in the world occur in 22 countries that are considered high-risk countries.

In this map you can see in the bright orange is the countries that have rates that are more than 300 cases per 100,000 population, and you can see that most of the countries are from Africa, especially Sub-Saharan Africa, and some countries in Asia. The country in America that has rates similar to those is Haiti. Otherwise the other countries in America are not as high.

So TB is the leading killer of people living with HIV, costing one-fifth of all deaths related to that. At least one-third of the people living with HIV in the world in 2012 were infected with TB, and people with a co-infection are 30 times more likely to develop active TB disease than people without HIV. So HIV and TB form a very, very bad combination. Each of these organisms affects and stimulates the progress of each other. In 2012, about 320,000 died of HIV-associated TB, and approximately 20% of the deaths among people with HIV are due to TB.

In this map you can see the countries where there is a high prevalence of the co-infection of HIV and TB. In red is shown the countries at high rates of co-infections that are 50 or higher per 100,000 population. And, again, you can see that the most significant countries are the countries in the Sub-Saharan Africa. However, in the lighter orange, you can see that rates of 20 to 49 cases per 100,000 of the co-infections, and in the Americas, the most important country in this rate range is Brazil. But there are other countries obviously in the whole world.

Multi-drug resistant TB, what we call MDR-TB, is present in virtually all of the countries that are plagued the WHO. 450,000 cases of MDR-TB were reported in the world in 2012. More than 50% of those were in India, China, and the Russian Federation. And of the cases of MDR-TB, about 10% of those have what we call extensively resistant drug TB, which is XDR-TB. The estimated number of cases of TB each year is declining, but very, very slowly. The death rate dropped from 45% between 1990 and 2012. An estimated 22 million lives are saved through the DOT program, which stands for Direct Observe Therapy course, and the Stop Strategy recommended by the World Health Organization.

Now, looking specifically at children, in 2012 the WHO estimated that there were 530,000 TB cases in children. Of these children, 74,000 were HIV-negative children that died of TB just in that year, in 2012. However, according to a recent study, using a mathematical model and taking into consideration the family dynamics and exposures in the different countries, in this study the authors feel that the actual number of TB cases is underestimated. They estimate that the real number is probably 25% higher than what the WHO estimates, and this is because the WHO estimates based on reporting of pediatric cases; however, as you know, confirmation of TB in children is difficult and very challenging, so underreporting is extremely common, especially in the areas in the world where TB is more common.

Now, turning to the epidemiology in the United States, we know that since the anti-TB drugs were available in the 1940s, the drops of TB decreased dramatically in the United States, to the point that in the late '70s early '80s, it was estimated that maybe by the year 2000 we would have eliminated TB from the United States. However, in 1985 something that was not estimated or taken into account occurred, and that is that the cases of TB started increasing in the United States, and there was a significant increase from 1985 to 1992.

The factors that contributed to the increase in the TB morbidity during that time was the occurrence of the HIV epidemic in the United States. Immigration from countries where TB was common increased, and also we started seeing transmission of TB in congregate settings, just like nursing homes, and jails and prisons. The other thing was the development of multi-drug resistant TB, which started popping up a lot more frequently. And at the same time these things were happening, there was a significant cut in the funding for the local TB programs.

So if we go back to the previous graph, you can see that since 1993, though, the rates of TB, the number of cases of TB in the United States, have continued to decrease, and every year it has decreased some. At the beginning, that decrease was more remarkable, and then in the last few years, it's kind of plateaued a little bit, but every year it has been less. The reason for that is because of increased funding to TB programs locally, which let them have increased efforts to identify people with TB promptly, initiate

appropriate therapy, and ensure completion of therapy. So these patients that are identified with TB are followed until the completion of therapy. Because of that, you see the decrease in the rates.

However, we have still some barriers for the elimination of TB in the United States, and this is largely because the populations that have TB in the United States are high-risk populations, and in these populations it is difficult to detect TB, diagnose, and treat. The other thing is the global TB epidemic is persistent, and the immigration of people from all over the world is still happening in the United States. Currently the control measures are limited. We need new tests, new vaccines, new drugs.

In this map you can see the TB rates by state. The states in blue represent states that have rates above the national average. The national average is 3.2 per 100,000 per population. That was in 2012. And you can see that there are several states that have more than that. In particular, there are four states that carry the TB bacillus in the United States, and those are California, Texas; Florida, and New York.

If we look at the TB cases reported by age group, you can see that the pediatric cases actually represent only 15% if you go from zero to 24 years of age; 5% is less than 15 years of age; and 10% between 15 and 24 years of age. Most of the population with active cases of TB are in the 24 to 44 age range, and some in the 45 to 64 age range, which means that this disease really affects people that are in their productive age.

When we look at the cases of TB and divide them, the rates, divide them by if the patients were U.S. born versus foreign born, you can see that the rates in the foreign born are extremely -- much higher than the rate in the U.S. born. In here the rates in the foreign born is represented in red, and the rates in the U.S. born are represented in blue, and the green represents the total population.

If we look at this in a different way, this graph really represents the number of cases in foreign-born persons in the United States and the trends. As you can see, the number of cases actually -- the actual number of cases have remained relatively the same. Only until the last three or four recent years you see a decrease in the actual number of cases. The decrease in the number of total cases in the United States have occurred mostly because of the implementation of the strategies have affected more the U.S. born population than the foreign born population. And because of that, the line here represents the percentage of total cases in the U.S. of foreign born people.

So in 2012 this percentage was more than 60%. So more than 60% of the total cases of TB in the U.S. occurred in foreign-born persons. This would be important to know. These are the countries from which these cases come, and, you know, it's no surprise for anybody that Mexico would be the first one, just because they're our neighbors. But the other ones are the Philippines, India, Vietnam, China, Guatemala, and Haiti.

Now before we look in specifically at the epidemiology of pediatric TB in the U.S., it's important to know how the cases are discovered, especially in pediatrics. So you can discover the cases actively or passively. Active means that the patients are identified through contact investigation and screening of high-risk groups. That just means that the patients are symptomatic present to the hospital, or to the doctors, and then they are diagnosed with TB because of their symptoms. Obviously, ideally, we would recognize and discover these cases by contact investigation and screening because these patients are not that symptomatic. They may have no symptoms or may have very mild symptoms.

In this graph we can see the division by age group of the pediatric cases. This graph only represents the patients that are younger than 15 years of age. But the important thing in this graph is that 60% of the cases occur in children less than four years of age, between four and less than that. And that is important to remember, because they represent, really, a high-risk population, as we're going to discuss a little bit later.

In 2012 there was a study published in Pediatrics, and it's the first time that we take a look at this data, including the adolescents. So in this study, they include the patients from zero to 18 years of age, and

also included that, that before was not recorded, and it's the first time that we can take a look at this; data on the parent or legal guardian country of origin, and if they have lived internationally.

So a total of 2,660 cases were identified, and of those, at least one-third were symptomatic. So those were discovered by passive investigation. But of all the cases, 75% had what we call an international connection. So they were either foreign born or have foreign born parents, or have reside outside of the United States. So 75% of all the cases in pediatric and adolescents have an international connection. Only 31% of the cases were actually foreign born, and of those, 52% were teens who had been in the United States for three-and-a-half years or more before the diagnosis. So these highlight or have a missed opportunity, because these patients should have been screened when they had arrived to the United States, but they have been here and they just presented with active TB disease.

Among the U.S. born, 66% had at least one foreign-born parent, and 13% had lived outside of the United States for more than two months. So a lot of things we can gather from this study. But it does highlight the importance of the screening questions that we do in our primary care settings about screening for risk factors for TB, and besides asking the country of origin, we need to ask about the country of origin of their parents and the history of living outside of the United States. It would be important things to include in our screening questionnaires.

Now, moving along to another area that is important to know is the rate of antidrug resistance. So you can see that the line on the top, the green line, represents Isoniazid resistance, and the line on the bottom represents MDR-TB. Fortunately the rate of MDR and Isoniazid resistance have remained relatively stable, with a little bit of an increase in the Isoniazid resistance. But the numbers are low. Isoniazid resistance is less than 10%, and the MDR is less than 2%. It's like 1.2% in 2012.

But when we look at these rates, dividing the population in U.S. born and foreign born, we can see that the foreign born have double the rate of the U.S. born. This graph, in this graph the primary Isoniazid resistance is represented, but the same phenomenon occurs when you look at MDR TB among U.S. born and foreign born. So the rates are low; however, the rates in foreign born are double the rates in U.S. born. So it's important to know this, because when you are evaluating a patient that could potentially have TB, if that person is foreign born, you have to take into consideration the possibility of either INH resistance or MDR TB.

XDR TB, which is defined as TB that is resistant to INH, Rifampin, Fluoroquinolones, and at least one of the injectable drugs, doesn't have a clear epidemiology or a clear trend in the United States. Fortunately the cases have remained -- the number haves remained low. In 2012 there were only two reported cases in XDR in the United States. And in this graph we see the rates of co-infection with HIV, and you can see that it has decreased significantly, and it we remains low in the U.S., about 10% for all ages, and a little bit higher for the patients that are between 25 and 44 years of age.

Okay, time to change gears, and now we're going to talk about microbiology. Mycobacterium tuberculosis complex is the etiology of TB, and it includes Mycobacterium tuberculosis, which is the most common species that causes TB, but also includes Mycobacterium bovis and Mycobacterium Africanum. They belong to the order of the Actinomycetales and the family of Mycobacterium BCA.

If you gram stain specimens, they may show a reaction weekly gram positive or not at all. However, you could see in the gram stain the presence of some organisms, so they are so-called "ghosts" because sometimes you can't really define if they're gram positive or not. So these organisms are acid-fast bacteria, which means that they are resistant to decolorization by the acids used during staining procedures.

The three classic staining of staining procedures are the Ziehl-Neelsen stain and the Kinyoun method, and in these the bacilli stains at a bright, bright red, under a background of blue or green, but there's also the Auramin-Rhodamine stain, which is specific -- it's very sensitive for AFB, and this uses fluoroscopy, and you can see that in the picture to the far right.

So these organisms are fairly large. They're nonmotile rod-shaped bacteria. They are obligate aerobes, and this probably explains a little bit why they like particularly the well aerated areas of the lungs, the upper lobes of the lungs. They're also facultative intra-cellular organisms, so they actually live in the macrophages and can persist in the macrophages for long periods of time. The cell wall of these organisms is very interesting. It does have peptidoglycan, but 60% of the cell wall is actually lipid, and it is known that a lot of the virulent factors for Mycobacterium resides in the cell walls.

In vitro, it only grows in special media. So we have solid media and liquid media. The classic solid media is the Lowenstein-Jensen medium, which is egg-based, but also the middle group medium, which is agar-based. They also grow well in liquid media, and this is the media that we use in automated radiometric systems like BACTEC. The difference in growth is significant, because in solid media it takes six to ten weeks to grow, but in liquid media they grow a lot of faster, and you can see growth even as short as one week to six weeks.

And this picture shows the colonies growing in the agar media, the small buffered colonies. If you actually stain these colonies and put them on a film, you can see what we call "serpentine quartz," and this is probably one of the -- produced by one of a billion factors in the cell wall, what we call the "quartz factor." And this quartz factor is important because it actually is [indiscernible] for the human cells, and it also inhibits the migration of [indiscernible]. So it's important factor in the virulence of the organism.

Now let's talk about pathogenesis of this disease. So the first thing that we need to know is that there are -- like I said in the epidemiology, there are persons that have higher risk for exposure or infection to TB, and it's important for us to know which are the populations that have higher risk. So this includes close contact of persons known or suspected to have active TB, foreign born persons from areas where TB is common, or persons that visit those countries, the residents and employees of high-risk congregate settings, and this includes nursing homes, jails and prisons. Also, the medically underserved, homeless, and users of illicit drugs have high risk of exposure or infection with TB. Health-care workers that serve those high-risk groups are also at an increased risk for infection. Children and adolescents who are frequently exposed to adults that have the increased risk factors for infection also have increased risk of exposure and infection.

So, the transmission of TB is airborne. It gets spread through what we call droplet nuclei. When a person that has contagious TB coughs or even sometimes sneezes or shouts or sings, if they have the TB in the larynx, they expel these droplet nuclei to the air. The transmission occurs when droplet nuclei are inhaled and they pass through the nasal passages and respiratory tract and reach the alveoli in the lungs.

So not everybody that is exposed to TB gets infected with it. The factors that affect when TB is transmitted are the susceptibility of the exposed person, so either the person has intact immune system or not, the infectiousness of the person that has TB, meaning the number of bacilli that they expel into the air, and that is related to the type of TB that they have. People with cavitary TB usually are more contagious than people that have nodulary TB for example.

The other factors are environmental factors that affect the concentration of TB organisms. So closed environments where there is not enough ventilation, versus outside places where the [indiscernible] kills some of these organisms. The proximity, the frequency, and duration of exposure is a very, very important issue. So the highest risk is for the close contact of an active case, meaning the people that live in the same household or that spend a significant amount of time with the person that has contagious TB. So a casual contact doesn't have the same risk or not nearly close to the same risk as the person that spends hours with a person who has active TB. TB can be transmitted from young children, although this is very likely due to the fact that children usually do not have a large bacterial load, and they don't have the force to expel the organisms in droplet nuclei. But it has been reported to happen.

So the droplet nuclei measure about five microns, and they contain about one to ten bacilli. The size of them allows them to remain suspended in the air for long periods of time. And it is estimated that 5 to 200 bacilli are necessary for causing infection. When the droplet nuclei are inhaled, they enter the lungs

and travel to the alveoli. An exception to this is Mycobacterium bovis, which is not transmitted usually by airborne, but it is transmitted by ingestion of unpasteurized dairy products. Once the tubercle bacilli reach the alveoli, some of them are killed there, but some of them, a few of them, continue to multiply. As they multiply, a small number of bacilli enter the bloodstream, and then they spread throughout the body. Through the blood, these bacilli can reach any part of the body, but there are certain areas that are more likely to be good environments for developing TB disease, and that includes the upper portions of the lungs, but also the brain, the larynx, lymph nodes, bone, and kidneys.

So, within two to ten weeks of the infection, when the bacilli reach the alveoli, the macrophages in the airways, the lower airways, ingest these tubercle bacilli, and they form a barrier shell around it that we call the "granuloma," and this keeps the bacilli contained and under control. So the MTB bacilli are in the macrophages can stay align and become latent, so their not actually multiplying but they're not dead, and this is what we call latent TB infection.

If the immune system cannot keep the tubercular bacilli under control, these begin to multiply rapidly, and if the immune system is unable to control it, and this causes TB disease. This process of rapid multiplication can occur, as I said, in different areas of the body, wherever the bacilli has gone through the bloodstream.

So let's talk a little bit more about latent TB infection, because that is an important concept to know and understand. These granulomas may persist for many, many years, and this is what we call latent tuberculosis infection. But some of them may break down and produce TB disease. It takes about two to ten weeks after the original infection for LTBI, for tuberculosis infection, to be detected via the two tests that we have, the tuberculin skin test, and the interferon-gamma release assay.

At that point, the immune system is usually, if it's an intact immune system, it's usually able to stop the multiplication of bacilli, and there are no symptoms. At this time, the chest x-ray is normal and the person is thought to have latent TB infection. People with LTBI are not infectious and they do not spread the organism to others. In the cases where the granulomas break down and the bacilli escapes the immune system, they multiply in the different areas and can cause TB disease. This can occur soon after the infection, or it can occur years later. Persons with TB disease are usually infectious and can spread the bacteria to others.

So the suits where TB disease occurs can be the lungs, which is by far the most common site, usually about 75 to 80% of the cases occur in the lungs, pulmonary disease, and are the most contagious of all the sites. Milliary TB can occur when the bacilli spread to all parts of the body and there are two or more organs systems involved, and it could be pretty severe, and fatal if it's left untreated.

Other sites of disease include lymph nodes, where it can cause a chronic or subacute lymphadenitis. It can cause meningitis, otitis media, chronic otitis media, or mastoiditis, osteomyelitis, gastrointestinal TB, renal TB. And pretty much TB once it spreads, it can go anywhere in the body. Extra-pulmonary TB is usually not infectious unless the person has concomitant pulmonary disease. So a person can have pulmonary TB and extrapulmonary TB at the same time, and these persons are contagious. If the extra-pulmonary disease is in the pleural cavity or the larynx, they also can be contagious, because only coughing or sneezing or even singing can spread the droplet nuclei into the air. Or if the extra-pulmonary site has an open site, and there are procedures that can aerosolize the fluid, that then becomes infectious.

Now not everybody that has acquired the infection, so latent TB infection, develops TB disease. In a person that has a normal immune system and they have TB infection, if it is left untreated, about 5% of these people with normal immunity will develop TB in the first two years after the infection, and then they have a risk of 5% later in life. So 5% in the first couple of years, and another 5% later in life. So a total of -- the risk in a person with a normal immune system in the general population is about 10% in their whole life to develop TB disease. That means that one out of ten people that get TB infection will go on to develop disease.

Now if the person that acquired the TB infection has a weakened immune system, the risk is much, much higher. The best example of this and the people with the highest risk are people that are co-infected with HIV, have the highest risk factors, and their risk is estimated to be 7 to 10% per year, 7 to 10% per year, versus the people that have a normal immune system, which is 10% in their whole life.

Other conditions that increase the risk include immunosuppressive therapy, so patients that have transplants or are post-transplant medication, prolonged and high dose corticosteroids, chemotherapy. And tumor necrosis factor alpha antagonist is the most recent one added to this list.

Other conditions that increase the risk of developing disease, if the infection is recent, we already discussed that the rate of -- the risk is 5% in the first couple years of life; however, in this group, the infants less than four years of age and the post-pubertal adolescents are at increased risk compared to the general population, and this is due to their immune system. In the infants it's usually because of the immaturity of their immune system. In the post-pubertal adolescents, it is thought that the changes in the puberty cause a little bit of a wane in the immunity, and if they get exposed to TB or have had TB, latent TB, at that point, at that time in their life, they have a high risk of activation of that and developing TB disease.

So the two picks that we see in the pediatric population are younger than four years of age and the post-pubertal adolescents. Other condition that is increase the risk include substance abuse, and also other conditions like Hodgkin disease, lymphoma, diabetes, chronic renal failure, silicosis, and malnutrition.

So a word about drug-resistant TB. So this is caused by organisms that are resistant to one or more TB drugs. It's important to understand that they are transmitted the same way as drug susceptible and they're not necessarily more infectious than drug-susceptible TB. However the importance of this is that a delay in detecting the drug resistance may prolong periods of infectiousness because of the delay in starting the correct treatment.

So multi-drug resistant TB is defined as a bacteria that are resistant to two drugs; INH and Rifampin. Extensively, drug-resistant TB is caused by organisms that are resistant to INH and Rifampin, plus Fluoroquinolone, plus one of the three injectable second-line drugs. As you can see in this graph, the rates -- the numbers decrease as we try to go to more resistant strains.

And it's important to remember that there are two types of drug resistance, primary resistance and secondary resistance. So we call primary resistance when a person gets infected with resistant organisms from the get-go, versus secondary or acquired resistance is when the person develops TB during therapy, and this is when they are not in the correct therapy or not in enough drugs or they are not adherent to their regimen.

So circumstances that increase the risk for drug resistant TB include people that have been exposed to persons that are known to have drug resistant TB or they have a history of prior unsuccessful treatment for TB and the drug [indiscernible] are not know; if they are coming from a country where drug resistant is more prevalent, and also we suspect drug resistant TB when they have positive smears and cultures two months after starting treatment, then that is an indication that we need to suspect drug-resistant TB.

Okay, so now, to finish, I just want to wrap up with going back to our original case. So to remind you, this is a six-year-old Boznian male who went to the emergency room with one history of fever and some vomiting. He's from Bosnia. The family had immigrated to the U.S. six months prior to his presentation. At the time of arrival to the U.S., he had a negative PPD, and he had this chest x-ray that we described a large pleural effusion with potentially some infiltrate there too.

So he was admitted to the hospital, was treated with IV Ceftriaxone first. Vancomycin was added. He was not responding, continued to have fever. And the questions that we were asked was about differential diagnosis, further evaluation, do we need to repeat the TST, what would be the best sample and what other tests should we need to do. Now, most of these questions are going to be discussed in

detail in the next webinar, and so I would encourage you to attend the series in order to have an understanding of this. But I'll give you what happened with this patient.

There was a chest ultrasound that was ordered, and it showed loculated organized pleural effusion, surgery was consulted, and they performed a video-assisted thoracotomy and decortication, VATD, and because we had suspicion of TB, of course that was our in differential diagnosis, we recommended that not only they would send the pleural fluid but to send also a pleural biopsy, and to send AFB cultures and the PCRs on the pleural fluid and on the tissue, as well as the bacterial -- the regular bacterial cultures. We did repeat the PPD, and it was read in 48 hours as 22 millimeters of induration. So if you recall, six months before he had a negative PPD, and now he has 22 millimeters of induration.

We recommended to do induced sputum, and one of them was done. However, the they changed the strategy to do gastric aspirates, and there was three of those were done. We also requested an HIV antibody, and that was negative.

The patient, based on these findings, would just be the PPD on his own, and the fact that he wasn't responding to IV antibiotics; was started on four drugs; INH, Rifampin, Pyrazinamide, and Ethambutol. And he improved with resolution of the fever, and he was discharged home to continue therapy, with direct observed therapy.

The final result is three gastric aspirates were negative smears and negative cultures. The induced sputum had a negative smear. The pleural biopsy showed multiple caseating granulomas. The pleural fluid and the pleural tissue were sent for AFB sneer and PCR, and they were negative. However, in about four weeks, the induced sputum and the pleural tissue cultures grew Mycobacterium tuberculosis, and it was resistant to INH.

So, just to wrap it up, things that we learned from this case, first of all, just a reminder about the epidemiology and risk factors. So TB should be considered in a child with pneumonia that is not responding to appropriate antibiotics, especially if the patient is foreign born. So that should be a red light in there just because they're foreign born. Remember that in regard to pathogenesis that it may take up to ten weeks from exposure to show a positive PPD.

So this patient had immigrated and had a PPD soon after immigration, and he obviously was in the incubation period, and he had not had time to convert to PPD. His parents actually did not have TB, and we could not find a source case for him. So he probably acquired the TB right before he left his country. So that's important to know the limitations of your testing. It could take up to ten weeks to convert.

Other things that we learned from this case is that it is very important to obtain cultures in children, especially when the source case is unknown, and that induced sputum may be actually better samples than gastric aspirates in older children, so we should be considering that in older children. And for treatments, remember that we need to suspect drug resistance in any foreign-born patient with TB and use the fourth drug, Ethambutol, until the susceptibilities are available.

So now we can have time for questions. Dr. Maraqa, I think is the -- I thank you for offering and volunteering to monitor and collect the questions. So if you have any questions, this is the time.

Sure. Thank you Dr. Alvarez. Can you hear me?

Yes.

All right, so we have a few questions from the participants. The first refers to the 2008/2010 study of pediatric and adolescent in TB, where the 2,660 cases were described and the parents status was determined. The question is were those 2,660 cases active TB cases or latent TB case, or both, as a far as you know?

Those were active TB cases.

Okay.

That was based on -- that study was CDC data, so the authors actually worked for the CDC, and this was based on cases, because the CDC doesn't collect data on latent TB.

Okay, thank you. And then the second question is regarding the graphs where it's not listed what age group we're talking about, were those graphs talking about TB cases only in pediatrics or was it referring to the TB in the U.S. as a whole?

Which -- I don't know if I go back to the -- can I go back to the presentation?

So the ones who were talking about MDR TB and the foreign-born versus US-born cases.

Let me see if I can get to those. So the drug-resistant TB or just the U.S. born versus foreign born.

It's actually not a question itself, but I presume both, probably.

So what is the question, again, now that I'm looking at the graph?

As you're looking at these, are these cases only in pediatric TB or refer to TB as a whole, in adults and pediatrics?

No, this is the whole. This is everybody, yeah, adults and pediatrics.

Okay, thank you. Another question regarding the high-dose corticosteroid putting patients at risk, does that include topical routes or only corticosteroids?

Only systemic corticosteroids, and this is really defined as high dose, and also duration, more than two weeks of duration. So, for example, short courses that are used routinely for something like reactive [indiscernible] disease or asthma are not going considered risk factors for developing disease. But it's the high dose longer courses are the ones that are considered a risk factor.

All right, thank you. Somebody is also asking, do you use Ethambutol in all your pediatric patients?

That is a good question, and as I said, a lot of the details about some of the management tests and treatment and all that we'll be discussing in other webinars. But just to answer the question, the only time -- yeah, we tend to use Ethambutol in most of the patients, and only we don't use it when we have, for example, the source case for the pediatric patient, the disability of the drug (inaudible) is known, and it is (inaudible), and the patient does not have a clear case of TB disease; for example, the patient that has just the high learning [indiscernible] and we know that they don't have any risk factors for drug resistant TB. Especially if we know that the susceptibilities of the isolate from the source, then we do not use it.

So basically the philosophy is that we use four drugs unless we don't need the Ethambutol. Before we used to only start three, and then only Ethambutol if we have suspicion for drug-resistant TB. So it did change a little bit on the philosophy. So we don't start Ethambutol on everybody but we have a low threshold to do it.

All right, thank you. And then if there is somebody who has never had a positive PPD and is low risk and gets seven-millimeter PPD, could you comment on what that (inaudible).

Yeah. There is -- I think your lecture next is going to cover that, but, yes, if somebody has no risk factors, a seven millimeter induration is considered negative.

All right. And could you comment on any general thoughts on the conversion lengths between the infection and disease. Are there any thoughts on how long it takes, and is it different in children?

Yes, actually there is -- I didn't put that in there, but maybe we can include it in the next one. There is actually a very nice pie table that was developed by this guy. I'm missing his name right now, but this doctor that took care of patients in -- in institutionalized patients. He started the -- this was many years ago, before TB. Studied the natural course of TB in these kids. This was in pediatrics. And basically he developed a time Table.

So, for example, from infection, the exposure and the infection to conversion is up to ten weeks, about ten weeks. The patients that developed pulmonary disease, especially the young kids that developed miliary disease and TB meningitis, so the more severe presentations tend to occur, actually, earlier, about three to six months after the infection, so from .0 from the infection. The ones that have milder disease, usually the range is around -- and I'm just going by memory here, but the range is about maybe six months.

Persons have developed, for example, osteomyelitis with TB, the incubation period or the time from infection to actual presentation is much longer, more like 9 to 12 months after the infection. And for example, renal TB presents years later. It could be a year or even five years after the original infection. So we do have an idea of the timeline, depending on where the presentation is. And, as I said, the more severe cases tend to present sooner because they also present also in the younger kids, in the less than four years of age.

All right, I think we have some more questions that will be covered by later topics in the series, so I think we can stop at this stage, Dr. Alvarez.

Yes, I think we don't want to get over that. But I would want to just encourage everybody that has participated to plan on participating in the subsequent ones. The next one is going to be September 11th by Dr. Maraqa. And the other thing that I would like to remind you is, please try to answer the evaluation survey, because that's information that would be very, very helpful to improve these webinars. Thank you.