

Advanced Concepts in Pediatric TB: Clinical Manifestations

Today we present Clinical Manifestations and Workup. Today's presenter is Dr Amina Ahmed. Dr Ahmed is a pediatric infectious disease specialist at Levine Children's Hospital in Charlotte, North Carolina.

Dr Ahmed completed her undergraduate education at Duke University and her medical school education at University of North Carolina at Chapel Hill.

She remained at UNC for residency and subsequently trained in pediatric infectious disease at University of Texas Southwestern in Dallas, Texas. It was in Texas that she developed a clinical interest in pediatric tuberculosis.

Dr Ahmed maintained strong clinical and research interest in tuberculosis. She runs a chest clinic where she evaluates refugees and other children with LTBI or TB.

She serves as the pediatric consultant for the North Carolina TB control program and thereby authors clinical advice to help departments and practitioners from around the state.

She has been an active member of the North Carolina TB Medical Advisory Committee since 1999 and has contributed to the North Carolina TB Manual, Policies, and Procedures.

Dr. Ahmed participates in research through the CDC's TB Trials Consortium through which she participated in study 26, evaluating Isoniazid and Rifapentine for the treatment of LTBI in children and adults. Currently, she is involved in a longitudinal study of LTBI through the CDC TBESC program.

Now we turn this over to you, Dr Ahmed.

Thank you very much. Can everyone hear me? Can you all?

Yep.

Okay, wonderful. Thank you.

I want to thank you all for inviting me to give this presentation. Tuberculosis is definitely a clinical love of mine.

I'm going to start out with some disclosures and I have no disclosures specific to me, but my institution does receive funding from Centers for Disease Control for the TBESC study on latent TB that we are participating in for the next several years.

My institution also receives funding from North Carolina Department of Health and Human Services for the consultation work that I provide to any provider in the state of North Carolina.

My last disclosure is going to be that I have been sick for the last three weeks and so I'm still coughing so please excuse me if I cough during this presentation. I will turn away and I will reassure you that I do not have tuberculosis because I did get a chest x-ray last week.

With that, as we were already introduced, today's talk is going to focus on clinical manifestations and evaluation and hopefully a lot of you have already participated in the prior lectures that will set the basis for this lecture.

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We're going to focus today on clinical disease, TB disease. The objectives of this talk are to recognize the clinical and radiographic manifestations of the most common manifestation of pediatric TB, which is pulmonary tuberculosis.

We're also going to highlight some aspects of extrapulmonary tuberculosis. It's not going to be a comprehensive review of all extrapulmonary tuberculosis, but I would like to discuss in detail the three most common manifestations of extrapulmonary TB, which includes lymphadenitis, meningitis and then miliary TB.

Then for the last third of the talk, what I'd like to do is approach it from the other side in terms of evaluation and diagnosis of pediatric TB.

We will not go into detail of all the diagnostic tests, but I just want to approach this from either an active case finding perspective, meaning you were screening a child for latent TB or TB and found disease and what to do there versus a child that comes to you who is symptomatic or has symptoms suggestive of tuberculosis and how to proceed with that evaluation.

Some of this is basic and we have already gone over it in the prior lectures, but I just like to review for the purpose of this talk. The terminology that we use in pediatric TB or TB in general is exposure, latent tuberculosis and then TB disease, which is just called TB.

Exposure is what it takes to transmit the organism. TB is transmitted person to person so once you've been exposed to someone with potentially contagious tuberculosis, you are at risk for infection and subsequently also at risk for disease.

Latent TB infection is defined as being asymptomatic and having no radiographic evidence of disease, but having evidence of having been infected with some exposure and that evidence is usually by immunologic test such as a TB skin test, the TST or an interferon-gamma release assay the IGRA test.

In these situations, the patient has no symptoms, x-ray is typically normal.

Latent TB is when the person is asymptomatic, no radiographic evidence, but the only way we know they have the infection is by some immunologic test.

Disease is when the patient's infection either reactivates or the patient progresses from infection to further multiplication of the organism in a particular site and that results in symptoms and signs of disease and/or radiographic evidence of the disease on chest x-ray or some other radiological testing.

It is important to remember that in this situation with disease, those immunologic tests that we use for latent TB may, in fact, be negative because that just has to do with the inherent sensitivity of those tests.

A negative immunologic test does not rule out disease whereas a immunologic test is usually the clue to latent tuberculosis infection.

Again, you've probably reviewed a lot of the pathogenesis, but what I would like to point out here is when the organism is transmitted person to person, it lands in the alveolar space. It multiplies and before the macrophages and the lymphocytes contain the infection in the immunocompetent host, before that occurs, there is what we call bacilleemia.

The organism does spread through the bloodstream and can land in different organs. The reason I bring this up is because this is the basis for extra pulmonary disease so during that lymphohematogenous spread early on in infection before the infection is contained, those organisms can land in the brain, in the

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meninges, in the bone, in the renal system and then later on, with multiplication of the organism or reactivation, can lead to extra pulmonary disease.

Now once the infection is contained, macrophages attack the organism and the lymphocytes respond with activation and it's those lymphocytes that now hold the memory for this infection and they're responsible for the reactive TST.

The delay type hypersensitivity, which is the TB skin test can take several weeks to develop, but what it indicates is that the patient, the host immune system has handled the infection and contain the infection.

The difference between pediatric TB and adult TB is that adult TB is typically reactivation type disease. The adult became infected some time ago. A year ago, two years ago, several years ago and now for whatever reason, the organisms have decided to multiply, reactivate and cause disease.

In children, especially in young children, the important thing to remember is that they can go from exposure to infection to disease within a matter of weeks.

They can go to disease even before their TB skin test or their delay type hypersensitivity demonstrates a positive TST. It could be part of the continuum of the infection to disease as opposed to reactivation, which occurs more commonly in adults.

We know from studies that were done years ago in the pre-INH era, for example, that the youngest child is at highest risk for developing disease after this infection.

In the pre-INH era, if a mother had tuberculosis, had active disease, they would separate the baby from the mother because there was no prophylaxis at the time. We know from those observational studies that 30 to 40 percent of those babies developed pulmonary TB and a high percentage also developed extrapulmonary TB such as meningitis, 10 to 20 percent.

We know that the younger the child, the higher the risk of progressing from that exposure to infection to disease. The risk of developing disease is definitely higher in the younger child.

Now when the child gets to be between five to 10 years of age, we call that the honeymoon period or the safe school years. Those are the children whose risk of developing disease after infection are at the lowest, two percent to five percent at most.

Once they get into adolescence, because of hormones, because of whatever you want to call it, meanness, whatever it is, they tend to have a higher risk of developing pulmonary TB again and then in adulthood, that risk of pulmonary TB goes back down to five to 10 percent.

What I want to point out again is that the risk of developing disease is significantly higher in the child under two years of age and then the rate of progression to disease is faster. Again, they can go from infection to disease in a matter of weeks, whereas adults tend to have reactivation type disease.

The risk of severe disease, that is disseminated TB or TB meningitis is also higher in this very young age group, which explains why the highest risk of disease overall, TB overall, is highest in the child under five.

Like adult TB, most pediatric TB is pulmonary tuberculosis. In children, extrapulmonary TB accounts for a slightly higher proportion of disease than it does in adults, but for the most part, it's going to be pulmonary tuberculosis.

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There are many manifestations of extrapulmonary TB and I have not listed them all, but I have listed some of the major manifestations. It's important to note that congenital TB can also occur, although it is a rare event.

Today, we're going to focus on the first three, lymphadenitis, tuberculosis meningitis and tuberculoma and then miliary tuberculosis.

This is one of several epidemiologic studies done in children in the United States in the last 10 years or so. This is the oldest one, but it's nice because it breaks down the type of disease that we see in children in the United States.

From '93 to 2001, there were several cases of tuberculosis disease that were reported to the Center of Disease Control and as you can see, in the end on the left corner.

In this time period, there were about 11,000 cases, 11,500 cases reported. Of those, the vast majority were pulmonary TB and it didn't matter if the patient was US born or foreign born. The vast majority of disease is still actually pulmonary disease.

You can see that the highest, the most common extrapulmonary manifestation of TB is actually lymphadenitis, which we'll talk about.

This is a chart that demonstrates the timeline of pediatric tuberculosis and in general, pediatric TB would be divided into early disease and late disease.

Within the first couple of months after becoming infected is when we're going to see most pulmonary disease and that's on the first line here indicated by uncomplicated lymph node disease. That's a fancy way of saying hilar adenopathy.

That's also the time period where because of that lymphohematogenous spread that we talked about, there's going to be miliary TB that's going to be noted or TB meningitis.

Then in the second half of the first year is when you may see complications from hilar adenopathy such as compression of the airways or hyperinflation. This is also the time period where you may see lymphadenitis, the most common extrapulmonary form of TB.

Then a year or two after disease, which is late disease, is when you see adult type pulmonary disease and this is typically in adolescents who have reactivated an old infection and you're going to get the classic cavitory lesions, the classic apical cavitory disease that you know about in adults.

Then also in this late period is when you will see other manifestations such as bone and joint disease and urinary tract disease.

I'm going to turn now to pulmonary TB for the next several slides. Different people have broken down pulmonary tuberculosis into different schema, but the one that I seem to understand the best is if we break it down into parenchymal disease and lymph node disease, recognizing that in children, lymph node disease is actually the most common manifestation, the most classic manifestation of pulmonary TB.

Parenchymal disease starts out typically in the ghon focus. That's where the organism initially lands, starts to multiply and causes a parenchymal process that you may or may not catch on chest x-ray. Then this resolves and you may not see anything except maybe a calcium deposit later on.

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If that Ghon focus also has a localized lymphadenitis associated with it with some edema or swelling or enlargement of adrenal lymph node, we call that a Ghon complex and again, not always recognized on chest x-ray because it may be a fleeting event.

Then the other classic parenchymal disease for pediatric pulmonary TB typically seen in adolescents is the adult type disease with cavitory lesion.

Lymph node disease is much more common in children, especially in young children, where they have an enlarged hilar node, a paratracheal node to the classic hilar adenopathy and this may or may not be complicated by airway obstruction or hyperinflation or even an associated pneumonia.

Progressive primary disease takes that Ghon focus and it actually has progressive disease in that focus so there's a caseous center. It spreads around into the paracardium, causes what look like bacterial pneumonia or a low-bar pneumonia. That is not very common in children unless, of course, they're immune compromised.

It's important to remember that in the United States, most children with pulmonary TB are relatively asymptomatic as opposed to low income countries and middle income countries. Most children with tuberculosis in the US are identified proactively so-to-speak.

They're identified by contact investigation typically as opposed to symptomatically. Most of them present fairly early on in disease because we've captured them. They haven't progressed to the point of being symptomatic. Most children will have relatively few symptoms. The exceptions are going to be infants and adolescents.

Infants, because they have smaller airways, that lymph node that may not be a big deal in a four year old may actually impinge on an airway. May cause airway compression, may cause hyperinflation and this will result in symptoms such as a cough or dyspnea or physical exam findings such as wheezing.

Adolescents similarly act like adults with tuberculosis. They have a huge bacillary load. They have reactivated their disease. Organisms have multiplied. They've got a lot of bacteria, a lot of inflammation.

They're going to have the classic signs and symptoms we learn about in medical school that are associated with TB, such as fever, cough, weight loss, hemoptysis, and night sweats.

They're also going to possibly have diminished breath sounds in their exam and you're actually going to be able to hear things like crackles on their auscultator exam.

For the diagnosis of pulmonary TB and we'll talk more about this in detail. It's important to remember for any TB in children, microbiologic confirmation of disease is difficult. They don't have a lot of bacteria. Most children don't.

Even if you can get the specimen, because of this paucibacillary disease, it's hard to get the culture to grow just because there's not a lot of bacteria.

Traditionally, we relied on other things such as putting together their epidemiology, their clinical findings, which may be non-specific. Results of immunologic tests and radiography.

Source case identification is also very important. Pediatric TB diagnosis. If you suspect TB and you can figure out who gave it to that child, then you can get the organism from that person and you will have a more likely chance of having probable TB diagnosis.

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You may not have it confirmed on the child, but if you put together the source case with everyone else, you'll have a diagnosis.

For pulmonary TB, radiography actually plays as big a role as anything else. They've got some characteristic findings that are very important.

Just like the other schema I showed you for the division of pulmonary disease in children, this is a proposed radiological classification. I've got the reference on the bottom and it matches up with the other slides that I just showed you in terms of dividing pulmonary disease.

This was an attempt for us to standardize how we diagnose x-rays that have suspected tuberculosis, partly for research purposes, partly for clinical purposes. Again, it's just broken down into parenchymal disease, lymph node disease and then added on is miliary disease, pleural effusion and also pericardial effusion.

This classification matches up very nicely with this cartoon, this diagram, of what we would expect to see on chest x-ray with children with pulmonary TB. Fortunately, the two articles are by the same person so it does match up nicely.

You may just see the child who had a ghon focus at one point that you can barely see here, but you may see enlargement of their lymph node ... I'm sorry. Let me bring my arrow out here. You may see enlargement of their lymph nodes here, uncomplicated lymph node disease not causing any problem.

This ghon complex ... This ghon focus, they multiply and start to form a caseous center and then cause a bronchial pneumonia or you may see the lymph nodes enlarging to the point that they're actually compressing the airway and causing airway compression atelectasis.

Or the lymph node may spill out into the ovalar space and cause a bronchial pneumonia that looks like a bacterial pneumonia or the lymph node disease may actually block the airways so much that there's hyperinflation of ball valve effect so the air gets in, but can't get out.

Now you've got hyperinflation or miliary pattern that we'll talk about. Pleural effusion, which is not commonly seen in children, but can be seen. Pericardial effusion and then of course, the adult type reactivation disease, which classically occurs in the apices.

The most common thing you're going to see in children is this uncomplicated lymph node disease because again, they typically tend to come to medical attention fairly quickly as part of a contact investigation and have not progressed to the point of either bronchial pneumonia or hyperinflation.

These next few slides are just radiological examples of what we've talked about. On the left here, you have this young man who came to me because he had cervical adenitis and because of his epidemiology, someone put a skin test on, thinking this may be TB adenitis.

The skin test was reactive and as part of the evaluation for determining whether this is tuberculosis adenitis versus non-tuberculosis mycobacterial adenitis, they also got a chest x-ray and the chest x-ray was specifically to look for disease.

Here is a soft tissue finding that's consistent with lymph node disease. This was not originally read by a pediatric radiologist so it was read as having just a pneumonia, but this is actually got very nice rounded edges that goes along with more of a soft tissue finding and lymph node disease.

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This child ultimately did get hospitalized, get evaluated for TB because we had no source case and he did grow out MTB from his gastric aspirates.

This is not so obvious as the one on the right. This young lady is actually the patient on the left aunt. She's just a year older, but she's his aunt.

When we were looking for the source case for the young man on the left, we found this young lady in the house. Also did a skin test on her, which was reactive and because it was reactive, we were looking to see if she had latent TB infection or TB disease.

She has here a nice density here, which is lymph node disease, which was not so subtle as it was for her nephew on the left. She also has some scoliosis here.

Again, these are two children that identified different ways. The one on the left is identified because he came in symptomatic with cervical adenopathy. The one on the right was picked up as part of, not a contact investigation per se because the child on the left is not contagious, but as part of a source case investigation.

This young lady was exposed to her uncle who had tuberculosis and as part of the evaluation, the contact investigation, she underwent a physical that was normal. Her skin test was actually negative.

Normally we would just repeat a skin test in eight weeks, but because of her age, because she is under five years of age, she warrants window prophylaxis, which would mean that we put her on isoniazid for eight weeks till we can repeat the x-ray ... I mean the skin test and that's mainly because she is at high risk for progressing to disease as I showed you in that chart earlier.

Because she's about to be put on isoniazid the last thing we want to do is put a child on isoniazid if they actually have disease and we just missed it because the TST was false-negative or hadn't converted yet.

We always get an x-ray before we put a child on window prophylaxis and when we did that, we found that she actually also had hilar adenopathy so she, in fact, had disease, not just latent TB.

Again, an example of a child coming to medical attention because of contact investigation and also an example of a child that has TB disease with a negative TST.

There's another x-ray with hilar adenopathy, which was not called by the radiologist. They're pretty ... Arrows in here. So because of the arrows, it's now obvious that he's got some soft tissue density there, but even without the arrows, if we lightened the film up a little bit, you'd be able to appreciate it.

What I'm showing here is the value of a lateral chest x-ray. A lateral chest x-ray shows the soft tissue density, which confirms that he has hilar adenopathy there. Always in a child that's being evaluated for TB, it's important to get the PA as well as the lateral chest x-ray.

This is another example of a child with hilar adenopathy, this time with complication. This density here shows soft tissue, which is consistent with a lymph node and then there's stuff that looks like consolidation and if you look on the lateral, you can see this nice white wedge shape consolidation, which is more consistent with atelectasis than it is with pneumonia.

Then around the trachea, the donut shape hilar adenopathy so this is hilar adenopathy with airway compression. This child actually has hilar adenopathy with hyperinflation. This film is skewed a little bit.

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The patient is rotated, but this child had a node right here and because air was able to get in and not get out because of the compression airway, he ended up with hyperinflation and presented with respiratory distress.

He also has aseptic meningitis with a high protein, which went along with TB meningitis so he actually had TB meningitis and still had an x-ray that indicated TB disease.

Here is a child that was just hospitalized this year at our hospital with a fever of unknown origin. She'd had a fever for about three to four weeks. As part of that evaluation, we did a TST looking for tuberculosis.

She didn't have any known exposure at the time, but we did a TST. It was reactive and then we went back and looked at her x-ray, which had been called pneumonia.

There was actually some fullness right around the right hilum, which cannot be very well appreciated of this one, but because there was some confusion as to whether this was just an infiltrate or some hilar adenopathy and she had some fullness here, too, we did a CT.

Again, we don't need a CT in the vast majority of cases of pulmonary TB in children, but this one was mainly to further evaluate her FOU and she had an enlarged node here.

Unfortunately her gastric aspirates did not pan out. We did not isolate the organism, but within a month of her starting empiric therapy, we did identify the source case so this is a child who's nine months old.

She's got hilar adenopathy, she's got a reactive TST and we have no other explanation for the hilar adenopathy so she was empirically started on TB drugs.

After she was discharged, there was a source case that turned out that this man had been sleeping in their house for a couple of months and had TB disease and was being treated for TB disease. That was probably her source case and she is now much better.

Here's adult type cavitary disease, classic apical disease that we see in adults. This was a teenager and this is another teenager from the Congo, who came in with fever, hemoptysis, night sweats and weight loss. He hadn't infiltrated. This had been going on for quite a while.

Then they did a CT of his in the emergency room. Again, not necessary because his sputums were already smear-positive, but it does show multiple cavities on the CT.

Pleural TB is another manifestation of pulmonary TB. It typically occurs within six to nine months of initial infection. We don't see this very much in children.

The thought is that with that lymphohematogenous spread may have sent a focus of infection to the pleural space or through parenchymal pulmonary involvement. You have a focus in your pleural space and then as the bacteria, the bacilli are discharged into the pleural space, there's a hypersensitivity response inflammation, reaction and then a build up of fluid.

It's typically unilateral. Typically doesn't always have the pneumonia, the parenchymal disease associated with it, but it can certainly.

These patients tend to have symptoms as opposed to the vast majority of children with pulmonary or intrathoracic TB. They don't tend to have symptoms, but because they've got fluid build up, they'll have

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fluoridic chest pain. They'll have diminished breath sounds in that area. They may even have some respiratory distress.

This is an example of a pleural effusion. Here's the patient heart right here. Then you can see here, the diaphragm on the left side is nice and clear and you lose the diaphragm on the right side. You can't see the diaphragm because it's obscured by all this fluid, which is tracking up.

Again, the diagnosis of pediatric TB, always confirmation means that you have to find the organism in a culture somehow, but barring that, the pleural fluid might give you some clues. There's a high protein, there's a low glucose and then there's some inflammation manifested by white blood cells.

Like most pediatric TB, mycobacterium tuberculosis is isolated and half or fewer cases just because they don't have a high bacillary load.

They don't have a lot of organisms to begin with, but if you actually get a biopsy tissue, whether it's node or pleura, it's going to have a higher yield on your isolate, meaning you'll have a higher likelihood of actually finding the organism.

Now that's a pulmonary tuberculosis so intrathoracic pulmonary tuberculosis in children as we talked about and then pleural TB, which is another manifestation of pulmonary, but not intrathoracic tuberculosis per se.

Now we're turning to extrapulmonary TB and TB lymphadenitis is the most common form of extrapulmonary TB that's recorded. Classically, it was called scrofula for mycobacterium scrofulaceum, which is actually a cause of non-tuberculosis mycobacterial disease, but that is what it was traditionally called.

The epidemiology of this disease is interesting. It's different from regular pediatric TB in that first of all, we tend to see it in older patients, the peak age being at 30 to 40, women more than men.

Then at least in industrialized countries, when we do see it, it tends to have a predilection for immigrants that are from southeast Asia. We see it in the Vietnamese population, the Filipino population, the Indian population, for example.

If you see it in a child, it's always important to ask about the history of ingesting unpasteurized dairy products because a child that has TB lymphadenitis, it might be regular old mycobacterium tuberculosis or it may be due to mycobacterium bovis, which is cow tuberculosis, essentially.

The United States does not have cattle that are infected with M. bovis, but certainly in places like Mexico, there are still some cows that are infected so we see children who have eaten unpasteurized dairy products from Mexico.

Certainly this is seen a lot in San Diego because those children cross the border and they will have unpasteurized products and then they can manifest with cervical adenitis, which is still TB adenitis, but actually due to bovis as opposed to MTB.

The clinical presentation of this, typically occurs in the first year after infection. Again, either through lymphohematogenous spread or in the case of mycobacterium bovis, it's probably due to ingestion and then drainage out. Lymphatic drainage into the cervical space at that time.

When this does occur, it's typically within a year of infection. Although, in the older southeast Asian population, I do wonder if it's just manifest years later as opposed to months later.

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It's typically unilateral, involves one to three nodes and it's usually painless. Not very tender to palpation. It may be slightly discolored, but it does not have the violaceous hue of non-tuberculosis mycobacteria and rarely, we may see some draining sinuses.

Because of when they present, when these patients present, you may or may not see pulmonary disease so their pulmonary disease may have self-resolved, you may have an infiltrate. They may still have some hilar adenopathy.

The first x-ray that I showed you in pulmonary TB is a child who is mong who's aunt also had TB disease. He actually presented with cervical adenitis and also had evidence of disease on his chest x-ray.

Putting those two together, you know it's probably TB as opposed to non-tuberculosis mycobacterium. Oftentimes, the pulmonary disease may actually be absent by the time you're evaluating the patient for TB adenitis.

In terms of diagnosis, your TB skin test may or may not be positive so remember if it's negative, it doesn't rule it out. Chest x-ray is abnormal in 10 to 40 percent of the cases, like the mong child that I showed you who had cervical adenitis.

A definitive diagnosis always requires isolation of the organism, either by culture or by NAAT, which is nucleic acid amplification test or PCR.

We know that more tissue is better. Excisional biopsy is going to give you a higher yield than a fine needle aspiration, which takes just a core of tissue, but you can always start with fine needle aspiration.

The histology's going to show granulomas or caseous necrosis langanhans giant cells, but the histology's not going to be able to tell the difference between mycobacterium tuberculosis, mycobacterium bovis and then non-tuberculosis mycobacteria because it's going to look very similar histologically.

This is a report of several theories of the TB lymphadenitis from around the world. What I want to point out here is that diagnostically, the excisional biopsy is always going to have a higher yield than the fine needle aspiration. It's a 93 percent versus 62 percent. This one was pretty equivalent, 18 percent versus 10 percent.

In general, the excisional biopsy's going to have a higher yield, but there is more morbidity of course associated with that surgery.

This is a 16 year old young lady from Vietnam. She come over as a refugee years ago. She presented with cervical adenitis. Because someone thought it was supraclavicular, they sent her to the pulmonologist initially, who given her epidemiology, put on a TB skin test looking for tuberculosis.

The skin test was reactive and she was in surgery clinic when they noticed that and they asked us to come read her skin test. In evaluating her further, her mother was with her, had on a scarf and it was August and for those of you who live in the southeast, it is too hot in August to wear a scarf, especially a wool scarf around your neck.

When we asked her why she was wearing a wool scarf ... This is something that we do with pediatrics and probably not in internal medicine, but she took off her scarf and showed us, the mother did, a scar in the exact same location where this child had cervical adenitis.

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The mother nine months ago had had a similar lesion removed. It was not cancer. She was relieved. They moved on. The lesion recurred. It was removed again. Cultures were not done so that mother probably in all likelihood also had TB. We weren't able to get her specimen for any cultures.

This child, we recommended excisional biopsy and TB was isolated. She got treated. It was actually very good that we isolated it because she was INH-resistant so we could treat her with appropriate drugs and we treated the mother similarly because even though she'd had the node excised, you still have to treat TB adenitis.

This is just ... This young lady's histology and this red mark here are her ... There's not a lot of it, but there is AFB, acid - fast bacilia that are lined up next to each other.

The confusing thing for us pediatricians is that there's probably a lot more non-tuberculosis mycobacterial adenitis than there is TB adenitis so we are always blessed with a child who has a subacute cervical adenitis like this young lady does.

Treated with antibiotics. No better. Her skin test is technically positive because she's symptomatic so five millimeters would be reactive in her case and her x-ray is normal.

Is it tuberculosis, is it non-tuberculosis mycobacteria? I don't know if you can appreciate this on the slide, but she has a very nice violaceous hue to this node. It looks more pink here than violaceous, meaning purplish, but it was very violaceous on exam. That's very classic for non-tuberculosis mycobacteria.

This mother happened to have a history of latent TB that was not treated, but she probably acquired that in Mexico where she was from and she did not have any disease at the time.

The bottom line here is for determining between non-tuberculosis mycobacteria and TB adenitis, unless you have a positive x-ray, which points you towards TB, then you're left with basically getting tissue to determine which one it is.

Both of these, mycobacterium tuberculosis and non-tuberculosis mycobacteria can have chest x-rays that are normal. They can both have skin tests that are reactive and you're not going to be able to tell them apart histologically.

In the end, you have to get tissue to be able to determine it and culture. That is what happened in this particular child that I just showed you and she had non-tuberculosis mycobacteria.

Because of her classic appearance, we did not start her on impaired therapy. She's at the right age for non-tuberculosis. Non-tuberculosis is just much, much more common than TB lymphadenitis.

TB meningitis is not as common as lymphadenitis, but it is a devastating disease if not caught in time. It typically also occurs within months of the initial infection and remember, young children can develop meningitis even before their skin test is reactive if it ever becomes reactive.

It's very important as we'll talk about later to take a young child who has pulmonary TB or TB elsewhere and evaluate them for meningitis even if they're asymptomatic because that can have devastating consequences if not diagnosed and treated appropriately.

The thought is with initial lymphohematogenous spread of the organism before the infection is contained in the alveolar spaces, that you may actually see your meninges and now you have a KCS focus there and your meninges that spills out the bacilli to the subarachnoid space, causing meningitis and as it does it, it settles down to the base of the brain.

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Basal meningitis is very classic for tuberculosis. As it settles down there, it causes inflammation. It causes infiltration of the cortical and meningeal blood vessels, essentially choking those blood vessels and causing infarcts.

Also as it settles down there, it obstructs the flow of cerebral spinal fluid so you end up where they communicating hydrocephalus, meaning it's communicating above in the ventricles, but it cannot resorb the CSF so you end up hydrocephalus or increased ventricular size.

This disease can be very subtle early in its course. Early on, there's going to be non-specific symptoms such as just fever or headache or irritability or maybe nothing at all.

Those of us that take care of tuberculosis have all seen children who look well, who were diagnosed with just aseptic meningitis and maybe were even walking out the door discharged when someone noticed that the protein was really high, can you bring the child back in and evaluate them and low and behold, they have TB meningitis.

It's important to remember that these kids can be relatively asymptomatic, which is why we tend to evaluate for TB meningitis in the very young child that has TB disease elsewhere, just to make sure we're not missing this.

In the next stage, you're going to get evidence of neurologic dysfunction, either by seizures or cranial nerve palsies and then finally, there's going to be coma or decerebrate/ decorticate posturing and ultimately death.

This is a review of cases of TB meningitis in South Africa and as you can see, nothing is 100 percent. Even fever only occurred in 67 percent of the patients overall. You can see the symptoms are not 100 percent at all.

The closest we get is this meningeal irritation, but only 27 percent of them had cranial nerve palsies. Again, just underscoring the point that we have to be vigilant in looking for this disease.

Diagnosis again, of course is going to require isolation of the organism, which is not possible in a lot of cases, but you need to keep in mind again that the skin test could be non-reactive, especially with overwhelming disease. The immune system is not working normally and your TST may be non-reactive.

X-ray may or may not be positive so by the time they present with TB meningitis, because it was from the original hematogenous spread, you have seeded a focus and now you have meningitis.

That patient may never have developed pulmonary disease. It's just from that hematogenous spread that you got that focus that now reactivation causes disease or now, bruise and causes disease.

Classically, these children will have a CSF pleocytosis so have somewhere between 10 and 500 white cells. Their sugar, their glucose, could be low or it could be normal. The protein is elevated and a high protein in the spinal fluid of greater than 200 or 300 should always be a clue that this may be TB meningitis.

You're not going to isolate TB in a lot of cases because again, you just don't have a lot of bacteria in that spinal fluid, but the more spinal fluid you submit, the higher the chance is that you're going to end up with a positive culture.

Ten MLs or two teaspoons is a lot of spinal fluid, but I always ask for at least five to 10 MLs and then that increases your yield on your culture.

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Imaging is very important in TB meningitis. It can offer a lot of clues. It's not always abnormal, but when it is, classically, what we're looking for is hydrocephalus and this basal or basilar meningeal enhancement because the exudate is settling down to the basilar areas of the brain.

Because it's choking those blood vessels, you're going to see infarcts. Occasionally, you'll see tuberculomas, which are actually foci infection that again, were seeded a while ago.

Then the MRI may be a little bit more useful than CT because you get to look at the brain stem a little bit better, but always remember to have contrast so you can see the enhancement in the basal meningeal space.

The same series from South Africa shows you that radiography is abnormal in the substantial portion of cases, but not always and early on, they're not going to necessarily have an abnormal scan so you can always repeat it later if you're suspicious or use other clues for the diagnosis, including the CSF.

Again, TST is not always reactive in these patients and the culture was positive only 19 percent of the time in this particular ... Sorry, 12 percent of the time in this particular case. Then you can also look for specimens at other sites for additive evidence that this is actually tuberculosis.

The definitive diagnosis requires the culture. You can make a presumptive diagnosis if you isolate TB. For example, from a BAL or from a gastric aspirate, especially if you have pulmonary TB disease and put that together with a clinical picture for presumptive diagnosis.

For those of you that are interested, there's a contestant statement on diagnostic criteria, which outlines clinical findings and has a scoring system. That's the reference that I have attached for you as well. The reference itself is attached. Just for your reference.

This is a young lady, also Vietnamese, who came in at 16 months of age and was basically obtunded in the emergency department. Her CSF shows pleocytosis with 56 white cells. Her protein is elevated at 129 and her glucose is very low at 11.

Her MRI showed basilar meningitis and infarcts. Basilar meningitis, infarcts and a child with a write-up epidemiology for being at risk for TB with a high protein, which you always think tuberculosis.

Her CSF smear was negative for TB. Her CSF culture was negative, but because she had x-ray findings and we were able to get a sputum because she was intubated, we did isolate MTB from her bi-culture. That was identified after her death, unfortunately.

When we went back for the source investigation looking to see who around her could have TB that might've given her TB, turns out that the mother had been diagnosed with latent TB months ago, but had not been treated and went on to develop disease and actually had positive x-ray finding.

On this MRI, I want to just point out hydrocephalus here. Enlarged ventricle space. Then here we're looking at a coronal section here and this is the base of her brain and all this white stuff is exudate. This is what we would call basilar enhancement.

In the child that has aseptic meningitis, meaning that the brain stem is negative and the culture is negative for bacteria. With hydrocephalus or basal meningitis, we should really suspect TB.

If you've got all those changes, basal meningitis, hydrocephalus, infarction of cranial nerve involvement and there's no other apparent cause, you should probably start TB therapy empirically until we know otherwise.

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Then the source case may be the key to your diagnosis. In this particular situation, we knew about the mother before we had her cultures and so it cinched the diagnosis.

Tuberculoma is another manifestation of CNSTB disease. The lesion may be singular or infratentorial, These patients may have headache or fever or may have no symptoms until they develop a lot of edema or swelling around the lesion.

This is a 19 month old who came in with suspected TB. Her mother had been diagnosed with tuberculosis recently so as part of the contact investigation, she had a physical exam. A TST that was reactive and a chest x-ray that was read as being abnormal, but it wasn't really clear if it was abnormal or not.

Her physical exam, according to the primary care physician, was normal, but because someone had noted irritability because she was very young with pulmonary TB, we thought she should perhaps have an LP done.

Here's her mother on the left here. Think it's there, with cavitory disease and here she is and this is how hilar adenopathy bilaterally on her.

We asked her to come in for a repeat chest x-ray because the initial one wasn't very clear and a lumbar puncture because of her age. She got the x-ray done, but got sent home because she ate a Tootsie Pop and so couldn't get an LP because she needed sedation.

Came back the next day for an LP. They couldn't do it so they hospitalized her and did a spinal tap and a spinal tap showed a protein of 466. Even with a bloody tap with 113,000 red cells is still very abnormal. She has white cells in there so she has pleocytosis.

Because she has evidence of maybe TB meningitis, we would image her brain and in her brain, what we found was one lesion with a lot of edema around it and multiple tuberculomas.

Here's one here. This white spot here. This white spot here. This white spot here. This white spot here. This white spot here. All of these are tuberculomas. I think she had 19 in all.

She was running around happy as could be, was never irritable. Completely normal exam, which underscores the importance of doing lumbar puncture in these young kids.

Lastly, miliary TB. This is when there's hematogenous spread with a primary infection as we talked about and the tubercules actually stuck in the capillaries and cause miliary lesions that we can see on the chest x-ray.

This is a fairly insidious presentation with fever, swollen lymph glands, big liver and spleen hepatosplenomegaly even before you see the x-ray finding.

It typically occurs either in the very young patient whose immune system is not very well-developed or an immune-compromised patient because they can't handle as the organism is multiplying, they can't handle the infection very well so there's miliary spread.

There's a second type that can happen when there is dissemination because the caseous focus erodes into the blood or the lymph vessel and then spreads out, but that actually happens rarely.

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These are some of the signs and symptoms that we see in miliary TB as opposed to pulmonary TB. These patients are symptomatic. Big liver, big spleen, swollen glands, fever and because it is miliary, you always have to evaluate for meningitis to make sure they didn't disseminate to the central nervous system.

This is miliary TB in the young infant. Because they're immune-compromised, relatively speaking, all this haziness here is the millet seed appearance of miliary TB.

This is a young man that was incorrectly diagnosed with juvenile inflammatory arthritis, got put on Methotrexate and became immune-compromised because of that and then he spread his organism all over the place, causing miliary disease seen on CT here.

Turns out he didn't have juvenile idiopathic arthritis. He had TB synovial septic arthritis and that's why when he got put on something that immune-compromised him, he developed miliary TB.

Again, with definitive diagnosis requires isolation of the organism, the x-ray is pretty classic in this so that would be a presumptive diagnosis. It's always important to look for dissemination to other areas, including the CNS in these patients.

I'm going to try to quickly go through some of these cases here, so primary reason, evaluated .

We're going to turn now. We've talked about the clinical manifestations of disease and how do these kids get evaluated and my approach to evaluation is to divide it up, either into active versus passive diagnosis or evaluation.

Active case finding implies that we have been screening a child or doing a contact investigation and then because of that contact investigation, we identify a child who may have TB disease so that's called active case finding, whereas passive case finding is when the child presents with symptoms. Then we evaluate the child to determine if they may have tuberculosis or not.

Like I said in the US, at least half of the cases are identified by contact investigation. This is another series. From 2009 to 2010, as you can see, for US born children, as many were identified by contact investigation so active case finding as opposed to passive, where they presented with symptoms.

It is important to remember that most of these kids will actually come to us through contact investigation and so may be asymptomatic.

When we do evaluate these children, in general because it's hard to confirm their diagnosis, we rely on a lot of other things, such as epidemiology, clinical presentation, radiographic findings.

If we're lucky, we'll have mycobologic confirmation of the disease, but again, it's as important to find who gave that child TB as it is to do the mycobologic confirmation because if you can find the source, it's very likely that you'll be able to isolate the organism from the adult who has TB.

The tools that we have are listed out here for you, which you're familiar with x-ray, TST, microscopy, PCR testing, including the expert testing.

I'm going to just briefly talk about TB skin tests and IGRAs the diagnosis of TB and you all are already familiar with this, but neither of them can tell you the difference between latent TB and TB disease.

Neither, if negative, can actually exclude TB disease so it is important to remember that because there is going to be variable sensitivity and various presentation.

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It is important, though, to remember that if you're really suspecting TB disease in a kid, you can use the two together and I have done that so the two together would increase your sensitivity.

Here's a series, for example, of patients with TB disease that's culture confirmed. If you look at the culture confirmed cases, only 76 percent have positive skin tests, 72 percent had IGRAs but put together, 94 percent actually had immunologic evidence of disease. When you're using these tests, you can put the two together.

Radiography, as we talked about, is very important in pulmonary tuberculosis, but it's also important in extrapulmonary as we saw from meningitis so it's important to use this tool as well.

Then remember to always review it with a pediatric radiologist if you can because the adult radiologist are just not very familiar with hilar adenopathy so you always want to review it if you can.

The thing that's going to be a clue always for pulmonary TB is hilar adenopathy and as we already discussed, both frontal and lateral films are recommended to pick that up.

Mycobiologic confirmation is always difficult in kids. It's hard to get them to hock up sputum for you so you're going to be dealing with gastric aspirates and BALs, which are difficult to obtain. Even if you get the specimen, then you're left with a kid who has very few bacteria and so it will be difficult to culture out.

Therefore, culture positive TB is not the rule. TB is isolated in fewer than 60 percent of the children and the smear has even a lower yield because again, you need to have a certain number of concentration of bacteria to be able to see it on smear and that does not happen very much in children with paucibacillary disease. A negative culture, a negative smear does not rule out TB.

When should you attempt confirmation? There are some kids that you just think oh, why even do it at all, but once you do, always try to isolate the organism. You should do it if you don't have a source case.

If you don't know what the children, how it's isolated, then you need to optimize therapy, then you should try to do confirmation. If it's not available or if you suspect resistance, then you should certainly try that as well.

Here are the specimens that you can use as various specimens. I'm going to skip over the next few slides and let you guys look at that at your leisure for the details of these different specimen types.

Now the approach to evaluation. Either we're going to screen and happen to identify a kid. Do a contact investigation, identify a kid or the child is going to come to us symptomatic and then we're going to definitely attempt mycobiologic confirmation because we will not have a source case.

Here's a child who was adopted from Guatemala, Friday four o'clock has a reactive TST. The physician sends her in for a chest x-ray and as you can see on the chest x-ray, there's evidence of hilar adenopathy here.

Positive skin test, hilar adenopathy and an asymptomatic child from a region where there's TB. This is TB until proven otherwise. We don't know where this child got it from. We don't know how much resistance she has so we've got to get the isolate.

We put her through gastric aspirates and given her age and subtle signs of TB meningitis, we did the lumbar puncture as well in the hospital. We were able to isolate TB from her and identify and tailor her therapy.

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Here's an example of a child with suspected pulmonary TB, identified by screening. Source case unknown. What do you do in that case? You attempt confirmation. Use whatever specimen you've got and remember, negative culture doesn't always exclude. If you really suspect it, still treat the child.

We're going to do an LP to look to make sure that the child in that lymphohematogenous spread did not spread to the CNS and always test for HIV because the two diseases go hand-in-hand.

Why the lumbar puncture? We already talked about this, but that meningitis may develop subtly and it may occur before the skin test is even positive. The younger the child, the higher the risk of meningitis so we recommend an LP, lumbar puncture in any child under one to two years of age. For North Carolina, we say two, who's diagnosed with TB disease elsewhere, like pulmonary TB like this child was.

We suspected pulmonary TB and we did a spinal tap. Unfortunately, it was negative. Remember, it's also going to impact how long you treat. You treat meningitis longer than you treat pulmonary disease.

I'll skip over this case in the interest of time. This five month old came in, was evaluated in the ED with a cough. There's a chest x-ray with hilar adenopathy noted and she was admitted for evaluation with gastric aspirates and then she underwent an LP because of her age and we started the source case investigation.

Again, you've got a symptomatic child with suspected pulmonary TB who has a source case unknown and here you do have to attempt to find her organism. One to confirm disease, but two to have an isolate for susceptibility.

Then we also started looking for her source case at the same time. Who around her gave her tuberculosis? We did further evaluation as recommended.

In her source investigation, we figured out that it was actually her uncle. Her parents had LTBI, but had normal x-rays. Then the uncle was found to have this x-ray on further evaluation after his skin test was reactive with cavities right here.

We actually got the isolate from him to grow before we got the isolate from the patient herself so we're able to optimize her therapy earlier.

Now, a nine month old was exposed to MDR tuberculosis. As part of the contact investigation, his initial skin test was negative, chest x-ray was normal. He didn't get window prophylaxis because there really is no window prophylaxis for MDR tuberculosis.

The repeat test was still negative, but he was coughing and in coughing, we do x-ray and there was some debate as to whether his hilum was full and had some adenopathy so then we did a CT and this area here is an inflamed lymph nodes so he had hilar adenopathy.

Now we already have a source case in this situation. We've already got the isolate from the source case, but because this source case has resistance and I'm about to put this child on highly toxic medicine, I would like to know, first of all, if it's really TB and second of all, is it more resistant than it was because in this particular case, the source case was not taking his medication very well.

We did go ahead and do mycobologic confirmation. We were able to confirm disease in the child. It was the same susceptibility pattern. His age dictated a lumbar puncture and HIV testing and the important thing is, we were able to put this kid on therapy, knowing that he wasn't more resistant than he was.

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This young man, seven month old, came in with lethargy, was apneic in the emergency department. Got intubated. His spinal fluid showed that he also had meningitis with 143 white cells and an extremely high protein. His CT showed hydrocephalus. These ventricles are all enlarged and then this circled area's an infarct.

A child who has aseptic meningitis with an infarct and hydrocephalus should always be presumed to have TB until proven otherwise. He was started on an antibiotic for regular meningitis until infectious diseases consulted and then he was put on TB therapy.

We've got all the appropriate specimens and started the source investigation. Then when we checked the father's x-ray, he had cavitory disease. He was on steroids so he never had fevers or cough or anything. We isolated the organism from him, the father, but not the child so we actually could optimize therapy based on that.

Again, if the child has suspected disease, the source case is unknown, you want to attempt bacteriologic confirmation, part of your investigation should be the source case investigation and then further testing as we talked about.

This last young lady had lymphadenitis as we discussed earlier. She had a skin test that was reactive, an x-ray that was normal so we couldn't tell if this was TB or non-tuberculosis mycobacteria.

Here it is erythematous. It's coming to a head so I was thinking this child is going to have non-tuberculosis adenitis, given her age. We did the biopsy and low and behold, she grew out TB and not non-tuberculosis. As a further surprise was that it was PCA resistant, which indicates that it's mycobacterium bovis.

Then the father admitted to us that he had unpasteurized milk and cheese in his store. He had a grocery store and he gives it to his child.

The lesson here is you can start your source case investigation, but sometimes the source is actually cheese and not another person.

In summary, young children are at higher risk of progressing to primary TB disease. They should be evaluated right away if TB is suspected.

Most disease in kids is still pulmonary, but extrapulmonary disease plays a bigger role and in evaluation of disease, it depends on whether the child is identified through active case finding with screening and contact investigation or passive case finding with symptomatic presentation.

The bottom line is if you don't have a source case, you need to try to do mycobologic confirmation. It's going to be important unless you have that isolate available from the source.

With that, I'm going to end and I thank you for your attention.