Thank you for joining us today, Dr. Starke. You may begin.

Thank you very much. Hello to everybody. I am honored that you’re giving up an hour of your time today to hear this. I thought about starting this talk by simply saying that research has recently shown that children are, in fact, little adults, and then we could all just hang up the phone. But, unfortunately, that turns out not to be the case, and it’s particularly the case when it comes to tuberculosis for the, hopefully, reasons that will become very clear as we go forward.

Just to tell you, I have put a lot of information on some of the slides, but it is my intention that that be for your reference when you download the slides as a handout. We won’t be going over every single detail of every single slide, but it’s there for you to have and study when you would like to, particularly when we get into adverse reactions of drugs.

So these are the objectives for this particular session. To understand the mechanisms and patterns of antimicrobial resistance in TB relevant to children. To understand the rationale for various treatment regimens of both drug-susceptible and drug-resistant TB. To plan the treatment for pulmonary and extrapulmonary TB in children and to plan follow-up evaluations including whether or not to get cultures, radiographs, assessment and management of common adverse reactions to TB drugs. But we’ll talk about a whole lot more.

I include this slide in almost every TB lecture I give because I think it’s a very nice conceptualization of how we approach TB, particularly from both the public health and the clinical point of view. People are in various boxes, and we design interventions to try to prevent the person from going from one box down to the next box. And this is particularly true for children and particularly in context of contact investigations where we’re trying to actually find children who have been exposed and either treat their infection or even prevent it from taking hold, hopefully helping them to not develop either disease or become ill. It’s particularly important in children, the distinction between diseased and sick because we can pick up about half of our kids in Houston through contact investigations, and these are kids with TB disease who have abnormal chest x-rays after exposure to someone close to them, but these kids have not yet become ill. And they have much easier to treat disease, lower burdens of organisms, and they do much better. Unfortunately, in most of the world where there’s high burdens of TB, children are not even discovered until they have become sick and it hasn’t been known, necessarily, they’ve been exposed to TB, so that means that it’s much harder to establish the diagnosis and the treatment is much more difficult because these kids have much more advanced disease.

So talking about what we do in the U.S and what’s done internationally is, in fact, somewhat different because of the patterns of epidemiology and the patterns of how children are actually discovered. The other issue with sick children, of course, is that we only can isolate the organism from about 30 to 40% of the children, which means our only hope of knowing that a child has drug-resistant TB is linking that child’s epidemiology to an adult with tuberculosis for whom we know the drug susceptibility testing. And this is a huge problem in high burden areas where TB control systems simply aren’t set up to make those links between cases and contacts.

So this is one of my favorite slides, the development of drug resistance in tuberculosis is the result of a conspiracy among the organism, the patient, the doctor, and the health care system. And what that simply means is given the nature of the organism, if the patient messes up by not taking drugs properly, the doctor messes up by not using the right regimen, or the health care system messes up by not providing the appropriate drugs, it will inevitably lead to the development of drug resistance, certainly in people who had high burdens of organisms as part of their tuberculosis disease. And the reason for this is because of the genetic basis of drug resistance for mycobacterium tuberculosis. For every known TB drug, so far there is at least one locus, one genetic locus. And in some cases, like ionized, there may be multiple loci that a certain mutation in that loci will confer resistance to the organism to that particular drug. Fortunately, for all the drugs we know so far, resistance to one drug appears to be independent of resistance to other drugs. And for the common drugs, we know how frequently these mutations can occur, so we actually can kind of predict what might happen depending on what drug regimens are used either appropriately or inappropriately. And what it also means is that the likelihood of developing
resistance is actually a statistical issue based on the number of mycobacterium in your body and the likelihood of having these drug-resistant mutant organisms that won’t respond to certain particular medications.

And to show this schematically, if you take an adult who has cavitary TB with maybe as many as ten to the ninth organisms, even though the laboratory will tell us that it’s drug-susceptible TB because the laboratory can only detect resistance down to a certain level, within that population there will be approximately 1,000 organisms resistant to INH and 100 organisms resistant to rifampin. So if we treat that patient with INH alone, it will kill most of the organisms, but those 1,000 INH-resistant organisms will multiply and take over as the dominant population. The patient will feel better for a while, but ultimately will relapse with completely INH-resistant tuberculosis. And this is the reason why tuberculosis requires multiple drugs for a cure.

If we take that same patient, however, and treat them with both INH and rifampin, then the ionized-resistant organisms will be killed by the rifampin, the rifampin-resistant organisms will be killed by ionized, and the patient will be cured.

What’s interesting is what happens when we talk about patients with fewer organisms. And, of course, the classic example of this is tuberculosis infection, that is, the person has a low number of organisms, so the likelihood of developing resistance, although not zero, is, in fact, very, very low. And that’s what has allowed us, for many decades, to treat tuberculosis infection with ionized alone.

I bring up all of this because the question then becomes where do children with tuberculosis fall on this continuum? And the answer is they probably fall somewhere in the middle, that is, they don’t have as many organisms as the person with cavitary disease. They probably have more organisms than a person who only has tuberculosis infection, although many patients that we see, even with abnormal x-rays are probably closer to the latent tuberculosis burden than they are to the caviar burden. And it’s one of the major reasons why development of secondary resistance while on therapy is much less common in children than it is in adults, and again, it’s strictly related to the body burden of mycobacterium that they have.

So to put it another way, we can kind of get away with some things in childhood TB that are more difficult to get away with in adult TB. But on the other hand it also makes it very difficult to know exactly what drug regimen the child needs, how many drugs, and for how long. And as difficult as this is with drug-susceptible TB, all of those issues are actually magnified if the child has drug-resistant or multi drug-resistant tuberculosis where we have virtually no randomized clinical trial data to guide us of exactly how many drugs that child needs and for how long. And that’s a very distinct difference between particularly smaller children and adolescents and adults with typical adult tuberculosis.

So the adage is more bugs and more drugs. And that's the thing that has guided us in TB therapy for decades, and, again, is particularly true for children in thinking about this.

So what are the roles of specific TB drugs? Well this is no different for children than it is for adults. Isoniazid is bactericidal and prevents development of resistance to other drugs as does rifampin. But I do want to say it appears that rifampin is a particularly important drug for children, and I don’t know exactly why that is. It may be because most of the organisms are located within fairly solid tissue. Children don’t usually have cavities with necrotic tissue. They more often have granulomas, and then the mechanical complications that occur. And rifampin may be particularly important for killing organisms in those locations.

Ethambutol, again, is mostly used as a bacteriostatic drug to prevent emergence of resistance. And pyrazinamide, as with adults, is really a shortening agent which allows us to treat kids for a shorter period of time.
So I have some cases intermixed in here and then some questions for you as part of those cases. So here’s case number one. A three-year-old girl who has been in contact with her uncle who was recently diagnosed as a TB suspect has been well. Her physical exam is normal, but she does have an 18 millimeter tuberculin skin test. Her chest x-ray is normal. So she is started on ionized. Straightforward so far. But two months later she develops a low-grade fever, a mild cough and a stuffy nose. She’s seen in an emergency department where diminished breath sounds are heard in the right upper lobe area, and because of her history of known TB exposure, her chest x-ray is as follows. And you can see the right upper lobe consolidation with actually the bowing of the horizontal fissure occurring in that particular area.

So here is more information. The CT scan of the chest revealed enlarged right hilar lymph nodes with external compression of the right upper lobe bronchus, which, of course, is a finding that’s pretty classic for tuberculosis. A bronchoscopy reveals some caseous material in the right upper lobe, but mycobacterial cultures and smears so far were negative. So what would you do? And here are your choices that you can weigh in on.

And you’ll see on your screen, as people start to press buttons, you will see some of the choices that are going to come into play.

I can see the percentages. I don’t know how many people have actually – oh, yes, I can. I’m sorry, I can see that. So you can see that the vast majority of people on the call would start this particular girl on full drug therapy, RIPE therapy. There are several different reasons why this particular thing could have happened. Number one is, of course, she may have had poor adherence with ionized. Number two is that she may have had good adherence with ionized but, in fact, her uncle’s organism was resistant to ionized. The third possibility is that we’re actually seeing the natural history of tuberculosis in children, and there are, I suspect, many children who, even though we give them ionized, actually do go on to develop some asymptomatic pulmonary findings, probably not as dramatic as this particular one in terms of the chest x-ray findings, but when ionized first came out it was pretty well shown it didn’t do that much to actually alter the natural history because, as you heard in previous talks, so much of the radiographic and physical findings in childhood TB are determined by the child’s immunologic response to the presence of the organism in large lymph nodes with subsequent blocking of various structures as opposed to the actual burden of organisms causing the manifestations of disease.

The fourth possibility, of course, is that there’s a completely different process going on here, that this child has RSV, or influenza, or something else.

I will tell you that we did start this child on full anti-tuberculosis chemotherapy and treated her for TB disease. We treated her with RIPE for two months, backed off the pyrazinamide and the ethambutol. Completed six months of rifampin and ionized, and she did very, very well with complete resolution of her chest x-ray. To be honest I don’t know if we had to do that, but that is what we chose to do because we thought the risk-benefit ratio favored that. And by the way, her uncle did have fully drug-susceptible tuberculosis.

So here are some points to ponder as we talk about treatment. What’s the real difference between TB infection and TB disease? Well, the organisms are present in both places. And we can even culture organisms sometimes from pulmonary or gastric aspirates of children who have recently been infected but don’t have any clinical or radiographic disease. We treat infection with a single drug and disease with three or four drugs, and again it goes back to mostly the burden of organisms. And the functional difference is exactly that. So I always ask my residents when we have someone who has a positive test for TB infection, why do we do a chest x-ray and a physical, and what we’re really doing is estimating the body burden of organisms so we know exactly how we have to treat. Do we have to treat for disease, for multiple organisms, or infection for fewer number.

So we have to remember for children infection and disease are on a continuum, particularly when you are finding children as part of contact investigations. And it’s not always so clear cut exactly what it is that we’re dealing with. Our convention is, if we can see it with our eyes, in other words an abnormal chest x-
ray, or feel it with our fingers, that is an abnormal physical exam, we consider that TB disease and we use the regimens.

Do we over treat some TB disease in children? I have no doubt that we do over treat it in terms of killing the organisms. But I’m also fine with that because the children tolerate the medicines so well, if anything, in children we would rather over treat than under treat. And that’s particularly true for young children, infants and toddlers, who are at increased risk of complications such as meningitis, disseminated TB and bad pulmonary TB.

Some other considerations, however. There have been very few randomized control trials that have been performed for any form of TB in children and virtually none for extra-pulmonary or multi drug-resistant TB. So we still get a lot of our information from adults. And those of us who work in childhood TB have pretty much decided if the regimen works in adults, it probably is going to work in children. And this may actually define the maximum treatment that children require. But it doesn’t, however, necessarily define the minimum treatment. Would some children do well with three or four months of therapy for TB disease? Probably they would, but those clinical trials have not been done, so we can’t endorse that.

Children do generally tolerate the existing drugs and regimens better than adults, so we do better there. But when we do probably need child-specific data is when we’re dealing with new drugs or shorter regimens. We need to make sure that those regimens still do work in children, although we think theoretically they likely should. But we would need child-specific data for those two things.

So if we’re talking about therapy for TB disease, and usually, again, most of the time we’re dealing with drug-susceptible TB, and we assume that’s what we’re dealing with, we start with either three or four-drug therapy. And this concept has changed over the last five or six years in the United States. For a while it was said start with rifampin, ionized, PZA – or I’m going to call that RIP, and only add ethambutol if you have risk factors for drug resistance. And most of the time those risk factors are either the child’s come from an area with high resistance rates or their source case has risk factors for resistance. And now we’re kind of back where we were before where more and more the trend is that if the child is at low risk for resistance, to go ahead and start rifampin, ionized, and pyrazinamide and only add ethambutol. It can be done either way, and it really depends on the epidemiology of your area and the population of patients that you tend to see.

And then we went through a period of time where the American Academy said, no, no, start everybody on RIPE therapy, and then stop the ethambutol when you know that the child has drug-susceptible TB. And now we’re kind of back where we were before where more and more the trend is that if the child is at low risk for resistance, to go ahead and start rifampin, ionized, and pyrazinamide and only add ethambutol. It can be done either way, and it really depends on the epidemiology of your area and the population of patients that you tend to see.

We still use pyrazinamide only for the first two months as our shortening agent unless we’re dealing with drug resistance. And we certainly, if we start ethambutol, we stop it once we know that the person has PAN-susceptible TB, so if I’m starting a child and I find out that the child’s source case has drug-susceptible TB, we will immediately stop the ethambutol. Which also brings up an important principle that when you’re dealing with a child with TB, you’re really managing two patients. You’re managing the child, but you’re also managing, or at least getting information from, the adult that that child got tuberculosis from because that may be your only source of information about drug resistance.

We anticipate in general a minimum of six months of therapy, but we do extend it longer. In our clinic, we get chest x-rays at diagnosis, two months into therapy when we’re considering stopping the PZA, and again at six months. We certainly have some patients with extensive disease, some patients who are very, very young who we may extend therapy to a longer period of time. Please remember all these things are just guidelines and you still have to manage individual patients. Children, as you know, it’s hard enough to establish their diagnosis by culture in the first place, but defining a more difficult course or even relapse with repeat cultures almost never happens. So we have to look at resolution of chest x-ray, the child’s growth and development being very, very important. And take all these things into consideration. So there may be times when you want to extend therapy to nine months based on your clinical experience and clinical acumen.
And as far as I’m concerned, the absolute standard of care for treating childhood TB disease is directly observed therapy. There would have to be an extraordinary circumstance for us to not do that.

I want to talk specifically about ethambutol since this seems to be controversial although it really shouldn’t be. Children metabolize it faster than adults, and that’s why now the standard dose of ethambutol for children is 20 milligrams per kilogram per day. Even at this dose the risk of optic neuritis is very, very low. The one population you have to be concerned about is people with renal disease because ethambutol is one of the only TB drugs that’s mostly renally excreted.

And I put on here you can feel very comfortable using ethambutol even in the pre-verbal child in whom visual acuity screening is challenging. We do not routinely do visual screening. We do not send them to the ophthalmologist, children of any age. And I have to say, knock on wood, I’ve never had any problems at all. Remember, however, that ethambutol doesn’t cross the blood-brain barrier very well, and in my opinion should not really be used for TB meningitis although, as you’ll see in a second, the World Health Organization does recommend it. To be honest it doesn’t make sense to me because there are better drugs that do cross the blood-brain barrier very, very well, so I know here in Houston we do not use ethambutol when we’re concerned about CNS, we use other drugs that we’ll talk about in a minute.

So there’s four different regimens, kind of standard regimens, to be used in adults, and they’re really the same drugs. This is for RIPE therapy, but it’s using different schedules and different timing.

So the first one is the standard regimen of giving the RIPE therapy daily for either five or seven days a week. There’s no data specifically for children that says anything about five days versus seven days. In Houston we give it by real DOT five days a week and then leave medicine with the families on Saturdays and Sundays and that’s because of budgetary constraints.

And then, that’s for the first eight weeks. And then when we drop the pyrazinamide and hopefully the ethambutol, then the INH and rifampin can be given either daily or intermittently. So a couple comments about this. We are more likely to continue daily therapy in young children, infants and toddlers, because of simply the volume and burden of medications that they have to take if they’re taking medication twice a week as opposed to every day. That’s particularly true during the first phase of therapy when they’re on four drugs often plus B6. To try to do that twice weekly in a very small child is extraordinarily difficult.

Also in the United States, our standard is pretty much that we give therapy twice weekly. Internationally there’s much more of a trend to give it thrice weekly. Actually in pediatrics there’s more data to support twice weekly medicine than thrice weekly medicine. Those of you who follow international standards will know that the WHO is kind of negative about intermittent therapy in children, and the reason for that really is because of HIV. We don’t want to treat kids with HIV with intermittent therapy, and because so much TB in high-burden countries is occurring in situations where HIV is a consideration, WHO has really downplayed the use of intermittent therapy. But in the United States, intermittent therapy has been used for a very long time with a huge amount of experience, and we feel very, very comfortable using it in children of any age if they can handle the burden of medications.

The second variation of this is, again, six months daily plus intermittent. And this is actually the regimen that we use in Houston and have used now for 25 years. And that is to start drugs daily for the first two weeks, and then switch to usually twice weekly therapy for the following six weeks with all four drugs. And then in the continuation phase, give ionized, rifampin two days a week for the following 18 weeks to complete approximately six months of therapy.

For most children with straightforward disease, particularly those picked up on contact investigation with fairly minimal disease, this regimen is extraordinarily effective. But we use it in a wide variety of patients with a lot of success, and I’d just tell you, we added up my numbers recently. I’ve treated over 1,000 kids with TB disease, and we’ve had exactly two relapses. And in both cases the children admitted that they had actually cheeked medication and spit it out after the DOT worker left the house. So we have pretty strong reason to believe that the regimens that we use are quite effective.
The third possible variation of this is to use intermittent therapy from the very beginning. This is not used very often in the United States, either for children or for adults. It is used in some countries like India and so forth, and there’s just not a lot of data on this particular regimen for children. There is some, but there’s not very much.

And then the final regimen is if PZA cannot be used for some reason, particularly if adverse effects occur, then we have the nine month regimen without pyrazinamide using just the rifampin, ionized and ethambutol, usually daily for eight weeks and then either daily or intermittently to complete nine months of therapy.

So we use variations of these same adult-type regimens in children depending on the circumstance, the age of the child, severity of the disease, whether or not they develop adverse reactions, and all of these are available to you depending upon the circumstance.

And please remember when you read something like the American Academy of Pediatrics Red Book, it tries to make recommendations or guidelines for the vast majority of patients. It is not intended to consider every single situation that you might encounter, and as with any therapy for anything, it is perfectly valid to have variations from those particular guidelines or recommendations depending upon the circumstances of the child.

So just to review what WHO does say, this is what they actually say about pulmonary and lymph node TB in children. They think the standard therapy is two months of daily RIPE therapy plus four months of daily ionized and rifampin. And where the prevalence of ionized resistance and HIV infection are low, then you can eliminate ethambutol from that particular regimen.

In HIV uninfected children with drug susceptible TB, they are okay with three times a week, thrice weekly, regimens used in the continuation phase, not even in the first phase. So they would treat daily for two months even under these particular conditions. But notice that these are even weak recommendations with what they consider very low quality of evidence. I'll be honest with you. I disagree with their evidence rating. I think the evidence for intermittent therapy is far stronger than this expert panel considered it to be.

And finally children with HIV infection should not receive intermittent regimens.

Now, when we talk about tuberculous meningitis, or osteoarticular tuberculosis, one of our problems is really a lack of data. Again, lack of randomized control trials. There are lots of case series, but almost no randomized control trials. What the WHO says is that children with these two conditions should be treated for 12 months with RIPE therapy given for two months and then ionized and rifampin given for the following ten months.

We have a little variation from this. The American Academy of Pediatrics recommends nine to 12 months for the treatment of TB meningitis, and I can tell you in my clinic our standard treatment is, in fact, nine months of therapy. And there’s actually a lot of data to support six months of therapy for TB meningitis, but most of us go for at least nine months. And also the American Academy of Pediatrics says that it really would not use ethambutol as the fourth drug for meningitis. It would either use ethionamide if an oral drug is indicated or amikacin if an oral drug can’t be given and you need that fourth drug. Some folks have recommended fluoroquinolones, but there’s virtually no experience in children with fluoroquinolones, although I have to say there’s data emerging from India and other places about very improved outcomes in adults with tuberculous meningitis using high dose rifampin and moxifloxacin. So this an area of thinking that may be evolving, and more and more pediatricians are using fluoroquinolones as part of the initial therapy. But until we get more published data, these recommendations, the use of ethionamide or amikacin as the fourth drug is usually considered pretty standard.

The WHO says for osteoarticular tuberculosis, the treatment also should be 12 months. Again, the American Academy is kind of softer on this and says for osteoarticular as other forms of extra-pulmonary
other than meningitis, usual regimens, the regimens usually used for pulmonary TB can be used. I know many clinicians in the United States who do extend therapy for osteoarticular TB to nine to 12 months in children. Again, there are no randomized control trials, and actually there’s very limited even case series guiding us in this particular area. There certainly are case reports, mostly of adults, who have not done well with six months of therapy with osteoarticular TB, but we really have virtually no data in this area when it comes to children.

A few notes on the standard tuberculosis drugs. Again, remembering ionized, the major toxicity in children, although it’s rare, is hepatotoxicity. We don’t see very much peripheral neuropathy in these particular kids, and as you’ll see in a minute, we don’t routinely give vitamin B6 except to children who are being breast fed, pregnant teenagers if they have a poor diet for some reason, or if they’re immunocompromised. Those kids we will routinely give vitamin B6 to.

One of the reasons, particularly in small children, is it’s one more drug. So if they’re already taking four drugs, which is hard enough for them to take, and then they have to take a fifth drug on top of this, sometimes you reach the level where the children just simply can’t tolerate it any more. So that has to be a clinical decision.

Rifampin, again, obviously important to remind people about the urine. But one of the most important points we always make is making sure that for teenagers it is understood that oral contraceptives may be inactivated by all erythromycins, and that these girls cannot rely on oral contraception during the period of time that they’re taking the rifamycin drug. And it is critical that you have that discussion with them.

We find, actually, we don’t see much hepatotoxicity, but we actually see pyrazinamide is our number one cause of hepatotoxicity. In fact, all of our adverse reactions, especially those that sort of require stoppage of therapy to figure out that PZA is actually sort of the number one culprit.

And finally, ethambutol, we see extraordinarily few problems. Again, it’s hard to even find a case report in the pediatric literature of any kind of eye problem, optic neuritis, in association with ethambutol, and as you’ll see in a few minutes, there’s other drugs, including ionized, that can cause optic neuritis, too.

So if we look at medication tolerance, the published reports suggest that about five percent of children have some kind of adverse effect while taking standard TB therapy. Most of these are minor. Abdominal pain without elevation in liver enzymes. But about three percent are elevation in liver enzymes, but most of those are asymptomatic. I am sure there are kids that have asymptomatic elevations that we don’t know about, but the natural history is that they tend to resolve spontaneously as the child continues to take therapy.

Again, in our experience, we’ve seen more hepatotoxicity from pyrazinamide than we have from ionized or rifampin, and peripheral neuropathy is very, very rare in younger kids.

In contrast, adults, three to four percent will have significant hepatotoxicity with INH alone, and up to five percent when INH and rifampin, they’re much more likely to have more severe liver involvement including symptomatic hepatitis. And up to four percent of adults will develop peripheral neuropathy while taking ionized.

So now we have a second case talking about adverse reactions. These are real cases, by the way. A 17-year-old boy with Crohn’s disease who has been on Remicade does poorly with conventional therapy. Before starting the Remicade he had two different TB skin tests which yielded no induration. But about six weeks after starting Remicade he develops fever, a five-pound weight loss, cough, some respiratory distress, and his chest x-ray looks like this. Pretty nasty looking disseminated TB with a lot of involvement obviously in the upper lobes.

He’s started on four-drug therapy, standard RIPE therapy for tuberculosis, and he does well clinically initially. His sputum culture is positive for pan-susceptible tuberculosis, and the ethambutol is stopped.
But after five weeks of treatment he develops abdominal pain and decreased appetite, losing six pounds. The physical exam reveals abdominal tenderness, worse in the right upper quadrant, and his liver enzymes, as you can see, are markedly elevated. What would you do? And here are your choices. Stop all the drugs. Stop the current drugs and start amikacin and the fluoroquinolone. Stop current TB drugs and start ethambutol and amikacin. Stop TB drugs and start ethambutol, amikacin and a fluoroquinolone, or do something else. And please go ahead and weigh in.

Well the vast majority of you, so far, interestingly, would stop all TB drugs with about ten percent of you – well, it seems – I should be quiet for a minute because the percentages are changing. About 70% would stop the drugs. About 16% would stop the current drugs and add another three-drug so-called liver-sparing regimen. So let’s keep going and see what happened.

So all his anti-tuberculosis drugs were stopped, and he was started on amikacin and ethambutol. Let me say, this is an older case, and if I were doing this case now, I would also start the person on a fluoroquinolone as well is what I would do now. But at this time, he was started on amikacin and ethambutol.

After two difficult weeks in the hospital, his AST and ALT came down to below 100. We reintroduced ionized, which again led to abdominal pain and an AST of 337 after only about three days. So now what would you do? Stop the INH until the liver cools down then restart RPE? Stop ionized and start RPE right away? Stop ionized until the liver cools down and then start RPE plus a fluoroquinolone? Or something else. And I’ll give you a few seconds to respond.

I see the percentages coming in, and the vast majority of people would stop the INH until the liver cools down, then start rifampin, pyrazinamide, ethambutol and a fluoroquinolone. Nothing here, I think, is necessarily an incorrect answer. What we actually did in this particular situation is we did number one, we stopped the INH until the liver cooled down, which only took about a week or so, and then we restarted him on rifampin, pyrazinamide and ethambutol. We did not start a fluoroquinolone in that particular situation. And we did this because he had already had great improvement, even in his chest x-ray, but in his tuberculosis symptoms, so we thought we had a little bit of time. And he ended up completing a nine month total regimen with rifampin, pyrazinamide and ethambutol, and did extraordinarily well with rapid clearance of the organism and no relapse in at least a two-year period of follow up.

So dealing with these adverse reactions can be tricky and deciding whether or not to stop medications, whether or not to continue other medications, are often very difficult decisions. I don’t think there’s sort of one right or wrong answer to these particular things. Fortunately they happen much less frequently in children than they do in adults.

Remember, also, that children get lots of intercurring illnesses while they’re on therapy, and so they can get, for instance, liver enzyme elevations in association with other infections, EBV, CMV, even influenza, so it’s important to consider other potential causes.

A few other pearls for medication administration. We have an INH suspension in the United States. It has lots of sorbitol, and when you get above five ccs, or above a five kilogram child, they tend to have GI intolerance of lots of diarrhea. So our cutoff for using INH suspension is usually around five kilograms.

Again, warning parents about rifampin and urine color, adolescents about oral contraceptives. If you have a child who is hospitalized, try to make sure, particularly young kids, that they can tolerate the medication dosage prior to discharges. And sometimes with little babies we actually have to divide medication during the course of a day because they just simply can’t tolerate the volume of all the medications being given at once as would normally happen with DOT.

And, again, intermittent therapy being difficult for infants and toddlers, so we are much more likely to prolong daily therapy in the very little kids simply because of the mechanical issues.
So how do we follow kids with drug-susceptible TB? We remind people that their tests of infection tend to stay positive forever, and we make sure we emphasize that in the letters we give them.

Frequent x-rays are not necessary. Things don’t change very fast. And we do them at diagnosis, about two months of therapy, and the end of therapy to document their new baseline after they finish therapy.

Please remember that approximately half of children will still have an abnormal chest x-ray at the end of successful therapy. It will be improved, and their symptoms, of course, will be gone, so it is not necessary to have a normal chest x-ray to stop therapy. In many situations, those findings, particularly if they are lymph nodes, will resolve. Some children will form permanent scarring in the lung parenchyma, and certainly they can also develop calcification as well.

If we have a child who still has an abnormal chest x-ray at the end of therapy, we stop therapy but we tend to see them back in a year or so and repeat the x-ray to get a better feeling of what their real final baseline x-ray will look like moving forward in their life.

Following growth and development is extraordinarily important, and it’s one of our best indicators of how well a child is doing. Making sure they get adequate nutrition. We do not routinely check liver enzymes even in little kids, and even taking multiple medications. And as I said, routine vitamin B6 not necessary except for a few specific indications.

Steroids are used when the host’s inflammatory response is causing more harm than good. And usually that means it’s affecting an organ. It may be affecting a structure or something that’s causing mischief. So we will virtually always give corticosteroids for TB meningitis. I actually don’t use it very much anymore for endobronchial tuberculosis, but some people do.

If they have miliary TB with alveolar block, in other words air hunger, pericardial disease with constriction, or vertebral or spinal root irritation in association with osteoarticular, we will then give steroids. And you can use either prednisone or dexamethasone. There are studies showing either one to be effective. We usually give it from four to six weeks with a two-week taper at the end.

So now let’s change gears a little bit. A 15-year-old girl from Nigeria arrives in Houston for her sister’s high school graduation. On her way to the ceremony, she stops off at the emergency department for some medicine for a mild cough. You hear diminished breath sounds and you find this chest x-ray. This is another real case.

You start her on standard four-drug therapy. The AFB smear of her sputum is positive and her culture grows M. TB resistant to ionized, rifampin, pyrazinamide and ethambutol. What do you do? Number one, continue the RIPE therapy and wait for the full drug susceptibility report. Stop all drugs and wait for the susceptibility report. Start moxi, immune glycoside, cycloserine, and PAS, start the regimen above plus (inaudible). Or something else. And please vote.

It looks like the sort of majority of people voting are voting to stop the medications and start an alternative regimen. This is a very, very tricky situation. And I will tell you that that’s not what we did in this particular case. As many of the adult TB people will tell you, one of the problems is when you don’t know the drug susceptibilities, there is a real possibility of burning additional drugs if you really don’t understand the drug susceptibility pattern. This is a teenager with adult-type disease, so she is much closer to an adult than a child. We also have, of course, public health considerations of the person potentially being infectious. So what we did in this case is we stopped her on her therapy and then did the best acceleration we could of drug susceptibility results for her.

And I want to make a point about this as well. When you have an adult with drug-resistant TB and you’re dealing with a child, many times the internal medicine people don’t understand how important it is that we get drug susceptibility information as soon as possible so we can get the child on the appropriate therapy, whether it’s for TB infection or TB disease. And it’s very common that we have to call health departments
or the people taking care of adult patients and say, please get this isolate off to the CDC for MDDR testing or something else because we need to know as quickly as possible what the drug susceptibility profile is so we can do the appropriate regimen.

So when we see teenagers that have adult-type disease and we really do have to worry about burning additional drugs, I think in many cases, unless the person is really critically ill, the advice would be to not go ahead and start other medication, but to try to get as rapidly as possible, drug susceptibility results and then act accordingly. And, of course, for little kids, we would say the same thing for adults from whom they contracted TB.

This is the amount of medication it takes to cure drug-susceptible TB. This is the amount of medication it takes to treat MDR-TB. And think about what this looks like to an adult patient, and then think about what this looks like for a two-year-old.

I had actually a 12-month-old two years ago who had MDR TB meningitis. And you can imagine what that ended up looking like and what that child and family went through in order to – and fortunately successfully – be able to cure that child’s tuberculosis.

We don’t know very much about treatment of drug-resistant TB in children in terms of actual data because there isn’t much. There are several international drug-resistant TB registries for children that are being started so we can at least try to gather information from around the world of how people are, in fact, being treated and what their outcomes are. It’s not as good as randomized control trials, but at least we’re trying to get some information to guide us more than just sort of expert opinion. We do know that if children of INH mono resistance, they tend to do very well with a six, usually nine, month regimen of rifampin, pyrazinamide and ethambutol. And that is what we would use in Houston for a child with ionized resistance but otherwise susceptible pulmonary tuberculosis.

For MDR and TB treatment, again, no randomized trial so it always has to be individualized. Depending on their exact drug susceptibility profile, the anatomic location of disease, the extent of the disease, how well the child is tolerating medicines, and fortunately the kids tend to tolerate them better than adults. And we think with children, just like adults, it usually does require four to six drugs to which the organism is susceptible with two being bactericidal. But, again, remember, as we said, children in general have a much lower body burden of organisms, and they may be differently metabolically active in adults.

So while we know adult regimens work in children, that may be the maximum therapy children need. And some children with multi-drug resistant TV probably needs much less medication and for a much shorter duration of time than adults do, but we just don’t know because we just don’t have any information.

There are some issues in the management of MDR TB in children. Again, clinical trial data very limited. Optimal drug combinations are unknown. Optimal durations of therapy are unknown. And we are lacking pharmacokinetic data even for the old drugs. I’m not talking about new things like bedaquiline, but even things like cycloserine and PAS in their current forms. We have no pharmacokinetic data for children, and particularly for infants. So we are constantly just making this up using dosages based on what would be done in adults. We certainly have no child-friendly dosing form, so as difficult as it is to treat drug-susceptible TB, it becomes even more difficult to, for instance, crush up those little Sudafed-looking tablets of ethionamide in order to get a child a proper dose.

Adverse drug effects are more difficult to assess in children, but they do tend to be much less frequent, which is a good thing. And, again, children have more intercurrent illnesses, so trying to decide number one, if the TB is not being properly controlled, number two if they are having adverse reactions to drugs as opposed to having an intercurring illness of some kind can be very difficult. And it’s important to be able to look for some of those causes of intercurrent illness.

Just a few notes on specific drugs. Amikacin, peak serum concentrations do tend to be higher in children than they are in adults for a given dose. In adults, amikacin, like capreomycin, is usually given IM.
children we are much more likely, if we need it, to put in a picc line and give it IV. And amikacin dosing is difficult because I get asked all the time, does it need to be given daily, can we give it three times a week. I will tell you that the answers to those questions are unknown. There is some data coming out of South Africa about treating children daily with amikacin for a shorter period of time, one to two months, and then backing off to giving it three times a week up to about six months of age. And most of us try to get rid of the amino glycosides by four to six months of age to protect the child’s hearing. That’s the most common adverse reaction in children being treated for MDR-TB is hearing loss due to amino glycoside therapy.

If you use levofloxacin, the dose should be increased to 15 to 20 milligrams per kilogram per day for children. We now have some very good PK data that shows that that is the better dose as opposed to the lower five to ten milligrams per kilogram. More and more amoxyfloxacin is being given to children, but I have to tell you we have virtually no PK data for any children and certainly none for infants and toddlers. So we’re just guesstimating on doses, but what we have found with levo is those children need relatively more medication, so it may be true that that ultimately is the case for amoxy, but frankly, we just don’t know.

Linezolid is being used more and more to treat multi drug-resistant TB in children. We use linezolid a lot in kids for short-term duration for staff infections, but limited for long term. There is a risk of optic neuritis, much higher risk than with ethambutol. They also can get peripheral neuritis and bone marrow suppression, and about ten to 20% of children started on linezolid for TB have to have it discontinued because of adverse reactions that are listed here.

Cycloserine we don’t know much about in kids. They don’t seem to have as frequent neurologic and psycho neurologic effects, but we would still give pyridoxine and serum levels.

The next few slides I have are adverse events associated with various drugs, and because of time these are drugs that I’m really putting in there for your reference. So I’m really not going to spend any time, and I’m just going to go to our last case.

So case four is a 14-year-old girl presenting with a mass in her right neck and an 18-millimeter reaction to a TB skin test. The mass started about two months ago and has grown, finally opening up and having a slightly bloody white discharge. There is minimal pain and tenderness. She has no systemic signs or symptoms. What would you do? There are no choices with this until we get to the very end.

She’s referred to your ENT surgeon, who performs and incision and drainage, which is not what we would have wanted done. We would have either wanted a needle aspiration or an excisional biopsy because of the suspicion of mycobacterium, but an IND was done. Histopathology of some of the tissue showed caseating granulomas with some AFB positive organisms. Culture is pending. Now remember, if this were a two-year-old, we’d be very suspicious about non-tuberculous mycobacterium, but in a child of this age, a teenager, that is a very, very rare infection, and this is almost always mycobacterium tuberculosis complex, either TB or m. bovis.

This girl was started on ionized, rifampin, pyrazinamide. Culture showed no growth. After six weeks of therapy she develops abdominal pain and a right upper quadrant tenderness. Her AST and ALT were elevated as you can see. We stopped all of her anti-TB meds, let the liver enzymes cool down, which they did, and we restarted rifampin and then pyrazinamide. She had no problems. So we took this as evidence that probably ionized was the culprit. So instead of rechallenging her, we added ciprofloxacin. And this is a bit of an older case, too, so that’s why it was cipro as opposed to levo. Now we would start her on levofloxacin.

So she’s on rifampin, pyrazinamide and cirprofloxacin. She took the medications twice weekly under directly observed therapy for a total of nine months. Did extremely well with minimal scar tissue. But four months later, we got a call from the family because she had again developed a draining lump at the previous site of infection. And you’re concerned about the diagnosis of possibly drug-resistant TB, so you refer her to the ENT physician who did do an excisional biopsy. Histopathology reveals a node with...
caseating granuloma and rare AFB-positive organisms, but you find out the entire surgical specimen was placed in formalin, so no culture was done.

I’d like to tell you I’m making up this case, but I’m not. This is a real case. And unfortunately these kinds of things happen.

So you start her back on rifampin, PZA and now levofloxycin. Two months later she informs you that she’s pregnant. Against your adamant advice. Now what would you do, and here are your choices. Quit your job. Transfer out of tuberculosis clinic. Declare her an adult and transfer her to internal medicine. Keep treating her and hope for the best. Or take her off all TB therapy. And obviously this is meant to be a little bit tongue-in-cheek at the end of a talk.

We ended up – I will tell you that we ended up, again letting her liver cool down. And actually we thought she most likely had an intercurrent illness, which she, in fact, did, and we put her back on therapy which she took – we actually stopped her – well, we stopped her pyrazinamide and treated her with rifampin and the fluoroquinolone. The problem is in a pregnant patient, what do you do. And it’s a question of trying to do the best of difficult choices. And we also added ethambutol at this point in time. She ended up getting treated for nine months. She did well. The baby did well. And I think it’s another example, maybe, of it’s more important to be lucky than good in this particular case.

So our final summary slide is that children tolerate treatment for drug-susceptible TB very well. Frequent biochemical monitoring is not necessary. A variety of regimens and schedules can be used as dictated by resources, drug tolerance, and psychosocial circumstances of the family.

Regimens that work in adults do tend to work in children, but the PK of new drugs needs to be established, amoxyfloxacin being an example.

Children tolerate drugs used particularly for MDR-TB pretty darn well, but there’s no clinical trial data for specific regimens, anecdotal experience suggesting they do well with individualized therapy.

And I will stop. Thank you so much for your attention.

Thank you very, very much Dr. Starke. I do have a few questions and even though we are kind of short on time, we’ll try to see how much we can get done in the next ten minutes.

So first question is do you have an age cutoff for intermittent therapy during the continuation phase?

No, we don’t. We do tend more often to use daily therapy in the little kids, but we certainly have treated some little kids with intermittent therapy, so age is not the only cutoff that we use.

So it’s more like if they are able to tolerate the volumes, right?

Yes. And we’ve had some kids that we’ve tried on intermittent therapy, found out they had difficulty tolerating it, and went back to daily therapy. Again, we work closely with health departments, and we’re very cognizant of limited resources. So we try to do the best. But the Houston Health Department in particular, is wonderful about doing whatever the child needs. They’re terrific.

That’s great. Another question is about the case of the 17-year-old with the (inaudible) disease. The question is did you consider maybe abdominal TB in his case, and if he was foreign-born, was there any risk of resistance?

This was an interesting case because he was born in the U.S. In fact he had lived in the same house his entire life. And in Houston, we do molecular typing of all TB isolets, and he had a completely unique islet. There was no other islet going back ten to 15 years that was the same. So to this day we have no idea where he got his TB. We did, of course, consider abdominal TB. He had no evidence of enteritis. He
wasn’t having diarrhea, and clearly with Remicade, and enteral TB can be an issue. So we considered that, but his lack of symptoms and then his rapid response improvement to taking away the ionized, we didn’t think that was an issue.

Very good. Very good. Another question. I know you said that you don’t necessarily routinely monitor blood work in the kids, but do you do them at baseline, like CBC, CMT, something like that?

We do no labs at baseline simply for drugs. We ask a lot of questions, finding out the child has a history of hepatitis and particularly if the child is on any potentially hepatotoxic drugs. Under those circumstances we would get baseline LSTs, but for kids not taking medications, no liver history, we do not get baseline labs. My mentor Catherine Sue (sp) always taught me that children don’t want to come back to see you when you stick them for blood, and I don’t think there’s much benefit to doing it in an otherwise healthy child with a clean past medical record.

Excellent. One more question. Since the guidelines usually give a range of dosing for pediatrics, do you always recommend to go with the higher of the range or just with some particular drugs?

The major reason for a range is because we don’t have pediatric-friendly dosage forms, there’s a practicality. I mean, ionized you can kind of break down into 50 milligram increments if you use 100 and 300 milligram pills with 250 milligrams being the hardest one. So that’s one of the reasons for ranges.

No, don’t necessarily shoot for the higher range. We just want to be within the range. Some people think if you have more serious disease you might benefit from a higher dose. There’s really not much data to back that up. So we’re just happy if we’re within the appropriate range.

Okay. Then the last question that we’ve got is do you think there is a role for streptomycin as a first-line regimen for TB meningitis in children?

Yes, I think streptomycin is an acceptable drug. You know, we all got used to not using it because it simply wasn’t available, and that’s why we flipped over to using amikacin. Certainly in an older child where you might be able to give an IM medication, if it’s susceptible, then I think streptomycin is a useful drug, and there is a fair amount of data supporting its use specifically for TB meningitis. So it is okay to use. It’s really not considered first line anymore, but there are arguments to be made for it.

And I think with that we’re going to conclude our session. Thank you very much, Dr. Starke. That was an excellent presentation.

Thank you. And thanks to everybody for listening.