Advanced Concepts in Pediatric TB:
Pharmacotherapeutics of TB Drugs

Welcome to the eighth of eight sessions on, "Advanced Concepts in Pediatric TB" sponsored by The Southeastern National Tuberculosis Center. Today we present: "Advanced Concepts in Pediatric TB: Pharmocotherapeutics of TB Drugs" Today's presenter is Dr. Charles Peloquin. Prior to coming to the University of Florida, Dr. Peloquin completed a hospital pharmacy residency at Duke University Medical Center where he also served on the clinical staff.

He completed a fellowship in infectious disease in pharmacokinetics at the Clinical Pharmacokinetics Laboratory, Millard Filmore Hospital in Buffalo, New York. For twenty years he was the director of the infectious disease pharmacokinetics laboratory IDPL at National Jewish Medical and Research Center in Denver, Colorado. He now serves as professor of pharmacy and medicine at the University of Florida, where the IVPL is now located.

Dr. Peloquin and his lab are a part of the UF Emerging Pathogens Institute. He is also a consultant to the FDA, the CDC, and the SNTC. Thanks for joining us.

Thank you for the introduction and welcome to the webinar. Today we're going to focus on pediatric patients and the use of drugs for patients who have tuberculosis. The objectives will be to look at the general principles of antimicrobial use, sometimes overlooking the treatment of tuberculosis, as well as the pharmacokinetic principles, monitoring for toxicity, spectrum of activity of these drugs, how they work. I'm not going to stress a lot of the details for a mechanism of action. Roots of administration, adverse effects, and so on.

Then we'll talk a little bit about therapeutic drug monitoring that may have a role in some patients that you will see. This is the list of drugs that we have at our disposal and you can see it's a pretty short list of drugs that are actually approved for the treatment of tuberculosis. For those of you following the NBA finals you might say that Rifampin is the Lebron James of TB drugs. You might be a Golden State Warrior Fan and then say it's a Steph Curry kind of drug. At any rate, Rifampin is the most important drug.

An alternative to Rifampin is Rifapentine, which is much more studied in adults than it is in children. Then we have other drugs, including Isoniazid, that is very important. Pyrazinamide that is very important. Then the rest of them are simply role players that have a particular role, especially in drug resistant cases. Among other drugs that we might choose to use for the treatment of tuberculosis are drugs that are not actually approved by the FDA for that indication. That's not necessarily a problem if you have a rationale for using the drug, you certainly may use the drug to treat your patient.

Nevertheless if you went to the package insert you would not see some lengthy approval discussion for tuberculosis. Other aminoglycosides besides Streptomycin that we might choose include Amikacin or Kanamycin. Amikacin is probably the one that most people use. It's readily available and you can get assays measured at most local hospitals. That's probably the most convenient. Among the fluoroquinolones currently available moxifloxacin and levofloxacin are the preferred agents for the treatment of tuberculosis.

There is no head to head study that shows that one is definitely better than the other, at least in long term treatment. At this point it's a choice and we can talk about why you pick one versus the other. Other drugs that we could consider that are not labeled for TB and may or may not have a big role include the macrolides: Azithromycin and Clarithromycin. These are indicated for Mycobacterium Avium Complex or MAC, but they're not indicated for tuberculosis.

At least in-vitro they're very weak drugs against TB. Whether or not in-vivo they have more activity is something that's being studied right now. Beta lactams including Amoxicillin Clavulanate have been used on a desperation basis for extremely drug resistant cases of tuberculosis. The role is clearly not established and there's no prospective randomized study to compare Amoxicillin Clavulanate Acid versus any other comparative.

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Clofazimine is a leprosy drug that's being reevaluated for tuberculosis. Initially it was developed as a TB drug but it was a wash-out at that time. People have circled back and there are some advantages of the drug. It remains to be seen on a clinical basis just how important those advantages might be. One main advantage is that it's still active even the presence of Rifampin and Isoniazid resistance. It definitely has that going for it.

Rifabutin is an alternative to either Rifapentine or Rifampin. We'll talk further about exactly where it fits in. Right now it's indicated for the treatment of MAC but it's also used for the treatment of Tuberculosis and it is listed in the TB guidelines. Linezolid and the newer oxazolidinones, Sutezolid and AZD5847 are all in the same class. Linezolid is the only one of these three that's on the market. It has been used for MDR-TB, which is multi-drug resistant tuberculosis. Again, as a minimum, resistant to Isoniazid and Rifampin.

Linezolid has a role, especially for XDR TB where you add resistance to quinolones and add resistance to an injectable. Once you get to that stage of drug resistance you're really quickly running out of classes of drugs and it's in those kinds of patients that Linezolid seems to have a role. A precise dose however has not been worked out. A few comments about pediatric cases of any disease state and in particular here, tuberculosis.

As a caveat I will say I'm not a pediatric specialist. I have been involved in the care of many children but per say I'm not a pediatric specialist. There's some great papers by colleagues, Greg Kearns and Susan Abdel-Rahman . You're welcome to look up those papers and they have really good discussions about the caveats of treating children. I'll try and do it justice here, so let's proceed.

Small children, as you already know, if you have children of your own, they can't swallow adult dosage forms. Various pharmacists, nurses, physicians, and parents come up with all kinds of wiley ways to get the children to take the drug. Crush them up or you open the capsules and you mix it in to whatever food the child likes. One of my favorite techniques is chocolate pudding, especially sugar-free chocolate pudding. Almost every child likes that so you're likely to get it into the child. It's important to realize that once they swallow it we don't have any data on the absorption from those dosage forms.

It just gets into the kid. These dosage forms may not be stable for storage. It's not like you could make a week's worth of chocolate pudding dosage forms and just keep them on the counter. I would definitely not recommend that you do that. Next children change over the course of time, you already knew that, but besides the obvious change of weight and height, inside the total body of water is changing. It highest in infants and it decreases over the first few years of life. In other words the kids are drying out.

Who cares? Well, you should care from the standpoint that some of the drugs really like to distribute to where the water is. If there's less water there's going to be more hanging in the blood, which of course is a lot of water. On the other hand if you're looking at a smaller child with a lot of total body water the aminoglycosides: Ethambutol, Cycloserine, and to a lesser extent Isoniazid are going to go those areas where the water is within the tissue spaces. The plasma concentrations are likely to be less.

Over the first six to twelve months the renal function of an infant changes and they become more adult like and then they actually exceed the renal function of adults. Renally cleared drugs, again some of these water-soluble drugs: aminoglycosides Ethambutol and Cycloserine are drugs you really need to be careful with when you're treating small children. You have two problems. You have drugs distributing into more places, but it also might be cleared more slowly. Then you have a third problem for the two oral drugs, Ethambutol and Cycloserine of getting the drug into the child in the first place.

This is not really a trivial undertaking. Total body clearance, which is the sum of renal clearance and hepatic clearance is often faster in children than in adults. If you give an equivalent dose based on weight only on a milligram per kilogram basis you generally are going to have lower plasma concentrations in children than in adults. Sometimes you might need twice the dose in a child to get concentrations that you see in the adult.

Combing the previous listed factors it typically means children need higher milligram per kilogram doses than adults after the first year of life. There are U.S. guidelines, WHO guidelines, and other guidelines out there. The doses are similar but they're not identical. Depending on what your personal favorite guideline is the doses that are going to be coming up in the subsequent slides may be similar but not identical to the doses that you're familiar with from your favorite guideline.

Here we go with specifics on the drugs, and if you heard other webinars that I've giving you might of seen slides very much like these here and that's because the drugs really haven't changed for the most part since the 1950s and 1960s. We pretty much have now what we had then with a couple of exceptions. Isoniazid is mentioned as one the primary drugs along with Rifampin for treating what we call drug susceptible TB. Let's stop and take a look at what we mean by drug susceptible.

It means that you've isolated the organism from the patient. That sample is worked up in the laboratory and it's tested against concentrations of various antimicrobials, and it shows activity at a particular concentration that's achievable in the patient. If the concentration cannot be achieved in the patient then you would consider that organism resistant to that drug. That has implications not only in the susceptibility testing end of it, but also on the drug delivery end of it. We'll come to that late in the presentation.

Isoniazid has the advantage of being giving orally, intramuscularly, or intravenously as a slow five minute bolus in about twenty-five millimeters of normal saline for an adult though, it's been proportionally less for a pediatric dose. The standard dose is three hundred milligrams, and I think you'll find in the upcoming release of the new ATS CDC IDSA treatment guidelines, I think I'm leaving out of the groups that affiliated but the national guidelines for the treatment of TB, the maximum word, the maximum dose designation is going to be removed from those guidelines.

Now that our population is getting larger and larger and there's in some cases an obesity epidemic and that does extend into the pediatric world then putting maximum doses may deprive these larger patients of the amount of dose they actually need. That's just a caveat to keep in mind. For children, usually it's in the ten to fifteen milligram per kilogram range. I'll just point out this fifteen milligrams per kilogram is going to be a recurring theme for many but importantly not all of the TB drugs.

Isoniazid is cleared by the liver. By an enzyme that shows genetic polymorphisms, so you have fast metabolizers and you have slow metabolizers. That might be an important clinical point, especially for regimens that are not daily. If they're three times a week or twice a week that might become an important variable. Some would argue even a daily dosing is an important variable.

The toxicity's associated with Isoniazid include toxicity to the liver or peripheral neuropathy. Sometimes central neuropathy. Happily children seem to tolerate these drugs pretty well. Dr. Stark I believe has recorded another lecture in this series and I will refer you to his discussion about how patients are treated and how these children tolerate these drugs.

Rifampin I've already mentioned is the key drug, it's the all-star for our team of TB drugs. It's used primarily with Isoniazid and some role players, if you will, in the treatment of TB. It is given either orally or intravenously. The standard adult dose is six hundred milligrams daily. The pediatric dose I would lean towards the twenty milligram per kilogram end of the range here, for the adults. Your standard dose of Rifampin is going to change.

It is cleared by the liver but it is not cleared by the cytochrome P450 system. It can produce either liver toxicity, at a pretty low rate, or a flu-like syndrome especially if the patient is taking the drug intermittently. Some studies a long time ago show that if you gave very large doses, once a week, eighteen hundred milligrams once a week, after several months ten to twenty percent of the patients would have this flu-like syndrome that would come and go after the dose of the drug. If you give it daily you should not be seeing that. If you are seeing it, and the patient is getting self-administered therapy, it's telling you that they're probably not taking it every day.

Rifapentine is a derivative of Rifampin, it's cyclopentyl Rifampin. It would be used instead of Rifampin and not with Rifampin. Just released by this reference here at the bottom in the American Journal of Respiratory Critical Care Medicine this year, 2015: The new dose was seven days a week with food, twelve hundred milligrams of Rifapentine. This dose here for children is probably now at the low end of the range. This Study Twenty-nine here did not include children so this dose may change upward in a couple years. Right now that's a ballpark estimate of a reasonable dose for children, and I'll have more in just a slide or two on that.

That will be this slide right here. Study Twenty-six, and the last one was Study Twenty-nine X, but Study Twenty-six was for latent tuberculosis as opposed to active disease. Everybody was getting a once weekly regimen as opposed to a daily regimen. This study included kinetics and tolerability in children and that was published in the Journal of Pediatric Infectious Diseases a year ago, June of 2014. The punchlines from this story are a two-fold greater Rifapentine dose for all children resulted in a one point three fold higher AUC. We doubled the dose but we barely got a hundred percent, we got a hundred and thirty percent on average of the AUC seen in adults. It looks like you have to double up the adult dose to get reasonably close exposure in children.

It made a big difference whether they could swallow the whole tablet, which was better or the crushed tablets, which was much more variable. Again as pointed out at the beginning of this presentation extemporaneous dosage forms might be necessary, but you cannot expect them to deliver the same kinds of concentrations consistently as you would get from a dosage form designed for children. Again the other conclusion here, uses of higher weigh adjusted Rifapentine doses for young children are warranted to get the exposures that are associated with successful treatment in adults.

Rifabutin was mentioned earlier, and it's a drug that's actually approved for non-tuberculosis micro-bacteria, specifically M. avium complex. It also is reasonably against TB. It is not a one to one switch for Rifampin however because it has some differences. You usually use it in cases of HIV positive TB or in other cases where patients have complex medical situations and they're on a lot of other medications. Rifampin is a very potent enzyme inducer and it changes the pharmacokinetics of a lot of other drugs. Rifabutin does so, but much less, so that's the advantage of Rifabutin.

Standard adult doses are three hundred milligrams daily but there's a range even up to six hundred milligrams daily. There's not good pediatric data for Rifabutin so we estimate, and it's purely an estimate, to five milligrams per kilogram. This would be a drug that I would definitely consider therapeutic drug monitoring because we really don't know if this dosage is right, but we have a really good idea of what the concentrations ought to be, and we'll talk about that shortly.

It's also cleared by the liver but the toxicity profile is different. It causes neutropenia, thrombocytopenia, and anterior uveitis. Generally that's not site threatening but it's certainly irritating and it's something to watch for. This seems to be concentration dependent, so Rifabutin if it's either overdose or if it's giving with other drugs that affect its clearance, because unlike Rifampin it is partially clearing by the cytochrome P450 system. If you give a drug like Ritonavir or if you give a drug like Cobicistat, it's going to block the clearance of Rifabutin and therefore you might run into a situation where you could have anterior uveitis.

It was most clearly seen back in the 1990s before the highly active anti-retroviral era when patients who had disseminated MAC were getting Fluconazole and Clarithromycin, two enzyme inhibitors and those patients could run into problems with anterior uveitis. It's not that common but it's something to watch for. Here's the comparative chart, both on the Cytochrome P450 3A4 induction and this enzyme is responsible for the clearance of about half of all the drugs that are cleared by the liver, so it's very important.

Previously it was thought that Rifapentine was less potent than Rifampin but Rifampin was tested daily and Rifapentine was tested twice weekly. If not surprising there was a difference. Now that we're dosing

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Rifapentine daily for active TB it's at least as potent as Rifampin. The flu-like syndrome was talked about, I talked about these toxicity's which are different for Rifabutin and then Rifapentine is very very highly protein bound. In our laboratory it's ninety-nine percent protein bound. That has implications because only the free drugs, not the protein bound drugs, is available to interact with mycobacteria.

Pyrazinamide is the ninja of the TB drugs. It seems to act against a particular group of the organisms that are slowly multiplying in an acidic media, such as certain portions of cavitary lesions. In general children don't have cavitary lesions so it's a little less clear how important Pyrazinamide is in the treatment of Hilar Adenopathy, which is the more common manifestation in children. Nevertheless we used it as part of the standard regimen and the doses for children are about thirty-five milligrams per kilogram.

Now the guidelines I do take some exception to because the guidelines even list as low as fifteen milligrams per kilogram, which is a dose that I don't believe was ever studied. When the British Medical Research Council studied it, they studied in adults thirty-five milligrams per kilogram. Over time people would dial that dose down more or less empirically. We can call that into question. I think we may be under dosing, at least in adults, Pyrazinamide.

It's cleared by the liver and then the metabolites go out in the kidneys. If you have a patient on dialysis you usually give it three times a week at the daily dose because these metabolites may or may not be the cause of this liver toxicity. Uric acid is very likely to be elevated in your patient. In fact if you're doing self-administered treatment and their uric acid is normal, they're almost certainly not taking their Pyrazinamide.

Ethambutol is used as a fourth drug at the start of the regimen, so we start with four, just in case there's Isoniazid resistant organisms or possibly Rifampin resistant organisms in the patient that we're about to treat. It takes sometimes many days if not many weeks to get your susceptibility data back. In children it's often hard to get an organism at all and you're based on known contacts or best guess for the susceptibility in that patient. Ethambutol is used until we're reasonably confident that the patient has fully drug susceptible TB. It's giving orally in the U.S. In Europe there's an IV dosage form but they generally speaking don't have it here.

The dose is fifteen to twenty-five mgs per kg. I would say again, the British Medical Research Council studies looked at twenty-five mgs per kg and then subsequently people started reducing the dose somewhat empirically. I am not sure that that is an appropriate thing to do. Ethambutol is cleared by the kidneys and that's something you really have to be careful about because patients with renal dysfunction can accumulate the Ethambutol and run into this serious problem of ocular toxicity. Again, if your patient has renal dysfunction or if they're on hemodialysis, you really have to be very very careful with this drug.

Streptomicin is rarely used anymore, it was the original TB drug, it along with PAS was discovered in the early 1940s. It can be given intramuscularly or intravenously. The dose range for children is fifteen to thirty milligrams per kilogram. Adults usually start with fifteen but again children having more total body water, you might want to start at least with twenty mgs per kg as far as the dose of this drug. Similar dosing would be true for Amikacin (or kanamycin). It's cleared almost exclusively by the kidneys so renal failure patients, you must be careful.

Ototoxicity, and there's two types: there's hearing loss and there's vestibular toxicity that are concerns in patients receiving aminoglycosides. Nephrotoxicity does occur though at least with the once daily or intermittent regiments used for TB it doesn't seem to be nearly the problem as it can be in patients in the Intensive Care unit. You can get magnesium, potassium, and calcium loss in your patients so it's easy enough to check the chem panel periodically. You have to correct the magnesium first if you're going to correct the calcium and the potassium. That's something to keep in mind.

Here are the other injectable drugs. The first two are true aminoglycosides. Capreomycin has the same toxicity and the pharmacokinetics so we throw it in the same pot but it's actually a polypeptides,

chemically distinct from the others. That's useful because you often have activity by Capreomycin in the face of streptomycin resistance and usually in the face of Amakacin resistance in-vitro. Turning to the fluoroquinolones, Levofloxacin is one of the two that we use most commonly. It's cleared almost exclusively by the kidney so the same caveat as with the aminoglycosides and with Ethambutol, you have to be very careful with this drug in renal failure.

It may be given orally and intravenously, it's very well absorbed orally. The dose is not a subtle matter for children but in an upcoming paper which I hope will be published shortly, we're looking at a dose of up to twenty milligram per kilogram for children. On a mgs per kgs basis it's higher than adults but based on our previous discussion that's exactly what you'd expect would be needed. Clearly more study is needed for Levofloxacin in children. Moxifloxacin really doesn't have a lot of good pediatric data. The adult dose is four hundred milligrams daily. You could choose to make a milligram per kilogram conversion to pediatric doses but that would be empiric and we really don't have a lot of data to support that that would be an adequate dose for children. Again if you felt compelled to use Moxifloxacin in a child, that might be a good situation to do therapeutic drug monitoring to make sure your achieving concentrations that are considered normal for the adults.

The advantage of Moxifloxacin is that it's cleared both renally and hepatically. If you have a patient in renal failure this might be preferred to Levofloxacin because it always has another way out. It has the liver to get out of the body. Like Levofoxacin it can cause CNS effects, it can cause stomach upset, it can cause tendinitis. More than Levofloxacin it causes QTC prolongation. Normally that's not a big problem and the prolongation is not that profound. Rarely, and that's why I have this in parentheses, rarely it can be associated with cardiac dysrhythmia's…Usually in a patient with a lot of preconditions that expose the patient to a higher risk. Or other medications that also cause QTC prolongation. That's something to be aware of but for the most part you're not going to have to worry about that in pediatric setting.

Ethionamide is actually better tolerated by children than it is by adults. The main intolerance is GI upset, and not uncommonly in adults causes emesis. It's really not a fun drug to take. It also can cause hypothyroidism, especially if it's used with para-Aminosalicylic acid.

There's not tons of published experience in children but a reasonable dose is fifteen to twenty milligrams per kilogram divided twice daily if you can possibly give it twice daily. I know that's a challenge on an outpatient basis. A lot of these weak second line drugs, they're better giving twice daily than they are once daily. Para-Aminosalicylic acid or PAS, just mentioned, it is usually given at the PASER® granules in most countries, not all but it's certainly in the United States. These are little granules that you should not chew. You just pour them in your mouth and then swallow with a liquid or mix in with yogurt and then swallow that down, but you don't chew these little granules.

The standard adult dose is listed here as four grams twice a day or three times a day. Most people cannot get around to three times a day dosing so twice daily I would say is the rule. This is the proposed dose for children, there's a lot of older experience with PAS in children in the 1940s and 50s, when it was one of the only three drugs available. This is presumed to be a reasonable dose for children but again, not a lot of recent published experience with PAS in children. It's metabolized and the metabolites go out in the kidneys. It seems to be reasonably safe, even in patients who decreased renal function. You probably need to give most people at least one dose per day. The toxicity's are GI upset, sometimes diarrhea, and hypothyroidism.

Cycloserine is a challenging drug to use because it causes central nervous system toxicity. The good news there is we know it gets in the brain so you might consider it in a patient who has meningitis. The difficulty of course is that if they started getting CNS changes it would be very difficult to know if it was the Cycloserine or the progression of the meningitis that's causing this problem. It's not the easiest drug to use. It's generally reserved for drug resistant cases. Standard daily dosing or the standard dose is two hundred and fifty to five hundred milligrams typically twice daily. I know that some people give it once daily. There's really not a lot of published experience with such an infrequent dose.

For children it's proposed, but not published data, that you give ten to twenty milligrams per kilogram ideally, divided twice daily. Cycloserine is cleared by the kidneys and so we have to be careful of accumulation of this drug in those patients. Now let's take a step back and consider what we're trying to achieve with the antibiotics. For every drug with a proven mechanism of action, this involves the drug entering the organism, binding to a target, and producing an inhibitory or lethal effect.

If this binding to the target doesn't occur either because the drug got destroyed by the organism's defenses or it couldn't penetrate into the organism or it never got to where the organism is hiding, if this binding doesn't take place nothing happens and the drug doesn't work. Even though it might be susceptible in-vitro, in the patient if this doesn't happen, it's effectively resistant. Now for every drug that we give either orally or parenterally, the only way for the drug to reach the organism or bug is through the bloodstream. If it not in the blood it's not in the bug. It's that simple and this is where the pharmacokinetics piece comes into play.

We trust that when we give the standard doses that all these things of drug delivery and drug entry into the organism and binding are going to occur. We're trusting, we're hoping, that that's going to be the case, often it is, but it's not always. We'll talk about the exceptions. Pharmacokinetics or PK is the study of the movement of the drug through the body. It's what the body does to the drug. Usually we're looking at serum concentrations.

Pharmacodynamics is what the drug does, in this case to the bug. It's how the drug does its work. It's the study of these relationships and we look at that in-vitro or in animal models or in human clinical trials with dose escalation. While the TB drugs did have human clinical trials, most of them did not have dose escalation. Somebody made a semi arbitrary choice, a priori, did that study, seemed to work, and those are the doses that we still use decades later. Whether or not they're the best doses - that often remains an open question.

Here is what I'm talking about as far as pharmacodynamics. There's two things that we're concerned about. The efficacy of the drug, which is the yellow curve and the toxicity. Now not every drug we give has concentration related toxicity. I would say Rifampin is example where this toxicity curve remains very flat for even much higher doses than we currently use, and that is being studied. Other drugs likes Ethambutol, I mentioned the ocular toxicity if you overdo it. Or Rifabutin, neutropenia or the anterior uveitis if you put too much drug concentration into the patient.

We have to concern ourselves with both the probability of response and the probability of toxicity. For anti-microbials we measure in the pharmacodynamics with one of these three variables. Usually AUC to MIC is a very good representation. Sometimes the Cmax is a little better. Then sometimes time of MIC is a little better, but most of the time if you default to choosing AUC to MIC, you're going to be pretty close to where you need to be for most of the TB drugs. What am I talking about? Well, we're super imposing the serum concentration versus time curve, on top of the in-vitro MIC.

Now when we're mixing in-vivo and in-vitro that's not ideal, but there is no way to directly measure the MIC in a patient who's under treatment. You have to get the organism out of them and you have to test it in the laboratory. You're stuck with this MIC being an in-vitro measure. Then we can compare this peak right here relative to the MIC or this area here under the curve divided by the MIC. Or that the time, from this point to this point, the concentrations remain above the MIC. All of them have some value, and I would say usually AUC to MIC has the most value.

There are drugs that we call concentration dependent and those include the aminoglycosides. Some of you may be old enough to remember, in training anyway, when Gentamicin was given eighty milligrams every eight hours. Now it's given four to five hundred milligrams or seven mgs per kg once a day. We take advantage of concentration dependent killing. We've also noticed that originally Levofloxacin was twice daily and then it moved to once daily, the very same reason. Unfortunately the rifamycins were not adequately studied in this regard. Those studies are happening now and I've already talked about Study

Twenty-nine X for Rifapentine. The dose changed from either twice a week or once a week at six hundred milligrams up to a dose of twelve hundred milligrams daily, at least in the adults.

This is a very important concept that's being revisited for all anti-microbials but in particular now for the TB drugs. We usually want to get a peak to MIC ratio, which is a little bit more clinically friendly than the AUC of about ten to twelve times the MIC. Here's the study that was done by Ludo Verbist back in 1969, this is a study that's older than most of the people listening to this presentation but the data holds true. If we look at this increasing dose in a chronic mouse model of tuberculosis, once they got up to forty milligrams per killogram they essentially sterilize the mice. This is exactly what we would want to do in people.

It turns out that the pharmacokinetics in mice are reasonably similar to the pharmacokinetics in humans so it's not because of some wildly different pharmacokinetics that they got this result. But this (10 mg per kg) is the dose that we currently use in humans. As in the mice, we still have lots of organisms, certainly after ten weeks, in humans. We have lots and lots of organisms sometimes out for months in humans. It would suggest that we need to revisit the dose of Rifampin.

Here's an acute mouse model, not that the mice are cute but it's an acute mouse model done by Jayaram and Colleagues, much more recently, published in 2003. They show the same kind of effect. That this is the ten milligram per kilogram dose, and this is the exposure that they got. You can see it's barely more active than giving nothing at all. It's not until you get much much higher doses and drug exposures that Rifampin really becomes an extremely potent drug.

We'll return to Rifapentine and what was mentioned earlier about Study Twenty-nine X. Study Twenty-nine X when they changed the dose to twelve hundred milligrams daily with food, and that was seven days a week in that study, the people with the highest Rifapentine exposures at an AUC or area under the concentration versus time curve had the best results. It is exactly what those two mouse models that I just showed you would predict because Rifapentine is cyclopentyl Rifampin and the business end of the molecule Rifapentine is identical to the business end of Rifampin's molecule.

Again, returning to this concentration versus response, we want to maximize the therapeutic effects while minimizing the toxicity of these drugs. There are clinical data to show that this is important. I'll just present one study here which is now a ten year old study. This is not a late breaker at this point. This was a study in HIV positive TB patients getting an intermittent Rifabutin based regimen. Unfortunately during this study, and much to our chagrin and it was not planned, we started selecting out for Rifamycin resistant tuberculosis. That is really really undesirable.

Now, there was a little discussion at the beginning when the parent study was published. There was a focus on the CD4 count being associated with the worst outcomes. The lower the CD4 count the worse the outcome. That really just turned out to be a marker for poor absorption of Rifabutin. You have the red guys who did really poorly, and not only did they fail a relapse but they have acquired rifampicin resistance, which for all intents and purposes is MDR TB. Then the guys in the blue, those guys did fine. Some of them had low concentrations and got away with it. One guy had high concentrations and didn't get away with it, but that's exactly what we saw in that response curve thing. It's a probability.

There's always some guy who is not going to respond and there's always some guy who's going to respond to even small doses or concentrations of the drug. On the whole you don't want your patients to have these low concentrations. Happily now, outside of a protocol where we could not change the doses, in your clinic if you're using Rifabutin you can measure the concentrations typically three and seven hours after the dose. If you had somebody in the red zone you could put them in the blue zone so that you don't get acquired rifampicin resistance.

Just to point out the variability of the kinetics in how children differ from adults, here is the volume and distribution and here is the clearance of Ethambutol. Focus on the third column here. You can see how

the volume numbers and the clearance numbers are very different for children than adults. What does that mean? It means that when you look at the concentration versus time curve the upper three curves are different populations of adults and these are the children. Clearly, they were getting the wrong dose and this was normalized here at twenty milligram per kilogram. Ethambutol can be a tricky drug and it's not unreasonable to consider checking serum concentrations in your patient. Especially if they're a heavy child or a very young child or a child that's having a lot of trouble swallowing the extemporaneous dosage forms.

Anything that makes that child an exception to the rule. I would consider measuring the drug. Now there are many reasons for slow responses, and slow responses are very common we'll look at that on the very next slide. Obviously if the patient has an adverse reaction and you have to stop the drugs it's going to take longer. If the patient leaves the treatment program for a while they're going to take longer to treat. In our experience there's a substantial portion of trouble that comes from low drug exposure.

The annual slide set for the CDC shows this slide, the years keeps marching out, but you can see that this looks like asymptotic process. It's zooming in on some kind of plateau. Things were not so great in 1993, which was the high point of the incidence of the resurgence of TB in the United States. It's gotten better but notice two things: First, this is eighty-eight percent. It's not ninety-five or ninety-eight percent. Secondly, it's at one year, it's not at six months. While this is good and we eventually get up to ninety-five percent of the patients to complete therapy, it's not six months and it's not ninety-eight percent.

The standard claim is that we have a six month regimen that does what I just said, ninety-eight percent success, three percent relapse which we don't explicitly track in the United States, for about ninety-five percent overall cure. You can certainly achieve this but if you look at the original studies this was per protocol under research conditions. What does that mean? That means that up to ten sometimes even twenty percent of the patients either didn't qualify for the study or they dropped out. They were not included in the analysis.

Now, if you have that kind of patient in your clinic they're still in your clinic. You can't say, "Well, I'm sorry you're not per protocol, get out of my clinic." You still have to treat them. It's highly unlikely that we'll ever get these kinds of numbers in a routine clinic situation because you have to take all comers. What percentage of U.S. TB patients complete the six month regimen in six months? The answer is eighteen percent.

That might be a shockingly low number for some of you. Now, you may clearly argue, "Well, what if they took six months and one week because of bureaucratic reasons? Paper trailing reasons, where they couldn't get their prescriptions right away." Okay, let's be fair and let's use the seven month instead of the six month time point. That's still forty-five percent. That's not ninety-five percent. That's less than half of what you might otherwise expect. Clearly there's something going on. Now the bulk of this data are adult data so I stress that, there are some pediatric data in here but it is predominately adult data.

In children, especially if they have minimal disease with hilar adenopathy, they tend to do really well. There are other cases which are actually excluded from this data set with miliary disease and meningitis, again excluded from this data set. Those are much more serious cases. This is supposed to be a six month regimen but it can take a year to get eighty-eight percent of the people to be completed in their therapy. It can take up to eighteen months in some cases. That would be like given three courses and of course you're paying for that. You're paying for them to be on three back to back to back courses of tuberculosis if you will.

Turning to the toxicity side of things. It is not possible to give drugs with the explicit purpose of avoiding toxicity. If you're going to give the drugs you have to accept that you're going to get some toxicity in some of your patients. There's no guarantee. If you really want a guarantee of no toxicity don't give the drug. If you find that you're forced to give the drug you're going to have to accept this probability and that was the lower curve on that probability versus concentration curve that I showed you twice already. You're going

to have to deal with this. The best way from my standpoint to avoid toxicity is give the most effective dose for the shortest possible time.

What we do for some of our cases here and I would suggest is available at several laboratories in the United States and in Europe, is you can consider therapeutic drug monitoring for any number of your patients. The decision to use therapeutic drug monitoring is the same as the decision to get a CBC with diff. or to get a CT scan or an MRI. None of these will guarantee the treatment outcome, what it allows you to do is make an informed decision. Am I delivering the drug? Am I delivering enough drug? Do I need to change the dose to get as much drug into the patient as I really want in the patient?

That's what this allows you to do. To quote our former president “doveryai, no proveryai” actually I never heard him speak Russian but I did hear Ronnie Reagan say, "Trust, but verify." More like that. At any rate that's what we try to do. Make sure that we're giving the right doses and I'd like to just close by thanking the folks in the laboratory who have actually measured the concentrations and these chemists, Jessica has recently left us for the FDA so congratulations to Jessica. If you call our laboratory you're going to be talking to Roger Sedlacek. Here are some current or recent graduate students and current or recent students who have done some data collection. With me today is Alyshia Wiggins who's our current student who's working on data collection for our laboratory.

With that I thank you for your attention and have a very good day.