

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

Welcome to today's webinar entitled "Learning from the Front Lines: Celebrating Ten Years of the Medical Consultation Database," sponsored by the Southeastern National TB Center. Today's presenter is Dr. Connie Haley. Dr. Connie Haley is an adult infectious disease physician and epidemiologist who currently works as a Medical Consultant for the SNTC. Dr. Haley received her medical training from Vanderbilt University, including specialization in Internal Medicine and Infectious Diseases, and a Masters of Public Health degree.

She has a long history working in the TB field, including serving five years as medical director of the Tuberculosis Elimination Program at the Tennessee Department of Health, three years as the director of tuberculosis research for TDOH, and six years as the principal investigator for the Tennessee site of the TB Epidemiologic Studies Consortium.

Dr. Haley is currently an adjunct professor of medicine in both the Division of Infectious Diseases and Global Medicine at the University of Florida, and in the Division of Infectious Diseases in the Department of Medicine at Vanderbilt University. She enjoys collaborating closely with the Centers of Disease Control and Prevention, and academic and public health partners across the U.S. to improve the clinical care of patients with tuberculosis and to advance progress towards TB elimination.

Today's moderator is Megan Ninneman. Megan is a PA from the Respiratory Care Unit of Jackson Memorial Hospital in Miami, Florida, and she's affiliate faculty for the SNTC.

Well, welcome, and thank you for joining us today as we celebrate our ten years of the MCD. We have a really great webinar planned for you today, with some really interesting cases taken from the MCD database, which Connie will be presenting for us. I just want to encourage you, if you have any questions, we will be monitoring the chat throughout the webinar and try to be answering them during our polling questions and at the end of each case. If we don't get to your question during the case, we'll try to get to them at the end of the webinar, time permitting. We have a full hour-and-a-half in front of us, so let's get going. Connie, I'm going to turn it over to you.

Hi everybody. It's so nice to be connecting with you all regarding our ten-year celebration of the MCD. I am making this presentation from our remote site in Tennessee. And I'm going to go ahead and get started. So our objectives today are to identify opportunities for educating field providers so that we can all work together to improve management of persons with TB infection or disease to ultimately help us stop the transmission of tuberculosis. And we also are going to talk about how we use the medical consultation system in the Southeast and how it's evolved somewhat over the past ten years to help benefit providers, nurses, and everyone in the field's knowledge and awareness of important issues in tuberculosis management. And, finally, to recognize the use of the MCD system so that we can identify clinical challenges that are commonly faced and help us evaluate how we're doing and talk about ways that we can improve as new challenges come up and old ones continue to persist.

So who are the SNTC consultants? So when I talk about us or the SNTC consultation system, we've had some changes over the past few years but currently Dave Ashkin, Mike Lauzardo, Ana Alvarez, myself, as well as Tom Dobbs, who is in Mississippi, and then our wonderful nurses Karen and Ellen. We all take calls. We usually have one nurse and one provider on call to answer questions, depending on what your need is. And then behind the scenes, it's really important to recognize Maria Gomez who takes all of our calls, keeps the system going, keeps all of us in line, and helps us to get all the documentation out in a timely manner. And also I really need to thank Donna Setzer and Steve Ryan, who are behind the scenes developing the MCD system and helping us with all of our systems issues and troubleshooting, and constantly working to try to improve our system. And I'll talk a little bit about some of those changes.

So our system has evolved somewhat. I have not been doing this for more than three years, but my understanding is ten years ago, before this existed, there were several warm lines for people to call and ask for help with TB cases and other TB control issues in both the National Jewish Medical Center and the New Jersey Medical Center. And my understanding is that, seeing how important those were and how much people relied on them, we then began

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

to set up a warm line as well. And, back in the day, a lot of those were calls coming in, people kept getting notes on their desk, you know, sticky notes, to call someone back, and it wasn't a great system of documentation or tracking what kind of calls we had and what kind of information was provided. And so CDC funded this system, this Medical Consultation Database, for all of the regional training and medical consultation centers, where we could track how many calls we get, who's calling, what we're being asked about, what are the challenges that people need help with, and also to allow us to provide documentation back to the caller so that they don't just have to think back later and go, "What did they tell me when they called?" It's nice to have this permanent documentation.

And I think that you all are aware that we're still trying to work on the system. Recently, in the last year or so, we started with submission of the caller, sending out a record of the call to state TB control offices, and I think that's helpful for the state to be aware of the challenges that are occurring in the field and what kind of topics they need to cover in training and education. It just keeps everyone in the loop. As consultants, we also try to contact TB programs about cases we get from outside callers, from private practice, hospitals, and others with questions, et cetera, to help make sure that public health is always in the loop when we have, in particular, TB patients that need to be managed in partnership with health departments.

And so it's evolving, and our documentation is getting better. I wanted to also say, this system was initially designed, the calls we were getting were one-point-in-time calls where we were being asked a quick question about a drug dose or what drugs we used in a certain circumstance. We really would not contact that person again or be contacted by them. Slowly, over time, it's been evolving where our calls are getting complex, requiring sometimes conference calls with multiple parties, sometimes follow up, helping to devise a treatment regimen and then check in and see how things are going. And so it's getting harder and harder to document all of that. We're trying to evolve the MCD system to help us be able to actually track this information.

We do have the current limitation that we don't have any way to store films or medical records. We don't get any private health information, and that's deliberate so that we don't have to worry about making a true -- doing a true order. We make recommendations to the field and let the providers make their own determinations if they agree and want to accept that recommendation. So, without any of that PHI [ph], sometimes it's hard, at times, to track calls that might come in three or four months later on the same patient. But we're really working hard to overcome that shortage. And I think that, with CDC's help and encouragement, this is becoming more user-friendly and more helpful to the field, to know that when they call us back about a patient, we still have that information handy.

And so, just going along with my talk, I have a few slides on data before we get into some actual examples of the calls, which I think will be the interesting part of the talk. But, over the past 10 years from 2006 to 2015, we documented more than 3,500 consults to providers in the field. And this, again, is just the Southeast region, but we do get occasional calls from outside the region. And we also get calls from overseas, and I'll tell you about that in just a minute.

I will tell you that there are a few limitations, and that is that the State of Florida has evolved as well. And while, initially, a lot of the consults we got were from Florida, Florida actually has their own funding and their own TB Physician's Network with different call lines. And so most of our consults now from Florida go to that and are not counted in our data for the overall MCD for the Southeast region. And so you'll see in just a moment how that trend has changed.

And also, when I tell you there's 3,500 consults, this doesn't mean that that's the number of calls that we get. Sometimes there's multiple calls on some patients, back and forth emails, and text messages. And so that doesn't, by any means, count the number of contacts we have with people. And then I'll tell you, too, that sometimes people call us directly. And we try to add this to the system, but a lot of times, if they don't go through Maria, a consult may not be formally opened in the database, and so there may not be documentation that we can send to you after the call. So, applause for Maria and for documentation. If you would like to have a record of your consult,

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

please go directly to her. You can call her or you can go through the website and put in an email consult, and that way you'll be guaranteed to get documentation back, hopefully in a timely manner.

And, as I mentioned, we do get some consults from overseas panel physicians. And the Southeast -- SNTC rotates with the other RTMCCs to take these calls, and they're always very interesting. And I hope to have a future webinar to include some interesting consults that we get from that system, but I'm not going to count them in our data today. But, as you know, overseas screening, prior to formal immigration, where people are coming here legally, long-term, not visitors or students or undocumented people, but those immigration requirements are received, and if they're challenged, they call us and we provide treatment information, just as we would for the United States using the same CDC standards for TB and for multidrug-resistance. But, again, that's going to be a separate future topic.

And one thing that's important to note is we don't take individual calls. We deliberately don't talk to patients about their case. We don't want to get mixed in with what the provider is telling them. This is a call -- the call line is only for providers. And I'll just tell you, there has been one time that I did get a call from a patient. He somehow found out about us online and called us. And there was a little triangulation of the patient trying to get us to give him a different answer than we gave to the provider. So we deliberately don't talk to patients.

So, just to kind of show you a little bit of our data, this is showing you, in the dark blue, calls from Florida, and in the light blue, calls from outside of Florida. And, as you know, Florida is a very large state, so a lot of the Southeast TB comes from that state. And so, by not counting those in our calls, you can imagine there's probably a lot of calls that don't get counted. But, as you can see, the dark blue has really gone down over time as their own hotline has picked up. What's interesting to me, in the last few years, in 2014 and 2015, is despite the lack of calls to Florida, we've had a pretty high number of calls coming in from the field. And I think that just goes to show that, consistent with the CDC's recent World TB Day epidemiologic report, you know, there's still a lot of TB out there and our progress isn't what it should be, and the cases that we have coming are very complex, and there's been a lot of TB drug resistance and TB and complex foreign-born patients. So this sort of plays some of that out.

When you look at the types of calls that we get, by far, the most calls we get are TB disease and latent tuberculosis infections. And when we document this, we put more than one category. These don't add up to the total of the number of calls that we get. So people might ask about TB disease, but also ask about diagnosis or they might ask about toxicity and also legal issues. And so you can see that we get a very large variety of patient calls on different topics.

We do put data on adverse effects, but, unfortunately, what I have for this chart wasn't very clean. I'll tell you, a lot of our calls around adverse effects are what you would expect, hepatotoxicity, gastrointestinal intolerance, rashes, CNS issues, and hematologic effects, as well as ophthalmologic and auditory questions. So we really do see the potential side effects that can occur during treatment for TB. It really is more now than treatment occasionally, although, hopefully, most patients do extremely well on treatment without problems.

Just in terms of who call us, as you can see when you look at the bright red and blue, the royal blue and the dark blue, we get a lot of calls from public health, from state offices, from local health departments, from regional offices. But if you look at the bright pink, we get a lot of calls from hospitals. Some of that is infection control issues. Some of that is just initial management of patients or trying to make the diagnosis for patients who might have TB. We get quite a few calls from private practice. Again, a lot of those are regarding latent infection, and diagnosis and treatment of infection. But we also get a lot of calls from corrections and other categories. It's sort of a catch-all. It's probably some miscoding. But you can see we get a lot of calls from outside of public health, and I think that's important because we try always to link public health back to these settings who are contacting us because we feel like we are a part of the public health system but also want to make sure that we can help spread education as much as possible.

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

When we talk about the type of caller, most of our calls come from nurses and providers. Occasionally, we'll get calls from respiratory therapists and administrators and DOT workers or social workers. But, again, by far, most of these are clinical types of issues.

So, with that, I want to move into some case examples. And I'd like to start with questions. So, Megan, if we're doing this polling question, maybe you can see if there were any initial questions on the MCD. This question is, "What is the standard treatment for patients with latent infection who's also taking a TNF-alpha inhibitor?" And I've gotten this call a number of times. So I'll be interested in seeing what the field thinks. The first choice is to complete a full course of treatment for latent infection before you start the TNF-alpha inhibitor. The second would be to start treatment at the same time as the Humira. You can defer Humira until after the patient has had at least a month of treatment for latent TB infection, or defer Humira indefinitely because -- this is key -- there's really a lot of increased risk of tuberculosis in patients who are immunosuppressed with these drugs, and the type of cases that we're seeing on TNF-alpha inhibitors are really quite unusual. I've seen a quite a few extrapulmonary and strange site, you know, very ill patients that have developed TB quickly after starting their immunosuppression with these TNF-alpha inhibitors and other biologics. So, Megan, any questions so far?

Well, I'd just like to point out, I think that there's no correct answer. So we're just interested in seeing what you guys think about this and what your own experience has been out in the field. I don't think we have any questions from the chat so far, Connie. So you're doing a great job for that update on the MCD and all the services that you guys provide for the community.

Thank you. Thank you. Well it's something that I really enjoy a lot. My role of the MCD for the Southeast National TB Center is to try to help improve the quality, and I just want to say as well that we use our MCD system for our own benefit. We do a lot of peer review. I read through almost all the cases, go through it, and use them for training and education among our own providers. And also really starting to use, just as with this webinar, trying to use these cases to teach others. We use them in our clinical course. We've presented them at the Southeast TB Controllers meeting and in a few other settings. And I find that we get some really interesting calls, and we want to share that information with others who may not see as much TB as we get to be involved in through our role as the Southeast National TB Center.

So, Emily, I think it's time to go ahead and close that question. And I'll just tell you that I agree with the two choices. I think people mostly felt that if you could get at least a month of treatment for latent TB infection that you'd have a benefit. Some people felt that it's beneficial to complete a full course of treatment. And I just wanted to apologize, I know that in field there's sort of a mixed feeling about whether or not the word "latent" should be accompanying TB infection. And I find it hard to make myself change that habit. So I'll do my best, but I know the CDC hasn't changed their guidelines yet. So this is an ongoing process for all of us.

I'm going to talk just a little bit about initiation. As you guys all know, the guidelines for treating TB infection were last updated in 2000. And, unfortunately, that was 15 years ago. And so there hasn't been any new recommendations [indiscernible] the agents have been more widely used. And we recognize that this question comes up a lot. And I think, ideally, being able to complete a full course of treatment for latent infection would be great. You know, if you could use a full month of Rifampin or 3HP, if appropriate based on the patient's clinical status, you know, or even if you could get nine months INH, that would be great, decrease your risk of tuberculosis by providing the preventative therapy in advance. But, unfortunately, many patients are just not able to wait that long. Sometimes the rheumatologist will tell you that they are very uncomfortable and the disease is progressing and they really need to take care of patients with Crohn's disease and other conditions that might use these drugs. And it's really important to have that ongoing communication.

You know, we don't tell people what to do, but we will often call up a provider, whether it's a rheumatologist or an oncologist, whoever is asking us questions, to help make that clinical decision with the best information possible. And those other providers know the patient well, so getting their input is helpful, and also gets their buy-in when

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

you're making recommendations that they may not want to follow. So I think, generally speaking, if you can get at least a month of therapy in, and that guideline is also put out for rheumatologic recommendations. But there is one review that's helpful that includes this recommendation from A. Vernon, and I put that reference there for all of you.

I'm going to just move along now. I put in some cartoons here to try to make it a little more interesting, and this is certainly one of my favorites. "I think we should cut back on my antidepressant. I watched 'Old Yeller' and it was absolutely hysterical." So, on the webinar, I can't hear if you're laughing or not, but I hope that makes everyone smile.

So the next question was regarding the skin test performance with Myasthenia Gravis. So this gentleman had had an annual physical and he had been diagnosed with Myasthenia two years ago. He had been on prednisone five milligrams every other day, and also getting gamma globulin, or IVIG, three times a month. And his last dose was about ten days ago. And he was coming in for his physical. He told the nurse that he had had a skin test in the past on this therapy and that both the skin test and T-spot had been negative. So the nurse is thinking, she just said, "You know, I want to know" -- and we get a lot of calls like this, people just wanting more information, even when it's not specific to a patient -- and she wanted to know what information is there regarding the skin test or the T-spot or other IGRAs in IVIG?

And so this was something interesting I had to kind of think about, but gamma globulin isn't known to affect the performance of any of these tests for latent TB infection. And, in fact, it's actually used as a treatment to strengthen the immune response, although it is based on humoral immunity with a B-cell response, whereas the skin test and the IGRAs are based on a T-cell response and cellular immunity. So there really shouldn't be an impact by the IVIG on the skin test or the IGRAs, but we did suggest that perhaps IGRAs would be the better choice to use. There really is no specific information on T-spots which addresses this question.

And I was talking about this with Dave Ashkin, and he was saying theoretically, interferon gamma response, the test gives you a reading for the mitogen, which is really the positive control. And so if the patient can respond to a mitogen, that shows you that they should have a pretty good intact cellular immunity. And so in essence it acts kind of like an (inaudible) test. And if the patient has positive mitogen, then you can see that they have the ability to manage the cell response and can therefore react to the test appropriately. I just want to point out that you always should consider the presence of comorbidities and what other treatment the patient is on when you're placing these tests. And the patient's probability is probably the most important part of these tests. I get lots and lots and lots of calls on IGRAs and also on skin tests. And you think about what kind of patient has the disease, not so much what kind of disease this patient has.

So you're trying to decide, you know, why would -- what risk does this patient have on the front end. And if you feel, on the front end, that this is a foreign-born patient with immunosuppression, is probably at a lot of risk, false-negative risk is possible, then you might say, "You know what, I'm going to test them and try to use any test that shows it's positive, and consider that a positive test," versus a low-risk person, when you don't want to test them, but you're going to have a low threshold with the [indiscernible] treatment if they have a test that you think could be a false-positive. I'm not doing a lot of justice to this. This is a big topic. And I'm happy to talk more about it later, but I'll refer you to a great webinar on biologics that Kevin Winthrop did. But also, we also had a great IGRA talk [indiscernible]. And both of those are on our website online, so you can either look those up and download the slides or listen to the webinar again.

So, again, we're going to move on. Megan, any questions that need to be asked right now?

I don't know if you want to go back, Connie, to the alpha-blocker case, or if you want to save those for the end. There was one question.

Learning From the Front Lines:
Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

I'll answer that real quick.

Okay, so the question was, "When using a TNF-alpha blocker, what is the time to develop active disease if the patient goes from LTBI to active disease?"

That's a good question. You know, I think that all of these clinical scenarios vary. And, you know, the time from infection to disease is probably -- the risk of going from infection to disease has been shown to be much higher in patients on TNF-alpha inhibitors, but I don't think that there's a set time that tells you how quickly that can happen. It can happen probably fairly quickly if you develop primary TB right after infection, and it's someone who's severely immunosuppressed and they have other comorbidity, maybe HIV or something else underlying it. And some patients may do well for a very long time, and then they suddenly develop TB down the road. So I think that's a really hard question to answer, but, you know, just, again, underline that there is significant risk of developing TB, if infected. And all patients about to get TNF-alpha inhibitors should be screened in advance. And if those tests show that there is disease, they should be treated. Thanks for that question.

I think that's a great -- thank you.

Anything else, Megan?

Well, I would just say, in my own clinical experience, I mean, I tend to see much sicker TB patients. But I've seen patients put on TNF-alpha blockers who have gone from LTBI to active disease in actually days to weeks. So it can be a very short amount of time. But I also agree with you, depending on the severity of their disease, they may be prolonged before -- you know, months before they become sick.

Right. Yeah, thank you. Megan has been working down in the Jackson Hospital to basically replace [indiscernible]. And Megan has seen the sickest of the sick and most challenging patients. So I rely on her a lot when I get some calls. And she's also been under Dave's tutelage, so Megan is an awesome resource for the Southeast National TB Center.

Okay, so my next case is a Peace Corps volunteer with a skin test conversion. So this young girl spent a year working in Swaziland as a teacher. And her skin test was done before she left, and then repeated on her return. So it was a documented conversion. And the caller reminded us that Swaziland has a very high incidence of both HIV and TB. The primary MDR rate, patients diagnosed with TB, about 15% of those patients already have MDR. And among patients who are relapsed cases of TB in Swaziland, about half of them are MDR, and, of course, there's XDR in Swaziland as well. So, a very high incidence setting that she had been working in when she became exposed. But she denied any knowledge of anyone who had been sick with TB, or MDR in particular, anyone she knew that had symptoms.

So my next polling question is how should you treat her? So she's converted her skin test after living in Swaziland. So would you treat her with nine months INH, self-administered; four months of Rifampin, self-administered; three months of weekly INH, and Rifapentine by DOT; would you go ahead and consider her possibly exposed to MDR and give her Ethambutol and quinolone for a year; or would you just provide education of symptoms of TB but not treat her at all since you don't know what her source case was and you don't want to risk any additional resistance? And, again, there's not one correct answer here. This is just -- and then I'll go through and provide my input on a lot of these cases. There may be those out there that disagree because there's more than one way in tuberculosis to manage a lot of these clinical scenarios. And so, you know, I often tell people that I provide consult to, it's not always black and white. And what we do in TB is definitely not easy.

So it looks like we've got -- we can probably go ahead and close the poll, Emily, but if you could leave the answers up for me. It looks like most people want to go ahead and treat the patient for latent TB using a standard TB regimen. And the choices we've seen, the nine months INH, which, as you all know, is very effective but very

Learning From the Front Lines:
Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

difficult to complete because of the long duration of therapy and the concerns over potential hepatotoxicity. Four months of Rifampin also is something that we recommend for treatment of latent TB infections. And then, of course, recently there's a lot more evidence suggesting that 3HP is equally effective, it is not inferior to nine months INH, based on the New England Journal study that was published by Ken Sterling and others. But any of those would have been fine.

I think in her situation, the main thing would be to be sure that she does not have any active TB right off the bat, and that would be my only concern is giving either the Rifampin for four months or the 3HP. 3HP would be great because you do give it as directly observed and so within 12 weeks you know that she's completed therapy, you've observed it. And if you've ruled out TB on the front end, then there's not really very high risk of resistance. Really, with Rifampin, there's very low risk of developing Rifampin mono-resistance unless the patient had active TB at baseline and has, you know, symptoms while they're taking the monotherapy. So I think any of those choices would be fine. But there's no benefit in providing prophylaxis for MDR on the front end. Those regimens aren't well studied. There's more toxicity and the effectiveness isn't well-known. And even though there is a lot of MDR TB in Swaziland, most of the cases still are susceptible to INH. So, just routine treatment would be appropriate here.

Okay, Megan, any questions?

No, you're doing great.

Okay. Okay. So this next one is a little -- it's an example of a little bit of a longer case, a patient we followed along with more than one episode. So this young woman came in. She was 29 years old and she had emigrated from El Salvador in 2014. She was healthy, but when she presented she was pregnant and was fairly close to her due date. She had about six weeks to go. She didn't have any history of TB and prior treatment that she reported and she didn't know of any exposures. When she had her routine screening in September of 2015, they found that she had a positive IGRA. She was HIV-negative and had no symptoms, but an x-ray was done. And I don't know how well you can see this. For those of you who want a better look, you can blow up your screen. But you can see this is not a normal x-ray. The radiologist read this a 1.7 centimeter nodule. So in this area is what they're talking about. And this actually is probably more than just a nodule. It looks like there's actually some disease here as well as some thickening of the minor fissure. And so, you know, this was concerning to us that this is real active disease and not just sort of an incidental finding.

And so our next polling question is how you do know when to evaluate this woman with a lung nodule? Do you want to wait until she delivers her baby, and then evaluate her lung nodule -- it's only six weeks away? Do you want to go ahead and deliver her and then evaluate the nodule? Do you want to further evaluate it right now, go ahead and do a full body CT to see if this could be something, cancer, widespread TB, or something else? Do you want to go ahead and empirically get sputum and treat her for TB if it's positive? Or do you want to get the sputum cultures and wait for rapid molecular testing for resistance before starting TB therapy? Megan, any questions?

No. I think this is a great question. I think it's one that can be very challenging. And, you know, I'm interested to see what the responses are for what people think would be the best thing to do for this pregnant lady at this point in time.

Yeah. So I think that people are really -- I see a few people are wanting to wait until she delivers the baby. And I will agree that she is not very sick. And so, you know, there's not an urgency to put her on treatment immediately. I think the two questions towards the bottom, D and E, you know, there's a few more leaning towards going ahead and doing sputum and culture and empirically treating. And then others, too, want to go ahead and wait for the rapid molecular testing. And, Emily, you can go ahead and close the poll.

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

So I think that in this situation, I think it is really important to try to get that culture. But I do think that it's not urgent. And so, ideally, the ability of the rapid molecular test, such as the nucleic acid amplification or the GeneXpert, which also gives you not just whether this is TB or not TB, but also can tell you if there's Rifampin resistance, and then the other nucleic acid amplification test that's important is the Hain test, which we do in Florida, and two other labs do. Hain just uses -- instead of telling you TB yes or no, but also Rifampin resistance or INH resistance. So you get just a little more information with that test.

And I will tell you that a lot of hospitals don't quite have the GeneXpert or the Hain, but most hospitals do have a NAAT, nucleic acid amplification test. And those can be done directly on a sample of sputum, so you don't have to wait for a culture to be growing. So that's a benefit of rapid diagnosis, you actually can get those back within a day. The test itself only takes about an hour-and-a-half to two hours, but by the time it gets to the lab and processed in a hospital setting, or even outpatient, you know, it may take a full day to get the results back. So, again, D would be great because you do get the cultures and susceptibility, and it's perfectly acceptable to empirically treat once you've collected your sample. We do that all the time in public health. But, again, if you can get that rapid test, that should tell you your resistance here, that's ideal, because if it is resistant, it's going to impact how you make your treatment decisions.

And so in this woman, I don't think they did rapid molecular testing. And when we were called on her, she had actually had the sputum sample collected, and multiple ones were smear-negative, but they grew culture-positive. And, as you know, once the culture starts growing in the liquid media, you could also do a DNA probe there that tells you TB or not TB and helps substantiate it. So the cultures were reported back as MTB complex. Furthermore, the results showed that she was resistant only to PZA. And although this lab didn't speciate down beyond the MTB complex, which you know *M. bovis* is part of MTB complex, the mono-resistance to PZA really suggests that this is *M. bovis*.

I'm not going to go into this discussion on *M. bovis*. And at the bottom you'll see that we had a webinar. There's a link there. You can get more information on *M. bovis* and how it's clinically relevant, and also becoming more common in the United States. But I also want to point out, MMWR had a great, really interesting case report of a couple of cases of *M. bovis* in the lungs, and actually were found to be contributing to person-to-person transmission. So that was really interesting.

Anyway, going back to our patient. Her baseline liver tests were normal. And they went ahead and started her empirically on treatment. And, you know, we tend not to use PZA in pregnancy at all -- we'll talk more about that in a minute. So she was started on INH, Rifampin, and Ethambutol, without the Pyrazinamide with the anticipation that you could cure her TB with this regimen and would just have to treat nine months instead of the six without the PZA, and that's also how we treat *M. bovis*.

So the day after therapy, she started having headaches and she began to take Tylenol. As you can imagine, TB cases are never easy. So she developed nausea, vomiting, and was admitted to the hospital with a pretty severe hepatitis. Her liver enzymes went as high as ALT of 600, and her TB meds were held. And her alk phos remained high-ish, but her bilirubin was normal. And so sometimes, with the different options of causes, etiology of hepatotoxicity in patients, sometimes you can kind of look at the lab results and kind of thinking about which medicine you think it might be.

In this situation, when it's mainly a transaminitis with the liver enzymes going up and bilirubin staying normal, I tend to think that it might be INH or PZA. Often, with INH, the liver enzymes will go up and they'll come back down almost as quickly as they went up. With PZA, you may have patients whose enzymes either stay elevated for a longer period of time or continue to go up, even after you've stopped the treatment. That's not always the case, especially in patients who might have underlying issues. In this situation, pregnancy is also considered a risk for toxicity, as you all know.

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

And so you all are quite familiar with the CDC guidelines. Again, they're quite old, 2003. And so there's a nice section on hepatotoxicity. And you all know, you hold your hepatotoxic meds, you hold them all while you wait for liver enzymes to come down, and you check for other causes. Does the patient also have hepatitis or HIV? Are they taking any other medications or drinking alcohol at the same time? And in terms of starting meds back, if the patient is really sick and you don't want to have a treatment interruption, you can start two or more anti-tuberculosis medications that have a good profile with low risk of hepatotoxicity while you're picking this out. If the patient isn't very sick, you can wait until the liver enzymes come down and just hold therapy. And then restart - you know, when the monitoring shows that they're better -- and we start with, again, sequentially adding back medications.

And also, you know, it's well-known that INH, Rifampin, and PZA can all cause hepatitis, but they're also the cornerstones for treatment, and Rifampin in particular because it enables six months of therapy, and PZA as well because it enables you to shorten. But, again, when you're looking at patients, you don't want to just think about the liver. You've got to think about what else is going on with that patient. And so while CDC gives three options for treating, Rifampin, EMB, and PZA without INH, or INH and Rifampin alone, without PZA, as long as you use EMB initially, or just Rifampin and EMB for 12 months, we also have to think about things like pregnancy, what drugs can I use that are not only non-hepatotoxic but also okay in pregnancy, or the patient has CNS disease to think about, what medications show well in CNS. They have renal issues, what medications can I use that aren't liver toxic but are also safe in renal disease?

And so I just wanted to give you some resources. Not only are the ATS guidelines out dated, but there are some new things that we do have that are much more up to date. First of all, the 2006 guidelines that came out from ATS, specifically for managing hepatotoxicity in TB and latent TB infection, those are very helpful and I still turn to those quite a bit. But the new Curry guide, "Survival Guide for Clinicians," for drug-resistant TB came out in February, and it's excellent. And it is up to date. And I turn to that quite a bit for all kinds of things outside of drug-resistant TB. And I think it's chapter five that has all of the medications listed, and it lists not only their dose and how they're administered, but it also tells you how they're metabolized, how effective they are in certain settings, when they need to be voided for renal versus hepatic disease. So I turn to those a lot. And then also, included down there, a reference for another liver hepatotoxicity review article.

Again, in this situation, Ethambutol is considered safe. There's only been one report of potential liver [indiscernible] disease, and it's really unclear. So that is recommended in liver disease. Quinolones as well, but I want to tell you all that quinolones are fairly safe. We tend to use Levaquin in patients who have underlying liver issues or hepatotoxicity because it's cleared by the kidneys, whereas Moxifloxacin is at least partially cleared in the liver. And so if you're going to use a quinolone, in this situation, I'll choose Levaquin over Moxifloxacin.

And Rifabutin -- I'm sorry the slide went [indiscernible] and got messed up, but underneath that reference is Rifabutin which shows that it's considered to be safe. There's a little bit of conflicting information between the 2003 guidelines and the Curry guide. But, compared to Rifampin, if you feel that a patient really needs to have Erythromycin because of the severity of the disease, large cavities, and you're concerned for their outcome, then I would probably go ahead and try to use Rifabutin instead of Rifampin if your patient can tolerate that.

And just other meds to think about, the aminoglycosides and Capreomycin are considered safe in liver, but in patients with advanced disease, some of us are careful not to use them because of potential for hepato-renal syndrome. You can use Cycloserine, Linezolid, or Imipenem/Cilastin safely, if you need to. And we recently recommended Linezolid for a patient who had cirrhosis, was extremely ill with CNS disease, but also had staph infection. And so Linezolid had benefited covering that as well in the patient can be given oral or IV.

And so, again, you know, in this situation, they had to think not just about liver and medications, they had to think about her pregnancy and what's safe. So, of course, aminoglycosides are not safe in pregnancies. There is well-documented teratogenicity, but INH, RIF, and EMB are considered safe. PZA, we do not use it, generally in the

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

United States, for pregnant people because we have the option of using INH, RIF, and EMB in this situation that are very effective. But, overseas, it's actually recommended by WHO and the International Union because the toxicity really hasn't been well-established, and it probably is safer than we think. And so if you get in a bind and you're looking at weighing the patient's risk or the TB or if you have drug resistance, it can be used. RIF, Cycloserine, and PAS have not been extensively studied, but they're thought to be safe in pregnancy.

And just in terms of quinolones, I looked this up because I was very curious. You know, if you really needed to use a quinolone, there's not very strong evidence reporting that there's risk to the fetus. There's a lot of concern about (inaudible) in animal studies. But looking back, some of the new data is showing that quinolones probably are safe, if you really have to use it in a situation like in drug resistance, especially after the first trimester, but, of course, we have many other options. So we don't typically have to rely on using quinolones. And the data really didn't look at long durations of treatment like we use in TB. They looked more at short courses for urinary infections and other things. And also the data is similar in children it is probably not as toxic as we have been led to believe, but the guidelines still do not say that you should use it.

Again, the most important thing is to look at the pregnancy. If the woman is very sick, then probably her fetus is going to have poor outcomes as well. And so you need to try to manage her as safely but as aggressively as possible. However, in our patient-she did not have significant disease. She wasn't very ill, and so we didn't have the leisure of not being as aggressive in her

This patient was hepatitis B- and C-negative. Her ultrasound showed the baby was actually doing quite well. The baby was normal but small. And providers felt like her situation was likely INH hepatitis, maybe precipitated by the acetaminophen she started taking for her headaches. So she was sent home and told not to take her medication. And as you can imagine there was miscommunication and she, unfortunately, continued to take it. But the very sharp, local health department caught it right away in her labs and realized she wasn't improving. And, again, they advised her to hold her medication.

She remained asymptomatic and her pregnancy continued to proceed normally. Liver enzymes came back normal. And the decision was made to start her on INH and Rifampin. And so it was restarted started and, unfortunately, within just a few weeks the liver enzymes began to be elevated again, up to ALT of 572. And so her TB meds were held. And, at that point, she'd only had ten doses of Rifampin and Ethambutol. They reevaluated her and there was no other evidence that she was drinking taking Tylenol or anything else. And so it was thought that she was highly sensitive to TB meds given her underlying pregnancy.

And so now we're at the next polling question, which is how would you manage recurrent liver enzyme elevation in a pregnant female? Keep in mind that she is due in a month.

Okay. So the question is how would you manage this? When her LFTs come back under normal, would you go ahead and start quinolones and Ethambutol, even before delivery? Would you hold meds until after the delivery and then start Levaquin and Ethambutol, both being very low risk of hepatotoxicity, and try to get her back on Erythromycin? Or would you hold therapy until three months after delivery and then restart INH, Ethambutol, and Rifabutin. And keep in mind that the risk of increased hepatotoxicity during pregnancy is thought to extend three months postpartum. So it takes the liver a while to come back to sort of this normal post-pregnant state.

And it looks like most participants favor either going ahead and treating her now or waiting until three months later.

Well, it looks like, I think based on the number of people here on the webinar, we've probably got most of our responses. So, Emily, you can go ahead and close that. So what we did in this situation, we actually went with B. She was only a month away. She had been doing really well. We didn't feel like she had a high burden of disease.

Learning From the Front Lines:
Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

And we felt like the risk/benefits that Levaquin was probably fine as well as the EMB but in this situation we just felt like it would be okay to hold therapy for a few more weeks.

In terms of number three, we didn't like the idea of waiting a few months after delivery, mainly because we felt like she would have prolonged period of exposure to the infant after birth, three months where she would not be on treatment, and we felt like that might be a sufficient amount of time for her to become culture-positive again. The problem with B would be, of course, if that you're taking Levaquin, potentially, you know, for two days right after delivery, there is the potential that Levaquin gets passed through the breastmilk. But, you know, you can always pump and dump, and she can provide that adequate formula in that interim.

What happened is that the mom actually got induced pretty soon thereafter. She was doing well. The baby was fine. And so the baby was just did great at birth. Unfortunately, we had talked to them about testing the placenta to help us assess whether or not the baby could potentially have congenital TB. If the placenta had a lot of granuloma or was culture-positive, that would be concerning for the infant. But [indiscernible] no culture was done, even though we had lots of discussions, I know the public health had been in very close communication with providers but as you know stuff happens.

The mom was seen in TB clinic. She was doing really well. And her cultures were still negative. And her AST and ALT returned to normal. The alk phos remained a little elevated, but as you know the placenta also produces alk phos. And her bili remained normal. She was able to be restarted back on Ethambutol and Rifabutin after delivery. She's done really, really well. She plans on breastfeeding, although I think, if I heard at follow-up, that she was not able to breastfeed. But, at the last follow-up, she was doing really, really well and was going to take a year of EMB and Rifabutin for five days a week.

And so the pediatrician evaluated the newborn at delivery, and the baby was very healthy and they felt it did not have congenital TB. Because we couldn't access the placenta tissue and just to err on the side of caution, even though the mother was not very infectious they went ahead and did an LP on the infant and it was completely normal. And the cultures for the baby were negative were negative from the spinal fluid. The baby's skin test was normal, as you would imagine at birth the skin test is not very helpful. But at about three to four months is when we typically replace the skin test in the infant after delivery. And also, putting the baby on INH right away is important, both to the baby's benefit but also because of the potential [indiscernible] mother. And so the baby was put on 50 milligrams, supplemented with B6. And a lot of communication with the pediatrician that had to monitor the baby and make sure that everyone was on the same page, between the mother and the baby doctors.

I just wanted to point out, I use this as an example, telling you that all is not lost [indiscernible]. I get a lot of calls about patients who cultures weren't done, their biopsies, their placentas, and lots of other tissues, and they still don't know whether or not a patient has TB. And I'll just tell you that we do have now the ability in certain specialized labs to extract DNA from a fixed specimen, both in paraffin or in formalin, and it kind of depends on the lab that you send them to. And if the DNA for TB is detected, we can actually then send that sample to the CDC and they can do molecular detection of drug resistance from that. So you really can still figure out how to treat the person appropriately, even when samples don't get cultures. And so here is the link for you to the CDC, National Jewish, University of Washington, and Vanderbilt Pathology Lab. There may be other labs as well, but these are the ones that I'm aware of.

And so one more question I want you to kind of think about. In this situation – the mom and baby were not separated. We didn't feel that the mom was very sick. And, if at all possible, you want to keep the mom and baby together. That early bonding is really, really important. But there are guidelines on this put out by the Red Book and there's also a nice discussion about it in Jeff Strake's Handbook of Children and Adolescent Tuberculosis. I put a link here for you. So if the mom is suspected of TB disease, it's really important to make that diagnosis and make sure that both the mom and -- is put on therapy quickly, and also the baby is put on INH as quick as possible.

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

And then when you reunite them, the mom should wear a mask if there's any chance of her being infectious, and that's just a surgical mask. So it's really important to make sure the mom understands that when she's holding the baby in close contact, she needs to have that mask on and make sure she's willing to adhere to all of these recommendations, and that she's taking DOT without any concern. And once that infant is on INH, it's really not necessary to separate them unless the circumstance is the mom has drug resistance. And because the outcomes could potentially be so severe in an infant, we would have much stricter criteria in that circumstance. We also had a [indiscernible] patient whose mom was cavitory and smear-positive and very, very contagious for a long period of time. And we actually did have to keep them separated for a bit just because we felt like the mom was really potentially infectious.

Breastfeeding really should be encouraged. This is a local recommendation in the U.S., but also worldwide. The benefits of breastfeeding are substantial. WHO recommends worldwide that breastfeeding should occur regardless of whether or not the mom is infectious because the benefits that benefit is so significant. But, in the United States, the recommendations are a little more stringent because we have good alternative formulas and safe water. So it's recommended that the mom should be clearly non-infectious and on treatment for about two weeks before allowing breastfeeding, because breastfeeding is much closer and prolonged contact than simply holding the baby. So, Megan, any questions for me right now?

Yes, Connie. There was just one comment. Was this mother smear-positive at diagnosis?

I believe she was actually smear-negative but culture-positive. And so that led to a little bit of a delay in the diagnosis, and then also I am not sure if she had two whole weeks of therapy -- I think she did -- but she had a lot of treatment interactions, giving her hepatotoxicity. But she had fairly minimal disease and had been on therapy. And they had done a culture -- her cultures and smears had been negative up to the time of delivery. Obviously, they did a culture at delivery and didn't have the results yet, but she was still smear-negative at delivery. The baby was delivered in isolation environment so that, you know, there were protections, just in case. But I believe that mother and baby were reunited very quickly.

Okay, and just going back to your polling question, I believe it was option C, about holding off for three months after the baby was born to restart TB meds, and there was a comment of if you wait that long then you would have to restart TB therapy, you know, you'd have to start therapy all over again. I don't know if you want to make any comments about that problem. You can wait between treatment versus having to restart the entire treatment over again. I know you wouldn't do this in this case for the reasons you gave, but are there other things where you started therapy and then stop for three months? Would you have to re--

Yeah, there's actually a nice table in the 2003 -- it's a figure actually -- in the 2003 ATS treatment guidelines. And it shows how long a treatment interruption can be. And I think three months is on the long side. I think, typically, if you go beyond two months, you really need to start over. And our goal, of course, is to get patients to complete therapy within a really short period of time. CDC looks at data for treatment completion within a month -- I'm sorry, a year. But, really, a year is a long time to complete six months of therapy. And so, ideally, patients don't miss therapy. And the more adherence, the more consistent therapy, the higher the efficacy of treatment, and the lower risk of relapse. And so I agree, that's another reason that we didn't want to wait three months. We felt like go ahead and -- you know, we were able to get her back on Ethambutol and Rifabutin, and she did do really well.

So I don't know about all of you, but I love this cartoon, and I think if I can put a crouton on a sundae and the calories don't count, I'm going to do that. And I'll celebrate the 10th birthday by having one. So the next case I want to cover is a child exposed to INH-resistant TB. This is a five-year-old girl born in the U.S. She had a skin test of 16 millimeters. She did not receive BCG. But it had been reported that she had potentially been exposed to an adult family friend who had been in the home and had INH-resistant TB, and had actually visited the house during an infectious period. This child had also traveled to Ghana for three months.

Learning From the Front Lines:
Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

I just wanted to make a point, when I heard the Jeff Starke talk at the TB Controllers meeting last month, you know, he made a point that I thought was really interesting. He was talking about the risk of TB in foreign-born children. And, you know, we always think about the risk of TB coming from their parents, but he said that there was a recent study -- I haven't looked at the reference -- that indicated that visitors in the home are actually a significant risk for TB among foreign-born children. And so this case kind of bears that out. It's important, as we do our histories of young children with positive skin test, to not just talk about family, but think about visitors to the home. And sometimes people don't want to disclose those visitors, as you all know, because sometimes extended family members or other people in community and may not be legal, or there may be other stigma issues, you know, a lot of reasons why. But it's just important history point.

Anyway, this child had had a really minimal cough, no other symptoms. The child was 95th% by weight. She was doing well, with no distress, displaying age-appropriate behavior, good development, lungs were clear, and no palpable lymphadenopathy. But, unfortunately, when they got the chest x-ray, they saw that the patient already had some significant abnormalities. And, as you can see here, there's pretty notable right hilar opacity, and the interpretation of this should be considered TB until proven otherwise.

So my next polling question is what would you do for this young child with a positive skin test, hilar adenopathy, exposed to INH-resistant TB? Would you go ahead and treat this with nine months of INH because this paucibacillary disease is often the case in children in this situation? Would you get a CT scan to confirm this and kind of look for other lesions, see if it could be something other than TB? Would you do sputum induction for AFB culture and susceptibility? Or would you hospitalize the patient for gastric aspirates? Or the last one is empirically treat the TB disease given risk factors and clinical challenges?

So go ahead and put in your answers to this. Megan any questions that you have seen or do you have any questions?

One question I would ask if a child this age who definitively had TB, what would you expect to see on a chest x-ray.

Yeah, I think this is really consistent with primary infections. Lymphadenopathy is a really common presentation for young children, and it's usually enough to diagnose TB. You can sometimes also see an infiltrate. A child like this you would not expect to see adult type cavitary disease consistent with reactivation TB. And so, you know, this chest x-ray is fairly competent.

I see that most people here want to either want to empirically treat this child for TB disease, which is something we do quite often, or to try to hospitalize the patient for gastric aspirates and even sputum induction. And so, I think that they're all appropriate choices. I agree we would not want to empirically treat with one month isoniazid. One, the child was potentially exposed to INH-resistant TB, although they could have been exposed on the trip to Ghana to anything. And I think we all agree there's not a need to get CT scan to confirm this. The chest x-ray is fairly classic as is the known exposure.

And so then the issue is really empiric treatment versus getting a sample. And so I just want to point out that because of the resistance, I think it would be very helpful in this situation to try to get a sample, a sputum culture so you can then get susceptibility. That is sometimes harder than it seems, especially if the child is undocumented and you don't have any funding to get the child authorized to pay for all this.

So in the first case, it's not certain, again, getting that susceptibility is really helpful. And she is five years old, so that could potentially be right on the cusp of whether or not you can get sputum induction. Spontaneous sputum is probably not going to be useful. It's very unlikely she can cooperate to give you a good sample of sputum deep in the lung. But induced sputum actually has been shown to have better yield of gastric aspirate if the patient can follow instructions. So it's worth trying to get in your clinic, and thereby, it will be much more cost effective for you. But if the patient isn't able, you could certainly hospitalize them and get early morning gastric aspirates. And,

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

again remembering that the yield of gastric aspirate is low, and so if you get a negative culture that doesn't mean it's not TB. It just means that you have too low of a sensitivity to detect TB. And so in this patient we're going to assume it's TB regardless, go ahead and try to get that [inaudible]. It's recommended that in children, especially when you're using the EMB get the baseline eye exam and monitor them with basic labs at baseline.

And in this circumstance, we were talking, they asked us what treatment to use, and we felt because it's possible the INH was susceptible, we recommend to go ahead and start on four-drug therapy. And, again, the risk of EMB in a baby -- in a five-year-old is fairly low. And optic neuritis has been reported in patients with normal renal function, it's probably not likely to be a problem as long as you're monitoring them closely.

But when you get the cultures back, you can certainly use that. If it's INH-resistant, you can certainly stop the INH and then go ahead and complete three-drug therapy. But if the cultures don't come back and you don't get an answer, probably in that circumstance, just to minimize, check to see if four drugs for a total of six months, I would probably just go ahead and stop the INH and use Rifampin, PZA, and Ethambutol for the duration of the six-month therapy.

I just want to point out that the chest x-ray is not a very good tool to follow in clinical progress in this situation. Most patients with pulmonary TB, the chest x-ray is very helpful if you get it after two months of treatment. You can tell that the infiltrate is improving and they're responding to your treatment. Similarly, [inaudible] you will also see some improvement during therapy, and we also get chest x-rays at the end of therapy.

So when you just have hilar or mediastinal adenopathy without infiltrate, we really recommend only that you get a chest x-ray at the end therapy and not during therapy. Even if you have successful therapy for six months, you may not have any improvement in the adenopathy at the end of treatment, and so that end of therapy chest x-ray is really kind of just to get a baseline. That adenopathy can persist for up two or three years, and so don't panic when you see that abnormal [inaudible] of therapy in children with adenopathy.

Okay. Megan, any questions? We doing okay?

I think we're doing great. I think that last slide was fantastic. You know, I think that's true for many people with TB, that, you know, even if they have an abnormal chest x-ray at the end of their treatment, as long as they completed an adequate regimen, that's sufficient. It's just to follow in the future to make sure there's no worsening in that chest x-ray.

Thanks. Good. Okay, so this is another call I had a few times, and this is actually something where I've recently changed my recommendation based on new information. But it's a 60-year-old woman who's taking inhaled steroids. Remote history of having had a positive skin test result, and so she's developed cough variant asthma and was put on -- and was offered a steroid inhaler, but she was uncomfortable taking that inhaler because she was afraid it would cause her tuberculosis to activate. And so the provider called me to ask if an inhaled steroid can be administered to an adult with positive skin test.

And so the polling question for you all is can they or not, or C, "I've been wondering about that." And so I see a lot of people choosing that, yes, we would go ahead and give the inhaled steroid to someone who needs it. And a few people have also been wondering about that, so great. Okay, Emily, you can go ahead and stop that.

So the answer is, yes, absolutely you can give it to an adult with a positive skin test. The question really is, so is there increased risk of developing TB in a person who is known to be infected affected by inhaled steroids. So I actually went back and looked at the literature again. I think I first did this consult a couple years ago, and so I went back yesterday to look at it to kind of see what was new. And, indeed, there's a little bit of new evidence.

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

So inhaled steroids are preferred in a lot of patients with lung disease, to oral steroids, because they are very effective for reducing inflammation, but it's very targeted toward the airways. And so that limits the unwanted systemic effects more so than giving oral steroids. But the question about whether inhaled steroids increases the risk of TB remains somewhat controversial. There's just never been a definitive study that's looking at randomized clinical trial, whether or not you really have an increased risk of TB through taking this type of steroid.

There are several observational studies that suggest there may be some increased risk. Unfortunately these, again, were observational risks, which means that they're risk factors that weren't necessarily adequately considered. And they were using insurance claim data, which means that, you know, you can't get a lot of the information you might want regarding an HIV status or whether they were contact, or even foreign-birth or ethnicity, which, as you all know, is common risk factors.

So one study showed an exposure with an inhaled steroids was not associated with increased risk if they are also taking oral steroids, but is if it's only in skin alone. And that was a study in Quebec. In another study they published a couple years ago, it was looking at the same thing in Taiwan and found that there is increased risk of TB in an infected persons using an inhaled steroids and that [inaudible] dose-response effect.

So, you know, thinking about this, the ATS guidelines suggest that 15 millimeter -- 15 milligrams or more a day of oral prednisone is considered a risk factor for developing TB if you're infected, usually when it's given for a month or more. And then recently there was actually a study that came out, Jick et al, that looked at the risk of TB at increased doses, again, of oral steroids, and said that maybe it doesn't even take quite that much, maybe 7.5 milligrams a day is enough to cause your immunosuppression and increase your risk of reactivation.

And so the study pointed out that Fluticasone, which is an inhaled steroid, is really about equivalent to ten milligrams of prednisone a day. So it's plausible that if you're using Fluticasone at the highest doses and using it for a prolonged period of time you may have enough suppression that's equivalent to the oral prednisone where you have an increased risk of TB reactivation. And so I think there's still a lot more to learn about this issue. But regardless of whether or not we there is risk, any patients who need inhaled steroids to breathe should be given that, and we should just recommend to them that if they have a positive skin test or IGRA, that you would then recommend that they take LTBI treatment and that will reduce their risk of future TB.

All right. I have a few more cases I want to get through. And so this next case is one that I just got, and I hope providers out there don't mind me immediately throwing it into my slide deck. But this is a Sudanese male who had lymphadenopathy. And he had immigrated in 2005. And last August he presented to the hospital. He'd had a few months of fatigue and weight loss. He had what he considered a chest wall sternoclavicular mass. And the way this was described, it wasn't described like a lymph node, it was really more described as a chest wall mass.

He had been given antibiotics and was discharged home but he came back a couple of months later with more of what he considered lungs. And this time he also had an oropharyngeal abscess. He had a positive IGRA. And, as you know, because he's foreign-born, probably had BCG-- the IGRA is a better test to use because it doesn't cross react with BCG. And so that was significant that he had likely a true infection. The chest x-ray and CT were done, and showed multiple enlarged cervical, hilar, and mediastinal lymph nodes. Unfortunately, I don't have a picture. And he was empirically started on TB meds, which is absolutely appropriate. I'm sure that they also chose to get a pulmonary specimen as well. Unfortunately, as you know, sometimes happens in the hospital, PZA was incorrectly dosed, and they also aspirated his chest wall mass. And it did grow to TB, but the DNA probe from the TB growth was never received. They didn't get susceptibility from him.

He was referred to the TB clinic, and, at that point, started appropriate doses five days a week. He rapidly got better. The clinical improvement within just three or four weeks, oropharyngeal, neck and chest wall masses had all resolved. And his sputum cultures had come back, and, again, they had been sent and came back negative. He was also HIV-negative and Hep C normal labs. He got a full initial therapy of 40 doses of daily RIPE, which is usually

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

five days a week. And then, in January, began continuation phase of INH and Rifampin, assuming full susceptibility, although his results had not been received yet. And I think there was just a lab mix-up. And as you guys know, this happens. Unfortunately, all of us, when something like this happens and the results that come back, you know. These are the situations where we learn something; right?

So then it was not until early February that preliminary results were received, and they came back showing susceptibility to RIF, EMB, and PZA. And so that was good news. And, unfortunately, there was further delay. And finally in -- just recently, the end of March, the provider received lab results that the INH was resistant, and it was resistant at .1 micrograms per ml, which is considered low level resistance. At this point, he had been on intermittent therapy for 18 doses during the [inaudible] phase, and he had been getting intermittent INH 900 and Rifampin 600, although he did continue to improve. And so we were called because there was concern that, oh, my goodness, he's now INH-resistant and he's been on two drugs for weeks. And so I believe I had a polling question next.

So if this is something that comes to you, what would you do? Would you, given the low level INH-resistance, would you stop the INH, restart RIF, EMB, and PZA five days a week, and complete six months of total therapy, counting the doses that he got of intermittent INH and Rifampin? Or would you stop the INH, go ahead and give him Rifampin, EMB and PZA five days a week and -- should have not counted that to complete six months with a full continuation phase of RIF, EMB, and PZA? Would you stop the INH and go ahead and change to bi-weekly Rifampin, EMB, and PZA to complete six months but not count the INH/RIF doses? Or would you stop INH, restart the three drugs, add quinolones, and complete six months? And the last one, would you just continue because it's only low dose INH, would you go ahead and continue INH and Rifampin intermittent to complete six months of therapy?

This is really interesting. And, I'm sorry, I know the second choice is a copy of the first, so you don't have the option of seeing that. There's a lot of people that feel comfortable that at low-level resistance you could continue INH and Rifampin.

So I think I'll, again, go back to the guidelines, and I also put a couple other references here. You guys are all aware INH is a very important first-line drug because it's got great early bactericidal activity against rapidly dividing cells. And it's also been shown in combination it prevents selection and emergence of drug-resistance. But resistance to INH is also really common, and the worldwide prevalence is about 13%, and that includes among new cases, like newly-reported TB, 10% have INH, and more than a quarter of patients who have been retreated have developed INH resistance.

And so the early data from the British Medical Research Studies show that you can easily treat patients with INH resistance, as long as you use PZA throughout and you continue Rifampin through the duration of therapy. And so the recommendations are, if you can't use INH, you can still use six months of Rifampin, PZA, and Ethambutol, and that's got a fairly high recommendation.

And so I just wanted to kind of talk a little bit about high-dose INH resistance. So INH resistance is conferred via two different mutations, and that's katG and inhA. katG is almost universally associated with high-level resistance, which is defined as 1.0 mg/ml of solid media, whereas inhA shows that you have lower levels of INH resistance, usually at a level of .2. And also, if you have the inhA mutation, those patients tend to also have Ethionamide cross-resistance.

And so in patients with MDR TB where we're relying on molecular determination of resistance, if we see that we get the molecular results first before we get the traditional susceptibility that actually give you that clinical concentration of .1 or .4, then you can say, "Oh, it's an INH mutation," and then the patient with MDR might possibly be able to keep using INH in the regimen, as well as other medications. Whereas, if you see that there's a

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

katG and it's complete INH resistance, you realize that you're not going to have any benefit from using INH in a regimen like you would when you use the inhA.

And it's theoretically possible to overcome low-level resistance by increasing the dose. There have been a few studies that have sort of looked at that. The intermittent therapy dose, typically around 15 mg/kg. And so one of the studies looked at one with a dose of 15 to 18 milligrams and found that there was some benefit when using high-dose INH.

So I just wanted to point out that I really, again, like going to the Curry guide for issues like this. And I looked up "how to treat patients with INH mono-resistance" and they really had a nice synthesis of the data which I have included the references for you. Basically, you can essentially treat INH resistance without using INH, even when there's low-level resistance if you continue to INH, Rifampin, and PZA -- I'm sorry, Rifampin, PZA, and Ethambutol, you can actually have pretty good outcomes equal to what you would if the INH had been susceptible.

So it's even shown that treatment outcomes are not very different if you have low versus high level resistance. And another study showed that if you added quinolones you could possibly also further improve outcomes. In fact, the RIFAQUIN trial was done looking at Rifampin, Ethambutol, PZA, and Moxifloxacin for two months, followed by once weekly Moxifloxacin and high-dose Rifampin. And found that that was as effective as using a standard six-month regimen when INH is susceptible. But it's very important, if you are using a quinolone, that you make sure that the isolate is susceptible to it.

The next slides shows the guidelines and recommendations now are slightly different from the 2003 ATS guidelines for drug susceptible TB, and I would go with these Curry guidelines. The same regimen is recommended, but now that regimen studied in the RIFAQUIN trial is actually recommended. And so you can use daily Rifampin, Ethambutol, and PZA, plus or minus a quinolones. If they can't tolerate PZA, you can use RIF and EMB, plus or minus a quinolone for nine to 12 months, or you can use this regimen used in the RIFAQUIN trial. And I'll be honest, I have never used this trial with the Rifampin and the Moxifloxacin, and I'm not sure I would in those circumstances if I could use one of these other two regimens. I think that's always a clinical decision based on someone's experience and comfort level. For our patient, certainly shows that we could have treated them very well without the INH, even though that low-level resistance was there.

So, really, the question was, with this patient, we could certainly go ahead and put them on Rifampin, PZA, and Ethambutol, and maybe they did get some benefits from having had intermittent high-dose INH with Rifampin. Maybe you could count it, but there's no data on that. And so I recommended that let's just go ahead and start the continuation phase over and not count that information, but also feel comfortable that we may not have lost much -- the patient may not have actually been on [inaudible] Rifampin because of the low-level resistance of INH being overcome possibly by the high-dose Rifampin intermittent doses. So that may be a little confusing, but I'm happy to answer questions about that as we near the end of the talk.

And I have a slide on intermittent regimens that we just talked about. And I'll just tell you, you know, there's only one study that I found about whether or not daily or intermittent Rifampin, PZA, and Ethambutol. That was done by Randall Reves and another group. And I think the problem is that when you do an intermittent therapy, you get such high doses of PZA, it's very, very difficult to tolerate for six months. And so there's evidence that it maybe is effective, but the tolerability is a whole other issue. And so, you know, I think if you can use daily therapy, that would probably be ideal.

And so, Emily, I think I'm going to skip the slide about adolescent TB and infectiousness. You all can just look at that on your own. I want to go to my last patient on -- I'm going backwards in my slides -- on the inmate.

So this is one of my favorite calls that I got, and I teach on it a lot. And so this is a 22-year-old African American U.S.-born prison inmate. He has a history of "underdeveloped lungs" from birth, but otherwise healthy. Other than

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

incarceration, hasn't had other TB risk factors. In January of 2015, he was admitted to the prison infirmary with a 40-pound weight loss over six months, fever, tachycardia, cough, shortness of breath, nausea, vomiting. He was just really sick. His HIV was negative. He was also tested for syphilis, and he had a pretty high pre-albumin suggesting he was really malnourished. His skin test was negative, but his QuantiFERON Gold was positive. Chest x-ray showed bilateral diffuse advanced lung disease. He had bullae and blebs throughout the left upper lobe, mid lung, alveolar nodule pattern in the remainder of lung. And no masses were seen. It's hard to tell, I think, how much of this is underlying lung disease from the TB, but he was smear-positive and culture-positive for pan-susceptible TB at diagnosis.

So he was started on standard 4-drug therapy at appropriate doses. And when he started treatment, he actually decompensated. I don't have a lot of information on the surge that was reported, but he was also given Levaquin and Prednisone, and apparently improved at that point. But he kept getting worse. And even though he was on treatment in the prison, it looked like the opacities were continuing to increase, as well as a left pleural effusion. Although this could have been an IRIS-type reaction, his cultures remained positive for quite a while. In February, again, continued to look worse.

He was then hospitalized for really a prolonged period of time. He kept having persistent fevers. His TB was susceptible to all drugs when it was checked again, which is appropriate. He was switched to INH and Rifampin fairly quickly, although he hadn't completed two full months of PZA. And the drug was sent to an outside lab for a therapeutic drug monitoring, and reported back as "low."

And just a plug for therapeutic drug monitoring, it's an excellent tool, and sending it was absolutely appropriate in this situation because patients who fail to respond to therapy, you certainly want to think about malabsorption of medications, drug interactions that might be affecting medications, acquired resistance, persistent areas of TB where the drugs may not be getting in. And the problem is when you send them to a reference lab that doesn't really do a lot of drug levels, it's really hard for us to interpret what those drug levels mean. And so I highly recommend using Chuck Peloquin's lab, which we use in the Southeast. And just to remind you all that thanks to a generous grant from the Virginia TB Foundation, we can actually send drug monitoring free of charge for you on request. Just call our 1-800-4TB-INFO hotline and we'll do that for you.

But that wasn't what happened here. It went to an outside lab. And so they found a low level. They put him on IV meds because they were worried he wasn't absorbing it. So he was put on Rifampin and INH, and he started to get better. So we switched him to PO meds and was sent back to prison. But, unfortunately, he continued to be smear- and culture-positive, and this went on through April. He continued to have intermittent fever.

So now we have another polling question. Why is this man with pan-susceptible TB, we have done another culture and proven that there's no drug resistance yet, although that was two months ago, why is he not improving or responding to therapy? Could he have a secondary infection or an underlying malignancy that is confusing the picture? Could he have acquired new drug resistance? Is he not absorbing his medication? Is it a possible IRIS because he had prednisone and then stopped it? Or is it something else?

I see a lot of people are still really concerned about a absorption , which, you know, based on the drug level, it's absolutely reasonable. And so I'm going to go ahead and stop that polling question, Emily, and move on. So I'm on slide five now. So, between April and May, he was hospitalized again. And there was concern that he had a renal abscess on ultrasound. And they were also trying to figure out why he had prolonged smear positivity and fevers. They did an extensive work up trying to find another cause of infection. If you remember, TB IRIS is also a condition that's based on ruling out other causes. So there were no other causes of new infection. He was started back on five-drug regimen, this time the other four drugs plus Moxifloxacin.

So, just to go onto slide six, I just want to point out that prolonged fevers in and of itself isn't that concerning. You can have prolonged fevers for a lot longer than two months, even if patients are otherwise responding. In his

Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

situation, he's also not converting his smears or cultures, and, again, smears can be positive for a long time if they are dead organisms, but his cultures were still positive. And, clinically, he would get back from the hospital, he would be tuned up in the hospital, he would come back home, and he would just be feeling bad again. And so, you know, there was definitely that concern for malabsorption. And so they called us and we recommended repeat cultures and susceptibilities again. Let's go ahead and get therapeutic drug monitoring at our lab. And we also recommended getting a rapid molecular test for resistance so that we could see quickly, by GeneXpert or Hain on a raw sample if there was any new drug resistance.

And we also wanted to make sure that we're just going to restart therapy and make sure he gets the full eight weeks of PZA. We didn't feel like he needed a quinolone. He didn't have documented resistance at this point. You know, we checked the doses for weight, made sure there weren't antacids given with his meds, things that might affect him. And we made sure that they -- we talked to them a lot about daily treatment. So, just to kind of get to the punch, Emily, go ahead and change to slide eight.

Just to get to the punch, what happened is we got therapeutic monitoring. We realized that this man was not taking his meds. He had trace levels of all of his meds. And so what was happening is he would go to the hospital and he would get IV meds and he would get better, and he would get the benefit of therapy. And then he would go back to the prison, he would be given sort of prison-type DOT, which is usually asking the inmates to show up at Med call. And then he would go back to the cell with his pills.

And so we called Ellen, and I said, "Ellen, what in the world can you do?" And she -- Ellen Murray, as you all know, is our corrections guru. And Ellen said -- she called up to the corrections and health department, and they ended up turning off the water in his cell so he couldn't use his toilet or sink. They "tossed" his cell was the term she used. They pulled up his mattress and went through all the things. They found a lot of pills. And they realized that he had gone to pill call then he would take his meds back to his room and not taking any of them. And so once they realized that, they instituted strict DOT, appropriate DOT the way we try to do it in public health where you actually have a patient sit with you for a prolonged period after they've taken their meds and swallow it.

And, lo and behold, the patient got enormously better. And when he started to feel better, and then he realized -- got a lot of education, and then he realized the benefit. He actually ended up being cured. Fortunately, no drug resistance developed from him selectively taking some pills and not the others. So this is just really a great case to me because, you know, it's difficult in settings like corrections, where your first priority is security, to have the standards that we have in public health, but that collaboration between showing corrections and public health is essential. And, you know, if they had been reaching out sooner, we might have been able to help a little sooner. However, hindsight is really perfect. So I hope you enjoyed that case, and the others. And I am happy to answer a few questions. I think we're at the end of our time, but I can stay on if anyone wants to ask questions. So, Megan.

Yeah, Connie, we have a few questions. I know we're at the end of our time, but if you can just stay on for a few more minutes. There was a question particularly about this inmate case, whether the patient was in general population or if he was in isolation, and if there was any kind of contact investigation that was done?

So that is a super question. Obviously those are really important aspects whenever we deal with cases on TB. My problem with the MCD consult is that I don't often get follow-up. I've reached out more recently. This was a consult we did over a year ago. Recently, my practice is to kind of reach out via email or phone call and ask how patients are doing. And because people call us for help but don't necessarily want us all in their business, I try not to press myself too much on people. But I love getting the follow-up because it helps me in situations like this to learn, and also to teach.

And so I believe that there were also maybe some issues with isolation, as you all have seen in your own practices, where being in the infirmary is considered isolation, whether or not it is a true negative pressure room situation. So my guess is that he was probably not adequately isolated and was probably a significant risk. I'm not sure of the

Learning From the Front Lines:
Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

results of his contact investigation either, so I can't tell you how many people were exposed. As you know he was transferred back and forth from the hospital to prison. So there were other exposures, in the hospital, in transportation, back and forth from the TB -- or from the medical clinic to the cell. So if he wasn't appropriately isolated, you know, that can be a nightmare contact investigation. Any other questions, Megan?

Yes. Going back to your case with the low-level INH resistance, you were talking about some treatment regimens. And there were some regimens that were recommended initially daily. And there was a question whether that daily recommendation was based on five times weekly or a seven times weekly regimen, or if there was any difference.

That's a great question, too. Actually, the intermittency of these regimens for INH resistance was something that I found, even looking at the guidelines, very unclear. I actually did go back and look at some studies, and noticed some of the original data didn't clarify daily five days versus seven days versus truly intermittent. The Randall Reves study was clearly intermittent. And a few others that were looking at Rifampin, PZA, and Ethambutol were clearly daily. And I think that it's perfectly fine to use five days a week as a target for seven. I think, you know, obviously, if we could be ideal and give a steady state of medication seven days a week, we would. But practical aspects of public health and our extremely limited resources are that that's almost never possible. We'll do it in patients who are extremely sick, drug-resistant, maybe HIV, or maybe on the front end while they're still highly infectious. The other alternative is to let the patients self-administer on the weekend days, and that's a good practice as well.

And so I think I put on the slide what I was able to find in the study regarding intermittent versus daily. I found it particularly interesting that in the Curry guidelines, that on the slide, that lists the actual three treatment options for INH-resistant TB. The first one said daily. You know, it clearly said daily Rifampin, EMB, and PZA, plus or minus quinolones. And the second one didn't say if Rifampin/Ethambutol was daily or not.

And I actually was talking to Dave about this last night to try to get a sense of that. And we both sort of felt like if you can do five days a week of RIF and EMB, that would be ideal. You're only giving two medications. And so daily would give you a steady state of drugs and it would give you more Rifampin exposure than bi-weekly, because, as you know, the bi-weekly dose of Rifampin is the same as the daily. So I would say daily would be ideal, but it's just not clear if the intermittent is appropriate for that regimen.

And then for number three, the regimen studied in the RIFAQUIN trial also showed that it was daily for two months, followed by once weekly. And, of course, once weekly therapy is easier for DOT. It's just that there's just not a lot of clinical practice using once a week Rifampin. When you get into these highly intermittent regimens, it does raise concern for me about acquired resistance if patients aren't carefully screened and followed. So, again, there is some data to support that. Anyways, I hope that was a helpful answer to that question. Megan, were there any other questions?

You treat resistance quite a bit. What has been your experience?

Well, I mean, my patients are captive audiences here in the hospital. So, I mean, we have the advantage of giving their medication by DOT seven days a week, so that's generally what we do. But even in our most complicated cases that we send into the community once they're discharged, if they're continuing on TB therapy, we'll treat them five days a week. And then we give the patients an option if they want to take the medication on the weekend, we provide it for them but it's not done by DOT. So they get the five days a week DOT and then the option to take on the weekend. And, I mean, we have pretty good treatment outcomes here in Florida by doing that.

Great. Any other questions come in?

Learning From the Front Lines:
Celebrating 10 Years of the Medical Consultation Database

April 5, 2016

We have one final question. It was a question about giving vaccines and placing a PPD on the same day. Is that recommended or is there any documentation that says whether you should do a PPD testing and then vaccines later on, or what do you recommend?

Yeah, that's a great question. And I think that does come up in clinical practice quite a bit, and we've actually been called about that as well. So the -- getting vaccines, those are immunogenic, and so can cause a [inaudible] immune response. And so it's recommended that if you are giving -- you're going to place a skin test and give the vaccine on the same day or draw the IGRA, it's probably okay. But if you've had a recent vaccine probably within about a month, you'd want to wait about a month or longer before -- if you have just had a vaccine you would like to defer to place the skin test until at least four weeks, maybe a little bit longer. That's a good question.

So I don't see any more questions out there. [Inaudible].

I just want to point out that the slides that everyone was looking at that is my family, and only my nine-year-old son, who is still a child and not an inhibited teenager, was willing to take a picture for World TB Day with a bear. So kudos to my son. But, anyway, happy World TB Day to everyone. I want to recognize all your hard, hard work in the field. We're so grateful for being included through the consult line and some of your cases. And always glad to help. If we don't know the answer, we will find out or help talk through the pros and cons, sometimes there's not a clear-cut answer. But please keep bringing your questions to us because it helps us to learn and it also helps us to share with others. Okay, so, Megan, thank you. And thanks, Megan, for doing this with me.

My pleasure. Thanks for having me today. And thank you all for joining us.