

**CDC Clinician Call:
Outbreak of Fungal Meningitis and Other Infections**

**March 13, 2013
4:00 pm CT**

Coordinator: Welcome and thank you for standing by. At this time participants will be in a listen-only mode until the question-and-answer portion. If at that time you would like to ask a question, press star 1.

Today's conference is also being recorded. If you have any objections, please disconnect at this time.

I'd now like to turn the call over to your host today to Mr. (Tom Chiller). Sir, you may begin.

(Tom Chiller): Great. Thank you, (Melissa), and good afternoon everybody.

This is (Tom Chiller). I'm the Deputy Chief of the Mycotic Disease Branch here at the Centers for Disease Control and Prevention. And I'm joined by Dr. (Anu Milani). He's the Medical Director of Infection Prevention and Control at St. Joseph's Mercy Hospital in Ann Arbor, Michigan.

And (Anu) and I will be speaking to you a little bit about updates with the fungal meningitis and other infections outbreak -- specifically focusing on clinical management issues -- and then we'll be taking questions on this call.

So again we appreciate those of you joining and we hope that we've been able to capture many of you after you've seen patients in clinic -- at least those on the East Coast.

I wanted to begin to talk a little bit about a couple of documents that we released recently and are now on the Web site.

The first document is the Health Alert Network document or HAN -- the CDC Health Update. And it's a notice to clinicians that is entitled "Continued Vigilance Urged for Fungal Infections Among Patients Who Received Contaminated Steroid Injections."

So before we go into a couple of the highlights of that document just to get everybody on the same page and to give everyone an update on where we are with in cases and infections reported to us at the CDC.

We now have 722 cases that have been identified. The majority of those cases are now paraspinal or spinal infections only, with 304. Those with meningitis only now number 239 and patients with both paraspinal and meningitis are 138.

So one of the things that we've noted in the epidemiology of this outbreak as it has progressed is that now we see more spinal and paraspinal infections at the site of the injection.

So with that in mind the vigilance that we're asking for clinicians and patients to continue has to do with those spinal and paraspinal mainly and that is that we are still seeing those infections occur months after the injection was performed. And in fact now have reports of patients with an injection longer than six months out and manifesting with an infection.

So our concern -- which we've emphasized throughout this outbreak -- is that fungal infections may be indolent for very long periods of time and we fully anticipate that there will continue to be infections identified in patients months after their last injection.

And we want to make clinicians aware that these infections will continue to manifest and present; although we hope that those will be in small numbers. But part of the Health Alert that we put out gives some guidance as to how one might evaluate a patient months after the injection.

And what we've found in speaking with clinicians who are managing many of these patients - like Dr. (Milani) who's on the line with us today - is that patients may have minimal if any change in their baseline symptoms for which they received the injection in the first place and therefore these symptoms may be very difficult to distinguish from anything new or worsening.

And even in those situations it warrants further careful evaluation of the patient and strong consideration to performing an MRI of the site of injection. There have been cases now noted will have the patients had no change in their baseline persistent symptoms but were identified with a focal infection -- a paraspinal or a spinal infection -- at the site of injection.

So the Health Alert urges clinicians and patients to continue to remain vigilant months now after their last injection and to consider performing that MRI scanning at the site of injection.

I want to now talk a little bit about the updated clinical guidance for patients that have already identified obviously as a case or as a clinically possibly infected patient and just to highlight some of the changes that we have added to the guidance this last week when we posted it to the Web.

I think the important things to note are as I've already mentioned incubation periods can be very prolonged. I think that the other thing to note is that patients on treatment are getting better and we can hear a little bit more about that from Dr. (Milani) when he tells us about the Michigan experience.

And then finally that we are trying to understand more about duration of therapy and make some recommendations as to if patients are discontinued on therapy, what kinds of ways they can be monitored after therapy is stopped.

So let me first talk a little bit about some of those points. And I first want to make it clear again that we do have an informal network of infectious disease clinicians who have a specialty in mycology that is available for consultation to physicians through the CDC.

And that clinician network continues to remain available and we hope that you are able to use those experts in consultation if you have patients and you have questions about patients. And we continue to try to update those physicians as often possible with information pertaining these patients as we find out new clinical information.

So a couple of points that I want to bring up about the guidance and then I will turn it over to Dr. (Milani) to give us a little summary about some of the clinical issues in Michigan.

I think it's important to note that we continue to recommend voriconazole as the first line therapy for patients. We continue to recommend it at the beginning dose of 6 milligrams per kilogram with a trough level in the fifth day and then adjusted the dose to try to maintain a trough between two and five.

I think it's important to note that we have seen a lot of side effects with voriconazole with our experience with this outbreak and that those side effects early on are the side effects that we would expect to see from voriconazole -- especially given at these higher doses -- and that is hallucinations.

And we think it's important that those side effects not trigger automatic removal of the medicine and instead should prompt clinicians to dose reduce, so lower the dose, recheck levels and reassure patients that those side effects can be managed and can go away and will go away with time and dose adjustment.

I think there are then other side effects that we've seen with more chronic use of voriconazole and in this outbreak because patients will be on voriconazole potentially for months. We are concerned about more chronic effects of the drug and side effects that we've seen.

There have been many reports of patients who, even though they have therapeutic levels, they complain of a foggy feeling, sort of being unable to make decisions and some forgetfulness. Sometimes nausea, anorexia and fatigue can be experienced. Chapped lips are very common. And I think you

will hear from Dr. (Milani) that alopecia we are noting is actually quite common and even photosensitivity can be severe.

So one of the things that we want clinicians to be aware of is that with many months of therapy there are issues with photosensitivity and skin cancer that have been noted with voriconazole and there also are rare side effects like periostitis that can occur.

And so we want clinicians to be aware that because we're dealing with months -- potentially months -- of therapy with voriconazole that we need to remain looking for these side effects. And again the clinician consultation network can help in dealing with these and identifying them if you need help.

To move on to some of the other potential antifungal agents that could be used if voriconazole is causing serious side effects, we have been continuously evaluating other drugs besides voriconazole and amphotericin B and those clinicians that have had to use them.

And what again want to recommend is that we still feel strongly with our clinical expert guidance that voriconazole and then amphotericin B -- especially liposomal amphotericin B -- are really the first lines of therapy.

If those drugs cannot be used due to very bad side effects as mentioned toxicities of the liver that can't be reversed, then we would consider itraconazole and posaconazole to be potential options.

Perhaps Dr. (Milani) can speak to his experience with itraconazole. We do not know of many patients on this antifungal medicines at this time. We do know of some that have been on this medicine but then had some recurrence of

disease and had to go on to other medicines. And we have very limited experience with posaconazole.

But these drugs, you know, do act with a similar mechanism to voriconazole. The challenge with these drugs for those patients with CNS disease is that they are not known to penetrate well in to the CNS like voriconazole.

But I think as we learn more about patients that have had to switch drugs we will provide more information via our Web site about these alternative therapies.

And I think finally a couple things focusing specifically on perimeningeal or spinal, paraspinal infections and again Dr. (Milani) can speak a little bit to this we encourage that as these are identified by MRI that a neurosurgical consultation is obtained.

I think that we have heard about many patients that have had these abscesses drained, these phlegmons removed that have had very good and speedy recovery in symptoms and pain -- which may be in part due to the procedure performed -- which is usually a laminectomy -- but may also be in part due to the fact that the infection was successfully removed or infectious material was successfully removed. And then those patients are now on an antifungal therapy post-surgery and we heard reports that these patients are actually doing very well.

And then finally and I'll stop talking and turn it over to Dr. (Milani). Finally I just wanted to mention something about duration of therapy and follow up.

I think we continue, you know, to remain cautious about recommending specific lengths of therapy. I think that the consensus from our experts is that

we're going to need at least three months of therapy and probably more like six months of therapy for many of these patients. I think there are going to be some categories of patients, like those with arachnoiditis, those with boney involvement, disc involvement that are probably going to need therapy even longer than six months, even up to a year or potentially longer depending on their response to therapy.

So we know that many of you who are following these patients and of course the patients themselves, you know, want to know when to stop therapy. I will say we are hearing reports of some patients and clinicians that have stopped therapy as early as three months but many of them have gone longer -- four months, five months.

Many of those patients that we've heard about have had meningitis early in the outbreak and have documented lumbar punctures that have shown no cells in the CSF and that has prompted clinicians to consider stopping therapy.

We are still evaluating and listening to clinicians tell us about ways in which to evaluate success of therapy. I think one possibility is performing a lumbar puncture and looking at the cerebrospinal fluid and documenting no cells or less than five cells in the CSF.

I think we're less inclined to recommend or even recommend thinking performing MRIs in follow-up because we do know from several clinicians and clinics that MRIs can remain positive for months after the infections has been diagnosed and haven't shown a lot of signs of improvement and change.

I think that we all know that MRIs can stay abnormal for lengthy periods of time and we wouldn't recommend serial MRIs with frequency in the weeks. You know, but instead if MRIs are done in follow-up would consider waiting

probably several weeks if not months before repeating an MRI as a way in which to evaluate patients' improvement.

So I will stop there and I will turn it over for the next few minutes to Dr. (Milani), where he will tell as a little bit about some of these clinical issues as they relate to the patients that he's taken care of in Michigan. (Anu)?

Dr. (Anu Milani): Thanks, (Tom).

So I'm just going to talk a little bit about our experience here at St. Joseph Mercy Hospital in Ann Arbor, Michigan.

You know, for the first month of this outbreak we mostly dealt with fungal meningitis. And since that time it's really been seeing these cases of spinal and paraspinal infections as (Tom) was talking about.

In regards to the 50-plus cases of meningitis that we saw, a very high number of these patients did have infections at their injection site kind of similar to the patients that have spinal and paraspinal infections except that that group actually never developed meningitis.

We've seen over 120 cases of spinal and paraspinal infection and a high number of these patients have undergone surgery. In taking into account the group with meningitis that developed infection at their injection site in this group we've taken well over 100 patients to the operating room.

I think most of the patients that had spinal and paraspinal infections that have undergone surgery seem to be doing quite well. And many of the patients that had meningitis that also developed infection at the injection site that required operative intervention seem to be doing quite well.

Throughout this time period we've also seen some peripheral joint infections and many of them have also undergone surgery.

Talk a little bit about treatment. Most of the patients that we've admitted have usually had two drugs. Usually the combination is voriconazole and liposomal amphotericin B.

I think the duration really varied on the disease presentation. The folks that had meningitis and had infection at the injection site they often received four weeks of treatment. Patients that just had spinal or paraspinal infections that underwent surgery they often got anywhere from seven to ten days of combination therapy and were sent home on voriconazole.

It is important to note that we have seen a couple of cases -- this is definitely not the norm but we have seen a couple cases -- recently that had meningitis initially that also had arachnoiditis that have required operative intervention in the last month because of what was felt to be worsening disease.

We have done MRIs on most of our patients that did have a spinal or paraspinal infection or injection. And in many of these patients as (Tom) alluded to that actually had little change in baseline symptoms, you know, and actually in fact in a third of these patients were actually found - we found abnormal MRIs. And many of these patients did require surgery and had confirmation of fungus.

In terms of treatments I think we really - I think it's important to highlight that most patients are in the outpatient setting. Most patients are doing relatively well. Most patients are being treated with voriconazole, but we continue to see side effects of voriconazole.

Probably the latest effect or the most recent effect that we've seen with voriconazole has been periostitis. Voriconazole contains fluoride. Fluoride can stimulate osteoblasts and you can have new bone formation. We've actually been able to get some fluoride levels back on patients and these levels have been elevated and these patients are at risk for osteomalacia.

And so this is something that we're beginning to see and I suspect that some of the effects that we're seeing as (Tom) had mentioned alopecia. Many of our patients have hair loss. Some of these side effects are likely dose related.

We've been using higher doses than we've ever used before to try to achieve levels often between two to five. And because, I think because, of some of these higher doses I think we are seeing some of these side effects accelerated.

I think the cognitive difficulties, the difficulties with memory loss, we're still seeing those and sometimes those seem to improve when we reduce doses.

We have switched a number of patients to itraconazole and those have been mostly patients that had peripheral joint infections or patients that had spinal or paraspinal infections that underwent operative intervention for various reasons.

We switched some of those patients to itraconazole. I think in our experience albeit the numbers are small it seems that itraconazole is probably easier to tolerate.

Limited experience with posaconazole. We have a couple patients but they seem to be doing well.

In terms of duration of treatment as (Tom) talked about I think that this is going to really kind of vary based on disease presentation.

It's also probably important to know that we have continued to see new cases as most recently as this week. Again the numbers are we continue to see a case here and there, but I think that it really highlights the need to be vigilant about, you know, symptoms and about imaging.

We have seen MRIs that were normal in November that unfortunately became abnormal, you know, in later months -- most recently even in February.

So I think that those were a lot of the points I wanted to talk about. I'll pass it back over to you, (Tom).

(Tom Chiller): Thanks, (Anu), and appreciate that summary. And I'm just going to end with just a couple quick comments and then we'll turn it over to questions.

I just want to reiterate that we have a clinical consultation network that's established. Again you can look on the Web site for that information or you can call 1-800-C-D-C-I-N-F-O -- CDC-INFO -- which is 1-800-232-4636 -- and mention that you are calling about the fungal meningitis outbreak and you want to be connected with the clinical consultation network.

That should connect you with a number where you can leave a message and we check that answering machine throughout the week, throughout the day multiple times. And so we hope that it's functioning. And if it isn't, you know, please let CDC-INFO know that you're not getting through so that they can get back to us.

I also wanted to then just end to mention something briefly about diagnostics and about testing. We recently published a study about the PCR method that we have been using to detect the fungus in this outbreak. We continue to offer that PCR test on CSF and other body fluids and tissues -- including fresh tissue and paraffin tissue blocks -- and we continue to collect fungal islets recovered from sites of infection as they come in.

We encourage you please to consult with your state health department prior to sending any specimen to CDC. Those specimens should be sent through the state health department or with the state health department.

We're also hearing that a number of clinicians have reported using a beta-D-glucan test and we've heard of other diagnostic tests that have been described for detection and patient management.

We do not -- CDC does not -- have any data on the performance of other tests and so we can't comment on their utility and certainly do not advocate those tests at this time without further data and validation.

But we can say that, you know, having examined here at CDC at least 20 autopsies that our pathologists have not been able to document any movement of the fungal organisms into visceral organs or outside the immediate spinal blood vessel walls except in the brain as we've talked about.

So we don't have any evidence yet of overt fungemia or circulation of intact organisms in the blood. So we're unclear about how serum or blood tests would perform in this outbreak.

And so we just want to make it clear that that's the current information we have available and it's important to work with your state health departments, your local health departments if you want to send specimens to get tested.

So, operator, I will stop there and go ahead and turn it over to questions.

Coordinator: Thank you. We will now begin the question-and-answer session. If you would like to ask a question, please press star 1 and record your name clearly. One moment please for the first question.

The first question comes from (Shannon). Your line is open.

(Shannon Burger): My name is (Shannon Burger). Can you hear me?

(Tom Chiller): Yes we can.

(Shannon Burger): I've been sending e-mails. I'm what you call a medical professional and I've been sending e-mails to (Tom Freidan), the Director, and a Dr. (Armstrong) at the CDC. And it's not really a question that I'm going to ask you. It's information that I wanted to give you.

My father, Kenneth Jungwirth -- J-U-N-G-W-I-R-T-H -- suffered death at Jupiter Medical Center and the Florida Department of Health is reviewing his medical records -- 1128 pages.

And I just wanted to give you information that the meningitis outbreak is not particularly what you think it is. My father died of sulfonamide poisoning. And I'm asking you -- I'm begging you okay -- to review your autopsies again -- the 20 that you were speaking of.

And the other 30 medical records - 30 patients that have now died out of the 50 to establish the exact cause of death of those poor United States citizens because I believe it's sulfonamide (trimeth) poisoning.

Again my father's records if you would like to obtain them are at the Florida Department of Health. I've asked several times in several e-mails that the CDC review it. The department of health has had his medical records since November 5 of 2012.

So again here's my information. I really hope that you take it to heart.

Man: Yes thank...

(Shannon Burger): I believe your meningitis outbreak is caused by sulfonamide (trimeth) poisoning and this is why. The medical...

(Tom Chiller): We really want this call to focus on clinical management of our current cases and so we obviously...

(Shannon Burger): Right. So this is how it's going to focus on it. The drugs that you're giving these 722 people are sulfa (trimeth) drugs.

(Tom Chiller): We have an etiology for many of these patients. We know it's a fungus. And although we know that sulfa toxicity exists and can cause serious complications we're focusing right now on the fungal element within the outbreak.

(Tom Chiller): Can we have the next question please?

Coordinator: The next question comes from (Jeanette).

(Jeanette Bluxrude): Hi this is (Jeanette Bluxrude) out of Minnesota. I'm calling in regards to my husband. I'm just wondering can this - he's had two of the injections. He's never gotten meningitis. But can it affect the neurological system?

Lately he's been more like in a zombie-like condition. A lot of times he can't sleep at night. Both his legs are dragging. He's very agitated and the pain in his lower back is getting worse and it's affecting - he also has chronic pain in his neck, so it's affecting his neck.

So I'm just curious if this even though he didn't get meningitis if this fungal infection can affect the neurological system.

(Tom Chiller): Yes thanks for that question. And I mean I think it's important - this let me just reemphasize that this is why it's important that if there are any symptoms that are concerning -- including continued pain that patients are having at the site of injection or where they got their injections originally -- it's important that they go back and get evaluated by a clinician.

And so I would encourage in this sort of situation and in any other like it to go and get seen and get evaluated and it may be that imaging with an MRI is important to elucidate whether there's a focal infection where pain is existing.

So I would encourage you and any other patients like this or with pain and even with baseline pain to go back and talk their physicians, get evaluated because we need to remain vigilant about the fact that these infections can occur many months after the injections have happened.

Next question please.

(Jeanette Bluxrude): Okay. Thank you.

(Tom Chiller): Sure thing. The next question.

Coordinator: The next question comes from (Sandy).

(Sandy): Hello I'm calling from Baltimore, Maryland. I'm a nurse case manager. And my question is I know you addressed it in the early conference call several months ago about patients that received a contaminated injection. You know, that we know that they received it. They were in the lot numbers. But yet we have providers that are continuing to request further injections and some of these patients have received further injections even though they had a contaminated epidural steroid injection.

So my question to you is, is there anything that you can put out to deter some of the physicians to really be careful about not recommending? Because some of these patients are not informed and they're going forward with the injections.

And given the new information with things coming up, my question was have any of these patients that have this recurrence or you feel like that it's the fungal infection is in hibernation and now it's surfaced again, did any of those patients receive any subsequent injections after receiving a contaminated one?

(Tom Chiller): Yes, thanks for that question and it has certainly come up many times. And we have certainly tried to address the subject by talking about the fact that there are going to be infections that are indolent, that are incubating as you say, that are going to occur as we've mentioned many times many months -- and you heard Dr. (Milani) such as that he just saw a couple cases last week -- after the injection.

And so we are concerned certainly about the risks of reinjecting steroids in to an area that was originally given an injection with a potentially contaminated lot of steroids.

But again we don't know when the safe period will be and we don't know which patients might be safer than others and when one can begin to consider reinitiating those steroid injections.

We realize that these patients are getting injections for a reason. They suffer from some sort of chronic pain and that their physicians have with in consultation with them decided that this is a potentially viable method to use to control that pain.

(Sandy): Right.

(Tom Chiller): I certainly think again we encourage, you know, all alternative methods to be used for pain control besides injections in these patients, you know, for, you know, a prolong period of time because again we just don't know how long people can potentially incubate with this infection before manifesting. But we do know it's months and I don't think any of us will be surprised if we continue to see a few cases go all the way out to a year after the last injection.

(Sandy): How about someone who had a contaminated injection and then you have a surgeon wanting to do a spinal fusion? I mean would that have the same advice -- try to do all kinds of other treatment modalities and stay away from surgery.

We're just concerned at this point because you have someone who we don't really know what this fungus is doing. It has a long incubation period and then you have doctors requesting well the person needs a spinal fusion.

And so we're very reluctant to authorize that on - you know, we're erring on the side of caution for the patient trying to think okay well you're going to be literally opening up the spine, going in there and doing a fusion.

(Tom Chiller): Yes. I mean again any other good question so and in fact I think (Anu) or Dr. (Milani), you guys have definitely done a lot of surgeries on those patients that are infected mainly for surgical debridement, et cetera. But since you've got a lot more experience with sort of dealing with the surgical aspects, I'm curious about your thoughts about this sort of question.

Dr. (Anu Milani): I share your concerns, (Tom). I think we - I don't think that we fully know what the incubation period is. And, you know, we've seen some patients that as I had noted earlier that had normal MRIs in November that unfortunately became abnormal in February.

So we try, you know, to recommend not giving epidural steroid injections to these patients that have had previous injections. We try to shy away from elective surgeries.

And, you know, in the case that you were bringing up, I would be concerned about putting potential hardware in to a site that had a previous history of a contaminated injection when don't fully understand how long the incubation period may be.

(Sandy): Okay. Thank you very much. This is very, very helpful.

(Tom Chiller): You're welcome. Next question please.

Coordinator: The next question comes from (Patricia).

(Patricia): Hi there. I was wondering what are the doses of itraconazole and posaconazole that you're using to treat the people who just cannot tolerate the voriconazole?

(Tom Chiller): Yes. (Anu), do you want to answer that?

Dr. (Anu Milani): Sure. Yes we've tried itraconazole. We usually load them 200 (T-I-P). We follow levels for three days and then we often go to 200 (D-I-D).

The posaconazole our experience is a little more limited. We've tried the four times a day dosing the q.i.d. and we're waiting for some levels to come back. And then, you know, depending on where the levels are we're going to probably try to the 400 milligrams twice a day dosing. In general they've been a little bit easier to tolerate in our experience.

(Patricia): Well I've got one patient who's tried voriconazole three times and it's just he just cannot take it.

The other thing that I'm finding is that, you know, if you've got somebody on amiodarone who cannot come off of it, you don't really have a choice except for AmBisome. And I've just been very hesitant to commit anybody to a long duration of AmBisome because of all those side effects.

Dr. (Anu Milani): I would agree, I mean with the risk of QT prolongation there with the amiodarone.

That being said, you know, there have been a couple patients that we have not - they've needed amiodarone and they've also needed voriconazole for, you know, CSF penetration.

And I can say that we were pretty vigilant about checking EKGs and monitoring QT prolongation. I think, you know, we had our cardiology colleagues also managing these patients, so we have done it. I mean not - I wouldn't suggest, you know, that that's the way to go. But in some patients we have had to do that and follow closely.

(Tom Chiller): And, (Anu), I was wondering if you could comment. I know that we've had discussions with our clinical experts about, you know, prolonged use of amphotericin and clearly there have been - I know that there are clinicians that have had to use amphotericin for prolonged periods and I know we've talked with the group about, you know, q.o.d. dosing and different ways in which amphotericin can be used.

Can you comment on a little bit of - I know you've used some prolonged amphotericin in some of the patients there as well.

Dr. (Anu Milani): Yes we've had a number of patients that have had I would say, you know, even four weeks or longer courses and there are many patients that tolerated daily AmBisome. Usually the dose was 5 milligrams per kilogram daily.

You know, they would definitely get fluid boluses often a liter before their infusions. And we had a lot of people also on maintenance hydration -- which I think seemed to help. There are some that did have some nephrotoxicity and some patients that we did put on every other day AmBisome.

And I think in our experience I would say that, you know, some of these patients I think, you know, that seem to either have worsening disease on just voriconazole alone like those that had meningitis and then they later presented with infections at their injections site they it seemed that many of them -- especially the ones with arachnoiditis -- seemed to respond to amphotericin and seemed to respond to it maybe a little bit better than the voriconazole.

(Patricia): Okay. Well I have two other questions that are quick. And one is I have a patient who's on voriconazole who's actually tolerating the medicine very well except for his face is so - looks so sunburned. He's just having a horrible time. He works outside and he says he's been on it for about four months and he says I just don't think there's any way I can take this stuff and work outside.

And so, you know, his MRI has improved actually over the last three months. So anybody - any recommendations for these people who have this horrible photosensitivity?

Dr. (Anu Milani): What type of disease presentation does he have?

(Patricia): He has a paraspinal. He actually had cervical injection -- cervical - yes cervical injection and he's one of those who got two injections and then he kept still having pain. And even after all of this came out about the meningitis outbreak, he went to another neurologist who gave him another injection.

Dr. (Anu Milani): So he never had meningitis.

(Patricia): No.

Dr. (Anu Milani): And did he undergo surgery?

(Patricia): No. He had the enhancement.

Dr. (Anu Milani): Okay.

(Patricia): They call it (unintelligible) enhancement but he didn't have any drainable phlegmon or abscess or anything like that.

Dr. (Anu Milani): Is he clinically improving?

(Patricia): Yes he is.

Dr. (Anu Milani): He is okay.

(Patricia): I mean he's one of the one's who really is but then he just says, you know, I just don't think there's any way I'm going to be able to do this and be able to work outside this summer. So I'm hoping that six months will be enough and hopefully I can get him there.

Dr. (Anu Milani): Well, you know, I mean and maybe in that patient maybe you're able to use itraconazole. I mean if you don't need CSF penetration and you're talking about a paraspinal injection as you said, you know, maybe that may be a consideration. You know, it's outside. You know, it's definitely not intradural, so you might be able to try that and see how you do.

We have done that in people that have had paraspinal infections, but I would say that most of our patients have undergone surgery. But there are, you know, as you said, there are some patients that just cannot tolerate voriconazole. Whether it's due to photosensitivity or for other reasons, they

just can't tolerate it. And we have stepped down some of the patients to itraconazole.

(Patricia): Okay. And my last question is I know on the Web site you talk about management of asymptomatic patients and that is just vigilance and, you know, continued monitoring. But I guess my question is, is there ever going to be a time that it is recommended that anybody who had an injection of a contaminated steroid lot have an MRI no matter what absolutely?

I mean you're kind of on the Web site and on the thing to kind of waffling on that. But is there ever going to be that recommendation that everybody absolutely needs to have that?

(Tom Chiller): Yes. And I think - and thanks for that and I appreciate you looking at the Web site and obviously you've studied the materials and the language closely.

Because what we've tried to do is base it on as much data as we have and have tried to evaluate that data. And because really there are really there's limited data on that type of patient and we sort of shy away from the term asymptomatic because again these patients all got injections for some type of symptom. So we've tried to use more the term no change in baseline symptoms.

And as Dr. (Milani) has already suggested in Michigan and as we've stated in the Health Alert as well as on the Web site there have been several clinics that have done some of this MRI screening on patients with no change in baseline and have found some disease. It's been around 10 or 15% in these one or two clinics. But it's been, you know, it's enough for us to raise this level of concern with all of you in the clinical community. But it's not enough data to flat out recommend MRI-ing everybody who's received an injection.

And so that's why, you know, we do think you should have based on that information you need to interpret it but we - you know, I think we do think you should have a very low threshold to evaluate your patients with an MRI at the site of injection.

I think that if you truly had a patient that was asymptomatic, let's say that their baseline symptoms were gone, that is certainly a patient that would be the lowest on my priority list to perform an MRI. Because I do think that at our experience in talking at this point is that everyone has some type of pain. It may not be any different than the pain that they had when they first came in to the doctor to get an injection. But everyone is having some type of symptomatology.

I think the challenge as we have described it is trying to understand whether that symptomatology is any different -- which would obviously prompt all of us as clinicians to try to obtain some sort of diagnostic testing.

But it is a challenging issue. We do want to put that in the hands of the clinicians that are there with the patient in their office evaluating them. But I think we all feel that you should have a very low threshold to consider getting an MRI if you're concerned.

(Patricia): I understand yes. And, you know, just recently when we also had a patient who had some enhancement on his initial MRI back in late December who got put on voriconazole. And because he was a fairly heavy guy, he had a very like 700 b.i.d. and his level came back like at 14 after five days.

And that's also what I'm finding is that putting these people on 6 milligrams per kilogram the doses don't come back in the two to five range. It always

seems to require a decrease in the dose. And of course they're all very symptomatic.

But this patient I'm mentioning actually when we rescanned him mid-February we had epidural abscesses and had to go to surgery so and his serology preliminary is positive.

So it makes a believer out of you when you see those enhancements and then they become epidural abscesses. It's very scary.

(Tom Chiller): Yes and thank you for that. And I think again we definitely hear about those reports from clinicians out there just like you describe and we definitely realize that starting on that higher dose - and as you know that there is correlation with even higher levels in obese patients. So we realize that that's going to get high trough levels at the beginning and so that's why, you know, we really want people to even though we continue to recommend starting at a high dose we really want you to, you know, that trough and then dose adjust right away.

And reassure your patients that yes you have a high level and we'll get rid of some of these side effects. We're going to take your medicine down to a lower level. But we still continue to recommend starting at that higher dose initially.

So thank you so much for those questions and those comments.

(Patricia): Thank you.

(Tom Chiller): Next question.

Coordinator: The next question comes from (Lori).

(Lori Basheto): Hi my name's (Lori Basheto). I'm just wondering if all the patients that were treated actually had positive fungal cultures, you know, that were treated with the antifungal or were people treated that actually didn't have positive cultures?

(Tom Chiller): Yes, thanks for that question. Fungal infections are a challenging group of infections to actually isolate organisms from oftentimes. And in clinic trials when one is evaluating fungal disease we characterize diseases -- actually infection -- in three different categories.

One is proven infection and that is where we actually see evidence of the fungus in tissue or we have a positive test for the fungal organism.

We also have a category of probable disease where we will characterize they will have classic findings consistent with fungal disease on radiology and a testing of serum or some other diagnostic test that is indirectly related to the organism itself.

And then finally the category of possible fungal infection where patients have, you know, all the signs and symptoms but they don't have any diagnostic tests that are indicating a fungal infection. And honestly the most common type of patient is that possible patient and that's for all fungal diseases unfortunately.

In this particular outbreak about 30% of the patients that are currently cases have a confirmed culture or PCR for a fungus and that is sort of not a typical to what we might expect to see. Unfortunately fungi are hard to grow, they're hard to isolate and they're often hard to find with the currently available diagnostic tests that we have.

So we base, you know, to a large extent our treatment strategies and our case definitions on someone who had the appropriate risk. In this case it would be getting a contaminated injection from one of those three lots and then symptoms consistent with what we're seeing in patients throughout this outbreak.

(Lori Basheto): Great. Thank you.

(Tom Chiller): Next question.

Coordinator: The next question comes from (Bill).

(Bill): Hello?

(Tom Chiller): Yes go ahead.

(Bill): I have a question. I'm a patient with side effects of fatigue, photosensitive skin, chapped lips, balance and headaches that seem to be either withdrawal or addictiveness to the voriconazole.

If the voriconazole has cleared the fungus, how is that defined and what is the chance of the infection or incubation coming back and what would the symptoms be?

(Tom Chiller): Yes. Well those are good questions and I'm sorry to hear that you're one of the folks suffering from this infection.

You mentioned that you're currently on voriconazole it sounds like and some of the side effects and the symptoms and signs that you're telling us about are known to be caused by voriconazole. And I'll turn this over to Dr. (Milani) in

a second who's obviously following a lot of patients like yourself that have many of these effects.

But I will tell you to address sort of the second part of your question -- which was about how do you know if the fungus is gone and then how do you know whether something recurs or relapses. You know, those are important but very challenging questions -- not only in this particular outbreak but in fungal diseases in general of this type -- which is one of the reasons why I think we are being very cautious about telling physicians to stop therapy early.

Because there are - it is challenging to know when the fungus is gone completely and so we do want to try to make sure that we've gotten rid of all the fungus. And in fact your body also helps get rid of fungus.

And so we are trying to understand from patients that have stopped their medicines on their own or from patients that have now been on therapy for many months whether, you know, there are certain time periods for certain disease entities that seem to be enough that we can actually stop therapy.

I think as far as recurrence or relapse again this is a challenging thing to diagnose early on. But we would want you the patient and your clinician that you're working with to continue to evaluate you once you were off the voriconazole and just to be concerned about any recurrence of any of those symptoms that you had prior to developing the infection or during the infection prior to stopping the voriconazole and then to evaluate those symptoms.

So I would ask Dr. (Milani) to maybe talk a little about some of the side effects you described and sort of how to deal with those.

Dr. (Anu Milani): (Bill), I think you mentioned chapped lips, dizziness. What were the other things you mentioned?

(Bill): Balance and photosensitive skin and the headaches.

Dr. (Anu Milani): Yes. Okay. You know, they are all possibilities. I think the chapped lips are something we see. Photosensitive skin is something we see. I think that especially as the weather becomes a little warmer, you know, I would recommend wearing long sleeves. I would recommend wearing sunscreen, maybe trying to stay out of the sun as much as possible, wearing a hat.

I think the dizziness and balance those can be issues as well with voriconazole. I think I'm not - I don't know the exact details of kind of your infection, but I think there are probably some important points to be discussed with your clinician.

(Bill): What is the protocol for ceasing to take the voriconazole?

Dr. (Anu Milani): Well I mean I think it depends, (Bill). I think that those decisions are really made on an individual level and they're made with your physician. And, you know, they have to take in to account what type of infection you've had, whether you underwent surgery, how you're feeling, have you had any MRIs. I mean there's a lot of things to take in to account and I think those are detailed discussions that probably are probably better suited honestly to take with your infectious discusses physicians.

(Bill): Okay. Thank you very much and thank you for taking my questions.

(Tom Chiller): Thank, (Bill). Next question.

Coordinator: The next question is from Dr. (Norman Bernstein). Your line is open.

Dr. (Norman Bernstein): Hi. Can you hear me?

(Tom Chiller): Yes we can.

Dr. (Norman Bernstein): Oh. Okay I'm Dr. (Bernstein). I'm from Fredericksburg, Virginia. I've had one case come here with originally after three contaminated steroid injections she developed meningitis and later relapsed on voriconazole with arachnoiditis.

And so with the arachnoiditis symptoms were quite - became quite severe. At one point she was hospitalized with a second bout of urinary retention and had to have narcotics for pain medication. And she seemed to respond to liposomal amphotericin.

The problem with liposomal amphotericin in the case was that originally when we gave the doses recommended by CDC we had problems with renal failure. And what we've done now is given doses of 4 milligrams per kilogram daily - - which is a little bit lower than what you've recommended -- and we were able to maintain the patient as an outpatient with infusions -- almost daily infusions of liposomal amphotericin.

I wondered what you thought about the dosing, how critical those higher doses are in these patients, whether any of the patients who have had surgical debridement are just are people who particularly have epidural abscesses or phlegmons or whether any of those people are just people with very severe arachnoiditis and whether sed rates seem to be of any importance in monitoring.

It seems with this patient that perhaps a steady drop in the sed rate seems to mirror some improvement in clinical findings and I wondered if there are any comments about that.

(Tom Chiller): Well thanks for those questions. And I think these are clearly some of the more challenging cases that are related to this outbreak. I think we have probably 50 or 60 cases. I mean don't quote me on those exact numbers. But I think we have around that many cases of meningitis with arachnoiditis like you're describing and they're clearly the most challenging cases to manage.

And again I appreciate the fact that you've been able to keep this patient going on AmBisome for so long even as an outpatient. I know that's an incredibly challenging thing to do, you know, with the amount of electrolyte loss, et cetera, that goes in to that.

And I'll probably - I mean I definitely want to turn it over to Dr. (Milani) who's certainly had his hands full of patients with the arachnoiditis in Michigan. But I just want - I mean just a couple comments in general, you know, from CDC.

And I think we haven't heard that much benefit from sed rates in general. Again as we all know with sed rates they're very nonspecific and sometimes they can be really helpful in some patients that have high ones that go down and other times they're not. But so far from what we're seeing with data we've gathered or with people we've talked to there hasn't been a good sort of nonspecific marker like that.

That being said, you know, it could be useful in individual cases depending on, you know, if it's high to begin with and you do see some change over time.

The other thing that I would say and then I'll turn it over to Dr. (Milani) is that, you know, I have been pleasantly - maybe a little bit pleasantly -- surprised just because I am a fungal disease person and I deal with arachnoiditis for other fungal diseases and they're incredibly challenging to manage and to deal with.

But we have heard of quite a few patients that were diagnosed with arachnoiditis that are doing much better. And, you know, that's been very heartening to hear that some patients are doing better.

And we haven't been wanting to recommend surgery based on what we've been hearing from other groups. But as you just heard Dr. (Milani) said that he's had to actually now I think take a couple patients to surgery that had arachnoiditis and these are challenging surgical issues.

So with that being said I'll let (Anu) talk a little bit more about his experience with arachnoiditis. (Anu)?

Dr. (Anu Milani): Yes. Thanks for the questions. Regarding dosing I think, you know, if your patient is clinically feeling better, then I think, you know, that's okay to use 4 (mgs per K). I think that's probably fine. And, you know, as I said before we even were using every other day dosing and some people that couldn't tolerate it we even used a little bit less frequent.

As far as sed rates and then maybe I can talk about surgery, we haven't really found inflammatory parameters to be quite useful, such as sed rate and CRP. I guess, you know, in your case if it was elevated and it seems to be coming down with response to infection, well maybe it is something you can follow. In general I would say our experience has been quite limited with that.

Our approach for patients with arachnoiditis it's really been if they had an epidural abscess or phlegmonous component in the epidural space that they typically underwent surgery. In people that solely just had arachnoiditis they did not undergo surgery.

Now we have seen and I would say some of those patients are doing well in the outpatient setting. Invariably most of those patients received combination therapy for an extended duration of time -- often four weeks, sometimes longer.

But there are a couple of patients in that group that we've seen recently in the last, you know, four to six weeks that even despite combination therapy and prolonged hospitalization did develop I think worsening of their disease. And one of those patients seemed to develop a real significant epidural component to their infection where it was primarily intradural.

And then there's a second patient that had kind of really worsening intradural disease. This was complicated by some hardware. It was unclear whether the hardware was involved. And because, you know, this patient had been hospitalized a couple different times and really had prolonged liposomal amphotericin, therapeutic voriconazole levels we actually elected to take that patient to surgery as well.

And in both of those patients they seemed to be clinically improved with surgical intervention. And based on some previous experience we had with really just mostly arachnoiditis it was felt that by our neurosurgical colleagues at least at the time that there was little benefit in patients that just had arachnoiditis. I mean they've gone in and intraoperatively really described kind of this phlegmonous-type material attached to the nerve roots and they

really felt that there was no way that they could, you know, to clean that. And, you know, when they irrigate and wash that out, it's like well maybe they're cleaning off maybe 1% of what was seen.

So primarily if it's just solely arachnoiditis, I would say for the most part none of those patients have really undergone surgery. But I think that what we are seeing is that those patients really do require still a lot of really close follow up and vigilance.

Dr. (Norman Bernstein): Thank you.

(Tom Chiller): Next question.

Coordinator: Our next question is from (Susan). Your line is open.

(Susan): Hi my question actually pertains to the recent findings. Actually they're not that recent. They were posted by the FDA back in December on other drugs where bacteria and fungus was also noted, such as like the betamethasone. Have you guys received any illnesses related to patients who have received betamethasone injections?

(Tom Chiller): Yes thanks for that question. I mean to date we haven't confirmed any illnesses that we can relate to another product, you know, that's associated with those bacteria or fungi.

I think FDA continues to keep their MedWatch reporting system open for clinicians to report to them. But again to date we haven't associated any confirmed infection in a patient with those products.

(Susan): But when you say confirmed, are you speaking in regards to, you know, laboratory confirmed? Like, you know, for example what I'm inquiring on actually pertains to - I actually received a betamethasone injection back in August and I've been suffering with bad neck pain, numbness in my head, numbness in my face.

And I see the posting out there for the betamethasone, so I'm just kind of curious to know if there's been any increased level in reports of, you know, neurological-related symptoms or increased pain related to people that have received these injections of betamethasone.

(Tom Chiller): Yes. No. I mean, you know, we obviously appreciate that and I feel for you. I think what we haven't found is any confirmed infections associated with these products. Now that doesn't mean of course that there aren't complications that happen with injections, that your symptoms aren't real, that they couldn't be caused by some other infection or something else.

And so it's important that you do go and continue to work with your clinician and your physician and try to figure out what's going on. But at least to date here with CDC and our partners we haven't confirmed a definitive infection...

(Susan): Right.

(Tom Chiller): ...associated with another product. So, I mean, that's all we know.

(Susan): Right.

(Tom Chiller): But again there are complications with every procedure out there...

(Susan): Understood.

(Tom Chiller): ...and so it's important for you to - it's important for you to be vigilant and definitely important for you to work with your physician and certainly report something if you find it.

(Susan): Yes see one thing that is kind of concerning that I think it would be helpful for you guys to be aware of in regards to the information that is posted up on the Internet and made available for absolutely anyone who has Internet access is that the doctors don't even recognize the fact that there could be a possibility for a patient to be in harms way who has received one of these other drugs.

Even though it's noted here that there's been bacteria and fungus, the primary focus has been on the methylprednisolone and my heart goes out to all the patients that have received that drug. I feel for them.

But the doctors they just totally disregard the betamethasone injection. And because nothing has been posted, they say well, you know, had that shot a long time ago. If something was going to happen, it would have happened.

And nobody has an answer as to what's causing this numbness in my head that has been there, that will not go away and nobody knows how to treat it. I've been to several pain management doctors and, you know, I went back to the one who initially did the shot and I went to another pain management doctor. I went to an orthopedist.

And everybody wants to do another shot even though we should be proceeding with caution, even though you don't have any documentation that somebody has become ill from a betamethasone shot. I've had other injections before and never in my life experienced a reaction like I have this time.

(Tom Chiller): Yes. No we appreciate those comments. Thanks for that and please, you know, continue to consult with physicians and again we will continue to do our best to investigate any associations that we find and certainly make that information available.

(Susan): Yes. And just if (unintelligible) - you know, if it's possible to just make it a little bit more clearer to the physicians that okay so meningitis hasn't been tied to betamethasone and we don't have any clear-cut laboratory-confirmed illnesses but to please, you know, please watch over these patients.

Because, you know, from what I heard you explain before, the incubation period is a long time. Hopefully nothing will surface in relation to betamethasone or these other drugs that have been known to be found with bacteria and fungus.

(Tom Chiller): No thank you. I mean I think it's a point well taken and we appreciate your comments.

(Susan): And thank you for your time. I appreciate your feedback.

(Tom Chiller): Absolutely. Next question.

Coordinator: Our next question is from (Yogish Brusal). Your line is open.

(Yogish Brusal): Hi. What recommendations do you have for patients who have low levels of voriconazole despite being on appropriate dosing of the voriconazole and they already have significant side effects from the dose they on right now? Do you have any specific recommendations, anything to enhance voriconazole levels or to switch to something else?

They have already been on AmBisome in the past and have developed acute renal failure and the patient is not too keen on going on AmBisome.

(Tom Chiller): Yes thanks for that question and I'll turn that over to Dr. (Milani) because I know he's also been talking about this for a while now as well.

Dr. (Anu Milani): Yes thanks, (Tom). Yes so I guess again I would go back and ask you what type of disease are we talking about, (Yogish)?

(Yogish Brusal): It was (paraspinus) infection in the L4-L5 area. She underwent surgery and debridement and she's been on voriconazole for the last three months now.

Dr. (Anu Milani): Okay.

(Yogish Brusal): She's taking the voriconazole as recommended. And the last two or three times I've been going up on the dose but it's hovering around one -- a little bit more than one.

Dr. (Anu Milani): And what is her dose?

(Yogish Brusal): She's around 76 kilograms. Her dose is now up to 450 milligrams twice a day.

Dr. (Anu Milani): Okay. And how is she clinically doing?

(Yogish Brusal): She is doing fine. She has a lot of fatigue, anorexia, she's lost weight, her liver enzymes bumped up, her (unintelligible) is climbing up. It's around 240 or two times in the upper reach of normal.

Dr. (Anu Milani): Yes. So I think that those are - and you said it was a paraspinal infection.

(Yogish Brusal): Yes.

Dr. (Anu Milani): So those are - these are challenging issues and I appreciate what you're going through. You know what, I think what we've seen is, you know, in cases like this I think that we did push the doses of voriconazole because I think, you know, we really wanted to try to achieve these levels between two to five.

But I think sometimes, you know, with the pushing the doses I mean the patient is already on 450 twice a day I think that, you know, as you alluded to I think that the toxicity, the side effects were probably more prominent. And some of the side effects that we are now talking about in addition not feeling well and memory loss are, you know, side effects related to fluoride levels, periostitis, alopecia, things like that.

So I can tell you that we've, despite some patients having lower levels than, you know, two to five if they are not able to really take higher doses and they're clinically feeling okay, they've undergone surgery and, you know, for whatever their disease presentation is and they seem to be doing okay. Their pain at the injection site is improved. We have actually watched some of those patients.

I guess I'm cautious about increasing the dose higher when they're having so many side effects. And I think, you know, in this type of a patient that you're talking about, you know, I wonder even if you go up on the dose would the patient even be able to tolerate going up on the dose.

And so I think sometimes and probably more recently we've tolerated levels being on the lower side, you know, taking in to account how they feel and how they're doing clinically.

(Yogish Brusal): Okay. Thank you.

(Tom Chiller): Thank you for that. Well it's getting - we're already - we're obviously a little over time but we obviously are here to try to help. So maybe we can take a couple more questions and then stop. Next question.

Coordinator: I'm actually showing no further questions at this time.

(Tom Chiller): Well then that works out well. So then we'll say goodbye and good evening. Thank you all for joining. And as mentioned this call was recorded, so this information hopefully we will have posted within the next several days. Thanks for your time. Goodnight.

Coordinator: This now conclude today's conference. You may disconnect at this time.

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