Multistate Fungal Meningitis Outbreak Investigation Update: Information and Guidance for Clinicians

Moderator: Leticia Davila

Presenters: Melissa K. Schaefer, MD, Tom Chiller, MD, MPH, Peter G. Pappas, MD, and Janet Woodcock, MD

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Coordinator:

Welcome and thank you for standing by. At this time all participants are in a listen-only mode. If you would like to ask a question during the question-and-answer sessions, please press star 1 on your touchtone phone. Today's conference is being recorded. If you have any objections, you may disconnect at this time. Now I will turn the meeting over to Ms. (Leticia Davila).

(Leticia Davila):

Thank you, (Corey).

Good afternoon. I (am Leticia Davila) and I am representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Communication System at the Centers for Disease Control and Prevention. I am delighted to welcome you to today's COCA conference call, Multistate Fungal Meningitis Outbreak Investigation Update, Information and Guidance for Clinicians. We are pleased to have with us today Dr. Schaefer and Dr. Chiller from the Centers for Disease Control and Prevention, Dr. Janet Woodcock from the Food and Drug Administration, and Dr. Peter Pappas from the University of Alabama at Birmingham. They will review the current epidemiology of the outbreak, describe clinical presentation and features of fungal meningitis, and review CDC's recommended treatment guidance.

There is no continuing education or slides provided for this call. Event-specific resources for clinicians are available on our COCA Web site at emergency.cdc.gov/coca.

Our presenter today is Dr. Melissa Schaefer. Dr. Schaefer is a Medical Officer in the Division of HealthCare Quality Promotion at the CDC. She currently works on the Ambulatory and Long-Term Care Team in the division. Her efforts focus on infection prevention in ambulatory care settings with a particular emphasis on ambulatory surgical centers and issues related to injection safety.

Our next presenter is Dr. Tom M. Chiller. Dr. Chiller serves as a Deputy Chief of the Mycotic Diseases Branch. He is board certified and is a faculty member in the Division of Infectious Diseases at the Emory School of Medicine. He practices infectious diseases at the Veterans Affairs Hospital in Atlanta. He has authored numerous articles and book chapters and given many lectures on public health surveillance and infectious diseases.

We also have Dr. Peter Pappas speaking with us today. Dr. Pappas is a Professor of Medicine in the Division of Infectious Diseases and Tinsley Harrison Clinical Scholar in the Department of Medicine at the University of Alabama in Birmingham. He is also the principal investigator of a national network of transplant centers, TRANSNET, in conjunction with CDC. Transnet provides important epidemiologic and treatment information concerning transplant recipients who develop proven and probably invasive fungal infections.

Lastly we will have Dr. Janet Woodcock. Dr. Woodcock is the Director of the Center for Drug Evaluation and Research at the Food and Drug Administration. She will be joining us for the Q&A section of today's COCA call.

At the end of the presentation you will have the opportunity to ask presenters questions. On the phone dialing star 1 will put you in the queue for questions.

For today's Q&A, we will take two questions specifically for Dr. Woodcock with the FDA immediately following her presentation. Then the next presenters will present, and then we will open up the lines for the second Q&A session.

At this time please welcome our first presenter, Dr. Schaefer.

Dr. Melissa Schaefer:
Thanks Leticia. And thanks to all of you for calling in today.

As Leticia mentioned, I'm going to give a very brief overview of the outbreak to date. I'll turn it over to Dr. Woodcock to give an update on the FDA investigation and the MedWatch report that was released yesterday. She'll take two questions after that. And then Dr. Chiller will give a brief update on clinical information. And then we want to spend the bulk of the time today doing question-and-answers, because I know you all have a lot of questions that we weren't able to get to on the COCA call last week.

So let me give you the brief overview and summary. And as I said last time, all the information I'm presenting here is available for your free access on the CDC Web site, through the COCA Web site, and

also through an MMWR, a report that was released last Friday evening summarizing the epidemiologic information and data that we've collected to date.

So if you haven't seen that report, I would encourage you to find it after the call and read it because it's going to have a lot of the information that you all have been looking for.

The Centers for Disease Control, along with state and local health departments and the Food and Drug Administration, have been investigating a multi-state outbreak of fungal infections among patients who have received a steroid injection of a potentially contaminated product from a single compounding pharmacy.

As of today, we have identified 233 cases, 15 deaths, 2 of these are joint infections associated with this outbreak investigation. All of these cases to date have occurred in patients who received steroid from one of the three lots of methylprednisolone acetate that was recalled by the New England Compounding Center on September 26, 2012.

CDC does not have any firm evidence that fungal infections have been caused by exposure to other NECC products. And as you'll see on the Web site and through the information you're going to be hearing, our investigation is ongoing.

At this point I'm going to turn it over to Dr. Woodcock to give a brief update on the FDA investigation and MedWatch report that was released yesterday.

Dr. Woodcock?

Dr. Janet Woodcock:
Thank you very much. This is Janet Woodcock from FDA. And I thank my CDC colleagues for the tremendous work they've been doing on this investigation.

The product in question that's been the - question in the fungal meningitis outbreak came from a compounding pharmacy - New England Compounding Center, or NECC. They make a large number of sterile injectables and ship them all around the United States.

Yesterday we issued a report through our MedWatch system. The company had already done a recall of all its products, and we had been following up and making sure that they were being pulled from health clinics and hospital shelves.

But now we have asked clinics and physicians to follow up with patients who were known to have received an NECC parenteral product since 5/21 and to follow up with them on their condition.

And we are not stipulating how this might be done. We're not, you know, it can be a letter, a phone call, patient had had a recent visit or so on. But we would like to have some follow up to see whether or not the patient remains healthy and has any signs of infection.

And this was driven by a number of things. FDA performed an inspection of NECC. And based on the condition of the plant and other factors that we take into account, we really can't assure sterility of any of these products.

At the time we issued the MedWatch report yesterday, we had three patients who had received other NECC products with suspect infections. That's been narrowed down to two patients at the moment.

Of course these infections may be completely unrelated to the NECC products. So I would reiterate with the CDC that the only infections that are definitely linked to an NECC product are the methylprednisolone at this point.

We are, however - since we made this announcement we've been receiving reports on our MedWatch system. As I said, these may all be unrelated to receipt of an NECC product. And in fact some of the patients may not have -- at the end of the day -- even gotten a product from that facility.

FDA will follow up, however, all these reports in our usual manner, and we'll coordinate that with CDC to make sure that no other product might be implicated in not being sterile and leading to infection.

And we will communicate any new developments with the clinical community as soon as we have information that is reliable.

We're urging health care professionals to report any infections where you have administered an NECC product to our MedWatch system. And the phone number, of the 1-800 line is 1-800-332-1088.

So that's where we are in this investigation. We are continuing to follow up with the firm and determine where the products are shipped and what volumes of various products were shipped. And as I said, we will communicate and provide information as it becomes available.

And so I think I'll take questions at this point.

Coordinator:

Thank you. At this time if you would like to ask a question, please press star 1 on your touchtone phone. You'll be prompted to record your name. Please un-mute your line and do so when prompted. To withdraw your request, you may press star 2. Again, to ask your question, please press star 1 at this time. Dr. Gullett, you may ask your question.

Dr. Norleena Gullett:

Hi, this is Dr. Norleena Gullett from ABC News. After reviewing the MedWatch report yesterday, our question was does this raise the number exposed from the prior 14,000? Since there is concern about other products, I realize you've not confirmed infection, but is that number increased now?

Dr. Janet Woodcock:

Well we know that NECC shipped large volumes of various products. We do not know how many, but we are currently compiling that.

None of these other products have been linked to confirmed infections, as you said. And I think the news really needs to repeat that for, you know, the (lay press). I'm not sure the public is getting that part of the message clearly.

So no other products have been linked to infection - documented infections right now. But we're concerned, we have reports of some that we're investigating. They may not be linked. You know, there's a good probability they are not linked.

But we would like clinicians who report to us - and clinics, and we'd like them to follow up with the patients. And if there are any people with suspect infections, we would like to hear about it.

Dr. Norleena Gullett:

Were there additional products other than the methylprednisolone? And I believe there were, (triam) I can't remember the...

Dr. Janet Woodcock:

Yes, there were infections in two patients who'd received other NECC products - or presumed infections. But we do not know whether there was any link between their, of course, receiving the product and getting the infection.

Dr. Norleena Gullett:

Okay, thank you.

Coordinator:
Dr. (Travetti), you may ask your question.

Dr. (Travetti):
My question was should we, at this point, inform the patients since they use other products of NECC of possible complications? Or just wait for them to call us and say that they have issues?

Dr. Janet Woodcock:
We are asking that clinicians who administered these products since the end of May would actively contact their patients in some way to make sure that they're well and that they don't have signs of infection.

Because we cannot assure right now that these products that were administered were sterile.

Dr. (Travetti):
Okay, thank you.

Dr. Janet Woodcock:
Thank you.

Coordinator:
(Scott Cormare), you may ask your question.

(Scott Cormare):
Thank you. You seem to be sending mixed messages. On one hand you're telling us that patients shouldn't panic and there's no other evidence that any other NECC product was contaminated. But on the other hand you're asking us to reach out to every single patient that potentially could have been given an NECC product and tell them that potentially they're contaminated.

And it's a bit confusing for us. Can you give us more details or give us some guidance about how we're supposed to accomplish this?

Dr. Janet Woodcock:
Certainly. I mean, I don't think we're asking you to tell them they may have been contaminated. We are asking you to reach out and make sure they are still healthy and have no signs of infection as a precautionary measure.

I recognize that this could be seen as sending a mixed message and causing patients concern unnecessarily. However, we don't know what kind of infections might have occurred from sterility breaches at this firm. Some of them may be indolent. And we would like clinicians to contact their patients to make sure they're healthy. And if we encounter reports of infections, we can follow up on those to make sure that there is no link.

Coordinator:
(James Marazeta), you may ask your question.

(James Marazeta):
Yes, thank you. My question is really directed to the FDA physician that just spoke.

Typically shipments from a compounding pharmacy of individual agents, like injectable steroids, come with a letter certifying that an independent laboratory has confirmed sterility of random samples from the lot that has been shipped.

Can you comment on whether or not this has been done in the case of NECC and their shipped compounded steroids?

Dr. Janet Woodcock:
Well I do not know whether they sent a letter or not. But we have looked at the practices at the firm, and we are concerned that we can't provide assurance of sterility.

(James Marazeta):
So as a follow up question, does that mean that there's no evidence in the investigation thus far that individual samples were routinely sent out to an independent lab to check sterility?

Dr. Janet Woodcock:
Well I can't comment because of confidentiality issues. I can't tell you about their procedures, all right, and I'm sorry.

But FDA is, of course, extremely experienced in evaluating sterile production, because that's one of the things we do for a business. Not sterile production, but overseeing it. And we are concerned that we cannot tell you -- whether you got a letter or not -- that there is assurance of sterility of these products.

It's more than just testing, of course. There's much more to it.

(James Marazeta):
Thank you.

Coordinator:
Thank you so much for your questions.

We will now turn it over to the next set of presenters.

Dr. Tom M. Chiller:
Thank you. And thanks, Dr. Woodcock and Dr. Schaefer.

This is Tom Chiller with the CDC's Mycotic Diseases Group. And I'm just going to give you a very brief update on some of the clinical issues and current situation.

And I'm joined today by, as you heard, by Dr. Peter Pappas. Dr. Pappas is serving on our clinical expert panel that we have gotten together to help give clinical advice. And so we look forward to clinical questions and Dr. Pappas will be happy to help answer some of those with me today.

So just a brief summary on some of the clinical aspects. The vast majority of the patients so far do have evidence of meningitis. We have only been reported two infections that are involving peripheral joints. Those happen to both be ankles at this point. And from those two peripheral joints infections we have not confirmed fungus in any of the fluids or in the patients to date.

(Four) of the fungal infections that we have confirmed, I think many of you know now that the majority of confirmed fungal infections are the black mold called *Exserohilum*. And that still remains the case. We now have -- in the CDC laboratory -- confirmed 26 *Exserohilum spp*. One, *Aspergillus fumigatus* infection, which was the index case, and one *Cladosporium* infection.

The *Cladosporium* is - since we had the last COCA call, *Cladosporium* is, again, another black mold like *Exserohilum*. It's common in the environment. We see it as a contaminant occasionally in laboratories. But we do feel that it could be part of this outbreak. As you all know, there have been multiple fungal pathogens to date, isolated *Aspergillus* and *Exserohilum*. So we have been cognizant of the fact that there could be multiple fungal pathogens still present in patients.

From the treatment standpoint, we know that *Cladosporium*, again, is a black mold like *Exserohilum*. And so treatment guidance is going to be similar to how we're managing and treating our Exserohilum patients as it stands now.

You heard the numbers of total cases from Dr. Schaefer of just above 230. And so we continue to remain vigilant with states to collect data on those 233 patients in order to understand their clinical situation and try to feedback some clinical guidance for all of you physicians out there managing these patients.

Just to highlight a couple of the changes to the guidance. We posted guidance I believe now two days ago on the Web site. We updated four different documents. One was the (CNS) treatment guidance. One was a joint infection treatment guidance. We also updated the (CNS) diagnostic testing guidance. And we also gave an update on dealing with asymptomatic patients who received one of the contaminated lots under investigation.

The main highlight from those documents is that we've changed our recommendation for empiric therapy in patients who are mildly or moderately ill to a single therapy with Voriconazole. And so for patients that are believed to be severely ill, for example with (CNS) involvement or are worsening on Voriconazole, we still advocate strongly the addition of (AmBisome) or Liposomal Amphotericin to the regiment.

We also, in the diagnostic workup we have eliminated the recommendation for galactomannan testing, as that has not been yielding. And considering only our initial case has *Aspergillus* to date, we don't feel this adds - this is adding much to our diagnostic workup.

Of course galactomannan testing should be done at the discretion of the treating clinician.

I think I will stop there. I want to reiterate what Dr. Schaefer mentioned, that all of this information, as it becomes available, is being posted on the Web site. And I would imagine, if not today, first thing tomorrow, we will also be posting a diagnostic guidance for joint infections.

So I will stop and we will open it up for more questions and answers.

We hope you guys can focus these questions on clinical aspects of the disease and the outbreak, as we have brought Dr. Pappas onboard to help us answer those questions.

Coordinator:

Thank you. At this time if you would like to ask a question, please press star 1 on your touchtone phone. If your question has been answered, please withdraw your request by pressing star 2.

Again, to ask your questions at this time, please press star 1 and record your name clearly when prompted.

(Muhammad Siki), you may ask your question.

(Muhammad Siki):
Oh thank you. I'm from Detroit, Michigan. I represent Ascension Health.

I have two questions. When the FDA came up with a statement yesterday, there was a comment about injectables. But there was something about, you know, the injectable being used in conjunction with eye surgery.

You know, for the epidemiology, someone - if I have a patient, let's say, who presents to me who had eye surgery but they used drops from that company into the eye, would that be one of these patients that I have to worry about?

Dr. Tom M. Chiller:
Thank you for that question. I just want to make sure I understood. So you're asking about a potentially NECC product that is used for eye injections?

(Muhammad Siki):
Correct. You know, the FDA statement came up with this - and I know, you know, this is a clinical question, issue. But I'm just going to read this. It's one sentence, "At this point in the FDA's investigation, the sterility of any injectable drugs, including ophthalmic drugs that are injectable or used in conjunction with eye surgery."

So it's not very clear for me if they're specifying only injectable or, you know, eye drops during that surgery. And cardioplegic solutions produced by NECC are of significant concern. And out of abundance of caution, patients who received these products should be alerted of the potential risk of infection.

Dr. Tom M. Chiller:
Yes, thank you for that. Dr. Woodcock, are you still on the call? I think she had to drop off.

Yes, I think Dr. Woodcock from the FDA dropped off.

I mean, I think what you heard from Dr. Woodcock today is that, as you just mentioned, out of abundance of caution, they put out this MedWatch report asking clinicians to contact patients who had any NECC product because of their concern for the facility and because of their concern of the sterility issue. And just find out if they were doing well and didn't have any signs of infection.

So that would include any product made by NECC. But they were particularly concerned about a couple of the products that they listed.

(Muhammad Siki):
Okay.

Dr. Tom M. Chiller:
And I want to reiterate that this Tom Chiller from the CDC. We here at the CDC are not actively involved in that part of the investigation, that's the FDA's role. And we have no firm evidence of any infection related to non-(MPA) products that we have already talked about.

(Muhammad Siki):
One (unintelligible) question additional. Can we know which states were involved in NECC products? I'm not just talking about the three lots, but, you know, all NECC products, is this available?

Dr. Melissa Schaefer:
So this is Dr. Schaefer. We'd have to defer to FDA and the Massachusetts Board of Pharmacy on, you know, what products went where from NECC.

But I believe that they did have licensing or ability to ship products to all 50 states, but the specifics of that we'd have to defer to FDA at this point.

(Muhammad Siki):
Thank you.

Coordinator:
(Robert Eisenberg), you may ask your question.

(Robert Eisenberg):
It has been asked and answered, thank you.

Coordinator:

(Brian Lampner), you may ask your question. (Brian), your line is open. Please check your mute button.

(Lisa McBride), you may ask your question.

(Paul Huffman), you may ask your question.

(Paul Huffman):
Yes. My question is the lots of steroid that were given, the FDA Web site is a little - or the CDC Web site is a little unclear about the dates. They say anybody that's gotten steroid injections or products purchased since 5/21. Does this include steroid lots that were produced before 5/21?

Dr. Melissa Schaefer:
Thanks for your question.

So on the CDC Web site we list the three lots of methylprednisolone acetate. These are the 80 milligrams per ML preservative-free product that was recalled by NECC on September 26.

I don't have the specific lot numbers in front of me, but they are on the Web site. The first of those three was produced on May 21, 2012, and the other two came subsequent to that. I believe it was June 29 and August 10.

So those are the three lots that we, at CDC with our public health partners, have identified as being associated with all of our cases to date.

So if you go to the CDC Web site, we list those three lots with the lot number on them. And the earliest lot that was produced was that May 21, or the 05212012@68 lot.

(Paul Huffman):
So if you were using a product that - say betamethasone that was produced before that, say 5/11/2012, but bought after 5/21, would I still need to contact patients in regards to that?

Dr. Melissa Schaefer:
I'm sorry, I misunderstood your question. So you're referring to the guidance from the FDA MedWatch report?

(Paul Huffman):
That's correct.

Dr. Melissa Schaefer:
So I'd direct you to ask your questions specifically to FDA for clarity. They have an 800 number on there for people that have questions like the ones you're raising.

(Paul Huffman):
Thank you.

Coordinator:
(Habul Tenduk), you may ask your question.

(Habul Tenduk):
Yes, hi. What is the role for intrathecal therapy with Voriconazole for people who are deteriorating (quickly)?

Dr. Tom M. Chiller:
Thank you for that question. And I will definitely ask Dr. Pappas to comment.

My one comment on intrathecal therapy, at this time we don't recommend intrathecal therapy, and that's based on a number of factors.

First is it is very challenging to give intrathecal therapy to patients. Second, we're not sure how much of these infections are going to be in the subarachnoid space where the intrathecal medicine would be getting.

And number there, we feel that both Voriconazole and if you need to add (AmBisome), both have very good (CNS) penetration. And so feel that these drugs are going to do the job they need to do.

And so that's where we're standing right now in intrathecal therapy. (Unintelligible) do you have any comment?

(Habul Tenduk):
I have one more question. Hello? I have one more question.

What do we do with patients who clinically - who are symptomatically having, you know, signs of meningitis, but their CSF tap is very mild, there is no real change, just several white blood cells or

lymphocytes, several red blood cells, but no alteration in glucose or protein. Are those (who) that we just empirically treat?

Dr. Tom M. Chiller:
Yes, thanks for that question. And again, I will get Dr. Pappas to comment as well.

But we are, you know, we're currently recommending that if patients have symptoms consistent with meningitis or if it's a joint injection consistent with a joint infection, that they be evaluated. And in the case you're talking about with a lumbar puncture, if those lumbar punctures are not abnormal -- and we're defining that as a white count greater than five -- then we would suggest close clinical follow up. And if the symptoms do not abate or get worse, then we would recommend a repeat lumbar puncture to reevaluate their CSFs...

(Habul Tenduk):
Okay.

Dr. Tom M. Chiller:
you know, with again, if an abnormal CSF is present, then clearly they should be empirically treated.

Dr. Pappas, you have any comments on that?

Dr. Peter Pappas:
Actually as to the first question, I think the issue of intrathecal therapy is a good one. It's commonly asked. And typically we're talking about Amphotericin because Voriconazole was chosen as our kind of cornerstone therapy because it does get into the CSF, about 50% of serum levels.

I think none of the people on our panel have ever been impressed with intrathecal Amphotericin and feel that (AmBisome), it gets very good brain concentration. And so the use of intrathecal drug of any kind we really discourage.

As to the second question, I think this is the person we had in mind, I believe, when we talked about symptomatic people who are not severely ill but have a mild CSF pleocytosis. Well certainly they should be treated. Many of them will be ambulatory and many of them can be managed with oral or initial IV Voriconazole followed by oral Voriconazole.

But I mean, those are individuals where dual therapy is probably really not warranted.

Dr. Tom M. Chiller:
Okay.

Dr. Peter Pappas:
At least to begin with.

(Habul Tenduk):
How long do these people get treated for? Once the Infectious Disease Team gets involved, how long are we looking at treating these people, you know?

Dr. Peter Pappas:
There's been a - this is Peter Pappas. There's been really no good experience with this. And that's one of the reasons that infections disease people need to be involved with these cases, because they're the ones with really what limited experience there is.

Opinions vary. They go from six weeks on the short end to six months and beyond or even a year.

Given that most of these patients are non-immunocompromised, although they're older, I think our consensus is that three months of treatment is probably a minimum. And that assumes that the patient is doing just extraordinarily well and can come off therapy clinically.

But three months is sort of the standard that we've set. And of course the clinician obviously has the, you know, the right to go up or down on that. But that was what we settled on as a reasonable length of therapy for patients where there's a strong suspicion of infection.

(Habul Tenduk):
Okay, thank you.

Dr. Tom M. Chiller:
And this is Tom. I just wanted to go ahead - we had an email question and I figure we'll go ahead and answer it really quickly. And it was asking about galactomannan antigen testing on CSF.

And as I mentioned briefly, CDC is no longer recommending galactomannan testing routinely in either CSF or serum. The galactomannan test for CSF is not an FDA-approved test and there's limited experience with it, although some people have used it for CSF testing, although there is no diagnostic approval for that use.

We're going to leave it up to clinicians to decide, you know, whether they want to order that test. But we have officially taken it out of our routine recommendations.

And I don't know, Pete, if you had any comments about galactomannan?

Dr. Peter Pappas:
I can't really add much to that, Tom, other than to reiterate that the *Aspergillus* case that was identified was the initial case, the (sentinel) case and then nothing since then.

They did use galactomannan in a CSF. But as you mentioned, it's not approved and we've not seen any sign of it since then. And so galactomannan as a routine, really it's hard to recommend.

Coordinator:
(David Klok), you may ask your question.

(David Klok), your line is open.

(Christopher Sifer), you may ask your question.

(Christopher Sifer):
Yes my initial question was - well I guess it's for the FDA. But actually I have another question.

We heard there was a heart transplant patient possibly with Aspergillosis, possibly related to cardioplegics. Could either one of you, I guess, comment on that? Thanks.

Dr. Tom M. Chiller:
Yes, this is Tom Chiller. The FDA did report on the patient that did have Aspergillosis infection following cardiac transplant and was given cardioplegia solution from (NECC).

As Dr. Woodcock mentioned, that case is under active investigation. We're not sure of any link from the (NECC) product to the *Aspergillus* infection. As you know, these are high risk patients for *Aspergillus*, and so it's not unusual at all for heart transplant patients to get Aspergillosis.

And so unlike the other patients in cases in this outbreak that are generally immunocompetent, although elderly, they do not have transplants and so the fungal infections they're getting are exceedingly rare and do represent an easier link to this contaminated product. This case -- with the cardioplegia solution -- does not.

So we're still investigating that case and do not have a firm association with the (NECC) product at this time.

Coordinator:
(Ashley), you may ask your question.

(Ashley):
It was for the FDA, thank you.

Coordinator:
(Alisa Stevens), you may ask your question.

(Alisa Stevens):
Yes, I was interested in whether or not any of the IB caffeine products had been identified as potentially contaminated?

Dr. Tom M. Chiller:
Again, we don't have any information on any other products that have been identified as contaminated at this time. I think FDA is investigating several products and continues their investigation, but we have no information of any other contaminated products at this time.

(Alisa Stevens):
All right, thank you.

Coordinator:
Dr. (Ray Demore), you may ask your question.

Dr. (Ray Demore):
Yes. I'm wondering if you have published or if you can say anything about the distribution of latency periods between exposure and onset of symptoms?

Dr. Tom M. Chiller:
Yes, thank you for that question. I mean, that is definitely something that we continue to look at.

Let me tell you a couple of the challenges with that as far as looking at the incubation or latency period.

One is many of these patients have had multiple injections, including multiple injections obviously with the three implicated lots.

And so it can be difficult knowing which injection is the culprit injection or is there actually a cumulative effect if there were multiple injections that were contaminated and administered.

And the second thing is that the much of the clinical data -- which is obviously being reported furiously by, you know, state health departments, local health departments through a tremendous effort -- is based on what they can find in charts often. And many of these patients may have actually had symptoms develop, for example, before hospital admission, which we know many have.

And so to really understand true incubation periods has been a challenge. So we, again, apologize for not getting more concrete evidence out there.

What we've been seeing though -- based on the evidence that we have -- is that typically patients have been presenting with incubation periods around one to four weeks. We have seen longer periods of incubation, up to two months. And we are concerned -- based on our experience with fungi and actually based on other outbreak investigations -- that longer incubation periods could be possible.

So we have been recommending that you continue to remain vigilant and talk to patients, even months after their injection because we do feel that there could be long incubation periods for these fungi.

(Ray Demore):
Thank you.

Coordinator:
(FE Narula), you may ask your question.

(FE Narula):
Actually it was for the FDA and it was already answered.

Coordinator:
(Marabuda Parik), you may ask your question.

(Marabuda Parik):
Yes, I have a question about the fungal infection on the joint, (unintelligible) said two of them were there. Is it identified and what species it is then?

Dr. Tom M. Chiller:
Yes, thanks for that question. We have not identified or confirmed fungus in either of these two joint infections.

And, you know, Dr. Pappas, I was wondering if you might give your thoughts just sort of on a fungal infection in a joint and what it might look like in these patients.

Dr. Peter Pappas:
Sure. And it's one of the reasons that Tom has suggested that we keep an open mind and follow these patients for weeks or months, and that's because we don't really know what the course of this is going to be.

But I think it's, you know, it's reasonable to assume that if someone is injected epidurally that the contaminated material, that the infection would probably show up within a few weeks.

But how's it going to differ if it's injected into a joint or a disk space or something, you know, some soft tissue, for instance?

And I think the answer is it may smolder for really quite some time. And so a fungal joint infection can be a very indolent process. And I think many infectious disease people know this from experience, that oftentimes these people walk in or limp in, they've had swelling, joint pain for weeks or months before, you know, that's identified as an actual infected joint. And then we're surprised to see that it's due to a fungus.

So I think the joint represents a unique sort of challenge, one that's going to remain - we're just going to have to be vigilant for really quite some time.

And so I think it's not clear to me at all what's going to occur as, you know, we watch this over the next few weeks or months as to how many people with infected joints are going to actually be identified.

(Marabuda Parik):
So you mean that the mold was already grown in these two patients?

Dr. Peter Pappas:

I think in the - Tom can answer this, but I believe that in the two patients that have been identified, I believe that - and Tom confirm this, but I think routine bacteria and crystal disease has been excluded. And I think the diagnosis of fungal arthritis is implied, if it's not culture-proven.

I don't really know. Tom?

Dr. Tom M. Chiller:
Yes, I mean, that's correct, Pete. But both of these two cases reported to us that we are calling possible joint infections have been ruled out for other etiology did receive injections with the contaminated lots, and therefore they count now as a case. But neither of them have actually had a fungal culture or PCR that is positive to date.

(Marabuda Parik):
Okay. Okay, thank you. So there's not too many.

Coordinator:
(Diane McDaniel), you may ask your question.

(Diane McDaniel):
Hey. This was really addressed to Dr. Woodcock with the FDA. Is there anyone there that could answer a question about the vials that we returned to NECC, if any of those had been checked to see if they had contamination?

Dr. Tom M. Chiller:
Sorry. No, we don't have any information on that. And perhaps calling the hotline at FDA might - they might be able to help.

(Diane McDaniel):
Okay, thank you.

Dr. Tom M. Chiller:
Sure thing.

Coordinator:
(Margaret Schmitt), you may ask your question.

(Margaret Schmitt):

It's been answered, thank you.

Coordinator:
(Carol Imes), you may ask your question.

(Carol Imes):
My question is with generic (unintelligible) that our doctor injects with this local - with a (retrobulbar) injection. He sees his patients at regular intervals, I think he said a day after, ten days and three weeks after. Since we're looking for an infection due to unsterile vials or maybe not sterilized vials -- I shouldn't put it that way -- is that sufficient? He felt very comfortable that he has no problem because he sees them at three weeks.

Do they need further notification or should we be calling them to ask more questions?

It might be an FDA question, I'm not sure.

Dr. Tom M. Chiller:
Yes, I mean, I think that those are - I think that, you know, again, I think you've heard from us repeatedly from the clinical side that we're really unclear about incubation periods for fungi, if these are indeed fungal infections, which we know they are at least for the (MPA) three lots.

For other (NECC) products that the FDA had just (put) forward the MedWatch announcement yesterday, I think that your clinician using judgment on how frequently they ought to follow and get in touch with their patients is going to be your best way forward. We just don't have any good information clinically on what to tell you.

So I think, again, that could be a good thing to reach out to the FDA and ask for their recommendations.

(Carol Imes):
Thank you. That does help, thanks.

Coordinator:
(Pam Bally Happy), you may ask your questions.

(Pam Bally Happy):
My question was really for Dr. Woodcock, thank you.

Coordinator:
(Lisa Lamure), you may ask your question.

(Lisa Lamure):
My question goes back to the beginning. You had said for clinicians to notify patients. I work in a hospital, I'm wondering how to handle this.

Dr. Melissa Schaefer:
And is your question related to the FDA MedWatch report or regarding notification of patients who received those three lots that we have associated with the infections to date?

(Lisa Lamure):
Actually the MedWatch report because there's quite a few medications listed there.

Dr. Melissa Schaefer:
Yes, I mean, I don't think we have any guidance that we can really provide at this time. I know Dr. Woodcock mentioned, you know, the FDA was leaving it to the facility and clinician to decide how best to contact patients, whether that be through letter or other mechanisms. But we don't have any additional information that we can provide at this time.

(Lisa Lamure):
Okay, thank you.

Coordinator:
(Jackie Sutton), you may ask your question.

(Jackie Sutton):
Yes. I just have a question regarding an inhalation product that we had purchased from NECC. I know that the FDA MedWatch specifically said to alert patients who received intravenous products. I wanted to see what the thoughts were possibly specifically from Mr. Chiller because there's always the potential of respiratory infections that we can be related to fungus, if he thinks that should be of concern and communicated to those potential patients.

Dr. Tom M. Chiller:
Yes, thank you for that question. And, you know, again, we appreciate the clinical community's concern about the announcement yesterday. And I think that, you know, all we can really say from our standpoint

is that we have not confirmed any infections associated with (NECC) products outside of the current three lots with the methylprednisolone.

And so it's completely unclear on what products we should or should not be concerned about. FDA I think has pointed out, as you mentioned, that they are concerned about the possible sterility of injectable NECC products.

And so I really have nothing to say about the inhalational drugs. And we just have no information that is either going to help you in searching or that has given us any inclination that there's a problem with any of those products.

Certainly I would stay tuned. And I know FDA is examining, you know, all kinds of options along those lines as far as the NECC products go. And certainly we'll inform anybody through their guidance, through their Web if they have concern for other products.

Coordinator:
(Brian Almany), you may ask your question.

(Brian Almany):
My question's already been answered, thank you.

Coordinator:
(Ellen Simonson), you may ask your question.

(Ellen Simonson):
My question was for the FDA, thank you.

Coordinator:
(Jeffrey Grossman), you may ask your question.

(Jeffrey Grossman), your line is open. Please check your mute button.

Coordinator:
(Erin McGee), you may ask your question.

(Erin McGee):

Oh hi. I was late to the conference call actually and I didn't - I wanted to know the total number of deaths. I understand the number of cases is not (unintelligible).

And also I wanted to know, Dr. Woodcock, what was Dr. Woodcock's first name, because I did miss that too.

Dr. Melissa Schaefer:
Yes, so from FDA it was Dr. Janet Woodcock. And the case counts that we presented are available on the CDC Web site, as they are everyday where we update them.

But the ones that we presented today are there are 233 cases, which includes 2 patients with joint infections and 15 deaths occurring in 15 states. The specific state counts will be available on the CDC Web site.

Coordinator:
Dr. (Selabeni), you may ask your question.

Dr. (Selabeni), your line is open.

Dr. (Selabeni):
Hello? Hello?

Coordinator:
You may ask your question.

Dr. (Selabeni):
Okay. Yes, I'm (George Selabeni) (unintelligible) hospitals in Tennessee with a number of these patients. And this is probably more appropriately FDA, but I'll put it to the clinicians in the room. Do we have a standardized reporting form for adverse effects of Voriconazole? Or is somebody compiling those data?

Dr. Tom M. Chiller:
Yes, this is Tom Chiller at the CDC. We at the CDC are not yet compiling any data on adverse affects of the anti-fungal drugs. And that probably would be a good question to pose to FDA. And I apologize, I think Dr. Woodcock's not on. But, again, you could reach out...

Dr. (Selabeni):
Right.

Dr. Tom M. Chiller:
on the 1-800 number.

Dr. (Selabeni):
Okay, thank you.

Dr. Tom M. Chiller:
Sure.

I want to just take this opportunity to, again, address a couple of email questions. There was a question on email regarding the incubation question that Dr. Pappas and I just spoke to.

And it asks specifically are we talking about epidural injection with methylprednisolone or are we talking about any injection site with other medicine?

So the information that we have on incubation period is obviously from our current cases. As we've mentioned, all of our cases that we have involved, one of the three lots of the (MPA). And so incubation for the (*Exserohilums)* and one *Cladosporium* and one *Aspergillus* are all based on the information from those injections since we do not have any non-(MPA) products that are associated with any firm evidence of infection.

So the majority - because we only have two joint infections, the majority of our information is from meningitis cases. And again, I want to emphasize that we think incubation could be quite long for these fungal infections.

And so we want you to remain vigilant for several months after injections.

I'll go back to questions, thanks.

Coordinator:
Ms. (Price), you may ask your question.

Ms. (Price):
Hello?

Coordinator:

Go ahead with your question.

Ms. (Price):
My question is the first instruction was to have fungal bacterial and mycobacterial cultures done on everyone, can we now rule out the mycobacterial ones for CSF in blood?

Dr. Tom M. Chiller:
Yes. Thank you for that question.

You know, again, we have - we were recommending a broad culture of CSF at the beginning of this outbreak, as we didn't understand the passages involved. I think as the outbreak is evolving, as we've mentioned we're seeing the vast majority to be black mold and mainly *Exserohilum*.

We do think that any patient clinically with meningitis needs to be evaluated for the possibility of bacterial meningitis and certainly if clinically relevant for AFB or for Acid-Fast Bacilli. But we do not have any association of Acid-Fast Bacilli with these particular injections. And so have dropped the recommendation for routine culturing at this time.

Ms. (Price):
Thank you.

Coordinator:
(Robin), you may ask your question.

(Robin):
Hi, thank you. Two questions actually.

I get that the latency period and the incubation periods are hard to pin down. But originally it was recommended that we call patients back to May 21st product. Is that still a recommendation? We're supposed to start from May 21st, anyone that's received any NECC product from that time?

Dr. Melissa Schaefer:
So the CDC recommendation has been that facilities who administered injections from one of those three lots that are on our Web site and that we've associated with infections to date, that those facilities contact their patients to make them aware of the outbreak and warn them of signs and symptoms that should prompt immediate evaluation by a physician.

The first of those three lots, as I mentioned, was produced on May 21, 2012, which is where that date came from. But the focus is really on, you know, when those lots were received by your facility and administered to patients.

So the timeframe is based on us knowing when that first lot was produced. But the facilities are the ones who know and would have to know when they received those lots in their facility and begin administering them to patients. Does that make sense?

(Robin):
It does, it makes perfect sense. I'm actually calling from a facility who uses NECC for other products, but we have not received any of the three implicated ones. And we're kind of looking for some direction as far as the best course of action on what patients to call and what timeframe to use.

Dr. Melissa Schaefer:
So I think you're referring to kind of the MedWatch guidance and report. And I'd advise you to direct those questions using the 800 number on MedWatch for, you know, physicians to get some more clarity on that.

(Robin):
Okay. That's fine, thank you.

And just one other quick question. The list by state on the CDC Web site, those are definitively patients that have received some type of fungal infection or fungal meningitis or the joint infection specifically from those three lots. And I'm just clarifying and confirming that for certain.

Dr. Melissa Schaefer:
So are you talking about our case count or are you talking about the list of facility names that we have on the Web site?

(Robin):
No, I'm talking about your case count by state.

Dr. Melissa Schaefer:
So our case count by state lists those people that we believe to have fungal infection associated with this outbreak. We do not have fungal confirmation in all of those, but testing and investigation is ongoing.

And if you look at the case count, there'll be an asterisk which will take you to the case definitions that CDC and public health have been using and applying to these patients so that you'll have a better sense of how we're classifying these patients.

(Robin):
Okay, thank you very much.

Dr. Tom M. Chiller:
And let me follow up a point that Dr. Schaefer made, because I think this is an important one and I can get Dr. Pappas to comment as well. And that is the ability to culture these organisms and to do PCR on them.

CDC is doing PCR on fluids in a research test that we are reporting back to state health departments to help with our case count and our confirmation of cases.

But neither test, neither culture, or PCR are being negative is something that rules out fungal infection so unfortunately the ability to test for this organism and not find it, does not mean that the patient doesn't have it and Dr. Pappas do you want to comment on just sort of culture and fungi in general and how challenging it is.

Dr. Peter Pappas:
Yes, no I mean it really is because a lot of these organisms become tissue based and all the culturing is the fluid and so it makes some sense that there has been difficulty isolating some these organisms, some of them are difficult just by their nature to be cultured.

So I think it's really a wise advice to keep a very open mind, people with unexplained inflammation in the joints and the CNS who have you know who are at risk due to this exposure, should be assumed to have this condition unless there's another better explanation.

Dr. Tom M. Chiller:
Thanks and I just want to add, and also get Dr. Pappas's thoughts again on this is that we received an email question that sort of addressed some of this, but it asks specifically about in terms of the time frame that we could expect to see some growth from CSF cultures and it also asks specifically about *Exserohilum* the -you know the similarity to ask to *Aspergillus* in the sense of is this a angio-invasive organism or is this a tissue invasive organism?

And so (Pete) do you want to take a crack at just talking a little bit about what we know about *Exserohilum* which obviously is limited.

Dr. Peter Pappas:
Yes, it's fairly limited. You know the classical angioinvasive organisms are *Aspergillus* and the Zygomycetes. With *Exserohilum* and other dematiaceous fungi, clinically they tend to produce more focal legions, parenchymal types of legions.

Yes they can be angioinvasive, but that's not their usual MO. They can, as we mentioned earlier, they can be difficult to culture, but if they're organisms that are in abundance, they will grow fairly easily, it may take several days.

So these are clearly organisms where it is suspected, the media needs to be held for, several days, couple weeks before you can feel comfortable that you don't have this infection.

Dr. Tom M. Chiller:
And again, they emphasize *Exserohilum*, we don't see this often at all in clinical practice, it is challenging to grow. We feel that these infections associated with this outbreak may have very low inoculum and therefore we may not find it even though patients are infected, it probably doesn't hang around in the CSF, which makes it even more challenging to culture from the CSF or to perform PCR on it.

It does invade tissue as Dr. Pappas mentioned and so we don't want anyone to have a false sense of security if the patient has received an injection from one of these three implicated lots and is having symptoms consistent with either joint infection or meningitis that has been ruled out for other causes. We want those patients to be treated with anti fungal medicines.

Coordinator:
(Anita Haller), you may ask a question.

(Anita Haller):
My question was answered already, thank you.

Coordinator:
(Andrea) you may ask a question.

(Andrea):
My question was answered, thank you.

Coordinator:

Just a reminder if you would like to withdraw your request and your question was answered please press star 2 at this time. Again to withdraw your request if your question has been answered, press star 2. (Robin Myanburg) You may ask your question.

(Robin Myanburg):

Thank you, I was wondering if there is any preliminary information or hypothesis as to the source of this fungal contamination, like the water they used, the sinks, the pipes or construction. Anything?

Dr. Tom M. Chiller:

Thanks for that question, obviously that's a topic under investigation from the FDA and I know that they are diligently working to try to understand the source, so I'm sure as soon as more information comes available that they have done, you will be hearing about it.

(Robin Myanburg):

Thank you.

(Leticia Davila):

Excuse me (Corey) can you please let us know how many questions we have in the queue.

Coordinator:

You have 28 left.

(Leticia Davila):

Thank you.

Coordinator:

You're welcome. (Andrea Smith) you may ask your question.

(Andrea Smith):

Yes, this is a question more from the public health side, than the clinical side. I'm wondering from where we're sitting, messaging is critical and we can see on the call with professionals there is a lot of confusion about who is at risk, who physicians should notify.

We're starting to get calls from folks who have gotten an injection from the facilities that were identified. So my question to you is are we missing somewhere, some sample scripts, sample notifications from

physicians to patients, something to help clarify with the public what an individual's risk is and who we're trying to reach out to.

Dr. Melissa Schaefer:
Yes, that's a great question and we appreciate the comment and suggestion for need and we will certainly take that back.

Coordinator:
Dr. (Kitel) you may ask your question. Dr. (Kitel) you may ask your question, please check your mute button. Dr. (Michelle Barain) you may ask your question.

Dr. (Michelle Barain):
This question is for Dr. Pappas, it's actually two questions. One is there a rule for repeat lumbar puncture as far as determining antifungal should be discontinued. And the second question particularly for remaining patients who are still receiving Ambisome how much toxicity do we allow? As you know from many other fungal infections these are very toxic, particularly with patients who have negative PCRs or cultures, what do we do about toxicity?

Dr. Peter Pappas:
Tom would you like me to answer that directly?

Dr. Tom M. Chiller:
That would be great, (Pete), thank you.

Dr. Peter Pappas:
Okay, so as to the first question, I think repeat lumbar punctures are going to be useful in these patients, but perhaps not as useful as you might expect and let me qualify that.

In the few reports that we've heard so far, some people who were getting better actually had a flare and had more white cells on repeat cap than they did at the original time and the only way to really explain that in a patient who is getting better is that they had lysis of the germs and started to call in more inflammatory cells.

Most of these are culture negative, so repeating the culture is not really the main reason for doing it, but rather sort of finding -having something laboratory based, an objective that you can follow.

I guess what I would say is, and again this is my opinion and that's all it is. I'd be inclined to repeat, assuming the patient's doing okay; I would be inclined to repeat an LP at a week or two and probably until their cell count were sort of at least heading in the right direction.

I wouldn't continue to do them until they're completely normal, because you'll end up doing a lot of unnecessary LPs in these patients. But I think one or two at least follow the LPs to be useful in therapy, but don't be too surprised if your second one comes back with pleocytosis.

You know the, let me see, what was the second question, did it have to do with link to therapy?

Dr. (Michelle Barain):
The second question is more so dealing with toxicity. For example I have a patient here that is considered a case who has arachnoiditis and meningitis.

Dr. Peter Pappas:
Right.

Dr. (Michelle Barain):
We initially had given AmBisome, she's a very morbidly obese patient and developed renal failure after several doses of AmBisome, which we discontinued, I guess the question and I know it's hard to answer, but is how much toxicity do we allow, particularly in cases who are not definite.

Dr. Peter Pappas:
Right. You're an infectious disease person, I presume, is that correct?

Dr. (Michelle Barain):
I am.

Dr. Peter Pappas:
I think the question, it is difficult to answer for every patient, but we all know that there are patients in whom giving them AmBisome or any amphotericin product is just absolutely critical to their survival.

And in that instance then you know you have to sort of sacrifice the kidneys, deal with the infusion toxicities, et cetera. In patients that are not so ill, you have a low threshold for stopping the therapy when it becomes too toxic. So you know and there are a number of ways to mitigate it.

The recommendation is to use a higher does; 7.5 mg/kg every day, but if your patient is really not tolerating it, and for whatever reason, creatinine or just infusion related to toxicity, there are some ways you can work around it. You can begin administering it every other day, if that works.

You could increase the dose and do it every other day, you could drop the dose back to 5 mg/kg , I mean dropping it below 5 is probably - I'm not sure it's going to be terribly useful unless there's synergy and we don't know if there's synergy.

So I think that every patient has to be individualized, it's not one size fits all, and in patients who really need it. That is they are ill, altered mental status, possible evidence of angioinvasion or mass lesions then I think you just have to forge ahead.

For those who are less ill and they're getting AmBisome and not tolerating it, then I would have a low threshold for stopping it or changing the course. But there is no good answer for every patient and I know you know that, but it really is going to have to be individualized per patient.

Dr. (Michelle Barain):
Thank you.

Coordinator:
(Anne) you may ask you question now.

Man:
If you're asking for (Anne) may I ask my question? Hello?

Coordinator:
You're line is open, go ahead.

Man:
Okay, for patients who have received other NECC injections, for example betamethasone or what not and its within eight weeks, number one if we call them up and they're asymptomatic and they've had the injection say three weeks ago, can they have another epidural injection or do we have to not do injections for eight weeks from the first injection?

Dr. Tom M. Chiller:

Yes, thanks for the question, we've heard several people ask a little bit about that and I know that's obviously something you guys are all thinking about, especially those who have been giving these injections routinely in your clinics, we just don't have information on that.

You know, our thought process is certainly that we wouldn't want, well we would be concerned about an injection going right back in the same location where a potentially contaminated lot was injected and we certainly would be concerned that if you were in a similar location and you were re-injecting steroids and there was potentially a incubating fungal infection there that you could potentially make it worse.

Again, we don't have any information on that at the current time so it's really hard for us to give you particular or specific guidance. We do think you should think with a relative level of caution. And I think giving injections at least in the shorter term that are really only absolutely necessary.

Man:
Okay, and the second question I have for you is products that were released by NECC, at least the ones we've received went to an independent lab, they were given to us after being quarantined by that independent lab, and they came to us and we were told that they passed the test of sterility and stability, can we put any confidence in that lab report? And these are for other products, not the methylprednisolone, but whether it's you know triamcinolone or betamethasone.

Dr. Tom M. Chiller:
Again, this is not our area of expertise and I apologize that FDA is not on the call, I know that at least all products from NECC were recalled so I think I would look to that guidance about any product from NECC and I again can't comment on an outside lab's ability to do that, that's simply not our area of expertise. Sorry about that.

Man:
Okay, thank you very much.

Coordinator:
(Ian Baer), you may ask your question.

(Ian Baer):
Oh thank you. I'm from Marion Ohio, where we've had - a large number of potential exposures. I'm actually interested in the clinical course of the 15 patients who died, specifically how many of those were microbiologically proven, did they die of a progressive infectious meningoencephalitis and were there any

mitigating factors as to why they died? Their basic underlying health was poor or was there a delay in diagnosis and therefore in treatment?

Dr. Tom M. Chiller:

Thank you, those are all great questions, and I will take a stab at some of them. So the preliminary information that we have on them, as I've mentioned when I began the call, we are making a very active effort right now as we speak to get more clinical information, to get that kind of clinical information as you can imagine those patients are scattered across the different states and have been reporting cases and so we're having to reach out to individual clinicians and go through medical charts etcetera.

So it's been a bit challenging to get that sort of information in a granular way, but I will tell you that many of those patients are patients that did suffer from basilar strokes. And there are, there is some autopsy information coming out where they are commenting of fungal invasion into the CNS.

And we're learning - we're trying to learn more about that physiology so that we can relate it. I think there is, I think there is - there clearly is a tendency for those patients to be earlier on in the outbreak where we were just identifying that there was a problem and so many of those patients did present late probably in their disease process and so did have already CNS involvement and we - it's a good question about were more of those had a fungal organism or culture identified certainly in a couple of the patients, where we now have some autopsy confirmation of fungus, there was fungus there, but I don't know the specific information about how many of those patients were cultured positive or PCR positive and have been confirmed and have a particular species of fungus. But that is a great question and it is something that we're actively looking into and we'll hopefully get back to clinicians so they'll have that information.

(Ian Baer):

If I may just expand on that slightly. So these people developed Basilar CVAs, Basilar strokes, presumably as a result of tissue invasion by the fungus, but they followed, I presume lumbar or low thoracic in spine injections? Or do we know?

Dr. Tom M. Chiller:

Well yes, we do know that from the ones that we know the majority that I recall, I don't have the data in front of me and again its scattered a bit, but yes many of them if not most were epidural injections, I'm trying to remember if they were all lumbar or if - I believe there were some cervical injections as well. But to my recollection they all were epidural injections.

(Ian Baer):

Okay, thank you very much, thank you.

Coordinator:
(Terry Sevlin) you may ask your question.

(Terry Sevlin):
Hi, We're an outpatient eye surgery center and we've used (NECC) eye drops for dilating the patients prior to surgery, so I have a couple questions, we then go ahead and prep the patient's eyes with betadine, will betadine kill these strains of fungus? These organisms?

Dr. Tom M. Chiller:
Yes, thanks for that question and honestly, you know, I think it's important to know about FDA's guidance yesterday about the particular products they're concerned about and dealing with those products and thinking about recontacting those patients.

As far as betadine, dealing with killing fungus, there's not a lot of experience with that per say, and I think in your particular situation with the eye, makes it more challenging.

I think that in this particular case again, the concern - although there is no recommendation about NECC products that are eye drops, I think the concern expressed from FDA is the sterility of the injectable products and in the cardoplegia solution so I don't have much to say about betadine and the black mold, I don't know Pete what is your feeling on betadine and black mold?

Dr. Peter Pappas:
You know, gosh I don't know any more than you do Tom, but I suspect it's effective. It's effective against most things. I guess I would add, and all this is speculation so this is kind of off the record, but it seems to me that the topicals, and whether that would be an inhaled topical or the ocular topicals, I think there would be - I would expect them to be extremely low risk.

Only because these are things we're exposed to every day in nature. We inhale *Aspergillus* and hundreds of fungal spores everyday and we inoculate our eyes every day with these spores as well through our unwashed hands and so forth.

So I would suspect, particularly with relatively low virulence organisms like these, the topical application to the eyes or inhalation would be very very low risk types of exposure.

(Terry Sevlin):

Thank you, I have one more question. We have a couple of vials of the dilating solution from NECC that I have set aside, but originally they were to be refrigerated and they've been at room temperature for a week now. Is it advantageous for us to go ahead and culture one of those? Would it be contaminated just from the temperature change, or what do you recommend?

Dr. Tom M. Chiller:

Yes, I would recommend that you, on that issue, call that FDA hotline number and let them know what you have and have them give you some advice.

(Terry Sevlin):

Okay, alright thank you.

Dr. Tom M. Chiller:

Sure.

Coordinator:

(Jennifer Boyd) you may ask your question.

(Jennifer Boyd):

Hi, I have a question about the (unintelligible) hello?

Dr. Peter Pappas:

Yes.

Dr. Tom M. Chiller:

Yes, what - can you repeat that please.

(Jennifer Boyd):

Yes, I have a question about voriconazole antifungal therapy if your patient has, (unintelligible) usually we go to PO, but if PO is not available what is the next line of therapy?

Dr. Tom M. Chiller:

Yes, thank you. So you're saying (IV voriconazole) stepping down to PO therapy and if PO voriconazole is not available what might be some alternative options?

(Jennifer Boyd):

Right will it be Itraconazole or Posaconazole or what will they be?

Dr. Tom M. Chiller:
Yes, thank you for that, (Pete), Dr. Pappas I'll let you answer that.

Dr. Peter Pappas:
Yes, we debated this and honestly there was no real consensus. Itraconazole is a lot cheaper, you can use the oral solution and I think I've said that itraconazole which has similar MICs to posaconazole is a little bit more predictable in its absorption. Posaconazole is probably the most active ofany fungal agent, but it's hard to get a lot of it in the system in its current formulation.

So I think we were kind of split and I think that probably because of expense and no evidence that one is better than the other, many clinicians would favor Itraconazole. The problem is with both itra and posaconazole, you sacrifice the ability to get into the CSF, and to the extent that it's important and we think it is that could be a very important feature that those two drugs lack.

(Jennifer Boyd):
Oh, because we have some patients with renal failure so we cannot use the (IV voriconazole).

Dr. Peter Pappas:
There again I would probably take issue of that, I think the company originally, Pfizer, originally did not study the IV formulation of voriconazole that has cyclodextrin in it because of the potential for aggravating renal toxicity so they didn't study it in patients that had creatinine over 2 or 3.

Subsequently, there has been a lot of data that the cyclodextrin given to patients with preexisting renal dysfunction does not aggravate renal function at all and we can't see that it causes a great deal of harm.

That's not to say we want to go administer IV voriconazole to just anybody, but again among people who need it, we do not let preexisting renal dysfunction preclude its use. And so I think that would be a safe statement as far as the consensus about the use of IV voriconazole.

(Leticia Davila):
Thank you. Operator we have time for one more question.

Coordinator:

Okay, our next question comes from Dr (Richard Creek), you're line is open.

Dr. (Richard Creek):
Yes, thank you. I was just wondering if you have any thoughts on epidemiologic patterns, such as in the state of New Jersey for instance. Where we have patients who have received injections from one or two facilities during a period of three months and then for instance the first reported case was the tenth of October and within six days now we have ten reported cases.

From an Epidemiologic standpoint, an infectious disease standpoint, does that make any sense?

Dr. Tom M. Chiller:
Yes, thank you for that question, and I think Dr. Schaefer who has been really working hard on the epi and the state, you can take a crack at that.

Dr. Melissa Schaefer:
Yes, I think it's something that we're looking at investigating and some of this to be active outreach through health department, facilities, and media, increasing awareness and actually doing outreach to patients to look for some of these very subtle symptoms that could have been missed, if not for knowledge of the outbreak and knowing what we're looking for.

So you know, obviously we have more investigating to do in looking at the information that is being detected, looking at particular associations with these particular lots or vials. Those are all things that we're doing; you know there could be a number of factors at play to address the question that you raised.

Dr. Tom M. Chiller:
And I think it's important to note that these are patients that originally had a health issue, that got their original injections for a health issue, so that adds to the challenge of then re-identifying them as having a worsening health issue, that is related to the injection and part of the fungal infection or that it is different from their current health issue.

Many of them suffer from chronic pain as you all know, so I think it presents the additional challenge that typically if we weren't - if the clinician wasn't concerned about it contaminated injection, symptoms that might not trouble them as much as they do now. So now I think as awareness has gone out, there is a much heightened level of suspicion for minor changes in symptomotology that is prompting much more thorough investigation which I think is exactly what we would have hoped happened after we made state health departments and clinicians aware.

So I think we're at - I think that was our last question and we want to reiterate our thanks to everybody who organized the call from our end. I'm sure Leticia will say more, but you know, we want to thank you for your questions and comments and concerns and continue to remain communicative with all of you and probably will have subsequent COCA calls as the time goes on.

(Leticia Davila):
Thank you Dr. Chiller, on behalf of COCA, I would like to thank everyone for joining us today, with a special thank you to our presenters. Dr. Schaefer, Dr. Chiller, Dr. Pappas, and Dr. Woodcock. We would invite you to communicate to our presenters after the webinar. If you have additional questions for today's presenters, please email us coca@cdc.gov, put October 16, COCA Call in the subject line of your email and we will ensure that your question is forwarded to the presenters for a response.

Again that email is C-O-C-A at C-D-C dot G-O-V. The recording of this call and this transcript will be posted to the COCA website at emergency.cdc.gov/coca within the next few days.

There are no continuing education credits for this call. Meningitis resources for clinicians are available on the COCA webpage. Go to emergency.cdc.gov/coca click COCA Calls and follow the links for the meningitis call.

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Thank you again for being a part of today's COCA call. Have a great day.

Coordinator:
Thank you for your participation, you may disconnect at this time.

END