Multistate Meningitis Outbreak investigation: Information and Guidance for Clinicians

Moderator: Leticia Davila

Presenters: Melissa K. Schaefer, MD and Tom Chiller, MD, MPH

Date/Time: October 10, 2012 2:00 pm ET

Coordinator:
Welcome and thank you for standing by. At this time all participants are in a listen only mode. After today's presentation we will conduct a question and answer session. To ask a question please press star one. And today's conference is being recorded. If you have any objections you may disconnect at this time. I will now turn the meeting over to Leticia Davila Ma'am you may begin.

Leticia Davila
Thank you (Tim). 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 multi state meningitis outbreak investigation - information and guidance for clinicians. We are pleased to have with us today Dr. Schaefer and Dr. Chiller from the Center of Disease Control and Prevention to review 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 website at emergency.cdc.gov/coca.

The first presenter 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.

She serves as a member of the health and human services ambulatory surgical center's workgroup, responsible for the development of the national action plan to prevent healthcare associated infections in ambulatory surgical centers. Her recent work has often included collaboration with the centers for Medicare and Medicaid services to develop an infection control worksheet evaluating infection control practices in ambulatory surgical centers during facility inspections.

Also presenting today is Dr. Tom M. Chiller. Dr. Chiller serves as the Deputy Chief of the Meiotic Diseases Branch. Dr. Chiller received his bachelor's degree from Dartmouth College and his medical and public health degrees from Tulane University. He completed a residency in internal medicine at the University of Texas Southwestern and then worked as an attending physician in HIV medicine. He completed a fellowship in infectious diseases with an emphasis on fungal diseases at Stanford University and then joined CDC as an epidemic intelligent service EIS officer in 2001. Dr. Chiller is board certified in infectious diseases and is a faculty member in the division of infectious diseases at the Emory School of Medicine. He practices infectious diseases at the Veteran's Affairs Hospital in Atlanta. He has authored numerous articles and book chapters and given many lectures on public health surveillance and infectious diseases.

At the end of the presentation you will have the opportunity to ask presenters questions. On the phone dialing star one will put you in the queue for questions. At this time please welcome our first presenter - Dr. Schaefer.

Dr. Melissa Schaefer:
Thanks Leticia. This is Melissa Schaefer. I'm going to start off today's call by giving you an overview of the investigation to date with some key activities that are going on and some key time line events. And then I'll turn it over to Dr. Chiller who's actually going to be discussing some of the clinical information that I think you're all waiting for as far as diagnostic and treatment guidance that is available related to this investigation.

So CDC in collaboration with FDA and state public health departments and state board pharmacies has been investigating an ongoing outbreak of meningitis associated with a potentially contaminated steroid medication which is preservative-free methylprednisolone acetate - 80 milligrams per ML - that was prepared by the New England compounding center located in Framingham, Massachusetts. CDC and the state public health departments have been actively coordinating outreach to patients who are potentially exposed to this medication and I've been working with clinical experts to develop the diagnostic and treatment guidance to help with evaluation and treatment of these patients. As of today -- October 10, 2012 -- a total of 137 cases including 12 deaths have been reported in ten states. CDC's laboratory has identified *Exserohilum* in ten patients with meningitis and *Aspergillus fumigatus* in one patient with meningitis. Dr. Chiller will be going over a little bit more details about that in his part of the presentation.

I want to take the next few minutes to talk through some of the product recall activities that have been going on related to medications produced by the New England compounding center. On September 26, 2012 the New England compounding center - again, located in Framingham, Massachusetts - voluntarily recalled three lots of methylprednisolone acetate - the preservative-free 80 milligrams per ML. And I'm not

going to go through those three lots on this call but that information is available on the CDC website. All cases identified to date have occurred after injections with methylprednisolone acetate products from any of these three lots. These lots were distributed to 75 facilities in 23 states and approximately 13,000 patients are believed to have had at least one injection with product from one of these lots. And again, on the CDC website we have the information about the lot numbers, the facility names who received this product and the states where these facilities are located. These injections - the product was not limited to just epidural injections. It was also used for other types of injections including joint injections. The Food and Drug Administration investigation into the New England compounding center facility is ongoing. On October 5th FDA reported observing fungal contamination by direct microscopic examination of foreign matter taken from a sealed vial of methylprednisolone acetate that was collected from the New England compounding center. Further analysis of that vial is ongoing. On October 6th the New England compounding center expanded its previous recall to include all products currently in circulation that were compounded at and distributed from its facility in Framingham, Massachusetts. And again more information about this recall and the products from the facility are available at the FDA website and CDC links to the FDA website from our page.

I want to talk about some of the main recommendations that have come out in recent days - again, on our website. One of our first and foremost recommendations and activities is that physicians should contact by phone or in person any patient who had an injection whether it be spinal, joint or otherwise. Any patient who had an injection after May 21st 2012 using any of those three lots that were recalled on September 26th and are believed to be associated with all of our cases. The May 21st date is significant because that is when the first of those three lots was produced by the compounding pharmacy. The CDC and the state local health departments have been working with facilities that received these three lots to actively conduct this outreach to make sure that all of these 13,000 patients are notified about the investigation and are aware of what symptoms should prompt evaluation by a medical provider and are directed to seek urgent medical evaluation if they are having those symptoms currently.

CDC in our recommendations have also said that healthcare professionals should cease use of any product produced by the New England compounding center, again, all of which have been recalled. CDC is currently not asking clinicians to actively contact patients who received other products beyond those three lots that I mentioned from the New England compounding center to asses for symptoms. But we do want clinicians to remain vigilant and report to state public health departments any infection that they identify in a patient known to have received a product from the New England compounding center.

Another important update that we want you all to be aware of is that CDC has been working with experts in the field and has been providing updated clinician guidance addressing interim instructions for diagnostic testing and specimen submissions, intermittent treatment guidance for these patients addressing role of anti fungal prophylaxis in asymptomatic patients and roles for lumbar puncture in

asymptomatic patients. And Dr. Chiller is going to be going through those in a bit more detail but I can't emphasize enough that these are all available on the CDC website. This investigation is evolving. We get new information every day. We update that website everyday and I would encourage you to continually check back to make sure that the diagnostic treatment guidance information that you have is the most recent because that does change. We are dating everything so that you will know what you have is what we're working with on that day.

Before I turn it over to Dr. Chiller I do want to go through the case definitions that we are using to capture these patients and kind of define what we are looking for. Again, this is a very detailed case definition with multiple parts that is on the website. But I'm going to read it to you know which will kind of help with the information that Dr. Chiller is going to be providing. So our case definitions for this outbreak - our case definitions for meningitis and septic arthritis - and they encompass a person who received an injection with methylprednisolone acetate produced by the New England compounding center who has developed any of the following - one, fungal meningitis or non bacterial or non viral meningitis of a sub acute onset following epidural injection after May 21st 2012. And I pause on that one because when we talk about non bacterial and non viral meningitis we're talking about a clinically diagnosed meningitis in a patient who has one or more of the following systems – headache, fever, stiff neck or photophobia, anesthesia profile showing a pleocytosis regardless of glucose or protein levels. And when I say a pleocytosis, for this outbreak case definition in these patients we are talking about more than five white blood cells in their CFF adjusting for traumatic cap or the presence of RBC. And Dr. Chiller will be explaining a little bit more about how we settled on those parameters shortly.

The next part of our case definition is again a patient who received an injection with methylprednisolone acetate produced by the New England compounding center who developed - we've already talked about the meningitis. Number two was a seizure or stroke following epidural injection after May 21st 2012 who had not received diagnostic lumbar puncture to evaluate for meningitis. Number three - evidence of spinal osteomyelitis or epidural abscess at the site of injection following epidural or sacroiliac injection after May 21st 2012. And for septic arthritis or osteomyelitis of a peripheral joint diagnosed following joint injection after May 21st 2012. And when we say septic arthritis we're talking about a clinically diagnosed septic arthritis meaning new or worsening pain with presence of an effusion or new or worsening effusion.
So those are our main buckets of case definitions related to this outbreak. We do have another case definition - a suspect case definition - that we have defined as a person who has developed an infection of a normally sterile site following use of a product labeled as sterile prepared by the New England compounding center. And this goes back to the point I made before about how we are not currently asking clinicians to actively call and contact patients who received other products beyond those three lots produced by NECC. But we do want you to remain vigilant and if you identify infections in patients who received a product from NECC we want to know about it. We want you to tell the state health departments so that we can continue to investigate and learn more about the situation.

So I know that's a lot of information. Again, it's available on the COCA website and the CDC website. And at this point I'm going to turn it over to Dr. Chiller to give you more information about diagnosis and treatment.

Dr. Tom M. Chiller:

Thanks Dr. Schaefer and thanks everybody for joining. I'm going to try and cover some of the basics from the clinical aspects of diagnosis and treatment. And I know it will not be probably as extensive as you like and hopefully we can field a few questions at the end of this call or at the end of my talk and answer some of the other burning clinical questions that people might have. But I will try to hit on some of the things that we are hearing from the field. Again, I want to emphasize this is an evolving situation as Dr. Schaefer mentioned. And the clinical information is especially evolving as we learn more about patients with earlier disease than some of the initial patients that probably had more advanced disease at the beginning of this outbreak.

So let's start just reiterating what Dr. Schaefer said about CDC laboratory's confirmed cases of fungal meningitis. We now have ten cases of exserohilum fungus and one case of aspergillus fumigatus fungus. It's important to note that the majority of confirmed cases where we have identified a fungus are exserohilum. Exserohilum is a black mold. You will often hear this group of molds called the black molds. And it is obviously a very rare and unique mold. And it's not something we have seen causing meningitis previously. So there is very little information known about this organism in the CNS. So what we are learning now about this organism and the other cases is really as I mentioned evolving with this outbreak. So briefly what we have seen clinically in the patients where we have clinical information is that the majority are presenting with headache and then there are a number presenting as well with neck pain and nausea and new neurological deficits. About 1/3 of the patients right now have reported neck stiffness, neck pain and fewer have reported dizziness, vomiting and sensitivity to bright light or photophobia. It's important to note that some of these patient's symptoms are very mild in nature. And the cerebral spinal fluid obtained from these patients have typically shown elevated white cell counts with the predominance of neutrophils. And as Dr. Schaefer just mentioned, some patients now are presenting with CSF white cell counts that are relatively low compared to the initial part of the outbreak. And so we want to emphasize that our case definition includes anyone with what would be considered an abnormal white blood cell count in the CSF. And we are defining that as any number of cells above five found in the CSF regardless of what the protein and glucose levels show.

So taking a step back to our recommendations in diagnosing these patients. Diagnosis is indeed a real challenge and we understand that this is going to be a challenge for clinicians. Currently we obviously recommend that if a patient presents with a symptom like headache, neck stiffness,

photophobia, dizziness, the things that I have mentioned that we have now commonly seen, we recommend that that patient gets a lumbar puncture. And we recommend that that lumbar puncture fluid – the CSF - be submitted for the typical microbiologic studies that you would submit that for. So both bacterial and fungal studies as well as viral cultures. We also want suspected cases to get as much CSF as possible. We are recommending if possible ten cc's of CSF be sent to the local microbiology lab for fungal culture. And then another one to five - five cc's if possible - of CSF be taken that can be that sent to your state health laboratory which will then go on to the CDC for PCR testing. If more CSF is available, we would then recommend that a galactomannan test or aspergillus antigen test be performed on the CSF if there is CSF available.

As far as diagnostic testing for non CNS disease patients - in other words, patients that receive the injections as Dr. Schaefer mentioned not in the epidural space but in a joint or other location. We also want that fluid collected and as much fluid as is available. Some portion of that fluid be sent to the microbiology lab for bacterial and fungal culture. And at least one CC if possible of that fluid being sent to the state health lab which will then forward it to CDC for PCR testing.

So to speak briefly about treatment - our treatment recommendations continue to evolve and are based on the current information that we have available about the cases. Currently for meningitis cases we are recommending starting treatment empirically with IV voriconazole at a dose of six milligrams per kilogram and to use that high dose voriconazole for as long as the patients are tolerating it. With that we want to also give high dose liposomal amphotericin B or the trade name is AmBisome at 7.5 milligrams per kilogram per day. And again this is a high dose to try to achieve adequate CNS penetration. We realize that these are two anti fungal medicines that carry with them toxicities - especially amphotericin B at such high doses. And given that many of the patients that are receiving these medicines are elderly, we anticipate and are already seeing problems with renal function due to amphotericin. But we remain concerned that the nature of this outbreak as it evolves is still unclear as to how many potential fungal pathogens could be involved. And therefore we do not feel comfortable yet recommending a narrower therapy. Although we'll assure everyone out there who's treating these patients that we are actively evaluating the situation and have an expert clinical panel that is reviewing with us patient data, clinical outcome data and the particular fungi that are being cultured in order that we might be able to narrow our fine tune the recommended therapy treatment - the CDC has not yet been officially notified of any joint infections although we do anticipate
that this could be an issue. Treatment recommendations for joint infections are currently being developed and we anticipate those will be up on the web very shortly. We again anticipate that we need to be aggressive in diagnosing septic joint patients. And if other causes like bacterial or osteoarthritic changes are ruled out in patients that have received injections into their joint then they should be empirically treated for the fungal infection. And again voriconazole should be used at a dose of 4 milligrams per kilogram. And we consider that the addition of amphotericin or AmBisome in these patients is also of note

and we continue to discuss whether both drugs should be used for these joint infections or whether it is possible to use only voriconazole. At this time we want clinicians to use their best judgment and I think because of the nature of the joint infections being less severe and without the danger of the high mortality that the CNS disease carries, we are less inclined to want to recommend two drugs for the joint infections up front but we are still cautious because of the nature of this outbreak being multiple organisms being involved. And we want to continue to use amphotericin B to treat organisms that would not be treated by voriconazole. Those organisms are going to be the class of zygomycetes or mucorales which are not susceptible to voriconazole. And that is why we continue to advocate the use of amphotericin or AmBisome.

A quick word of prophylaxis - we do not recommend prophylaxis in these patients. And the main reason for that is it is for concern about under treating patients that have a true infection. Prophylaxis would give lower doses than we would want to use for treatment. And we would be concerned that we might mask two infections with lower doses of the antifungal medicines needed. So we continue to not recommend prophylaxis and recommend aggressive diagnosis in this setting.

As I mentioned, the clinical situation continues to evolve and we continue to collect information as Dr. Schaefer mentioned from all of our state and local health partners and clinicians that are treating these patients. And we will continue to update the website with clinical frequently asked questions as well as treatment guidelines on a daily basis. And I'd like reemphasize what Dr. Schaefer mentioned in that going to the website and checking out the current recommendations should be done on a daily basis if you're dealing with these patients as we are trying to make recommendations daily with changes to the clinical situation as we gather that data.

So I think with that I'll stop talking and I will open it up for questions. Again, I want to emphasize as Dr. Schaefer already did that although we are focusing our case definitions on the three lots that are listed that we think are associated with all of our cases to date, we do want clinicians to remain vigilant about patients that received other New England compounding products. And we would want clinicians to report any specific cases with those products to their state and local health authorities. Thank you.

Leticia Davila:
Thank you Dr. Schaefer and Dr. Chiller for providing our COCA audience with such a wealth of information. We would like to apologize that we had some inconveniences when you guys were logging in today's call. So we would like to apologize for that but we also want to thank you for joining today's COCA call. We will now open up the lines for a question and an answer session. (Tim)?

Coordinator:

Alright. And if you do have a question, please make sure your phone is un-muted and press star one. When prompted, record your name slowly and clearly. Once again it is star one if you have a question. And we do have questions queuing up. One moment please. Our first question will come from (Michael Vella). Your line is open.

Michael Vella:
Yes. I was just wondering since NECC is a compounding company, is there any concern about the source methylprednisolone that they've used to compound. So, any upstream concern?

Dr. Melissa Schaefer:
I think that investigation and evaluation is ongoing with FDA and the Massachusetts board of pharmacy. We don't have any additional information at this time.

Michael Vella:
Any news at all of what their source methylprednisolone was from or who it was from?

Dr. Melissa Schaefer:
We don't have that information at this time.

Michael Vella:
Okay.

Coordinator:
One moment please. Next we have (Susan Sullivan). Your line is open.

Dr. Patella:
Yes. Actually she left. This is Dr. Patella at Skyline Medical Center. A couple of questions - the PCS testing that you're doing - is it specifically for this fungus or an area of organisms? And who's picking up the samples? Do we have to tell them to pick them up? We have a couple of samples here at Skyline. I'm not sure they've been picked up for the CFS for the CDC.

Dr. Tom M. Chiller:
Yes. Thank you. The PCR test again is a research only test that we just basically developed. But no, it's a pan fungal PCR. So it should pick up any fungus. And then that fungus if we identify a band we then sequence that DNA to identify the species. And you should be sending your samples to the state health department. And they know what to do with them once they get that. So your clinical lab is probably very used to sending things to the state reference lab, et cetera. And so they should be able to get it to the state lab which will be able to send it off to us.

Dr. Melissa Schaefer:

And I think to be clear to add the testing that Dr. Chiller was talking about is focused on those patients that meet the case definitions that we have on the CDC website. So it's not for all patients. It's for those that meet the case definition.

Dr. Tom M. Chiller:

Right. We just want to receive CFS or joint fluid samples from cases that meet the case definition.

Dr. Patella:

Right. And I have a follow-up question. If a patient is unable to tolerate the first line agents, what is the backup - echinocandins or anything else?

Dr. Tom M. Chiller:

Yes. That's a great question. I think I would certainly try to use voriconazole and amphotericin and we certainly realize there are going to be patients out there that don't tolerate one or even both of those. I think I worry a little bit about echinocandins. They are not great drugs for exserohilum. They do not penetrate into the CNS well at all. And so I'm a little concerned about recommending those. I would probably consider something like posaconazole as a good alternative. The problem with posaconazole as you know is it's only available in an oral solution at this point in time. So honestly voriconazole and amphotericin are your best bets if you can, you know, and you have some toxicities with one. You know, you may have to drop one and use the other. We know voriconazole has excellent CNS penetration which is one of the reasons why we see some side effects in the eye. So we know it penetrates very well. And we know that AmBisome at higher doses does a pretty good job of penetrating into the CNS as well. And so that's why those two agents are being recommended. And there's not a lot of alternatives after those unfortunately.

Dr. Patella:

Thank you.

Coordinator:

Are you ready for another question?

Dr. Tom M. Chiller:

Yes.

Coordinator:

Okay. (Carla Miller) I'll open your line.

Carla Miller:

Thank you. Can you comment on outpatient treatment for these patients? We're concerned about the availability and cost of outpatient treatment.

Dr. Tom M. Chiller:

Yes. So, can you be more specific? Are you talking outpatient treatment for someone who's potentially been on IV therapy for a while and then you're transitioning to an outpatient. Or are you talking about...

Carla Miller:

No. That's absolutely correct.

Dr. Tom M. Chiller:

Okay. Yes. Well we fully expect that patients will probably need to be on antifungal therapy for months – certainly weeks to months. Unfortunately with fungi, you know, we know that short course therapy does not work - especially with molds. And we would even be concerned about, you know, recurrence after therapy has stopped. And again we don't have a definitive time yet established for how long we would recommend therapy. We are continually reviewing that based on the data coming in and with our clinical expert panel to see if we can't come up with some recommendation about duration of therapy. As far as outpatient therapy - let me better address the concept of IV and PO or oral voriconazole. Voriconazole achieves the same levels in both IV and PO. There is an issue though with taking pills in that you need to take it on an empty stomach. And you need to, you know, to check levels to make sure people are being compliant and are absorbing it. But it works very well orally. So I think we would feel comfortable with both IV and PO formulations of voriconazole getting into the CNS and getting the levels you need. I think the problem you're going to have is the AmBisome. But you can do IV therapy with AmBisome as an outpatient although that may be a little challenging. As I mentioned we would hope that there would be a

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we hope that we can modify treatment recommendations in the future where we might be considering voriconazole as the primary choice. But for the time being as we don't yet know the full extent of the fungi involved in this outbreak, we think it's important to continue to use both agents.

Carla Miller:

Thank you. We are really struggling with the transition from inpatient to outpatient and the patients being able to afford the treatments post discharge. Has the CDC considered releasing any of the voriconazole to the strategic national stock pile?

Dr. Tom M. Chiller:

Well thanks for that question. And we do realize that, you know, the challenges in antifungal therapy is in outpatient. We have not had any extensive discussions about the national stockpile. But we certainly will bring that up with others here who are much more informed about that.

Carla Miller:

Okay. Thank you.

Coordinator:

The next question comes from (Tom Farris). Your line is open.

Tom Farris:

Thank you. I realize it's early yet in this situation but some patients have been treated for over a week now. What have we learned about the clinical response to treatment for those who are currently hospitalized? And have we identified any prognostic indicators to suggest who's doing well versus poor responders.

Dr. Tom M. Chiller:

Yes. Thank you very much for that question and that is definitely something that we are looking at with the clinical team. We do have some small cohorts of patients where there is more intense clinical follow-up. And we are actively analyzing that data. So unfortunately you are right. It's a little early. We don't have any good prognostic indicators at this time. We do know that some people are stable on therapy. We also know that some people unfortunately have progressed to strokes and even death. What we do think is that early in the outbreak we were obviously identifying people with more advanced disease. And so we expect that there would be poorer outcomes in some of the earlier cases. And I think now that the outreach that Dr. Schaefer described has gone on with active case finding, we are seeing people with clearly what would be considered mild or early disease and I think we'll expect better outcomes. But we will definitely be getting that information out on the web as it becomes available with clinical updates for clinicians.

Tom Farris:

And just a quick follow-up. Even for the best cases we don't know if they were immunosuppressed or had other significant mobility's?

Dr. Melissa Schaefer:

We're looking at all of those things as Dr. (Chiller) mentioned. And as, you know, we get information, we'll make sure that we're putting it out there to help you all.

Tom Farris:

Okay. Thank you.

Dr. Tom M. Chiller:

And I do want to mention - I want to take the chance to mention something that Dr. (Schaefer) reminded me that we didn't mention in our summary. And that is the question of the incubation period of these organisms. What we're finding with the data that's been reported to us is that and as we've said on our website that we're seeing a typical incubation period between one to four weeks. But we're clearly seeing some shorter incubation periods into the four to five day range and also longer incubation periods.
So we don't want you to feel that someone is safe after four weeks. That is clearly not the message. The message is that although many patients have an incubation period of one to four weeks, there are clearly cases that have shorter and much longer incubation periods. The exact length of which we're going to begin to feel comfortable with an incubation period is still unknown. And unfortunately with fungi, they can remain very indolent for long periods of time. So we're hopeful that we can learn more as we hear more about cases coming in. But it's important to emphasize that incubation periods can be quite long and we expect some will be for these patients.

Coordinator:

Our next question comes from (Kelly Stephsinsky). Your line is open.

Kelly Stephsinsky:

Hi there. I was wondering how many specific cases you have reported in Indiana as well as deaths. Do you have those numbers available?

Dr. Melissa Schaefer:

That information is detailed on the website. I don't have the state - I'm sorry. Actually I do have the state specific information. So for Indiana we have 15 cases, no deaths reported as of today.

Kelly Stephsinsky:

Okay. And do you have specific pockets? I'm sorry. Go ahead.

Dr. Melissa Schaefer:

For all of you just to save state level questions - if you go to the CDC website http://www.cdc.gov/hai/outbreaks/meningitis-map.html we have a table listing by state, case count and death information that we update daily.

Kelly Stephsinsky:

Thank you. And is that broken down by county as well?

Dr. Melissa Schaefer:

It is not.

Kelly Stephsinsky:

It is not. Okay. Do you have specific pockets obviously of places who may have gotten bad doses?

Dr. Melissa Schaefer:

As I mentioned in the beginning, on our website we have a list of the facilities who received medication from these three lots by state. So you're able to check there. Anymore details about county distribution and others - I'd direct you to the state health department.

Kelly Stephsinsky:

Okay, great. Thanks so much,

Dr. Melissa Schaefer:

Yes.

Coordinator:

Next we have Dr. (Norlena Gullin). Your line is open.

Dr. Norlena Gullin:

Hi. Yes. For those of us that are not infectious disease physicians, could you help with some of the spelling of exserohilum as well as the various classes of fungus that are not susceptible to the Amphotericin B?

Dr. Tom M. Chiller:

Yes. The specific names, et cetera are all on the website.

Dr. Norlene Gullin:

Oh, okay.

Dr. Tom M. Chiller:

Yes. So it's probably easier instead of me spelling it out for you if you just look on our website. This is a category as I said exserohilum represents one of the black molds. There are many. And so they traditionally are not as susceptible to amphotericin as so of the other molds but should be very susceptible to voriconazole. So that's one of the reasons we feel more comfortable using voriconazole. I

will say that we are actively trying to get MIC or minimum inhibitory concentration susceptibility type information on the current isolates that we have. And they are difficult to grow. So we are struggling a little bit to get that information. But we hope to have that within the next couple of days. That will also help us if we need to make any changes to the current recommendations for treatment.

Coordinator:

Our next question comes from (Timothy Burke).

Timothy Burke:

Yes. Thank you. What can you tell us about the causes of death in the fatal cases at this point?

Dr. Tom M. Chiller:

Yes. Thank you for that question. Almost all of those cases have died of stroke or some complication of a stroke. And we do not have autopsy information on all of them. And only have received I think so far one case here at the CDC. And the rest is from reporting. But we can say that in one case we have seen that the *Exserohilum* was directly invading into tissue. And so we anticipate that invasion into tissue and invasion into blood vessels is what causes brain ischemia and stroke and that was the cause of death. I don't know in specifics in many of the other cases unfortunately. Again, we're trying to compile that information and learn more as we collect it.

Timothy Burke:

A follow-up - is there any of that sort of clinical detail that's up on the website now?

Dr. Tom M. Chiller:

Not in that detail yet. We know that you and others have been asking for that and we are well aware. And we want to put clinical detail up on the web as soon as we feel that it is verified and that, you know, it can be of some use. So we know you guys want that. We are well aware of that and we are trying to get it up there as fast as we can. We just do not want to put information up that gives a different picture than what we're seeing. So we want to make sure that we verify anything we put up.

Timothy Burke:

I understand.

Dr. Tom M. Chiller:

Great. Thank you.

Coordinator:

Next we have (Dana Cartier). Your line is open.

Dana Cartier:

Hello. Hi, this is (Dana) calling from a pain practice in Pennsylvania and our understanding was there was two pain practices in the state of Pennsylvania that received one lot. And there has been no reported cases due to this lot as of today. We had two questions regarding that. The first one is we screened our patients for all the symptoms that the ADHD sent us regarding these patients. And if a patient is not having any type of symptoms, is it safe for them to come back within a week or two to have another epidural injection even though they're showing no symptoms right now because the incubation period has been extended?

Dr. Tom M. Chiller:

That's a great question and we haven't heard that yet very often. So we don't have really any information on that. I would think the, you know, again I would be cautious. I think what we're telling people is that those who got an infected - a potentially infected lot injection - should be, you know, continually followed for the development of symptoms. And as I mentioned those symptoms could take some time to develop. I would think that if - I may not have heard you correctly. But if you are talking about non potentially infected lot injection being done and then being able to follow up with one of those patients who feels completely fine several weeks later to repeating an epidural injection then I think you guys will need to use your best clinical judgment.

Dana Cartier:

Okay because this is from one of the lots that was recalled.

Dr. Tom M. Chiller:

Excuse me.

Dana Cartier:

Their initial injection was from a lot that was recalled. But I know initially they were saying the incubation period is 28 days. So if we had a patient at the beginning of July - is it safe to give them another epidural injection if they are having no symptoms?

Dr. Tom M. Chiller:

It's a great question. And again, I mean, I think that, I mean, I can't answer you that. Specifically we don't have information on that. But I think what we do have information on is that incubation periods can clearly extend beyond four weeks. And so I think you do need to remain conscious of the fact that a patient with an injection could have a much longer incubation period than was previously suggested. And you need to take that into consideration if you are going to continue to treat. We realize some of these people need continued treatment for their pain management. That's clear. Otherwise they wouldn't have been coming

to you in the first place. So I think you're just going to have to use your best clinical judgment and decide how to manage that. But it's a good question and I will put it to our clinical team.

Dana Cartier:
Okay. And one other question that I did have - we were under the understanding that all three lots were pulled and it was not determined yet if all three were contaminated. They were still being tested. And one of our unopened vials was sent I believe to the FDA to be tested. Will we receive a report from the FDA or whoever is doing the testing on this vial to state that it was or was not definitely contaminated?

Dr. Melissa Schaefer:
Yes. That's not a question that we can answer. FDA would have to speak to that and how they would be reporting back information. I don't have the answer for you.

Dana Cartier:
Okay. Thank you.

Dr. Tom M. Chiller:
But I think we can, I mean, we definitely could confirm - right Dr. Schaefer - that each of the three lots has had patients linked to the injection, correct?

Dr. Melissa Schaefer:
Yes. Our concern extends to all three lots. We're not focused on any one at this point which is why, you know, why the guidance that we issues has been there to actively call any patient who receives an injection with products from any of those three lots.

Dana Cartier:
Okay. Thank you.

Coordinator:
Our next question comes from Dr. (Michael Njar). Your line is open.

Dr. Michael Njar:
Thank you. This is Dr. (Michael Njar) in Tennessee. We did not receive any of the tainted drugs from NECC although we did use other drugs from NECC. So we seem to have dodged a bullet if you will. Obviously I'm concerned - my patients are concerned. When they call in if they are having any of these symptoms and some of the symptoms are non specific - headache for example. But if I'm concerned

enough, should I still seriously consider sending them on for lumbar puncture to the local emergency room or should I simply reassure them and try the whole staff? What are your thoughts please?

Dr. Tom M. Chiller:

Yes. Thank you. That's a very good question. I think we are still concerned that other NECC products could be contaminated. We have no evidence that that is the case to date. But we are certainly still concerned. And so I do think that if you feel that there's a clinical condition or clinical symptoms consistent with, you know, something that could represent meningitis or something that could represent some of the clinical findings as we've seen in the other cases that are associated with a contaminated product. I think we would think you should think and consider performing a lumbar puncture on those patients.

Dr. Michael Njar:

And a follow-up question - with the emphasis on diagnosis, obviously we're looking for more than five white blood cells in the CFS. Are there any stains at all that may be helpful? Obviously I'm not an expert in this field. And secondly when they send these samples off for culture - how many days are we looking at before we get a yes or a no from the lab - two days, four days, et cetera. Thank you.

Dr. Tom M. Chiller:

No. And thank you for bringing up that question because it's actually a very, very important one. So just, you know, from the microbiologic evaluation of CFS, it's important to obviously do the routine microbiological evaluation because these patients could be coming back with bacterial meningitis, et cetera. And stay-ins can help with bacteria at times. Unfortunately for mold stay-ins will not generally be helpful. And in fact the culture is useful if it's positive. But it's not useful if it's negative. In other words it is very difficult to culture mold out of the CSF. So what I definitely want to convey to everyone is unlike bacteria where if it's sort of culture negative you might be able to sort of rule it out. You can't rule out fungus if it's culture negative. In fact I would expect as we are finding that the majority of these patients will be culture negative. And in fact many of the PCR positive patients are also culture negative.

Molds are very hard to culture on a CSF. They don't tend to stay in the CSF. They tend to invade into the durra and then on to wherever they're headed unfortunately in the parameningeal foresee. So we don't expect that the CSF necessarily to harbor large amounts of these organisms and therefore they're going to be very difficult to culture. So unfortunately there is no magic data to say okay, culture negative after two weeks. We're done. We don't have to worry about it. In fact a culture negative really doesn't tell us much about the disease. If the case is consistent with the definition clinically then we would continue to presume it's a case and continue to treat as though it's a fungal meningitis whether or not we have a culture or a PCR positive.

Coordinator:

Our next question comes from (Carrie Meyers). Your line is open.

Carrie Meyers:

Yes. I understand that the incubation period is still kind of a moving target. But patients are actually calling and asking questions about potential for dormancy and occurrence for illness at a later date whether it be six months, a year or even longer down the road.

Dr. Tom M. Chiller:

Yes. I mean I obviously wish I could shed light on that issue because I'm sure it's a concern for people. You know, I can only speak as a clinician on this which, you know, we don't have any information on it obviously yet for this outbreak. But I do know the CDC has investigated unfortunately a couple of other outbreaks in the past. And one that we investigated about ten years ago had an incubation period I think for one of the patients of like 150 days. So we know that fungi can be indolent. I wouldn't say dormant purse but they can be indolent and the progression can be slow. So we don't know in this case whether the incubation period could extend out that far. And there is relatively no experience on this kind of stuff out there in the world. So we're learning - all of us as we go. But we are certainly concerned for longer than one month incubation periods because we know we've seen those already. But I don't know how far out to tell you to think. I mean I certainly think that we need to, you know, we need to continue to remain in touch with our patients as needed. But I think we need to, you know, reassure them that those sort of long incubation periods are going to be, you know, the exception I think and not the rule. But we can't say for sure that they won't exist or haven't.

Carrie Meyers:

Thank you.

Leticia Davila:

Thank you Dr. Chiller. Tim do you know how many questions are in the queue?

Coordinator:

We have at least 40 more to go.

Leticia Davila:

Okay. We'll only be able to take about two more questions.

Coordinator:

Okay. Our next question then will be from (Amy Peterson). Your line is open.

Amy Peterson:

Yes. Hi, Dr. Chiller. Another question about incubation period although I know you answered most of what I had to ask about this. Coming from a perspective of forward surveillance that we're going to need to do here in our population - once we establish a covert that's been exposed where in our beneficiaries going forward - and I know it's going to be a moving window and we'll just have to keep apprised of what you find out. But can you tell me what the current far reach extent is for the incubation period that's known just so I can use that for forward planning until we get more data? Thank you.

Dr. Tom M. Chiller:

Yes. Thank you. You know, part of the problem is we haven't received that kind of information on all the cases yet. So any numbers I quote you are going to be on a subset of the patients and so I may not be quoting you the exact outlier. What I will say is this is that again, we know we've had confirmed patients with - because remember there are patients that received multiple injections. And those that received multiple injections, we have to figure out what was the contaminated injection? Was it the first, second or third? And so we're fudging a bit the calculations there. Is it the last injection - the first injection? For those patients with one injection in one cohort, we know that it went out to 40 plus days. There are some reports of some patients longer than that already. But again, we just don't have the full story. So I don't want to quote you on a specific number. But clearly we do have confirmed cases beyond 40 days.

Amy Peterson:

Okay. Thank you. I was also just partly curious because of the media saying things like three months. I think I heard on NPR this morning. So I know that there's conflicting data out there and I realize that's partly because this is just an unknown. But thank you.

Dr. Tom M. Chiller:

Yes. And I think the three month period came from the Tennessee group potentially where they've done a tremendous job in collecting a lot of information on their cohort. And I know that I believe they reported a patient out to 40 plus day and then therefore sort of extrapolated to say that we should be thinking about things, you know, at least three months, you know, within three months. So I think that's where some of that information is coming in. You know, again we're trying to not be that specific yet just because we keep seeing more and more people with longer incubation periods. And so we want to try and get a better handle on that.

Leticia Davila:

Yes. I just wanted to jump in real quick. And (Tim) we will be taking calls or questions and answers for

another 15 minutes. Thank you.

Coordinator:
No problem. Next then we'll have (David McKinney). Your line is open.

David McKinney:
Yes. I'm calling from Tennessee and I'm an emergency room physician. And we've probably seen 65 plus stations over the last four to five days. And universally all of these patients have had headaches. Some of them - we've done about 32 LP's in the last five days and a couple of questions about that. Number one is would you recommend really just probably going ahead and doing LP's on all of the patients that have been exposed to these lot numbers? And the reason I say that is because just about every one of them or actually every one of them have had headaches. The number two question would be that we've had some CSF's that come back with just minor elevations in the protein with no pleocytosis. And for those patients that have headache and have been exposed, would you recommend re-tapping them at some point? And another question about the re-tapping - have we thought about that to help us guide therapy specifically with maybe switching over from the intravenous to the oral preparations that we talked about.

And also another question that we've had as far as treatment - are you recommending treating for bacterial and viral infections in patients that we do, you know, hospitalize and treat until at least the bacterial and viral cultures come back. And I think that was about all that I had. Are any other solutions besides sending patients to the ER because we've really been overwhelmed to be honest with you. Thank you.

Dr. Tom M. Chiller:
No. Thanks for that. And we certainly appreciate - Dr. Schaefer's an ER doc. So we certainly appreciate that you guys are out there on the front lines getting hit with obviously a lot of referrals now. So we appreciate all the hard work that you're doing. So I'll try to address your questions. So basically our recommendation is any symptoms - so a patient who received one of these lots who has a symptom like headache and like you said unfortunately probably many of them have headaches that is post an epidural injection. We would recommend an LP. If those LP's as you mentioned do not have greater than five white cells - so no pleocytosis - and have other abnormalities, we are calling those non cases. But we do think you should - someone, if not the ER - their physician should clinically stay aware of them and monitor them. And I think if we would recommend it clearly that if their symptoms worsen that they should have a repeat LP. If their symptoms pretty much stay the same, I think one could also consider an LP. But I think if they clinically are improving with obviously no intervention then I think you would warrant another LP.

So we are recommending that you stay vigilant on those patients that do not have cells and that you do have a low threshold to consider repeating an LP if you feel the clinical symptoms have worsened or not improved. And then finally you also mentioned transitioning using the path to help guide a transition from IV to oral therapy. We don't really have any information on that yet. We are talking with our expert clinician panel about the concept of looking at, you know, CFS parameters after a week of treatment and what we would be expecting. I mean I don't think it's going to help guide whether we switch from IV to oral. As I mentioned at least voriconazole, that's going to depend really more on the patient's adherence to medicine and compliance because the vial availability of IV and PO voriconazole are equal. It's the AmBisome that will be more of a challenge because there is no oral obviously as we all know – oral amphotericin B.

And then finally the bacterial and viral treatment - we certainly want patients that are being ruled out for bacterial and viral positives - we certainly want them to continue on their bacterial treatment until you feel that there is not a bacterial component. We don't think they need to be continued on bacterial treatment once that is ruled out and you now consider this a suspected fungal meningitis case. We haven't had any - early on we had reported propioni acnes bacteria but we don't think that that had anything to do with any infection in our cases so far. So we don't think that bacteria are involved at this time.

David McKinney:
Very good. Thank you. Just one other follow-up thought. One of the things that just to let the folks know, I mean, we have considered doing is trying to set up an LP clinic and staffing that separately from the ER. And I didn't know if you'd heard of any other creative solutions for, you know, sort of infusing the ER. Dr. Schaefer might have some thoughts on that.

Dr. Melissa Schaefer:
Yes. We haven't heard of that. I appreciate you bringing it up and sharing it. And we don't have any more information at this point in time. But thanks for bringing it up.

David McKinney:
Okay. Thank you.

Coordinator:
Our next question will come from Dr. (Steven Long). Your line is open.

Woman:
Hi. Dr. (Steven Long) had to walk out for a minute. But his question is, is the CDC making any suggestions about using or not using other preservative free steroids prepared by other compounding pharmacies?

Dr. Melissa Schaefer:
We haven't made any recommendations beyond looking at the New England compounding center. As we said, all of the New England compounding center products have been recalled. And so, you know, clinicians and facilities should make sure that they aren't using any of those products at this time. But we don't have any updated guidance directing products from other compounding pharmacies at this time.

Woman:
Thank you.

Coordinator:
Next we have Dr. (Sherive). Your line is open.

Dr. Sherive:
I actually (unintelligible).

Dr. Melissa Schaefer:
I'm sorry. We're not able to hear the question. Can you either repeat or maybe we need to move on to the next question?

Coordinator:
Hello. Dr. (Sherive)? We'll go ahead and go to the next question. It comes from (Roland Shelifow). Your line is open. Excuse me. He's not responding either. One moment please. Next we have (Peter Pandelitis). Your line is open.

Peter Pandelitis:
Yes. I have a couple of questions. Thank you for taking them. Can you confirm the earliest date that someone has been injected and has been infected with the recalled methylprednisolone lot?

Dr. Melissa Schaefer:
I don't have that information in front of me. We're still looking through all the case reports that we have. And as we get, you know, an epidemic curve and timeline available, we'll be releasing that.

Peter Pandalitis:
Okay. Another question - I'm sorry. The lots that have been identified to have direct - that they've directly noticed fungal contamination and has that been noticed in all three lots directly or specifically one lot or two?

Dr. Melissa Schaefer:

We don't have that information at this time. The FDA is performing testing and evaluation of the vials from those lots. And so we'll have to defer from them on the information. But I think the important take home for you all is that we have associated infections with all three of these lots. So I would be concerned as we said to actively contact all patients who received an injection from any of these three lots.

Peter Pandalitis:

Is there any recommendation regarding let's say for peripheral joints or other joints for repeating injections in asymptomatic patients with nonsteroidals or has that been considered at all?

Dr. Tom M. Chiller:

No. Currently our recommendations are to monitor those people who got one of these lots of steroid injected into their joint and to monitor for a more of aseptic arthritic picture. We think this will probably be sort of insidious and in the (unintelligible). But we would be concerned about fungal and septic arthritis. And so we haven't gone beyond wanting to evaluate that and then treat it with antifungals. We haven't thought of other possible treatments into TGS. And again we haven't been officially notified yet of any cases although we do know that some of those 13,000 patients that got injections did obviously get injections into the joint space.

Peter Pandalitis:

And one final quick question - you mentioned briefly or there may have been a response briefly to a question earlier about monitoring patients that had other abnormalities other than an increased white blood cell count but perhaps decreased glucose or increased protein. If those patients remain symptomatic, do you have a timeframe which we should consider doing another tap on them?

Dr. Tom M. Chiller:

Yes. We don't have an exact timeframe because we again don't really know. I can tell you that talking to the clinical expert panel. So again here you have a patient that has symptoms - let's say a headache and some nausea. You perform an LP. You have less than five cells. You may have a glucose or protein abnormality but may just be a completely normal path but has the symptoms. And what we're recommending is to continue to monitor that patient clinically - probably every couple days or have some close contact with that patient. And I would think if the patient didn't have resolution in that or wasn't getting better or clearly was getting worse. Then I think, you know, in a week's time you would consider re-tapping them. Again, that is not CDC's recommendation. That's just sort of a general feeling from the expert clinical panel.

Peter Pandalitis:

Thank you.

Coordinator:

Next we have (Kim Bether). Your line is open.

Kim Bether:

Yes. Thank you. I'm an infectious disease pharmacist at the University of Minnesota. I was just curious. I have two questions. First, was there clinical consideration by the teams who came up with the recommendations regarding some literature that does suggest in vitro antagonism between the Azole antifungals and the polyene antifungal agents? I know that there's very little literature to support the antagonism in vitro but I was wondering if that was a consideration when the double antifungal recommendation was made. And then my second question is for the treatment recommendations that are forthcoming for the septic joint infections, do you anticipate a preference of one of the Amphotericin products - either the lipid formulation of Abelcet or liposome or AmBisome as the recommendation. I'm just not aware of any superiority literature between the two products in this type of infection.

Dr. Tom M. Chiller:

Yes. Thank you for two very interesting questions. So the first question about the antagonism issue - yes, this has been sort of an age old issue as you know with the azoles and the amphotericin products being antagonistic in some in vitro data. I mean, I know that this clinical panel obviously is well aware of that issue in vitro and certainly thought about it. But there are also, you know, we're all well aware - those of us that are dealing with fungi - that at least clinically that hasn't bared out. And we've looked at that in lots of different ways - never systematically unfortunately but certainly in many, many patients that have been treated with dual agents. So absolutely that was thought of but we really don't think that those in vitro data pan out in the patients. But it's always been an interesting point of discussion. And I think it continues to remain that way but thankfully it doesn't seem to be playing itself in the clinic. And then your second question about the AmBisome ableset for joint I think is a very good one. And I think we are reviewing that as we speak or as soon as we get off this call we will continue to be looking into the septic arthritic specific recommendations. But thank you for that point. And I think we are definitely thinking along those lines as well. The reason we're recommending AmBisome for CNS infections as you know is that there is good data that that is probably the best lipid formulation as far as penetrating into the CNS. So that is why we are recommending AmBisome for the CNS. And I do agree that we need to be thinking about different considerations - certainly price, et cetera for the joint infections.

Kim Bether:

Thank you for that and I agree with your assessment on the in vitro data. Thank you.

Dr. Melissa Schaefer:

Thank you and operator I think we're prepared to take one more question.

Coordinator:

Okay. And that question will come from (Jennifer Lions). Your line is open. (Jennifer Lions)?

Jennifer Lions:

Hello. Sorry, I was on mute. I was just wondering where and when the first case was reporting. And in follow-up to an earlier question if there had been any connection or correlation between severity of systems, IE those who died with rapidity of onset after they were exposed to the methylprednisolone.

Dr. Melissa Schaefer:

So the second part of your question first - that is information that we're looking at with the case report forms and details about the cases that are coming in. The first part of your question was the first case that was reported. That came out of Tennessee. The dates and specifics of that are available on the CDC website.

Jennifer Lions:

Okay. Thank you.

Leticia Davila:

Okay. On behalf of COCA I would like to thank everyone for joining us today with a special thank you to our presenters - Dr. (Schaefer) and Dr. (Chiller). While we had anticipated that many of you would be interested in this topic, we were very surprised to learn of the overwhelming response of almost 2000 participants who joined us for today's COCA call.

We apologize for any inconvenience that you experienced while attempting to join the call. We invite you to communicate to our presenters after the webinar. If you have additional questions for today's presenters, please email us at **coca@cdc.gov**. Put October 10th COCA call in the subject line of your email and we will insure that your question is forwarded to the presenters for a response. Again, that email address is **coca@cdc.gov**.

The recording of this call and the transcript will be posted to the COCA website at http://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 http://emergency.cdc.gov/coca/ , click COCA calls and follow the links for the meningitis call.

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

Coordinator:
Today's call has ended. Please disconnect at this time.

END