Multistate Outbreak Fungal Meningitis and Other Infections: Updated Clinical Guidance

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Presenters: Melissa K. Schaefer, MD and John Jernigan, MD

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Coordinator:

Welcome. Thank you for standing by. At this time all participants are on a listen-only mode. After today's presentation we will conduct a question and answer session. If you would like to ask a question please press Star 1 on your touch-tone phone. Today's conference is being recorded. If you have any objections you may disconnect at this time. I would now like to turn the conference over to Ms. Leticia Davila. Ma'am you may begin.

Leticia Davila:

Thank you (Juliann). Good afternoon. I am Leticia Davila. And I'm representing the Clinician Outreach and Communication Activity, COCA with the Emergency Communications System at the Centers for Disease Control and Prevention.

I am delighted to welcome you to today's COCA conference call, *Multistate Outbreak Fungal Meningitis and Other Infections: Updated Clinical Guidance*. We are pleased to have with us today Dr. Schaefer and Dr. Jernigan from the Centers for Disease Control and Prevention.

They will provide updated information on the multistate investigation of fungal meningitis and other infections including epidural abscess as well as other clinical syndromes being diagnosed in exposed patients. They will also review CDC's diagnostic and treatment recommendations for clinicians. There is no containing 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 first presented 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 Division 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.

We also have Dr. John Jernigan speaking with us today. Dr. Jernigan is the Clinical Team Lead of the multistate meningitis outbreak and Director of the Office of Health Associated Infections Prevention Research and Evaluation in the Division of Healthcare Quality Promotion at CDC. He is also a Clinical Associate Professor of Medicine at the Emory University School of Medicine in the Division of Infectious Diseases.

In addition to today's presenters Dr. Anu Malani will be available to answer questions during the Q&A section of today's COCA call. Dr. Malani is the Associate Medical Director for Infection Prevention and Control and the Medical Director for Antimicrobial Stewardship at St. Joseph's Mercy Medical Center in Ann Arbor, Michigan.

At the end of the presentation you will have the opportunity to ask the presenters questions. On the phone dialing Star 1 will put you in the queue for questions. At this time please welcome our first presenter, Dr. Schaefer.

Dr. Melissa Schaefer:
Thanks Leticia. So as Leticia mentioned I'm going to start out by giving a brief update and then I'll turn it over to Dr. Jernigan to go through the health advisory alert that was released by CDC last week. And then we'll open it up for question and answers.

So this is our fourth COCA call on this multistate outbreak of fungal meningitis and other infections associated with three lots of methyl prednisolone acetate from the New England compounding center. Per usual the details of the investigation including all the materials we've discussed here, case counts, case definitions, diagnostic and treatment guidance are all posted on the CDC Web site. We update that frequently so please check back frequently and look at the date for the document you're using to make sure that you're using the most up to date information.

The focus of this call is to give some updated numbers for the investigation and to describe some of the syndromes that we're currently seeing in patients presenting from this outbreak. As I mentioned this was described in the HAN we released last week. So the case counts are posted on the CDC Web site every Monday, Wednesday, and Friday currently. And so the case counts that we have as of yesterday November 26 are that CDC has received reports of 510 cases including 36 deaths in 19 states associated with this outbreak.

Dr. Jernigan I'm going to turn it over to him now to give an update on the HAN and to describe the kind of transition that we're seeing and the types of cases being reported to CDC currently.

Dr. John Jernigan:

Thanks Melissa. As Dr. Schaefer mentioned we're continuing to see new cases reported more than now eight weeks after the three implicated lots of methylprednisolone acetate were recalled. However the majority of the new cases that have been reported to us in the past have been meningitis. And we're seeing a transition in the types of the clinical presentation to cases that are being reported to us more recently. We've recently observed an increase in the number of patients presenting with evidence of epidural abscess, phlegmon, discitis or vertebral osteomyelitis or arachnoiditis at or near the site of the injection. And we've seen these complications occurring in patients both with and without evidence of fungal meningitis. Of the cases that have been reported to CDC in the last few weeks a majority actually have - of them had not been cases of primarily meningitis but rather these spinal and paraspinal infections.

It's important to note that the overall trend in the number of cases being reported is still going down. It's just that a larger proportion of those that are being recently reported are some of these paraspinal or spinal infections. We - our current diagnostic and treatment guidance addresses management of these patients that have abscess, epidural abscess and other complications at or near the injection site.These infections may occur in isolation or in patients previously diagnosed with fungal meningitis as I said.

It's important to note that although these patients - patients with these localized infections frequently have new or worsening back pain. The symptoms may in fact be quite mild or very clinically difficult to distinguish from the patient's baseline chronic pain that called for the injections in the first place. We have made some slight alterations to our guidance last week. It's currently active on our Web site based upon this new information and I'll relay that to you now.

Our recommendations are that in patients with new or worsening symptoms at or near the injection site physicians should obtain an MRI with contrast of the symptomatic areas if the MRI is not contraindication - contraindicated. This recommendation also applies to patients being treated for meningitis. In some cases radiologic evidence of abscess or phlegmon has become apparent on repeat MRI studies performed subsequent to an initially normal imaging procedure. Clinicians should therefore have a very low threshold for repeat MRI studies in patients who continue to have symptoms localizing to the site of injection even after a normal study. However we - we're not sure what the outcome duration between MRI study should be.

We have received reports of patients being treated for fungal meningitis who had no previous evidence of localized infection at the site of injection but who were subsequently found to have evidence of localized infections such as epidural abscess on imaging studies. Therefore in patients who are being treated for meningitis even in the absence of new or worsening symptoms at or near the injection site clinicians

should strongly consider obtaining an MRI of the injection site approximately two to three weeks after the diagnosis of meningitis. Early identification of new disease at the injection site may facilitate additional specific interventions such as drainage and provide information for measuring effectiveness in therapy thereafter. For patients who are demonstrated to have epidural abscess, phlegmon, discitis or vertebral osteomyelitis we think that - or early consultation with a neurosurgeon can be beneficial to discuss whether surgical management including debridement is warranted in addition to fungal - antifungal therapy for these patients. As always for information about antifungal treatment and management of these patients please go to our Web site where we have treatment recommendations.

We are always continuing to investigate this ongoing outbreak gathering new data. And it's possible that as we get more information these guidelines could change so make sure to check those frequently. I will also say that CDC has set up a clinician consultation network, a network of ID physicians who have special expertise in treating fungal infections who are being made available through the CDC to clinicians who are caring for patients involved in this outbreak if you need additional assistance or additional information on individual patient management. In order to access this clinician consultation network you can call CDC Info which is 1-800-CDC-INFO telling us you're a physician managing a patient that's involved in the fungal meningitis outbreak and that you'd like some expert clinical care and they will connect you with the appropriate person.

I - we will - with that I'll end my prepared comments and we will open it up for questions. And we're delighted today to have join us - joining us to participate in the question and answer phase Dr. Anu Malani. He's already been introduced to you. Dr. Malani has been really the lead infectious disease clinician in caring for a large number of patients in Michigan. Around 140 patients have been treated in St. Joseph's Mercy Medical Center. And Dr. Malani has been overseeing treatment of those patients and has great front-line experience. And it's helpful to have him on the call today to help field some of the questions. I will - I will emphasize that, you know, any comments that are made on this phone call today shouldn't be considered official consultation on any individual patient management. For that you should consult local ID physicians or access this Clinical Consultation Network. But we'll be trying to get general concepts and impressions based upon what we've seen here at CDC and perhaps more importantly what front-line ID clinicians who are accruing great experience with many of these patients are seeing on the front line through Dr. Malani.

So with that we'll end our formal comments and open it up for questions.

Coordinator:

Thank you. At this time we are ready to begin the question and answer session. If you would like to ask a question please press Star 1. You will be announced prior to asking your question.

One moment please. Our first question comes from Dr. (Hatavi).

Dr. (Hatavi):
Yes I got a quick question. Can you hear me?

Dr. John Jernigan:
Yes. We can hear you.

Dr. (Hatavi):
The question I have for you is if patients are completely asymptomatic when is it clear for us to possibly do injections on them again? I have quite a few patients who are not doing well with their pain ever since this occurred. So I'm just wondering when is the time to clear these patients who are completely asymptomatic to proceed with injections for them?

Dr. John Jernigan:
You know, I wish we had a solid answer to that question. And the answer is we simply don't know. There obviously is a theoretical risk that an exposed patient may have, you know, active infection of their epidural space that may not be clinically manifested yet. And we simply don't know what the implications of injecting an anti-inflammatory medication into that potentially infected space could be. There is certainly the theoretical concern that that could make things worse, could alter the immune response such that an infection that was, the immune system was starting to clear you might tip that balance away and actually exacerbate things. But we don't know. That's a theoretical risk. And I wish I had a great answer for you on that. We simply don't know. I think that it's going to have to be an individual decision between the clinician and the patient balancing theoretical risk that's there with the, you know, the clinical implications, the pain syndrome that they have. And I think it's just going to have to be an individual decision.

In terms of, you know, giving a time course as to, you know, when it's safe to do we don't know. We know from previous, you know, outbreaks of fungal meningitis associated with epidural steroid injection the incubation period has been at least in a few patients quite long, many months suggesting that there could be viable organisms present in the epidural space for some time. So, you know, there should be some concern for several months. Beyond that I simply I can't give you a better answer than that. I'm sorry for that.

Dr. (Hatavi):
It's okay. Thank you.

Coordinator:

Thank you. Next question (Chris Henderson) - (Hendrickson).

(Chris Hendrickson):

Hi. I'm in infection prevention at the University of Minnesota Medical Center and Amplatz. And currently for infection preventionists looking out for potential new cases we've been monitoring, we have three emergency rooms. We've been monitoring patients coming in. They're looking for, you know, headache or anything that sounds like it may be meningitis. And we're also tracking all the cerebral spinal fluids, those cultures looking for anything unusual. And now when we get into the osteomyelitis or some of these other newer complications for us to try and monitor all MRIs done across this campus would be probably impossible. But do you have any other ideas or discuss with any other IPs on in large multi-center facilities how they're doing this or is there - are we kind of doing the best that we - that you think we can right now with what we're doing?

Dr. John Jernigan:

Well I'll make a comment and Dr. Schaefer may want to comment as well. I think the - in my opinion the surveillance should focus on patients who've been - who have been exposed. That is patients who have known injections with one of the three contaminated lots of methyl prednisolone acetate formulated by New England compounding center. And among those patients you should be carefully monitoring, you know, for onset of symptoms, not only of meningitis with, you know, headaches, fever, stiff neck and all that stuff but also new or worsening pain symptoms at the site of the injection, you know, that might imply a localized infection associated with the actual injection. So I think that if I were you I would try to focus my surveillance at this point on the cohort of patients whose actually exposed through one of the implicated lots. I don't Dr. Schaefer do you have any additional comments on that?

Dr. Melissa Schaefer:

No I don't. I don't think I have anything to add. And, you know, it sounds like you guys are, you know, doing a very diligent effort here. And I'm sure that your clinicians and your front-line staff are very aware of the outbreak and the guidance that's being put out and what folks are seeing. And I think that's critical because they're the ones who are actually seeing the patients come in and taking the history and exams and can elicit, you know, that potential exposure from these folks. For those who haven't been on the prior COCA calls, you know, we've mentioned on the CDC Web site we do list the 76 facilities that received these three lots of methylprednisolone acetate that have been associated with the outbreak. I mean that's another way to kind of figure out if they were potentially exposed to these medications.

(Chris Hendrickson):
Thank you. That was helpful.

Coordinator:
Thank you. Next question comes from Dr. John Bolinger.

Dr. John Bolinger:
Yes thank you. I'm the Chief Medical Officer at Union Hospital in Terre Haute, Indiana and we've had about 100 exposures to the recall medication. The question I have now is how low should our threshold be for screening these patients with MRI looking for abscess formation?

Dr. John Jernigan:
I'll make the comment first and then I'll let Dr. Malani relay some of his experience. I think that one of the purposes of putting out the HAN last week was this, you know, this emergence of spinal and paraspinal infections as, you know, the predominant calls of newly identified cases. You know, and it's pretty clear that this is emerging as a late manifestation of exposure. And I think part of the reason for the HAN was to express that we think there should be a pretty low threshold. So if a patient's been exposed, has had a paraspinal injection or an epidural injection with one of the implicated lots and they have anything in the way of new or worsening symptoms I think there should be very, very low threshold. I think they should get the MRI in that case. And again if patients are being treated with fungal meningitis even a lower threshold later on in the illness they might consider getting an MRI.

Anu do you want to comment on that?

Dr. Anu Malani:
Sure yes. So I would agree and echo what Dr. Jernigan just said. I guess, you know, if there haven't been a lot of MRIs that have been done yet I would probably prioritize. I think now, you know, you're at least last injections given September 26 so you're probably seven weeks or maybe even longer out. I think probably the cases of fungal meningitis that we'll see - actually no, we're well more than seven weeks. We're actually couple months out. So I think fungal meningitis by itself presenting now I think that those case it's probably going to be a little unusual. I mean you might see a couple cases here trickle here and there. But I think the predominant manifestations are going to be some sort of infection at the epidural site. I think in terms of priority I would probably image the people that had fungal meningitis initially. And then I would probably if I were going to have a tiered approach -- and this is kind of an approach that we've undertaken -- we would, you know, I would, the group too would be anyone that has increasing neck or back pain. I would image those folks as well.

The third group would probably be those that are asymptomatic I guess, quotation mark asymptomatic. And I think as Dr. Jernigan was saying I think it's sometimes difficult to sort out in patients where they're, you know, they're really truly asymptomatic or do they have a little bit of symptoms. I think again in this patient population there's a reason why they got epidural steroid injections in the first place. They have some sort of chronic pain. And many of them kind of deal with the chronic - deal with chronic pain. And I think sometimes the pain is subtle and it's not till they maybe undergo some sort of operative intervention do they realize that, you know, actually I feel much better. So I would have a very low threshold to MRI folks. And then the question is is and again I don't think anyone knows the answer to this is if you have a negative MRI now does it mean you're out of the woods? And I am not sure that we can say that.

I think as far as we know right now I think the longest duration of symptoms that we that at least heard about has been about four months from injection to an epidural infection. And so I suspect that we're going to even see longer duration of symptoms as we continue to image folks. So hopefully that helps a little bit.

Dr. John Bolinger:
Yes it does. Thank you very much.

Dr. John Jernigan:
Yes and it's Dr. Jernigan again. Let me just emphasize that currently CDC actually does not recommend MRI for exposed patients who are completely asymptomatic. So that's not our current recommendation. I do think that what Dr. Malani points out is that these are patients who, you know, the reason they got epidural steroid injection is because they have chronic pain syndromes at the site of injection usually. And then many times as I said, this is chronic. And so sometimes it can be very difficult to sort out what's baseline chronic pain and what are new symptoms. And that can be a tricky business. But so I think that's where you, the physician needs to be very vigilant, have a low threshold if they think there's any hint that things are getting worse or not, you know, responding clinically the way they want. But currently it's CDC's recommendation is we do not recommend MRIs in exposed patients who are completely asymptomatic. So I just wanted to clarify that.

Coordinator:
Thank you. Next question (LL Singh) - (LL Saint), go ahead please.

(LL Saint):
Oh okay I'm sorry. Yes this is my first call that I've joined about this. And somebody actually sort of answered my question - well asked the question that I was going to ask about patients coming in and if

they're, you know, chronic pain and they've been getting a series of the steroid injections is there any adjunct test results that we would also order to kind of, you know, decide whether to give the MRI? And then I work in a rural facility so we would probably either have to have them admitted or probably transferred to a facility that would be able to provide the MRI with the contrast. So in that kind of case it's like, you know, how, you know, I guess which patients would I really be like okay I need to have them either admitted so they can get the MRI or transferred to a facility if there are any subsequent labs or test results or tests that we would order to or is it just more clinical?

Dr. John Jernigan:
I'm not - I think that probably the best diagnostic test that we know of at the moment is an MRI with contrast if there's some concern that they may have an infection localizing to the site of the injection or nearby there.

(LL Saint):
Okay.

Dr. John Jernigan:
So I think that is the test. You know, the tricky part is whether you're, you know, went to get it exactly. And I guess if there's, you know, what we're saying is that for patients who are having pain who've been exposed the threshold should be pretty low to get that.

(LL Saint):
Okay. Okay.

Coordinator:
Thank you. Our next question comes from (Marlies Churney).

(Marlies Churney):
Yes hi. I was wondering if you could comment or update us on any issues with the cardiopalegic solutions that were mentioned? I haven't really heard much.

Dr. Melissa Schaefer:
Yes this is Dr. Schaefer. I don't think we have any updates to provide at this time. On the CDC and FDA Web site you'll notice that we have been posting results as they've been available of testing of product from the New England compounding center. But as far as any additional cases have been identified associate with cardiopalegia we're not aware of any confirmed cases that - confirmed infections that have been associated with use of that drug.

(Marlies Churney):
Thank you.

Coordinator:
Thank you. Next question (Janel Alicea).

(Janel Alicea):
Hi. Thanks very much. I have a question about I wonder how - what proportion of the new cases that are presenting are these ancillary infections such as the abscesses and arachnoiditis? Is it all of them? Is it - what proportion if you could tell me?

Dr. John Jernigan:
I don't have the exact numbers right in front of me. But I will refer you to, you know, to our Web site. And you can actually look at that health advisory notice. And there's a graph there that shows. And you'll see of the case, the last bar on this is looking at cases that were diagnosed between 11-11 and 11-17. And you can see that the vast majority of those were in fact either osteomyelitis or abscess. As of November 4, now this is a little older data but I think this is the last hard data I have, 67% of the cases had spinal or paraspinal epidural abscess or osteomyelitis. Am I reading that correctly?

Dr. Melissa Schaefer:
Yes so...

Dr. John Jernigan:
Yes.

Dr. Melissa Schaefer:
...in the HAN, you know...

Dr. John Jernigan:
Yes.

Dr. Melissa Schaefer:
...which as John mentioned was from last week so the numbers are a little outdated although not significantly outdated we mentioned that the 91 cases had come in since November 4 at the...

Dr. John Jernigan:
Yes.

Dr. Melissa Schaefer:
...time the HAN was released. Of those 91 about 2/3 of them were patients who were presenting with final or paraspinal epidural abscess or osteo.

(Janel Alicea):
And those infections alone without fungal meningitis or both in conjunction and alone?

Dr. Melissa Schaefer:
I believe those were alone.

(Janel Alicea):
Oh okay. All right thank you.

Coordinator:
Thank you. Dr. (John Lang).

Dr. (John Lang):
Yes hi. Yes two questions. First I mean you mentioned doing these studies to look for local infections. Any evidence that shows that drainage helps? Again this must be very complex being right near the spine if there can be spine surgeons to operate on these?

Dr. John Jernigan:
Yes we do think that for patients who have epidural abscess there is some suggestion that surgical debridement and drainage may be of benefit. And that's one of the reasons why we encourage folks to involve neurosurgeons early. I'll let Dr. Malani comment on his experience in Michigan.

Dr. Anu Malani:
I would concur with that. We've had many patients that have gone for operative intervention, probably well over 60. And the majority of these patients feel dramatically better after their surgery. I think there's a couple differences with this I guess second wave of infection as opposed to the fungal meningitis. And many of these patients seem to have fungus or organisms seen on their path. Many of them also have fungus that actually grows in their cultures as opposed to the, if the meningitis patients where there's kind of few - only a few of them probably actually grew. But I would say, you know, the majority of the patients they go for operative intervention they feel much better. And in terms of just again talking

about symptomatic, asymptomatic, not about screening but sometimes these patients actually don't realize how symptomatic they were till they undergo operative intervention. And as far as, you know, we still don't know exactly how they're going to do because it hasn't been long enough. We're only about eight or nine weeks into the outbreak. But a lot of our patients that we've seen, in the last few weeks I mean most of the cases that we've seen have really been epidural infections or some sort of process in epidural space. And many of these patients have now gone home and most of them are actually doing quite well.

Dr. (John Lang):

The other one is a patient here that originally presented more of a meningitis, went on voriconazole, had improvement. However they had new pain down their left leg which they've never had before. And MRI showed progression of arachnoiditis nerve involvement on the left. Then went on liposomal amphotericin and even a further follow-up study will while on amphotericin and the voriconazole show's progression of the arachnoiditis further up the cord area. Anyone seen this type of - while on therapy?

Dr. Anu Malani:

So I guess I can comment a little bit on that. So we've seen several cases of arachnoiditis. And I think that's also one of the, I don't know if we completely understand the pathogenesis of this infection. But clearly we've seen patients some patients that seem to have the infection starts off epidurally and seems to spread to the inter-dural area. And some and some have developed arachnoiditis. I think, you know, our experience here and I think this is shared by other - there's been some other surgeons, neurosurgeons in the country that have seen this that there are some patients that when they underwent biopsies of their inter-dural area they actually had some fungus seen there. And once it involves the nerve roots or arachnoiditis I think that that - that's kind of - that's felt and in terms of the neurosurgeons is that that's probably an area that's not really amenable to surgical treatment. We have, you know, a lot of cases of arachnoiditis. I would say that most of them have improved on combination therapy. And in fact we had some people recently go home after prolonged stays of combination therapy.

So I think that people can improve and people seem to be improving on combination therapy. I think as far as the imaging that you're talking about I think, you know, we've seen imaging kind of stay the same even, you know, two to four weeks out. I'm not sure what that really means. I suspect imaging lags behind. And maybe, you know, in this patient population those that have arachnoiditis really imaging at four weeks or longer it may be more appropriate. But even despite their imaging staying stagnant or being about the same clinically they're better. They're much better. So I guess I would say for that patient the patient that's on combination therapy I would ask you if they actually feel better?

And as far as surgery if there is not really an epidural component to their infection I'm not sure that the arachnoiditis by itself it's probably not amenable to surgical treatment.

Dr. (John Lang):
Okay. I actually have a third question. Have they done any fungal testing on these *Exserohilum* and what is the MIC they've been obtaining?

Dr. John Jernigan:
Yes there have been a number of clinical isolates that have been looked at. And in general I don't have the figures right in front of me but the MICs have been mainly in the 1 to 2 microgram per milliliter range.

Dr. (John Lang):
For voriconazole?

Dr. John Jernigan:
Sorry?

Dr. (John Lang):
For the voriconazole?

Dr. John Jernigan:
(Conazole) yes.

Dr. (John Lang):
Okay.

Dr. John Jernigan:
And much lower for amphotericin B.

Dr. (John Lang):
Thank you.

Dr. John Jernigan:
Okay.

Coordinator:
Thank you. Next question (James Mulnar).

(James Mulnar):
Hello. Can you hear me?

Dr. John Jernigan:
Yes.

(James Mulnar):
Okay. I've got a couple of questions. Number one is I have a couple of patients with the arachnoiditis presentation. And the question often comes up is on the imaging is there any other - any way to better discern inter-dural from exter-dural? Because we will debate around the films back and forth frequently, is that exter-dural is that inter-dural. Has anybody found any particular points of view or items? Because some of these patients are - well both the patients have continued to slowly deteriorate in kind of a stutter step way despite dual treatment? And was just wondering if anybody had any feedback about that?

Dr. John Jernigan:
Anu why don't you take that one.

Dr. Anu Malani:
I think that that's - I think it's difficult. You know, we've had some multidisciplinary spine conferences where we've had our neurosurgeons, our radiologists, our anesthesiologists, infectious disease present. And clearly there is, you know, it's not always clear even when you have a neuro radiologist looking at the MRIs and a neurosurgeon and sometimes they look at things differently. In terms of imaging I know our radiologists really like some of the T1 fat suppression images. I think that that's helped in delineating some of the processes a little bit better. But I think that that's - I think the axial views also. But I don't really have much more to add about that. I think it's difficult and I share your I guess I share your concern and agony.

(James Mulnar):
Yes. That's a good word for it. Just two follow-up questions, in terms of people when they're not clinically improving are there - I mean some of the patients we've been struggling to maintain their voriconazole levels above one and if not two simply because they're obviously some rapid metabolizers. Has anybody gotten more aggressive in their dose titration?

Dr. Anu Malani:

We - so I - that's funny, you know, because we have troughs all over the place. We have troughs less than one and up to 16.

(James Mulnar):

Wow.

Dr. Anu Malani:

And clearly, you know, the toxicity of voriconazole is real. I mean, you know, it's all over the place from people hallucinating to photopsia to QT prolongation to people just kind of generally not feeling well to LFT abnormalities. And we've had I'd say just offhand if, you know, most people we start off at 6 mgs per kg twice-daily. And pending levels we'll back down a little bit, you know, shooting for troughs probably, you know, three to five-ish. But there have been a couple hypermetabolizers. And I can tell you in one patient we actually tried using Omeprazole, you know, which is a CYP219 inhibitor.

(James Mulnar):

Yes right.

Dr. Anu Malani:

We tried using Omeprazole twice daily, actually seemed to bump up her levels. And her, you know, she's almost on 10 mgs per kg twice daily.

(James Mulnar):

Wow.

Dr. Anu Malani:

And we really had low levels and we really needed to get it in her. She had arachnoiditis and...

(James Mulnar):

I - and that's what I was trying to do. Both my cases are arachnoiditis and wanting to make sure we keep as good of a level up.

Dr. Anu Malani:

Yes and I think it's the fine balance between toxicity and achieving a level that, you know, seems to be okay for them and making sure that they don't develop a hepatotoxicity with the increased dosing.

(James Mulnar):

Yes.

Dr. Anu Malani:

I think that that area becomes especially important as people, you know, eventually leave the hospital and probably are not going to be on AmBisome treatment.

(James Mulnar):

Well my other question is about people that are falling on the cracks. I have a couple of patients who had exposure. MRIs have shown some minimal uptake on enhancement like not in a particular area but like the dural line. And but those have been stable and unchanged now since their injection back in late September 14 on two separate MRIs separated by three or four weeks and two LPs also negative for any pleocytosis although they do have a slightly increased protein normal at our institution being about 50 and they're about 75 or 80-ish of which the majority of that is albumin when I had it broken down reflecting serum uptake. And I didn't know if anybody else has had any reports of this because I'm suspicious that they had something but I'm not able to show that they have anything at all?

Dr. Anu Malani:

Are they symptomatic?

(James Mulnar):

Only in terms of their usual symptoms. And again most of these people have fairly significant stenosis complaints. And they will have waxing and waning sort of complaints. They'll have a little numbness here when they sleep wrong. It's like while you've got bad stenosis at C 5-6 but neurologically they're unchanged. They have no headaches, no sign of a meningeal pattern. And they've been this way since 9/14.

Dr. Anu Malani:

And your MRIs are they a month apart or how far apart?

(James Mulnar):

About a month apart, three or four weeks apart as are the LPs.

Dr. Anu Malani:

Yes.

(James Mulnar):

I've been basically doing seeing her every other week and repeating the studies basically every other week after that. So...

Dr. Anu Malani:

Yes.

(James Mulnar):

...we're at what, 70 some days now?

Dr. Anu Malani:

Yes I suspect that that what you're describing is an area that we're all facing right now is these people with these subtle MRI changes, are they real, are they not real, what to do about them? And I don't know but at least from our experience thus far and I don't know if it's clear yet I mean we have patients like you're describing that we're following...

(James Mulnar):

Okay.

Dr. Anu Malani:

...off of therapy repeating MRIs.

(James Mulnar):

Okay.

Dr. Anu Malani:

I can also tell you anecdotally that we've also had people, folks that have had very subtle changes, subtle changes and not even really clear why they got an MRI. But they got an MRI and they happen to get admitted and they happen to undergo surgery and then they've actually had infection present. I think it's an area just it's not well defined. I think we'll probably learn more in the coming weeks as we continue to repeat MRIs and see if some people are progressing. But I think in that patient if they seem to be doing well and you have stable MRIs but seems reasonable to me that I would maybe watch them clinically and again have a low threshold for performing imaging. It's, you know, it seems at least in the ones that developed infection they often seem to have progressed a little bit. And if you have two stable MRIs that are a month apart and they're clinically doing okay I, you know, I think maybe you watch them and see. It sounds like you know you probably have to repeat an MRI at some point in time again.

(James Mulnar):

Yes.

Dr. Anu Malani:

And I think that's the difficult part because, you know, even if you MRI these folks right now is, you know, when can you say you're out of the woods? And I don't think we have those answers yet.

(James Mulnar):

All right, thank you.

Coordinator:

Thank you. Our next question comes from Dr. (Kedobi).

Dr. (Kedobi):

I was just wondered if there there's been any legal actions against physicians that you know of?

Dr. John Jernigan:

I can't comment on that. I'm - not information that I'm privy to so sorry.

Coordinator:

Thank you. Once again if you would like to ask a question please press Star 1.

Leticia Davila:

Operator excuse me, how many do we have in the queue?

Coordinator:

I have - just have - I just have one participant left in the queue.

Leticia Davila:

Okay. We'll go ahead and take that one question.

Coordinator:

All right thank you. Have not recorded your name. If you would like to ask a question your line's open. Please go ahead. Pick up your handset or check your mute button. I'll clear their question now. Did you want to take any more questions at this time? I have three that just queued up?

Dr. John Jernigan:
Sure that's okay. Go ahead.

Coordinator:
Thank you. One moment please. (Robin) go ahead please.

(Robin):
Thank you, hello. Just want to clarify that all of the cases that are being reported up to this point are indeed those that have received one of the three lots of the methylprednisolone acetate, even the newer ones that are showing up with the osteomyelitis and the epidural abscesses?

Dr. John Jernigan:
Yes that's correct.

(Robin):
Okay. And my second question follow-up is is there any information available on the new reports from the betamethasone or the triamcinolone from that same company?

Dr. John Jernigan:
So as I mentioned FDA posted on their Web site the results of testing of that they performed in the FDA lab. And I think that's what you getting at and mentioning that there was fungal growth with identification pending in betamethasone and in triamcinolone two different lots. CDC has received the isolates and is looking at those. And I don't have any more information right now but as soon as we do we will - we'll get that out to all of you.

(Robin):
Okay. And just really quickly the triamcinolone that's been listed on the FDA Web site do you know if it's preservative free or with preservative?

((Crosstalk))

Dr. Melissa Schaefer:
I only know what is posted on the Web site and I don't know that it's indicated. Let me see here. Yes I don't see that specifically in here so I'm not certain about that.

(Robin):

Okay, all right. Thank you for your help.

Dr. Melissa Schaefer:

Yes.

Coordinator:

Thank you. Next question, (Camille Jones).

(Camille Jones):

Hi. I was just wondering is there any sort of financial assistance available for the cases from any of the manufacturers for before the monitoring surveillance?

Dr. John Jernigan:

I am not aware of such. Anu have you heard of anything like that?

Dr. Anu Malani:

Say that again I'm sorry?

Dr. John Jernigan:

Financial - the question is financial assistance for patients with regard to treatment or monitoring et cetera?

Dr. Anu Malani:

I know Pfizer, one of the manufacturers of voriconazole they have a I think it's called an RSVP program. So it's a compassionate use program. And I know that we've - and I believe we've had at least some patients get assistance with voriconazole through that mechanism. I don't know of anything else.

(Camille Jones):

Okay.

Coordinator:

Thank you. (Sue Eastland)?

(Sue Eastland):

Yes hi. Thank you. Earlier in the call it sounded like the emphasis for the diagnostic treatment guidance was for those patients who were known to have received one of those three tainted lots of

methylprednisolone acetate. But based on the conversation that we just had with (Robin)'s question should we follow that same guidance if we have a patient present that did receive a NECC product after 5-21?

Dr. John Jernigan:

Well I would say that our guidance is focused right now exclusively on those that have received one of the three contaminated products. We know that there's - we can't consider other products from NECC to be safe and that physicians should always be vigilant that there might be, you know, that their patient could have something going on. I will say that CDC has not confirmed, does not have laboratory confirmation of any fungal or other infection caused by other NECC products other than the three implicated lots.
So our guidance is geared toward those who are exposed to one of those three lots. But, you know, there should be some level of vigilance as always in patients that there could be some complication for an injection. But I don't think the guidance would be exactly the same.

(Sue Eastland):

Well if we were in a state and we had a patient who had an epidural abscess that was from - and had received a related NECC product, not one of the three implicated lots, and we provided that information to the state how would we know if that had been forward onto the CDC? Because this was early in the scheme of things before these other epidural abscess cases cropped up. It was just something that our physicians were in tuned to and on top of and said oh by the way we did have an epidural abscess patient. And that patient did receive next (triamcinilone). But it was like I said it was early when all of this was going on.

Dr. Melissa Schaefer:

So I think you can follow-up with...

((Crosstalk)

(Sue Eastland):

And we did report it to...

Dr. Melissa Schaefer:

Okay.

(Sue Eastland):

...our State Department of Public Health. And at that point then they don't let us know whether they pass that on to the CDC or not.

Dr. John Jernigan:

You can follow-up with them and find out if that was the case and...

(Sue Eastland):

Okay.

Dr. Melissa Schaefer:

And then we'd also...

Dr. John Jernigan:

Yes.

Dr. Melissa Schaefer:

...encourage you to report any potential adverse events that you think are linked to a product from NECC to FDA and MedWatch. They are also, you know, collecting this information, tracking it, looking for signals or, you know, associated with products from NECC. So it's also important that they're getting, you know, any information about these reports.

(Sue Eastland):

We did. We did report it to the FDA concurrently.

Dr. Melissa Schaefer:

And what state are you from?

(Sue Eastland):

Alabama.

Dr. Melissa Schaefer:

Alabama, okay.

Dr. John Jernigan:

I think it's also important to keep in mind -- and I'm not saying this is the case in your particular patient -- but, you know, there is a background rate of complications associated with epidural injections that extend beyond, you know, this particular outbreak. I mean...

(Sue Eastland):
Right. And the gram-positive bacteria that grew with - I mean we worked it up and submitted it because of fell into the reportable definitions that...

Dr. John Jernigan:
Right.

(Sue Eastland):
...we were not concerned about it being NECC related. As this has gone on however, you know, we certainly I guess at our facility have a heightened sensitivity to it. And that's why I was wondering if the guidance regarding the MRIs et cetera was expanded to those other NECC products. But I understand your point that currently it is not, that's not the focus.

Dr. John Jernigan:
Next question?

Coordinator:
Thank you. Ms. (Wagner)?

(Wagner):
Yes. We have a group of patients that were wondering about future procedures, elective surgeries -- those type of things -- for both the patients having received contaminated injections. And I'm speaking of elective surgery outside of the spine area or other procedures. And then also the group of patients who have received other NECC meds, what is - what are the thoughts about doing procedures, elective surgeries or implants or other spine injections on those who received NECC meds which have no - not so far been linked to contamination or infection?

Dr. John Jernigan:
So as I mentioned before we - we're not aware of any laboratory confirmed infections caused by other NECC products. So we don't have any recommendation on that specifically. With regard to patients who were exposed these are patients who were exposed but not known to have an infection?

(Wagner):
Yes.

Dr. John Jernigan:

I think - I don't think we have any formal recommendation on that. Just to my own clinical opinion if the patient's not manifesting any evidence of infection and if in fact the procedure has nothing to do with that particular body site I don't see any major, you know, contraindication to proceeding. I think again at the end it's going to be a decision between the clinician performing the procedure and the patient discussing risk benefits. I think again this is pure supposition on my part but in a patient who's been exposed but has not manifested any evidence of infection and who is not going to have any procedure having to do with the site of injection the risk has got to be pretty low.

(Wagner):

Thank you. Would you think there'd be increased risk with an implant surgery like when they're placing any implants like a knee replacement?

Dr. John Jernigan:

I have no way of quantifying that risk. If, you know, I think in an abundance of caution if they could put it off for some period of time that might not be a bad idea. I don't know Anu do you have any thoughts on this issue?

Dr. Anu Malani:

Yes I mean I think we as an institution really - and again I mean for right or wrong I point that out we have tried to hold off on elective surgeries. Again as we've kind of mentioned on this call I don't know when you can effectively say the folks that received ESI injections are out the woods. And one thing to keep in mind is if they do develop an infection and say they undergo some sort of procedure or are going to get a procedure, I mean, you know, there are some risks of drug interactions and drug toxicity and antifungal's are not easy to take. So I guess if - I mean I would agree that the risk is probably low. But just to have a blanket policy I mean our policy is going to be let's hold off until we can really kind of - again elective procedures until we can effectively say that, you know, okay we think people are probably not going to develop infection. The same thing I think it was mentioned before I think the first respondent had mentioned about repeat epidural steroid injections. I would kind of say the same thing about those in almost the same class again for right or wrong is that, you know, we are trying to hold off on those types of procedures for this cohort of patients.

Coordinator:

Thank you. Your next question (Susan).

(Susan):

Yes I was going to ask about the betamethasone that was reported on the FDA's Web page? You commented briefly that you were waiting for additional information. Do you have anything else that you could add or if you could repeat what you mentioned earlier?

Dr. Melissa Schaefer:

Yes I don't have any additional information at this point. You know, on the FDA Web site as I mentioned they have a table listing, you know, what products they've tested and found to be contaminated. And as I mentioned, you know, they posted it for betamethasone and (triamcinolone), two different lots that they detected fungal growth and identification was pending. You know, I don't have any additional information at this time but certainly when we do, you know, we'll make sure that you all have it as well.

(Susan):

So have there been any reports of illness associated...

Dr. Melissa Schaefer:

You know, is Dr. Jernigan mentioned we don't have any laboratory confirmed reports of infections associated, you know, with these other products. And, you know, we'll - we've been looking and as I mentioned FDA is certainly collecting, you know, MedWatch reports and again encourage all of you if you, you know, have any adverse events that you believe to be associated with any medication but certainly any of these products from NECC to be reporting that to FDA so that we're getting them in a systematic way and can look for any signals associated with a particular medication. Obviously again as Dr. Jernigan, you know, reiterated earlier you know, the sterility of any of these products is not - we don't think that they're necessarily sterile which is why they've been recalled and why, you know, FDA made the recommendation that patients be notified, you know, a certain subset of patients be notified. So, you know, these findings are not necessarily surprising or unexpected of as far as contamination in these products.

(Susan):

So should patients follow the same type of protocol then to proceed with caution in terms of elective procedures and surgeries?

Dr. Melissa Schaefer:

So I think that was the question that was just asked.

(Susan):

Right.

Dr. Melissa Schaefer:
And I think...

Dr. John Jernigan:
Well I mean I think our - the guidance we're talking about, the guidance on our Web pertains to patients who have been exposed to one of the three implicated, one of three contaminated lots of MPA associated with NECC. So, you know, we just we don't know the risk associated with other products. As we've said there's no - there's been no laboratory confirmed evidence that these other products have caused infection. So this, we have no recommendations on them for those patients. Again I think, you know, clinicians for any patient even outside of this outbreak, you know, need to be vigilant for what's going on with their patients. And if there's something going on clinically that suggests that they might have an infection at a site where one of these products was used they need to investigate it. And if there's something that suggests that there's an infection that related to a contamination event they should report it to the FDA. And if there's a pattern, you know, that emerges certainly we'll be looking for those things so...

(Susan):
Thank you.

Leticia Davila:
Operator we have time for one more question.

Coordinator:
Thank you. Our last question comes from (Christine Segera).

(Christine Segera):
Yes hello. I'm one of the patient care supervisors or assistant managers of Southdale Emergency Room in Edina, Minnesota. We've gotten at least 100 patients come in that we've - I - my responsibility as part of the ED is to log into report to our infection control and our infection department. And I have been getting recently some repeat patients coming in. Most of the time, you know, they tell us that they've been exposed. And the question I've been getting is one patient I had last week actually had been tested at another facility in the Minneapolis area two weeks ago had a negative tap. But then she came back in with abdominal pain and other symptoms not related. I did put her on the board and I did log that you have that reported just to send it in. But are we still tracking patients who did say they got the contaminated even if they have symptoms that may not be related to this? Is this information you still want to receive?

Dr. John Jernigan:

I think that basically the follow-up of those patients who have been exposed but have shown no evidence of infection related to their injection the follow-up is primarily between the patient and their clinician. And we think that the clinicians, their physician should follow them closely and, you know, be vigilant for signs or symptoms that could be related to an injection related infection. Obviously people are going to have other things that go wrong. In this case, you know, the abdominal pain. You know, sounds like it's probably unrelated but that's an clinical judgment that the physician's going to have to make whether they need to be evaluated for either meningitis or an infection at the localized site of the injection. So I think just to summarize for those patients again who've been exposed but have shown no evidence of infection to date the follow-up should be primarily between, you know, the physician and the patient. And they should both be informed of what signs and symptoms of infection might be and be vigilant for those. And should those particular symptoms develop then they should be investigated accordingly.

(Christine Segera):

So do you want us to still send in the information if they come in and it's a symptom that's not related to their previous injection?

Dr. Melissa Schaefer:

So are you asking about reporting to your health department? Because CDC hasn't been getting reports of, you know, patients who don't meet the clinical case definition per se. So I think your question is I don't know if your hospital is keeping the - is in close contact with the health department and they're the ones who you're sharing this information with? If so they'd be the one to direct that question to.

(Christine Segera):

Yes they're the ones. We send it to the health department and they forward the information to you.
But I have - physicians have been asking me that question, because they've been exposed in the past if they have new symptoms is this something we're still supposed to be tracking? And I wasn't sure on that answer if it was not related to injection but because there were possibly other medications involved that's what the physicians are questioning.

Dr. Melissa Schaefer:

So I think, you know, what CDC is collecting reporting are those the meet the clinical case definition come to us from the state health department. I think I'd follow-up with your health department on how they want you to report or track these other potentially exposed patients who have not yet converted over to meet a case definition.

(Christine Segera):
Okay thank you.

Dr. Melissa Schaefer:
Yes.

Leticia Davila:
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. Jernigan and Dr. Malani. 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 November 27 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 address is coca@cdc.gov.

The recording of this call and the transcript will be posted to the COCA Web site at emergency.cdc.gov/coca within the next few days. There are no continuing educations for this call. Meningitis resources for clinicians are available on our COCA page. Go to emergency.cdc.gov/coca, Click COCA calls and follow the links for the meningitis call.

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Coordinator:
This concludes today's conference call. Thank you for joining. All parties may disconnect at this time.

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