

Good afternoon. I'm Commander Ibad Khan, and I'm representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Risk Communication Branch at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA call; Interim Recommendations for Diagnosing and Managing Suspected Fungal Meningitis Associated with Epidural Anesthesia Administered in Matamoros, Mexico. All participants joining us today are in listen only mode. Continuing edition is not offered for this activity.

After the presentations, there will be a Q and A session. You may submit questions at any time during today's presentations. To ask a question using Zoom, click the Q and A button at the bottom of your screen then type your question in the Q and A box. Please note that we often receive many more questions than we can answer during our webinars. If you're a patient, please refer your questions to your healthcare provider.

If you're a member of the media, please contact CDC Media Relations at 404-639-3286, or send an email to media@cdc.gov. I would now like to welcome our presenters for today's COCA call. We're pleased to have with us Dr. Tom Chiller, the chief of the Mycotic Diseases Branch in the Division of Foodborne, Waterborne, and Environmental Disease in the National Center for Emerging and Zoonotic Infectious Diseases at the Centers for Disease Control and Prevention.

Lieutenant Dallas Smith, an epidemiologist in the Mycotic Diseases Branch in the Division of Foodborne, Waterborne, and Environmental Disease in the National Center for Emerging and Zoonotic Infectious Diseases at CDC. And our final presenter will be Dr. Luis Ostrosky, professor and chief of the Division of Infectious Diseases at McGovern Medical School at the University of Texas Health Center in Houston, and the chief epidemiology officer at Memorial Hermann Healthcare System. It is now my pleasure to turn it over to Dr. Tom Chiller.

Dr. Chiller, please proceed.

Thank you very much, Ibad, and it's a pleasure to be with all of you. I see our numbers are approaching 900 and oh, they just went over. It's definitely a pleasure to be here on a COCA call and really to engage you all in this current ongoing and developing situation that we're having with fungal meningitis associated with epidural anesthesia. I'd like to give a little context and just you know, present a little bit of information about some of the previous experience that we've had with fungal meningitis and some of you may recall it over a decade ago now, we had the largest outbreak ever recorded from a nosocomial source that indeed was a fungal meningitis due to spinal steroid injections for the most part, in people receiving those injections for back pain and other conditions. Our clinician, Luis, also worked on that outbreak with us to rapidly develop clinical guidance and help for clinicians and other healthcare providers that was a fungus called *Exserohilum* predominantly, and you know, that was a completely new fungus for us to deal with in the CNS and so I think we learned a lot during that process.

Patients did well once we got them identified and got them evaluated with a lumbar puncture to understand whether they had meningitis and successful treatment was really indicated by the rapidity in which we were able to diagnose them. Next slide. So fast forward now 10 years and last year, in November, we heard about an outbreak of fungal meningitis where possibly 1,400 patients plus were exposed to contaminated epidural anesthesia and in this case, our colleagues in Mexico were able to identify ultimately around 80 patients with meningitis. But 39 of those died, so a case fatality rate of almost 50 percent. *Fusarium solani*, a fungus, was isolated from several patients and one patient actually also had *Alternaria* isolated from their CSF.

Ultimately Mexico determined that the most likely culprit was poor IPC practices from anesthesiologists that may have been the cause and in this context, we were then made aware of two cases in Texas of unknown meningitis and that is what sparked the current situation and investigation that we're in now. So I'm going to turn it over to my colleague, Dallas Smith, to walk you through the current situation and then of course to Luis to tell us more about managing these patients and the challenges that we have with them. Over to you, Dallas.

Thank you so much, Tom. Next slide, please. So I just want to take you through an outline or a timeline of this current fungal meningitis outbreak. So on May 8, through the Emerging Infections Network, CDC learned of two unusual meningitis cases that were recorded by an astute clinician in Texas with prior epidural anesthesia. The Emerging Infections Network is a list serve of ID physicians who are able to use this platform to talk about cases they're seeing and ask for any advice.

Over the next few days we worked with our colleagues in Texas and learned of several additional cases of suspected meningitis. Throughout this time, we've also had, before May 13, we also learned of positive [inaudible] which we will talk about later and that's what made us suspect fungal meningitis. We worked with our colleagues in Mexico on May 13, and closed down two clinics that were implicated in this fungal meningitis outbreak. Over the next several days, we worked with other colleagues at CDC, including DDMQ and a level, and on May 16, a Level 2 travel health notice was published. And this Level 2 travel health notice cautioned or advised any patients in the U.

S. to cancel all elective procedures in Matamoros, Mexico. In order to raise awareness among clinicians, public health professionals, and the public, on May 17, a HAN Health Advisory was published. On May 20, our colleagues in Mexico was able to get a list of all patients, U. S.

citizens, who were exposed at these two clinics in Mexico. We were able to turn those lists around the same day on May 20 and send out state specific reports so that states know call these patients and inform them of their exposure and get them in to treatment and evaluation. On May 26, in order to provide more education to clinicians caring for patients with fungal meningitis, CDC worked with the Mycoses Study Group, which is a group of ID physicians and people interested in fungal diseases and who are considered experts in their field. And we worked with this group to help organize a webinar focusing on diagnostic and treatment recommendations for this fungal meningitis outbreak. On May 28, UCSF, which is a university in California, identified *Fusarium solani* species complex in a CSF specimen through metagenomics.

A few days later, on May 31, CDC's Mycotic Diseases Lab and the University of Washington also identified *Fusarium solani* species complex in CSF through a pan-fungal PCR test. And finally, this past weekend, on June 3, we received a list of patients from a U. S. based patient coordinator of one of the clinics, Clinica K-3, and on this list we identified six additional patients that were not included on the original list. And more importantly, we received updated contact information for patients who were on the first list but we weren't able to get ahold of.

Next slide, please. CDC worked together with our colleagues in Mexico to submit a public health emergency of international concern. We were able to, on May 19, we were able to complete the international components by working with our colleagues in Mexico as patients on these original list that Mexico sent over had patients from Mexico, the U. S. , Canada, and Columbia.

On May 28, I'm sorry, May 20, a risk assessment was completed by CDC through the Public Health Emergency of International Concern Assessment Team. Finally, on May 21, the actual public health

emergency of a national concern was submitted to the World Health Organization and is still under their consideration. Next slide, please. I want to briefly go over the case definitions we are using in this outbreak, and so we have four different case definitions and all of them are in patients who received a procedure with epidural anesthesia in Matamoros, Mexico since January 1, 2023. Our first case definition is a person under investigation, and these are individuals who have not had a lumbar puncture done yet, and have, and the symptoms are unknown or have no symptoms.

A suspected case are those patients with symptoms suggesting CNS infection. So symptoms such as fever, headache, stiff neck, nausea, photophobia, or altered mental states. However, their LP, or their lumbar puncture results are not yet available. A probable case are patients with an abnormal lumbar puncture and we're defining this by, with a CSF profile with greater than 5 white blood cell counts. And we also account for the presence of red blood cells.

However, probable cases have not had fungus identified or detected from the CSF or tissue. Finally, a confirmed case is an individual who has had fungus detected from CSF or tissue, either via culture, PCR, or metagenomics. Next slide, please. And as of June 7, here are our current case counts. We have 184 people who are under investigation.

We have 13 suspect cases. Ten probable cases. Four confirmed cases, and unfortunately, we are up to three deaths currently. Out of these three deaths, we've had one probable case and two confirmed cases. We've also been able to rule out 19 cases, mostly, most of these patients were ruled out because they did not have the exposure criteria, so they'd never had an epidural.

Next slide, please. With want to go over just demographic characteristics of those who are exposed in the United States, or I'm sorry, of U. S. residence. And so when we look by clinic, the two clinics that are implicated in this outbreak, there is about a 50/50 split, so 117 are from Clinica K-3 and 94 are from Riverside Surgical Center.

When we look at the breakdown by sex, we see the majority of them are female, however, some of-- we at least have one probable case that is male currently. And as you can see, there's at least 18 people, 18 males, who had procedures done during our exposure period. When we look at the age, we see that the mean age was 34, however this range from 14-69 years old. Next slide, please. Although the majority of the cases are in Texas, we do see that there's a wide distribution across the United States, and so we've been working and engaging our state and local health departments to be able to provide care for these patients, provide information to clinicians, and to notify patients to get them in for evaluation.

Next slide, please. When we look at a breakdown of race/ethnicity, we do see that fungal meningitis has been diagnosed most frequently in Hispanic and Latino patients. Next slide, please. We also put together an epidemiological timeline with the procedure dates of those patients who have suspected, probable, and confirmed cases. And as you can see, this is a pretty large timeline, ranging from January 17 to April 28.

Next slide, please. When we look at the clinical summary of the patients that we have been able to interview, we see that for the symptom on-- the symptom frequency of symptoms that patients initially present with, we see that headache is the most common with 12 patients, however, a variety of other sometimes are also common. We see stiff neck, we see nausea, fever, vomiting, and other symptoms that we've listed here. What was really interesting is that we did some analysis to look at days from the procedure in Mexico to symptom onset. We saw that the average time period was 19 days, however, this

ranged from 2 days all the way to 32 days, and so we can see that the incubation period can be at least a month if not longer.

We also looked at days from the procedure in Mexico to hospitalization and we see that the average was 56 days, however this also ranged from 14 days to over 100 days. And we just wanted to re-emphasize and show this data because we want to get patients in early to get evaluated but as you can see from this data, we see that there are delays in diagnosis, there are delays from seeking care, and so we want to use this data to get patients in early, even if they are asymptomatic, which my colleague, Luis, will go into, even asymptomatic should be evaluated for fungal meningitis if they've had our exposure criteria. Next slide, please. And so I also want to provide a brief breakdown of laboratory summary of those cases that we have information on. And so when we look at the lumbar puncture results, we see that the average glucose was 32, we see that the white blood cell count average was 757, however, this ranged from 24 to over 1700.

Unfortunately, to date, all CSF, so cerebral spinal fluid, and blood cultures have been negative. However, as I mentioned in the beginning of the presentation, we have had six CSF beta-d-glucan results have been positive, highly positive. And beta-d-glucan is a component of a fungal cell wall and so although this does not point out the exact fungi, this does give us an indication that the meningitis is fungal ideology. We've also had two blood beta-d-glucans be positive as well. As I mentioned before, we have had success in a pan-fungal PCR test, as of today, we've had the pan-fungal PCR tests that have identified *Fusarium solani* species complex.

And as I mentioned before, this has been done at the CDC's Mycotic Diseases Branch's lab and at the University of Washington. UCSF, as I mentioned in the timeline, identified *Fusarium solani* species complex through metagenomics, also, our colleagues in Mexico have identified six patients that have tested positive for *Fusarium solani* from CSF by PCR. Next slide, please. We have a variety of resources that we would like to share with those attending the call today. And what I really want to highlight here is that we have a fungal meningitis outbreak webpage.

This webpage is in English and Spanish, it's updated weekly with our current case counts, and any emerging information that we have. I also wanted to highlight that we released an updated HAN last week and this updated HAN, which I've identified as HAN number 2, describes important updates, which includes talking more about the multistate outbreak, talking about the importance of asymptomatic screening and testing for patients exposed. And so I wanted to point out this updated HAN. I also want to point out that we have worked with our colleagues at the Mycoses Study Group to develop interim recommendations for clinicians who are caring for patients with fungal meningitis. And these interim recommendations are updates quite frequently.

The link does not change, but we are updating and expanding these recommendations based on a variety of factors, including outpatient care. Next slide, please. And I will turn it over to our good colleague and honorary MDB, of the Mycotic Diseases Branches member, Luis.

Thank you very much, Dr. Smith. My name is Luis Ostrosky-Zeichner, and I'm a professor of medicine and epidemiology at the University of Texas Health Science Center at Houston. I also do epidemiology for Memorial Hermann Healthcare System. And I'm the current president of the Mycoses Study Group.

It is my pleasure to represent our colleagues and on behalf of the writing group and MSG, I am going to go over the interim recommendations for diagnosis and management of this disease. Next slide, please. These are my disclosures, I do research and consult and occasionally speak for multiple companies that

develop antifungals and diagnostics. Next slide, please. And I want to walk you through the interim guidance process.

This started as a multidisciplinary group that first convened on the evening of May 19, 2023. And we wanted to make sure that several groups were represented to have a truly multidisciplinary sort of set of recommendations. So, represented disciplines were epidemiology, public health, with the local health authorities, pharmacy, medical mycology, and we had the fortune to have a neurologist with us. We do, from our experience, from the recent outbreaks that Dr. Chiller mentioned, and unfortunately in mycology we do have to rely a lot on expert opinions because there's no randomized trials on *Fusarium* or *Exerohilum meningitis*, but we have been fortunate enough to be able to serve the community and help with the management of these outbreaks.

The end product is hosted in our website and again, we aim for this to be a living document and to update it as information becomes available. Next slide, please. So I'm going to first walk you through some of the experience we were able to gather from the recent outbreaks. Next slide, please. And I'm going to start with the *Exerohilum* outbreak, as Dr.

Chiller mentioned, this is the largest systemic fungal meningitis outbreak documented in the world probably, 2012, like Dr. Chiller was mentioning, [inaudible]. And this was an outbreak of meningitis, spinal or para-spinal infections and peripheral joint infections related to the injection of contaminated dexamethasone in patients that were undergoing mainly pain management procedures and the culprit ended up being this mold, called *exerohilum*. As you can see here, we have this really, really large peak but we continue to have many cases over several months, primarily in the Michigan area, but this really ended up being an international outbreak. And we ended up with more than 700 patients.

Next slide, please. And as you can see here in this 749 cases, we ended up with a real attack rate of 5 percent over 13,000 people exposed. And the presentations were very different when people were getting spinal blocks as opposed to peripheral joint injections. Meningitis and stroke tended to present within the first 30 days. We saw local paraspinal infections presenting a little bit later with a median of about 60 days, and the peripheral joint infections were also presenting a little bit later, about 60 days.

So again, there is a very broad range for incubation period for these infections but what we did notice is that the most severe ones do tend to present earlier. Next slide, please. And then going to the Durango outbreak, this was again an outbreak that was first reported in November 2022, when physicians in the state of Durango, started to notice cases of meningitis, what they saw as atypical meningitis, in women after childbirth and when public health authorities investigated they noticed that all of these women were getting epidurals for their childbirth. And eventually they were able to track down 1,800 exposed, primarily women, out of which they diagnosed 80 cases, documented 39 deaths. And again, as Dr.

Chiller mentioned, 31 of these cases tested positive for *Fusarium* by sort of ad hoc developed PCR for this particular outbreak. As you can see here from the Mexican Public Health website, the majority of these patients were presenting between Day 0-7 with a few stragglers for a month out. And a quarter of these patients were presenting more than 20 days out. So again, a broad incubation range for these diseases and as in our current outbreak, their most frequent presentation was headache, 94 percent of the patients, and about a third of them presented with nausea, [inaudible] rigidity, and vomiting. So again, we were able to assist the local health authorities in Durango in managing these patients.

We had many, many basically Zooms where we were co-managing some of those patients and were really impressed by the high frequency of neurovascular complications that were being reported. A lot of

strokes, a lot of vasculitis, intracranial hypertension, and we drew from the experience with this outbreak to create some of the guidance that we're going to be presenting today. Next slide, please. So going to the interim guidance or recommendations. Next slide, please.

Two very important tenets that we emphasize is that this is a disease that does require infectious disease and neurology consultation. And we do understand that some of these cases are happening in rural areas or areas where you don't necessarily have access to an ID or neurology specialist, and this is when we think that consulting with the Health Department can help people liaise and find resources for clinical consultation in these disciplines, and the other reason to consult with the Health Department is that we are collecting information on these cases and health departments are helping us do some very detailed case report forms where we learn about the CSF parameters, incubation periods, the specific exposures that they had within Mexico, so again, another important reason to liaise with your local health department. Next slide, please. As far as the diagnostic approach, we feel that both symptomatic and asymptomatic patient should have a very extensive workup, the reason why we are recommending to be aggressive with asymptomatic patients is because both in Durango and in general, in medical mycology, we found that early therapy or primitive therapy, goes a long way in avoiding complications. So what we're recommending for people that have the documented exposure, is starting with a lumbar puncture, documenting the opening pressure, doing the routine CSF testing, like color, cell count, protein, lactate, and glucose, and we do find that the cell counts, the protein, and the glucose are very useful in diagnosing the cases and in monitoring the response to therapy, so having a baseline CSF is very important.

Because we, everything's pointing to a fungal etiology but we then know that that's the only etiology at this point. We do recommend doing bacterial, mycobacterial, fungal stains and cultures. As Dr. Smith was mentioning, Fungitell, or beta-d-glucan, has been a very, very reliable marker for these patients. We find it elevated and people ask me what's the cutoff for the CSF, we don't have that information, but in general terms, we don't expect to see any beta-d-glucan in the CSF.

So any detectable beta-d-glucan should be a red flag for your patients. Again, we're also, because we're still trying to rule out other etiologies, we're recommending an Aspergillus galactomannan, which has been found to cross react occasionally with Fusarium. And we do recommend when you have access to this, to do molecular testing by multiplex PCR, these are the typical multiplex panels that many hospitals in the U. S. have that test for the most common etiologies of meningitis and we are asking our partners to send for a pan fungal PCR or metagenomic testing to the University of Washington or UCSF, where we've been able to detect some of these organisms.

In addition, we're asking people to reserve or store some CSF for future or additional testing as we gather more information from this outbreak. And it is very interesting to also mention that we have seen occasionally positive serum beta-d-glucan or Aspergillus galactomannan, again thinking that Aspergillus galactomannan may cross react with the culprit that we're suspecting. We suggest that all patients within a normal lumbar puncture, undergo a brain MRI with and without contrast to start looking for complications. I'm going to talk about the complications later on. And for patients who are also complaining of back pain, or any neurological deficit in the extremities, we also recommend a spinal MRI, although to date we have not seen many local complications at the site of the epidurals.

Next slide, please. So for asymptomatic patients with a normal LP, what we recommend is do not administer empirical antifungal therapy, in fact, we have found some patients with alternate explanations for minor symptoms, not really headaches but it's very important to really recommend that people with a normal LP should not be treated empirically and for those patients we do recommend very close

monitoring, perhaps even repeating the lumbar puncture in about two weeks, or sooner if the patient has any symptoms or has any symptoms that are progressing. Again, this is a population that you want to watch very, very closely, but we are not currently recommending empirical therapy. Next slide, please. For patients with an abnormal LP, by abnormal we really are very holistic, any elevation in white blood cells, any low glucose, high protein, we do recommend being aggressive and currently we are recommending two antifungals administered together; Liposomal amphotericin B, we are recommending 5 milligrams per kilo daily, with the ability to escalate to 7.

5 to 10 milligrams per kilo. And we want to remind clinicians that Liposomal amphotericin B is a nephrotoxic toxic agent and to minimize the nephrotoxicity, we recommend aggressive hydration and aggressive monitoring a replacement of electrolytes. We are currently recommending to avoid [inaudible] B, and [inaudible] B requires a skillset to administer it and has been associated with meningeal fibrosis and very, very acute headaches so we currently do not recommend using this strategy up front. And for the second agent, we're currently recommending Voriconazole, 6 milligram per kilo, every 2 hours for indication, followed by 4 milligram per kilo q12, we do recommend measuring weekly, Voriconazole levels with a target of 4-5 micrograms per ml. We do recommend starting IV to make sure that we're frontloading the patient but as the patient tolerates it, you may be able to transition to oral.

Voriconazole has relatively good bio availability and if the patient is tolerating the oral route, you can consider doing this pretty soon. Again, we recommend monitoring for liver toxicity, as well as hallucinations, which are one of the main toxicities of this drug and they're usually self-limited. Drug interactions are very important when you work with Voriconazole so always having a pharmacy partner look over the drug interactions is very useful. And for patients that do not tolerate or develop toxicity to Voriconazole, we're currently recommending either Posaconazole or isavuconazole. The suggested duration of treatment is a minimum of three months, but most patients will likely need more than that.

And we're working on criteria for when you can stop therapy, but in general terms, you want to make sure that your patient is improving clinically, there are no complications, [inaudible] to tolerate the meds, and we have some sort of improvement in imaging and laboratory parameters as well. Next slide, please. So as I was mentioning, close monitoring is going to be very important, after you stop therapy. Having a very low threshold for repeating a lumbar puncture to detect recurrences very early on. And in mycology we've learned that radiologic abnormalities may persist for months and do not necessarily signal failure but what you don't want to see is progression in the imaging lesions so, again, while you don't completely expect to have resolution of any imaging findings when you find them, no resolution does not signal failure, but progression is very important in assessing people that may need escalation of therapy.

The complications that we have been seeing in these cases are multiple. They are ranging from increasing intracranial pressure to vasculitis and brain edema, to the most extreme cases where we have seen strokes and intracranial hemorrhages, and those typically happen in sort of the base little areas of the brain, brain stem hemorrhages, which all of you know are incredibly bad prognosis. So again, we're trying to manage these complications with serial LPs oxygen mannitol, we're starting to think about lumbar drains and BP shunts, and the use of steroids has always been controversial in medical mycology. Our colleagues in Durango reported good experience using them at the right time. Not too early and not too late, but just when vasculitis was starting to be developed and if steroids are going to be used, we did see in Durango that if they were tapered too fast, people would have a recurrence in the inflammation.

So again, this is a controversial topic, but some patients, particularly those with vasculitis or a lot of edema and inflammation, may benefit from steroids with a slow taper. Next slide, please. I do want to acknowledge the writing group for this interim recommendations, we have representatives from CDC, Cameron County, and the Mycoses Study Group, and this is my last slide, and I'm going to turn it over back to our host. Thank you very much.

Presenters, thank you for providing this time and information to our audience. We will now go into our Q and A session. Please note that we will be joined by Dr. Jeremy Gold, from CDC's National Center for Emerging and Zoonotic Infectious Diseases during this Q and A session. For our audience, remember to ask a question using Zoom, click the Q and A button at the bottom of your screen, then type your question in and please note that we often receive more questions than we can answer during our webinars.

So, our first questions, our first question states; were you able to rule out any drug manufacturing or medical device manufacturing issues as a source, and if so, can you talk a little bit about that?

I can start, Dallas, on that one. You know, the infections occurred in Mexico as we stated here, so obviously the Mexican authorities, both the federal and state have been investigating this from the moment they found out about it, and we're working with them to support them. There are some, you know, there are some hypotheses or thoughts about sources, this is associated at least at this time with only epidural anesthesia, there are basically two types of things used in epidural anesthesia, one, the anesthetic, which is a product produced and quite widely distributed across Mexico, and then morphine as an additive. And then of course there are different anesthesiologists that practice in these clinics and do the procedures with a group of various surgeons. So, as I mentioned before in Durango, after the investigation there they were concerned about practices and infection prevention control, used during the epidural anesthesia and they didn't find or conclude that there was a contaminated medicine at that time.

But I think it's still unclear and they're still investigating that. So, they don't have a particular source and know whether or not there is a medicine contamination at a manufacturing type of facility versus an in-sit to contamination of medicine at the site of practice, so to speak, and obviously Mexican is in charge of that investigation and we are trying to support them however they need.

Thank you very much. Our next question asks; the data that you shared stated that the fungal meningitis was diagnosed in approximately 10 times more, or more than 10 times more women than men. Can you talk a little bit about that dynamic?

Yeah, I think it's a really great question and I think it goes back to those who are, a lot of the patients at these clinics were seeking cosmetic surgeries and so we did see that more females did present to these clinics in Mexico for cosmetic surgeries, but I don't, that doesn't mean that females are more at risk than males. I think it's, as I mentioned, we have at least one probable male case, we have multiple suspect male cases and so we, no one sex or gender is more at risk for fungal meningitis, it's those who sought care at these facilities for cosmetic surgeries, or cosmetic procedures.

Thank you very much. Another question about the data that was shared, the information listed mentioned the probable and confirmed deaths. And the question asked for the deaths, [inaudible] do you need to change that one probable case to confirmed as well?

Yeah, so in order to change a probable to a confirmed case, there needs to be some detection or edification of the fungi, which in this case has been *Fusarium solani* species complex in all of our

confirmed cases. And so a probable case would be with someone with an abnormal lumbar puncture but the fungus has not been identified. In order to transition to a confirmed case, the actual fungus would need to be identified or yeah, identified through either CSF or tissue.

Thank you very much. Next question is about the therapeutics, we have a question from clinicians at a clinic that share a personal case study of using IV [inaudible] and Voriconazole and having some relapse issues and they want to ask about the, any guidance you can share, any recommendation on intrathecal amphotericin B.

I'll take this question. So the management of these patients is very challenging, in general terms, we are seeing that people, at least initially improve with the dual therapy and then some of the people start presenting complications. Most of those complications are inflammatory so we recommend aggressive shunting, or management of their [inaudible] pressure, or maybe even the steroids in this situation. We are currently not recommending intrathecal amphotericin B for the reasons that I mentioned. There's an association of neurotoxicity with intrathecal ampho and not many people know how to do that as well.

So it's challenging to do it. So at this point, we do recommend for people that are not doing well, to maybe try pushing the doses and making sure where therapeutic and of course managing the mechanical and inflammatory complications.

And Luis, if I could just, you know, just add, I do see in the chat that this group specifically is from Arizona that's asking this question and as you and I know, both groups in Arizona and the Central Valley of California, have a little bit of experience with intrathecal ampho due to [inaudible] mycoses and meningitis and so some of them have experience and it looks like this group does have some experience using it. If I, I don't recall, Luis, that anyone went that route even in the fungal meningitis outbreak in 2012, but do you, I don't recall.

No, I don't recall ever having to go to that route in Michigan and Mexico, Durango did not use that either. Again, it's complex to use, I fully acknowledge our colleagues from Arizona who have perhaps the best experience using it, but I'm more concerned about mechanical and inflammatory complications, perhaps rather than a true antifungal failure in this case, yes.

Thank you very much. Our next question asks; can you share what would be the right time or the safe moment to be discharged from the hospital?

So that's a great question, this is a question we're talking about actively in our working group. We are very reluctant to put out a very specific guidance because there's going to be a variety of ways to discharge people in different settings, whether they're going to a long-term care facility or they're going home, or they're going to have access to care, whether they're funded to continue the therapy or not. But in general terms, I favor holistic approach, where people are resolving their clinical signs and symptoms, CSF parameters are improving, and maybe [inaudible] is stable or improving as well. And there's a good way to follow them, I think that would be the sort of sweet spot to discharge people.

Thank you very much. Our next question asks; have you observed or do you have any guidance for any long-term effects patients may suffer from fungal meningitis on recovery? And if so, can you please share some of that guidance.

So this is where Michigan comes into focus, we did see some patients from Michigan experiencing very long-term complications, primarily fibrosis of the affected areas for those with the lumbar infections,

intracranial hypertension, meningeal fibrosis as well, long-term headaches, so unfortunately some of these people do require very long-term management of symptoms and follow-up. In Durango it's too early to tell, but again, we are seeing some patients with ongoing mechanical problems and inflammatory problems.

Thank you. You addressed some of the concerns about basal stroke or intracranial hemorrhage, can you talk a little bit about the recommendations you might have for supportive care in those instances, please.

Yes, so this is where working with neurology is crucial. Our neurology colleagues have many, many, many things they do to maintain perfusion, to make sure we don't have basal spasm, and some of our groups have been using endovascular therapy to stent areas that are narrowing or to coil aneurysms that have been reported as well. So, again, any neurovascular complication is, in my opinion, a reason to escalate to a higher level of care where basically vascular neurologists are involved in the care of these patients.

Thank you very much. Based on what you and the other presenters have shared about the, there are still so many unknowns about this outbreak, can you talk a little bit about what your expectations are for how long we should see these cases emerging?

I can maybe jump in for this question. I don't know if we have a great answer yet, we know that fungal meningitis can have a very long incubation period, it can be weeks to months. Based on current epidemiological information, we, in the data that I showed earlier, we did see that from procedure to hospitalization, so this may be the first time that we were aware of this fungal meningitis in a patient, was almost 100 days, over 100 days. And so if we think about when the last patient could have been seen, which was May 13 when the clinics were closed, it could be 100 days out from there. While we do see that the incubation period, so that would be from procedure to symptom onset, is about 30 days.

And so we're kind of using that 30 days right now, but we don't want to rule anyone out. And so, we're still trying to gather data to better answer that question, but I hope that provides some context about what numbers we're kind of working with based on the available data, but I guess our main message that if a person had this exposure, even if it's a month or two out, and they're having symptoms of meningitis, they should have a very low threshold of getting a lumbar puncture done and going into emergency room.

Thank you very much, that actually answers multiple questions we've had about the duration of patients showing symptoms and some of the things that should happen there. Along the lines of the lumbar puncture, we have quite a few questions on that as well. So one question asks; should patients receiving therapy for suspected meningitis undergo repeat or serial lumbar punctures to assess improvements in their CSF parameters?

I think I'm going to take this one. We have found that in general terms, following the CSF parameters correlates with outcomes. So, we are recommending currently, repeating lumbar punctures and analyzing the CSF. We don't, we're very reluctant to give a specific time frame, but in mycology we like the two-week mark for other fungal meningitis and that would be probably a good point to repeat the lumbar puncture and make decisions about de-escalation from Liposomal amphotericin B and switching to oral Voriconazole and with the caveat that if the patient is not doing well, it can also be done sooner than the two weeks.

Thank you for that answer. You mentioned during the therapeutic section about the controversial use of steroid therapy, can you talk a little bit also about if any of the patients have been suffering from any immunocompromised conditions and what your recommendation would be there.

So far, the cases we're aware of are, tend to be healthy women, we have not seen reports of immunocompromised patients being affected. And we don't see a lot of immunosuppressants in the background for these patients. Again, steroid use, in my opinion, may benefit patients who are primarily experiencing mechanical or inflammatory complications.

Thank you very much. We also have a question about the patients in general. Can you talk a little bit about if they are residing in the United States and if they are not U. S. citizens, were they currently residing in the United States when they traveled to receive treatment?

So again, I can jump in for this one. So the patients that were included in our data are all U. S. citizens. But of course, they did travel to Matamoros, Mexico for these procedures.

The vast majority of patients are being treated and cared for in the United States, however, by working with our colleagues in Mexico, a few are being treated in Matamoros, Mexico right now. As I mentioned before, the initial list we got from Mexico did have patients from a few other countries, and those countries are following up with those patients that were their citizens. And those countries were Canada, Columbia, and then the U. S. and then Mexico.

Thank you very much. Our next question is about therapy again, and the question asks; can you talk about the criteria for amphotericin step down.

I'll chime in here. So again, we're trying to be very holistic and not have specific cut offs or specific time frames. Most of us are thinking that at about two weeks, we would repeat the lumbar puncture and imaging, and if the patient is improving from a clinical standpoint, CSF parameters are improving as well, imaging is stable or improving, that may be the right time point to deescalate the Liposomal amphotericin B, and move onto oral therapy with the Voriconazole.

Thank you very much. Can you talk about if there's any known link between the Durango and Matamoros cases.

Yeah, I can talk about that briefly. As of right now, the only clear similarity is that *Fusarium solani* complex was implicated in both of these outbreaks. We don't know whether or not these are related, we are working with our Mexican colleagues to, you know, to try our best to see if we can determine that by sequence analysis. Unfortunately in this cluster in Matamoros, we still do not have a culture positive, so we don't have an organism. They did have, I believe, two or three cultures positive from the Durango outbreak where those were sequenced and some of that information may be available but at the time, we don't have that information for this cluster.

Clearly that is something we would hope to be able to get and if so, to make some comparisons. This is a relatively new field in terms of *Fusarium solani*, as Luis and Dallas both mentioned, this is a rare organism, so there's not a big genomic databank of isolates. That being said, you know, we are really hopeful that fungal genomic epidemiology and comparison of genomic sequences can help look for sources and it certainly has been successful in previous situations. So we will be continuing to, you know, work with our Mexican colleagues to try to do this.

Thank you very much. Our next question asks; is treatment recommended for patients with mild symptoms, such as headache, when the lumbar puncture is normal but the patient did have an epidural at one of the implicated clinics?

I'll be happy to take this one. That is a very tricky situation. That's why the question is being asked. So we have found some patients that have the epidemiological exposure and have some very mild symptoms with a totally normal lumbar puncture. And in that setting, what I would recommend is focusing on finding other causes of the symptoms.

And at least in some cases, we have been able to identify [inaudible] or another infection happening that was accounting for the symptoms. So, again, we do not recommend empirical therapy with a normal LP, we would really focus on finding the cause of those sometimes and I do want to take that opportunity before we close to thank all the clinicians in the field like our colleagues at UTRGB, and in all the rural counties that are seeing these patients, because they're really sharing their experience and providing some of the clinical pictures that we're sharing today.

Thank you very much. We have time for one more question, and our question asks; do you have a recommendation for an alternative therapy if a patient does not tolerate Liposomal amphotericin or Voriconazole, or is the combination therapy the sole recommended course for the duration?

So, those are two agents that are known to have activate against the possible culprits that that we're thinking about in this case. And the other thing that [inaudible] and Voriconazole have in common is that they have very good CNS penetration and concentrations. So ideally, we should work through the toxicities and try to administer the combination of the two agents. In cases where Voriconazole is not tolerated, we do give the option of using the two other second generation [inaudible]. And as far as [inaudible] goes, it is the formulation that is associated with best CNS penetration so we feel that we can work around the toxicities and really try to get that medication in for the patients.

Great, thank you very much. Again, at this point I want to thank everyone for joining us today, with a special thanks to our presenters for sharing their time, expertise and for answering these questions. Today's COCA call will be available to view on demand a few hours after the live call, at emergency. cdc.gov/coca.

A transcript and video will be available on demand on the COCA calls webpage next week. We innovate you to join us for an upcoming COCA call next Thursday, June 15, from 2:00 pm to 3:00 pm Eastern time. the topic will be Evaluating and Supporting Patients with Long COVID in Returning to Work. You can visit emergency.cdc.gov/coca.

cdc.gov/coca for more details about this COCA call and other upcoming COCA calls. You may sign up to subscribe to receive announcements for future COCA calls by visiting emergency.cdc.gov/coca/subscribe.asp.

You will also receive other COCA products to help keep you informed about emerging and existing public health topics. Again, I want to thank you for joining us for today's COCA call and have a great day. .