

Update on the Multistate Outbreak of Fungal Meningitis and Other Infections

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Presenters: Anurag Malani, MD; Michael Kasotakis, MD

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Operator: Welcome and thank you standing by, at this time all participants will be in a listen-only mode. After the presentation we will conduct a question-answer session, at that time to ask a question dial star one on your touchtone phone. This conference is being recorded, if you have any objections you may disconnect at this time, I would now like to introduce your host, Mr. Tom Chiller, sir you may begin.

Tom Chiller: Thank you and good afternoon everyone and thanks for joining us on such short notice, today's CDC webinar is going to discuss some recent data in the ongoing fungal meningitis and other infections outbreak and what their implications are for the treatment and management of patients exposed to contaminated lots of steroid injections from the New England Compounding Center.

My name is Tom Chiller, I'm a medical epidemiologist and Deputy Branch Chief of the Mycotic Branch at the Centers for Disease Control and Prevention and I'll be providing a real brief overview of CDC's recent health alert network update which should be going out today. Following this overview we'll hear from our colleagues Doctors (Malani) and (Kasotakis) who are both physicians at St. Joseph's Mercy Medical Center in Ann Arbor, Michigan and have been dealing with many of the patients in this outbreak throughout the last several months.

They are going to present a series of cases that's going to high- that will highlight the current clinical presentations, diagnostic findings and treatment strategies for these infections. Once we've heard from our presenters we will open the line for a question-and-answer session. During the presentations please make sure your phone lines are on mute as - and we will take questions again after the presentations are complete.

So I now want to just briefly mention as I talk to you about the agenda today, we're going to look at an overview of the CDC update, we're going to then hear presentations of clinical case findings and strategies for treatment from (Anu Malani) and (Michael Kasotakis) from St. Joseph's Mercy and then we're going to have the Q&A session.

Just to highlight some of the new findings that we've been discussing and working on with states in this outbreak, there has been new data provided that has shown evidence that a substantial proportion of patients have developed localized or focal infections at the site of injection following exposure to the contaminated steroid injections that we've been talking about and that are associated with this outbreak.

The signs and symptoms of these spinal and paraspinal infections can be very subtle and difficult to distinguish from the patient's baseline chronic pain so we want clinicians to consider obtaining an MRI for patients with persistent but baseline symptoms. And it's important that this decision be made on a case-by-case basis after discussion between the clinician and patient and taking into account the patient's history regarding past and current systems.

This is a summary of the health advisory that's going to come out later today and we encourage you to go to our Web site listed here on this slide to get a more detailed overview of these recommendations. Now I would like to again

introduce Dr. Malani and Dr. Kasotakis who will tag team the following cases that will be presented to illustrate treatment and management issues, Anu.

(Anu Malani): Thanks Tom, at St. Joseph's Mercy Hospital, Ann Arbor we've seen well over 165 cases of fungal infections associated with the contaminated methylprednisolone injections. While the early cases primarily presented as meningitis for the last six to seven weeks we have primarily been seeing patients with paraspinal and epidural infections.

I want to highlight five cases that illustrate the various presentations we are now seeing, Case 1 will be a parameningeal infection, Case 2 will be related to an epidural abscess, Case 3 will be an epidural/paraspinal abscess with minimal symptoms, Case 4 will be vertebral osteomyelitis and discitis and Case 5 will be sacroiliac osteomyelitis.

So starting with the case of parameningeal infection, here are the key points of this case, in terms of diagnosis, parameningeal infection is a potential complication of fungal meningitis and may occur despite medical therapy. A MRI at the epidural injection site as indicated in patients presented with fungal meningitis and probably should be completed two to three weeks after presentation. MRI findings can be difficult to interpret in the post-operative setting and may lag behind clinical improvement.

In terms of treatment, a prolonged course of liposomal amphotericin or amphotericin may be necessary in some cases of (eract myditis). Case 1, this was a 72-year-old female with a history of a contaminated L-3, L-4 epidural injection, her chief complaint was when one week of headache, neck stiffness, chills and fatigue 15 days after her injection. Her lumbar puncture showed 549 white blood cells and confirmed a diagnosis of meningitis; although the PCR was negative her fungal DNA.

Medical treatment was initiated with voriconazole combined with liposomal amphotericin for five days, her clinical symptoms improved and she was discharged 26 days after her injection and continued an oral voriconazole as an outpatient. Unfortunately the patient returned to the hospital 36 days after her injection with a chief complaint of back pain and lower extremity weakness. I will now ask Dr. (Mike Kasotakis) a neuroradiologist from our hospital to interpret her MRI findings.

Dr. (Michael Kasotakis): Okay thank you (Anu), I'm going to show you a series of two slides showing the lumbar spine MRI images on this patient. On the first slide you can see my arrow here pointed on the left is a T-1 sagittal post-contrast image and you can see there's an area of kind of bulky mass like enhancement with an (endorselapse) of the approximate level of L3, L4.

To the right of that is a similar post-contrast image but this one is a fat suppression, you can see much more clearly the area of abnormal enhancement. Now it's sort of hard to tell if it's epidural or intraspinal but on the next slide here this is a representative axial image through the area of interest, you can see the arrow and my arrows pointing to an area of enhancement that is clearly intradural and basically representing clumping and enhancement of the nerves of the (clottapuana).

(Anu Malani): Thanks (Mike), given these MRI findings, our neurosurgeons performed an evacuation of the epidural abscess and an L3 laminectomy. Intraoperatively they described flood line like material adherent to quantum nerve roots and a small amount of pus. This is an intraoperative image from a patient with a similar presentation showing the fecal sac with visible phlegmon.

Pathology from an intradural abscess showed inflammation on (H&E stain) in the top right-hand corner and fungal hyphae on GMS stain. Given these operative and pathology findings the patient was restarted on voriconazole and amphotericin in continued combination therapy for five weeks. She had a follow-up MRI 62 days after injection which showed stable (epidural) with intradural involvement and post-operative changes and enhancements at the laminectomy site.

At 71 days after injections her symptoms had improved sufficient for discharge and she's now continuing treatment on oral voriconazole as an outpatient. To summarize the key points of this case, in regards to diagnosis parameningeal infection is a potential complication of fungal meningitis and may occur despite medical therapy. An MRI of the epidural injection site as indicated in patients presented with fungal meningitis and probably should be completed two to three weeks after presentation.

MRI findings can be difficult to interpret in the post-operative setting and may lag behind clinical improvement. A prolonged course of amphotericin may be necessary in some cases of (epidural). The next case I will discuss is an epidural abscess, the key diagnostic points here are that epidural abscesses can develop many weeks after a contaminated methylprednisolone injection therefore you should maintain a low threshold for ordering an MRI in patients with persistent, worse or new symptoms.

In regards to treatment, neurosurgical consultation is critical when evaluating and treating epidural and paraspinal abscesses and optimal treatment duration and selection for an epidural abscess is unknown. Case 2 is a 47-year-old male who received a contaminated C6, C7 epidural injection. He presented repeatedly after his injection with the chief complaint of headache, confusion, malaise, neck pain and spasms.

During the 30 days after his injection, he had three unremarkable lumbar punctures, also during this time he had three unremarkable cervical MRIs. A fourth MRI was ordered 42 days or six weeks after his injection which (Mike) will discuss.

Dr. (Michael Kasotakis): Okay thank you (Anu), I'm going to show you a series of two slides, on the first slide here we have two MR images through the cervical spine that are separated in time. On the left you can see its 31 days after injection and on the right 42 days. The MRI 31 days after injection, this is a post-contrast central key one which was negative and then on 42 days you can see the arrow and my arrows pointing to an area of abnormal enhancement which has a (lentaform) appearance that's consistent with an epidural location.

On the following slide, again you see the two MRs, they're (T2 weighted) images and you can see the collection on the right that's developed 42 days injection within the epidural space. Our findings are consistent with a cervical epidural abscess or phlegmon.

(Anu Malani): Thanks (Mike), given these MRI findings our neurosurgeons performed an evacuation of the epidural abscess and C5 to C7 laminectomy - abscess and pus were visualized interoperatively. Pathology from epidural abscess showed acute inflammation next to a bony (stikiel) on each stain and rare fungal hyphae on GMS stain in the right-hand bottom corner.

The patient was then medically treated with voriconazole and amphotericin for ten days, his symptoms improved and he was discharged 57 days after his injection and continues on oral voriconazole. To summarize, the key diagnostic points are that epidural abscesses and paraspinal abscesses can develop many weeks after a contaminated methylprednisolone injections

therefore should maintain a low threshold for ordering an MRI in patients with persistent, worse or new symptoms.

In regards to treatment, neurosurgical consultation is critical when evaluating and treating epidural and paraspinal abscesses and optimal treatment duration for epidural abscesses is unknown. Now I'll present Case 3, and epidural abscess with minimal symptoms - the key points in this case first, patients with minimal or baseline symptoms may harbor epidural and paraspinal infection, therefore you should maintain a low threshold for ordering an MRI in these patients. And finally operative findings may not always correlate with microbiology or pathology results.

Case 3 was a 43-year-old female who received a contaminated L3 to L4, and L4 to L5 epidural injection 34 days apart. She presented to her physician complaining of lower back pain which was similar to her baseline pain which she rated as three out of ten. She had a lumbar puncture 12 days after her last injection which showed a white blood cell count of one and not consistent with meningitis. She underwent a lumbar MRI 41 days after her last injection and (Mike) will go over her MRI.

Dr. (Michael Kasotakis): Okay thanks (Anu), I'm going to show you one slide here, a series of four images. In the left upper-hand you can see the arrow pointing to the right L4/L5 neuroforamen and this is a contrast with the fat suppressed image so you can see the bright area here which represents abnormal enhancement. To the right of that you can see the arrows pointing to the right neuroforamen at the same level and you can see there's asymmetry in the fat.

Here's normal fat surrounding the nerve right here, but here there's abnormal enhancing soft tissue. Here's the same slice right here in the sagittal plane, you can see some enhancements at the disc margins here. In the lower right-hand

corner you can see a parasagittal, this is a non-contrast image, so you can see normal white fat surrounding the exiting nerve roots above and below the area of abnormality, but within the frame on the right here you can see some what I call fuzzy soft tissue which faces the fat surrounding the nerve root, these findings are concerning for neuroforaminal and paraspinal phlegmon.

(Anu Malani): Thanks (Mike), given these MRI findings our neurosurgeons performed a right L4/L5 laminectomy and (mediofisotectomy) with foraminotomy of the L4 root. No abscess or pus was seen interoperatively, however anatomic pathology showed and L4/L5 epidural fungal abscess. Pathology from the paraspinal abscess showed acute inflammation with pigmented septate hyphae fragments.

The patient was medically treated with voriconazole and amphotericin and she systematically improved by 52 days after her injection, she was discharged on oral voriconazole. To summarize patients with minimal or baseline symptoms may harbor epidural and paraspinal infections therefore once you maintain a low threshold for ordering an MRI in these patients and finally operative findings may not always correlate with microbiology or pathology results.

Now I will present a case of vertebral osteomyelitis and discitis, the key points here are that osteomyelitis and discitis are potential late to applications of contaminated methylprednisolone injections - a proactive outreach may help identify patients earlier in their course. In regards to treatment, surgical consultation is critical for evaluating and treating osteomyelitis.

Case 4 was a 28-year-old female who had a contaminated L4/L5 epidural injection, she presented with the chief complaint of three weeks of left lower extremity weakness 90 days after her injection. She had previously undergone a lumbar puncture at an outside hospital 20 days prior, which was normal. An

MRI was performed on this presentation which is shown in the next slides, (Mike).

Dr. (Michael Kasotakis): Thank you (Anu), I'm going to show you a series of two slides here, on the first one on the left is a sagittal stir image through the area of abnormality, on the right is the post-contrast fat suppressed image. You can clearly see that there's abnormal bone marrow edema within the L4 and L5 for table and abnormal (unintelligible) within the L4/L5 (interoteble) disc.

To the right of midline here you can see that this (floridly enhances fallen) contrast administration and there's also enhancement in irregularity of the (rotebal) body (implate). The next slide I'm going to show you two side-by-side images, on the left is a pre-contrast P1 through the area of abnormality and on the right is the contrast image. You can see that there's florid (herarotebal) enhancement surrounding the disc space, there's also enhancement within the disc and within the ventral epidural space - this is a classic case of discitis osteomyelitis.

(Anu Malani): Thanks (Mike), because of these radiology findings, the patient underwent an L4/L5 microdiscectomy with irrigation and debridement of scar tissue in the L5 nerve group, pathology showed fungal hyphae in GMS stain and chronic inflammation. Microbiology confirmed the presence of mold which has yet to be speciated; the patient has been medically treated with voriconazole and amphotericin.

She's still hospitalized but her symptoms have improved and will probably be discharged later this week, about 107 days after her last injection. She will continue on voriconazole as an outpatient. In summary osteomyelitis and discitis are potentially complications of contaminated methylprednisolone injections. A proactive outreach may help identify patients early in their

course, in regards to treatment surgical consultation is critical for evaluating and treating osteomyelitis.

Now I will present the last case, a case of sacroiliac osteomyelitis, the key diagnostic points for this case are sacroiliac osteomyelitis are a potential complication of contaminated sacroiliac injections, therefore once you maintain a low threshold for ordering an MRI in patients exposed to contaminated sacroiliac injections. In regards to treatment criteria for surgical intervention are not clear.

Case 5 is a 60-year-old female who had a contaminated right sacroiliac joint injection, she presented with the chief complaint of progressive right-sided pain and difficulty ambulating. And MRI was performed 44 days after injection and (Mike) will present her radiographic findings.

Dr. (Michael Kasotakis): Thank you (Anu), I'm going to show you one slide with a series of three images, where my arrows pointing to is the fat suppressed post contrast image and you can see where the level of the right sacroiliac joint, you can see the abnormality is centered at the level of the joint but also involves the (septates) and sacrum and ilium. You can see up here in the left upper-hand corner that there's abnormal signal intensity manifest by this bright signal involving the bony surface.

In the lower right-hand corner is the P1 non-contrast image to show you how there's normal marrow here built with fat but abnormal here - abnormal marrow here secondary to the edema, this is a case of septic sacroiliitis.

(Anu Malani): Thank you (Mike); given these radiographic findings our orthopedic surgeons performed an arthrotomy and debridement, a iliac crest bone biopsy. Interoperatively they noticed a small amount of (perion fluid) - pathology

findings from the Iliac crest biopsy showed neutrophil and plasma cell infiltration next to bony (spiceals) consistent with osteomyelitis.

Market biology confirmed the presence of (exer highland), the patient was medically treated with IV voriconazole and the patient symptoms improved to the point where she was discharged 58 days after her injection - she has continued on voriconazole as an outpatient. To summarize this case, remember that sacroiliac osteomyelitis is a potential complication of contaminated sacroiliac injections, again once you maintain a low threshold for imaging or an MRI in patients exposed to contaminated sacroiliac injections and the criteria for surgical intervention in sacroiliac osteomyelitis is not clear.

In conclusion, parameningeal infections, epidural abscesses, vertebral osteomyelitis with discitis and sacroiliac osteomyelitis are potential complications of contaminated methylprednisolone injections. Proactive outreach may help identify patients earlier in their course, therefore once you maintain a low threshold to order imaging in an MRI with or without contrast if the spinal or paraspinal injection site in patients with persistent, worse or new symptoms.

Early surgical consultation is essential for management of spinal or paraspinal infections and finally optimal duration of medical treatment for these infections is not yet known. I'd like to acknowledge the following persons for their contributions and thank you.

Tom Chiller: Thanks (Anu) and (Mike) for that great summary of cases and again for your - for all your hard work in dealing with these complicated patients over the last several months and we appreciate you taking time out of your busy schedules to be with us today and with the clinical community that's been able to join.

I want to just remind everybody that there are two different ways to ask questions, you can type in a question via the live media Web site that you're logged into now and we here at CDC can receive that question and our - and can respond to it in this webinar. And then secondly the operator will also be able to queue you up and take calls on the phone line directly. So as you're hopefully getting ready to ask some questions, I'd like to start with the first question.

And (Mike) I don't want to put you on the spot, but I think all of us appreciate the challenges in getting MRIs and reading MRIs, especially in this particular outbreak and given the fact that the health advisory that has just come out and the health alert that's just come out actually from us today at CDC that really tells patients and clinicians to have a very low threshold to get an MRI at the spinal, paraspinal areas that are affected or that were injected.

We - I just thought I would give you a chance (Mike) to comment on your experience with MRIs and whether there are a few take home messages or thoughts that you could give us about reading these MRIs as abnormal and whether there were things that we should be looking for or asking about?

Dr. (Michael Kasotakis): Yes well that's a good question Tom, thank you so much. You know, as you alluded to, it really is a, you know, large multi-disciplinary concerted effort - it's going to take multiple, you know, facilities of the hospital to bring such a program together. You know, here at Michigan we, you know, got authority from the State of Michigan to bring in a new MRI scanner to address capacity issues - we're a CON state - a Certificate of Need state.

So once you get that in line and you address those capacity issues, the next step is, you know, finding the qualified readers to read these, reading them in a timely manner, having a consistent, unified vernacular on what disease means and how we classify it and then knowing who to disseminate the results to. And here at St. Joe's we're very successful at that because we did have a multi-disciplinary team approach.

We had almost daily meetings, we had a fungal outbreak clinic where we as radiologists could contact, that we as radiologist could send the results to immediately - given that we basically guaranteed them a 24/7 365-one hour turnaround time on these reads. So it was really a multi-disciplinary concerted efforts and it's an evolving process too, we were lucky in that - although we are a private practice radiologist group, we're not an academic institution, we are very sub-specialized.

And Tom what that means is that all these neuro- all these spines and MRIs were read by neuroradiologists, so we did have the comfort level when it comes to specialization. And we, you know, it was a learning process, there was a lot of consultation between colleagues, there was a lot of evolution, there was a lot of (red path) correlation. There were conferences where, you know, we discussed this with the ID docs and the surgeons to provide pretty quick feedback so we can - so we could gauge our sensitivity, okay.

And we sort of, you know, oscillated on the balance between being, you know, too sensitive or not as sensitive and because what really happened here is and (Anu) can discuss this too is once we started the screening program which when we talk about later, you know, MRI really became, you know, where the buck stopped. You know, for the first time as I know, MRI was used as a screening study and that really brought up a lot of unknowns and new areas that we had to address.

Because as you know there was a (plush amount) of information on these MR images, some of which may or may not pertain to fungal disease and we came up with so-called, you know, equivocal findings. And whether or not it was related to true fungal disease or not, we weren't sure, the only thing we could do in at least in radiology was to recommend a follow-up examination. So there were quite a bit of patients that underwent follow-up, so it's not only the initial screening MR, but it's the follow-ups that go with that.

And it's having a really tight group where you can provide feedback across disciplines and evolve as readers and clinician's is really key to this.

Tom Chiller: Great thanks (Mike) and thanks for explaining some of the logistics in putting this together and I think we'll have to - we'll probably have to time to - I'm sure they'll be more questions about radiology. While we're waiting for people to queue up on the phone, I think we have received a couple questions here at CDC via the live meeting, so maybe we'll go ahead and read those and then we'll take those first couple questions. (Ray) do you want to...

(Ray): Sure, the first question probably would be fielded for (Anu), what is your experience in collecting microbiology samples - PCR samples interoperatively? In my experience many of the LP samples, fungal cultures and PCR negative are interoperative tissue sample studies more like (reach) results and positive results.

(Anu Malani): So we saw about 53 cases of meningitis and, you know, many more cases of paraspinal and epidural related infections. I would say that first that is that there's definitely a higher proportion - or a higher degree of positive cultures from the epidural and paraspinal cases. In terms of the meningitis patients, it's

really a minority of them that had positive cultures, its - I can count them on one hand, so it's only a few.

In terms of molecular testing in that group, it's probably - oh it's about maybe 15 or so and it did not always correlate to level of pleocytosis, I mean we had patients with as low as, you know 20 to 50 cells that had positive molecular testing. In regards to what we've really seen in the last six to seven weeks, you know, that epidural and paraspinal infections it seems that these patients have a much higher degree of positive cultures, also positive paths meaning that, you know, as seen in a couple of these cases we presented that they actually had evidence of fungi and histopaths.

As far as PCR from these tissues we are still getting results on some of those tissue samples, frankly if they had mold growing or they had evidence of fungi on histopath, I'm not sure that we always have the tissues for PCR. I think maybe an order of Tom can count it a little bit on PCR and that setting because I think we still are maybe waiting to get back some of those tissues.

Tom Chiller: Thanks (Anu), I think it's important to note that PCR and culture for fungi in general are not a very sensitive test and so we know that many people who truly do have infections will still not have a PCR or a culture positive. I think that we are working on our tissue PCR here at CDC we are able to PCR fungi from tissue, but this is a chal- this is again a challenging and more of an experimental test.

But we are in this outbreak trying to do that and have had some success and so we continue to work on that and continue - and we'll be happy to continue to tissues from suspected patients to try to perform PCR. So let's move on to the next question, we'll take one more from the Internet and then we'll go to the phone lines.

(Ray): Okay there was a question here, do you have any ideas about identifying these infections in patients with implantable devices that make MRI - the devices that they would - if they are not able to get an MRI because of some kind of medical device? I think I mangled that question, but I think it's a question for (Mike).

Dr. (Michael Kasotakis): Yes, no I got to thank you - that's a really good question. So first of all I want to say that by far and away MRI with contrast is the gold standard for diagnosing this disease, but there are patients as you mentioned that cannot receive MRI due to contra-indications, those include patients with pacemakers and patients with bladder or spinal stimulators.

What we've done is we have experience with that, we've tried to do CT with contrast and we have a case in particular where we did a CT in a patient with a spinal simulator and the CT didn't show any infection or at least, you know, couldn't identify anything. We thought that was clinically necessary based on the risk and benefits after discussion with the neurosurgeon we actually - he removed the stimulator, then we put the patient into the MRI scanner with (contrast) and found positive disease, okay.

So it may be very important to have that difficult discussion, we have not yet had any patients with pacemakers ironically, although we are under clinical trials that allow us to scan patients with pacemakers in a controlled setting with a cardiologist. Finally, the role of nuclear medicine like gallium scanning is really minimal and we haven't done it at our institution - the test is pretty simple and non-specific.

And then one more point is that, you know, if all bets are all, if the patient cannot get in the machine, I would certainly do the CT scan with contrast

because we have diagnosed disease on CT, although again it's less sensitive than MRI, especially in bigger patients where there's a lot of paraspinal fat. And what happens is that the disease, the infection, the fungus fills in the fat and you get asymmetry of the fat and we have the UTC to diagnose it.

So MRI if you can with contrast, if you can't CT and then if you really need to consider working with the surgeon to address these stimulators and pacemakers, thank you.

Tom Chiller: Thanks (Mike), operator should - can we go to the phone line if there's anyone queued up?

Operator: Yes thank you, and as a reminder to ask a question over the phone, dial star then one. We have a question on the phone waiting, Dr. (Steven Pile) your line's open. Please check your mute button Dr. (Steven Pile) your line's open.

Tom Chiller: Perhaps go to the next question.

Operator: We do have another question in queuing, one moment.

Tom Chiller: We can take one quickly then through the Internet while we're waiting for that question to queue up.

Operator: Yes we...

Tom Chiller: Go ahead (Ray).

(Ray): All right so next question over the Internet, is the incidence of localized infection similar in Tennessee and Virginia?

Tom Chiller: So this is Tom Chiller at the CDC and I think I'll take that question and I think that you can see on our recent updates to the web page for numbers of cases that right now the majority of paraspinal and spinal infections are in Michigan and Tennessee and partly this could be due to geographic differences in the way this disease is presenting that are unclear to us right now for the exact reasons and risks. But there could be geographical differences in presentation and there also could be differences in the aggressivity of clinicians approaching the patients that have very minimal symptoms, if not symptoms the same as their baseline symptoms.

And that is one of the reasons based on the preliminary data that we have from Michigan, Tennessee and North Carolina that we have put out the health advisory today that strongly encourages clinicians and patients to evaluate their pain and consider obtaining an MRI in order to diagnose localized infections that may be very subtle clinically. So, operator could we take - is there a question on the phone?

Operator: We do have a couple more questions over the phone. Our first question comes from (James Mulner). Your line is open.

(James Mulner): Hi. Thanks to all for putting together this seminar by the way. Actually, I have a series of questions but the first one is probably we've been again still working with Voriconazole serum levels and improving our turn around time but just wondering if other people have seen an adequate response rate with levels in the 1 to 2 serum range as opposed to pushing them up between 2 and 5 as some of the CDC notation represents and we have been doing dual therapy with Amphotericin B as well during this whole time period.

Tom Chiller: Yes. Thank you for that question. (Anu) do you want to give your thoughts and experience?

(Anu Malani): Sure. So, you know, we've seen Voriconazole troughs all across the spectrum. It seems that when we started people initially we saw quite a number of people with elevated troughs and often backed down on the dose and it seems like more lately the trend with increased amount of time that patients have been on Voriconazole we have actually seen troughs on the lower end and they seem to be tolerating it a little bit better.

I think generally we have tried to tolerate troughs between 2 and 5. Some people, if they didn't, you know, if they had arachnoiditis and it was pretty severe, I think we have erred on the side of maybe even a little bit higher as long as they are tolerating it well. You know, maybe even the low 5's.

In patients that also had osteomyelitis, like sacroiliac osteomyelitis, we have seen a number of those cases or tubal osteomyelitis, almost the same. We've maybe even erred on the side of being a little bit higher as long as they are tolerating it well. I mean, we have had several patients that have had low troughs of late and we have kind of struggled with in terms of how to bring their troughs up.

I think turn around time has been an issue for us. It definitely was an issue very early on where we were getting troughs back probably, you know, for five to seven days and sometimes those are delayed on the weekends. Our lab testing is done through the Mayo Clinic and so the turn around time is anywhere from two to three days to five to six days. It just kind of depends on when it happens because I think they ended up batching tests Monday through Friday and sometimes if you do a trough on Thursday or Friday it takes a little bit longer to come back.

And I would add that, you know, for a couple of the peripheral joint infections, I had one patient who really had significant ALT elevation, probably 10 times normal, that didn't really seem to go away. She's on Itraconazole, doing really well, seems to be tolerating it okay and I think we also have a shoulder and an ankle type infection that are both on Itraconazole.

(James Mulner): Okay. That was helpful. Thank you. In followup, what are you using as a criteria of when you feel it's safe to discharge patients home? We have one gal who really has done remarkably well, good levels on IV, now off of Amphotericin less than a week, and abscess or phlegmon intradural it seems to be has diminished in size by probably anywhere from 40 to 60%, depending on how you measure it. But are you guys having any particular criteria that you are using when you are willing to change them from IV to oral and are you doing that as a slow transition or just making the leap? And are there other criteria you are using to ensure that you don't have the patient coming back now that we have gotten this intermediate term improvement? She is now at probably six weeks here in the hospital.

(Anu Malani): And she has an intra - did she have meningitis before?

(James Mulner): She had no meningitis symptoms, increasing low back pain and that the first MRI at week three and a half was entirely normal and within two weeks later presented with worsening back pain that the MRI was very positive.

(Anu Malani): So it sounds like kind of - and no surgical inter?

(James Mulner): No surgery yet, no.

(Anu Malani): So it almost sounds like arachnoiditis.

(James Mulner): That's what she seems to have with, you know, a dense sort of adhesion at one level and some slight enhancement on the caudae region descending.

(Anu Malani): So I guess I would say a couple of comments on that is one, in terms of how long we treated patients for it, I think it depended on what type of infection they had, whether or not they underwent operative intervention. For a case like that, we saw several cases of arachnoiditis. I would say that many of them did not undergo operative intervention because there really wasn't an epidural component to their infection and many of these patients actually, their symptoms improved.

Actually, I mean almost all of these patients improved with time. Many of them received long courses of combination therapy, four to five weeks, and I think what we kind of tried to do internally amongst myself and three other ID partners who are primarily seeing these patients as well. We tried to treat these types of patients, those with arachnoiditis, with about four weeks of combination therapy.

I think we have to realize that the MRI is often difficult to interpret, often not changed, but if they are clinically doing better we also felt that, you know, the IV, we are using IV AmBisome here, was also difficult to tolerate for a long period of time that potassium wasting, the magnesium wasting, the significant renal effects, the IV hydration. You know, we had people gaining 30 or 40 pounds of fluid because we were hydrating so aggressively, is really hard to take after, you know, beyond that period.

And in terms of those that had, you know, that did have arachnoiditis or intradural involvement that had epidural or paraspinal infections and they underwent operative intervention, we were treating many of those patients with combination therapy for anywhere from seven to ten days and then

discharging them on oral Voriconazole. In terms of the transition, I would say that if you have a level back, probably can transition them right away, especially if the level is okay, given the bioavailability.

And that may also help in terms of when they are getting ready for discharge so you are not waiting to see if they can tolerate it or if they have nausea or things like that. So I think you know, we didn't always do that initially on, but I think the trend more so probably in the last, you know, month to six weeks, as we are probably transitioning people to oral Voriconazole much sooner, especially when we had levels back.

Man: Thanks (Anu) and (James) thanks. I hope you don't have more. I want to cut you off just so we get.

(James Mulner): That's fine, no I'm done. Thank you.

Man: Thanks, (James) I really appreciate it. So, operator queue up another person. In the meantime, we will ask one Internet question.

Man: All right so this next question, what is the timeframe for treatment in patients with meningitis? If still three months, if they start doing well on treatment, and how are patients doing off of treatment?

Tom Chiller: So, thanks for that question and I guess I'll start (Anu) and then I'll give you a chance to respond as well. Obviously duration of treatment has been an issue that all of us have been thinking about since the beginning of these infections and I think that as we are learning more about how patients are doing and as we are hearing about different manifestations of disease, I think we are probably going to have different lengths of therapy based on severity and location of disease.

For example, I think we all know that osteomyelitis due to fungus requires lengthy therapy, usually a year, if not longer. I think that some of the arachnoiditis patients or maybe all of them will also require lengthy therapy that will potentially go months to a year, but I think that the optimal duration for these various conditions is still unknown and I think that as we as a clinical community begin to feel comfortable that our patients are improving and then maybe push that therapy a little bit longer and begin stopping, we will probably learn unfortunately more about whether that was a sufficient therapy or not.

(Anu) do you have any specific comments from your experience?

(Anu Malani): I agree with what you said, Tom. I think that treatment duration is going to depend on probably what bucket of spectrum or disease you have and those that have arachnoiditis, those that have vertebral osteomyelitis, sacroiliac osteomyelitis, you know, probably most of our patients that had meningitis, they all presented, you know, over two-thirds of them re-presented with infection at their epidural site. Many of those were operated on and I think that even those patients are going to require a long course of therapy. Many of those patient presentations were on oral Voriconazole.

So we here, recently in Ann Arbor, have not really done repeat spinal taps yet. There are I think other centers that are doing that and I think as Tom alluded to earlier there are probably different geographic, depending on where you are in the country you may be seeing a different type of disease but I think that those answers are not yet known. And then the other thing I would add, even in epidural and paraspinal infections, I think that surgical intervention is probably, our feeling here is that this is probably something that really has a

strong role in these patients and that may play a role in how long you treat patients as well. Maybe those patients can undergo a shorter course of therapy.

Man: Thanks (Anu) and again a challenging issue, duration of therapy, but I think one that we will continually address with our clinical experts and with people like (Anu) out there treating these patients and will try to give some guidance when we learn more information. Why don't we see - operator is there anyone queued up on the phone? We can take a phone question.

Operator: We do have a couple in queue. Dr. (Fark) your line is open.

Dr. (Fark): Yes. I have a question here. Why is it that we are seeing more localized disease now, and (unintelligible) more meningitis?

Tom Chiller: Yes, thanks for that question and I think we are asking the same thing of ourselves and of the clinical community. It does seem that if we look back now at the prior three months or so that we have been in this outbreak, in the initial stage or the initial days they were very severely ill patients presenting, many of them had strokes. Some of them died unfortunately.

And then with the, as we gained knowledge that there were contaminated injections and as we mounted a public health response, we brought back in hundreds if not thousands of patients to be reevaluated. Many of them had lumbar punctures. As you all know, were diagnosed with meningitis based on the lumbar puncture findings, and those cases of meningitis were quite diverse, so we had cases that had very few cells in their CSF, two cases with many cells, but I think in general there were meningitis cases that were not as severely ill as some of the first initial cases.

And now as you have just heard over the last month or so, the majority of patients that are presenting, and that we are diagnosing as part of this outbreak, do have these focal infections. Of course as you heard (Anu) mention, in his experience and in experiences from some other clinics and states, a large proportion of those initial meningitic cases did develop a focal infection at the site of injection concurrently or slightly delayed to when their meningitis was diagnosed.

So that is sort of the look of the clinical disease that we have seen in this outbreak. You know, but specifically to address the issue of why certain people have localized infection and why this late, I think would be challenging and I think that the pathophysiology of this disease and of this infection is something we are grappling with and trying to learn about as we go, since the unprecedented nature of this particular outbreak and the fact that fungus was injected with a steroid into a sterile space allowing for minimal inflammation to initially occur probably presents some sort of complication into how the pathophysiology of different people progressed.

So suffice it to say, I don't think we have a very good answer for that question, although it is a great question and I think we still continue to consider different options and I don't want to theorize on this call but I do think it presents a very interesting clinical syndrome.

Dr. (Fark): Can I have a followup?

Man: Okay one followup.

Dr. (Fark): Yes. That's going to be significant, given that patients would have residual back pain from their underlying initial pathology while they initially received the steroid injection and if you consider repeat imaging, the whole issue of

artifacts from their previous pathology and artifacts from scarring from the surgical intervention that they have done. So, see more localized disease, I'm seeing risk and made decision when to stop work on as though it even more difficult.

Tom Chiller: I think you present two very important points and you are absolutely correct. The first one being the pain that they initially received the injection for, it's clearly complicating our ability to diagnose patients with a subsequent infection clinically, which is why you heard today and why we are recommending that clinicians consider doing imaging and then you bring up the point that the imaging could potentially be hard to interpret, given the fact that they may have chronic changes there or they may have had surgery to alleviate their back pain.

And I do think that does present challenges. I think as (Mike), our neuroradiologist on the call with us today, has alluded to, there are plenty of patients that have had negative MRI scanning done earlier post-injection that then go on to develop a positive MRI finding and so we are cautious to say that if there is an abnormality on MRI at that site of injection, it should be closely evaluated and I think a low threshold to consider that it might actually be relevant and be part of an infectious process.

I want to just give (Mike) a chance to respond specifically to the MRI issue. (Mike)?

Dr. (Michael Kasotakis): Yes, thanks Tom. I think in regards to the question, absolutely. History is vital and I don't mean exposure history but I mean where they were injected and which site and which level and often, again, these are very subtle findings. There may be, you know, things ranging from, you know, a little, you know, more enhancement than what we expect but if we here and if we

find out that they have been injected at that level, we tend to be very cautious and our only tool, like I alluded to earlier, was temporal imaging, in other words getting a followup to see if that area in question evolves into something more obvious.

And so I think that is how you need to approach the MRI with caution, with a low threshold, a high sensitivity, and with clinical correlation as to where they were injected, and then finally using temporal imaging, followup imaging to see if that finding is real or not.

Man: Thanks, (Mike), I appreciate that. And thank you for the question. Why don't we queue up another phone, but in the meantime we will read a quick Internet question and address that. (Ray)?

(Ray): All right. What is your experience with death associated with these injections? How many? And do you always request an autopsy on such cases? Finally, are the autopsies performed as hospital cases or within the realm of the medical death investigation symptoms, so the coroner or medical examiner?

Tom Chiller: Thanks for that question. To date, I believe we are at 39 deaths that are associated with this outbreak. I think the important thing to point out about death is, as I just mentioned, the outbreak has sort of been in these three phases as I look back, and the first phase was clearly very severe disease. Most deaths occurred from patients that were diagnosed or identified early in the outbreak that had very severe meningitis or complications thereof, many of which developed strokes.

And so it appears that the majority, again the majority, the vast majority of deaths occurred early in the outbreak or as part of patients that were diagnosed early and were unable to be successfully treated for either their meningitis or a

complication thereof, like stroke. I think that we are certainly encouraging these clinics and hospitals to perform autopsies. Many of them have been performed at the hospitals themselves. I believe some of them have also been performed through the state and medical examiners and we here at CDC are working with anyone who is willing to do an autopsy and are happy, our pathology group here are happy to receive tissues, process them, and review them with local and state pathologists.

So, why don't we take a call now from the phone line?

Operator: Thank you and once again to ask a question on the phone, dial star then 1. Our next question comes from (David Kaufman). Your line is open.

(David Kaufman): Hi Tom, how you doing? This is (Dave Kaufman) in New Jersey. (Anu) and (Michael), thank you so much. That was very illuminating. We are here in New Jersey. I think our experience has been a little bit different, but maybe in the next two weeks it will become more similar. So I had a bunch of questions. Tom knows I always do so sorry about that.

When you were looking, particularly when you talked about talking devices out of patients, did anybody ever consider PET scanning these people? Did you have any experience with that out in Michigan?

Tom Chiller: (Mike) any comments?

Dr. (Michael Kasotakis): Yes. No, (Dave) I don't have any experience with that. It's a good thought, you know. You know, PET as you know was metabolic imaging and looks for glucose uptake and, you know, I guess any infection would be, you know, hypermetabolic or positive, if you will, but again it's probably not as

specific. It's probably sensitive but no I don't have any experience with that. That's a good thought, though.

(David Kaufman): Yes actually when we started our outbreak I wanted to kind of PET scan everybody as a research project but nobody was happy about that. The other question I had mostly for (Anu) and any other ID docs that are in, I'm, you know, I'm not too smart but I'm having trouble understanding the wisdom of using dual therapy for an extended period of time in these folks. So I'd kind of like some ideas on the rationale of that.

Tom Chiller: Sure. I mean, yes go ahead (Anu) I think I'd be interested in hearing your thoughts.

(Anu Malani): Sure. And then you can add in, Tom. So you know I think some of the way we approach patients changed a little bit, probably towards the end of October, maybe a little bit before that when we started seeing a number of patients, mostly you know, the first month of this outbreak was mostly folks with CNS meningitis and then by, you know, week three or four, the third and fourth week in October we were seeing a number of them to come back that were already home on oral Voriconazole, coming back with, you know, second processes at their epidural site.

So we started treating all those people with combination therapy because well, you know, it progressed on oral Voriconazole. You know, was it failure to medical therapy or would it have just happened as a part of their disease? You know, maybe not fully clear. So we know that Amphotericin or, you know, Ambisome, is fungicidal. We know that Voriconazole may be fungicidal at high doses. I think in the epidural and paraspinal cases, I think probably my own feeling is the key there is probably if you can operative intervention probably really plays a large role.

We figured, you know, and you're right. No one really knows is one drug better than two drugs? You know, which drug should be used? Should you use Ambisome as opposed to Voriconazole? One thing is, you know, if you use Ambisome and they are only going to be here a week, well then you have to start them on Voriconazole and as you know a lot of people had difficulty probably tolerating Voriconazole, especially initially with hallucinations and photopsia, etc.

So, you know, we kind of took an approach of using both drugs that are here. I think surgical intervention is probably really something that plays a large role and I can tell you our readmission rates from that group of patients which is, you know, really the majority of disease we have seen in the last six to seven weeks, it's nothing at all what it was like for the patients with meningitis. So, you know, so I mean I can't tell you that our way is the right way. I do think that surgery is very important and to engage your neurosurgeons and to have, you know, we were fortunate to have kind of these multidisciplinary conferences with neurosurgery, neuroradiology, infectious disease, anesthesia, and really kind of talk about some of these cases which I think, you know, we are seeing so many that it really kind of helped us to have some sort of, I don't know if I should say standard but maybe a uniformed approach for how we kind of.

(David Kaufman): I think you are absolutely right. At our little community hospital we have had the hospital set up a clinic where we see all these patients rather than try to scatter them throughout anybody's office day or whatever and I think it has helped and we have had a dedicated team and yak, yak and blah, blah.

Tom Chiller: And (David) I'll just comment. I'll comment. Again, thanks for calling in. It's good to hear your voice. I, just to comment on the dual therapy aspect, I mean

I agree. As you know, we are on untreaded ground here a bit and I think that in CDC's guidance we still continue to recommend consideration for dual therapy in people that have new findings or worsening or have very severe disease and I think there is, I mean there is some rationale in the antifungal world where dual therapy may be better than monotherapy in some particular cases, hitting, you know, hitting it at different, you know, different sites, different targets.

The cidal versus the static effect of azoles versus the polyene's and just maybe hitting the infection hard at the beginning. I think that the real challenge, as (Anu) pointed out, is that there are these patients that progress, these patients have progressed on drugs. It's unclear to us whether that was simply already happening and whether that was a failure of monotherapy or whether giving them more dual therapy up front might have stopped some of that progression.

And here's the challenge that we are sort of faced with. We know that these people got injections with steroids and we know on many of the pathology slides that we have looked at there was minimal to almost no inflammation in some of those epidural spaces around the fungi which of course would lead to minimal or no symptoms at the site and also minimal or if not no findings on MRI or imaging where you need some sort of inflammatory reaction for that to be present.

So some of the thoughts are that a lot of the epidural and localized infections that accompanied the meningitis that showed up later might have already been there or might have already been established because the fungi were already invading, but there just wasn't the time for the body to respond to it. So I think that the dual therapy question is still a challenging one. I think we have heard from clinicians that are treating a lot of these people, you know, like yourself

that some of them have opted for dual therapy in some initial settings for a certain period of time and then have been transitioning to Voriconazole.

(David Kaufman): So one last question, I hope, when you guys have gotten your pathology on your localized infections, has there been sign of vaso invasion, just out of curiosity?

Tom Chiller: You said signs of what again?

(David Kaufman): Blood vessel invasion.

Tom Chiller: Yes. So on and I think we tried to post some images now on our website of pathology but what we have seen in pathology sections and in slides with our pathologist here at CDC is we have seen angio invasion. We have seen evidence of hematogenous spread but only in the post-air circulation so it doesn't seem to be a systemic hematogenous spread but just within the post-air circulation of the CNS, and pretty robust vasculitis as well as subarachnoid hemorrhage, etc., and I think if you go, if anyone goes to the website we have a pathology page and I believe there are representative images of some of these different conditions and disease states on the web.

Man: And Tom I would also add on imaging and radiology, we have noted, you know, angioinvasive mycotic aneurisms of the basilar artery. They are almost a centimeter to a centimeter and a half in size. So clearly angioinvasive. Unfortunately that patient did die. She did have basilar strokes as well.

Tom Chiller: Thank you. (David) one more question and then we've got to let some other people. Are you done?

(David Kaufman): I'm done.

Tom Chiller: Oh fantastic, (David), thanks for joining. Good to hear your voice.

(David Kaufman): Best thing you've heard from me, I know.

Tom Chiller: So why don't we queue up another phone question and in the meantime we will do an internet question, right?

Man: All right. And we use Itraconazole if the patient does not have intradural collection, if they are having trouble tolerating Vori and Ampho.

Tom Chiller: Yes thanks for this question and we clearly get and have gotten these questions a lot about alternative therapies, if Vori and Ampho are causing too much toxicity. I know (Anu) has a little bit of experience with Itraconazole so (Anu) I will let you address this one.

(Anu Malani): Sure. I think if they don't have the CSF involvement, they don't have meningitis, you know, it's probably okay to use Itraconazole. I guess, you know, it depends on the ones with the epidural infections and how much epidural involvement there is. I think, you know, we have, I have a couple of patients that have sacroiliac osteomyelitis, they have, you know, ankle related infection and I even this week was on the fence about switching someone with vertebral osteomyelitis to Itraconazole. She did have a little bit of a rash and I've just been kind of watching her on Voriconazole.

But I think the criteria for switching really is going to depend on whether or not they have CSF involvement and, you know, how much epidural space involvement they have because clearly, you know, Voriconazole does get into the CSF. My own experience, I think just, you know, there are not many patients I have on Itraconazole but in those cases they really couldn't tolerate

Voriconazole and they all seem to be doing fine on Itraconazole. I think in our, we have about three patients thus far on Itraconazole. And we have used Itraconazole over Posaconazole just because of, you know, the more frequency of dosing, you know, absorption issues with Posaconazole.

Tom Chiller: Thanks, (Anu) and just to comment on Posaconazole, I think that there are a few people using it out there. It is available. As you all know, it's oral solution only. The MICs for Posaconazole are very low. It's a drug that gets actually really good tissue levels and even in the CNS, although it's not known necessarily yet as a CNS drug. I think, you know, we still are learning about Posaconazole and as (Anu) mentioned there are issues with dosing and absorption that one needs to consider. So I think it could remain a second or third line drug if needed and certainly can be considered along with Itraconazole.

And just to direct susceptibility, since I brought it up, we have now posted susceptibilities for the (unintelligible) organisms that we've tested here at CDC. They are on the web and we continue to test more isolates as they come in, so for anyone's information, although we can't interpret these MICs yet because we have no idea about break points per se, you can get a look at the MICs on our website so please visit CDC's website to see the minimum inhibitory concentrations for the drug.

I think we are getting on to the hour and 15 minutes and I think (Anu) and (Mike) both have clinical patients to see and so we thought we'd cut this off here in the next minute or two. We could take one more question from the phone and then maybe try to do a couple more Internet questions. Can we take one more from the phone?

Operator: We have no questions in queue over the phone.

Tom Chiller: Okay perfect. Then maybe we are at the perfect time to stop so again, thanks everybody for joining today. Please tell your colleagues this will be on our website and you will be able to watch the slide presentations and then hear some of the questions and answers so your colleagues will, please let them know. I want to thank (Anu) and (Mike) and (Ray) and everybody else who helped organize this webinar. I hope everyone has a happy holiday and Happy New Year. Thanks for joining.

Operator: And this concludes today's conference. Thanks for participating. You may disconnect at this time.

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