

**Panel Topic:** Treating Acanthamoeba Keratitis (AK) and specific physician experience in using miltefosine.

**Date/ Time:** Thursday, 9/29/22 at 7am

**Place:** World Cornea Congress: McCormick Center, Chicago Illinois



**Panel Participants:**

**Dr. Elmer Tu:** Joel Sugar, MD Professor in Ophthalmology; Professor of Clinical Ophthalmology; Director, Cornea Service - Illinois Eye and Ear Infirmary - Chicago

**Dr. Christopher J. Rapuano:** Chief, Cornea Service, - Wills Eye Hospital- Philadelphia Professor of Kimmel Medical College at Thomas Jefferson University

**Dr. Jamie D Martinez:** Assistant Professor of Clinical Ophthalmology – University of Miami Health System - Miami

**Dr. Beeran Meghpara:** Director of Refractive surgery, Wills Eye Hospital  
Clinical assistant professor of ophthalmology, Sidney kimmel medical college - Thomas Jefferson University

**Dr. Gerami Seitzman:** Clinical Professor of Ophthalmology, Medical Director, Francis I. Proctor Foundation, Director, Cornea and External Disease Fellowship. H. Bruce Ostler Chair in International Ophthalmology and Prevention of Blindness, University of California San Francisco

**Todd MacLaughlan:** CEO Profounda, Inc.

**Background on Acanthamoeba Keratitis (AK):**

Acanthamoeba keratitis is a serious, rare, and painful eye condition which affects the cornea of the eye. The condition is caused by a single celled amoeba, called Acanthamoeba and is commonly associated with contact lens wear.

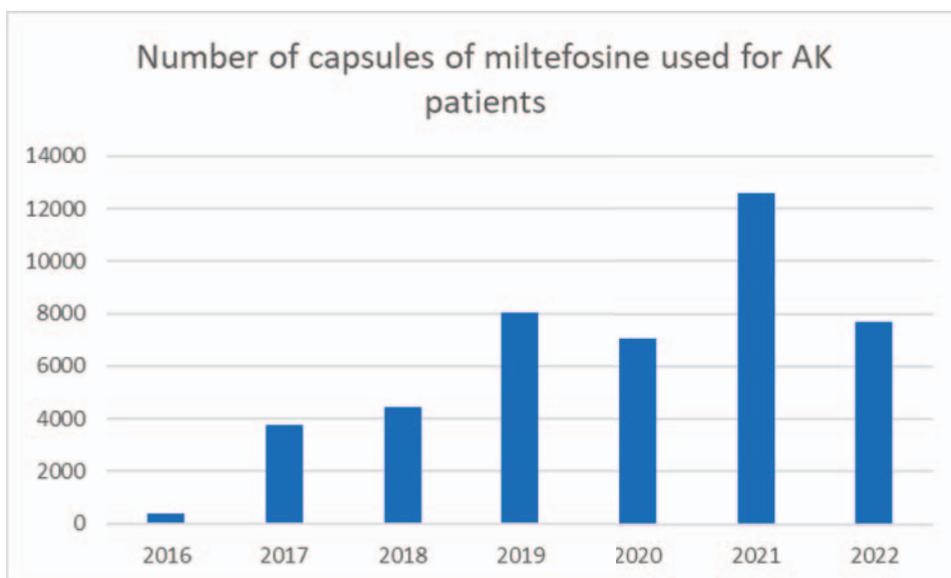
In addition to the approval for the treatment of Leishmaniasis, Impavido (Miltefosine) has also received orphan drug designation in treating the free-living infection primary amebic meningoencephalitis (PAM), the brain infection caused by the water-born amoeba Naegleria Fowleri, Granulomatous Amebic Encephalitis (GAE), invasive candidiasis and for Acanthamoeba Keratitis. It is available in oral dosage form and requires only one to two 28-day treatment cycles.

Cases of atypical keratitis require a high degree of suspicion for Acanthamoeba keratitis (AK) and prompt referral for Acanthamoeba cultures, particularly in contact lens wearers, according

to a study conducted at Wilmer Eye Institute in Baltimore.<sup>1</sup> Easy to misdiagnose. This retrospective study included all patients (n = 43; 45 eyes) with culture-positive AK seen at Wilmer between 2012 and 2019. The patients' mean age was 41 years, and they had been symptomatic for a mean of 52.6 days (range, 6-231). Before referral, 17 (37.8%) and nine (20%) eyes were misdiagnosed with herpetic and bacterial keratitis, respectively. An additional 13 (29%) received no initial diagnosis.

Risk factors and symptoms. Contact lens use was the strongest risk factor for AK, with nearly all eyes affected (95.6%). Notably, only five eyes (11%) presented with the classic ring infiltrate of AK.

Use of Miltefosine has been used to treat AK starting in 2016 and has been increasing in use as part of the overall treatment of this rare, but serious disease.



The purpose of this discussion was to share experiences about treating patients with AK and with the drug Miltefosine which has shown to be helpful in many cases.

Todd MacLaughlan:

Good morning. Everybody can grab their breakfast, and we'll get going here shortly. My name is Todd MacLaughlan, I'm the CEO and founder of Profounda. Today we have a very distinguished panel of experts in the field of acanthamoeba keratitis. Each of them will talk about a case or so that they have so they can walk through it, and then again, we'll have a chance for some questions and answers as well. With that, I'll start off if everything works. Here's the list of experts to my left here. Dr. Elmer Tu is probably the first person I know who had experience miltefosine in treating acanthamoeba keratitis. Then Dr. Chris Rapuano was actually one of the first ones to actually use it when the product received the Orphan Drug designation approval. Then, Dr. Martinez is from Florida. Hopefully they're having a good day in Florida. Our power is out in Orlando. We're from Orlando as well. Dr. Beeran Meghpara also from Wills Eye Institute. Then, Dr. Gerami Seitzman from UCSF is also here.

Miltefosine was actually approved for another condition called, Leishmaniasis. Three different forms, cutaneous leishmaniasis, visceral leishmaniasis, and mucosal leishmaniasis. That's a very rare disease here in the United States, and probably less than, I would say, 100 cases here in the United States. Usually caused by people traveling. It is a pretty significant worldwide disease, and it kills about 30,000 people a year worldwide. It's a female sand fly that bites you. It is present in the United States, as well as being endemic in Texas. It's endemic in eighty other countries. Usually the people in the states who get it usually go down to Costa Rica, and come back with it after their vacation. Impavido is also used for treating a free living amoeba infections of which acanthamoeba keratitis is one.

You may have heard of the brain eating amoeba, which is also a free living amoeba There's historically been about 156 cases of brain eating amoeba where people swim in fresh water, goes up their nose. Usually they're dead within 10 days. There's only been four survivors officially, although there's one survivor actually that's ongoing right now. There is technically five out of 150 cases. It's also used for amoebic infections in the brain, as well as for skin infections, disseminated amoebiasis. There's also used for systemic fungal infections as well. These other uses I'm mentioning are all off label uses, but they are being used and recommended by the CDC. The symptoms of acanthamoeba keratitis, obviously you're probably very familiar with it, but it's pain in the eye, eye redness, blurred vision, excessive tearing, sensitivity to light. We always think that you look for that ring to know that it's there. The problem with that is, it comes much later in the disease process. That's not necessarily the right sign. A time to diagnosis for acanthamoeba keratitis can vary from days to months to get the right diagnosis.

Usually they say it's a scratched cornea, then they say it might be herpes, and so they go through a bunch of different things. Be aware of it as a possibility in contact lens wearers, especially as the weather's getting warmer and warmer, the chance of acanthamoeba is getting higher and higher. The estimate of keratitis in the United States is estimated to be one to two new cases per million. Contact lens wearers, about 90% to 95% of cases of acanthamoeba keratitis come from people wearing contact lenses. If you hear contact lenses, probe for use of water, storage of water, not drying your hands properly. That's something you should be looking for. There has been a couple other cases. One case was with a policeman actually going through tear gas training. He basically got the tear gas exposure , his eyes get irritated, but because of that, he actually got exposure to acanthamoeba keratitis from the water. It can happen in other places, but usually it's contact lenses. Early diagnosis is important. Obviously, the earlier you diagnosis and start treating, the better. The physicians here will talk about their experiences

There was a case study by the CDC, and you'll hear more of it in the case studies here, where it basically showed that the miltefosine may have a role in the treatment of Acanthamoeba. It's not a perfect solution, but it does seem to help some people along the way. In terms of just US data, because miltefosine is primarily used in the US to treat acanthamoeba keratitis. The drug itself is not widely available in the rest of the world. We have treated some patients at Moorefields Institute in the UK. We have a case ongoing right now in Switzerland. You can see here that we're seeing an increased number of treatment months of patients being treated with miltefosine. Again, it's prevalence is growing, so be aware. of the availability of miltefosine You also won't be the first to use it in the USA. In terms of how often it's being prescribed, I would say most of the time it's being prescribed three times a day, twice a day, and then sometimes it's less than that.

How long? About half of the patients will use it for one month, but about half will use it for two months, and then there are some that have used it for as long as 10 months, believe it or not. The majority is one to two months. The purpose of today's discussion is really to just increase the awareness overall of acanthamoeba keratitis, and just a forum to talk about miltefosine, how it's used, what are some of the drawbacks to it, what are the pros, and how to manage through a case with AK. With that, Dr. Tu, I'll turn it over to you. This is just the last slide. There is a patient support group out there as well for

acanthamoeba keratitis, and it's a very active group, so it's possible you may hear from those patients who found this group on Facebook. Basically their feeling is, treat early, make sure when you hear contact lenses and water basically be aware. It is a very traumatic disease for these patients. They're very worried when they come to see you. Dr. Tu, with that, I'll let you take over.

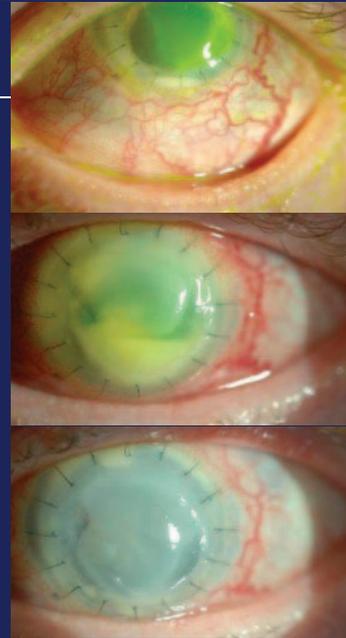
Dr. Tu:

Good morning. Thank you, Todd. The one thing I will tell you, working with Todd has been great. Profounda is a very responsive company. You can text, or not text, but email at 3:00 in the morning, and you'll have a response pretty soon. He's been a real patient advocate, and so it's really been wonderful to work with him on these very difficult patients. Let me just start off with a case presentation. If you look at this, this is pre-approval, okay? To my knowledge, this is the very first case that was ever treated with miltefosine. I wanted to walk you through this with me, because I had never used this drug before. There was no clinical experience, and this patient was desperate and this is how it came about. In October of 2011, we had a patient who had basically been treated for several months with progression of disease, despite maximal tolerated medical therapy. She was on PHMB she had been on chlorhexidine for almost seven months.

At that point we're like, "Well, we are not able to control this medically, so we're going to go ahead and do a corneal transplant to see if we can eradicate the disease, or at least remove the bulk of the infection if at all possible." Interestingly, the confocal was positive, but all the cultures to date had been negative. A negative culture doesn't, in most cases, tell you that you don't have disease. It's helpful if it's positive, not as helpful if it's negative. In fact, if you look at the studies, only 30% to 50% of patients are going to have a positive culture. It really depends on how your laboratory handles these things. We did a transplant, her visual acuity immediately afterwards was pretty good, but we were confirmed on pathology that it indeed was acanthamoeba. We continued chlorhexidine afterwards, she was doing pretty well. You can see the eye below looked great after the transplant, but that's only the beginning of the story, unfortunately. We did add, at the time, systemic voriconazole. The origin of the systemic therapy was really a paper by Govinda Visvesvara from the CDC. He tested two drugs against acanthamoeba, and a couple of other free living amoeba, voriconazole, and miltefosine. At the time, the Voriconazole was effective, but it was more static. Miltefosine had a higher kill rate, so that's actually where I originally got the idea to use miltefosine, because I started voriconazole, which I had used in a couple of other patients that had a positive response. In this case you can see that unfortunately afterwards, our patient did still have some inflammation, which is not unusual after an eye has been transplanted for a chronic inflammatory response. You see the hypopyon there. Then, as you follow along, the cornea is clear, clear, then you see the hypopyon in the upper right. Then, this is the telltale sign unfortunately, here is, you see this crescentic area of inflammation coming in from the sclera or from the peripheral cornea. That's a hallmark of recurrence of acanthamoeba keratitis. Now, could you have picked it up earlier because of the persistent inflammation and suspected earlier? Possibly, but in this patient, they're on maximal therapy at this point. Now we have a recurrence.

## Clinical Course

- Maximal Known Medical Therapy
  - Low Dose systemic steroids ( scleritis)
  - Voriconazole oral ( multiple intracameral tap and injects)
  - Topical Chlorhexidine 0.02%
  - Started miltefosine 50 mg bid x 28 days
- Increased inflammation noted week 3
  - Added corticosteroids
- Finished course of miltefosine
  - Inflammation subsided by week 2 off therapy



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## Presentation 10/31/2011

- Progression of disease despite PHMB/ CHX therapy for 7 months
  - Plan for Therapeutic PKP
  - All cultures to date were negative for Acanthamoeba
- 11/8/2011
  - VA 20/60
- Pathology results positive for Acanthamoeba cysts
  - Continued topical Chlorhexidine 0.02% Q2h
  - Added systemic voriconazole



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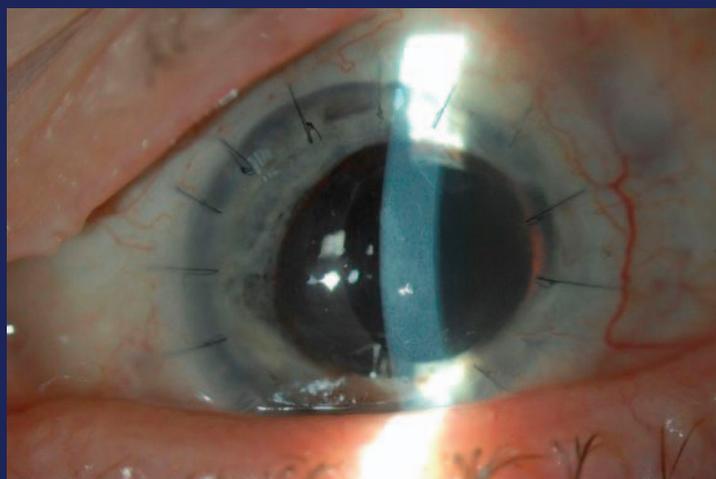
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The patient has been on topical medications, is on voriconazole. We're are kinda stuck, what do we do next? Again, this is a patient on a maximal known medical therapy. We started some low dose systemic steroids because she's developed scleritis at the time as well. Inflammation continued to worsen. We started miltefosine at that time, and this came under an emergency FDA IND in 2011. We treated her for one month. Luckily she wasn't a larger individual, so we treated based on the WHO criteria for Leishmaniasis in terms of dosing, either twice a day or three times a day, depending on the patient's weight. What happened at this point was that she got worse. Her inflammation got worse. She started to develop a larger hypopyon, a clunky coagulum in the anterior chamber. At that point, the eye is either lost or the drug's working. I was like, "Okay." I mean, I had no other options, so I was like, "Okay, I'm going to have to assume the drug is working, that the inflammation is because the acanthamoeba are dying. I'm going to add some steroids.

I added steroids, finished out her course of the month of therapy, and you can see she did quiet down eventually after a couple weeks, and then we re-transplanted her, and she maintained 20/60 vision for at least a decade until she moved to Arizona. I don't know what happened to her afterwards. This is a little bit of the wild - wild west of the early days of miltefosine, and we have a lot more experience with it now in terms of how to use it. I just wanted to present historically how... I mean, everything was a unique case. In this case, in terms of having the inflammatory response afterwards. People get worried that that's the disease getting worse, but if you've ever treated these patients, any time you give them any type of medication, you don't see much of a response initially. Then, this is the first time that I gave somebody something, and two weeks later, something's happening. At that point, nobody had ever treated anyone with this before.

## Optical Keratoplasty



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It turns out, and I'm going to finish up here, that if you look at some of the Leishmaniasis data, it's a little unusual that when patients are treated (with miltefosine) for Leishmaniasis, they'll sometimes get hyper inflammatory responses, and sometimes even in the eye. This may be a characteristic of the drug and there may have been some Leishmaniasis in the eye, but there's a hyper inflammatory response also seen with systemic treatment for Leishmaniasis. I think that this is probably part of it. It was part of the point of the paper that Chris and I were on to try to point this out to people when they're using miltefosine. That inflammatory response is not necessarily a negative thing, and then you just need to control it until they're off the drug. All right, great. I'm going to turn it over to my good friend Dr. Rapuano, and he's going to go through his experience.

Dr. Rapuano:

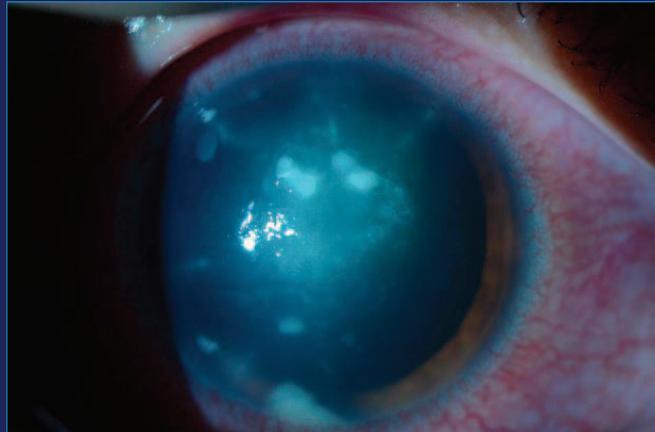
Great. Thank you all. Thank you, Todd, for including me. I work with some companies unrelated to this presentation. This is the first patient that Todd mentioned that I treated with miltefosine. 25 year old woman comes in with about an eight week history of redness and pain in her right eye. She's an extended wear, soft contact lens wearer. She was in a hot tub, but the last time was several months ago. Her symptoms started after she delivered her baby about two months ago. That's what her cornea looked like on presentation. You can see that there are radial keratoneuritis and multiple infiltrates poking down here. We were very, very suspicious for acanthamoeba. We scraped her for path smears, and multiple cultures. We started her on Brolene and Bacquacil every hour around the clock, which is my standard treatment. The pathology of acanthamoeba came back positive the next day. She's on this, she's home.

On a Saturday, I'm reading my emails three days later, and I read about miltefosine. Miltefosine had received an Orphan Drug FDA designation approval, which is some intermediates... It's not fully FDA approved, but it's okay to use from my standpoint, conservative me. I'm at home. There's an email at the bottom of this little blurb on whatever I'm reading, so I emailed Profounda. Todd MacLaughlan called me back on the phone that Saturday afternoon. I couldn't believe it. We arranged to learn about this, and get the drug. I see her back the next week, and she's actually looking a little bit better the next

week. I discussed starting miltefosine with her, because it's definitely strong wall, and looks this bad, the results are not that great. We obtained systemic testing, and she started miltefosine, and the recommended dose at the time was 50 milligrams, three times a day on January 14th. It's about 10 days after I first saw her.

# Acanthamoeba keratitis

- 25-year old woman with ~8 week h/o redness and pain OD
- H/o EWSCS wear and hot tub use but last time was several months ago
- Symptoms starts after she delivered her baby 2 months prior



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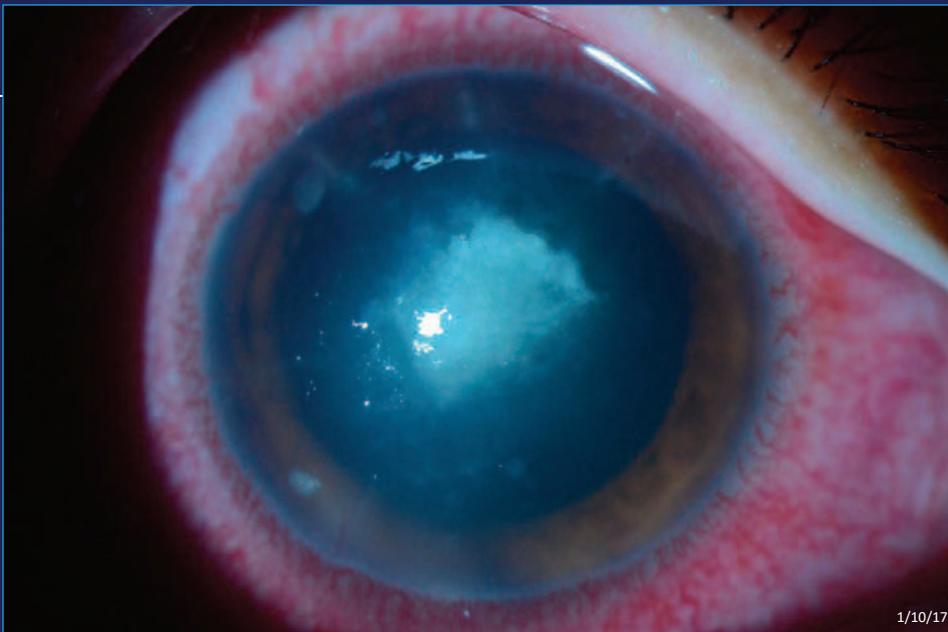


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It's hard to see in the bottom right, but I think about 10 days later this is how she looks. Overall looking a little bit better. We did not get that severe inflammatory reaction in this patient. Overall it's improving.



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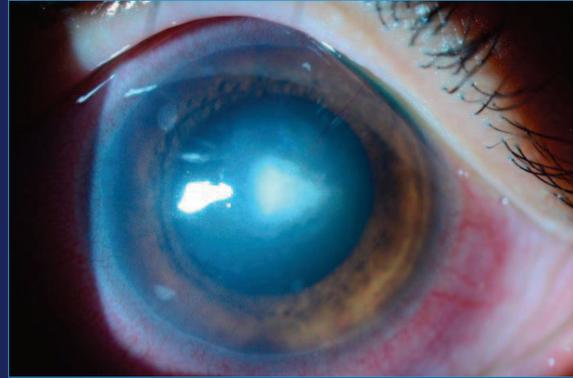
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She developed some nausea and vomiting after the second dose of miltefosine, but not after the third dose. What I did was, I decreased miltefosine to twice a day instead three times a day. She did develop

some inflammation, nothing severe. We started loteprednol three times a day, and saw her back, and overall doing pretty well. That's February 7th.

# Acanthamoeba keratitis

- Overall AK improving
- Pt developed N/V after 2<sup>nd</sup> dose of miltefosine, but not after 3<sup>rd</sup> dose
- Told to use miltefosine bid
- Due to inflammation, start loteprednol tid in 5 days and f/u in 7 days



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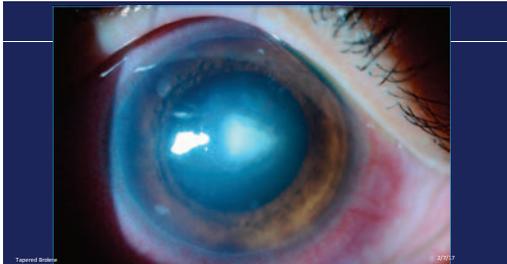


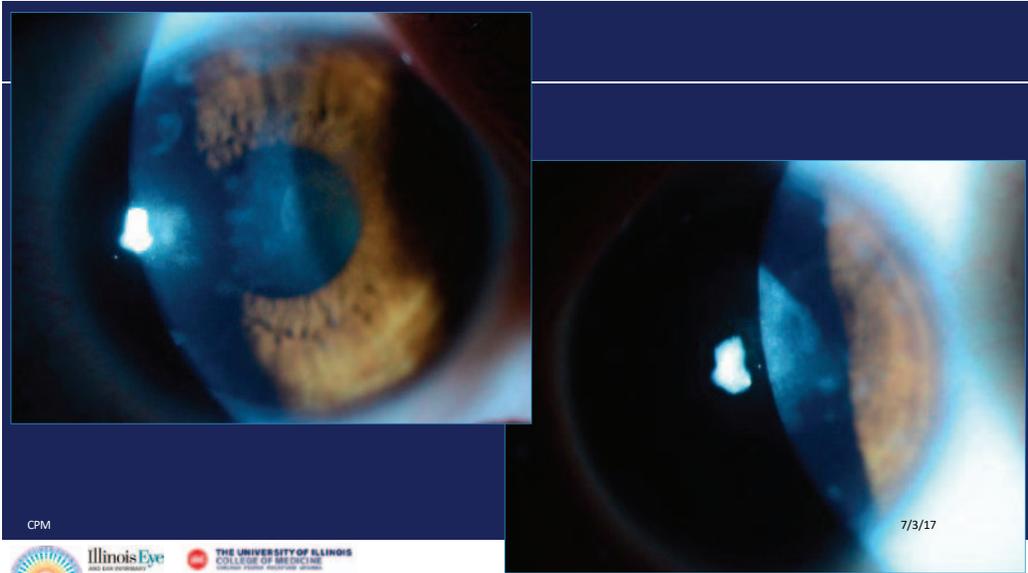
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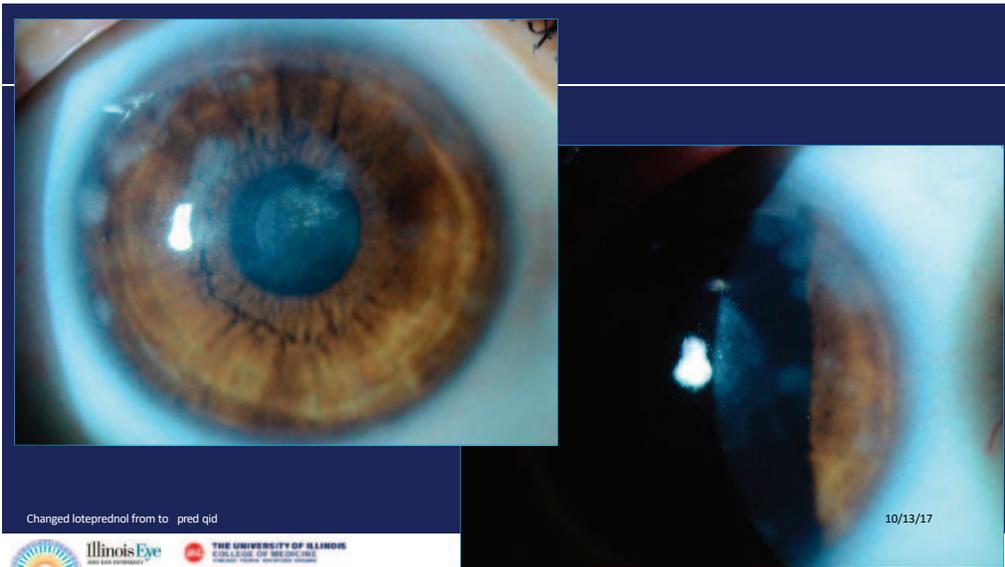
Then, March 3rd, looking pretty good. Very pleased with this. She's obviously off miltefosine at this point, because she was on it for just one month. We did a four week course that was recommended at the time. Here, April 25th, looking pretty good. I'm very happy. May 30th, it's a little hard to tell, but we see some SEIs coming up.





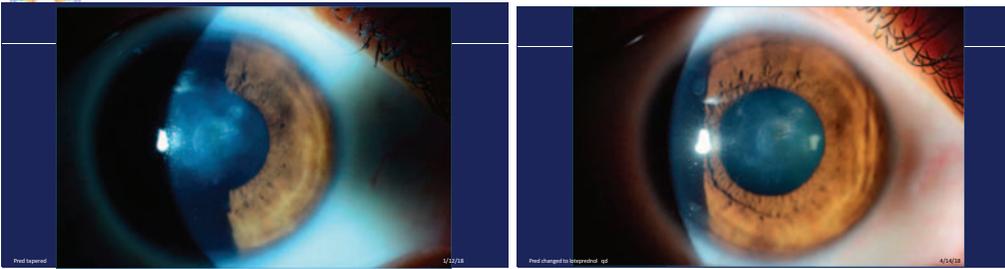
CPM

7/3/17



Changed loteprednol from to pred qid

10/13/17



Pred tapered

1/2/18

Pred changed to buprenolol qd

4/24/18



I think "Eh, we'll just have to ignore those." Then she got some more SEIs. I think, "Well, I really can't ignore it anymore." Just more SEIs. More SEIs. Eventually I start her on loteprednol increase her [and then I put her on Prede forte. The SEIs go away, and here January of 2018, so a year later, she's doing well with just a stable scarring, and basically no SEIs anymore. Here is stable scarring in April of '18. I last saw her in June of '18. She was on loteprednol once a day still, and her vision was 20/60. We keep hearing about this inflammatory reaction. Certainly we don't get it in all patients. This patient didn't get it, and I haven't seen severe ones like the one Elmer showed, but I've certainly seen more inflammation

than this patient had within a few weeks of starting it. Again, I think you don't have to be afraid of adding steroids at that point, because it's going to be very helpful. Thank you very much.

Dr. Tu:

Thanks. Next we'd like to welcome Dr. Martinez with the Bascom Palmer Institute, and with his experience.

Dr. Martinez:

Hi, thank you very much for this presentation. I have to acknowledge all of my mentors and my fellows that help me to get experience with this difficult patient with a corneal infection. Acanthamoeba, it's our top 10 organisms at Bascom Palmer that we are concerned of in about 2% of patients in our top ten You can see at the bottom of the table.

**Top organisms isolated in BPEI**

Rank	Top Isolates 2011-2015	Number of Isolates	% of total (N=876)
1	Pseudomonas aeruginosa	405	27
2	Staphylococcus aureus	234	15.6
3	Fusarium species	117	7.8
4	Serratia marcescens	78	5.2
5	Viridans Streptococci	63	4.2
6	Staphylococcus epidermidis	59	3.9
7	Herpes simplex virus	56	3.7
8	S. pneumoniae	39	2.6
9	Candida albicans	31	2.1
10	Acanthamoeba species	30	2.0

Table courtesy of Darlene Miller, D.H.Sc., M.P.H., C.I.C.



We know that our goal here is to prevent the therapeutic cornea transplant, because the risk and complications after a therapeutic cornea transplants. We always tell patients to get an optical point of transplant once the eyes quiet. Last year, we published a case series of five patients we treated with systemic miltefosine. Our results, as I mentioned, five patients, which three of them unfortunately developed inflammation, and have required a therapeutic cornea transplant, and two of them did really well and end up having an optical cornea transplant.

## Results

Five females from 16-53 years-old, with a microbiologic diagnosis of *Acanthamoeba*, were treated with MLT and standard medical treatment.



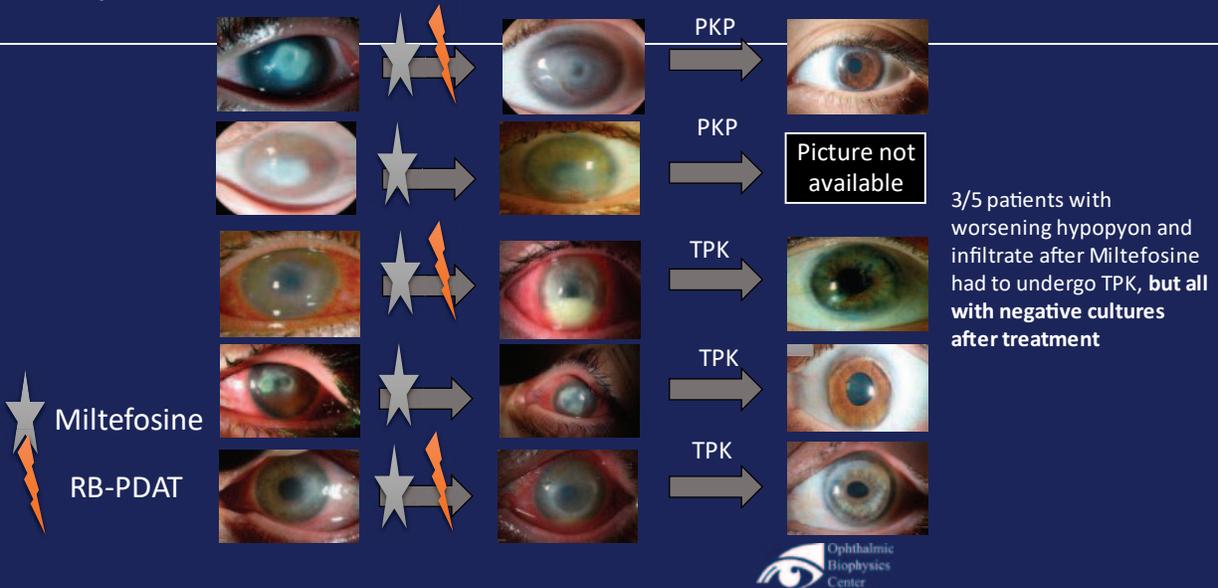
Three of five cases deteriorated. (increased pain and inflammation) after initiating treatment and required a therapeutic keratoplasty.



Two patients improved after one week of MLT and optical penetrating keratoplasty was performed after clinical resolution.

You can see here the first two cases of patients that did respond to miltefosine. Patients were stubborn did not respond to treatment, and we started on miltefosine, and we saw some great results afterwards.

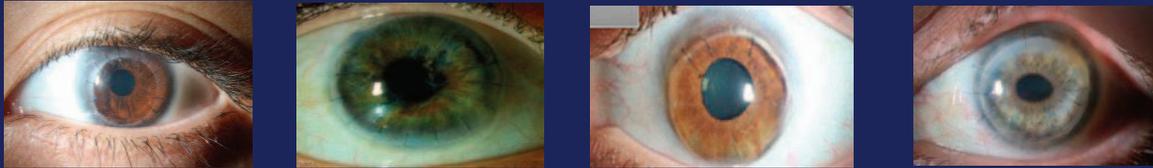
### Our experience with Miltefosine



Now, they have their optical cornea transplant and its been more than four years actually, the first case. It's been more than four years, and patients are doing great. The other three cases, as my previous colleagues mentioned, we've seen this inflammation response after miltefosine. The first cases that we saw this was concern, of course, and we get worried. We ended up doing a therapeutic point and transplant on these patients. Now it's been really more than three years for most of them. Interestingly,

these corneas actually, there has not been any reinfection afterwards, and the culture is actually from the cornea often that we removed at the time of the therapeutic cornea transplants was negative.

## Results



Cultures negative on the corneal host tissue



This is reassuring that we were doing the right treatment. At that time we did not do any steroids, because we're new to this, but now we're moving forward and doing the steroids at the time where we see these hypopytium, and increase in inflammation. Definitely, one thing from the experience after this, I do recommend to do cultures. You guys do cultures when we see this inflammation just to reassure we're creating this inflammatory response, rather than the worsening of the disease. As I mentioned, these cornea as do really well. One of them is already almost five years after optical cornea transplant, and as well as therapeutic cornea transplant, they're doing well. Definitely be aware of this environmental response. Also, I will say, with these sort of topical steroids now, systemic, maybe it would be a discussion for later on. Thank you very much.

Dr. Tu:

There will be an opportunity to ask questions, and we'll have a little bit of a panel discussion after this. We have the five cases, we want go through those first, but if you have questions, try to think of them, and we'll have a mic for you if you need it. Next, I'd like to invite up an Illinois native here in Dr. Meghpara. Here from Wills Eye Hospital to present his experience with miltefosine.

Dr. Meghpara:

All right, thanks, Elmer. Thanks, Todd, for the invitation. This is one of my cases. These are my disclosures, none of which are relevant to this case. I think this was 2018, so this was one of our first patients that we used this medication on. This was a 22 year old female, a contact lens user. She said she took care of her contact lenses well, but I mean, she's 22, so who knows. She presented with two weeks of worsening pain and redness. She was diagnosed with herpes at an outside institution, and started on oral Valtrex one week prior. This is what she looked like on presentation.

22 year old CL user

2 weeks worsening pain and redness

Diagnosed with HSV keratitis and started on Valtrex 1 week prior



In contrast to maybe some of the other photos you saw, this was maybe a little bit of an earlier presentation. This was mostly epitheliitis, with a regular epithelium ridges, whirls, If you look at the cobalt blue light, you can maybe see how this could be confused with herpes maybe. You can call this a pseudo dendrite. Same patient, same time, just using different lighting. You could really see that radial keratitis really jump out at you.

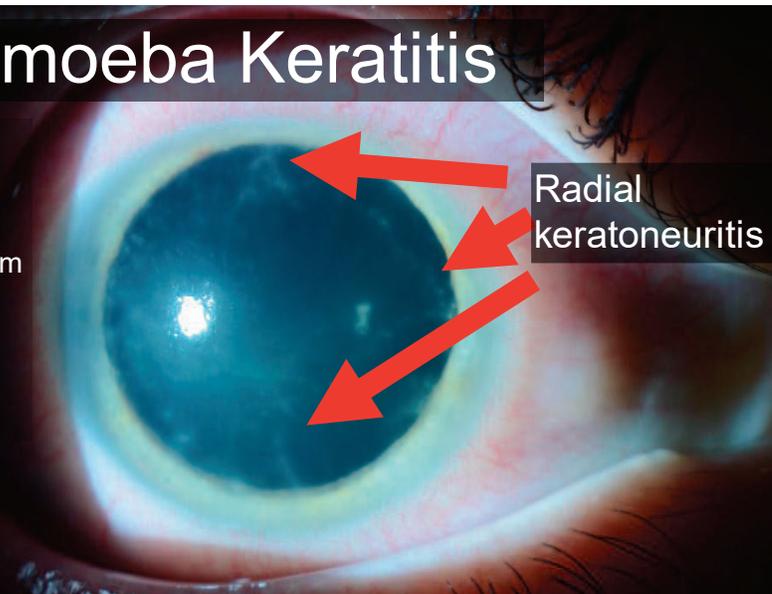
This patient was diagnosed with acanthamoeba, but started on PHMB every hour while awake. At this time, there was also a difficulty of getting Brolene. I work at Wills and the kind of the global that we do is, we do PHMB and Brolene together. We couldn't get it at that point, so we just did Bacquacil.

## Acanthamoeba Keratitis

Start PHMB Q1hr while awake

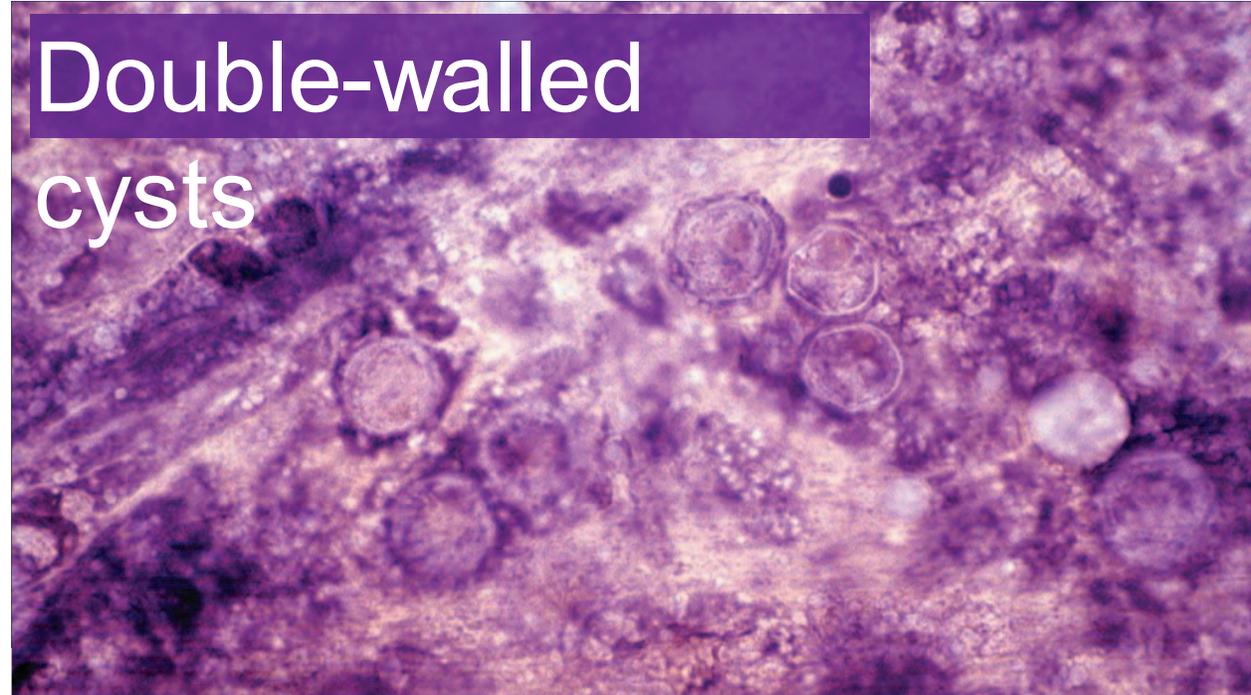
Epithelium sent to pathology to confirm diagnosis

Introduced miltefosine as a possible treatment



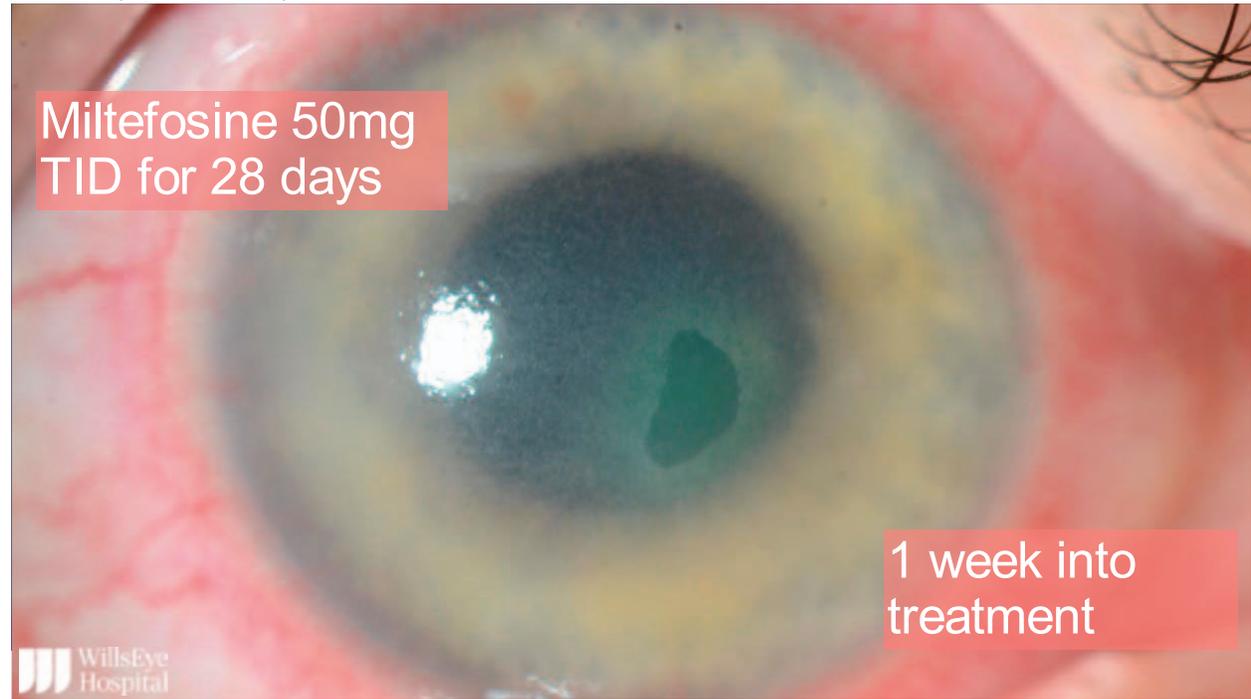
We don't culture, we like to send the epithelial specimens to pathology so that they can look at it under a microscope. We did send an epithelial sample to confirm the diagnosis, and introduced the idea of

starting miltefosine to this patient. We could talk about this later on, but I'd like to have a tissue diagnosis that confirms the patient does have acanthamoeba before starting the medication, although this is pretty convincing. This was the pathology specimen. This is a beautiful photo was provided by our ocular pathologist, Oh, geez. Okay. You can see the nice, classic double-walled cysts. There's multiple in that photo. I count one, two, three, four, five, six, seven, maybe eight. This confirmed the diagnosis.



# Double-walled cysts

At this point, we went ahead and started with miltefosine, 50 milligrams a day, with the goal of treating for 28 days. This is the patient one week into treatment.



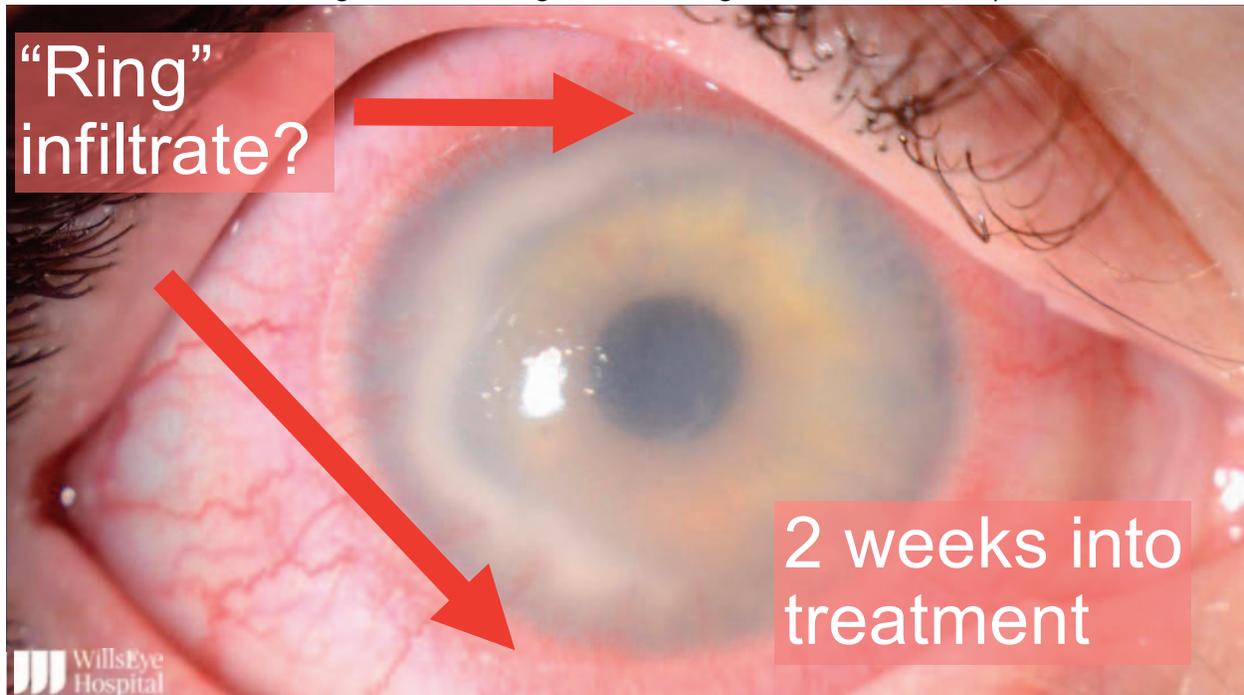
Miltefosine 50mg  
TID for 28 days

1 week into  
treatment

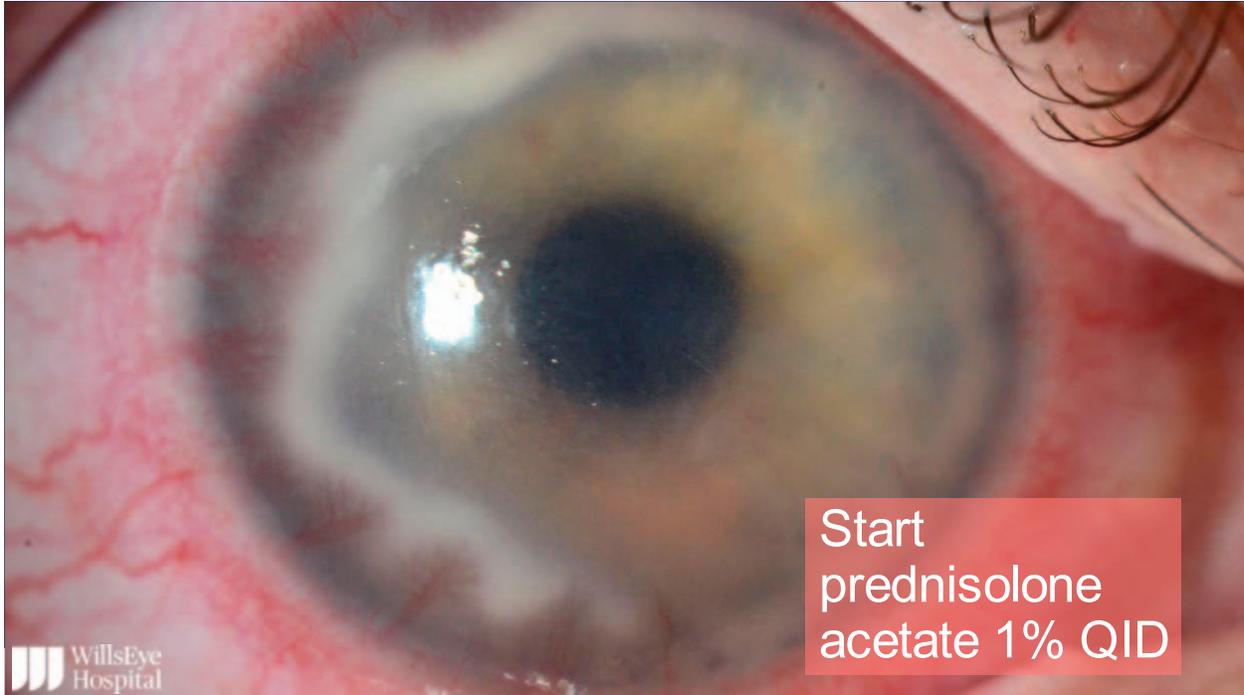
WillsEye  
Hospital

Para centrally you could see the epithelial defect healing. That was the biopsy site. The patient looks a

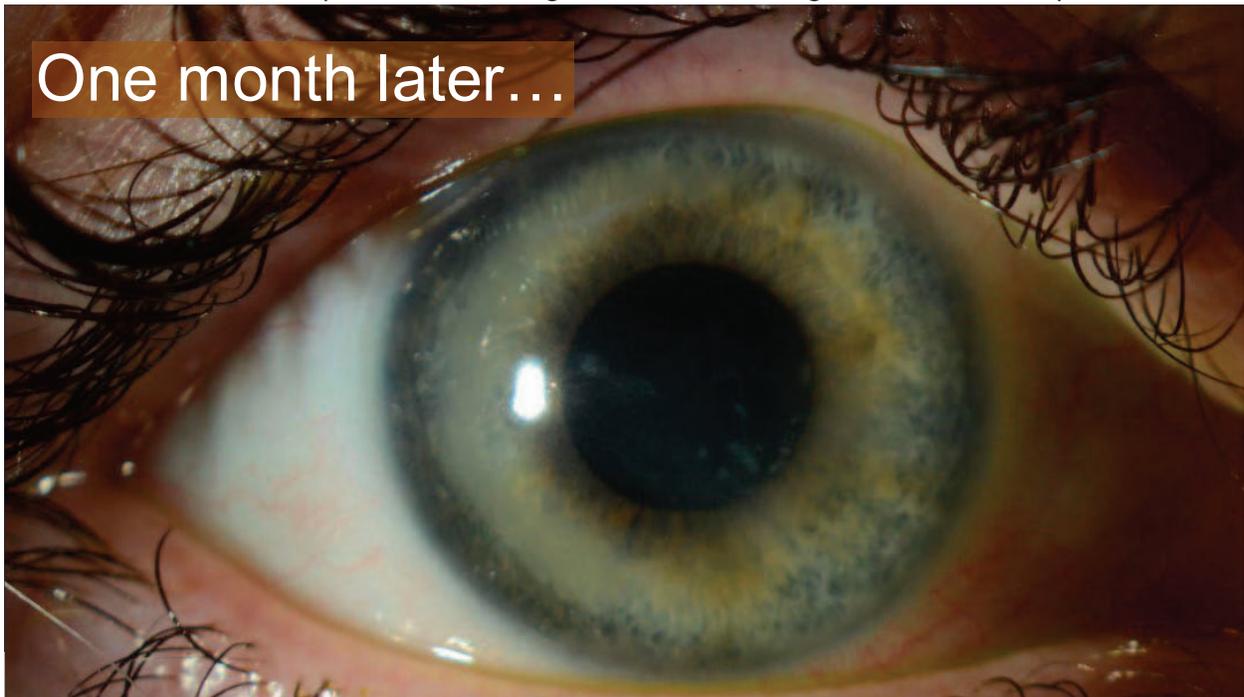
little bit different than they did at that initial photo. There's this more granularity, maybe there's something that's developing in the cornea. Two weeks in this treatment, the patient comes back and the person that saw this was concerned. "Well, are they developing a ring infiltrate now?" Then, "Do we need to change treatment? Do we need to add something? Do we need a transplant?" A few days later they came back and saw me, and this isn't a ring infiltrate, and you can tell, that inflammation is at the terminus of those vessels, right? It's not a ring, it's undulating, and it's almost scalloped.



This is one way how this post-treatment inflammation can present. Instead of being worried that this is worsening disease, we went ahead and started prednisolone acetate 1%, four times a day. One month later, I would say this is probably our biggest success story.



This cornea looked quite great one month after treatment, after the full one month course of the miltefosine. With this mild paracentral scarring, vision was 20/30 in glasses, and she did quite well.



Interesting enough though, after following this individual for now a few years, she did have, We got her off all her topical therapy, obviously just one month miltefosine, but we had to keep her on steroids for years, and sometimes it was just one drop of steroid twice a week or three times a week, because she would get these, almost like Chris had, these SEIs, or very faint areas of inflammation. Then eventually three, four years later, we just stop steroids and she's done fine. She did have this acute inflammatory

response, but also this prolonged small drain inflammatory response that lasted quite some time. Thank you.

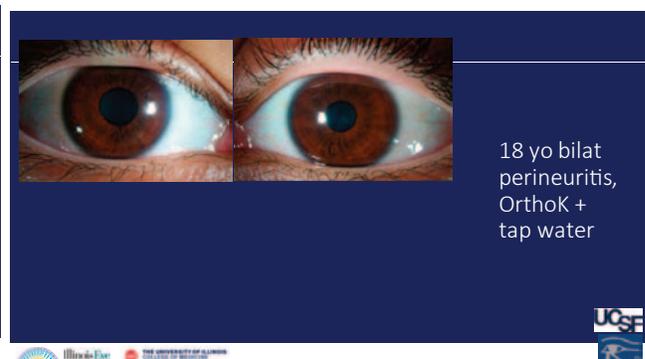
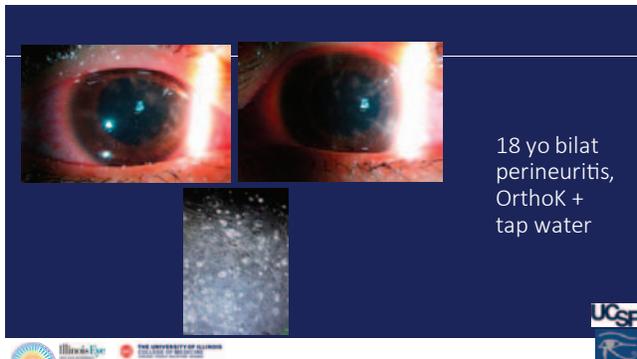
Dr. Tu:

Next up, Dr Seitzman from the UCSF Proctor Foundation, who will give us her experience.

Dr. Seitzman:

If there were a perfect way to treat acanthamoeba, we'd all be doing that, and we'd probably be done with the conference right now. We all have different ways, and we all feel pretty strongly about our different ways. There's no wrong thing to do, except for to start steroids before the acanthamoeba treatment. It's a disease of a tremendous of heartbreak, as we all know, and I just want to echo that Todd's been incredibly responsive, and on his honeymoon, pulled over and called the Walgreens for us. On numerous occasions, thank you for partnering with us in a rare disease with lots of suffering. There's no proctor, even though we're really nerds, so we take pictures ourselves of every patient. We do our confocals ourselves of every patient, so we really have a sense of if they're culture positive, confocal positive, and how deep their cysts are. Yeah. We all want to catch disease sooner than later. There's early acanthamoeba patchy keratitis. These are my patients we treated at UCSF with monotherapy and biguanide We can't get PHMB in California. Long story.

We start chlorohexidine 0.04 hourly through the night for 48 hours, and then we keep on hourly for a while. This is early disease. We love to scrape the cornea. These patients both recover really well. What happens when we have a 18 year old with bilateral perineuritis, the stakes are higher. Ortho K and tap water. To be fair, we do what we always do. Hourly chlorhexidine monotherapy. At three to four weeks we do start a little steroid, especially if they're in pain, and there's inflammation in the cornea. Beautiful double-walled cysts. It turns out three months later monotherapy patient does well. Okay, terrible disease. 17 year old showering. This is awful. We agree it's awful. There are cysts that go one third into the cornea. Also, at some point, can we discuss why are some double-walled and some are just in chains and cysts? I don't understand the different formation. What do we do here? Severe? To be fair, we use monotherapy, the same thing we always do. A month into treatment, he' s clear peripherally. We start



a little steroid, and this is just last month.

We're out of the woods with this severe case. We lucked out. Then there's this case who's been treated for two months before they even gets to me with this terrible full thickness corneal inflammation.

17 year old  
SCL  
+Showers  
+ lots of steroid prior  
to presentation

UCSF

This is not maybe that fifth person on miltefosine. I say, "You've been on our typical treatment. We will start miltefosine, 50 TID." A week later, we put you on some steroid. He already had Lotemax so we use Lotemax. We thought he had scleritis, so we start him on 40 milligrams of prednisone at one month. Oh my goodness, he's clearing. This is great. His kidney function goes up. We follow kidney function and liver function in his CBC in all different regimens. At proctor, we do live immune suppression ourselves for a severe case, and we're used to following blood work. We follow these people weekly until we figure out how we're going to manage this disease. We pause his miltefosine, we start Voriconazole . His liver function goes up. Long story short, we struggle with the neurotrophic defect, and end up doing an optical PK. He does beautifully.

Start Miltefosine 50mg tid  
Loteprednol tid -> 40mg pred

Creatinine= 1.40  $\uparrow$   $\mu$ M 1.08  $\mu$ M  
1 month later

4 month struggle with neurotrophic defect

36 yo monthly SCL +  
showers  
treated for hsv w  
Valtrex and durezol

Then treated with  
PHMB/Chlorhex for 2  
months on lotemax  
daily

UCSF

In our heads we think severe, deep disease, failed treatment. We start miltefosine, no problem. Then, here's a case. We met him nine days into treatment, sort of a patchy epithelial apathy. Early stromal disease.

**71 yo SCL**  
**Sleeps and**  
**showers in them**  
 tx with topical steroids but  
 we met 9 days into course

UCSF

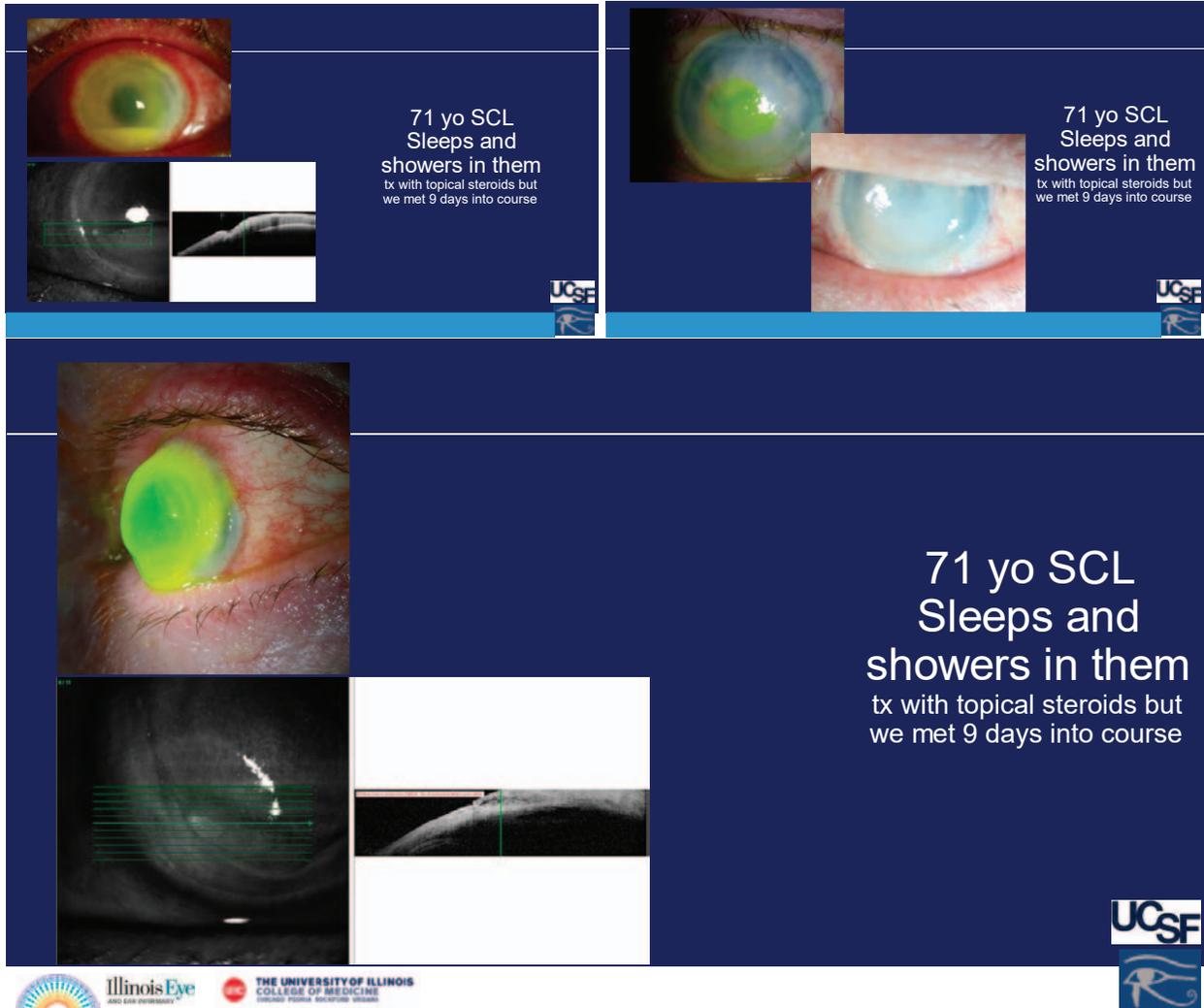
4 weeks

Start Miltefosine 50mg tid  
 8 days later

Start PF tid

**71 yo SCL**  
**Sleeps and**  
**showers in them**  
 tx with topical steroids but  
 we met 9 days into course

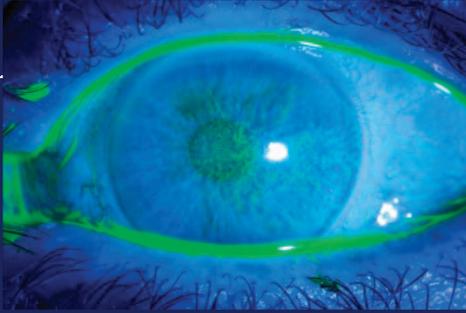
UCSF



You see dendritite cells on confocal. Not a high cyst load. I actually said, "We caught it early, you're going to do great." Never say that. Oh, where are we here? Yep. Yep. Bottom line, he doesn't do great. The cysts start to penetrate deeper, and so he had superficial disease now into anterior muscle. We do start miltefosine. It's okay that it's getting inflamed after a week. You're getting this now, we start Pred Forte. Here we go. Hypopyium, peripheral gutter. We know that it's inflammatory, but to be fair, this is where evidence-based medicine fails us, because the patient's in so much pain, and he's worsening. We really think it's a miltefosine response. The patient wants everything we send him to across the country for Rose Bengal PDT. The peripheral guttering just goes around 360 degrees. He has an ectatic cornea, he perforates in the peripheral Exactly the story we don't want to hear.

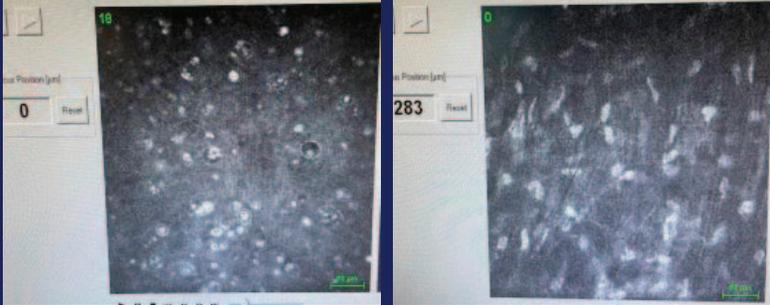
We do this large PK with a neurotrophic defect, but here's the crazy thing is that, the transplants clear. Sorry, the TPK was clear. This is him, honest to God, about few weeks ago. He has a swollen cornea, failed transplant. He's going to do fine with an optical. He wondered if miltefosine helped us.

Now I just was on the phone with this patient yesterday.



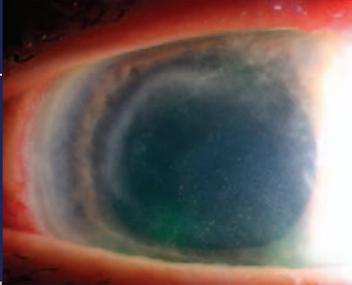
64 yo SCL  
swam in river  
in Africa  
tx with topical steroids  
but we met 10 days into  
course

+Culture  
acanthamoeba



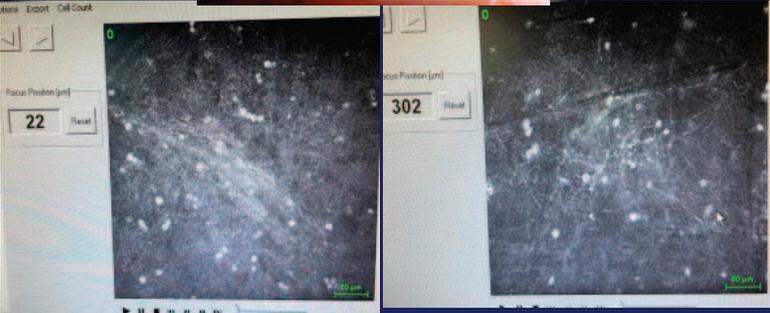
Early disease, patchy keratitis. Look at those beautiful double-walled cysts. Anterior stroma is clear. We treat her like we do everyone, monotherapy except for she's got a ring at four weeks.

4 weeks



64 yo SCL  
swam in river  
in Africa  
tx with topical steroids  
but we met 10 days into  
course

Start Miltefosine 50mg tid



We start a steroid. The trouble is the cysts. Look at them, they double down. They're in cyst chain formation. Now she's at 300 microns. Oh no, let's start miltefosine. Ugh, everything's getting more inflammatory. We think that's okay. Let's just double down a second month. That is a lot of inflammation. We think it's just miltefosine, I'm not sure. Then what happens is that now her creatinine

went up, her white blood cells went down, we had to stop for a week. We've restarted just yesterday, last night, miltefosine BID.

8 weeks 2<sup>nd</sup> month miltefosine

12 weeks 3<sup>rd</sup> month miltefosine

64 yo SCL  
swam in river  
in Africa

tx with topical steroids  
but we met 10 days into  
course

Increasing creatinine  
Decreasing WBC  
Cysts >330

UCSF

When I look at that I think, "Is this a case that I'm going to present?" I wish I would have TPK'd her earlier. I'm not sure. I think, in general, in nuanced acceptance, like a million, we start everyone at UCSF on the same treatment, except for if they progress at three to four weeks and we get deeper into the cornea, then we do start miltefosine. If they failed reasonable medical therapy, we consider miltefosine. A lot of cases do well with topical therapy, but sometimes they don't. Severe case sometimes does well with topical therapy. Severe cases can do well with miltefosine. Sometimes mild cases progress no matter what you do. Cysts are terrible, and you take it personally. How do we decide? Well, gosh, we need ROCT of how to treat these patients. The trouble is, we need a treatment. We need a trial of everyone at the exact same stage of their disease. The people who were pretreated with steroids, the people who weren't. That's really limited by the end of the disease, and it's hard to do, but we're all capable of hard things.

Dr. Tu:

That's awesome. Thank you, Gerami. I'll open it up to the floor for questions, but I think maybe the panel, we can start talking about... I mean, whenever we have a new hammer the question is, when is it proper to use right? Maybe a poll of everyone here, what stage are you going to consider using miltefosine? What criteria? I know this is difficult, but-

Dr. Rapuano:

I'll start. I've had pretty good experience with it. I haven't had the really bad inflammation, so obviously my experience is tainted or better than average perhaps. I'm starting in people who have strong disease. If it's just epithelium, I'm not starting it right away. If they have radial keratoneuritis then I talk about it, and I usually will start it within a week or two, especially if they're not getting a lot better quickly.

Dr. Tu:

Dr Meghpara?

Dr. Meghpara:

Yes, as Chris' younger, more aggressive partner, I probably started a little bit earlier than you do. Like I mentioned in my case, I want a tissue diagnosis, so I want to prove that it is a acanthamoeba, but we don't have a confocal, so we rely on our pathologist. Although, I guess, technically my case there, that was probably the earliest that I've ever started it. I guess there was current neuritis there, so maybe it was stromal.

Dr. Rapuano:

Stromal

Dr. Meghpara:

Yeah. Certainly I'd probably start a little bit earlier, especially now that we've used it a fair amount and have had good success. I guess, Elmer, a follow up question would be maybe, after everyone goes through their answers, what things do we worry about systemically for those of that haven't used the medication? What do we check lab-wise? There's no standard for that either. I think we were talking earlier, and we all do different things as well. Maybe we can talk about that next?

Dr. Tu:

Yeah. Jamie, you want talk a little bit about when you decide to start the miltefosine

Dr. Martinez:

Same thing. When there's strong disease, no response to standard medical treatment. It's sometimes difficult to get the drops probably for the patient, so wait at least two weeks to see how progression. One week maybe, but two weeks to see no progression. I mean, sorry, if there's progression, then definitely start on miltefosine.

Dr. Tu:

Gerami, you made a great point. This is unfortunately not a reportable disease, and there's so many different ways to treat it, and the presentations don't always clue you in necessarily as when medications should be changed, and when you can start. I mean, how do you go about, not just miltefosine, but do you change your treatment based on the appearance or are there criteria for use?

Dr. Seitzman:

We do. We change our treatment based on clinical worsening, which is really multifactorial. We start with chlorhexidine, and if we... We don't even understand how to assess drug resistant acanthamoeba. We don't tests for that, so we use a gut feeling. Gosh, if chlorhexidine isn't working, we'll switch to the other biguanide shipped in illegally in California if we use PHMB. Also, these drugs don't penetrate quickly. Nothing we do penetrates deeply, and we don't get how deep rose bengal works so far. When we see cysts at 300, 400 microns, I don't know... I know what an inflamed cornea will get a little deeper, but with deep cysts, I think then the gut feeling is, you need something systemic to get deeper.

Dr. Rapuano:

I mean, what strength of PHMB or chlorhexidine do your people use? We use 0.02%, but yesterday at one of the meetings they were talking about using higher strengths. You use 0.04? They were talking about 0.6.

Dr. Seitzman:

We do 0.04. Then of chlorhexidine and PHMB, if we use it, and then if it progresses or we think we want to escalate because of Dart's paper with the 0.06, sorry, 0.08 . We'll go up to 0.08. Nobody knows,

Dr. Tu:

No, and since Dr. Dart's paper, we've actually been continuing with 0.06 as a standard initial therapy. I don't know if...

Dr. Martinez:

You commented something on rose bengal. We have the rose bengal therapy.

Dr. Seitzman:

We've heard.

Dr. Martinez:

Yeah, so that's also ... cases were so severe, just you do everything you can to treat it. We do miltefosine. When they're waiting for miltefosine, Sometimes we overlap on that area, but definitely rose bengal penetrates about 200 microns. Sometimes these patients they have, so we don't know, maybe it could be deeper in these kind of cases where they have sort of like...

Dr. Seitzman:

Did any of you debride a superficial lamella surgically to allow for penetration of something deeper?

Dr. Rapuano:

To remove stroma?

Dr. Seitzman:

Yeah.

Dr. Rapuano

No

Dr. Tu:

I mean, there was a report of someone who PTK, basically just 200, 300 microns, and it seemed to work in that particular case. I don't know the kind of confocal that does that perfectly in terms of exactly where it is. Just a comment about, it's been the experience and international experience that if you have a patient with deep disease that's been posterior half or posterior third, if you do collagen crosslinking they get more much worse. I mean, their corneas melt, much like you showed with the patient that you had. They melt very rapidly, and the cornea basically dissolves afterwards.

Be careful with deeper disease if you're thinking about at least collagen crosslinking that's a problem. Any other comments about... What about testing? Beeran brought this up. I mean, we were talking about earlier, I'm hands off. You tell either the infectious disease people if you're working with them, which we don't, or their general physicians, because they're on miltefosine. Do your thing, because I learned early on when I was treating someone with cyclosporine that I can bag their kidney. Ever since then, I've always handed this over to their general PCP to determine.

Dr. Rapuano:

What I do is different from what Beeran does, but you have to make sure they're not pregnant. If they're of childbearing age, woman, make sure they're not pregnant before going on it, and I get a CBC, and then just a regular kidney test, liver function test, and CMP, and then I'll write their medical doc and say, "Here, I got these tests, now you follow them."

Dr. Meghpara:

What I do, I get a pregnancy test, but my wife's an internist, and she hates when she gets letters like that, and fax them over to her. I check before I start treatment. A CBC, a CMP, to check kidney and liver. Then I'll recheck it myself two weeks into treatment, and then recheck it again at the conclusion four weeks afterwards. Then if I see anything, then I'll say, "Call your PCP." I just check it myself.

Dr. Seitzman:

As I mentioned, we get a pregnancy test only before we check weekly. I've asked a few PCPs, they say, "I hope you know how to follow up, because I don't know how to follow it." We get weekly. Maybe too conservative, although we pick up a lot of that dysfunction.

Dr. Tu:

One thing to remember, I don't know if Todd has this information, but this is not a new drug. I mean, this is 20, 30 years of worldwide experience in developing countries. That's usually where Leishmaniasis is, and it's safety profiles on it are pretty good.

Todd MacLaughlan:

Normally we recommend that you check the levels for kidney and liver every two weeks. Normally the kidney function doesn't change a whole lot, although Gerami saw some increase. Liver can go up. Of the 200 plus cases in Leishmaniasis, we only have one case but we stopped because of the liver enzymes. This is a worldwide drug that's been around for a while. Lot of experience with Leishmaniasis. In terms of AK, mostly US experience.

Dr. Tu:

Any questions from the audience?

Speaker 9:

Thank you so much for this information, and just I'm asking a question about the initial treatment for acanthamoeba. Do you push combine chlorhexidine and Brolene at the same time? Many times, this combination gives better results. This is the first question. The second, regarding the coinfection fungal infection of acanthamoeba. It's very common in long term treatment when the patient doesn't respond. We find fungal infection. Do you repeat the cultures every now and then, and how frequently?

Dr. Tu:

Wow, those are loaded questions. Thank you.

Speaker 9:

Thank you.

Dr. Tu:

I'll go down the line. Gerami, why don't you start first?

Dr. Seitzman:

Everyone's going to have a different answer, which means we're all equally right, I think. We start monotherapy. At UCSF, we don't use Brolene because of the NV3 data, that we think the BAK of Brolene does most of the cysticidal activity, so we just use an antibiotic that's high in BAK. The second part of that question was...

Michael:

Fungal.

Dr. Meghpara:

Combined.

Dr. Seitzman:

Oh, great point. The last patient I showed with this, we caught early with the superficial epithelial apathy was acanthamoeba positive and VZVPCR positive. We have to always remember the multi organism diseases, and we do re-culture to get a feeling of where we are. Although, remember if you re-culture and they're on hourly by one eye, the drop itself is going to limit your culture. If you really want to re-culture, you should cease treatments for two days.

Dr. Meghpara:

Yeah, our initial therapy usually is Brolene and PHMB. We can get that compounded by our pharmacy at Jefferson. As far as re-culturing, I don't do it routinely. I guess I probably should, but I do it if I see signs that things are getting worse.

Dr. Martinez:

I do use Brolene but it takes a while to get it, so I want to get ahead of the game, so just try to find it because it takes a couple days, maybe weeks to get it. I do start doing therapy. Also, that's a really great point to re-culture. We see these inflammations two weeks after surgery. I mean, sorry, after miltefosine. I think it's really important to culture. I do a lot of biopsies in these cases, because sometimes scraping you can get negative results, and if I know that initial diagnosis was negative scraping and positive on a biopsy, then if you're going to follow up and we do a re-scrape, you may not get anything. That's also where I have some problems. I have maybe even repeat a biopsy to make sure we're dealing with all the organisms. Thank you.

Dr. Rapuano:

As I mentioned, we do PHMB and Brolene. What we do is, I buy Brolene on the internet. It's over-the-counter in much of the world, although much of the world's pharmacies won't ship to the US anymore, you've got to look around and find one. Then I have stash of Brolene, which we then give to patients to treat them. I don't usually re-culture unless I see something that needs to be cultured.

Dr. Tu:

I mean, I've stopped using Brolene. As Gerami mentioned, we had an invitro article maybe 10 years ago that showed that it's really BAK that's the effective agent in that. Then Moorfields just had a study three years ago which showed that for Brolene, almost the entire acanthamoeba effect is from BAK. I'll usually treat them with a topical BAK containing antibiotic to get the dual purpose of hitting any bacteria that might be there, but also adding anti acanthamoeba activity. Polymicrobial is definitely an issue in many of these patients, because acanthamoeba is actually not there for your corneal tissue, they're there for the bacteria.

It's like hitchhikers guide to the galaxy. Dolphins are here for the fish, not you. That reference I'm not sure. Anyway, it is good to keep an eye on that. Now, the other question about combined therapy with biguanides, you had so many questions in that short time span, I appreciate it. I do not. I do not usually use it, because I think there are compliance issues, and there's not been really any studies that suggest that one is necessarily superior to the other. I would prefer to dose more frequently and be compliant, than have to juggle medications. I don't know other people's thoughts

Peter:

I have a question here from a hot, humid Mobile, Alabama. We're actually having a little outbreak about two or three a month. I think some of the etiologies have to do with ER doctors prescribing tobradex and in two cases, tetracaine. I think tetracaine anesthetic abuse is sometimes one of the reasons these end up so bad so quickly. Actually, when I land on Monday morning during patient rounds. I've been adding ivermectin. There's supposedly some anti acanthamoeba effect of that. Could you comment on that, and whether or not that might be synergistic with miltefosine?

Dr. Tu:

I haven't had any experience. I don't know, ivermectin and COVID is another issue. I don't know. Does anyone use ivermectin? Let us know how that works out, Peter. Well, that's a good question. Can I have a show of hands from the clinicians in the audience? How many of you have seen an acanthamoeba keratitis one in the last year? Wow, that's why you're here at breakfast. About many of you seen have seen five? Whoa. That's bad. Okay. What about 10? Okay, we're getting there. Yeah. Yeah. Well, I mean, there have been papers recently, you guys published one about how it's becoming more difficult to treat. I think we're all seeing more cases. What do you think?

Dr. Rapuano:

Kristen, what do you think?

Kristen:

There was a paper recently, was it you and...who looked at the MICs for acanthamoeba

Dr. Seitzman:

Yeah.

Kristen:

I thought that was interesting, because it was different outcomes, but it turned out that the MICs were the same. There's a lot of different factors than just what's going on with the bugs

Dr. Seitzman:

Another complication of polytherapy is that we always think it's going to be synergistic, but you have to remember you can have antagonistic if you use too many different types, and your therapy can be less effective.

Dr. Tu:

Gerami, you also mentioned, and I think all of us understand that the sensitivity testing is not valid. No, I mean it's completely invalid-

Dr. Rapuano:

For acanthamoeba.

Dr. Tu:

For acanthamoeba. I mean, it took them 30 years to get a semi valid test for fungal. I mean, they've been working on that since 1984. Just over the last few years it's become reasonably comparable for bacteria to this, but acanthamoeba is completely not correlated with clinical activity. That's part of the problem. We just don't have a way of testing drugs.

Todd MacLaughlan:

Just as a side note, Florida hospital just announced a test for that, for the brain eating amoeba, and it's also for acanthamoeba. I was talking to the person who developed the test. It's a PCR test, and they're looking at doing that test now for the time as well. That's something that they need to coordinate with you guys on.

Dr. Seitzman:

We just have to say out loud, we've got CRISPR gene technologies for a lot of diseases, and we're still in 2022 using pool cleaner. It's not the most sophisticated.

Speaker 12:

Can I just quick question? We usually do chlorohexidine and Brolene on our patients. We currently have two patients that are recalcitrant patients, and we started them both on miltefosine, and they seem to be doing good. They're responding. One of them is doing it for roughly two months, and the other one, two weeks. Good results so far. My question is, when do I know how to stop? When should I stop? It's working, but they need to stop it eventually.

Dr. Tu:

I'll start, and Todd may not want to hear this, but usually . No, at first it was very difficult to get this drug. In the first few patients that I treated, it was not with Todd. I mean, I was importing it from Germany. I was glad that the first patient was not heavy, because I could use it just twice a day but

extend therapy to about four to five weeks, because they only give you enough for 20 days, 28 days. It was a TID. I usually treat for a month, and if they get an inflammatory response, I stop it, and let them rest for a bit. I might give them a second month, and then usually if they're going to have a therapeutic or transplant or an optical transplant and there's still some information, I might give them some more at that time. I usually don't extend therapy out to more than a month or two initially. I don't know. I think this is a good question. Thank you.

Dr. Rapuano:

I mean, my standard's been a month, and then I would add it only if I needed to, and I haven't had to yet.

Dr. Martinez:

The maximum I've done is two months, but I do have a case that I was hesitant to do three months because there was no response. The patient had no worse, the side effects of nausea, they're not fun. She don't get her therapeutic transplant, but she's doing great right now after transplant. Definitely two months. One month to two months is mine depending on response, but no more.

Dr. Meghpara:

I think I'm pretty consistent with everyone else. The majority of my patients are a month. I've had one patient where I've had it on for two months. I typically do three times a day unless, as Chris mentioned, if the patient has significant nausea/vomiting, then we'll see if they could tolerate twice a day.

Dr. Seitzman:

I don't have anything else. That's very similar, when we do a transplant we put them back on that to be safe. The other thing, I don't know if we've mentioned, it's really common to have one severe episode of diarrhea or nausea/vomiting. It doesn't tend to repeat itself. We've had a few people that have just low grade nausea, and we actually pushed them through with zofran to tolerate the nausea a little better.

Dr. Rapuano:

I just want to mention, I know we have to end. I'm on the board of OMIC, the Ophthalmic Mutual Insurance Company and the malpractice company for many US ophthalmologists, and some of the biggest losses, malpractice losses for OMIC have been missed acanthamoeba cases. I mean, multimillion dollar cases. I know I'm preaching to the choir here to cornea specialists but there's a reluctance sometimes to refer patients to cornea, and people get in real big trouble. Not only the patients, but the doctor.

Dr. Tu:

Did you... Oh, sorry.

Ken:

Can I just say one thing? I know we're running out of time. Hi, my name is Ken from Albuquerque. First of all, I've seen six patients over the past about a year and a half or two years with Acanthamoeba. About five of them were scleral lens wearers. I don't know if other people have had that experience too. I've treated three of those patients with miltefosine and seen severe inflammatory reactions, including one which was shocking bilateral case, and with the worse avascularization I've ever seen in my life. It

went on for months, and months, and months. After treatment it kept getting worse, worse, worse. He was treated for two months.

All patients were treated for two months. He's done well. He's relatively low, considering. He's had a therapeutic graft and then an optical graft done elsewhere in one of his eyes. All three were treated for two months, and one of the patients treated for two months have recurrence in her graphs. Even two months on miltefosine, issue is BID, is not necessarily a cure-all. I just wanted to say, my experience may be different, but the amount of inflammation was honestly shocking, and it scared me from using it. I would just like to caution people that you can see just incredible inflammation with this medication. It least that's my experience.

Dr. Tu:

Yeah, it shocked me too in that first case that I did I use it in. We're almost out of time. I did want make one comment is that, we had a publication recently on scleral lenses, which was an abstract, and then also ortho K has an extremely high rate of acanthamoeba keratitis. One of the things is that, you think about infectious keratitis is contact lenses. Overnight, soft contact lens wearers is an issue, overnight wearing gas permeable lens wearer is an issue. Then, one of the problems with scleral lenses, as you mentioned, we had a number of cases, we also put that series together as well. We usually think of soft contact lenses as being the problem, somebody's wearing a GP can't possibly be an infection, but it's actually very high. Orthokeratology in the Pacific Rim, it was as high as, 33% of them were acanthamoeba. The other ones were mostly pseudomonas. Final comment, as usual.

Ken:

Thank you, Dr. Tu.

Speaker 14:

Good morning, everybody. Dee from Pittsburgh. Here's the deal about that orthokeratology issue, contact lenses and tap water do not mix. We need to make this very, very clear to our patients. It's not the orthokeratology, it's the tap water use, and after they changed the behavior pattern, the rate went down. Tap water and contact lenses, we got to educate our patients. We have an epidemic of acanthamoeba keratitis. How many hands went up? It's not a rare disease. Thank you, Profounda, for helping us cure this disease or manage it at least. Education, critically important, number one. Number two, can we all agree that a dendrite in a contact lens wearer should be considered as acanthamoeba before herpes so that we can get this disease early? If we do, you got it. We don't have to have this patient do a year of therapy. I really believe in extensive superficial keratectomy when you see that dendrite form. That's where the cysts are, right Gerami? I mean, that's where they are.

Any abnormal epithelium, get rid of it. You can send it for PCR too. If you don't have a lab, you can do acanthamoeba PCR, and that is very effective as well. I just think that early aggressive intervention, any irregular epithelium is likely infected. The downside is very low to doing this early, and the upside is super high, and we've had some big wins by doing this, and then you don't have to miss the diagnosis and all that. The other thing, is the tap water. You did some great work, Elmer, with looking at the tap water in Chicago with Dr. Joslyn. The tap water is not the same today as it was 40 years ago, because they're changing the amount of disinfectant in the tap water. People who used to clean their contacts in tap water 30 years ago were okay, not anymore. I think we really need to educate our patients. We're working through UCLA, and all this. We need a huge patient education campaign. Maybe we can partner together, and do this. Thank you.

Dr. Tu:

Great. Thanks Dee. I guess my final comment is that I think from presentations you realize acanthamoeba is not all rainbows and butterflies. There are very individual cases. We're seeing a lot more of it, and the more that we can add to our armamentarium, the better. I want to thank our panelists.