Hello, my name is Francis Mah, I’m in the University Department, Ophthalmology Department. I’m on the cornea service and I’d like to talk to you today about adenovirus, HSV or Herpes Simplex Virus and Herpes Zoster Virus and how it affects the external eye as well as management and diagnostic techniques and kind of an update for 2011. Obviously these diagnoses are very old but every year I think we need to update our background information in order to help treat patients with the best evidence. I am a clinician primarily however I’m also the Medical Director of the Charles T. Campbell Ophthalmic Microbiology Laboratory and I’m fortunate to have this laboratory because we do a lot of research in order to help us with diagnostic techniques and looking at new diagnostic techniques as well as looking at some of the newer agents to treat some of these agents. So we will go through some of the newer agents for potential treatment.

As far as my disclosures, the Campbell Laboratory has several members including Jerry Gordon who is now Professor Emeritus, Regis Kowalski who is the Chief Microbiologist and then Eric Romanowski who is the Director of our Laboratory. Also as far as disclosure these groups including the NEI have supported the research that we’ll talk about today.

So this case kind of represents exactly what we are talking about in terms of the difficulty in diagnosing as well as the morbidity to patients and why diagnostic techniques as well as management techniques need to be updated and hopefully improved through research. This is a case, the patient that came into the cornea service is a 41 year old Pittsburgher and for the past 2 weeks he’s had foreign body sensation, he’s had redness in both eyes, he’s seen several eye physicians and you can
see that he’s been on various different treatments ranging from Viroptic, which is a topical antiviral all the way to steroids and Depo-Medrol injections as well as Penicillin injections in order to, to treat various different types of infectious disorders. Unfortunately for this patient not only did he have to endure all of this treatment as well as time spent away from work, but none of these treatments actually helped him. He had no improvement over 2 weeks, and you can see he’s pretty uncomfortable.

On our exam in our clinic we saw that his vision was slightly down in the right eye, his left eye was 20/20. He had lid swelling, follicles, erythema, corneal subepithelial infiltrates and he was diagnosed in the clinic at this stage, 2 weeks later, with EKC, or Epidemic Keratoconjunctivitis as well as Medicamentosa with the typical medications that he was on including an anesthetic Proparacaine. We did a culture in the clinic and it was positive unfortunately as is typical for viral cultures, the culture came back 10 days later. So this poor fellow had to actually endure not only 2 weeks but 10 extra days of discomfort as well as not knowing exactly what we were treating.

So as far as adenoviral infection, so this would be the first of three topics that we cover in terms of antiviral, ex – or viral external ocular disorders. The problem with adenoviral infections, number one is there is no real specific diagnostic tool. The treatment, management, the morbidity to the patient is extensive, there are incorrect impaired treatments, there is multiple doctor visits, just like this gentleman had to endure. There is loss of work, even if it’s a child that has this, you know the parents have to find either a nanny or a babysitter or they’ve got to stay home from work in order to
make sure that the child is taken care of. So you can have loss of work, loss of school and that’s obviously going to impact the finances of the, the household. There is also morbidity, obviously the patient you know is not enjoying the situation as well as the fact that he doesn’t actually know what’s happening to his vision, does he have a blinding condition that’s going to progress. These are all issues that the patient has to go through for a “simple” adenoviral infection. The final problem is there is no treatment for adenoviral infection. So even if we can tell him that he’s got an adenoviral infection there is no FDA approved antiviral which will take care of his infection.

So what are some recommendations clinically? How can we treat these patients and give them the best medical care despite the fact that there is no approved treatment? Well, some of the current treatment or therapies for adenoviral infections, which have kind of been passed on from clinician to clinician and through residencies and internships, are very broad advice to these patients. Number one, for example, is there is symptomatic relief, you can have vasoconstrictors, artificial tears, topical non-steroidals, none of these are specific to cure the adenoviral infection but they do help alleviate some of the discomfort that the patient may be going through. We also want to avoid topical antibiotics and topical steroids, and we’ll go through why we want to avoid topical antibiotics and topical steroids several slides from now; but these are all the academic guidelines that we currently teach to our residents. Finally you want to have some isolation, you want to have handwashing, you want to make sure that for example towels, pillow cases, they all are used separately from the patient that has the infection versus the rest of the household.
Current practice patterns however may be a little bit different compared to the academic guidelines that are listed here. For example, the use of antibiotics and steroids, approximately a quarter to a third of those people in practicing ophthalmology offices are using routine antibiotics and steroids for adenoviral infections. This may promote potentially antibiotic resistance and even epidemics because of the resistance. In terms of isolation or minimizing, the isolation, people want to get back to work quicker, people want to not have to keep their kids home from school and so they try to minimize that, they try to send their kids back to school a little bit earlier, or they try to go back to work a little bit sooner than is recommended by their treating physicians. As far as handwashing, it’s variable. It’s very difficult to tell a patient to stay away from their eyes even though their eyes are bothering them, or to make sure that these patients are washing their hands or using separate towels. It’s very difficult to break these kind of routines that we all get into, and so as far as what happens in daily life versus what we tell the patients it may be very different in terms of what’s happening.

So some of the pearls that we have here as far as clinical management, adenovirus unfortunately is the most common ocular viral infection worldwide. Apparently there is about three major syndromes, one of them is EKC, which is the most devastating in terms of its morbidity. There is also follicular conjunctivitis, which is the most mild and then there is pharyngeal conjunctival fever. It is the most common viral infection worldwide, in Japan they have over a million episodes per year which obviously could be very impactful you know in that country. It’s actually a reportable infectious condition.
So some of these questions and whether you have the answers to these. So today, 2011, if you have a patient with potentially EKC should you shake their hand? What we have found in our laboratory, probably not unless you are wearing gloves. So we did a clinical study where we actually cultured the hands of patients that had adenovirus and EKC and we found that 42% of these patients had positive cultures from their hand and so since adenovirus is spread by contact you probably don’t want to shake their hand, you want to be polite and so forth. And that’s the other thing is these patients didn’t know to wash their hands or they didn’t wash their hands and they did reach up and they touched around their eyes prior to coming to the doctor’s office. So as far as shaking hands, you probably don’t want to shake their hands unless you know for sure that they don’t have adenovirus.

What about in bottles? In the offices we often have Proparacaine or we often have Fluorescein bottles, dilating drops and they all contain Benzalkonium Chloride, how about those? And what about surfaces in the office like chairs with cloth or doorknobs or tables or the slit lamps themselves, how long can an adenovirus survive on some of these office surfaces when these patients show up for their visit? Quite surprisingly it’s a long time, depending on the surface as well as depending on the serotype even up to 7 weeks on some surfaces in offices. And so you can imagine that if you see one patient in the office that has EKC for 7 weeks you may be spreading unknowingly this patient’s EKC depending on the strain as well as what they touch. So in general you’d like to get these patients if they call in and they say that they’ve got an infection of their eyes, or you are thinking that they might have pink eye not to have them sit in your offices but go directly to an exam room and
wait there, because it’s much easier to clean the exam room than it is to clean the entire waiting room.

So for example desiccated adenovirus 819 and 5 survive 8 days on paper surfaces like magazines in the waiting room. You can imagine that these people are picking up magazines and for 8 days the adenovirus is living on these magazines; 10 days on cloth, for example the chairs that the patients are sitting in; 5 weeks on plastic surfaces and then 7 weeks on metallic surfaces like doorknobs and so forth. So again, if you suspect that a patient has an adenoviral infection you’d like to get them right into a room from the front door as soon as possible to prevent the spread of adenovirus.

What about the Benzalkonium Chloride question? Again, we use many drops, we don’t use disposables typically, we typically use multidose bottles, for example Fluorescein, how long can adenovirus survive? Adenovirus can actually survive in bottles containing Benzalkonium Chloride for 3 to 4 weeks, depending on the serotype. So again it’s a perfect mechanism of spreading the adenovirus. So you’ve got one patient that comes in, you touch the eye by accident with the Fluorescein bottle or Fluorescein tip or a Proparacaine bottle, that bottle is now infected and you could potentially transmit this virus for the next 3 or 4 weeks to unknowing patients. And so it’s very important that if you do have a patient again use disposable products, for example the 2% Fluorescein in the little vials or the Fluorescein strip when you have patients that you think may be infected with adenovirus.
Is there a new diagnostic technique? There are several newer techniques one is immunochromatography, or IC. It’s very, very simple, it’s very, very fast. Accuracy is pretty good, 88% sensitivity, specificity is excellent so if you get a positive test you pretty much know that the patient has adenovirus. There’s also two different versions of the IC test with two different companies that have immunochromatography tests that are available commercially. One is the SAS Adenotest which is FDA approved and then there is the RPS Adenodetector which is more of an office base. So you could potentially have a very quick, almost like a pregnancy test where you put some tears in the well and then several minutes later you’ll know whether it’s positive or negative.

How good is the RPS test, Adenodetector test? Should I go out and buy a bunch of these tests for the patients that come in who potentially have adenovirus? It may be a little too early to tell, we tested this in our laboratory, we had masked observers looking at the different tests and we found that our sensitivity and specificity was a little lower than optimal. We found 81% sensitivity and 91% specificity. Interestingly we found that actually women were better examiners of the test than men were and once we kind of did a little research we found that as many of you may know, women actually have more cones and therefore have better color vision than men do and so we were surmising that that was probably why women actually got better test results in terms of leading these tests than men did. It was 9% sensitive versus and 100% specific and again women were much, much better at the reading the tests. It may be a little early for them, they are trying to perfect it, they are in clinical trials and they are going to publish a paper regarding a clinical trial. What about other rapid diagnostic techniques? We actually do PCR, a polymerized chain reaction, it’s a very rapid,
very, very sensitive, very specific test. The problem is it costs a lot of money, and so therefore it’s not really an office based procedure. We have this in our laboratory, and fortunately we are able to do this for our patients and hopefully in the future this will be much cheaper and smaller so that it can be an office based procedure.

What about if you want to send your culture? So let’s say you are going to send your sample from a patient to a laboratory where the sample actually survives and where you get a viable result from this culture that you’ve sent to a central laboratory? We actually did this study and it does look like it would survive a trip, specifically we sent a sample from Minnesota to Pittsburgh and it survived the trip. The storage temperatures varied anywhere from 20 degrees to zero degrees and all the samples survived. So if you were going to send a sample, you felt it was very, very important to get a sample read and to make a diagnosis quickly and you wanted to send it to either us or a central culturing center or a central laboratory, you would find that the result or the samples would survive the trip.

What about antibiotics, topical antibiotics? Are they indicated for EKC patients? Obviously this is a viral infection, the simple answer is no if you are definitely positively sure that the diagnosis is adenovirus. Yes, if you think it may be bacterial conjunctivitis. Interestingly as far as those physicians that treat the academicians treated with antibiotics for a known viral infection about 25% of the time, and comprehensive is about 32% of the time. There’s a lot of pressure obviously from patients who come in, they don’t want to leave empty handed if they’ve got an infection, and so I
think it’s you know very easy for a clinician to write for an antiinfective agent even though they in their minds may know that it’s not going to be effective.

Two considerations, number one is we actually did a test, a survey of comprehensivists as well as cornea specialists, academic cornea specialists. And academic cornea specialists actually got it wrong 50% of the time whether the patient had bacterial infections or viral infections. There was a flip of the coin, there are no scenarios if you really don’t know which one it is, you are really not going to do much harm by prescribing a topical antiinfective. Also if you are using it at the FDA approved dosages, for example either twice a day, 3 times a day or 4 times a day, you are probably not going to promote resistance if they use it at the approved dosage for the approved length of time, in other words 7 days. So you really are not going to do that much harm in terms of for the community and again if you are unsure of the diagnosis at least if it is a bacterial conjunctivitis they will feel better if you do prescribe the antibiotic.

What about topical steroids? Obviously these people are miserable, they’ve got a lot of inflammation around their eyes, is it right to use topical steroids in the treatment of EKC? And the situations where it is appropriate is rarely. Typically if significant vision is lost, if they are ptosis, iritis or pseudomemembranous conjunctivitis those are the indications for topical steroids. Interestingly when you ask clinicians, comprehensivists as well as academic cornea specialists the academic cornea specialists are using more steroids, probably because they are getting the worst case of EKC but they are using it about 40% of the time, comprehensivists about a third of the time in terms of
their topical steroids. So you should probably not really use topical steroids. Why don’t you really want to use topical steroids? Well it actually increases the spread so you may be benefitting that one patient, but the community, their family, their friends may be worse off because you could actually lengthen the shedding and therefore increase the spreading of this infection.

What about topical steroids to treat subepithelial infiltrates? Again, this is sometimes. So as we know, subepithelial infiltrates happen probably about 10 days, maybe 2 weeks after the beginning of the infection. They can cause a lot of discomfort, they can affect vision, so if they are causing significant vision loss, if they are you know not working, if they are not doing what they need to be doing in order to for example work, feed their kids, you know do their daily activities, then yeah, definitely you should be giving them some relief by using topical steroids. However again this may actually lengthen the overall course. In the literature these subepithelial infiltrates have lasted up to 66 years because of the use of steroids in promoting kind of the rebounding of inflammation that happens in the cornea. So what you want to do is you want to discuss with these patients you know the fact that steroids will in fact help, however it may lengthen the overall course and then obviously we’ve got the steroid related issues such as cataracts and intraocular pressure spikes, which you need to discuss to the patients.

There are some other ways of taking care of subepithelial infiltrates from EKCs that are in the literature. One is topical Cyclosporin has been reported to be effective, and then another procedure
is actually PTK or phototherapeutic keratectomy has been reported to be effective in removing or eliminating these subepithelial infiltrates.

Why is it wrong? So kind of back to the question of steroids and why we shouldn’t use steroids for EKC, what’s so wrong about it besides you know obviously the issues of cataracts and intraocular pressure spikes which are inherent to corticosteroids topically? Well, again it prolongs and it spreads the epidemic, and it can increase the days of shedding by up to 9 days. So again, you may be benefitting the patient, and the patient may be feeling better but overall the community may be worse off because you may be actually promoting the spread of these infections.

What about topical nonsteroidals? With steroids you probably want to stay away from as much as possible, what about topical nonsteroidals? We’ve found in our studies that they really weren’t that useful. They did not increase the shedding, so they were not as harmful but they really didn’t help the patients either. And in clinical trials it seems that it really did not benefit patients either, so often times in the clinic I’ll often tell the patients they can use some artificial tears, we can use some nonsteroidals. If they help, great, you can continue them. If they don’t, then they don’t have to use them because it’s not actually killing the virus or treating the infection. It’s more of a symptomatic relief similar to like Tylenol or Advil when you’ve got a head cold.

What about how long people should stay away from work or school if they do have EKC? You know the old time recommendation was not until you see the white of the eyes, not until all of the
symptoms were completely gone could they return to school or work. And it turns out probably 7 days is a reasonable amount of time, unless they continue to have symptoms. So about 90% of patients are not infectious after 7 days, it does depend on the serotype so if a patient after 7 days still has symptoms then they probably should not be going back to work or to school, they should be reexamined, but 7 days is typically I think a good recommendation because 90% of the serotypes will be gone by that point.

Can you prevent transmission of EKC in the home? We kind of touched upon some of the advice that we give people. It is difficult, adenovirus is spread by contact, it’s very difficult for the home again when you get in your normal routine, but you need very, very conscientious hand washing, you want to make sure the patients do not reach up towards their eyes, no sharing of towels, wash cloths, linens, no sharing of reading glasses or soap, no sharing of TV remotes, things like that. And you want to make sure that you know as much as possible you are kind of away from the rest of the family and using separate towels and wash cloths. As far as pillow cases you’d like to change the pillow cases every 3 or 4 days because you may be reinflecting yourself by using the same pillow case, so you do like to – you would like to change the pillow cases every 3 or 4 days.

What about transmission in the office? So let’s say by accident you’ve got a patient came in with EKC, they sat in your waiting room a little too long, or they you know accidentally got some contamination in the BAK bottle can you stop transmission in the office? This actually happened at Johns Hopkins at Wilmer. They had a very, very severe outbreak, they had a very lengthy spread of
EKC and they were able to eradicate and decrease the transmission within their office. Again, very meticulous hand washing, gloves, they had a dedicated red eye room so if a patient came in they would escort them directly into that red eye room, they would not stop at the front desk. You want to sterilize your instruments, tonometers and lenses, anything that might be near patients. You want to do that with heat or 1 to 10 dilution of sodium hypochlorite or Clorox. Actually the alcohol swabs do not kill the adenovirus so just doing the alcohol swabs will not kill adenovirus so you do want to use other measures in order to kill the adenovirus. Unit dose solutions, you know treating immediately in terms of a red eye room so again in 1999 at Wilmer in Johns Hopkins they were able to control a very bad outbreak and the outbreak went from 39 to .5 outbreaks a year. So they had a real significant problem and they were able to reduce it by implementing some of these measures.

What about contact lenses? Often times patients with contact lenses get these infections and they want to know when can I put my contact lenses back in? Do I have to get a new pair, especially if they’ve got gas perm contact lenses or if they’ve got the soft contact lenses where they get rid of them every year instead of disposables? Can they in fact reuse their contact lenses? So we looked at this in our laboratory and we found that you probably cannot reuse soft contact lenses. We looked at various different methods of cleaning contact lenses, the very best method for cleaning contact lenses and getting rid of adenovirus in contacts from soft lenses is heat. Unfortunately there isn’t a single manufacturer left in the United States that has heat sterilization units for contact lenses. So then you are left with hydrogen peroxide or the multipurpose solutions. The multipurpose solutions were the worst at cleaning contact lenses, hydrogen peroxide actually did a pretty good job, so what we would
recommend is if you know financial you are in dire straits and you just can’t get a new pair of contact lenses and you really want to use the old contact lenses, we would recommend using hydrogen peroxide but maybe going through the cycle 3 or 4 times and then again kind of advising the patient you know this may or may not work, you may reinfect yourself. So the best advice is going over to either a rigid gas permeable contact lens or just getting rid of everything that you’ve got and starting all over with a brand new contact lens as well as new solutions.

What about treatment? You know we’ve already talked about the fact that there is no FDA approved treatment for EKC or for adenovirus. Well they are looking at different antivirals, again it’s the number one viral infection worldwide so there is a big need for an antiviral for EKC. There are several candidates, these are all in Phase II clinical trials, so we may be several years away. One is the Aganocide, which is a stable derivative of N Chlorotaurine, that’s actually part of us, it’s in PMN as part of our innate immunity and this is a synthetic version. Alcon, in conjunction with Nova Bay is testing this agent. FST100 is actually Povan and Iodine mixed with Dexamethasone. It’s made by Foresight Bio-therapeutics and again they are in Phase II clinical trials to look at whether this is going to be an effective method not only for the microbiologic cure but also for the clinical cure of adenovirus. There is Doxovir, which is a Cobalt Chelating Agent, and it’s being looked at by OPKO Health and then finally there is Ionic Contra-Viral Therapy which is Digoxin and Furosemide. There have been some interesting reports that this has some efficacy against adenovirus and this is being looked at in the UK. So there is some hope that very soon we will have an agent to treat EKC and adenoviral infections.
So in conclusion for this part, treating ophthalmologists face daily challenges in the diagnosis and optimal treatment of EKC and in the prevention of adenoviral transmission in the clinic and the hospital and the community, treatment of adenovirus remains symptomatic with some academic guidelines, but promising new antiviral agents are currently under development.

So the next topic is herpes viruses. The herpes viruses have been around for over a billion years, there are various different forms of herpes viruses and there is only 8 that have been known in humans to cause infections. There was a nice review done in 2003 and epidemiologically there is approximately 59,000 new or recurrent cases in the US every year at a cost of approximately 17.6 or $18 million to treat. Now interestingly these patients that are affected number about 30,000, so even though you’ve got 60,000 new or recurrent infections obviously many of these are recurrent issues.

How do we diagnose infectious herpes? It’s mainly a clinical diagnosis. It’s got a very distinct pattern as we all know, people have a past history of these dendrites or geographic ulcers so it’s a very clinical diagnosis. There is no rapid sensitive office based test which is available, there are cultures, there is also an Elvis test and real time PCR, again nothing really rapid you know as far diagnostic techniques for herpes simplex virus of the eye. But we do have advancement by for example PCR which is very, very specific and can make the diagnosis within one hour.
What about the current treatment for epithelial keratitis? So there are various different forms of herpes simplex in the eye, and first we’ll talk about epithelial keratopathy or keratitis, and basically that is a classic dendrite, so now the treatment is either topical or oral. Topically there is Trifluridine, which is Viroptic, it’s 9 times a day and then you taper. Number two is Ganciclovir, which is 5 times a day and then taper. This is approved in Japan, in Europe and the United States. And that’s a newer agent in the United States, it does seem to be a little bit more tolerated than Viroptic in terms of the eye, the dosing is a little bit less; however it is a gel so it may blur the vision compared to the Viroptic.

Another agent is Acyclovir 3%, this is not available in the United States, it is available in Europe as well as Japan. This is an ointment, so in terms of blurring effect this would be the worst and it is also 5 times a day. Oral agents include Acyclovir, Val Acyclovir, Famciclovir, all of these have been shown to be effective, Acyclovir and Val Acyclovir are now generic so they are an inexpensive option for oral agents. For children you would use oral Acyclovir 12 to 15 mg/kg/day in divided doses. In general I typically will use either an oral agent or Ganciclovir since it is much better tolerated in the eye.

Can you tell about recurrent HSV from topical antiviral toxicity? Again Viroptic, which is very efficacious, is also very toxic. It has two preservatives include Thimerosal and Benzalkonium Chloride, you have to use it 9 times a day, patients complain about burning and often times I’ll get a referral because the patient will have been using the Viroptic for approximately a month, two
months, three months, they still have irritation, redness, they’ve got a lot of punctate keratopathy and the referring physician wants to know, is this HSV or is this just toxicity from the medications?

First of all herpes simplex keratitis is a self-limiting condition and so therefore after 2 weeks or a month whether you are on the drops or not typically it is resolved unless you get a secondary type of episode such as a metaherpetic type of a phenomena. So usually 2 to 4 weeks later you can stop the agents and so most of the times these referrals we advise the patients to stop, to use some preservative free artificial tears, to use some lubricating agents and that typically takes care of it. So after 2 weeks, 4 weeks you can stop the agents unless you’ve got a metaherpetic phenomena going on, in which case you would use other agents, for examples steroids, in order to help resolve the problem.

What about HSV and bottles containing Benzalkonium Chloride? So it turns out that HSV is not as strong as adenovirus and it does get affected by Benzalkonium Chloride. So as far as HSV in a bottle of Fluress for example, it will become eradicated in less than 1 hour, whereas again adenovirus can live in those bottles up to 3 or 4 weeks. So with HSV a little less concern about Benzalkonium Chloride, still probably be advisable to use disposable types of multi- or sorry, single use vials.

What about the treatment for immunogenic herpes? So we talked about epithelial keratitis, which is an infectious herpes simplex, this is immunogenic herpes. For example, stromal keratitis or iridocyclitis, so the HEDS Study, landmark study showed us that what we need to use is a topical
steroid and an antiviral cover. Many people were doing that already, but this showed that this was in fact the proper way to treat immunogenic herpes. So you want to control the infection with the steroids, you do not want to cause a recurrence, which is why you have the antiviral coverage. In terms of the antiviral coverage, either topical or oral agents are effective, and that’s what HEDS II found out. So as far as the agents you could either use Trifluridine or Acyclovir, most likely you can also use Ganciclovir although it was not studied, and then as far as oral agents you can use the Acyclovir as cover, 400 mg twice a day. My personal choice is Acyclovir 400 mg. twice a day, and then using my steroids to help with controlling the inflammation.

I think one of the concerns that many people have is long term use of steroids in immunogenic herpes; and so patients get caught up kind of a bouncing up and down in terms of getting significant inflammation, being put on some steroids, being tapered all the way off and then the inflammation coming back. I think one of the keys is that clinicians should not be afraid of using long term low dose steroids if it’s going to keep the patient from having rebound inflammation. As we all know, inflammation can cause scarring, it can affect vision, obviously increase the, the morbidity of the, the disease. I’d much rather deal with the cataract than an central corneal scar in these patients. So long term steroid use is okay as long as you are managing a cataract as well as monitoring the intraocular pressure.

When should you use long term antiviral suppression? Again this was answered by HEDS II and as far as the HEDS II it basically told us that recurrent disease is where we should start our long term
antiviral suppression. Single episodes, initial episodes it probably was not warranted in everybody.
The way that I like to advise is if there is a significant scar and the next episode may cause permanent vision loss, then I would advise it even if it was the initial episode. If there is a stromal keratitis which is recurrent, I would advise long term antiviral suppression even epithelial disease if it’s recurrent it is warranted to advise long term antiviral suppression in order to prevent these episodes. And that was borne out in an epidemiologic study by Lairson in 2003 and he showed that it is not cost effective to try to prevent every single episode but recurrent episodes would be warranted and it would be fiscally responsible.

What about antiviral suppression in preop patients? So if you’ve got a cataract surgery patient coming up and they give you a history or you know that this patient has had HSV in the past, what do you do to prevent a recurrence of HSV, because obviously the incision could cause the HSV to recur, the stress alone from having anticipation in terms of the surgery could cause a recurrence of the HSV, so in general for short term prophylaxis for surgeries where patients are not going to be on long term steroids such as cataract surgery, refractive surgery, glaucoma surgery, we typically would recommend two days preoperatively and then 7 to 10 days postoperatively with an oral agent. You could also consider a topical agent such as Ganciclovir or Viroptic or Acyclovir. I typically would choose an oral agent because it’s so well tolerated and it’s not adding another drop to the regimen postsurgically.
As far as long term prophylaxis, for example in defects or penetrating keratoplasties or DALKs we typically use oral Acyclovir, again for longer than a year to prevent rejections, recurrences. You can also use MMF or CellCept in addition to your Acyclovir and this has been shown to act synergistically to help prevent not only recurrence of the virus but also rejection. And so these are some of the recommendations for preop prophylaxis of known patients with HSV or a history of HSV.

What about possible future therapies for herpes simplex keratitis? There have been some studies looking at some potential agents, for example Loteprednol. Loteprednol is a safer synthetic steroid, there does not seem to be as severe in terms of the steroid responding types of intraocular pressure spikes and cataracts, and so people have looked at Loteprednol, it does seem to be effective in terms of treating immunogenic herpes simplex stromal keratitis as well as iritis. Amniotic membrane transplants can be adjunctive and helpful, and then animal studies have shown the down regulation of inflammatory cytokines and chemokines are a potential future mechanism of trying to treat or adjunctively help these patients that have had issues with their herpes simplex keratitis.

When should you suspect HSV in patients presenting without a prior history? So if you get a patient who has no history of HSV when you suspect HSV in these patients? One of the scenarios is unilateral anterior uveitis with iris atrophy. This is also in consideration with herpes zoster iritis. But anterior uveitis unilaterally, sometimes in unilateral blepharitis you can have HSV, and then focal endotheliitis with and/or trabeculitis can also cause – or also be caused by HSV. So if you’ve got a
patient with iritis and they’ve got intraocular pressure increase again a lot of people will think about HSV in terms of their diagnosis and they would be correct in thinking that that could cause increased intraocular pressures.

Van der lelij did a study and in 31 patients with anterior uveitis with iris atrophy 83% were positive for HSV and 13% for VZV. Obviously older patients are more prone to VZV or zoster whereas younger patients would be HSV.

What about an antiviral? Again, the Aganocides are looked at for HSV in addition to adenovirus the Povidone Iodine has efficacy against HSV in addition to Doxovir as well as the ionic contra-viral therapy, it’s the same list as the adenoviral list. Most companies and industry in general feel that in order for a drug to be a viable option to be manufactured that it should have efficacy not only against adenovirus but also against herpes. These are some other antivirals in preclinical development for adenovirus. And then we’ll move onto zoster.

So varicella zoster virus, which is our final topic, is a very I would say recognizable condition. The photo that’s off to your right obviously is a classic, obviously this is a very severe but it’s very recognizable. You can make the diagnosis from the doorway as you are walking in to see the patient. There are some issues though with the research involved with varicella zoster compared to herpes simplex. So the knowledge that we have is less and poorer than adenovirus and herpes simplex virus.
One of the issues is that it grows very poorly in cell culture, it’s highly cell associated, there is no animal models of varicella, there is no animal reactivation models of zoster, there is no experimental reactivation of latency in zoster. So unlike herpes simplex and adenovirus, we have very few mechanisms where we can actually study the virus. So a lot of the studies are more clinical studies. They may be retrospective, but these are the primary studies that we have available to us in terms of herpes zoster.

One of the more recent studies which is very important, one of the key slides in this lecture is by Severson, and basically what they looked at was they looked at herpes zoster and when they started antivirals and if the antivirals did impact ocular zoster. So we know that within 72 hours starting an antiviral for systemic zoster is very important because it decreases the chances of neuropathy. And so the study was looking at whether antivirals would decrease the chance of ocular comorbidities such as neurotrophic keratitis as well as iritis, stromal keratitis, corneal edema, uveitis and glaucoma. And it turns out that yes, if you start the antivirals, the sooner that you do, even one day difference can significantly impact and reduce the possible complications of zoster. And so very, very important that even though it’s been 3 days or 4 days, that you start the antiviral for these patients and you give it for the full 10 amount, 10 day amount, and it’s for the full dose. So Acyclovir is 800 mg 5 times a day, Valacyclovir is 1000 mg 3 times a day, and you do want to do that for the full 10 days.
Various different oral antivirals are used in the treatment of zoster. As far as the Viroptic, Viroptic has no efficacy against zoster so do not use Viroptic if you have a patient with zoster. Ganciclovir does have some effects against zoster but shingles and zoster are a systemic disorder so you’ve got to treat systemically with oral agents. So the different agents that we have orally are Acyclovir, Valacyclovir, Famciclovir, BVDU as well as some newer antivirals such as Foscarnet and Cidofovir. So again, the key thing is getting these patients started on an antiviral.

What about corticosteroids in the treatment of acute zoster ophthalmicus? So there are some conflicting studies. And what we probably would recommend is work with the PCP or the infectious disease person in terms of starting steroids and in terms of managing pain which is really the key with these patients.

In terms of pain management there are various different agents which can be used, but again very important to co-manage these patients with their PCPs or their infectious disease people, or with pain management. There are things such as the tricyclic antidepressants, there is Neurontin, a narcotic, all of these agents again I would probably want to co-manage these agents.

Another key slide regarding zoster ophthalmicus is this slide where we look at Hutchinson’s Sign. I think we all remember from residency and training that if you have any of the pustules going down the nose that’s the nasociliary branch of V1 and if you do have any of the pustules going down the nose that’s a positive Hutchinson’s Sign. And it turns out Hutchinson’s Sign is very predictive of
issues like iritis and neurotrophic keratitis. So iritis and cornea denervation such as neurotrophic keratopathy are much increased in terms of their incidence when you compare positive Hutchinson’s Sign versus negative Hutchinson’s Sign; so for these people I follow them a lot closer. So if they come in, they’ve just been diagnosed with zoster, they’ve got even a single you know little pustule on the nose, then I’ll bring them back within a week and follow them very, very closely for iritis as well as for corneal issues. If they don’t, then I’m a little less concerned about them, I’ll see them back maybe after 2 to 3 or 4 weeks unless they’ve got some issues.

There is a syndrome with Ivan Schwab described called herpes zoster sine herpete, this is something that we also need to remember. About 10% of the time zoster can be evident without the typical rash. If you get an acute granulomatous uveitis without the skin eruptions it’s in the V1 pattern, you get significant corneal anesthesia, you get the atrophic sector in the iris and then you get significant loss of accommodation, iridoplegia, and it is important to consider zoster as well as CMV as well as herpes simplex viruses and so therefore you may want to stick a needle in the anterior chamber and do a PCR to make the appropriate diagnosis.

What about immunosuppressed patients? So typically any patient under 40 or 45 I’d be very suspicious for immunosuppressive conditions such as AIDS or cancer, or immunosuppressive agents being taken such as high doses of steroids. With chronic VZV you can have immunosuppression and you’ve got to make sure that you look out for these patients. AIDS came up 33% of the time, bone marrow transplants 50% of the time and cancer 25% of the time in these patients with chronic
replication, so chronic shingles that’s occurring over weeks and weeks. And for these people they may need to be on chronic antiviral agents, again for weeks or indefinitely until the immunosuppressive agent or disorder is reversed or treated.

What about the differences between varicella and herpes zoster and zoster ophthalmicus? These are the basic different terminology that we use. So varicella, which is chickenpox, that’s about 4 million cases a year. So this is the classic chickenpox that most kids will pickup. There are some complications, 175,000 complications per year, typically from pneumonitis, from the chickenpox, and there could be 100 deaths from the chickenpox. Herpes zoster, that’s shingles, the incidence is about 3 or – 3 to 500,000 cases per year, lifetime risk is about 10 to 20%. And then there is ophthalmicus which is more specific around the eye in the V1 distribution. As far as eye issues with zoster ophthalmicus it’s about 50% of the time, again increased risk with a positive Hutchinson’s Sign.

There was a huge study regarding the zoster vaccine and this was published in the New England Journal of Medicine in 2005, there was a vaccine to prevent herpes zoster and postherpetic neuralgia in older patients. It is effective in approximately 50 – of decreasing the incidence by about 50%. So it is important that patients, older patients who never had an outbreak of shingles or zoster ophthalmicus get the vaccine in order to prevent the devastating effects of zoster.
So in summary for zoster, for a younger patient you know kind get the little red flag up for HIV, AIDS, cancer 20 times more likely. As far as immediate treatment the minute that you see these patients ask them if they are on an antiviral agent, if they are not you’ve got to put them on an antiviral agent. As far as pain management or steroids, leave that to the PCPs as well as the pain management folks. Hutchinson’s Sign is very, very important, watch these people a little bit more carefully for some of the complications that shingles or zoster ophthalmicus can cause. As far as the issues of shingles, hopefully these will reduce with the advent of the vaccine and as more and more older folks get the vaccine so that we can prevent shingles, and then obviously remember that not all shingles causes the rash and so make sure that that’s also kind of in the back of your mind.

So in conclusion for zoster, in the near future it probably will increase as Baby Boomers age, early and aggressive antiviral therapy is essential and hopefully the vaccine will help us in reducing eventually the number and the severity of zoster in the near future. Thank you very much.