Feline Infectious Peritonitis (FIP)
Dr. Elizabeth Berliner
Video Transcript

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Introduction: Dr. Elizabeth Berliner is the Janet L. Swanson Director of Shelter Medicine at Cornell University College of Veterinary Medicine. She holds a BA in English literature from Union College in Schenectady, and an MA in English from Binghamton University. In 2003, she earned her DVM from Cornell and is boarded in canine and feline practice with the American Board of Veterinary Practitioners. She serves on the ASV Board of Directors in the organizing committee for the new shelter medicine specialty.

At Cornell, she directs the internship in shelter medicine, trains veterinarians in both classroom and shelter settings, and consults with animal shelters regarding best practices. Her interests include shelter level consultations, diagnosis management, prevention of infectious diseases, and innovative outreach programs promoting accessible veterinary care, humane behaviors, and the human animal bonds.

Dr. Berliner also acts as a seasonal lead veterinarian for the HSVMA's Rural Area Veterinary Services program, which facilitates mobile spay neuter programs, spay neuter and preventive medicine clinics in rural areas of the U.S. to communities without access to veterinarian care. *[Applause]*.

Dr. Berliner: Thank you. So thank you for all being here at the last talk on the last day of the conference. I expected to have about four people in the room so this is pretty exciting. Even more exciting because I consider FIP to be kind of the trifecta of craptastic diseases in shelter medicine. So we used to talk about that in private practice, you get a bad disease with a nice animal and a nice owner, and that is the trifecta of craptastic. Right.

In a shelter scenario, we kind of have that with FIP, a really bad disease, and I'm going to talk a lot about that – a bad disease, usually really nice kittens, right. And then we have people that are really invested in those kittens because a lot of times they've been in foster care, so they've been hanging out with us for a while and people are bonded to them, or they are kittens that have gone into adoption and people have bonded with them. So it is the trifecta of craptastic diseases and we're going to wrap up the conference with it, so I appreciate you for sticking with me.

I chose this picture realizing it was going to be poor quality, but it was one of the earliest pictures I could find of FIP because it is a relatively new disease out there, and I'll talk a little bit about why that might be with some history. I'm going to do some review of clinical signs and diagnostics and a little on treatment, and then I'm going to talk about kind of the implications for shelter, and then some of the new research that's out there and what may be coming down the pike.

Caveat: I'm not a researcher. So I talk to researchers. I am a clinician and I'm in the shelters. And so my goal here was to kind of look at what's out there in the research now and be able to report to you what we know and what we don't know, and where we might be headed. This is also a new talk for me, so like Dr. DiGangi pointed out, this is the first time I'm really talking about this in this kind of audience and so I'm completely open to questions, feedback, and all of that. I'd really like to hear from you to know what else you need to know or what could be more useful for you.

So a little bit of review about the virus without getting too detailed. Again, I didn't want you to nod off or think you were back in virology, your second year of vet school. So it comes from a coronavirus. So FIP is a mutation of a coronavirus, and coronaviruses are called that because they are these beautiful little things that kind of look like sunshines, but they don't bring any sunshine or rainbows; they usually bring sadness, right, and lots of coffee or wine depending on your choice.

A coronavirus, itself, is a self-limiting intestinal virus in cats. So it causes a little bit of diarrhea, but not that much of a big deal, except for what its future ramifications might be. Important to know; here is the part that comes out of virology, that it is a positive-stranded RNA genome. And why do we care other than passing boards when we were in vet school? We care because that actually impacts the biology and the pathogenesis of how this works and become something like FIP. And so being a positive-stranded RNA genome, it functions directly in approaching synthesis. And so it promotes protein products that then enable that virus to continue to enter cells and replicate. And so by doing that because it is directly involved in the protein synthesis stage, there is less opportunity for repair than DNA viruses, and there is a lot more opportunity for mutation. And

so the area that we've been focused on is really these little S-spikes, all those pretty sunshiny parts.

Because the S-spike is what allows the coronavirus to enter into other cells and replicate, and usually that's just entering other intestinal cells and replicating and causing a mild disease that may or may not be a big deal. When it mutates to become FIP, it becomes a big deal, and that's where it occurs is in that little beautiful spiky protein. It's important to know that coronaviruses primarily affect epithelial cells. That becomes important in figuring out where is this virus going to cause a problem, and where is FIP going to cause a problem, so we'll talk about that in pathogenesis.

And this is another important thing to know, which I didn't know because this wasn't covered in my virology is that we actually have two stereotypes of feline coronavirus. So that FCOV is going to stand for coronavirus through this whole presentation. Both of them can cause FIP, but this is a primary area of interest right now in terms of research, potential prevention and treatment. So type I feline coronavirus predominates in Europe and in America, and it's the one we've talked about historically.

The type II stereotype is actually a recombination event, and, boy, do we hate these recombination events, right, when viruses find other types that are kind of like them, but not really, and then mutate and join together and create these super viruses, right. And so the type II is a combination of the type I feline and a canine coronavirus. So those two have recombined and now they're making this type II stereotype. And this is one that we're really watching. This is one we're really concerned about, and I'll tell you about an outbreak actually.

This is happening more in Asia, and this isn't that surprising because what else is a coronavirus? SARS. And if you remember back to when SARS became an issue about a decade ago, there was this perception SARS being the human respiratory virus in Asia that quickly spread and was very serious, and the fear that was that was going to be an epidemic that just kind of wiped out large amounts of people because it was so mutable and because we had no way of preventing or controlling it. And so these coronaviruses being as mutable as they are, being able to recombine, can be really scary events.

The other aspect is they can sometimes recombine and then mutate again in a way that makes them essentially not as effective, and so they can burn out. And SARS essentially burned out at that point with that epidemic. The other important thing about that is that's when people started paying more attention to coronavirus again. And when we actually started looking at veterinarians back at the feline coronavirus and FIP and saying,

"Is there something that we can learn from this that maybe can impact our ability to help these cats?"

So how does feline coronavirus transmit? Most of you know this. This is a quick review. But it is primarily fecal-oral, although it can be transmitted in salvia and it can be transmitted transplacentally, so two kittens from the mother. But primarily, we think of it as a fecal oral transmission. And so for us as shelter people, that's primarily litter boxes or our environment, and those are things we can control to some level. So it will be transmitted fecally in the litter boxes.

It can be shed from months to years so this is a long-term shedding process. It can be carried on coats and it can live in an environment if the environment is not cleaned sufficiently. They are widespread. And this is what we talk about when people want to talk about doing serology, and I'll go into that specifically with diagnostics. But coronaviruses are very widespread. Up to 90 percent of cats were positive in studies in densely housed populations.

So in shelters just looking at prevalence across the board, you can have up to 90 percent seropositive for exposure. One shelter study, 33 percent of cats entering the shelter were positive, and within one week, greater than 60 percent of them were positive. So we know that it is spreading in shelters, and it's not just by directly sharing litter boxes, it's also by activity in the environment, it's by fomites, it's our hands, it's our clothes, it's everywhere, so it's really throughout the environment.

I was going to show this video, and we'll see it if works. This is not because I think you guys need see this video, but I wanted you to know it was out there. I don't know if you ever have this experience, but sometimes when I talk to the people who work with me, or I talk with my mom, who raised me, I can give her all sorts of advice, and it doesn't mean nearly as much is what her next-door neighbor, her groomer, or her own veterinarian tells her.

And sometimes it's true in your shelter too. I hear from quite a few of you in your shelters that are like, you know, I have this questions, blah, blah, blah, and I'd give an answer back and they say, "Well, that's what I said, but they don't believe it from me. Can you tell them that answer because they might listen to you?" So this video, and I actually think it's pretty entertaining too, is – let's see if this works without playing. This is how we do it. *[Video starts playing]*. It has a lovely French accent to help people pay attention, and a creepy cat cartoon.

So if they won't listen to you, they might watch the video for the accent, and Augustus, who is unknowingly about to contaminate the environment.

[Audience laughter]. Right? Only the French. Yes, they won't look like that in the litter box. *[Video continues playing]*. Poor Play-Doh. So I don't know that we need to go into the intestinal villi biology, but as you can see, sometimes your staff, other people that you're working with, may actually pay more attention to Play-Doh than to you, if it's anything like my life.

So that cartoon is out there. That is actually – Dr. Diane Addie is part of that, who I'll be referring to quite a few times through this presentation. I just think it's a really nice different representation maybe to show your staff in terms of kind of educating in how this is passed, and then some of the sad effects that can come from it. So I'll make the switch now because I've kind of given the background on feline coronavirus to really talking about how that becomes feline infectious peritonitis, and then how we find ourselves in the sad story of having a disease we can't treat, and in some cases one that we even struggle to try and diagnose.

And so there is a lot that's not understood, but we do – there are several theories going about in how coronavirus becomes feline infectious peritonitis, and we've really kind of settled now. So the researchers seem to be pretty happy with this internal mutation theory. And that's the one we've learned and we kind of explain to people *[inaudible]* about the way this happens. And so the idea is that a mutation allows entry of the virus into macrophages. So this is important. Feline coronavirus, itself, has a propensity for epithelial cells.

So those spike proteins, those beautiful sunshiny proteins allow entry into intestinal cells. The genetic mutation that occurs to become FIP allows the virus to enter macrophages. And that macrophage tropism is what enables the disease to be as virulent as it is, and to be something that we can't get under control. And then what it allows is that virus can now survive and replicate in the macrophages themselves in tissues, and then they lead to all the kinds of clinical signs.

So that's the mutation that occurs. How it occurs, we still don't exactly know, but this has been the focus in the last decade, and really in the last five years is when this has taken off. And so because we are now looking at mapping the entire feline genome, researchers have been able to narrow in a lot more in terms of which mutation is causing this. Then there are at least three mutations that have been credited with allowing coronavirus to now become FIP. And so, again, this is not my area of expertise, but there are three different papers out there that kind of symbol.

The ORF3c was the first one that people talked about, and indeed that has been shown to allow that tropism to occur, that change, but then there was also some recent research, Dr. Chang is here at Cornell on the S-gene, and

then recently in the Whitaker lab at Cornell as well. It has to do with S-gene cleavage sites. It's very possible that any one of these can cause this change, and so it may be multiple mutations that allow this to happen. But you don't necessarily need all of them for it to happen, which is why it can actually occur as frequently as it does.

And so even the pathogenesis of FIP is not truly understood. It's a really hard disease to study, and especially because we've gotten a little bit more sensitive about challenge studies and inducing disease in animals even in laboratory settings. And so what actually happens once that mutation occurs is not always the same in every animal, and that's why we get different clinical presentations. And one thing that we have learned is that actually some of the animals may eliminate it.

There are some animals who may actually experience the mutation for FIP but not actually get sick. And what they think that is, is it's because they have an appropriate T cell response. And T cell responses are responsible for some of the changes that we've seen even in HIV management. And so some of the animals may have enough of a T cell response that they can eliminate the virus and actually not get ill. And that is a relatively new idea.

There is a pathway that takes it through complement activation. So if you reach back into your immunology for the different inflammatory pathways that can occur when a disease enters a system, if complement is activated, that's when you tend to get pyogranulomatous vasculitis, not necessarily the leaky effusive form of the disease because that tends to be more antibody-antigen complexes, so the antibody and the antigen combines plug ups all the – creates leaky vessels, and then that fluid kind of pours out into spaces.

So the truly effusive disease tends to be more of the antibody-antigen response, but the complement activation also results in those kind of small deposition of little granulomas that you see on vascular surfaces. And both of these can occur simultaneously so it's not one or the other necessarily. And then there is an element of a cell-mediated response. So when you get the dry form and you just get granulomas, and truly it's a spectrum. Every cat has a little bit of dry and a little bit of effusive, but they end up on side of the spectrum or the other, that tends to be when the T cell response is depleted.

And so if an animal has had some form of T cell response, but then they kind of use up their T cell response, that's when you will get more of the non-effusive granuloma formation and something that becomes a little bit more chronic and a little bit more insidious and hard to diagnose. And so how the animal responds is ultimately responsible for the clinical signs

that we see, and why we see such a spectrum of change. Okay? And sometime it's a fuzzy as this – I'll have a couple of eye pictures. I was in Dr. Vallone's talk this morning, and I'm sure some of you were too. He showed a lot of really great slides on uveitis.

And indeed when I talk to students, uveitis is one of the things that I tend to focus on with these disease because it can be so tricky to diagnose. But truly the eyes, I think, are one of the earliest signs where you will see something brewing with an animal. And this is indeed a cat with FIP reflecting what is a relatively obvious case of uveitis. Even I could spot that one. I wouldn't necessarily have spotted some of the ones that Dr. Vallone had up this morning if you were in his lectures.

So what we think we know about FIP, this is what we've kind of talked about over time, is that the conversion to FIP is thought to be spontaneous. It just kind of happens. It's unique in a particular animal, which therefore makes it not contagious to other animals. This is what we've believed historically. New evidence suggests that we may be wrong, at least in some cases. That's kind of where I'm going at the end of this talk.

It was also thought to be uniformly fatal with a grave prognosis, but the truth is there are animals that respond in immune response and do recover, and we may just never know that they actually had that mutation and that that was possible. But it has occurred in laboratory settings. And this poor cat is really glad he is not sharing a litter box with Play-Doh. So a little bit about epidemiology in this. It is a disease of young cats.

So like I said, usually it's those cute kittens, right, they're the ones that you just want to send out into the world with sunshine and rainbows, with happy children who will frolic with them, and then they come down with this horrible disease. So it's our young cats, six months to years primarily, more common in males than females. Not tremendously more common, but that is true. And, again, it's the younger cats that are more likely to shed coronavirus, they're more likely to have diarrhea. They have compromised immunity, and they can have concurrent infections that can contribute to this.

A comment on this, there was a study that was done – actually it might have been with Florida a few years back, on looking at the prevalence of parasites, bacterial populations, and viral populations in animals – cats entering shelters. And they split it between 50 percent of the animals had diarrhea, and 50 percent of the animals did not have diarrhea. They had perfectly normal stool. They collected samples and they just kind of analyzed it across the board to see what was there.

Comparing the healthy animals without diarrhea and the animals with diarrhea, there was absolutely nothing that was significantly different in terms of the prevalence of roundworms, hookworms, salmonella, clostridium, and campylobacter, nothing significantly different in those two populations. The only thing that was significant is that the cats with diarrhea had a much higher rate of coronavirus, and that was sero, that was their serology.

And so interesting in that when it really comes to comparing the two populations, coronavirus may actually be the one that's contributing more to our cats having diarrhea in the shelters. It's possible. Especially when we have done fecal tests and all these other things, and kind of ruled out infectious organisms that we can account for. And this is sometimes how I feel. Anybody feel like this right about now in July? Does your shelter look like this? Because ours does. Yeah.

So it also looks like this. Kittens bounding out bins, coming in from foster care. So other things to know, obviously densely housed populations are much more prone to see FIP when we have lots of cats being housed. The incidents in shelters and in catteries are five to ten percent, which is much higher than in the average population. In a research cattery where they took a thousand exposed cats, they had only .8 percent incidents in that research population when they exposed them.

In Joliet, what we tend to stick with is that rates higher than one percent in a shelter are something to be concerned about. It is expected that about one percent of your young cats will develop FIP. That is something that may be beyond your control, at least as far as we've understood historically. If you have a rate higher than that, then it's time to be concerned and start looking at if they are some things to help control that.

Risk factors; certainly multi-cat households. Not surprising. Catteries, animal shelters; hoarding scenarios is a big one because of the stress and exposure. Stress, recent surgery, vaccinations, new home environments can all cause increase shedding of coronavirus, can all cause increased opportunities for mutation and increased opportunities for disease. And then purebred cats? So a lot of thoughts about the genetics of this disease. Again, we talked about how in different cats; there are different immune responses. There is a feeling that certain purebred cats are more prone.

This is certainly complicated by the fact that purebred cats come out of catteries usually, and so there has been some concern that we're not exactly sure how much of it – which comes first, the chicken or the egg, which is more important how the cattery is operating or that it's a purebred cat. But certainly some of the interest in this and some of the

research has been driven primarily by Birman cats, and some of the Persian breeders for sure.

And I see people nodding because they like Birman cats out there and now they're scared. Is there a pre-genetic disposition to this disease? At least for now, the research seems to indicate there certainly could be. Clinical forms, this what you all know. This is the stuff that sticks in everybody's mind in what you see, right. So the wet form, you get effusions; abdominal effusions primarily, thoracic effusions and granulomatous disease.

With the dry form, they tend to be non-effusive so you get central nervous system signs, you can get seizures, you can get ataxia, you can get ocular abnormalities with either of these. So that's the some of the earliest signs, again, I think. And then abdominal masses can arise where you actually are feeling enlarged kidneys, enlarged spleen, and enlarged liver because those granulomas grow to the point where they are essentially just large masses within the abdomen.

And so uveitis can look like almost anything. There are actually retinal infiltrates from the disease as well. The biggest thing is usually that non-specific ill- thrifty, cyclic fever, not really eating kitten. That's my first warning. If I've ruled out other things and I kind of have just this kitten that's failing to thrive. And temperatures, we don't take temperatures a lot in our shelter, personally. We take them when the animals are ill, but temperatures can be a big sign in this because they really wax and wane, and they tend to run these fevers that kind of go up and down.

They can get icterus, but that's usually later on in progression. So, again, I watch for fevers, anorexia, and kind of ill-thrift first. And then I check the eyes, for me, and try to do a good ophthalmic exam. The uveitis can be very subtle. You may just see a little aqueous flare. You may just seem some injection of vessels in the iris, itself. You may see infiltrates if you're doing a fundic exam, and that is a huge warning sign to me that uh-oh; something bad is brewing. I don't have jaundice yet. I don't even have fluid yet, but I've got a kitten with uveitis and a little bit of a fever and I'm really worried at that point.

Other things, like I said, neurological signs or abdominal masses are all possible. And so this is indeed is a cat with uveitis, and these little infiltrates, in my normal life, I would look at that and wonder if it wasn't a herpes sequestrum. It's pigmented. It's kind of floating back in there, but those are actually keratic precipitates that are forming from the aqueous flare and the aqueous chamber. And the way I know it's different is that sequestrum is not in the surface of the cornea like our sequestrums usually are. Instead, it's behind the eye.

If you saw Dr. Vallone's lovely drawings this morning, it's behind that eye. It's kind of attached to the inside of the cornea. It's in that interior chamber, and, indeed, we also have aqueous flare that's occurring on that side and that is actually FIP in that eye. So initial databases, we don't have good specific tests for FIP in blood work, but some of the things you're going to spot: lymphopenia, so they'll have a low lymphocyte count; they'll have a non-regenerative anemia, which won't surprise you because it's an ill-thrifty kind of sick-looking animal. You may have neutrophilic leukocytosis. The biggest thing is hyperglobulinemia. So the globulin will be up in over 50 percent of the cats.

Again, this is a non-specific finding that could be up for any degree of inflammation, but when you have that in a young animal that's showing these other signs, it becomes part of the clinical picture, and FIP becomes high on your radar. They may have elevated liver enzymes if they're at the point of having granulomas plaques or depositions in their liver that are contributing to disease. They may have an elevated bilirubin. You may have fluid. And certainly you can get into looking at kind of breaking down where you have a monoclonal or polygonal gammopathy. Most people don't get to that point. But if you do run it, then you're looking at something that this is normal inflammation across your globulin analysis, and this, you'll end up with a lot more of the gamma globulins in particular. But it still doesn't look like a cancer; it looks like a high-level of inflammation, which is exactly what it is.

Everybody knows this picture, right? You pull that straw-colored sticky stuff out of the abdomen and you – most of you are probably ready to call it at that point, yes? People make a diagnosis based on straw fluid from the abdomen. And that's mostly where we end up, especially if you're working in a practice or a shelter. So straw-colored, my line in the sand has always been a total approaching greater than 3.5 in that fluid.

So if the protein is lower than that, then I pause and I think, wait a minute, could this be something else? Could I be missing something? If it's higher than 3.5, if it's 4 or 4.5, 4.6, if it's sticky, then I'm ready to call it at that point based on a combination of clinical signs. The other thing is that you look at it under a microscope, and remember you can always treat your fluid just like urine. That's how I think about it, and that's how I teach my students and trainees. Treat it like urine. Spin it down, look at the cells and make a slide of the sediment.

Look it under a microscope. What kind of cells do you have in it? You can do a lot with just a microscope in your shelter to kind of analyze this fluid and not need to wait to send it to the lab. The other thing is that if you take this fluid and you do submit it to look at albumin and globulin,

this a relatively specific test for FIP, and one that they recommend if you're really struggling. So it's not your albumin and globulin ratio in blood; it's your albumin and globulin ratio in the fluid that you withdrew.

And so if the ratio is high, then you – the ratio between albumin and globulin has to be less than .9. And so what that means is your globulins are super high and your albumin in that fluid is low. And so if that ratio exists, then that's really specific for FIP in a very sensitive test. And so if you're struggling – now most people aren't at this point. Most of the time when you pull this fluid off, your protein level is high and you've kind of solved the problem and you've made the diagnosis.

But there are ones that can really start to fool you, and that's when people want more testing to be sure – because making this decision, it's often an euthanasia decision, is a big decision and it involves a lot of players and so you want to be sure of your diagnosis. Your major differentials are lymphoma, heart failure, liver disease, and peritonitis or pleuritis. Those diseases can happen in kittens, and so it's important to know that it's not something else.

I recently had a case that came into a community clinic I was doing. It was kind of classic to me, three-year-old male cat, perfectly round, like this cat was just round with abdominal effusion and muscle wasting over his back. I called that FIP from across the room. When we drew the fluid off it, we actually had a really, really low protein level, and that cat actually ended up having cardiac disease. It was still a poor outcome for that cat. It was still – he was in advanced stages of disease and not doing well and he presented for euthanasia.

But certainly in my mind, that was clearly FIP from across the room, and indeed wasn't. So there are other diseases that are going to come to you. We don't tend to think of cats as getting large amounts of abdominal effusion from cardiac disease, but it can happen so don't leave it off your list. Rivalta's test; I actually don't do Rivalta's test a lot. People talk about it. What it's actually testing for is the protein level in the fluid. And so if you've already looked at the protein level, and it's high, then you kind of know you're going to get a positive test. So people hold it out there as a test to do.

I don't tend to do it myself, but it's always talked about, so I wanted to make sure I included it in the talk. It's acetic acid or people would use vinegar, which is not exactly the same but it's pretty close. You put a drop of effusion in. If the drop disappears, then you have a negative test. If the drop retains its shape, then you have a positive test. So if you have the fluid that you took out floating around in your acetic acid, it's a positive test and you can be pretty sure that is FIP. Having said that,

people will talk about the fact that you can be absolutely sure that it's FIP because the positive predictive value and negative predictive values that have been reported are so high.

And so if it's positive, it's FIP. If it's negative, it's not FIP. The truth is that this came from a study where the prevalence of the disease was 51 percent because it was a controlled study so that affects your predictive values. So in reality, it's not a total slam-dunk if that test comes up positive, but it's a slam-dunk for a really high protein level in the fluid, which you already knew because you stuck on your refractometer. So, again, my go-to is usually the refractometer, and I don't tend to do Rivalta's testing myself.

You can do molecular testing. And this is where things get hard because what we really want is a molecular test that we can do on blood because we want to do it on the cats that we aren't sure have FIP. We want to do it on the ones that don't have fluid collecting in their abdomen. And unfortunately that does not exist. There is a not good test on the blood. But you can submit the fluid, and they can do a reverse transcriptase pcr, but what you're actually testing for then is coronavirus, not necessarily FIP.

So if you really want to know, you would need to know that that coronavirus had entered the macrophages. So to confirm that it's FIP, they actually have to identify the virus, itself, in the macrophage, which means, okay, it went through that mutation, and it was actually able to do enter the macrophages. And the reason that that's actually tricky is because the cell count in that effusion is so low. So if you ever had spun that fluid down and actually looked at the sentiment to make sure you didn't have just some sort of neutrophilic effusion or some kind of peritonitis, there is not a lot of cells in there.

So there aren't a lot of macrophages usually in the fluid. The macrophages are deposited on the endothelial layers of the organs, and they're causing the effusion but they're not showing up in the effusion. And so that test, itself, is actually – the negative predictive value is actually low. If you don't find it, it may still be FIP; you just didn't have enough cells to be able to visualize, to be able to see that virus in the macrophages. Does that make sense? Some of you are nodding, and some of you are like, "Oh lord, I should have totally gotten in my car and gone home by now." Right. *[Laughter]*. Okay. Good.

In development what's important here is they really are working on reverse transcriptase PCR tests specific for FIP, and even better, if they could find one that's in blood. But we don't have that yet. We don't have one that's available. All right. I'm not holding it as a secret in my back

pocket; it's actually just not out there. Of course what you all know is that biopsy or histopathology is the gold standard for this. So if you have a question, you don't have effusion, it might be FIP, the next recommendation is explore the cat and collect some samples, right, and send it in.

See what you've got. See if you have granulomas, and see if you can find evidence of it on histopathology. And the confirmation, again, is finding the coronavirus antigen in the macrophages because it doesn't belong there, and so that's what they're looking for. So it's really important that you sample multiple samples and multiple tissues because it may not be in every organ. And if you don't see it grossly, you may still want to get samples if this is indeed the path you're going down and you've done an explore.

Classic legions, most of us, if you're actually doing a gross necropsy or if you are doing an explore and you find this sort of granulomas pattern through the liver or thought the kidneys, then you're pretty much ready to call it on that, I think, right. And I think if you really need diagnosis, you collect a sample, you send it in, and then they look for the coronavirus in the macrophages in the tissue. Titers. Titers are not very useful – not useful at all in diagnosing FIP. They may be useful in talking about some prevention or control measures…maybe.

So it is not helpful, and I'm assuming everybody in this room knows that, to do a coronavirus titer to try and determine if an animal has FIP. A positive titer for coronavirus is not FIP, and a positive titer for coronavirus is not a reason to euthanize a cat because as I said before, it's ubiquitous. Sixty percent of cats in shelters, maybe up to 90 percent of cats in catteries, will have up positive coronavirus serology and it may stay positive. And so you never want to euthanize a cat for a positive coronavirus titer.

It may be useful as a point of control. It appears that cats that have high coronavirus titers indeed may be shedding high numbers or organisms. So there may be a correlation between the increase in the titer, and how much they're actually shedding. And this might be important if you are particularly in an area where you are experiencing an epidemic. So taking titers of some of your cats that you are suspecting, or the cats that are in the lobby, or the cats that have access to your whole facility, checking them to see if they're really shedding high amounts may be useful if you're really trying to decide how to handle an outbreak or an ongoing issue in your shelter.

But the key point, diagnosis of FIP is based on a combination of clinical signs. My students hate to hear that. My trainees hate to hear that. There

is not a test that's going to tell you if it's FIP. It's going to be a combination of clinical signs. You are going to have to actually use your problem solving skills to decide if this is the case, and you're going to have to make a call. And that's just the truth in FIP. No single test is going to help you. Treatment; now this is really disappointing because really there isn't any. You can use anti-inflammatory suppression of the immune system for palliation mixed signals on whether this works or not.

In most cases, if you use Prednisone, it's going to increase the animal's appetite and they might feel a little bit better, and it might control their fevers. And so that may seem to be a positive outcome in some scenarios, but it's not going to change the clinical course of disease. The progression is going to be exactly the same. It may just make the animal feel better. And so that's really the only thing that people are still talking about. Interferon does not help. People have tried to use it, but it really hasn't been successful in that. Areas of research in this are looking at antiviral control of replication of a virus, so they're looking at things like protease inhibitors, which are in some of the combination drugs that have been used in HIV control.

And looking to see if those drugs can help clinically affected animals to decrease the replication of the virus and to prolong the clinical signs. There seems to be some success. The biggest concern is that most of them are toxic to cats, and so finding that line between toxicity and therapy has been extremely difficult. And right now, there is nothing that's recommended. Absolutely nothing that's recommended, but it is an area of research.

If you need reminders on how to handle this, I wanted to make sure I include this source. I love algorithms and pictures and charts. And so when you're really standing there and kind of emotionally dealing with needing to make a decision on an animal, this is available from ABCD Vets. And I have all the references at the end of this talk, which is a really nice algorithm for how to kind of think through the clinical signs, the risk factors of exposure, what you're seeing on exam, the laboratory tests that are available, and how to make the call or the decision that indeed this does look like FIP.

And I need to not only deal with this, but also figure out what I'm going to do with the animals that were in contact with this cat. I have an FAQ section, which I am headed to because that's usually the calls that I get. So what does this mean for us? And this is what I always try to come back to when I've read through the papers and I've talked to researchers is what does this mean about what we do? People call me because they want to know what to do, not because they necessarily want me to read them the latest paper from JAVMA, right.

So part of what I find interesting about this disease is that is such a new disease, and I think part of it is because of what we do as shelters. Cats weren't necessarily housed in multi-cat populations until the 50s or 60s when cats became popular in this country. So catteries started breeding more cats and shelters started collecting cats off the street and putting them in shelters together, and we actually – and that's when FIP was reported. So essentially, we didn't create the disease, but we are exactly the environments where this disease has been allowed to kind of mutate and come into fruition.

And the other aspect is that because of the combination aspects of coronavirus that exposure to multiple species, whether it's coronavirus of pigs or coronavirus of dogs, mixed coronaviruses of cats, have actually contributed to the virulence of this organism. And so we are kind of a part of this FIP history as animal shelters, and we're also the ones that continue to wrestle with it, I think, the most.

So what does this mean for you? Clean all the things. All right. Please clean all the things. I stole this from one of my former interns who stole the picture from Ally Brosh, if you guys know her work. But minimizing feline coronavirus in the environment is absolutely key. And it's difficult because it's so ubiquitous, but it's not difficult to kill. Mechanical cleaning and basic cleaners, disinfectants will kill it. So it's not like parvovirus. It's not super hardy in the environment. You just need to clean and mechanical removal.

This is one of my recommendations in terms of litter boxes. I truly believe that kittens, young cats, anything with diarrhea should have a disposable litter box, not a plastic litter box that they continue to use day-after-day. That's for multiple organisms, not just coronavirus. But I generally am not a fan of cardboard, the small cardboard litter boxes in most cat cages, but if they're kittens or they've got diarrhea, or there is some other clinical issue, I am very much a fan of disposable litter boxes. They get tossed every day. And that's when I pull them out.

So I would recommend that if you're not doing that, that you really reconsider that for your kittens, your young cats, or anything with diarrhea so that they are starting with a fresh litter box every day. And not something that although you may have scrubbed it and you may have soaked in bleach, it still has kind of the plastic damage and all of that where things can collect. If you are experiencing an outreach, whether it's an outbreak of coronavirus that's causing diarrhea in everybody, or if you're experiencing an outbreak of FIP, then there is talk about trying to have a clean break in your intake animals and the animals that you have.

So closing the intake is not completely outrageous for a couple of weeks in order to sanitize, clean, and get things under control. Do some titers even to figure out who may be your high shedders. Try to figure out who your point of exposure is. All of these things have their place. But it needs to be done strategically and not necessarily in a panic. Again, coronavirus is everywhere. You're not going to eliminate it. You are not going to eliminate it.

But it is possible you may have a hot strain come through that's causing kind of a diarrhea outbreak, or it is possible that you might see a high rate of FIP in your kittens, where suddenly you say, okay, we need to stop for a minute and try to get this under control by cleaning – by making sure we're not exposing new populations to the old population by trying to be strategic. Other things are of course let's keep the kittens in the shelter as short a time as possible. I know that's obvious, but the use of foster care can really help in this.

Not mixing litters of kittens can really help in this, fast tracking your kittens through so that spay and neuter at eight weeks of age out to adoption, not holding onto them I think is important. I am not a fan of kitten rooms in particular. I like my litters to be kept separately and coronavirus is one of the big reasons for that. Long incubation periods, so you've got a cat that's shedding, should you hold onto it and try to let it clear the virus? I already you they can shed for months to years.

There is no point in quarantining a coronavirus-positive cat that's got a positive serology. They're going to shed for a while. You may manage where you keep them, but do not quarantine them for that reason. And of course you hear this from every shelter talk you ever gone to, please try to minimize overcrowding and stress. The more overcrowded they are, the higher the viral loads, the higher the viral shedding, the more likely they are to be sick, continue to circulate at capacity for carriers. The key, I think, to managing any disease in a shelter – of course if you only had one cat, then there is no right – I realize that is not possible. But minimizing the overcrowding and stress is really important.

And this poor mom had eight kittens. I don't think any mom should have eight kittens. And her little tongue is sticking out right there, and I just felt like she was just looking at me like, "Oh lord, please, am I not done yet? Do something about this." Communal housing is another big area, and I'm a huge fan of communal housing, which I was not when I was working in the shelter and somebody first proposed the idea to me. I was like, "Are you kidding me? Like, I just taught everybody put gloves on and not go between cages, and now you want me to stick cats in together."

I think it's the best thing that's happened to cats in shelters, but I do think that it's, again, not something to just be done as routine with every single cat. If the cat has diarrhea, it shouldn't be in communal housing. If the cat has had ongoing diarrhea, I would not recommend communal housing. I don't recommend multiple litters together in communal housing. And, again, if you're having an outbreak or this is an ongoing issue in your shelter, then there may be a role for serology titers just to try and figure out who your big shedders are and maybe manage them differently.

FAQs. So I tried to capture some of the biggest questions, and then we'll see what other ones you guys have for me. What is the status of the FIP vaccination? The status is this guy's says don't do it. Everybody says pretty much, "Don't do it." So FIP vaccination was a modified live vaccine intranasal administration. Because coronaviruses are highly mutable, it really has not been efficacious. I'm not even sure I could not find whether it's actually still for sale or not, but it is not recommended in situations or shelters.

So this kitten says, "Please do not give me the FIP vaccine." There is at least one study that showed that it actually made the cats more likely to get FIP because of the mutation of the virus. It's an older study, but still of concern. This is the big question that I'm interested in and where the research is going, "Can cats pass FIP between themselves?" And the story has always been no. Right. Each mutation is unique in each cat, maybe if they're genetically related; they are more predisposed.

But indeed there was an outbreak in Taiwan in 2011. A litter of kittens came into shelter in August, there was progressive illness in that litter between August and September, and ultimately through the shelter, 13 of the 46 cats in that shelter died of FIP. So a really high percentage of cats died over the course of the next year. Thirty-three percent remained healthy, but 26 of those 33 were actually positive for coronavirus. So getting the coronavirus in question didn't necessarily all result in FIP, but when they analyze this virus, it was indeed the exact same mutation across the population in these kittens.

And so what it was, it was actually a unique type II virus that was amplified out of the sick cats. It was the same virus and it passed across the population and it was a type II. And what they actually found in collecting is that it just wasn't in the organs, but it was also in feces, in nasal swabs, and in urine. So it was actually being shed into fluids that we didn't know could actually transmit the virus before, and should not have been able to transmit actual FIP virus. But the FIP virus, itself, was in the feces and in the urine.

So in particular, this type II mutation does appear to have horizontal transmission. Does anybody want to panic about that? Because please don't because that's one story, one recombination event that occurred in one shelter. It's not the one that you see in your shelter at this point. It's not the one that's reported in most shelters, but it is of concern, and it's garnering a lot of attention and discussion. That's what's really taken us to kind of looking at this challenge of the type II cerotype.

The other important thing to know is that line of coronavirus that is being studied in the labs is actually a type I. That's the one that's available for study in labs, and that's the one that can grow. The type II cerotype is not easily kept in a laboratory for study. So it's really hard to study, and we don't really know what direction we're headed in. What we do know is it doesn't seem to be common. It was in Asia, which is indeed where type II is found more predominantly, and where we expect we're going to continue to see this sort of activity.

But it does, I think, cause us all a bit of concern in terms of what does that mean. We have always said it's not transmittable, and indeed we now see there is at least one form that appears to be. How about this question? Anybody ever ask this question? "So a kitten in our shelter developed FIP, it was a singleton kitten, but it was mixed with other singletons. So there has been environmental exposure. They are not genetically related. What is the risk? Are those other kittens at risk?" They've been exposed to that coronavirus; are they more likely to necessarily develop the mutation?

The feeling at this point is no. And so if they are not genetically related, they should have no increased risks. Now, they were exposed to that coronavirus and we're going to assume that it's not a particularly hot one, and that this is going to be a typical presentation. But the current recommendation is go ahead and adopt that kitten out. You may want to educate that it was exposed, but the truth is, again, 60-90 percent of cats were exposed to coronavirus most likely in your shelter.

Unless you're really controlling for that at this point and wrapping them in saran wrap, which is what I always want to do. *[Laughter]*. Let's just put them in plastic, right. Nobody touch them. Don't breathe on them, and somebody adopt them really fast. But that wouldn't help their immune system either. A little dirt is good for you. So this kitten, as a singleton, may have been exposed to coronavirus but truly, it's not at greater risk unless it was genetically related. That's what we currently believe. So I would adopt that kitten out.

What about a kitten that developed FIP, and this kitten is in this entire litter of lovely kittens with little pointy ears, and they all seem to be kind

of closely related, or maybe clones. *[Laughter]*. So this developed FIP. What do we do with these guys? How many of you in your shelter would adopt them out, just adopt them out? How many of you would adopt them out with disclosure to the owners? Okay, a lot of the same hands went up and a few more. Like, you would disclose to them the littermate had FIP.

Tricky question, but it's dark in here, euthanasia on the docket for anybody, and you don't necessarily – but yeah, certainly in some cases, particularly if you are a shelter that's even euthanizing healthy cats, there is potential that euthanasia may be on the line for that because it's going to be harder to find them homes even with disclosure. So what do we do with the siblings? What is the risk? If they're genetically related, they do have a higher risk of developing FIP, a two to ten times greater risk of developing.

So it's at least twice, if not ten times higher that they're going to develop FIP. And that's genetics and exposure we think, a bit of both. And that ten times is a little bit scary, right? So they do have a higher risk. I think you have to have some disclosure to adopters that they could be getting into a scenario where they're going to adopt a kitten that could develop this disease. Now, truly, any kitten you adopt out could develop this disease, but there is a higher risk in this litter.

Anybody here foster them for a longer period of time or try to keep an eye on them before adoption, hold onto them? Yeah, and I think that's an option if you've got a good foster system, or even a foster-to-adopt system. I couldn't find anything on the exact timeline like when do we expect these kittens to develop, but it generally takes months to – weeks to months. So if you can hold onto them a little bit longer and kind of monitor them for signs, give them a good screening physical exam, monitor their weight gain, make sure they're not developing fevers or uveitis, look for the early clinical signs, then I might be inclined to do a little bit of that, just for the heartbreak aspect.

If I got people who could foster them, hold onto them another month or so, make sure that they look like they're going to be okay, and then still adopt them out with a disclosure. I think the information is key, similar to what Dr. DiGangi said. A lot of times people are upset because they weren't given information so they couldn't make an informed choice.

They might still be upset that they lose the kitten, but I think it will be less upsetting if they knew the risks they were getting into. And so foster to adopt potential, and certainly any of these disclosures that I do to try and encourage people to take animals that may be more prone to disease is always put in the context of this is how we save lives.

There are some people who are going to want the cat with the absolute best opportunity to be 100 percent healthy, and I totally get that. There is also this population of weirdoes, like myself, that are willing to take the ones that might be more challenging or more likely to be broken. And because I am lucky enough to be associated with the veterinary school and a veterinary school community, I have lots of weirdoes like me that are willing to sometimes sign on for risks.

So if you're out there educating your volunteers, your foster parents, your community about the fact that this how we save these animals. We get people who are willing to take chance on them, and then your chance at lifesaving is slightly higher, I think. So the other thing I did in preparing for this, and I can't see the clock so I don't exactly know how much time we have. 7:00? Okay. Good. This is perfect. As I sat down with researchers, who I don't really understand what they do in their laboratory, so I might be the only one in this room that doesn't totally understand what they're doing up there with all those lights and buttons.

But I'm assuming I'm not. I'm assuming some of you are kind of with me out there in the world where you just deal with the dirty kittens and the dirty puppies and like to pick poop and look at abscesses, like, that's me. All right. They like to push buttons and do things like that. This is one of my favorite comments I got from them. As we were talking out diagnostic tests, what's possible? What's coming down the pike? How can we make this better? This is what people want to know. I heard feces-based tests are hard. And I was like; feces-based tests with coronavirus are soft and squishy. *[Laughter]*.

But the point here as she said this to me, and I kind of giggled because I'm funny like that in like weird puns, is that because it's not normally shedded feces, and that type II in Taiwan is exception. But because you don't see the FIP tropism in feces because you're not getting a lot of microphages in feces, then a feces-based test is probably not going to happen for FIP. So we can look at coronavirus shedding, but we can't necessarily look at FIP.

The goal, even though we haven't figured out how to do it, is still some sort of test that could be done on blood that would help us recognize FIP, and that is not out there. We really need the tissue because we need tissue macrophages. But everyone will tell you that the goal is still an antemortem, a test on a living animal that can tell you that they have FIP when it's not completely obvious. The best positive predictive value on a test with blood involves these steps.

So when I heard this, it helped me understand why it's so complicated. You can get blood from a cat, then you isolate the white blood cells, then

you grow them in culture, then you do IFA for the antigen. This is extremely labor intensive. It's not a very sensitive test because, again, you may have low levels of antigen in those particular circulating macrophages because what you really want are tissue macrophages. So the ones that are circulating are not going to have a lot of the antigen.

So this is not commercially available, but if you took the researcher and held them against the wall and said I absolutely have to have something I can do with blood, they would tell you this is possible, but it's still probably not going to be a very good test and it's going to take a long time and it's going to cost you a lot of money and patience so they don't have it out there. There is a test coming out from ANTECH, so there will be a commercial test that will be.

You can submit blood on it. It's going to be reverse transcript PCR. They will tell you it's not going to be as good as if you submit fluid. If you submit fluid, what they're actually looking for there is to kind of amplify the antigen in the cells, and then they are thinking that they will be able to tell you whether there is FIP from that effusion. Again, a lot of times just analyzing the effusion can help you with that. They will accept blood samples, but they'll tell you that it's not going to be as good a test.

But it is out there for 2015. So those are my references, and I'm happy to take any questions in the last few minutes. And, again, I really thank you for sticking around for this sad topic on the very last day. *[Applause]*.

[End of audio]