Announcer: Welcome back to the Mayo Clinic cardiovascular podcast series, interviews with the experts. I'm your host, Sharonne Hayes. I'm a non-invasive cardiologist and vice chair of faculty development and academic advancement for the Department of Cardiovascular Medicine here in Rochester, Minnesota. Today I'm joined by my colleague Dr. Allen Luis, who is associate professor of medicine, co-director of the Pericardial Disease Clinic here in Rochester. He also leads a number of clinical trials related to treatment of inflammatory pericarditis. Today our topic is contemporary management strategies and recurrent pericarditis. Welcome, Allen.

Dr. Allen Luis: Thank you very much, Dr. Hayes. For the invitation and the opportunity to discuss this important topic with you,

Dr. Sharonne Hayes: Dr. Luis is gonna share with us contemporary management strategies for recurrent pericarditis, including indications and limitations of the IL one receptor blocker therapy. You'll also discuss the role of radical surgical pericardiectomy in the treatment of patients with recurrent pericarditis. So to start with, tell us which is the this problematic patient population that we're gonna really be focusing on today.

Dr. Allen Luis: That sounds great. So we are really looking at the patients that are called to have recurrent pericarditis or complicated pericarditis. And this term really refers to people that have had more than one episode of inflammatory pericarditis. So you have those patients with acute pericarditis, they have their one episode, it goes away and it never comes back again. And that is ideal. But we all know that there's a proportion of people even up to a quarter or a fifth of patients that have pericarditis that comes back again and again and again. And the spectrum of recurrent pericarditis really is quite broad. It tends to be those patients that have frequent flares after their initial episode, but sometimes patients can have flares of pericarditis that are a number of years apart or really longer durations than that apart. But really the topic of interest or the patients of interest are those patients that tend to have a cluster of flares, of pericarditis all in close succession and close together.

Dr. Sharonne Hayes: So you've got somebody in your pericardial disease clinic and you and I both work there and see these challenging patients. What's your initial approach when they come into first time visit and they've had one or more recurrences?

Dr. Allen Luis: So that's a great question and I think the first thing to do is to step back, take the clinical history again, examine the patient again carefully. Because what I've noticed is we are all in this paradigm in medicine where we are told and taught that if something has happened before, it's most likely to be the cause that happens again. But when you step back and look at it, you sometimes realize that there are a number of people who, yes, had an episode of pericarditis a long time ago. Yes, they had a recurrence of pericarditis, but now they have chest pain that's labeled as pericarditis and they don't actually have pericarditis anymore. They have musculoskeletal chest pain. They feel overly sensitive in

their chest because they've had these previous things to worry about and a variety of other causes. And so I think confirming your diagnosis, first of all is the most important approach to pericarditis and then comes the treatment approach. So when we come to the treatment approach, the important thing to look at is to really start at the bottom of the ladder every time you have a flare and then work your way up the ladder. There is no reason if you get a, a flare of pericarditis resolved to start at the top of the ladder because your previous intervention didn't work. And so really in all my patients, I try to start wherever possible using a non-steroidal anti-inflammatory in conjunction with colchicine and exercise restriction in those patients. And exercise restriction is really important and it's often underdone. We forget to tell our patients not to exercise during an acute flare of pericarditis. And that's really important. I started a good dose of either A, any of the nonsteroidal anti-inflammatories at a good dose or aspirin, add a dose of about a gram three times a day. Colchicine, you really want to dose well, you wanna give as much colchicine as they will tolerate. And really the recommended dose if you're over about 70 kilograms is a dose of 0.6 milligrams twice a day. And so by and large, most people tolerate their colchicine just fine. And that really vastly decreases your rate of recurrence in those patients who don't calm down with just a non-steroidal, anti-inflammatory and colchicine, then you really have multiple options now in as to how to treat them. And if you go to different experts throughout the country or throughout the world, different people will advocate for different next steps in the treatment of pericarditis. The traditional next step in the treatment of pericarditis has been to go to a corticosteroid, namely prednisone in combination with Colchicine and to use that in the treatment of pericarditis. If you choose that approach and choose to give prednisone, it's important to start at a low dose and you're really looking for 0.25 milligrams per kilogram. And my typical starting dose is between 20 milligrams and 40 milligrams. It takes longer for the pain to resolve than if you go to a higher dose upfront. But I really find if you have patients and wait a couple of days, the 20 milligram dose is quite efficacious along with colchicine in combination. And so starting on steroids, it, if you choose to embark on steroids, it's really important to recognize that this is a long-term treatment strategy. You can't give an asthma dose pack regime of treatment and have your patient off steroids in two weeks 'cause you have insufficient suppression of inflammation. And if you try and read your therapy too quickly, those are the patients that recur. And so I would check inflammatory markers, ensure normalization of inflammatory markers, and then really slowly taper my patient off the AP prednisone at a dose of 2.5 milligrams every two weeks or so. So I would come down in 2.5 milligram increments every two weeks. And then when I hit the 10 milligram mark, I would consider slowing my taper even further.

Dr. Sharonne Hayes: So let me, let me just because I, I really want to to emphasize the need to take that history, right? I mean, I've had somebody who had pericarditis in the past referred to Pericardial disease clinic who really needed a stent. I mean they were having exertional pericardial pain, which turned out to be their tight LAD lesion. So really important. One thing you didn't mention is something that we routinely do low yield, but how important is making sure that this isn't somebody who has undiagnosed lupus, rheumatoid arthritis, or the patient who comes in who we know they have that condition, are are, are we gonna focus just on the truly idiopathic here or do you have something to say about those who likely have an under an underlying cause or targeted cause

Dr. Allen Luis: That, that's a great point there Dr. Hayes. And thank you very much for bringing that up. So yes, in your examination it is widely important to make sure that they don't have an autoimmune cause for their pericarditis. They don't have an any other cause for their pericarditis. And really to examine them carefully, see if there is any evidence that makes you suspect autoimmune disease. Also, in some cases you would consider a panel of auto antibody testing and potentially want to want to screen for myeloma as a potential unusual cause. But really that's guided by the history and the examination where you identify that patients have an autoimmune cause for pericarditis, really treatment should be geared towards that autoimmune cause. And all the data that applies for idiopathic pericarditis really doesn't apply to those patients with autoimmune disease and therapy should be targeted to the underlying cause there.

Dr. Sharonne Hayes: Let's shift gears a little bit to some of these new medications that some people are a little less familiar with using beyond steroids. When do you use IL one receptor blockers?

Dr. Allen Luis: So I think that there are two potential avenues for where I would use an IL one receptor blocker. The first is in my patients on steroid therapy already who failed to come off steroid therapy. So I've tried and tried and every time I've weaned them down they flare. And you really have no other choice but to escalate therapy to something else in order to get them off. If you've tried to really slow taper and not really been successful in getting your patient off therapy. Some would advocate in patients with severe inflammation on a non-steroidal anti-inflammatory and colchicine that an IL one receptor blocker may be a reasonable next step where in your experience you know that you're unlikely to get this patient off steroids and steroids are likely to be problematic. And then of course there are those patients with contraindications to steroids or patients that have quite a lot of side effects for steroids in whom you would consider using an IL one receptor blocker up upfront. And so those are really the three groups. It's sort of an individualized decision. The 2015 European Society of Cardiology guidelines had placed IL one receptor blockade below corticosteroids on their treatment algorithm as the next step. But really this paradigm, this treatment paradigm has shifted and there has been a move to avoid steroid side effects, avoid the difficulties of weaning steroids and really to use these earlier on. And I really don't think that there's a right or a wrong approach, whether they use steroid first or whether use an IL one receptor blocker first.

Dr. Sharonne Hayes: And sometimes it seems to depend upon the difficulty or lack thereof of getting the reimbursement for these very expensive medications.

Dr. Allen Luis: Absolutely, yes, these medications can be incredibly expensive. It depends on the patient's insurance and coverage and things like that that really do play a significant role as well.

Dr. Sharonne Hayes: So say you've committed to an IL one receptor blocker and you know, aside from the, the limitation of getting it into the patient's hands, but what are some of the limitations or cautions that we need to consider when we're using these medications?

Dr. Allen Luis: So really when we start the therapy, I think it's really important to keep in mind that you really want to exclude infection. And so in these patients I will routinely screen for hepatitis B and C, I will routinely screen for HIV and I will do tuberculosis testing. And all my patients that I put on these IL one deceptive blockers, they really are quite potent immunosuppressants and they really do risk unmasking these conditions. The medication is generally contraindicated in those people with a history of malignancy or recent active malignancy because that immunosuppression is thought to increase the risk of progression of cancer. And so those are the things that I really think about when I, when I think about putting a patient on these medications, the limitations I've generally found these medications to be highly effective. When you put people on it, they get relatively rapid resolution of chest pain, they get relatively rapid resolution of symptoms, they do incredibly well when they're on them. But in saying that, there are a few patients that I've had that have managed to have flares of pericarditis despite these medications. So just because they have a flare of symptoms does not mean that this is not pericarditis or that the treatment will necessarily be completely ineffective. So to keep that in mind and the other really the big limitation that I worry about is the duration of treatment. I think that's a big unknown at the present time, but traditionally used some for 12 months, some for 18 months. And the data seems to suggest that there is an incredibly high risk of recurrence following discontinuation of an IL one receptor blocker in terms of recurrent pericarditis occurring after these episodes. If we look at the data from Anakinra, that was published in the, in the IRAP registry that we were involved in. And you can see really there was sort of a up to 50% rate of, of recurrence or, or even more in some cases. And when we look at comparable data with rilonacept we see a very, very similar rate with the only case series or published from the end of the a Rhapsody study showing as much as a 20 as much as a 75% rate of recurrence in just 25% freedom from recurrent episodes of pericarditis. And so that's really where I see challenges in management. It's when the patient is ready to come off treatment and you're left with the paradigm of do you stay on this life long, do you come off this, what do we do with you at this point?

Dr. Sharonne Hayes: That kind of transitions what's left after that. So one thing that is left but less often used is radical pericardiectomy. So when, when do you consider surgery or a patient with recurrent pericarditis? Is it ever right at the beginning, you know, before trying all these medications, is it only after failure? Sort of tell me what's your thought process?

Dr. Allen Luis: Absolutely. So I, I think really this is a very important discussion to have with the patient. I find it very important to be honest with your patient upfront. And you know, I'd often talk to them about the challenges of an IL one receptor blocker at the end of their therapy. Really in all my patients I would've tried and failed a non-steroidal anti-inflammatory and colchicine before I consider surgery. I think that's fairly basic run of the mill usual medical therapy. When it comes to next steps, I would've tried either steroid or an IL one receptor blocker before I consider surgery. In terms of those patients that are coming off steroids and failing to come off steroids, I really offer them an option. I offer them

the option of either having cardiac surgery for pericardiectomy or moving on to an IL one receptor blocker. And the reality is, by and large, most patients want to avoid surgery. And so they're all keen to try an IL one receptor blocker. It's few and far between that you find a patient who has just had enough of medications and just wants to be off medication altogether. They don't wanna be an injectable and they choose pericardiectomy fairly early on in their, in their treatment paradigm. And, and that is reasonable as well. There are patients that have contraindications to an IL one receptor blocker as we discussed earlier, infection and malignancy who would be treated better with a surgical pericardiectomy of steroids are not working. And those patients that have side effects to both sets of agents. And as I mentioned earlier, the handful of patients that do have true episodes of recurrent pericarditis with elevated inflammatory markers despite adequate therapy with an IL one receptor blocker.

Dr. Sharonne Hayes: So I know we're hoping to have our surgical colleagues to give us more information about the surgery and outcomes, but you know, what in your experience is the symptom free or recurrence free outcomes of patients who have a radical pericardiectomy? Because even though it's radical, we know we leave some of that tissue there and, and, and, and I think that how do we counsel patients when they're making that choice?

Dr. Allen Luis: Absolutely. And so one of the things that you just mentioned, Dr. Hayes, that I wanna highlight is that Pericardiectomy really needs to be done by a surgeon with expertise doing pericardiectomies, not for constrictive pericarditis, but rather for recurrent pericarditis. The reason I say this is the traditional pericardiectomy is an anterior and inferior pericardiectomy. It's called complete, but it's anything but complete when you leave all the pericardium posteriorly along the lateral wall of the left ventricle. And so really you need to find a surgeon with expertise in pericardiectomy that can truly strip the pericardium in its near entirety, barring what runs along the phrenic nerves and barring the little bit between your pulmonary veins. And so really you need an expert surgeon that does a lot of these and is capable of doing these. The long-term outcomes after surgery are extremely good. Patients do well and when, and the only real data published in this patient population is from our colleagues here at Mayo Clinic that looked at their experience doing radical pericardiectomy in patients with recurrent pericarditis. In that particular study, the operative mortality was exceedingly low and the risk of perioperative complications was also extremely low. But what is really interesting to see is the marked improvement in 10 year progression-free survival, 10 year recurrence-free survival, and that is over 90% at 10 year follow-up and far exceeds those people that were managed with traditional medical therapy with steroids and nonsteroidal anti-inflammatory. So really these patients do extremely well and they, if their pericardiectomy is done right, you're really looking at a 90% or so freedom from recurrence at 10 years.

Dr. Sharonne Hayes: I think you've really provided us with a comprehensive approach. Now you've made it seem simple and these patients are, in my experience, very tough 'cause no one's the same. But I I think that if we think about this, the way you have is making sure that you've got the proper diagnosis, that we start with the basics and then move forward and, and escalate, so to speak, and keeping surgery

in the right hands on, on the table for folks. They will do better, I think, than they have traditionally done, many of whom have really suffered either from the recurrence or the side effects of steroids.

Dr. Allen Luis: That's absolutely right.

Dr. Sharonne Hayes: I really wanna thank you for, for joining us today, Dr. Luis. This wraps up this week's episode of Interview with the experts. We'd really like, we've enjoyed discussing this important topic and I hope we will hear more, particularly some of the details about surgical outcomes in the future. We look forward to you joining us again next week for another interview with the expert. Be well.