BroadcastMed | chp_crystal-arthropathies-720p.mp4

SPEAKER: Hi everybody. We're going to go ahead and get started. Thanks a lot for doing this. I know that everybody has been super busy with [INAUDIBLE] all the services. So we appreciate that you had time to come. We'll take a quick break [INAUDIBLE].

Today I have the pleasure of introducing Dr. Leslie Kerr, who is one of our professors of medicine in the division of rheumatology. She's going to be talking today to us about conditions that we frequently see in our patients [INAUDIBLE]. And those are crystal arthropathies. Thank you, Dr. Kerr.

LESLIE KERR: Thank you very much. It's a pleasure. And I don't know what year you'll be starting, Andy, but I'll be starting my 40th year here in July.

[LAUGHTER]

SPEAKER: Not quite.

LESLIE KERR: So I've started here as an intern and have been here ever since. My job description's changed a little bit.

But one of my favorite set of diseases are the crystal [INAUDIBLE]. I have the pleasure of spending all day Tuesday in the geriatric practice. And just to sort of emphasize how common these things are, the last patient I saw before I came upstairs had gout. And the one before had pseudo-gout. So once you can recognize crystals, you see them all over.

The reason that I call this crystal arthropathies is that I want you to keep an open mind, that we are probably going to discover additional crystals from the three that I'm going to discuss today that cause human synovitis.

And just to sort of have that as a background to be able to then incorporate the new knowledge that we will hopefully acquire about other crystals that cause human disease. And of course, on the inpatient service, when I am a consultant, I think, you know, we call it dessert. When we get to see all the patients who have polyarticular gout and pseudo-gout, because there is no more gratifying thing to diagnose and treat, because patients are in severe pain. You recognize what's causing it, and you get them out of trouble very quickly.

So here we go. So I mentioned that there's more than one crystal that causes human synovitis. The most common is monosodium urate monohydrate. We recognize acute gout. We recognize tophaceous gout. And we also recognize that most patients with either of these things have a long period of asymptomatic hyperuricemia.

The second most common crystal that causes human synovitis is calcium pyrophosphate dihydrate, CPPD. We recognize it as acute pseudo-gout. It can be a poly-articular destructive arthropathy. The pseudo-rheumatoid pattern of pseudo-gout. A great mimicker of rheumatoid arthritis.

And again, we have a major branching point. If you think it's rheumatoid, you go off into a [INAUDIBLE] direction, which you wouldn't want to do if it was pseudo-gout. So this is a very important clinical distinction to make. And then there are many people who have asymptomatic chondrocalcinosis who never go on to develop any synovitis.

The third most common crystal that we know that causes human disease is basic calcium phosphate, also known as calcium hydroxy-apatite. When clumped together, it can cause an acute calcific tendinitis, or periarthritis. It can also cause an acute arthritis, very rarely, mostly in dialysis patients.

But the most famous synovitis that we know is called Milwaukee Shoulder. And I'll be telling you about that.

And then calcium oxalate-- I've never seen it. It's just for the completeness. Again, this is only in dialysis patients. Sometimes we have some very beautiful synovial fluid crystallography where we see little fat globules that are in the joint. There are lipid cholesterol crystals. They're very pretty, little sheet-like crystals. But we don't think they really cause synovitis.

And so that leads me now to talk about the three crystals that do cause human disease, with 2/3 of cases being due to monosodium urate, namely gout. And gout, unlike rheumatoid arthritis, is truly an ancient disease, with a lot known about it, even in ancient times.

Hippocrates' aphorisms on gout, that men are predominantly afflicted, that women don't get into trouble until after their menses have ceased, is still true today. Estrogen is uricosuric. That's why. OK?

We then went on to realize that uric acid was a crystal that was visualized, that these crystals were a gouty tophi. That colchicine was effective for gout in 1814. That's a medication that's really stood the test of time, huh? OK?

Hyperuricemia was associated with gout. We've known that since the 1840s. The key agent that lowers uric acid, allopurinol, was developed here at Mount Sinai, by Doctors Gutman and Yue. This is a Mount Sinai medication.

What other medication in the modern era has withstood the test of time like allopurinol? And then on and on and on. So, a very long and rich history, and a Mount Sinai history in the milestones of the treatment of gout.

So as I mentioned, there are a few phases. Many patients go through a phase of asymptomatic hyperuricemia. And in my many years in medicine, I've seen the pendulum swing back and forth. And I can't really tell you whether asymptomatic hyperuricemia is harmful or not, but in general, we don't treat it.

OK. But there is a lot of controversy. And the voices on either side wax and wane depending on which you're in.

We do, however, recognize acute gout. Once you've had an acute attack and your joints settle down, you then enter what's called the intercritical period, the period between attacks. And that period is highly variable.

Your next attack may be never. And your next attack may be next week. So you're looking at the patient's comorbidities and clinical factors to figure out whether you need to intervene or not in the intercritical period.

And then a minority of gout sufferers go on to precipitate uric acid in their soft tissues and around their joints, known as chronic tophaceous gout.

So hyperuricemia seems to be the key pathogenetic factor. In 90% of patients, it's due to under-excretion. And many of those reasons we can't do anything about, like renal insufficiency, or renal failure. And that's why we see it so often on the inpatient service.

There are medications that, obviously, are risk factors. Think of the millions of people who take aspirin in one form or dose or another. So low dose aspirin, which is what we're giving as cardiovascular prophylaxis, blocks uric acid excretion. So that's a risk factor.

We don't take patients off aspirin. We have to work around it.

Diuretics, sometimes we can do. So as an example of somebody whose intercritical period I would not treat, a 45-year-old man comes to me with his first attack of gout. The history is that a month ago, he was diagnosed with hypertension and put on hydrochlorothiazide.

Clearly, if I go back to his primary and say, could you treat this man's hypertension with anything other than a diuretic, he will never have another attack of gout, needs no other treatment. So where you can modify, that's great. But again, on the inpatient service, they have problems with volume control. They have severe congestive heart failure. We are often stuck with the diuretic therapy.

And then the other reason why we see these patients often on the inpatient service is that acute metabolic stress leading to dehydration, ketosis, et cetera, is a risk factor for acute gout.

Then we have the over-producers, which is a minority. And actually, ethanol, as you see, alcohol's on both sides. So this is the double whammy.

And in fact, the most intractable, difficult gout patients that I have had to treat have been patients who use alcohol. And alcohol blocks your ability to excrete uric acid. And it increases turnover of purines.

So that's why it's the double whammy. And those patients can be very difficult to treat.

Then when you're seeing a 24-year-old guy and your family history demonstrates that all of his uncles, his father, his male cousins, they all have gout at a young age, you know you're dealing with one of these families that has a mild deficiency, or hyperactivity, in the synthetic pathway of purines. These are a partial deficiency of HGPRT.

Remember, the complete homozygous is Lesch Nyhan disease. And those people tend to die young, and I don't see them. So it's partial deficiencies, or deficiency of G6PD, or hyperactive PRPP synthetase. I'm now bringing you back to your first year of biochemistry, which none of you, including me, remember very well.

But anything that increases cellular turnover. You're going to have increased purine turnover. So I have many patients with polycythemia, for example, lymphoma, psoriasis. So we don't see gout and rheumatoid arthritis. That's usually a confusion of diagnostic thinking. But you can commonly have gout superimposed in the setting of psoriatic arthritis if they have extensive skin disease and a lot of skin turnover, or just psoriasis alone as a risk factor for acute care.

So these are some of the things to think [INAUDIBLE] viable, in terms of your approach to preventing gout. And then gout can come on in two clinical fashions. 80% of first attacks are monoarticular, with the most common joint affected in a monoarticular attack being the first MTP, followed by the instep, followed by the ankle, followed by the knee, and then subsequent attacks upper extremity joints are fair game. But that means that 20% of attacks, first attacks, can be polyarticular. So you could have two toes, two ankles, two knees, a wrist, et cetera thrown into the mix.

It's the abrupt onset of severe inflammation. It often occurs at night because, remember the solubility of uric acid decreases with decreasing body temperature. So those cool places like your toes get the coolest when you go to sleep. And that sets up the precipitation of uric acid crystals. If you do nothing, what happens to acute gout or any crystal cellulitis?

It tends to go away. I'm not recommending that. Patients are in agony. But it should temper your enthusiasm for poisoning your patient too much. OK? 75% occur in the first MTP. What we love about this as rheumatologists is, for every other type of disease we spend the first 20 minutes of the lecture apologetically explaining how little we know about etiology and pathogenesis. But for this series of diseases, we see the etiologic agent in the synovial fluid, which is very satisfying, namely, the intracellular uric acid crystals in gout or CPPD in pseudo gout.

Residents and fellows initially love to quote uric acid levels to me when I'm on rounds. And basically, an acute attack, it doesn't matter to me. Because the uric acid level could be high. It could be normal. And particularly in a polyarticular attack, where all of it's precipitated into joints, you could have a low serum uric acid during the attack.

So I only really want to know what the serum uric acid level is in intercritical period, three to four weeks after everything has subsided, and only in those people who I feel I now must step up my therapy to lower serum uric acid. If they don't meet the indications for uric acid lowering, I don't really need to know what the uric acid is. Because again, within that controversy of that asymptomatic hyperuricemia, my own reading of the current literature is I wouldn't treat. So I have very strict criteria for whose uric acid I'm going to lower and I'll get into that shortly.

So here is a description from the 1600s when they really knew how to write English. And it's as true and as fine a description today as it was then, by Sydenham. The victim goes to bed and sleeps in good health. At about 2:00 in the morning, he is awakened by a severe pain in the great toe, more rarely in the heel, ankle, or instep.

This pain is like that of a dislocation, yet the parts feel as if cold water were poured over them. Then followed chills and shivers and a little fever. The pain which was at first moderate becomes more intense. With its intensity, the chills and shiver increase. After a time it comes to its full height, accommodating itself to the bones and ligaments of the tarsis and metatarsis, now a violent stretching and tearing, now a gnawing pain, a pressure tightening, so exquisite and lively meanwhile is the feeling of the part affected that it cannot bear the weight of the bedclothes nor the jar of a person walking in the room.

The night is passed in torture, Sleeplessness, turning of the part affected, et cetera, et cetera, et cetera, hence the vain effort by change of position, both in body and limb affected, to obtain an abatement of the pain. And this is why we want to treat it. Its really miserable, but much better said in those days.

And here's how it looked to them. This was a lithograph from the 1700s. You had a devil gnawing on your big toe.

And here's how it looks in the flesh-- pretty inflamed. This is actually an oligoarticular attack because you can see podagra. You can see tenosynovitis over the dorsum of the foot, and a hot ankle.

So what can't this patient do? Walk. OK, this is disabling.

And again, if it was just this hot ankle, you didn't have these other components, there's nothing clinically that would dissuade you from considering septic arthritis of the ankle. This is as hot as any septic arthritis. The fact that you've got two other joints, however, makes septic arthritis unlikely because septic arthritis is almost always acute monoarticular arthritis.

And again, another rendition-- you've got a devil heating up that foot with a hot iron. And so risk factors. For a minority, there are genetic predispositions. Obesity-- either when you gain or lose weight, you will have increased purine turnover. So that's the risk factor.

Advanced age-- probably by virtue of the fact that you lose GFR as of the age of 65. So if your serum creatinine is normal, you'll have decreased GFR. And therefore, you are going to have decreased ability to excrete uric acid.

Aspirin, diuretics-- I've mentioned. Heparin-- it's in the literature. I'm not really clinically convinced of that. In the days before CellCept, when we relied heavily on cyclosporine, as a transplant center, we would see terrible intractable gout, and they were stuck with cyclosporine. Now, with CellCept, it's less of a problem because it doesn't interfere with uric-acid excretion the way cyclosporine. Does.

Alcohol-- I've mentioned. Renal insufficiency-- you're kind of stuck with that. And acute illness. So this explains why we see so much gout on the inpatient service.

And as inflammatory as it looks, clinically, it is also inflammatory when you aspirate fluid, with white-cell counts as high as 100,000 and 90% poly-predominance. The glucose, if collected properly, however, will be reassuring in that it will be normal rather than low, the way it would be in a septic arthritis. The gram stain will further reassure you because it will be negative. And the diagnostic observation that gets you off the hook for septic arthritis and confirms that the synovitis is due to gout is the observation of negatively birefringent uric-acid crystals intracellularly because it is the phagocytosis of the crystal by the white cell that engendered the clinical synovitis that we see.

So if you've got a white-cell count of 100,000 and it's poly-predominant, and you see a crystal or two floating around in that fluid, but the location is not intracellular, be very scared because those fluids in real life, as well as all the staph exams, are going to grow Staph. aureus. So you're only off the hook if they are intracellular.

And here's what we seek to see. It's really fun with a polarizing scope because they're very bright, very strongly negatively birefringent. Birefringence is a manifestation of knowing where the long axis of your crystal is in relation to the polarizer on your microscope. So when it's yellow in a polarized field, that means it lacks color. And so to be negatively birefringent, when the long axis of the crystal is parallel and lacks the color-- which is yellow is the lack of color-- that's the definition of negative birefringence.

If you then rotated your polarizer 90 degrees, it would be blue or purple. And so positive birefringence, which is the physical-chemical property of pseudo gout has the opposite. So when the polarizer is parallel, it's purple. And when it's switched 90 degrees to make it perpendicular, it looks yellow. You don't need to know that-- just that uric acid's negative, birefringence and calcium pyrophosphate is positive [INAUDIBLE].

I could also tell by the morphology without doing the polarizer that this long-needle-shaped crystal is uric acid. That's how it looks. But you don't need a fancy microscope. This is 40x. You need a slide, you need a drop of synovial fluid, and a cover slip.

And if you see this crystal harpooning this cell, by its morphology and the fact that it's intracellular, A, you know it's crystal synovitis, and B, the shape of the crystal. And you'll see the difference when I show you the pseudo-gout crystals tells you this is gout. So that's all you need, really, to make a diagnosis.

AUDIENCE: What is the cell? Is it a macrophage?

LESLIE KERR: It's a poly.

AUDIENCE: I see,

LESLIE KERR: Yeah, and it's 90% polys.

So how do we treat? And I'm not going to spend a lot of time on the treatment of pseudo gout because in the acute phase, it's almost identical to that of gout. So in a world where your gout sufferers are all young or middle-aged people, have no comorbidities like severe high-blood pressure, renal insufficiency, bleeding diaphysis, or on blood thinners, suffer from dementia, et cetera, you could use a high-dose nonsteroidal anti-inflammatory. But basically, none of the patients I take care of at Mount Sinai would be safe candidates for that.

And the nonsteroidal anti-inflammatory with the greatest potency is indomethacin 50 milligrams, three times a day. It wouldn't matter which nonsteroidal you picked, except it's got to be the high end of the range. So sometimes, the mistakes that I see is that a patient presents to an urgent care or an ER is given ibuprofen 400 milligrams twice a day and still limps into my clinic two days later. It's not that they picked the wrong drug. They just didn't give anti-inflammatory dose.

So if you've got to give a really high dose, you better look carefully at your patient because by and large, the majority of the patients that I've seen, certainly on the inpatient service, would be poor candidates. It would be poor clinical judgment to give them high-dose nonsteroidal anti-inflammatory drugs because of the toxicities due to their comorbidities.

Colchicine is an interesting drug. It inhibits the chemostasis of the white cells into the joints that have the crystals being acutely shed. It works well in acute attacks only if the attack has been going on for less than two days. So if the history is that this has been going on for four or five days, there's no point giving somebody colchicine [INAUDIBLE]. You're just going to get toxicity. You're probably not going to get efficacy.

I reserve oral colchicine loading for a patient without a clear past history of gout who has an acute monoarticular attack not involving the great toe-- because the great toe is 99% gout and 1% pseudo gout, and never septic-- but say, a joint which is more likely to be septic, like an ankle, a knee, or a wrist, and I can't get the fluid out because anti-inflammatories will make even a septic joint transiently appear clinically improved, but then you go on to irreversibly destroy the cartilage, whereas colchicine acutely will treat gout, pseudo gout, the arthropathy of FMF, sarcoid, and Gaucher's disease, with the other three being lower on the list, but will not make a septic arthritis look better. So it's much more specific than an anti-inflammatory.

I only do oral colchicine loading, which is one pill every hour, no more than six pills, assuming they have normal renal function, stopping way before that sixth pill if they feel very much better because then I got an answer. If nothing happens, then it's not acute crystal synovitis, or if they develop any GI symptoms. So before each pill, you say, are you nauseated? Are you having stomach cramps? Are you having diarrhea? If the answer is yes, you don't give another pill.

In that way, by using the gut as your monitor, you can avoid colchicine toxicity. About 15 years ago, I moved to get IV colchicine removed from the formulary-- and I think it is off the formulary-- because I was convinced that I had seen three IV colchicine-related deaths?

What happens if you don't treat gout? It all goes away. So death from a gout therapy is completely unacceptable.

And the story was there were always postoperative patients who could not take PO who all had renal insufficiency. Their attack had been going on for a while they got 1 milligram of IV colchicine. They didn't get better, but the attack had been going on. So they got repeat doses.

There was no gut to tell you you were getting into trouble, and colchicine is nondialyzable. There is no way to get rid of it. And so they died of fulminant myocarditis with intractable arrhythmias, hemorrhagic pancreatitis, and the other one had the bone marrow wiped out.

So colchicine is a nasty drug. Once you go beyond the gut toxicity, it's multi-system organ-- severe inflammation, which is completely unacceptable. So that's why, thanks to me, when you call for IV colchicine, you're probably not going to get it. But call one of us instead. We'll help you get the patient out of trouble, all right?

And then to me, the most elegant topical therapy-- if you know it's gout, and it's only one or two joints, and it's a 99-year-old with a bleeding diathesis whose blood pressure is uncontrollable, why not just inject the joint with steroids. Drain the fluid out, you take the crystals out physically, and then you inject the Depo-- 40 of Depo-Medrol. The job is done.

The problem is many of those patients had eight joints, so you can't inject eight joints. That only works for one or two. Is that your comment?

AUDIENCE: Will they do that in a patient?

LESLIE KERR: What are we doing all day? In our pockets on rounds, we carry ethyl chloride and little bottles of Depo. All we need from the floor are the syringes. Yes.

AUDIENCE: Can you put a little bit of Marcaine as well?

LESLIE KERR: You could, but that's another stick. So I just spray on ethyl chloride.

AUDIENCE: Wouldn't they--

LESLIE KERR: That's a topical.

AUDIENCE: When you mix the steroid and the Marcaine, a lot of people--

[INTERPOSING VOICES].

LESLIE KERR: A lot of people do it, but if you look at it, you see the steroid begin to precipitate out.

AUDIENCE: I see.

LESLIE KERR: And I always wonder about the efficacy. And also, steroid can crystallize. And there's a rare number of people that go on to get a hot synovitis v after they get an injection.

AUDIENCE: Another crystalline property-- steroid crystal property.

LESLIE KERR: Right. So I don't mix. Some of my colleagues may inject a little Novocaine or lidocaine first, and then inject.

AUDIENCE: Well, then the drug--

LESLIE KERR: Right. I spray on the spray and give it. Yeah, you have to wait a little longer. You can't be like a faith healer, where suddenly, they can bend their joint, but they get better within a day or two. It's very dramatic. And it's a completely safe therapy, as long as you know that it's not a septic joint.

But for the most part, in the inpatient service, We're using parenteral steroids. And the dose is usually significant, and it's proportional to the number of inflamed joints. If you've got six inflamed joints, you can figure roughly 60 of prednisone or it's equivalent. Four inflamed joints-- 40, et cetera. And you keep it up for a few days until they start to get better, and then you rapidly taper and discontinue.

So what if I think that somebody meets the criteria for uric-acid lowering? The last thing I will ever do during an acute attack is initiate uric-acid lowering. Why?

There is a marked inflammatory milieu. You've got high levels of interleukins, et cetera. If you start to have fluctuations of uric acid across those membranes, you will convert a three-joint attack into a 12-joint attack. Your patient will hate you forever, and they will never take that drug again no matter what.

So if you think that this is someone who should have uric-acid lowering, make a mental note of it. Get them out of the acute attack, and then a month later when they're completely cooled off and blocked with prophylactic colchicine, which is a whole different way of using colchicine, then you can slowly introduce your uric-acid lowering.

And ACTH is of interesting historical significance because, again, that was Dr. Yue of Gutman Yue, who recognized that ACTH was far more effective for crystal synovitis than parenteral steroids. And she taught that to me.

And then one of my Fellows asked me, where is it in the literature? And I said, it isn't, so let's put it there. And so we collected a whole bunch of patients, and we showed that compared to the historical studies of steroids and gout, the patients got better much faster. And because it's ACTH, they didn't become as hyperglycemic, and they didn't become steroid dependent, you didn't have steroid-withdrawal symptoms, et cetera, et cetera.

And as soon as we wrote that, it went off the market as an orphan drug. And then it came back more recently as Acthar Gel, which is unaffordable. And the reason it might work better is that there are ACTH receptors on white cells. And the white cells, as you know, is the key mediator of the inflammation, as well as a whole melanocortin anti-inflammatory pathway that's activated by ACTH that is not activated by steroids. So when ACTH if and when it ever becomes affordable again, that may be a more effective and safer alternative.

So then you get your patient out of the acute attack, and they enter what we call the "intercritical period." And so again, you may not have to do anything more than to look at the medications and get rid of the diuretics if that's feasible. Educate the patient about diet if that's something you feel was the major trigger. If alcohol intake can be modified, that's a very good place to go if that was the major trigger.

If not, however, the patients we have with creatinines of 3 and we're stuck, or they're in severe congestive heart failure, we're stuck with a diuretic. And if the history is that this is their third attack in three months, you can make a bet that the intercritical period is going to be very short. And it's very disabling to have attack after attack. So that's somebody who should be on prophylactic colchicine.

So the rationale behind prophylactic colchicine is that you're going to give a small dose at a regular interval to have a steady-state low level of colchicine around at all times, such that in this patient in whom you are hypothesizing that crystals are going to be continuously deposited, you are telling the white cells, so what-- don't get excited about it. And so that's the strategy.

And so what's a prophylactic dose? Well, again, you're looking at the creatinine and asking about the gut. So it could be one pill a day for somebody with a creatinine of 1.2. It might be two pills a day for someone with a creatinine of 0.8. For someone with a creatinine of 2, it will be one pill every other day or 0.3 milligrams daily. For a dialysis patient, it's one pill a week. Remember, it's nondialyzable.

And in-between, you sort of figure it out. But if you ask about nausea, stomach cramping, and diarrhea, you will not overdose the patient. And again, if it's somebody with no risk factors except that they went to this barbecue and they binged, if you make them aware that, you may not have to treat them at all. Yes.

AUDIENCE: [INAUDIBLE] if they're already on allopurinol--

LESLIE KERR: Keep it going. Don't stop it, don't start it, don't change the dose. Steady state. If you stop it, you induce fluctuations. If you increase the dose-- so just keep it going.

It may not be the right dose, but that's an outpatient problem when they're cooled off and on colchicine. And if they're already on colchicine, keep it going because even if it fails, the attack is likely to be fewer joints, and less intense, and a shorter duration if they're on colchicine than if they're off it.

Then a minority of patients enter what we call "chronic tophaceous gout phase." The common locations are the ears, as imaged here, and the distal digits. Again, these are cooler places of the body, so you can think of people with tophaceous gout as essentially being super-saturated solutions of uric acid. And where are they going to get the precipitates? It's going to be in areas that are cooler because the solubility of uric acid is decreased by.

And this is something that we, fortunately-- the panel rarely see these days. Only really an intractable alcoholics do I see something like that. And sometimes, these patients are misdiagnosed as rheumatoid because it can be highly deforming.

But you can see uric acid draining through the skin. You have DIP involvement, you have asymmetrical PIPs. This could never be rheumatoid arthritis. There's tophi everywhere.

AUDIENCE: Does ambient temperature play a role, or is it just body temperature? In other words, do people worse in colder-- so they move to Minnesota--

LESLIE KERR: Alaska or something. Yeah, I haven't heard that. Yeah, I don't know.

And so here are the X-rays. On this side, it's a mild presentation of gout. You can see this erosion of an overhanging edge, but the joint space is preserved. And that's why it's not osteoarthritis.

And you can see some lucencies in the soft tissue with a soft-tissue mass. So this would be mild tophaceous gout. This is a much more severe image. This distal digit's been replaced by this lucent mass, which is a tophus.

So if you stuck a biopsy needle in there, you would get out sheets of uric-acid crystals. OK, here are the more common. This is the first MTP. You eventually got the joint space narrowing of destruction, but all these classifications are within the tophus. Here's a big tophus here, big tophus there, and a big soft-tissue mass on the side of the foot.

So if I have a patient who has a bunion in the setting of gout-- a bunion gives you hypertrophy of the first MTP-- in order to decide whether he or she is a candidate for uric-acid [INAUDIBLE], they'll often take an X-ray of the feet, [INAUDIBLE] of the feet, because it's easy to distinguish osteoarthritis radiographically from a tophus radiographically. And the tophus would change my management. Osteoarthritis obvious doesn't. But clinically, a bunion and a tophus of the first MTP look identical.

So here's the microscopy. So remember, with an acute gouty synovitis, you've got lots of white cells, and they phagocytose the crystals. A tophus is a sequestered precipitate of uric acid. And so the most beautiful crystallography that happened to aspirate one-- you see crystals in all directions.

So what are the indications for uric-acid therapy? Again, allopurinol has withstood the test of time and given the longevity of it in the millions of patients who have used it, it's a relatively safe drug. But that's not to say that it's completely safe-- and so Stevens-Johnson syndrome, severe rashes, bone-marrow suppression, hepatotoxicity.

And these things don't have to happen in year one. They can happen year 10 or year 20. So you have to have a good reason. You don't just throw these things around because somebody's had one attack.

So here are what I consider to be the indication-- recurrent attacks, despite colchicine prophylaxis. So if you think somebody is going to have problems with recurrent episodes of gout, the way you get to first base for uric-acid lowering is to put them on prophylactic colchicine and demonstrate that they fail. If they don't fail, your job's done.

So anyone who's had a few attacks, you give them prophylactic colchicine, they don't have attacks, you don't have to do anything more. However, if they do go on to have attacks, it's so disabling that that is an indication for uric-acid-lowering therapy. And I would say that's the main indication for the majority of my patients. They still go on to have attacks despite [INAUDIBLE].

The second indication is uric-acid stone. If you don't ask, have you ever had a kidney stone, as part of your history taking, you don't get to that indication, because the patient isn't going to make the connection. If the answer is yes, they go right into a uric-acid-lowering strategy.

And then tophaceous gout-- if you don't examine the patient for tophi, or you don't take an X-ray of the feet to differentiate a tophus from a bunion, you don't get to that indication. And so the rationale for the stone formers and the tophi is we think that chronic uric nephropathy is a relatively rare occurrence. And that's the rationale for not just lowering everybody's uric acid who has asymptomatic hyperuricemia.

But among people, uric acid stones, you get a uric-stone nephropathy, which you don't want to have, plus the individual episodes of renal colic are quite disabling. And for the tophi formers, if you can form tophi in your soft tissues and your joints, you're probably making microtophi in your kidneys, which is the risk factor for chronic urate nephropathy. Not all people with tophi will have them in their kidney, but there's no way to differentiate. So in addition to wanting to prevent that destructive arthropathy that tophi can do, you also want to make sure they're not damaging their kidneys. So those are the main indications.

And then one that's not really relevant to the field of rheumatology is somebody who is about to get a chemotherapy that's going to lyse a billion leukemic cells to prevent acute urate nephropathy, which is not within the complications of gout and tumor lysis. So those are the indications.

And so what do we do? Well, in an academic world, you would like this to identify the underexcretors versus the overproducers. Almost all the patients I see in the in-consult service are underexcretors, and there's nothing I can do about it because when you're creatinine is 2, you're an underexcretor. There's nothing I can do.

And so anything I give you to increase uric-acid excretion isn't going to work because you're not going to deliver that distally to distal tubule, which is where the uricosuric effect would be. So I'm not going to bother with somebody who's got renal insufficiency or who's on a diuretic to show they're an underexcretor because they are, and there's nothing I can do about it.

But if it's a young person who has normal renal function, and you're looking at this guy, and you're thinking, I'm going to put him on allopurinol for 60 years, really? And I said, allopurinol's a great drug, but the side-effects can come back to bite you decades later. It's kind of a nice trick to show that that person's an underexcretor, and therefore, by the book, treat him with something that increases uric-acid excretion which works only at the level of the distal tubule and has more systemic effects, like a uricosuric. So I will define that status in that situation.

f vast majority of patients will end up on xanthine oxidase inhibitors because they are either overproducers, or they are underexcretors, and there's nothing you can do to increase their excretion. So the only uricosuric that we commonly prescribe in this country is probenecid, known as Benemid.

And again, if you didn't take the history that they have a renal stone, then you're going to be in trouble because the main contraindication to the use of uricosurics is someone who is a uric-acid stone former. Why? Because the only side-effect of uricosurics is stone formation.

So you would not give it to a stone former. That person already has a more-than-sufficient excretion distally of uric acid. Anyone whose on a diuretic for renal insufficiency-- it's just not going to work because you don't have-- the cut-off is basically a creatinine of 1.6 or greater. It's just not going to help you. You're not going help the patient.

Sulfinpyrazone just fell out of favor. Benzbromarone is FDA approved in Europe, but because there was a hepatic-toxicity signal, the FDA never approved it here. It worked up to a creatinine of 2.5 I'm told.

And then the mainstay are the xanthine-oxidase inhibitors, of which allopurinol is the mainstay, the Mount Sinai drug, the devil we truly know, with a long track record. In 2010, the FDA approved a new xanthine-oxidase inhibitor, one that it's more selective, known as "febuxostat," or "Uloric." There was a signal early on of retroperitoneal hemorrhage in three patients for unknown reasons, and a cardiovascular signal as well that was suppressed by the company. In post-marketing data, we now know that there was a cardiovascular risk associated with the use of Uloric. We don't understand why.

And so for me, that's always been a niche drug because any new drug, you don't know the long-term side-effects until it's been out for a while. But I did have a fair number of patients who were completely intolerant of allopurinol with severe rashes, other allergic reactions, thrombocytopenia. And there was really nothing for them. They were quite miserable. So now, at least we have something that's structurally completely different. So for patients who are intolerant of allopurinol, or you can't control the allopurinol, I will prescribe Uloric.

The other thing that was manipulation by the company that makes febuxostat is that is that they compared 80 milligrams of febuxostat which is their fairly fullest dose-- I have very few people on 120-- with 300 of allopurinol to show that it was more effective in lowering serum uric acid, when, in practice, I don't stop at 300 allopurinol. I push it as high as 800 milligrams.

So if I gave 400 or 500 allopurinol and 80 of febuxostat I don't think you'd see a difference. But that's why it's in the literature that it lowers it more effectively, it lowers it lower. I take that with a grain of salt.

Lesinurad-- we had in combination with allopurinol. I never really used it, and the FDA just pulled it, so we're not going to be using it.

Interleukin-1 inhibitors-- you remember, there's a lot of interleukin-1 enhancements in the gouty milieu. And so experimentally, the interleukin-1 inhibitors, there are case reports that document its efficacy when you can't give anything else or nothing else is working. So it's experimental. It's not FDA approved.

There was a short trial of canakinumab, which lasted for a month. When you're giving it to elderly, diabetic patients, and you wonder why you see increased risk of sepsis, well, no great surprise, right? So these are not FDA approved.

And then a brave new world for me as someone who treats gout, pegloticase. And the story is absolutely fascinating. So again, this is the type of treatment you can develop when you know something about etiology and pathogenesis, which is what we're missing for all the other connective-tissue diseases.

So the story is that throughout the animal kingdom, all of the animals walk around with a serum uric acid between 2 and 3 milligrams per deciliter, except for humans and a couple of nonhuman primates. I always forget whether it's a orangutans or baboons. We two species-- baboons and humans-- walk around between 56 and six. And the solubility of uric acid and serum is about 6.2. So we're right near the cut-off.

So it's clear why we get into trouble with gout and the rest of the animal kingdom doesn't. The rest of the animal kingdom has an enzyme called "uricase," which we lost in our evolutionary progression as humans and as baboons. So knowing that uric acid is the problem and understanding why we are in trouble with relatively high serum uric acid levels because we lost uricase, you could then rationally develop a form of uricase to infuse into people.

So uricase, if you remember your biochemistry, which most of us, including me, do not remember, converts uric acid into allantoin. And allantoin is 200 times more soluble in urine than uric acid. So that's why the animals that kept the uricase have no problems with uric acid. And so we have patients who have failed or have severe allergic reactions to everything on this list and can't use it. And they are suffering with recurrent polyarticular attacks and have tophi everywhere.

And so this was a brave new world. In fact, Dr. Gorevic was one of the initial study centers for allopurinol. Pegloticase. And the Fellows who were doing the study would say to me, before the infusion, their serum uric acid was 14. A half an hour later, it was 0.0.

And you know what-- this tophus they had there-- in two hours, I saw it start to visibly shrink. This was like amazing. Amazing.

I have three patients on it. It's not something I throw around. It's very expensive. You must have a normal G6-PD or you can't metabolize it. And it's a porcine uricase, which means that it has the potential to develop blocking IgG antibodies, and so you must get a serum uric acid before each infusion. And it should be less than 2.0. And if it starts to rise, you know the next infusion is going to cause an anaphylactic reaction.

So it's not a forever drug, but so far, my three patients who are on it are doing so much better. It's like a relief to remove horrible gout from their lives. And their serum uric acids have not bumped up yet. So it's such a wonderful thing to have in this era of knowing something about etiology and pathogenesis.

So that's the gout story. Any questions before I move on to the other two crystals that will be much quicker? Yes.

AUDIENCE: In an acute attach, if you give systemic steroids, does that increase your risk of having more recurring attacks?

LESLIE KERR: No, no, no, no. If you give it, and then you taper it off. And if you think they're going to have more attacks based on their history or risk factors, you put colchicine on at the same time. And that continues after the steroids. Yes.

SPEAKER: We have five minutes left, so I don't knoq how much you have left to go.

LESLIE KERR: We started almost 15 minutes late, and you're only giving me five more minutes?

SPEAKER: I'm sorry.

LESLIE KERR: I'm going to do quick because you've got to hear about pseudo gout because this is the one you missed-- monoarticular, polyarticular, but a different pattern-- the knee, followed by the ankle, followed by the wrist. A hot wrist is going to be much more likely to be pseudo gout than gout, just from that distribution, never having had a hot toe. Inflammatory, but not as inflammatory as gout, positively birefringent crystals.

Here's how they look. So they're short and stubby. They don't harpoon the cell. They're much harder to see with just plain microscopy, but polarizer brings them out. When you see that intracellularly, you know you're dealing with pseudo gout.

A hint can be visualizing chondrocalcinosis on an X-ray. So here's chondrocalcinosis in the wrist. Here it is in the knee. And here it is lining the humeral hip. Again, these are the common places where you see pseudo gout.

But lots of people have chondrocal without ever having pseudo gout. So if it's monoarticular, you got to tap it to rule out septic arthritis. Demonstrate the intracellular crystals to prove it. But having this on a prior X-ray increases your index of suspicion. Same as gout for the acute attack.

Here's a list of metabolic abnormalities that are associated that you should know particularly-- hypoparathyroidism, hypothyroidism, and diabetes. And so when you look at advanced-stage acute illness diabetes, hypothyroidism, and a hot wrist, that's a clinical scenario that screams pseudo gout.

And the others are rare. If you see pseudo gout in a young person, think about Wilson's disease and hemochromatosis. That's pseudo gout. We're done.

Third crystal you probably haven't heard of-- calcium hydroxyapatite. But you've seen it-- that hot, severe, periarthritis of the shoulder, where there's no shoulder effusion, but it's exquisitely tender. You can feel a little rock here-- calcific tendinitis.

And sometimes you can see the calcium hydroxyapatite precipitated as a clump on the supraspinatus tendon. You give a shot of Depo right there, and you relieve them.

Milwaukee shoulder-- McCarty is a rheumatologist who worked in Milwaukee. He saw a lot of women who had worked on farms who had severe synovitis of the shoulder that would come and go. He had the feeling that it was a crystal. He kept looking. He didn't see anything.

One day, he gave a sample to somebody with an electron microscope. And lo and behold, intracellular calcium hydroxyapatite. So calcium hydroxyapatite, when dispersed in synovial fluid, you can't see it with traditional microscopy. So he proved that it was-- a crystal synovitis-- older women.

This is always on the Geri boards, OK? Trauma, overuse, rotator-cuff tears, severe pain within range of motion, big infusions. Nothing works that well. We try all these things. They usually end up needing a rotator-cuff repair and/or a total joint.

And here's how it looks in the flesh-- big, painful effusion, severe osteoarthritis of the joint. And because the humeral head is so high up in the glenoid, you know there's a rotator-cuff tear.

So those are the three crystals. And I find this topic so satisfying because we know what the etiology is. And so think about that with your glass of port after dinner. Hopefully not with your hot toe. Thank you very much.