Dr. Kendal Williams: Welcome everyone to the Penn Primary Care Podcast. I'm your host, Dr. Kendal Williams.

When we look back at our previous podcast, we found that the most popular podcast to be downloaded was the one on hypertension, "Clinical Pearls on the Management of Hypertension." And we had promised at the time that we would bring back Dr. Cohen and Alison Purcell to talk more about the details of hypertension management and that's what we're going to do today.

So I had introduced Dr. Cohen and Alison before, but I'm going to do it again: Dr. Jordana Cohen is an Assistant Professor of Medicine at Penn in the Renal and Electrolyte Division. She's a researcher in hypertension and is part of the Center for Clinical Epidemiology and Biostats.

Jordy, thanks so much for coming again.

Dr. Jordana Cohen: Thank you so much for having me again to talk about my favorite topic.

Dr. Kendal Williams: Alison Purcell is a family nurse practitioner in the Department of Family Medicine and Community Health at Penn. She runs the hypertension program and the hypertension clinic and has a lot of experience in the practical management of hypertension. Allie, thanks for coming again.

Alison Purcell: Thanks so much for having me.

Dr. Kendal Williams: And I'm really excited to be joined by a wonderful colleague and friend with a great deal of experience in this area as well, Dr. Matthew Rusk. Matt is a full professor of medicine at Penn. He's the former Director of the Primary Care Residency Program, is a primary care physician himself. He also runs with a colleague the Penn Employee Hypertension Program. Matt, thanks for coming.

Dr. Matthew Rusk: Thanks for having me. Looking forward to it, Kendal.

Dr. Kendal Williams: So, what we want to do today is to really generate a great discussion among these terrific colleagues about some of the scenarios that we face that are more challenging in the management of hypertension.

I really would encourage everybody to go back and listen to our first one if you haven't already. There was a lot of I found very helpful points that were brought out. I myself have gone and bought my potassium salt replacement and using that almost exclusively for myself, but there was a lot of great points.

I think, you know, for me, and Allie, maybe you can speak to this as well, I mean, I think the thing that came out of that discussion for me was really the use of combination medications as well as the discussion about the treatment goals. I don't know if you had any other sort of pearls that you took away from that discussion.

Alison Purcell: Oh, I agree. And the discussion about the diet interventions and specifics on self-monitoring at home, that was helpful.

Dr. Kendal Williams: So I think we're just going to dive right into it and talk about the thing that everybody wants to talk about. And that is what do you do when what you've done isn't working anymore?

So you have to choose when you're starting a patient on a blood pressure medicine between an ACE and ARB, you don't do both. But then you have thiazides as options and calcium channel blockers as options.

But now, what happens when you have somebody on all three? You've chosen an ACE or an ARB and you have a thiazide and calcium channel blocker, and you're still getting high blood pressure readings, high enough that you need to manage further, and you need to add something further.

So the first question we want to delve into is how much do we need to work up patients that in which we face the situation? Jordy, how often is secondary hypertension an issue?

Dr. Jordana Cohen: This is a great question. So the patients that you described, if you still have an elevated blood pressure on optimal tolerated dosing of the three first-line antihypertensive agents, those patients are called resistant hypertensive patients. It also applies to the group of individuals who require that fourth medication to reach control.

So if someone's on four medications and has well-controlled hypertension, they're also called resistant hypertensives. And then if they require five or more anti-hypertensives, the new category for that is called refractory hypertension. I think it's been around for a little while, but it's been studied more and more recently because these are the patients that are really the highest risk.

And we really should be evaluating all of these patients for secondary hypertension. Literally every single person who has refractory hypertension, we should be evaluating further. There are very few situations where there's no added value to looking a little bit deeper. The extent of that workup and how much we need to do

depends on the person's risk factors. But typically at least about 20 to 30% of these individuals have a cause of secondary hypertension. So there is value in working it up.

Dr. Kendal Williams: So, what do you start with? What's your basic workup?

Dr. Jordana Cohen: So every single one of these patients, definitely we should be looking for kidney disease. As a nephrologist, I'm not just biased, but we see so much of it. It's one of the most common causes of resistant hypertension that shoves that number of secondary hypertension actually even higher, probably closer to even 50% if you include CKD in that group.

And, of course, obviously these patients are usually undergoing at least annual monitoring with the basic metabolic panel since they're on an ACE inhibitor and ARB and a thiazide or thiazide-like diuretic.

But on top of that, it's a really good idea to be checking a urine microalbumin in those patients or at least a urinalysis to be looking for underlying albuminuria or hematuria, which could give you a clue that they have significant kidney disease, but that might not be necessarily reflected in their basic metabolic panel.

More and more also, especially in African-American patients, we are recommending getting a Cystatin C also for screening for chronic kidney disease since that can give us a more accurate assessment of their kidney function than the creatinine alone. It's not quite as prone to issues with race in terms of classification of CKD. And it's also not susceptible to confounders like muscle mass as creatine is. So that's our first and foremost, the most important screening.

Everybody with resistant hypertension should also be screened with a renin and aldo to assess for primary aldosteronism.

Dr. Kendal Williams: Serum test, right?

Dr. Jordana Cohen: Serum, yeah.

Dr. Kendal Williams: So one would not expect to have hypertension as a result of pure kidney disease until you reach stage III and above. Is that what you would think?

Dr. Jordana Cohen: Not necessarily. We sometimes see, for instance, people coming in with glomerular disease, like for example, lupus patients who don't necessarily manifest as having a particularly elevated creatine, but can come in with hypertension. Typically, you'll see the creatinine elevated or the Cystatin C elevated though.

Alison Purcell: Well, Jordy, can you talk a little bit more about Cystatin C? Are we doing this for everyone whose GFR comes back a little bit down? Are we doing this on a certain age group? Or did you mention just, you know, focusing on our African-American patients?

Dr. Jordana Cohen: Personally, I would check a Cystatin C in any Black patient with resistant hypertension out of concern that I might be missing underlying kidney disease. I think that it's quite feasible that we can miss it in patients if they are being misclassified based off of creatine alone, especially if a patient has very little muscle mass, is frailer, which is particularly problematic in very obese patients because it's very hard to know if they have much muscle mass.

People are very sarcopenic under their obesity and we can't really tell and they tend to hyperfilter their kidneys, so what that can do is it can show falsely normal kidney function in someone who actually does have clinically significant kidney disease.

The Cystatin C can at least help somewhat with some of that. It's not a perfect metric, but it is a really good tool. So I think any Black patient with resistant hypertension, checking Cystatin C, it's not necessarily being recommended across the board and absolutely every patient, yet it costs about $15 compared to your basic metabolic panel, which is typically about $8 for everything. So it's a little more expensive, but I think it's worth checking.

And if it becomes sort of our heuristic to be checking it in everyone with resistant hypertension, I'll be really happy because I think that'll really give us a much better picture of the prevalence of chronic kidney disease in these patients.

Alison Purcell: And is the microalbuminuria also now a definition for CKD that we should be thinking about?

Dr. Jordana Cohen: Yup. So that's been part of the definition actually for a few years for our definition of chronic kidney disease. So you either have chronic kidney disease if you have an elevated creatanine with an EGFR less than 60, or you have CKD if you have microalbuminuria, so more than 30 of urine microalbumin. More than 300 is considered macroalbuminuria. That's what we start to consider quite more clinically significant and higher risk of adverse cardiovascular events and progression of kidney disease.

Dr. Kendal Williams: And Jordy, just to clarify, you're checking these to find out the effects of the blood pressure on the kidney to the degree to which it has been affected and you're also trying to sort out if that kidney disease may be a cause of their hypertension, correct?

Dr. Jordana Cohen: Correct. Great question. It's bi-directional. So kidney disease is very often the cause of hypertension. But hypertension, we think can also cause kidney disease. This is not perfectly teased out in terms of the pathophysiology of it and there's some controversy.

But in large scale observational studies, it's been suggested very highly that hypertension can cause chronic kidney disease. And so we're also looking for target organ damage.

I think that part of that is because we often underdiagnose primary aldosteronism and aldosterone is highly toxic to the kidney. It's profibrotic and causes kidney disease and cardiac disease. And so I do think we're going to find out over time that a lot of the hypertension-induced kidney disease, where we don't always know the true cause, that it's often due to excess aldosterone,

Dr. Kendal Williams: So when. You get your renin and aldo levels back, you'll have an elevated aldo and low renin?

Dr. Jordana Cohen: Correct. And so I prefer to check renin activity. There are two options when you order it. You can either get renin activity or a direct renin level. And so I prefer renin activity because I find it easier to interpret because it's been around longer. It's something that we're just much more comfortable with that and in terms of interpreting the ratio.

So when I check a renin activity, I'm looking for ideally a renin level less than 0.6, which to me that's telling you a hundred percent that this is somebody who is very likely either primary aldosteronism or at least has excessive aldosterone for what they should have. And then an aldo level of typically more than 20 is the upper limit of normal that we look for.

But if they have a low renin and an aldo level in the mid-teens, I'm still doing confirmatory testing and looking deeper, because what we really care about is that aldosterone to renin ratio. And if that ratio is more than 20 to 30, then we're thinking this is a very high risk person for primary aldosteronism.

Dr. Kendal Williams: Matt, when you're doing workup in your practice, I'm assuming you're doing the renin and aldo as well. Are you thinking about some of these other concerns as well, some of the other hormonal causes?

Dr. Matthew Rusk: Yeah. So when we get to the sort of endocrinopathies phase of things, so, you know, in primary care, you're seeing a lot of patients and you

don't want to have to have people come back for blood work any more than they have to, because they're going to get grumpy if you keep making them come back.

And so one of the questions I have is should you try that as sort of batched together with some of the testing to try to make it more expedient for the patients.

And so, some other more obscure endocrinopathies you might be thinking about are pheo and Cushing's as an underlying cause of hypertension. So I've always thought, you know, how could you test for all three? Now, you might argue you really shouldn't test for Cushing's or pheo, unless there are other symptoms that fit in with those diseases like pheo. Do they have, you know, flushing and paroxysms of hypertension?

But a question I had for Jordy was, one thing I've sometimes done is tried to combine the testing altogether with one blood draw by having the patient take a dose of dexamethazone between 11 and 12 the night before, come in at eight in the morning, do a renin and aldo level, do a cortisol level and do plasma, and then metanephrines and you're sort of testing for three different things all at once.

And, you know, in primary care, we're trying to sort of sort out wheat from the chaff and none of these tests are perfect screening tests, but it's the way to screen for all three very quickly and efficiently. So if I want to test for all those at once, I'll do it that way.

But I'm curious as to whether Jordy thinks we ought to do a more sort of parsimonious workup and only check for those other things if we have a higher level of suspicion? And, you know, I think Cushing's in particular can sometimes be hard to clinically diagnose. People might not have classic symptoms, and that may be one thing we don't test for enough of.

Dr. Jordana Cohen: Yeah, this is a great question and there is not an easy answer to it. So in our practice and with myself training under our very experienced senior hypertension specialists, Debbie Cohen and Ray Townsend, both of them really felt strongly about not over-testing for pheo and for Cushing's, but you should look for it.

If there's somebody who's a diabetic with resistant hypertension and central obesity, then I think it's very appropriate to check for Cushing's. If somebody is having labile hypertension and refractory hypertension and palpitations or any other symptom, headaches, I think that it's reasonable if you have a level of suspicion to check for pheo. And I think your approach is appropriate to try to batch it all together.

One thing that I do want to mention about the primary aldo testing along with all of this is it needs to be done after the person's been walking around and ambulatory. So the worst thing is to check a renin and aldo in the hospital when someone's been lying down. So I do think a great time to do it is in ambulatory practice and in the way that you describe, having them come in the morning after they'd been up for a little bit and been sort of doing some activity and then have it checked. At least an hour or so after they wake up is perfect.

In terms of the pheo and the Cushing, I think there should be some level of suspicion that we shouldn't just be checking it in any patient who has resistant hypertension. There has to be some other reason, but think there's a wide range of reasons that we can use to justify it. So I don't think it's incredibly narrow and we shouldn't be ever checking these. We just need some rationale.

In terms of interpreting the pheo results though, the metanephrines, so couple of things I've seen people doing recently that I do want to call out is I think a lot of folks don't check the plasma metanephrines, instead they either check 24-hour urine or they check plasma catecholamines. What we recommend for screening for pheo, and this is based off guidelines as well, is to check just plasma metanephrines. The 24-hour urine is okay to do, but it's actually just so problematic because it's so frequent that patients undercollect 24 hour collections. The lab won't even run it if they undercollect and so that can really frustrate a lot of patients.

And similarly, with the 24-hour collections, they're not quite as good of a screening test as the plasma metanephrines. In terms of the plasma catecholomines, they don't really give us the same information. And what we're looking for typically in interpreting whether someone has a pheo, are those plasma metanephrines, looking at the normetanephrine and the metanephrine.

We look for those to be two to three times the upper limit of normal to consider it positive. So if it's just slightly elevated, we don't consider that positive. That could be stress-induced particularly in people who have it checked when they're in-patient.

But also for instance, if the dexamethazone maybe can cause a little bit of stress and you see a slight elevation, I wouldn't over-interpret, which I know we haven't seen anyone, I think really over-interpreting that lately, but just something important for people to be aware of.

Dr. Kendal Williams: Jordy, you had mentioned in our last podcast that in terms of imaging, you would start with a renal Doppler, right?

Dr. Jordana Cohen: Yeah. So I do start with a renal Doppler if someone is thin.

We have a lot of trouble interpreting renal Dopplers in obese patients or even overweight patients. And they're also just not a fantastic test if they're being done by a technician that is not very experienced in doing it. So it's very operator-dependent.

So if we know we can get them to do it here at Penn, and we know that it's like a patient that doesn't have a very large body habitus, I think it's reasonable to start with Doppler since it's so safe and inexpensive. And a lot of insurance companies won't even let us check the next step of imaging if we haven't done a Doppler first.

But if you have a high level of suspicion for renal artery stenosis due to atherosclerotic disease or due to fibromuscular dysplasia, the latter being more of something that we would see in younger patients more often, then that's a situation where we go to the next level of imaging.

For renal artery stenosis, we can do either an MRA or a CT angiogram. CT angiogram is a good option because it's both our assessment and the treatment if you do think somebody as a stenting candidate. But of course, the prior trials have shown that stenting in renal artery stenosis for atherosclerotic disease often isn't beneficial because it's a high risk of restenosis and that becomes very challenging to manage.

But for patients with fibromuscular dysplasia, the treatment is often angioplasty and those patients can be very responsive to it. So in younger patients in whom you have a suspicion for it, we will send them for CT angiogram.

Dr. Matthew Rusk: So, you know, and I was always taught that, you know, most of the renal artery stenosis we see in clinical practice is older folks with atherosclerotic arterial disease and the management after the stenting trials came out sort of negatively that the way to manage that problem is with medications basically. So I guess I've always thought, if they're older, if they have renal artery stenosis and risk factors for atherosclerosis, that's probably what's causing it.

Do we need to look for it? If we can control it with medications because medications is going to be a therapy anyway.

Dr. Jordana Cohen: I agree. I tend not to look for it with those patients in whom I have a high level of suspicion unless a couple of reasons where I would look for it. One being that they have very labile refractory hypertension, where every single time that I add on a new medication like an ACE inhibitor or thiazide, that their creatinine increases by like 40%. That's the patient I'll definitely look for it because they're not going to be tolerating optimized therapy because of their severe renal artery stenosis.

So that's one person. If they've got truly refractory hypertension also, just where you're adding a seventh and eighth medication, those are people that we'll look for it because they very potentially may benefit from trying to stent, even if they are at a risk of restenosis, if they really aren't responding to therapy. And then individuals who have a rising creatanine. Once it goes over the 1.8 or 2 depending on their age, we'll start investigating to see if we can preserve kidney function potentially if it's becoming a critical issue with regard to potentially putting them on dialysis in the future.

Dr. Kendal Williams: So let's follow the pathway down that their aldo level is high, so they have a hyperaldo state, what do you do?

Dr. Jordana Cohen: So, this is a very important question. So if they have a hyperaldo state which isn't always a cut and dry diagnosis, because a lot of our patients end up with that suppressed renin, but an aldo of 10 and what do you do in those patients?

So first, before you make the diagnosis, if you're struggling and you're worried that you're not getting a good quality test, that's when we'll sometimes do 24-hour urine aldosterone because that's a good confirmatory test. It requires salt loading though.

And so what I usually will do is check with the patient what their usual sodium intake is. And if it's less than about 4.5 grams a day, I tell them have an extra couple of salty bowls of soup the day before the testing and the day during the 24-hour urine testing, to make sure that they're adequately salt loaded. Most American diets do get close to where they need to be. So that's a good sort of confirmatory test if you're really not sure about interpreting the results.

One other thing I wanted to mention about the original renin and aldo testing is there were some older literature and older thoughts that you had to hold several antihypertensive medications in order to check the renin and aldo. And I just want to make sure folks know we tend in our hypertension clinic not to hold most antihypertensive agents when checking the renin and aldo. It's very important to hold spironolactone or eplerenone if they are on it, since those will impact our interpretation of the renin and aldo.

Other antihypertensive medications can affect the renin and aldo, for instance, calcium channel blockers, thiazide diuretics, ACE inhibitors, ARBs can increase your renin. Beta-blockers can decrease it. So you can see a slight impact, but they shouldn't be able to do it that substantially in somebody who is a true primary aldo patient.

A real primary aldo patient, often going to capture it, even if they're on those interfering medications. And if you have that really high level of suspicion and it was borderline results, that's a good time to move forward either with repeat testing or doing 24-hour urine aldosterone.

Then once you've confirmed the diagnosis, really the best thing you can do next, in my opinion, which is a little controversial, is just send the person right to Scott Trerotola for adrenal vein sampling. And we're always happy to facilitate that in our hypertension clinic.

The reason being is that he's published some really great not high quality evidence. It's small studies, but some really compelling evidence that when you do a CT scan to look for an adrenal adenoma, you can miss the actual secretion, which side is secreting aldosterone?

So some patients have unilateral adrenal hyperplasia and not necessarily an adenoma. And so those patients will still lateralize on adrenal vein sampling, meaning that adrenal vein sampling will see that they have one dominant adrenal gland that's secreting most of the aldosterone and that wouldn't show up on a CT scan.

There are some bigger observational studies that have actually shown that this may happen in up to a third of people with primary aldosteronism where they're misdiagnosed by the CT scan as having either no adenomas, so people don't send them for adrenal vein sampling or where it shows that they have it on one side and then they go for adrenal vein sampling, and they're actually hypersecreting on the opposite side.

And so that's just things to be aware of, that the CT scan isn't the end all be all.

Dr. Matthew Rusk: I had a quick question about that, Jordy, and I fully confess it when I have hyperaldo patients that are difficult, I send them to Jordy.

But what about the patient who let's say it's an elderly patient who doesn't want to have a lot of procedures. And it is a bunch of procedures to get adrenal vein sampling. What's wrong in a patient like that? Let's say you confirm they have hyperaldo and just saying, "I'm going to suppress it by giving you eplerenone or whatever or spironolactone."

And if we can get your blood pressure under control, why not just do that, it's a bit of therapeutic nihilism, but is there anything wrong with that approach, particularly in a patient who's older and doesn't want to go through all that testing?

Dr. Jordana Cohen: I think that's the perfect approach. I think it's all about having the conversation with the patient before you even start the testing and say, "What would you want to do based on the results?"

And if it's someone who's older, who's not a surgical candidate, or if they've had hypertension for 40 years, 30 years, we're not going to see a huge benefit even if we were to send them for surgery because they've already had stiffened blood vessels from their hypertension. They've already have some target organ damage from it.

Our goal is to try to reduce further damage and the best thing you can do in somebody like that is just get them on a mineralocorticoid receptor antagonist. So I think that's really the perfect approach. I don't think it's one-size-fits-all where every patient has to go through this extensive workup.

There is some additional benefit that's suggested by doing surgery in people who are good candidates for it, because it removes that aldosterone source so you're not getting that constant risk of target organ damage. Whereas the medication, if someone's not fully adherent to it, it could leak through or if their dose isn't optimized, they may not get as much benefit. So it's possible that the medication might not be as good as surgery for everyone, but I think it's often a really outstanding option.

And if somebody is found to have bilateral hyperplasia, we're going to be treating them with the mineralocorticoid receptor antagonist anyway. We don't remove both adrenal glands. So I really think that it's a really great approach if you just start them on treatment.

The main issue is that a lot of providers around the country aren't starting people on mineralocorticoid receptor antagonists. We did a big nationwide study in the VA where we found that all people with resistant hypertension, only 14% of people were started on one out of those people who had no contraindications for a mineralocorticoid receptor antagonist over a 20-year period. So we really need to be doing better.

So I think whatever we'll get people to start that mineralocorticoid receptor antagonist is really the best way to go.

Dr. Matthew Rusk: That's great, Jordy. And I guess, you know, I think one of the things that most of the people who get put on a mineralocorticoid antagonist or most doctors who are prescribing it are worried about causing hyperkalemia because most of those patients are on an ACE or an ARB. And I found that just not that many people have a problem with hyperkalemia.

And I'm wondering if you can comment, do you think that concern is overblown or, I mean, obviously you need to check it, but how much do we need to check it? How often does that even happen?

Dr. Jordana Cohen: It's a great question. So I'd always check basic metabolic panel one to two weeks after starting a mineralocorticoid receptor antagonist. In most people, I start spironolactone 25 or eplerenone 25. Spironolactone's a bit more potent at that lower dose than eplerenone is.

Most of the people in our practice now are starting most men on a player unknown though to start, understanding that it's not quite as potent, but that you'll have less gynecomastia.

But in terms of the hypokalemia, lower doses from 25 to 50 milligram equivalent in spironolactone really aren't associated with that high of a risk of hyperkalemia than in people who are on ACEs and ARBs.

The PATHWAY-2 trial was a really elegant trial that was done in the United Kingdom about five years ago where they randomized patients in a crossover fashion to 12 weeks of spironolactone versus a beta blocker versus an alpha blocker versus placebo. These were just patients with resistant hypertension that were all on an ACE or calcium channel blocker and a thiazide or thiazide-like diuretic.

And they found that in those patients, there were really low rates of hyperkalemia on the spironolactone in 12 weeks, but their blood pressure control was phenomenal compared to the other agents.

And so I really think that I agree with you. I think it's overblown. And more advanced chronic kidney disease patients, if they have CKD stage IV and V, that's when we start seeing a higher risk of hyperkalemia. And in those patients, we can often get them onto the new safer potassium binders to help facilitate treating them with them.

Dr. Kendal Williams: So I just want to step back for a second because we've bled into the discussion. We started out with a hyperaldo state, but assuming the patient does not have a documented hyperaldo state by the testing you described, the next step beyond those four basic medications we talked about before, based on the trial, you just stated, Jordy, is to reach for a mineralocorticoid blocker like Aldactone or a eplerenone. Is that correct?

Dr. Jordana Cohen: That's correct. And so I think a lot of people ask why even check a renin and an aldo if you should be starting it anyway.

So that study that I described, what we were checking also is to see just general practices of how people do that. Are people empirically starting mineralocorticoid receptor antagonists when they're not checking renin and aldo?

And what we found was that the people who were not checking renin and aldo were very rarely starting mineralocorticoid receptor antagonists. Whereas those people who were checking renin and aldo in their patients were about four times more likely to be starting people appropriately on mineralocorticoid receptor antagonists, regardless of the results of the renin and aldo.

So we think it was just that good behavior begot other good behavior. But I think that it's just really important that we treat patients with these medications, whether or not it's empirically, because it will protect them if they do have undiagnosed primary aldo.

We should be using it across the board in everybody with resistant hypertension, unless they already have advanced chronic kidney disease with hyperkalemia, in which case send them to us in nephrology clinic and we'll help figure out if it's appropriate.

Alison Purcell: So Jordy, could you talk a little bit about the difference between using eplerenone and spironolactone? I've had a lot of providers bring up the concern of cost and if there's going to be prior auth issue at the pharmacy and I was just wondering if you could speak to that a little bit.

Dr. Jordana Cohen: Yeah, I'll speak to it a bit and I'd love to hear your experiences too, Allie, on it.

So from our experience, eplerenone historically, like even just five years ago, was very expensive and we were having a lot of trouble getting it covered for patients by insurance. You'd have to very frequently put in a prior authorization justifying that they hadn't tolerated spironolactone and that now we have to try the eplerenone. And that's no longer quite as much of the case.

We still hit some barriers to prescribing eplerenone first before spironolactone, but we're having better luck. It is still quite more expensive than spironolactone. Spironolactone is often covered very well by insurance with almost no copay with several insurances, whereas eplerenone is still very expensive with insurance.

What I found though is that if you go to GoodRx, there are several local pharmacies that will give it for less than a dollar a pill, if not even less expensive, for a 90-day supply. I saw one recently for about $60. So it's still money, it's not cheap, but it's much better than it used to be for eplerenone. So I have that

conversation with my male patients, and I say, "Here are the risks of spironolactone for you. You do have a small risk of getting gynecomastia. We see it in about one in 10 male patients who start on spironolactone. Sometimes it's irreversible, which is really quite concerning to a lot of male patients." So the majority of the time, they'll ask to start a eplerenone first and I just explain that it may cost money and here's how to go about bypassing that cost or at least minimizing the cost.

So I think it's always worth that conversation. Obviously, there are still barriers to it. And I've had lots of men that I've successfully started on spironolactone without any problem whatsoever. So I do think it's still a great option to do spironolactone in those situations. Allie, have you had any similar or other experiences related to that?

Alison Purcell: Yeah, I've seen it a little bit easier. I tend to go to the spirinolactone first and having those conversations cost-wise, but I too have not had a lot of pushback at the pharmacies in recent months. I've also wanted to ask about the eplerenone and spironolactone daily versus twice daily dosing. I know I've read that and I've seen eplerenone, you know, increased to b.i.d., have a little bit stronger effect on the blood pressure control. I was wondering if that's the same with spironolactone, if you tend to titrate up doses or you tend to rather than a hundred milligrams daily, a separate spironolactone 50 and 50 or 25 and 25. I'm wondering about that as well.

Dr. Jordana Cohen: Yeah. Based on the drug label and the pharmacokinetics, I tend to be a little more comfortable spironolactone once a day, and eplerenone twice a day once you go to higher doses of it. That's also part of why I prefer spironolactone just because it can be a little bit easier to take since it's better for once daily. So it's, again, balancing those risk factors of the side effects for men, particularly with the eplerenone. And also some women, if they have lightheadedness or other sort of more obscure side effects with spironolactone, they tend to tolerate the eplerenone better. So that's where I'll be okay with doing it. But I personally try to avoid twice daily medications as often as I can. And the eplerenone's not as good when you give the higher doses at once a day. You can do it, but it won't be quite as long-acting.

Alison Purcell: And before we move on from the renin and aldo discussion, I thought I'd ask because one of the other concerns I have for patients, especially commercial patients with deductible plans, is how much money they're going to get for this, you know, big workup of their hypertension? And I was wondering if you knew the costs offhand at Penn Lab for the renin and aldo testing and the metanephrines, et cetera.

Dr. Jordana Cohen: I don't know, offhand. I know for research studies, we

recently researched it. And for renin and aldo, I think it's somewhere around $30 to $50. But I don't know for the metanephrines offhand. if someone else is talking in the next few minutes, I can pull up the costs though because I have access to how much it costs. So just give me a few minutes.

Dr. Matthew Rusk: Yeah. I was going to say, I send those tests pretty often. And if people have a regular commercial insurance that covers the lab, I actually haven't had any pushback from the insurance companies about covering them, like I do for some blood tests. So I haven't had any difficulties with that.

Dr. Jordana Cohen: Yeah. I've never had a patient complain, right? I don't think I recall any patients coming back and saying, "How could you order these incredibly expensive tests?"

Alison Purcell: Yeah. That's only happened once or twice to me. I was trying to avoid the more obscure commercial insurances for that reason.

Dr. Kendal Williams: So if you have a patient, like I had earlier in the week who was on all the agents we talked about, is on Aldactone and is still getting blood pressures of systolics 165 at home. Now, I think you're into a little bit of an area where there's just expert opinion. I'm curious for Matt and Allie, what drugs do you then turn to?

Dr. Matthew Rusk: And just to clarify, Kendal, this is someone who's maxed out on a calcium channel blocker or an ACE or an ARB, a diuretic and eplerenone?

Dr. Kendal Williams: Yes, exactly.

Dr. Matthew Rusk: Yeah, that's always a tough one. If those are all maxed out, there are, you know, other sort of fourth line drugs I would think about. I don't feel great about prescribing any of them. But I might prescribe, you know, a mixed alpha beta-blocker, like labetalol or Carvedilol if I was trying to throw something else out. If they had, you know, more advanced kidney disease or something like that, another drug I might get somewhat begrudgingly would be something like Clonidine, but I never feel great about it because I feel like they have a lot of side effects. And then there's some other ones that I would very rarely use, like minoxidil or something, which is incredibly powerful. But you're right, once you get to that point, you're sort of just randomly trying different things and just seeing if they work.

Alison Purcell: Yeah, same. I think as some patients are already coming in on lower doses of beta-blocker and then maybe after those initial four champion classes are gone through, yes, use the beta-blocker, Carvedilol. The only downside of course is the twice daily dosing.

And then, also if they come to BP clinic on hydralazine, maybe we'll do some adjustments of that. But I too, I mean, a three times daily dosing or just the labile ups and downs of that, try them to avoid. I am curious, I did want to talk about and hear from Jordy about the use of loop diuretics and how they start to fold in a lot of elderly patients and, again, overlapping cardiac disease and kind of thinking of when to kind of pull out that loop diuretic and transition over from a thiazide. I rarely see patients come out of the renal clinic on both, but I've seen a couple.

Dr. Jordana Cohen: That's a great question. And so I have a lot of opinions on the topic of what to do for refractory hypertension. And so the first thing, to answer Allie's question with loop diuretics, especially if someone has even minor kidney disease, so much of their hypertension is probably volume-mediated. So what I do with somebody who once they've failed those four top antihypertensive medications, I take a step back and try to think what's driving their kidney disease. We've done secondary workups so far, at least what we think is reasonable.

And if kidney disease is there, then the next thing I do is make sure that their hydrochlorothiazide has been switched to chlorthalidone because chlorthalidone is more potent in kidney disease. There was a beautiful trial that came out in the New England Journal two weeks ago by Rajiv Agarwal's group, which demonstrated the efficacy of chlorthalidone in advanced chronic kidney disease too.

So you'll see us using that more and more in our chronic kidney disease patients now. But I'll often add a loop diuretic at that point. I'm probably a little different than some of my colleagues, but this is because so much hypertension in kidney disease is due to volume and its hidden volume.

They don't necessarily have to have edema. They really can hide their volume very differently than non-renal disease patients based off of what's happening to their handling of systemic blood pressure, of plasma volume. And so I really think that there's a lot of value to adding-- actually, I love torsemide at that point, a low dose of torsemide because it's a once a day loop diuretic. And so you're not worried about them for getting that second dose later in the day, at which point they can develop sodium avidity with their salty dinner and would have nocturnal hypertension as a result. So I really value using torsemide in that situation.

If they're not chronic kidney disease, but if it's somebody who has maybe a touch of anxiety or you think may be a little more sympathetically driven in terms of their refractory hypertension, my next step is actually exactly what Matt had said. I love Carvedilol for this. I'm not as big of a fan of labetalol just because I don't think it has this favorable pharmacokinetics as Carvedilol. But think that they're both good options. The Carvedilol twice a day is the only downside, that adherence issue. But I'll often go to that because of that dual beta alpha and antagonist activity, which can be quite helpful and it's the most potent antihypertensive of the beta blockers.

Alternatively, what we'll often do is in people, especially if they have a bit of labile and refractory hypertension, but even if not, rather than doing a Clonidine pill which can actually worsen blood pressure lability unfortunately in a lot of patients because it has very odd pharmacokinetics. And even if it wears off just a tiny bit before they get their second dose in, you can see that rebound hypertension starting. And so it's a very challenging medication to really have patients on long term. They love it because they see their blood pressure come down immediately after they take it, unlike most of their other very long-acting antihypertensives, which takes several days to reach peak effect. But I think it's just not as good for long-term management. But that's my bias.

I love using the Clonidine patch when we can, but it obviously creates issues because people get rashes with it. That's the biggest complaint. But 0.1 of Clonidine two to three times a day is about equal to 0.1 Clonidine patch a week. And I find it very long-acting. And so it tends to be very good for people with labile hypertension at leveling out that lability or with sympathetically-driven hypertension.

If they don't tolerate the Clonidine patch, an alternative that I really like using that I learned from several colleagues at the Vanderbilt Hypertension Clinic, which is one of the top autonomic clinics in the country, is to use guanfacine. Guanfacine is another central alpha agonists, which has the exact same mechanism of action as Clonidine. It's a medicine that's actually often used for ADHD, but it's a very potent antihypertensive. And it's dosed very similarly to Clonidine. I recommend giving it to patients at night before bedtime. And you can give 1 milligram of guanfacine, is the equivalent of 0.1 microgram Clonidine patch. And so it's really a good alternative option to take once a day.

It's a very long-acting antihypertensive medication. It's half-life as longer than 24 hours. And so it can really be a very good option also for people with blood pressure lability and with sympathetically-driven hypertension.

I also love it for people who have ADHD and hypertension, where you're worried about the effects of their ADHD medications on maybe contributing to their hypertension. And this is something that is a good option for them in particular, because it can hit two birds with one stone.

Dr. Kendal Williams: So guanfacine is an older medication. I remember learning about it in medical school. I assume it's fairly cheap. But does it have side effects like Clonidine in terms of the dry mouth and orthostasis and some of the other issues?

Dr. Jordana Cohen: Yeah. Not really orthostasis, but the exact same side effects

in terms of the dry mouth and the fatigue. So I recommend taking it at bedtime. I try to keep the dose low. I try not to go above 3 milligrams but I often will keep people just at 1 or 2 milligrams and that tends to minimize the adverse effects.

Dr. Kendal Williams: It used to be that the Clonidine patch was expensive. I think that's changed now, right?,

Dr. Jordana Cohen: Correct. It's gotten a bit better. It's usually covered by insurance, especially if people are on multiple antihypertensive agents, so the insurance company can see that there's someone who's refractory.

Dr. Matthew Rusk: So you had talked about patients with CKD using chlorthalidone. And when the CKD is more advanced, they tend to go to a loop and I love torsemide, as you said. Should I be using chlorthalidone more in people with more advanced kidney disease? Does it work if people have a GFR say less than 30 or should I be going to a loop in those people?

Dr. Jordana Cohen: So we used to think that we had to go to a loop in all of those people, but this paper that just came out two weeks ago in the New England Journal suggests otherwise. These were people with chronic kidney disease stage IV and V that did fantastically on chlorthalidone. So I think you're going to see us using it more and more in these more advanced chronic kidney disease patients that we don't have to necessarily stop it when they're more advanced and that they're still seeing really good antihypertensive benefit from it.

But I do think that personally, like I had mentioned, I love using both when you need it. But I think that before switching to a loop, I think right now, we'll be seeing more people switching them to chlorthalidone first.

Dr. Matthew Rusk: That's really helpful. I'm really glad to learn that.

Dr. Jordana Cohen: Yeah, good news. And then the other thing that I was going to add is I just looked up the cost of the metanephrines and they've really come down a lot. I remember when I was in training, I think that it was about $400 to check them. It's down to $32 at the Penn Labs.

Dr. Kendal Williams: So, this has been a great discussion. I really appreciate all of you participating.

Before we wrap up, are there any other sort of pearls in hypertension management that you'd like to share with the primary care audience?

I know, Allie, you had brought up something about, you know, when ambulatory blood pressures are an emergency.

Alison Purcell: Yeah, Jordy, I was able to listen to your talk at the Penn Hypertension Seminar this year. And I think all primary care providers would feel comforted hearing about the data about asymptomatic patients and being referred to the ER for an elevated blood pressure. And I think we all feel pressured to do so if they call from home with their 180 to 200 blood pressure and everybody's upset and the nurses are upset and we're upset. And I guess the easy answer sometime is to go to the ER, even though they have no symptoms.

Can we take better care of them by not sending them to the ER?

Dr. Jordana Cohen: Yeah, we can. And we now have data to support that, actually. So there was a really good article in JAMA Internal Medicine in 2016. The first author, his last name is Patel. And this was an article that showed that in asymptomatic people that were referred to the ER, that they were more likely to be admitted, but not more likely to necessarily have good outcomes and that they had the similar blood pressure control six months out from the study.

So it doesn't do anything for their blood pressure control. They may potentially have more adverse outcomes in the short term from going to the hospital.

And so if they don't have any evidence of target organ damage by history, then if you can get them in the office to do an EKG, that's amazing. But I don't think that there's really a reason just for a number to send them to the emergency room. There needs to be some suspicion for target organ damage to really merit them going in, because we really should be only treating hypertensive emergency in the emergency room.

And there really should no longer be a term hypertensive urgency. It should just be chronic uncontrolled hypertension. And those are the people that we need to decrease their blood pressures low and slow over a long period of time because we can cause a lot of damage by lowering it too quickly.

And that's been shown in two other recent really high quality studies in JAMA Internal Medicine, one in 2019 by Tim Anderson. Another one that came out this year by Dr. Rastogi that actually had one of our top fellows who was one of the co-authors. Both of which showed that when you send someone to an emergency room and they're admitted to the hospital and you escalate therapy for their chronic hypertension, it's associated with adverse outcomes with more readmissions, more falls after hospitalization often or other adverse events after their hospitalization and more ischemic events during their hospitalization, like more risk of MI and more risk of acute kidney injury.

So it's not benign to send someone to an emergency room for hypertension, unless you really are worried that it's for hypertensive emergency.

Dr. Matthew Rusk: It's so great to hear Jordy say that. I was going to say the best place to treat chronic hypertension is in your office.

Dr. Jordana Cohen: Yes.

Dr. Matthew Rusk: Never in the emergency room. So I couldn't agree more.

Dr. Kendal Williams: I want to stand up for some of those hospitalists who might be listening who are constantly called about moderate blood pressure elevations in the hospital. When I was a hospitalist, I got called maybe a hundreds of times at 4:00 AM for blood pressures at 165 or so. You know, hospital-based treatment is also overdone, and you have to give these drugs some time to work.

So, I am constantly teaching the residents not to aggressively treat people in the hospital, but rather to get them started on something and then follow that.

Well, I want to thank you all for joining again. This has been a great discussion.

These are practical problems that we all face in our clinical practices all across Penn and around the world. And Jordy in particular, thank you for shedding the light of your knowledge here. And I really am very appreciative of Allie and Matt joining as well.

So, thank you all, for the great audience out there, for joining us and keeping with us in our podcast experience. And please come back soon.