Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/cushing-syndrome-strategies-diagnosis-management/39896/

Released: 05/29/2026
Valid until: 05/29/2027
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Cushing's at the Core: Leading-Edge Strategies for Diagnosis and Medical Management of Cushing Syndrome

Announcer:
Welcome to CME on ReachMD. This activity, titled *Cushing's at the Core: Leading-Edge Strategies for Diagnosis and Medical Management of Cushing Syndrome*, is provided by Cornerstone Medical Education and the American Academy of CME.

Prior to the beginning of the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Host:
Thank you for joining us for *Cushing's at the Core: Leading-Edge Strategies for Diagnosis and Medical Management of Cushing Syndrome, Hypercortisolism*. This educational activity is presented by the American Academy of CME and Cornerstone Medical Education and is supported by an educational grant from Corcept Therapeutics.

Joining us today are Drs. Honey East, Amir Hamrahian, and Rosario Pivonello. Dr. East is Director of Metabolic Medicine of Mississippi in Jackson, Mississippi. Dr. Hamrahian is Associate Professor of Medicine, Division of Endocrinology, Diabetes, and Metabolism at Johns Hopkins University in Baltimore, Maryland. Dr. Pivonello is Associate Professor of Endocrinology in the Department of Clinical Medicine and Surgery at University of Naples Federico II in Naples, Italy.

Disclosures, accreditation information, and learning objectives are provided here. To claim your credit for this activity, please be sure to complete the post-test and evaluation at the conclusion of the presentation. Thank you for your participation.

Dr. East:
Hello. My name is Dr. Honey East. I'm an endocrinologist in Jackson, Mississippi, and I'm very excited to be here. So I'm going to kick us off today talking about patients that we need to consider, who we need to screen, as well as the prevalence of hypercortisolism that we see in our patient population.

As you know, cortisol obviously has a very important physiologic role. However, when the balance of cortisol secretion is disrupted, we can see many different signs and symptoms.

Some of those comorbidities that we do see in clinical encounters include neuropsychiatric diseases, such as anxiety, depression, difficulty sleeping, cardiovascular disease. Patients with hypercortisolism, Cushing's disease, Cushing syndrome have increased incidence of heart disease, stroke, thromboembolic disorders, etc.

Also, reproductive and sexual disorders. Females often present either with irregular menstruation or with infertility. It's important for us to realize that PCOS is a diagnosis of exclusion, and one of the conditions that we need to exclude is hypercortisolism.

We see different dermatologic manifestations, including easy bruising, easy bleeding. Immunological disorders—patients with recurrent infections, severe infections that perhaps are not explained. Metabolic disorders—you think about fatty liver, nonalcoholic metabolic-associated changes in the liver. Muscle damage—we see sarcopenia, we see weakness, we see the typical central adiposity with the loss of muscles in the extremities and the associated weakness with that. And we see skeletal damage, increased chance of osteoporosis.

The best way to learn about hypercortisolism is in those patients that we all see all too frequently, and those are the patients who have iatrogenic hypercortisolism from exogenous corticosteroid therapy. And when you think about those patients, they may have a steroid psychosis or a steroid sarcopenia, and they may develop steroid-associated hyperglycemia or diabetes. And so please keep that in mind.

A lot of these signs and symptoms can certainly be nonspecific, so we want to look for groupings of these different signs and symptoms. But there are some signs and symptoms that can be a little bit more specific, and I love this slide because it really highlights how significant some of the changes that we can see with hypercortisolism can be.

So this is a patient with excess cortisol, and what you see is you'll see the thickened, discolored abdominal striae. So because of the thin skin, we have visible the blood vessels up underneath the skin because the skin has become so thin, and we see the characteristic wide changes. So a lot of the times these patients will have discolored abdominal—we call this—violaceous striae that are over 1 cm. So this would be a person that, if you saw this on exam, you would definitely want to screen this patient.

In clinic, some of the more common presentations that we might see, though, are those conditions that we know are clearly linked with hypercortisolism, including hypertension, diabetes, and osteoporosis.

So previously, it was estimated that hidden hypercortisolism was somewhere around 0.2% to 2% of the general population; however, maybe even estimated up to 10%, but really difficult to say.

We certainly today are going to focus on the association with hypercortisolism as with patients who have type 2 diabetes as well as hypertension, but I don't want you to forget the effects that hypercortisolism can have on the neuropsychiatric disorders, including treatment-resistant depression, and also the unexplained bone disease or fragility fracture.

And, you know, sometimes I think, as clinicians, we get, you know, laser-focused, and this is where I found it very helpful where other members of the team can say, "Hey, this is unusual. What do you think about this?" You know, the physical therapist who calls me and says, “This patient has a fragility fracture, and they don't really fit into the typical scenario that we see.” The counselor who calls and says, "You know, this patient's depression is very treatment-resistant. Could there be an underlying cause?" And so certainly, in those cases, we want to consider Cushing syndrome and screen those patients when appropriate.

So let's talk a little bit more about hypercortisolism and those comorbidities that we see in our clinic patient population, focusing on hypertension and diabetes. The association of cortisol excess and high blood pressure is well known. You'll see here on the left numerous studies that have shown the association of excess cortisol and the relation to hypertension and difficult-to-control hypertension.

On the right, you'll see that elevated cortisol levels are shown to be present, particularly when we have additional comorbidities and complications. When we think about our patients with hypertension and uncontrolled diabetes, certainly those patients who have microvascular complications, such as the diabetic retinopathy, the diabetic kidney disease, are at higher risk to have an underlying cause such as hypercortisolism, as you see here.

It’s important to mention that for those treatment-resistant patients, you know, please think about this. You know, if you have a patient who has atrial fibrillation, you're certainly going to think about an underlying cause of that atrial fibrillation, such as hyperthyroidism. And so for your patients who have difficult-to-control hypertension, difficult-to-control diabetes, we really need to not miss an underlying cause such as hypercortisolism because we may not be able to get adequate control if we don't get to the root cause.

When we look at the prevalence of hypercortisolism in patients with type 2 diabetes, there have been several studies throughout the years looking at the prevalence, and this is a really heterogeneous patient population here. You'll see some of these studies looked at outpatients, some looked at newly diagnosed diabetics, some looked at inpatients, some looked at diabetics who were living with obesity, and you'll see there was really a pretty wide range, anywhere from 0% up to 9.4% prevalence of hypercortisolism in these patients with type 2 diabetes.

Really, this leads to just a lot of questions. And so we ask ourselves, well, really, where are we now? You know, in 2026, where are we as far as the prevalence of hypercortisolism underlying conditions such as uncontrolled type 2 diabetes and hypertension?

Well, what we should focus on then is maybe looking at those patients who have advanced type 2 diabetes or those patients with difficult-to-control diabetes, those that are requiring insulin treatment. You'll see the studies here looking at specifically the odds ratio in those patients who have type 2 diabetes and hypertension. The odds ratio was 2.1. When we move along to those patients who have type 2 diabetes that required insulin treatment, the odds ratio was even higher at 2.5. And as one might expect, those patients who had advanced type 2 diabetes—we're defining that as having those microvascular or macrovascular complications, or being on insulin plus

hypertension, or having difficult-to-control resistant hypertension—we see that the odds ratio is even higher at 3.6.

So these would be some clues and some tip-offs to the patients that we certainly need to be screening, and we do not need to miss an underlying disorder that would be causing them to have such resistant or advanced disease.

So, as mentioned, there are all these questions that are going on now. You know, we have these ranges from 0% to 9.4%. Well, where are we? And so the CATALYST trial was developed to try to give us a little bit more information on that. And this is looking at over 1,000 patients who have difficult-to-control diabetes who underwent a 1-mg overnight dexamethasone suppression test and had a cortisol level over 1.8 on dexamethasone suppression testing. And the dexamethasone level was confirmed, by the way. So this really looks to give us an answer of what the prevalence is that we're looking at today.

I do love the way that CATALYST was set up because the exclusion criteria really took into account a lot of other physiologic conditions that could cause a false elevation in the dexamethasone suppression testing, and that was taken into account for this. There also was a treatment phase to CATALYST looking at what happens when we treat those patients for their hypercortisolism.

But right now we're talking about the prevalence of hypercortisolism. And based on the CATALYST trial, we had over 1,000 patients who had an A1c of over 7.5 despite optimal type 2 therapy in really good centers, many centers of excellence. They were very aggressively treated. And what we found was that the prevalence of hypercortisolism in patients with difficult-to-treat type 2 diabetes was higher than we had seen previously, and we saw this at 23.8%. So, you know, encroaching up upon 1/4 of these patients had cortisol levels of over 1.8 in dexamethasone suppression testing.

Even more interesting was a prevalence rate of 36.6%. So that's over 1/3 of these patients had hypercortisolism if they had difficult-to-control diabetes and required more than three antihypertensive therapies.

So you say, well, what about resistant hypertension? We know now that with diabetes, the prevalence in difficult-to-control type 2 diabetes is much higher than previously thought. Well, what about resistant hypertension? And for this, we have the MOMENTUM trial. Similar to the CATALYST trial, we looked at around 1,000 patients, and they were adequately screened for other physiologic or other conditions that might cause abnormal dexamethasone suppression tests. They were excluded from the trial. The remainder had dexamethasone suppression testing done, and looking at those patients who had that cortisol level of over 1.8 with an adequate dexamethasone level.

And drum roll, please. This is straight off the presses 2 days ago from the time of this recording, we have the results from the MOMENTUM trial. And quite amazingly, these are patients who have resistant hypertension defined as inadequate control on three or more hypertensive agents, including a diuretic, or four or more hypertensive agents that are not adequately controlling their hypertension. And I think about, you know, oh my goodness, this is a lot of my patient population.

And what they found on the MOMENTUM trial was very interesting—27.3% of these patients did have a post-dexamethasone suppression level over 1.8. And we are all anxiously awaiting the paper so that we can really dig in, get more details, and learn more about this. But certainly the prevalence was higher here in the MOMENTUM trial than I think any of us expected.

So I'm now going to turn this over to Dr. Hamrahian, who's going to speak with you more today about what we do when we suspect hypercortisolism and how we really need to be screening, the appropriate way to be screening these patients.

Dr. Hamrahian:
Thank you, Dr. East.

I'm going to talk about how to screen for Cushing syndrome. Every screen for Cushing syndrome starts with the clinical suspicion for the disease. This can be due to a finding during routine exam, it can be related to the patient's symptoms, or related to the presence of multiple comorbidities, which are usually progressive.

The first thing to keep in mind is that we need to make sure that we are ruling out an exogenous Cushing syndrome, and that is very important. And sometimes the patients may not identify, for example, multiple glucocorticoid injections as part of their medical treatment, and we need to specifically ask for them.

Once the exogenous Cushing syndrome has been ruled out, we have three main tools—diagnostic tests—for evaluation of patients suspected to have Cushing syndrome. These include the late-night salivary cortisol, the 24-hour urinary free cortisol, and the 1-mg dex suppression test.

And here is a strategy. If the clinical suspicion is low, then it is reasonable to use one single test initially, and this can be based on what you are more comfortable with as the screening test. And if that test is negative, you can stop there and have the patient return in the case of progression of the clinical picture.

In the case of higher suspicion, when there is an intermediate or high suspicion for the Cushing syndrome, it is better to do a couple of tests, two to three tests, as an initial screening, just to make sure that you are not dismissing the disease because of a false-negative result due to one of these tests. And if the result is normal, then usually you can stop there and again tell the patient to return in the case of progression of the signs and symptoms.

But you need to keep in mind about the cyclic Cushing syndrome. I have come across this several times in my practice, and it's important to keep that in mind. The important point is that these patients usually look Cushingoid when the intervals of hypercortisolism are too far apart, so that can be a clue when you have a normal result in a patient who looks Cushingoid and there is no evidence of exogenous glucocorticoid intake.

There are different ways to tackle this problem. I like the idea of getting a 24-hour urine cortisol once a week for 4 weeks and then once a month for 6 months. I have seen other people have done salivary cortisol at bedtime once a day for 7 days and then once a week for 4 weeks and then once a month for 6 months. So there are different approaches, and usually by doing this, you are able to catch this condition.

Now, once the patient has abnormal screening tests, based on the severity of the disease, I mean the abnormal results and the patient's clinical picture, sometimes you may need to repeat some of them, especially if they are borderline.

It is important to kind of remember about the non-neoplastic causes of hypercortisolism; some of which have been put in this box here, including severe depression, anxiety disorder, uncontrolled diabetes, severe obesity, people with excessive exercise, malnutrition, and all of these can cause elevated cortisol levels.

And once these have been ruled out, and sometimes you need to treat the underlying condition and then repeat the testing, once these have been ruled out, then would be the next step to move forward in the diagnostic evaluation of the patient with Cushing syndrome.

This is a slide was published in *The Lancet Diabetes & Endocrinology* in 2021 after the Pituitary Society workshop that had more than 50 clinical researchers and experts in the field that came around this workshop and published this paper.

Here's a table with information about the sensitivity and specificity of different diagnostic tests for Cushing syndrome. I should say that there is no test in the world that provides 100% sensitivity and specificity in Cushing syndrome. And if you see sometimes a number like that, that may be related to the specific population that was in studies, or maybe the sample size was not too large, and that's why you may see numbers as high as 100% sensitivity or specificity for a specific test.

Each of these tests—the 1-mg dex suppression test, the 24-hour urinary free cortisol, and the late-night salivary cortisol—there are some caveats for their use and interpretation. We all know about the CBG effect, that in the case of increased CBG, you will have a false-positive dex suppression test. The patient may be taking medication that may increase the dexamethasone clearance. And there are some patients, rarely, that we see that we don't have a good explanation and are likely fast metabolizers, so measuring the dexamethasone level helps with interpretation of the test.

We measure creatinine during the 24-hour urine collection for cortisol to ensure that the collection was adequate. The patients who have a high urine output, they can have falsely elevated urinary free cortisol, and we see that at least several times in the year, people who are taking more than 4 or 5 L of fluid per day. So the free cortisol gets filtered to the glomeruli and it gets reabsorbed and metabolized in the kidney. The amount of the urine that is filtered is about 20 times more than the amount that you see in the urine. So in a state of high water intake, you can have some changes in the dynamics of the reabsorption of the cortisol, leading to an increased cortisol level in the urine. So that needs to be kept in mind.

The proper collection of the saliva is very important. We tell the patient always to do it at bedtime. And despite that, the patient may get different messages from the lab staff, and it's very important to confirm with them that indeed the collections were done at the proper bedtime. Of course, this would not be also a good test for shift workers with an erratic sleep pattern.

There are some other tests that has been listed in this table that we may use in special circumstances. These include the 2-day low-dose dex suppression test for patients, especially when there is a suspicion about non-neoplastic hypercortisolism. We don't have CRH available now. A test that I used to do a lot, the 2-day low-dose follow-up CRH stimulation test, and I'm a big believer in this test, but unfortunately CRH is not available. And we really don't know whether vasopressin in addition to the 2-day low-dose dex suppression test does the same kind of—or provides the same diagnostic accuracy or not. That's something that needs to be studied.

It is important to realize that there are certain situations when a specific test would be better than the others. For example, when we are dealing with mild autonomous cortisol secretion, the 1-mg dex suppression test to stick out as the best diagnostic test. This has been shown in several studies looking at the association with comorbidities, the development of hypercortisolism after surgery, resolution of

the comorbidities after surgery, for example. So in this population, for example, the 24-hour urinary free cortisol is not a good test. About 80% of the patients would have a normal 24-hour urinary free cortisol. And the late-night salivary cortisol also has shown to have a poor sensitivity and specificity in this particular population. So sometimes the choice of the test also depends on what we are looking for.

As you may know, in the CATALYST study, when they looked at the patients with difficult-to-control type 2 diabetes and they screened them with a 1-mg dex suppression test, there was a significant improvement in hemoglobin A1c and some of the cardiovascular risk factors when the patients were treated with the glucocorticoid receptor blocker compared to placebo. So that would be another population of patients who may benefit from a 1-mg dex suppression test when they have difficult-to-control diabetes.

There is a relationship between the urinary free cortisol and the glomerular filtration rate. This was a study from Hong Kong and from a population of the patients in the nephrology clinic. It is not mentioned in the paper what kind of way the glomerular filtration rate, or eGFR, was measured, but definitely they did not have any suspicion for Cushing syndrome. So they found there was a correlation between the UFC and the creatinine clearance. And this especially becomes much more tighter, this relationship, when the patients have more severe CKD, and you can see that on the picture on the right side.

And here, for example, the normal range for this assay, which was RIA, was about 100 to 370s—in that range—mmol/day. And as you can see, all of these patients had their levels less than 60 mmol/day. So when the creatinine clearance is less than 20 mL/min, the UFC may be unreliable.

This also applies to the mass spect assays that we use commercially in this country. So even using mass spect, the creatinine clearance significantly decreased kidney function has an impact on the urinary free cortisol level.

Here is a little busier slide, a little more about the additional caveats about the different diagnostic tools that we have, and some of these we already mentioned about that. It is important to think about the absorption of the dexamethasone in some conditions. Patients who have had partial small intestine resection, chronic diarrhea, I have found this not to be a significant problem. Even people who have had a significant amount of their small bowel resected, they still have a good absorption seems to be.

Having a history of medications that can induce CYP3A4 enzyme and then cause increased metabolism of the dexamethasone is very important. Of course, some medications like estrogen, the presence of, of course, pregnancy, some chronic liver disease that can be associated with increased CBG—all of these can cause a false-positive test.

The commercially available urinary cortisol that we have are mass spect in most major commercial labs, and these all perform much better than compared to the immunoassays that we had in the past. However, still there are some reports of, for example, the carbamazepine and fenofibrate that can cause falsely elevated levels in some of these mass spect assays, so that's something to keep in mind.

We ask the patient not to brush or eat anything for about an hour before their salivary cortisol collection. We ask them to avoid any tobacco products for at least 4 hours. And if they're using any imported black licorice, we advise them to avoid it for about a week before the late-night salivary cortisol collection.

There are some reports that salivary cortisone may have better diagnostic accuracy compared to salivary cortisol, but it's not commercially available in the United States right now. We're hoping that we can have that available in the near future.

Now, once the patient has been diagnosed with hypercortisolism and the non-neoplastic causes have been ruled out, the next step would be to measure the ACTH level. There is an overlap between the ACTH level in patients with Cushing disease, as you can see on the left side, and patients with ectopic ACTH syndrome.

Now, usually the levels of ACTH more than 225 or 250 pg/mL are consistent with ectopic Cushing syndrome. The patients with adrenal tumors and ACTH-independent Cushing syndrome usually have a suppressed or low ACTH level. In most patients it is less than 15 pg/mL.

Now, in the picture on the right side, in this study, they have looked at the ACTH levels in patients with ACTH-independent Cushing syndrome. The black diamonds and circles are the RIA assays, and the white squares and circles are immunochemiluminescent assays. And as you can see, these sandwich assays, immunochemiluminescent assays that we use commercially in the United States, the majority had a level less than 15 pg/mL, and almost all had a level less than
20 pg/mL.

So in general, when I have a level less than 15 pg/mL for ACTH, I feel very comfortable that this is an ACTH-independent Cushing syndrome, and levels above 25 pg/mL usually indicate that the ACTH-dependent Cushing syndrome. And when I have levels between 15 to 25, I may repeat the fasting early morning ACTH at a different time, and usually I get the answer, and sometimes I may perform a

vasopressin stimulation test to kind of differentiate that.

These ACTH levels may not apply to patients with mild autonomous cortisol secretion, so keep in mind, while most patients have low levels, not every patient has that, and they can have a normal ACTH level.

This is a slide about ACTH-independent hypercortisolism. As we discussed, ACTH is usually undetectable or low in this population. We mentioned that most patients but not all patients with MACS, have a low side ACTH level, usually less than 15 pg/mL. And the DHEAS can also be measured and can be additional important diagnostic evaluation in these patients, and usually the level is less than 55 to 60 mcg/dL in patients with MACS.

Once the ACTH-independent Cushing syndrome has been established, the CT of the abdomen would be the next step. And in the patient with a unilateral adrenal mass, that points to a unilateral hypercortisolism in this population, when there is an isolated abnormality on one side. Patients with bilateral adrenal masses, the approach to them would be usually going after the larger adrenal tumors, or sometimes we use adrenal vein sampling to differentiate about where the excess cortisol is coming from, especially when there is no significant asymmetry between the adrenal masses. And I should say that adrenal vein sampling has not been very well established with it as a diagnostic criterion to determine the laterality of the excess cortisol secretion, so we need more data on that regard. And in rare cases, you may not find a significant abnormality, and this can be related to micronodular adrenal hyperplasia, which is usually a bilateral disease.

Now, further going down the diagnostic workup, so we have established a hypercortisolism, and we have measured the ACTH, and based on the ACTH level, we have two different kind of diagnostic algorithms. So one is ACTH-independent Cushing syndrome, and as we discussed, we want to get a CT scan and look at the adrenal glands. In the patient with ACTH-dependent Cushing syndrome, the next step would be to get a pituitary MRI.

If the pituitary MRI shows a discrete lesion and the clinical picture is suggestive of Cushing disease, usually that can establish the disease. And there are different criteria that has been used in the literature about what's the best kind of cut point for the size of the adenoma during the pituitary MRI. And I would say that, in my opinion, rather than a specific number, it's the appearance of the tumor. And when you see a nice, well-defined hypodensity on the pituitary MRI, even if it's 5 mm, to me that's more important than having an 8-9 mm lesion that is heterogeneous and not well defined. And so sometimes it's important that we are comfortable with our radiologists and neurosurgeons and look at these images and we have a well-defined abnormality. And sometimes you may get additional testing, like a vasopressin stimulation test, to further confirm that the source of the disease is pituitary.

In the absence of a well-defined lesion, there are different approaches, and that can include doing IPSS, and that require expertise in centers that do it regularly. In the absence of having IPSS in the institution or in a nearby institution or referral medical centers, a combination of the vasopressin stimulation test and, of course, pituitary MRI and the body CT, including the chest, abdomen, and in some cases neck imaging and a gallium DOTATATE scan, can help to differentiate the etiology of ACTH-dependent Cushing syndrome.

Cushing syndrome is a high-maintenance illness. It requires a team to take care of this. These slides show you some of the components of this team care.

The medical office and my medical office coordinator is very important for me and my patients to obtain prior authorization when it comes to medical treatment, providing them with the timely appointments, keep an eye on my schedule for cancellations, and opening slots.

My nursing staff is crucial with patient education, communication, finding about their adverse events, ensuring their well-being.

I get alerts from the pharmacy about drug interaction alerts. I mean, other physicians may put the patient on a treatment that can affect my medical treatment plan with a drug interaction, and I get alerted from pharmacies.

Some of the pharmaceutical companies, they have patient support services, and I think they do a good job communicating with the patient. They help out with start of medication for the patient so they can get on treatment as soon as possible while their insurance approval is pending. They can help with the insurance communications, give us some help in that regard. Monitoring the patients, some of them have a very good interaction with the patient, and we get sometimes news from them sooner than our nurses or staff tell us about the patient having an adverse event. For example, they can alert us that a patient's potassium has not been measured, for example, and needs to be evaluated. We get these alerts, and we appreciate it. I mean, that, as I mentioned, it's a teamwork. And timely prescription delivery is important for our patients, so there is no interruption in their care.

The medical team—you have the list of them here. These are some of the important ones, but not all of them. We work closely with other disciplines to take care of these patients.

And at the end of the day, now with the availability of the medical health records being online, the patients are able to reach out to us directly and keep that line of communication very, very well. So we get notified by the patients with their questions, with their adverse events, and we can respond to them ourselves or through our nursing staff and have the issue resolved and make sure that both us and the patient are on the same page and for the best outcome.

Here, I'm going to hand over to Dr. Pivonello, who is going to discuss treatment options for patients with Cushing syndrome and go over some cases with you.

Dr. Pivonello:
Thank you, Doctor. I will focus now on the advances in medical management of Cushing syndrome.

So we know that nowadays surgery represents the first-line treatment for the majority of patients with Cushing syndrome, but we know that it is not always curative and not always suitable, so medical therapy has acquired in the last year a major role.

Also, considering that we have different categories of drugs available, including pituitary-directed agents, adrenal-directed agents, glucocorticoid receptor antagonists. And according to the fact that we have so many drugs available, we can also tailor the treatment to the single patient, considering the patient's comorbidity, the mechanism of action, and the availability of the drug, and of course the clinical scenario.

So surgery, as demonstrated, to achieve inadequate control of Cushing syndrome, but especially of Cushing disease which is the most common form of Cushing syndrome, in around 65 to 90% of patients. But many patients can have also postsurgical recurrence, which is calculated to be 35% within 5 years and 69% within 10 years.

So medical therapy can be employed in different steps of the journey of patients with Cushing syndrome. For instance, when the disease, of course, persists, or the disease recurs after successful surgery, when surgery is not an option or is refused by the patients, when we have a severe condition which requires emergency treatment, or while we are waiting for, I mean, the surgery or the efficacy of radiotherapy.

So we can now start with the first category of drugs, which is the glucocorticoid receptor-directed agents. Among this group, the actually used drug is mifepristone. But in general, glucocorticoid receptor-directed agents work by blocking the binding of cortisol to the glucocorticoid receptor. And mifepristone is actually the currently used glucocorticoid receptor antagonist, but it is not so selective for the glucocorticoid receptor because it's also able to bind the progesterone receptor. And this may cause consequences like vaginal bleeding and endometrial hypertrophy.

The new investigational drug, which is selective for the glucocorticoid receptor, is, I mean, relacorilant, which is a modulator designed for the treatment of Cushing syndrome. It is highly selective for glucocorticoid receptors, so with no activity at the progesterone receptor and others, and this, of course, avoids unwanted off-target progesterone receptor effects like the endometrial hypertrophy and the vaginal bleeding.

Moreover, because of the lack of increase in ACTH, it does not induce hypokalemia, and it is also not associated with adrenal insufficiency and QT interval prolongation.

The majority of the data coming from the literature regarding mifepristone are derived from the SEISMIC study, which aimed at evaluating the efficacy and safety of the drug in endogenous Cushing syndrome after 24 weeks of treatment.

As you can see in the slides, mifepristone has demonstrated to be very effective in two comorbidities of Cushing syndrome, which is hypertension and also glucose impairment. Actually, in patients with Cushing syndrome associated with diabetes or impaired glucose tolerance and/or hypertension, the drug was able, during the study, to control around 60% of, I mean, glucose parameters in patients with Cushing, and in around 40% blood pressure in the same patients. So actually, it also was able to improve other clinical comorbidities of these patients, including the weight and the waist circumference and also the body fat, with a safety profile which is characterized by nausea, fatigue, headache, arthralgia, and vomiting, which are, I mean, associated with glucocorticoid withdrawal syndrome, hypokalemia in 34% of cases, and, as mentioned before, endometrial thickening in around 20% of patients.

So actually, mifepristone seems to be really effective in controlling the clinical pictures and comorbidities in patients with Cushing syndrome. And it was also demonstrated by another more recent study which is the second part of the CATALYST study, in which patients with inadequately controlled diabetes and hypercortisolism, mifepristone was able to control glycated hemoglobin in a good percentage of cases.

Indeed, in the study, patients were divided into two groups, one having mifepristone and the other one having placebo, and you can see that after 24 weeks there was a big difference between the two groups, in which, of course, placebo has almost no change, whereas a

significant decrease of glycated hemoglobin was demonstrated with the use of mifepristone in this group of patients. However, I mean, this mifepristone, as we know, is characterized by the non-selectivity of the binding of the glucocorticoid receptor.

But, I mean, we also know that another drug, relacorilant, is actually the drug demonstrated to be very selective for glucocorticoid receptor, as has been tested in a phase 3 study quite recently, which is called the GRACE trial. In this trial, which is a phase 3 study including an open-label phase followed by a 12-week double-blind placebo-controlled randomized withdrawal phase, it was demonstrated that this drug, I mean, was able, again, to control comorbidities of patients with Cushing syndrome.

In this case, you can see in the slides that during the open-label phase there was a clear decline of diastolic and systolic blood pressure in these patients, which actually confirmed the effect on hypertension of the glucocorticoid receptor blocker.

And during the withdrawal randomized phase, you can clearly demonstrate that, I mean, the group of patients maintaining the mifepristone treatment and taking the drug during the randomization phase had a stable control of blood pressure, whereas the patients switched to placebo had a loss of control of hypertension, so an increase in systolic and diastolic hypertension.

So relacorilant, I mean, has this advantage to be very selective for glucocorticoid receptors, so the safety profile reflects this action. You see indeed in this list that we cannot see the classical symptoms and signs of progesterone blocker, like endometrial hypertrophy, for instance, but we have extremity pain or back pain, which is more typical of this drug. And you see from the safety profile that no clear symptoms of adrenal insufficiency or glucocorticoid withdrawal syndrome were found in the safety profile, and also no clear QT interval prolongation was also found.

Let's go now to another group of drugs used in patients with Cushing syndrome, which is the adrenal-directed agents, or steroidogenesis inhibitors. I mean, these are a group of drugs which has been used a lot in the past. For instance, ketoconazole and metyrapone has been currently used for decades in the treatment of Cushing syndrome and Cushing disease.

These are working, I mean, blocking one or more enzymes which are necessary for cortisol synthesis, thereby reducing cortisol. So the most recent ones include levoketoconazole, which is able to inhibit several enzymes in steroidogenesis, and osilodrostat, which is more, I mean, a blocker of 11β-hydroxylase. And these, I mean, two drugs has been tested in recent important studies.

So let's start to look at the data on levoketoconazole, which represents the levoisomer of the racemic classical ketoconazole used in the past. We have two different studies which has demonstrated the efficacy and safety of the drug. The first one is the SONICS study, in which you can see that the drug was able to decrease rapidly the urinary free cortisol concentration in patients with Cushing syndrome. And then after 6 months, it was calculated that the control of urinary free cortisol was found in around 1/3 of patients. But if we look only at the group of patients which ended at the 6 months of treatment with available urinary free cortisol at the baseline and at the last observation, this percentage raise up to 62%. And in this study, you see that the safety profile include nausea, headache, and peripheral edema, which we are currently, I mean, found with the use also with ketoconazole. And an increase in transaminases, which seems to be a little bit lower than what we expected from ketoconazole, in this study, was around 12 to 15% of cases.

The data were confirmed by the LOGICS study, which was a phase 3 placebo-controlled randomized withdrawal study with an open-label titration maintenance followed by a double-blind randomized withdrawal and restoration. And the study

demonstrated that when the patients, I mean, switched to placebo, they lost the control of urinary free cortisol in 95.5%. And on the other hand, the study demonstrated again that the control of urinary free cortisol with levoketoconazole was around 50%, compared to only 5% in the patients, I mean, which was addressed through the arm of the placebo.

Osilodrostat represents another kind of drug, which is the classical blocker of 11β-hydroxylase, like metyrapone, but is more potent and also easier for administration because the half-life permits the use of the drug just twice a day, or only once a day.

The LINC 3 study was the main study demonstrating the efficacy of the drug in the great majority of cases, especially in controlling the urinary free cortisol, with the consequence of having hypocortisolism in 51% of patients and adverse events related to adrenal hormone precursors occurring in 42% of patients. This reflects, from one, the potency of the drug; from the other side also the mechanism of action which blocks cortisol production and induce an increase in the precursors and also in the androgens.

In the LINC 3 study, actually, the rates of normalization was around 66% at week 48, but also very high, as much as 81% after 72 weeks, with the consequence of improvement in cardiovascular- and metabolic-related parameters, physical manifestation, quality of life, and actually, so the drug is quite manageable, and also the adverse events were quite well manageable, and still represent probably one of the most potent drugs that we have available now in controlling urinary free cortisol in patients with Cushing syndrome.

So we also tested osilodrostat efficacy and safety in the LINC 6 study, which is a real-world study demonstrated now, not in a phase 3 study but in real-world evidence, that control of urinary cortisol was found in a great percentage of patients. You see 74% after 3 months

and 63% after 6 months. And also, this control was associated with concomitant control of late-night salivary cortisol in a good percentage of cases. So, I mean, the safety in the LINC 6 study was similar to the LINC 3 study.

So the last category of drug that can be used, at least in Cushing's disease because they are directed on the pituitary tumor, that is the pituitary-directed agents, which are the aim to block the ACTH. Therefore, I mean, they can block also the cortisol production in patients with Cushing's disease. The classical nowadays the used drug is pasireotide, which is a somatostatin analog which binds to the somatostatin receptor in order to block ACTH from corticotrophs. But also cabergoline, which is a dopamine receptor agonist, has been used in an off-label manner in some, I mean, experience of some groups treating patients with Cushing syndrome.

We can say that pasireotide is generally used in the long-acting release formulation, and the phase 3 study dedicated to this drug demonstrated that after 7 months of treatment, the responders are around 40%, and actually they can reach 52% of cases in patients with mild disease. So this kind of drug it is more, I mean, used and can be more effective in patients with mild or moderate disease.

And the data coming from the phase 3 study also demonstrated that together with the control of urinary free cortisol, the drug is able to control also the mean late-night salivary cortisol, so in a way trying to restore the circadian rhythm of cortisol in around 30% of patients which is, I mean, a good subgroup of patients in which the drug can also act on the late-night salivary cortisol.

But the safety profile of this drug includes the development of hyperglycemia, which is quite common. Up to 73% of patients can have hyperglycemia during treatment, together, of course, with the classical adverse events associated with somatostatin analogs. And of course, we can have some QT prolongation, which has been also associated with the other drugs used for Cushing syndrome. Six percent of patients, unfortunately, discontinued due to this hyperglycemia, which actually has to be taken into account when we use this drug in patients with Cushing's disease and has to be monitored, I mean, during the treatment.

There are also some experiences with the combination of pasireotide LAR together with cabergoline, demonstrating that the combination of the two, in case pasireotide alone is not effective, can double the percentage of patients which actually can control the urinary free cortisol.

So we can now, in this summary slides, make a comparison of the different classes of drug, emphasizing that when we use the pituitary-directed agents, we can have hyperglycemia, which is quite common, especially during the first months. And of course, we have to take in mind that this kind of drug can be used only in case of Cushing's disease. When we use an adrenal-directed agent, so the classical steroidogenesis inhibitors, we have to know that the overtreating can cause adrenal insufficiency or hypotension or hypoglycemia. We have to monitor carefully QT prolongation and also the consequences of the accumulation of adrenal hormone precursors.

On the other hand, when we use glucocorticoid receptor blockers or modulators, we need to titrate close the dose slowly in order to prevent glucocorticoid withdrawal syndrome, and we can have sometimes an increase in blood pressure, which has to be taken into account, and considering also the use of spironolactone even for hypokalemia.

So these are, I mean, the different things to take in mind when we are using the different drugs for our patients with Cushing disease. And one of these is the QT interval, which is very important and crucial because almost all the categories of drug has been found to be associated with some QT prolongation, or at least the potential for QT prolongation. That's why we have to take care when we use these drugs to consider when there are other drugs that the patient is taking which also influence the QT.

Dr. East:
Thank you, Dr. Pivonello. Now we're going to discuss a case based around a patient with hypercortisolism.

Our case is a 52-year-old woman who has a 10-year history of type 2 diabetes and hypertension for the past 8 years, and she presents for her yearly annual exam. She does note that over the past year and a half, her blood pressure has remained elevated despite treatment with four blood pressure medications that included a diuretic. It's defined, as we were speaking about earlier, as resistant hypertension.

So she's had progressive a weight gain, specifically central obesity. She's had worsening fatigue, the proximal muscle weakness, easy bruising, new-onset facial rounding, poor glycemic control despite escalation of diabetes therapy, and importantly, she has not had any recent exogenous steroid use and denies alcohol excess.

So right now, with all we've talked about today, hopefully you've got all these little warning bells going off in your head that she is showing signs and symptoms of cortisol excess.

Her A1c has historically run around 7.5%, but recently it's been worsening. She has this resistant hypertension, dyslipidemia, and osteopenia on previous bone density testing. Her medications include metformin 1,000 twice a day, basal insulin, as well as four different antihypertensive medications, two of those are diuretics, and medication for pharmacological therapy of hyperlipidemia.

Despite four-drug therapy for her blood pressure, her blood pressure is elevated at 168/98, and we did repeat this sitting. Pulse is 84. Her BMI is 33, and she does have that proximal muscle weakness.

So, you know, I think we were all taught, you know, if a patient has to reach up and get out of their chair using their arms, they don't have that hip flexor strength, they're not able to get out of a chair into a standing position, that also should be making a lot of those bells ring in your head that we need to screen this patient for hypercortisolism, whether it be endogenous or even exogenous with iatrogenic corticosteroid use.

So her lab results: she was at 7.5% for her A1c, and now she's at 9.2%. Her fasting glucose is elevated despite basal insulin therapy at 190. Her potassium is low at 3.2 despite treatment with spironolactone. Despite lipid-lowering therapy, she continues to have elevated triglycerides, and her creatinine was normal.

So this astute clinician did have some bells going off and said, "Hey, we need to look for an underlying cause of why this lady had unexplained worsening of her diabetes and of her blood pressure over the past 18 months." And so a dexamethasone suppression test was done, and it was significantly positive at 12.4, and her ACTH was suppressed.

So the decision was made to go ahead and see if we could find a source of her hypercortisolism. Because of the suppressed ACTH, she was considered to have ACTH-independent hypercortisolism. CT of the abdomen was done, and lo and behold, we did see bilateral adrenal macronodular hyperplasia. She was diagnosed with endogenous Cushing syndrome due to an ACTH-independent, aka adrenal, source.

In order, you know, to get her diabetes and her blood pressure under better control, it is important to get to the source and to address the underlying etiology, you know, here in this case, the macronodular hyperplasia that is autonomously secreting cortisol.

So she was not a surgical candidate because the macronodular hyperplasia was bilateral, and there was concern over permanent adrenal insufficiency with a bilateral adrenalectomy. And so medical management was chosen and certainly should be discussed with this patient. Because she had an elevated hemoglobin A1c and severely uncontrolled type 2 diabetes, in this particular case, mifepristone is considered to be the best option.

So I will turn it back over to you, Dr. Pivonello.

Dr. Pivonello:
To the end of this presentation, I just would like to present one case of a 52-year-old woman which was referred for the evaluation of resistant hypertension. And so the history of the patient demonstrated the progressive, I mean, occurrence of symptoms and signs which are typical of patients with Cushing syndrome, together with impaired glucose tolerance. And also the features of Cushing syndrome, like mild facial plethora, scattered ecchymoses, and also dorsal cervical fat pad, were found in the patient. And biochemical evaluation demonstrated a mild elevation of urinary free cortisol, but the cortisol was not suppressed by the 1 mg dexamethasone test, and plasma ACTH was completely suppressed.

So the diagnosis in this case was an ACTH-independent Cushing syndrome. And actually this was confirmed by an abdominal computed tomography, which demonstrated the presence of an enlargement of the right adrenal gland with multiple nodules ranging from 1 to 2.5 cm, whereas the left adrenal gland appeared to be normal in size. So the diagnosis was unilateral cortisol-producing macronodular adrenal hyperplasia.

The initial treatment, as usual, was laparoscopic right adrenalectomy. So the pathology confirmed that we are facing with an adrenal gland with multiple cortisol-producing nodules, no carcinoma, and after surgery the patient had adrenal insufficiency requiring hydrocortisone replacement.

And after 1 year, the patient had control of the blood pressure and also in the glucose parameters and the other parameters; that's why the hydrocortisone was continued for a long period of time.

But after 4 years, you see that the patient returned with again the development of symptoms and signs which resembled the recurrence of Cushing syndrome. So again, fatigue, hypertension, diabetes, and also the increase in weight. And unfortunately, the biochemical evaluation confirmed again the increase in urinary free cortisol, which was mild, and the ACTH was again suppressed. The imaging demonstrated that the previously normal left adrenal gland started to be enlarged, and the size was almost 4 cm, and there was also development of one macronodule of 1.5 cm. So actually there was a progression of the disease to a bilateral macronodular adrenal hyperplasia, which was initially asymmetric.

This is the reason why we have different options. We can propose to the patient a contralateral adrenalectomy, or we can propose a medical therapy, or just a watchful waiting. But because the hypocortisolism was moderate, and the patient wished to avoid a lifelong

steroid dependence, and there were not severe features in our patient, there was medical therapy chosen for them. And the patient started to be treated with osilodrostat.

The initiation strategy was more conservative, so we started with 1 mg twice daily, and then we titrated every 3 to 4 weeks the dose of the drug. And the monitoring of the patient was every 2 to 4 weeks, controlling, of course, all the symptoms, signs, and also the other parameters for looking at the efficacy and also the safety of the drug.

After 6 weeks, the urinary free cortisol decreased, actually, but not normalized, and there was an improvement in blood pressure and glucose parameters.

And after 4 months, finally the urinary free cortisol normalized, with also stabilization of weight, improvement of glycated hemoglobin, and without hypokalemia or adrenal insufficiency. That's why the dose was maintained at 3 mg twice daily.

The follow-up at 2 years demonstrated that the patient had a sustained biochemical control with a 5-kg weight reduction, with no need for contralateral adrenalectomy and a stable situation with good tolerability.

So demonstrated that in this case the use of first surgery and then of the medical treatment to complete, I mean, the control of a recurrence of disease was a good strategy.

And with this case, I mean, I will end my presentation. Thank you.

Host:
Thank you again for joining us for this educational activity. To claim credit for this activity, be sure to complete the post-test and the evaluation. For additional educational activities, please visit www.cornerstonemeded.com. Thank you for your participation.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Cornerstone Medical Education and the American Academy of CME. To receive your free CME credit or to download this activity, go to ReachMD.com/CME. Thank you for listening.