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Podcast Issue

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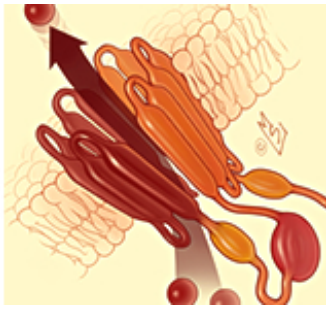

VOLUME 2 — ISSUE 1: TRANSCRIPT

Featured Cases: Cystic Fibrosis-Related Diabetes

At the conclusion of this activity, participants will demonstrate the ability to:

- Discuss how diagnostic criteria were chosen for cystic fibrosis- related diabetes
- Describe the appropriate screening tests for diabetes in CF
- Explain the evidence-basis for insulin as accepted therapy for CFRD.

This audio activity has been developed for clinicians caring for patients with issues related to cystic fibrosis. You can also read the **companion newsletter**. In this edition Dr. Moran also reviews the results of The Cystic Fibrosis Foundation (CFF) consensus conference to update existing guidelines, convened in September 2009 at the CFF headquarters in Bethesda, Maryland. It was co-sponsored by the CFF, the American Diabetes Association (ADA) and the Lawson Wilkins Pediatric Endocrine Society (LWPES).

Unlabeled/Unapproved Uses: The author has indicated that there will be no reference to unlabeled/ unapproved uses of drugs or products in the presentation.

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Guest Faculty Disclosures

Dr. Moran discloses that she has no financial relationship with commercial supporters.

CME/CE INFORMATION ⇩ **PROGRAM BEGINS BELOW**

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LAUNCH DATE

This program launched on January 12, 2010, and is published monthly; activities expire two years from the date of broadcast, ending in January 11, 2012.

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MR. BOB BUSKER: Welcome to this eCysticFibrosis Review podcast. eCysticFibrosis Review is presented by The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Genentech, Eurand Pharmaceuticals, Vertex Pharmaceuticals and Axcan Pharma. Today's program is a follow-up to the November, 2009, eCysticFibrosis Review topic, "Cystic Fibrosis-Related Diabetes," or CFRD. The accreditation and credit designation statements can be found at the end of this podcast. For additional information about accreditation, Hopkins' policies, expiration dates, and to take the post test to receive credit online, please go to our website newsletter archive, www.ecysticfibrosisreview.org, and click in the December, 2009, podcast link.

At the conclusion of this audio activity, participants should be able to discuss how diagnostic criteria were chosen for cystic fibrosis related diabetes, describe the appropriate screening test for diabetes and CF, and explain the evidence basis for insulin as an accepted therapy for CFRD.

I'm **BOB BUSKER,** managing editor of eCysticFibrosis Review.

On the line we have with us our November issue's author. Dr. Toni Moran is a Professor of Pediatrics and the Director of Pediatric Endocrinology at the medical school at the University of Minnesota.

She has disclosed that she has no relationships with commercial supporters and that her presentation today will not include discussion of off-label uses.

Dr. Moran, welcome to this eCysticFibrosis Review podcast.

DR. TONI MORAN: Thank you, I'm happy to be here.

MR. BUSKER: Dr. Moran, you co-chaired a recent conference on cystic fibrosis related diabetes. Tell us a little bit about that, if you would?

DR. MORAN: The Cystic Fibrosis Foundation has actually held three conferences on cystic fibrosis related diabetes, and I've been privileged enough to be part of all three of them. The first one was back in 1990 when we really didn't know a lot about it, other than that we were just beginning to recognize it was a serious problem.

The second one was in 1998 when we had some new data and could start to make some recommendations. A lot has happened since then, and we have learned a lot since then. But you know that was more than ten years ago, and so in September of 2009, the Cystic Fibrosis Foundation held a third CFRD consensus conference, and what was exciting about this one was that it was co-sponsored by the two major pediatric and adult diabetes associations: the American Diabetes Association and the Lawson Wilkins Pediatric Endocrine Society. So we have a whole new set of recommendations, we had a group from Johns Hopkins that did an evidence review for us, so that they could be evidence based guidelines, and we really carefully reviewed the literature. Dr. Bonnie Slovis and I were the co-chairs, and we had a group of experts in the field and have come out with new recommendations.

MR. BUSKER: To put those recommendations in context, I'm going to ask you to start us out with some deep background, cystic fibrosis related diabetes, CFRD, how does it differ from other types of diabetes?

DR. MORAN: CF-related diabetes is unique. It has features of the other two forms of diabetes. Type 1 and type 2 diabetes are the forms of diabetes that affect the general population. Type 1 diabetes occurs primarily in children and is an autoimmune disease. The immune system attacks and destroys the islets. So people with type 1 diabetes eventually can't make any insulin and will die without insulin therapy.

Type 2 diabetes is usually found in adults, although we are certainly seeing adolescents now with type 2 diabetes. To have type 2 diabetes you need to have two defects. You need to be resistant to insulin, and the most common reason to be resistant to insulin is obesity. But not everybody who is insulin resistant gets type 2 diabetes, you also have to have beta cells that are able to make a usual amount of insulin but not extra insulin.

So CF diabetes occurs in patients who have had half of their pancreas destroyed by fibrosis. These are insulin insufficient patients. Insulin is not completely absent, but they don't have enough insulin to meet

their needs. They have very mild insulin resistance most of the time, but any time they become severely ill, which happens quite often in CF, they become very insulin resistant. So they are insulin insufficient, but not insulin absent, and they have waxing and waning insulin resistance, which makes them very unique.

MR. BUSKER: And again, still as background, the diagnostic criteria for diabetes?

DR. MORAN: The diagnostic criteria are criteria that have been developed by the American Diabetes Association include a fasting blood sugar greater than 126, blood sugar during an oral glucose tolerance test that is greater than 200 at the end of the test, and there is now a third new criteria that is coming out in January 2010: hemoglobin-A1c greater than 6.5. There has been talk for years about using hemoglobin-A1c as a diagnostic criteria for diabetes, but there were problems with having a uniform assay. That has been taken care of worldwide now, and so probably for the general population hemoglobin-A1c is going to become the screening test of choice for diabetes. But those three can all diagnose diabetes.

MR. BUSKER: Since CF related diabetes is so different from type 1 and type 2 diabetes, do the American Diabetes Association diagnostic criteria really apply to CFRD?

DR. MORAN: Well yes and no. The ADA criteria are based on risk of microvascular complications, and CF patients get microvascular complications at probably the same blood glucose levels. So certainly, if someone has a fasting blood sugar of 126 or a 2-hour OGTT glucose of 200, those criteria apply. The hemoglobin-A1c criteria are a little bit more problematic. If someone has a hemoglobin-A1c of 6.5 or above, clearly they have CF-related diabetes. The problem is if the hemoglobin-A1c is less than that.

So many CF patients have spuriously low hemoglobin-A1c levels. The problem there is that if you get a high level, you know it's diabetes, but if you get a low level you can't use that to exclude a diagnosis of diabetes. This is the first issue about the ADA criteria: they do apply to CF, but the hemoglobin-A1c level lower than 6.5 does not exclude diabetes.

The second question though, which is a really interesting question that the committee grappled with for a while, are these criteria strict enough for patients with CF? Because even though we do worry about microvascular complications and don't want our patients to get them, our real concern in CF is that hyperglycemia affects CF lung disease and can affect morbidity and mortality in these patients. And there is some data that forms of glucose tolerance that are less severe than diabetes, like impaired glucose tolerance, may have a very negative effect on CF lung disease.

So the real question is, should we develop stricter criteria for patients with CF based on their risk of worsening lung disease and should we be diagnosing and treating them earlier? The conclusion the committee came to was that even though we all really thought there probably was something there, there just are not enough data yet to assign specific glucose thresholds. We really need more research and until those research questions are answered, the committee elected to continue to use the ADA criteria.

MR. BUSKER: The date of onset of diabetes, why is that so important in CFRD?

DR. MORAN: The date of onset is important for any form of diabetes. We know that duration of diabetes in general is related to complications. It's related to risk of microvascular complications, like eye, and kidney and nerve disease. In the general population, it's related to risk of macrovascular complications, heart attack and stroke. Actually those macrovascular complications do not seem to occur in CF, but we know in CF that not only does microvascular function decline, but pulmonary function decline and mortality also have a relation to the duration of diabetes.

In particular for research studies, but also just to have a sense of patient's risks, it is really important to have a date of onset of diabetes. You wouldn't think that would be so difficult because it is not difficult in other forms of diabetes, but it is difficult in CF.

And the problem is that there are two things going on in CF. One is that slowly, over time, these patients are losing their ability to make insulin. But acutely, from day to day, week to week, insulin resistance can wax and wane. They get sick, they're very insulin resistant, then they're not sick anymore and their insulin sensitivity returns. And so blood glucose levels can go up and down.

A patient might be hyperglycemic this week and might not be hyperglycemic next week, so do you say

the diabetes started this week or did it go away? Do you wait until the patient is continuously hyperglycemic to diagnosis diabetes? This was really a tricky question to answer.

What we know is that some patients with CF are first recognized to have diabetes when they have an abnormal oral glucose tolerance test when they are clinically stable. But this year that test might show diabetes, with a fasting blood sugar two-hour level of let's say 210, and the next year maybe their two-hour level is 199, so they just miss the threshold. Are those two numbers really different? There are other patients who get diagnosed during physical stress like hospitalization, when they're sick and they're hospitalized, their blood sugars are really high and they need insulin, but about a month later they don't need insulin. So do they have diabetes?

What the committee decided was that once you are diagnosed with diabetes, you always have diabetes. This was based on the longitudinal data that we have in CF, most of which has come out of the University of Minnesota. Here at the University of Minnesota, the first time a patient has an abnormal diabetic oral glucose tolerance test they are diagnosed with diabetes. The first time they have prolonged hyperglycemia during a hospitalization, they are diagnosed with diabetes, even if their blood sugar levels return to normal afterwards. Based on that diagnosis, we have been able to say there is a relationship to risk of microvascular disease and we can predict the rate of lung function decline. And there is a relationship to mortality. So that diagnosis has important prognostic implications.

This is in some ways similar to type 2 diabetes. If you have a patient with type 2 diabetes who's obese, and then they lose weight and their blood sugars get normal, do you say their diabetes is cured; no, their beta cell defects are still there, so you don't say the diabetes is cured, you just say it's controlled.

The CS patient who comes two or three times a year and is hypoglycemic and needs insulin has diabetes, even if in between those hospitalizations their blood sugar is normalized. Because every time they get sick, every time they come in, that hyperglycemia is going to occur.

So the bottom line is that the committee decided, based on clinically important outcomes, based on the fact that we know that the hyperglycemia recurs again and again and again, once a patient meets diagnostic criteria, they have diabetes, and diabetes doesn't go away but it may be controlled without treatment during periods of stable health.

MR. BUSKER: In 1998, the consensus conference recommended that CFRD patients be identified as either having or not having fasting hyperglycemia. Do patients still need to be identified that way?

DR. MORAN: Well, the reason that that was recommended in the first place was that CFRD without fasting hyperglycemia is really a milder form of diabetes. It is all part of a spectrum, and those patients without fasting hyperglycemia have less severe diabetes.

So the question was do they need to be treated the same, and back in 1998 we really didn't know the answer to that. So it was recommended that until we could determine that, we should identify them separately. It was actually identified at that conference in 1998 as the most important future research question, to figure out whether these patients should be treated with diabetes therapy or not.

That led to a large, multicenter, multinational study funded by both the CF foundation and the National Institutes of Health. There were 14 centers in the US, and Canada, and Great Britain, and it took place over a number of years. But we specifically took patients who had CFRD without fasting hyperglycemia and treated them in one of three ways. We treated them with either insulin before meals, repaglinide before meals, or placebo before meals. Repaglinide is an oral agent, it's a pill that stimulates endogenous insulin secretion.

Our hypothesis was that if we increased insulin in these patients we would prevent clinical decline. Specifically, what we were looking at was weight and body mass index, so we tried to increase insulin either by giving insulin or by trying to stimulate endogenous insulin.

Patients were treated for a year, and what we looked at was the change in BMI the year before therapy versus the year of therapy. What we found in these patients who had diabetes without fasting hyperglycemia was that all of them had a slight but significant drop in BMI the year before therapy. So

we're averaging about a couple of pounds and you can imagine if patients are losing a couple of pounds a years chronically, that that would certainly be significant.

During the year of therapy, insulin reversed that. Not only did they not lose two or three pounds, but they gained two or three pounds. So insulin therapy clearly benefited those patients. Placebo did nothing. The repaglinide patients actually did have a bump in weight initially, but then they weren't able to sustain it, so at the end of the study year they were losing weight just as fast as before. We believe that is because they have so few beta cells, so you can stimulate those beta cells but you can only push them so hard, and then they just can't do it anymore.

The results of the study clearly indicated that insulin therapy in these patients without fasting hyperglycemia reversed chronic weight loss. Because of that, the recommendation is now that they be treated the same as patients with fasting hyperglycemia. From a strictly clinical standpoint, there is no reason to separate the two kinds of diabetes.

There may still be research reasons, in particular trying to figure out if there are different insulin regimens that might work better or different ways of treating them with insulin, however from a clinical standpoint, it is not necessary to differentiate the two.

MR. BUSKER: And we will return in just a moment with Dr. Toni Moran from the Division of Pediatric Endocrinology at the University of Minnesota.

MS. MEGAN RAMSEY: Hello, I'm Megan Ramsey, nurse practitioner and clinical coordinator for adults at the Johns Hopkins Cystic Fibrosis Program at the Johns Hopkins University School of Medicine. I am one of the program directors of eCysticFibrosis Review. These podcast programs will be provided on a regular basis to enable you to receive additional current, concise peer reviewed information through podcasting, a medium that is gaining wide acceptance throughout the medical community. In fact, today there are over 5,000 medical podcasts.

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MR. BUSKER: Welcome back to our December, 2009, eCysticFibrosis Review Podcast. I'm Bob Busker, Managing Editor of eCysticFibrosis Review. Our guest is Dr. Toni Moran, Director of Pediatric Endocrinology at the Medical School at the University of Minnesota, and our topic is cystic fibrosis related diabetes.

Dr. Moran, we've been talking about some of the recommendations that came out of the recent CFRD consensus conference, I would like to ask you now about screening. Based on those recommendations, what should be the screening test of choice of CFRD?

DR. MORAN: The test of choice for CF related diabetes is the oral glucose tolerance test. This is based in large part on the poor performance of other tests. You know, I talked earlier about hemoglobin-A1c. In actual practice worldwide, hemoglobin-A1c is going to become the screening test of choice for both type 1 and type 2 diabetes because it's so easy to do, it's just a one-time test and the patient doesn't have to be fasting. In CF patients, if it's 6.5 or above, that is sufficient to diagnose diabetes. The problem is a large, large number of CF patients with diabetes have hemoglobin-A1c levels less than 6.5, so hemoglobin-A1c is just not sufficiently sensitive to be the screening test of choice for CFRD.

There are other tests that the committee looked at. Fasting glucose for example, has until recently been the screening test of choice for type 2 diabetes, but

the problem is that it doesn't pick up the patients who have diabetes without fasting hyperglycemia. We know now that those patients need to be treated and they can only be picked up by OGTT.

There are tests like fructosamine that may be more sensitive in CF because of their rapid red cell turnover, but there are just no data comparing outcomes to fructosamine levels in CF. No one would know what to do with it.

Random blood glucose levels and urine glucose, have all been shown to have low sensitivity in this population. Continuous glucose monitoring where you wear a sensor at home is something that many people, especially Europeans, are excited about. What we know is that if you have a patient with normal glucose tolerance and you send them home and measure their blood sugars at home, they have high blood sugars at home. Once you get them on their usual diet they have little spikes in blood sugar during the day and you can pick that up with CGM, or continuous glucose monitoring.

But we have no idea what it means. Even in type 1 and type 2 diabetes it is not recommended as a screening tool because there just are no prospective longitudinal outcome data telling us it's significant.

So we considered all of those things and none of them were sufficient, and that got us right back to the oral glucose tolerance test.

MR. BUSKER: The OGTT, the oral glucose tolerance test, doesn't that have a lot of variability?

DR. MORAN: Yeah, you're right, it's not an ideal test, no one would tell you it's an ideal test. So the test, itself, is variable. I don't have diabetes, and if I took the test on three different days, there would probably be some variation in my results. The test itself is variable, and then CF patients are variable. Their waxing and waning inflammatory and infectious status also influence the results.

It is not a perfect test, but we really don't have anything better. What we do have with the OGTT is longitudinal outcome data. The OGTT correlates with important outcomes like the rate of lung function decline over the next four years, the risk of microvascular complication, and risk of early death. In the CFRDT study it identified patients who responded positively to diabetes therapy.

So, yeah, it is not a great test, but we know that CF patients who have ever had a diabetic pattern on the OGTT have greater risk for clinical deterioration than those who have never had a diabetic OGTT.

While it is not perfect, it does have prognostic significance and at least at the moment it's the best test we have.

MR. BUSKER: At what age should OGTT screening begin and how often should it be performed?

DR. MORAN: There was some difference of opinion in the consensus conference about this, and, you know of course, a consensus conference involves what everybody can live with.

What we know is that the risk of diabetes begins to sharply rise at the age of about 10 years. It is very rare to have diabetes in CF patients younger than 10, but about a quarter of CF patients, 20 to 25 percent, of CF patients between the ages of 10 and 20, have diabetes.

The committee elected that 10 years is recommended as the minimum starting age for OGTT screening. At the University of Minnesota, we start earlier, we start at 6 and there are data that individuals who don't have diabetes but have abnormal glucose tolerance between the ages of 6 and 9 are at very high risk for early development of diabetes, diabetes within 3 to 5 years after the oral glucose tolerance test.

So I'm going to continue to start at age 6 and the other centers will have to choose how early they want to start, but certainly by age 10. And then the test should be done annually. The reason it should be done annually is that CF patients can start to have clinical deterioration 6 to 12 months before they get diabetes and you don't want to miss that. Prolonging it might put undue risk on the patient for clinical deterioration.

MR. BUSKER: The treatment goals for CFRD, define those for us if you would, please?

DR. MORAN: The treatment goals are the same for other forms of diabetes. We know that if your hemoglobin-A1c is 7 or above and you have CF,

you are at risk for eye and kidney complications similar to type 1 and type 2 diabetes. The goal is to maintain the hemoglobin-A1c level less than 7, and to maintain glucose goals within the same ranges that the ADA recommends. Those differ by age and they are slightly more lenient in younger patients than older patients.

MR. BUSKER: And achieving those treatment goals, what is the best evidence based therapy to do that in patients with CFRD?

DR. MORAN: The only therapy that there is evidence for is insulin. There is good evidence that insulin therapy reverses chronic weight loss, that's from the CFRDT trial, and then there are also good longitudinal data that mortality is significantly reduced when there is aggressive screening and aggressive treatment with insulin.

We know insulin therapy improves weight, improves protein catabolism, improves pulmonary function and improves survival. So in patients with diabetes there is really not question that insulin is the therapy.

There is some question yet in patients with lesser forms of abnormal glucose tolerance, like impaired glucose tolerance. Should those patients get insulin therapy or maybe some other diabetes therapy? There just really is not enough information right now to determine that, and that was actually what was identified at this consensus conference as the most important research question moving forward.

MR. BUSKER: In patients who become acutely ill, if hyperglycemia develops, how should that be handled?

DR. MORAN: We know that when patients are acutely ill they are very insulin resistant. For example, if you have somebody who already has diabetes and is on insulin, their insulin at least doubles and sometimes it triples, sometimes it quadruples. They are tremendously insulin resistant and need a lot of insulin while they're sick. And then, even though the illness tends to appear to be resolved in a couple of weeks, it usually takes a month or so for the insulin resistance to return towards normal.

Now the question is in patients who are not on insulin who come into the hospital and become hypoglycemic. There are not a lot of CF specific data on intensive insulin therapy in the acute illness setting, and we know from other populations that prolonged hyperglycemia might delay clinical recovery, might have a negative impact on nutrition and on infectious status, so the goal is really to have near normalization of blood glucose.

There are some patients who come in and you start therapy and right away their hyperglycemia gets better. So we tend to wait about 48 hours and then if patients are still hyperglycemic, they are diagnosed with diabetes and started on insulin. There's a number of different ways the insulin can be given, but the goal is just to achieve the most normal glucose levels you can achieve safely without causing hypoglycemia.

And you keep the patient on insulin as long as they are hyperglycemic. Some of them will need it continuously even after they get better. Some of them will be able to come off of insulin, at least until the next illness.

MR. BUSKER: One final question, Dr. Moran, look at the future for us, if you would, what do you see as the top research considerations in CFRD?

DR. MORAN: This is actually perhaps the most fun part about the conference; to really put our heads together and decide what were the most burning issues. We came up with five. The first one we already mentioned, and is the one that everyone really agreed was the most critical right now: what do we do with patients who don't quite meet diabetes diagnostic criteria but have abnormal glucose tolerance? Would they benefit from some form of medical therapy and, if so, what should that be?

The second question had to do with what the obstacles are to oral glucose tolerance screening. We know that a number of centers have a difficult time getting OGTT screening up and running, so how can we overcome those questions and problems at those centers?

The third question that was identified was why does the additional diagnosis of diabetes negatively impact pulmonary function and survival and what is that relation? The forth question was should the target goals for glucose and/or hemoglobin-A1c be different in CFRD compared to ADA target goals; should they be stricter? And the fifth question was a psychosocial question: how do we assess and improve patient

acceptance of the diagnosis of diabetes to improve patient self management and psychosocial well-being.

Those are the five top areas that were identified, and actually one of the participants in the conference was from the NIH. The NIH is looking towards its future goals for CF diabetes research and will certainly take these into account.

MR. BUSKER: Dr. Toni Moran from the Division of Pediatric Endocrinology at the University of Minnesota, thank you for participating in this eCysticFibrosis Review podcast.

DR. MORAN: Well thank you, it was my pleasure.

MR. BUSKER: This podcast is presented in conjunction with eCysticFibrosis Review, a peer reviewed CME and CNE accredited literature review e-mailed monthly to clinicians treating patients with cystic fibrosis. This activity has been planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education, with a joint sponsorship of the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing.

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