

Division of Diabetes Treatment and Prevention

Advancements in Diabetes Seminar Insulin Management

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Chris Lamer:

Thank you, Jan. My name is Chris Lamer and I've been with the Indian Health Service for a number of years. I'm not sure how many they are right now but I've had the pleasure of working at the Cherokee Indian Hospital where I got my start with IHS. And currently, I'm working with the Office of Information Technology and I have a couple of different applications that I oversee and I have been working with the Division of Diabetes Treatment and Prevention as a Pharmacy Consultant, which brings me to my disclaimer in talking about insulin therapy that I am not seeing patients and managing insulin. My experience is based on some of the limited dose adjustments and things that I did back in Cherokee. It focuses mainly on my limited knowledge that I have of being a pharmacist on insulin and the differences about insulin. So that's where I'll focus in this presentation.

The objectives, we've already talked about those. Just to start off, what is insulin? Insulin is a hormone that is released by beta-cells in the pancreas in response to elevated level of glucose. It's a protein. It prevents excessive glucose production and it helps the body utilize glucose as energy and store it as glycogen.

Glucose is continuously produced by the body through gluconeogenesis and glycogenolysis through various organs, especially the liver and muscles. Gluconeogenesis is the creation of glucose from amino acids and free fatty acids. Glycogenolysis is the breakdown of glycogen into glucose. Glucose levels will increase after we eat meals. Many factors can affect the blood glucose level such as exercise, insulin resistance, stress, emotion, illness, or even temperature.

When we talk about insulin, insulin is secreted as a basal release, first-phase and second-phase insulin release. Together, this helps to reduce the response to elevated blood glucose levels.

Basal insulin release refers to the constant release of insulin from the pancreas in response to the constant glucose levels in the blood. Basal insulin is relatively peakless and it makes up about 50% of the amount of insulin that the body makes each day.

After a meal our intestines and enzymes break down carbohydrates into simple sugars, which are rapidly absorbed into the bloodstream. High levels of glucose passively diffuse into the beta cells of the pancreas and this triggers the release of insulin, C-peptides and amylase. This is called first-phase insulin release. The main purpose of this short rapid spike in insulin is to tell the liver and the muscles to stop making glucose.

Elevated blood glucose levels continue to stimulate the pancreas to release insulin. This is then called second-phase release and it lasts for a much longer period of time. The insulin helps to return the glucose levels to normal by enabling absorption of the cells. Insulin also helps to convert excess glucose into glycogen, amino acids into proteins, and free fatty acids into adipose tissue.



As insulin resistance progresses over time, the pancreas' ability to secrete enough insulin diminishes and may be unable to release any after 10 or more years. This is very patient variable. Some people will go much longer with a functional pancreas. Other people may have problems very early on. Loss of first-phase insulin release results in postprandial hyperglycemia and that's when we start to see blood sugars rise.

Insulin secretion continues to decline over time. Estimates are that by the time a person is diagnosed with diabetes, about half of the functional beta-cells have been lost. Nutrition and physical activity are the mainstays for diabetes treatment and should be initiated at the earliest possible time and continued throughout life. While the body is still able to secrete insulin, non-insulin medications may help keep blood glucose levels under control. Eventually, insulin will be required.

Insulin should not be thought of as the last line therapy though. Insulin is effective at any point after diagnosis of diabetes and could be considered as part of a patient's treatment plan at any point in time.

There are two ways insulin is used. There's probably more than that but two general categories that I think of. The first is called augmentation where insulin is added onto current therapy to provide additional blood glucose lowering.

It's often supplemental and usually it's given as a basal injection although it can also be given as bolus injections. The pancreas is typically still functional and capable of producing insulin. It's just that the extra insulin helps to bring the blood glucose under better control.

The second method is called replacement which tries to mimic the function of the pancreas through the use of combined basal and bolus insulin. Insulins can be used as replacement therapy when the pancreas is still functioning. However, if you get to the point where the pancreas is no longer secreting insulin, replacement therapy becomes necessary.

People who have highly elevated blood glucose levels should get insulin as primary therapy, at least until their blood glucose levels come under control. When glucose levels are very high, non-insulin medications like sulfonylureas or Metformin will not be able to get control of the blood glucose levels until they're brought down with insulin. High glucose levels can be identified by patients who have fasting plasma glucose that's greater than 250, consistent casual glucose greater than 300, a hemoglobin A1C greater than 10%, ketonuria or signs and symptoms of diabetes such as polyuria, polydipsia, and weight loss.

Today, I'll be referencing the type 2 diabetes insulin treatment algorithm. This pocket card can be found on the DDTP website under Clinician Resources. There's a heading called "Clinician Tools" on the right and you can select the diabetes treatment algorithms or you can go straight to the insulin algorithm. This algorithm demonstrates one method for initiating and modifying insulin therapy. There are many different ways that insulin therapy can be initiated. This is just one example.

Before getting into discussions about the different kinds of insulins, I want to take a moment to discuss what makes them different. When it comes down to it, there are really four things that separate out the different kinds of insulins we use today. The first thing is the onset which tells us when the insulin will start to work. It's the time between giving the injection and the time that the insulin begins to pass into the bloodstream. This is very important when we talk about bolus insulin to help people know when they need to take their insulin and how to plan for taking it.

The peak, which usually happens halfway through the duration of action, or sooner with the short-acting insulins. Peaks are necessary for bolus insulin or mealtime insulins because they mimic natural process of first and second-phase insulin release. Peaks are usually not too beneficial for bolus insulin therapy where a flat or peakless insulin level is preferred in many cases. This isn't to say that peaks

are bad for all patients with basal insulin therapy. Treatment and insulin selection should be tailored to the individual -- tailored and individualized to the patient, because insulin resistance patterns vary and different people's lifestyles can be very different. Some insulins will match up better with patients than others.

The duration determines how long insulin will lower blood glucose levels. It's important to know when the patient may need more insulin or when the patient may be getting too much insulin. A long duration is generally necessary for basal insulin therapy to improve continuity and to reduce variability.

Finally, how concentrated is the insulin? In the past, almost all insulins were U-100. Today, there are U-100, U-200, U-300, and U-500 insulins. Concentration means how many units of insulin are contained in each milliliter. In the U-100 vials, there are 100 units in each milliliter. U-200 contains 200 units. U-300 contains 300 units and U-500 contains 500 units in one milliliter. So if a patient receives 0.5 milliliters of a U-100 insulin which would be 50 units and you withdraw 0.5 milliliters of U-500 insulin, you'll be giving them 250 units of insulin which is about 200 units more than they were supposed to get. So, in addition to knowing what kind of insulin people are taking nowadays, we also need to make sure that we try to recognize the concentration of the insulin that they are receiving. For the most part, people are getting U-100 insulin but there may be cases where somebody may come in taking something different.

So, why are there different concentrations of insulin? There are a couple of reasons. For one, you can give a larger dose with one injection versus having to get two different injections. So if you have a concentrated insulin, you can get more units of insulin with one shot whereas to give that same amount, you may need to use two or more injections. There's an ability to store more insulin in insulin pens and for some insulins, concentrating the insulin to extend the duration of action, and we'll talk about that a little bit later on.

On this slide I have Rx who is a fictitious 58-year-old man whose image was from a Royalty-Free Stock photo website. We're just going to pretend that he has type 2 diabetes and he's had it for 14 years. His A1C is about 9.9% and his casual blood glucose is elevated at 248 milligrams per deciliter. He is currently taking a max dose of Metformin, max Glyburide and max Pioglitazone. After talking with him, he seems to be a pretty serious kind of guy. He doesn't spend a lot of energy on thrills or entertainment. He has been working hard all his life and doesn't have a whole lot of time in the day to do much else. His diabetes is something that he tolerates. It's not something he thinks about much. He eats three meals a day at scheduled times, goes out with family and friends a couple of evenings during the week and he says he takes the doses as prescribed. His life is pretty structured by day but less so in the evenings.

So if we think about different options of getting his A1C under better control, we can think about newer medications such as the DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors. But it's very likely even in combination that these won't be able to lower his A1C enough. So we need to look at insulin. If we go to our treatment algorithm, the first step is to target the fasting blood glucose with basal insulin.

For many patients, there's a target range of 70 to 130 milligrams per deciliter. However, all blood glucose level targets should be individualized based on the patient's condition, their health, and their preferences. We can start basal insulin at 10 units and increase slowly every three days based on fasting plasma glucose readings or we can start off at 0.2 units per kilogram. It's important to note that the dosing will start slow and increases slowly. This is done to enable safe titration. This reduces the risk of hypoglycemia and also helps the patient not feel miserable. When people have blood sugars that are high and they've been high especially for a longer time, they get used to that. If you lower the blood sugar too rapidly, it could make them feel miserable or even hypoglycemic although their blood sugars are in the normal range or even still remaining high, therefore a slow titration of insulin is always recommended.

Even though we know that insulin is the next step, there's a number of things that we need to consider before starting it. First of all, what is our goal of therapy going to be? We may have one goal of therapy while the patient is taking non-insulin medications, but they may have a different goal whenever they're taking insulin. We need to look at the immediate goals such as preventing hypoglycemia as well as long term goals like preventing complications and reducing morbidity and mortality. These goals will vary depending upon the age of the patient, their health, how sensitive they are to the insulin therapy. The main point is that the goals of therapy must be individualized for each patient. And there must be a collaborative process between the clinician and the patient and a good understanding of what's to be expected. We tend to think of lab tests as our goals of therapy; they are often our targets, and the ADA has set some basic targets for diabetes treatment in the insulin therapy. However, again, these should be modified to fit the patient's needs.

Insulin administration is not a simple process for everyone. It requires manual dexterity, adequate vision and comprehension of how it works. A patient who has arthritis or dementia may have a much harder time with insulin administration than someone who does not. In these kinds of cases, you have to start thinking of other things like what kind of caregiver support is available to assist the patient with the insulin administration? In a patient who may be very sensitive to insulin therapy, what kind of support exists if they become hypoglycemic or unable to manage their hypoglycemic state? Is there somebody around who's going to be able to help them and do they know what to do? Poor vision, language barriers and fine motor skills deficits can contribute to improper insulin therapy, risk of hypoglycemia, and also poor insulin administration. These barriers can be documented in RPMS as health factors, and these kinds of things needs to be recognized, assessed and addressed prior to starting insulin. Use of appropriate health literacy techniques and teach back methods can help improve understanding and overcome some of these barriers and help the patient to make sure they're taking their insulin correctly.

We also have to think about monitoring as another consideration. If somebody's on insulin, they'll need to be checking their blood sugars, so we need to think about how often will they be checking it, when will they be checking it and educating them on how to perform the testing. The patient also needs to know how to assess the results and they also have to be aware that hypoglycemia is a risk and be prepared with a plan on how to address it.

And so those are some of the clinicians' concerns but the patient is going to have a whole lot more concerns as well. There are issues associated with fear and intimidation around insulin injections and sticking yourself for blood glucose monitoring. If we talk about issues such as hypoglycemia, the patients may get concerned about their own safety. There are lifestyle concerns; how is this going to affect my work? Will it change the way I feel? Can I still drive? Since insulin is often talked about as a last line of therapy, oral meds and if this doesn't work or this and if that doesn't work, well then you're going to have to be on insulin. People have the feelings that is insulin going to be the last step before death? Do I have to start planning my funeral now that I'm taking insulin? I think these are all legitimate concerns by people. And clinicians face these daily when helping people to take control of their diabetes and start insulin. It's a lot to take in for a patient and clear plans and preparation by the healthcare team can assist in this transition. And of course, they've mentioned it here but weight gain is another major issue that goes along with insulin. Insulin is an anabolic hormone and there will be weight gain with any medication that either increases insulin or improves insulin sensitivity. So even though we know that insulin is the right next step for our patient, sometimes it's not always that easy to put into place.

As we would assume, this patient would use some basal insulin to start off to help lower his fasting blood sugars, help get his A1C under better control. In general, basal insulin suppresses overnight hepatic glucose production and lowers the fasting blood glucose.

Up until about 2000, NPH was the only available basal insulin on the market. Other long-acting and peakless insulin products have come to the market and have been shown to lower blood glucose and A1C with less instances of hypoglycemia and weight gain.

NPH has an average duration of action ranging from 12 to 16 hours. So it often requires twice daily dosing to provide full basal insulin coverage. One of the downsides to NPH insulin is that it peaks anywhere between 4 and 12 hours after a dose. This can result in lower blood glucose levels during those peak times. So if a patient takes a dose at night, it may peak at two or three in the morning resulting in nocturnal hypoglycemia. Although NPH does not mimic natural basal insulin, it may be a reasonable choice among many people who have insulin resistance or may benefit by its peaks in duration. NPH remains a commonly prescribed insulin based on its lower cost and the familiarity of people having using it. It's available in a vial and as a pen and it can be mixed with short-acting insulins. It's always important though to draw up the fast-acting insulin first and then the NPH second to prevent contamination with the protamine zinc in the NPH that prolongs its duration of action.

Long-acting insulins can also be injected once daily and lower fasting glucose levels with lower risk of hypoglycemia and less weight gain than NPH. There are two long-acting insulin products, Glargine which was FDA approved in 2000 and Detemir which is on the IHS Core Formulary. Detemir has a peak of six to eight hours although that peak is relatively lower compared with NPH. Both agents can last 24 hours, although sometimes especially at lower doses, they may not, and patients may need to take a dose twice daily. Both of these insulins are available in vials and as pens. Neither glargine nor Detemir can be mixed with other insulins.

You may be hearing about the newer ultra long-acting insulin products that have recently come onto the market. These products provide steady insulin levels over 24 or more hours. Insulin Glargine is a concentrated version of the long-acting insulin Glargine and Degludec is a new insulin.

Glargine U300 or Toujeo is three times as concentrated as Glargine. This is the exact same insulin, the same medication. It's just much more concentrated. After injection, it gets released more slowly providing a very long duration of action of up to 36 hours. This long duration of action assures that there's a constant basal release of insulin without a peak so there's less risk of hypoglycemia in waking as compared to NPH or long-acting insulins. Glargine U300 is available as a pen and it cannot be mixed with other insulins.

Insulin Degludec or Tresiba -- I'm not sure if I'm saying that right -- is a new insulin that has a very long half-life and duration of action of up to 46 hours. And even though it has such a long duration of action, if you have somebody who's taking NPH or a long-acting insulin, there's still a one-to-one dose conversion when switching from NPH or other insulins. However, if the patient's taking insulin plus they're taking Detemir twice a day, there's a recommendation to decrease the dose by 20% and then make dose titrations every week. Because it has such a long half-life and long duration of action, weekly dose titrations are recommended versus two or three days as we see with other drugs.

And the reason why these very long duration of actions are beneficial is that they end up providing a flat and constant basal release of insulin with very little variability. In fact it also allows for a little bit of flexibility. A dose can be administered between 8 and 40 hours of the scheduled dose. So if somebody is taking their dose every morning and then one day they get real busy, they forget about it, go to work and come home. If it's within 40 hours, they can take their next dose without any change in their plasma steady state concentration. Degludec is also available as a pen and like the other long-acting agents, it cannot be mixed with other insulins.

Going back to the algorithm, once we have the fasting blood sugar under control, we can then start to look for pattern management and look at our pre-meal blood glucose levels, how they're looking before meals and how they're looking after. And it looks like I lost connection.

So on to the next slide, when recommending self-monitoring blood glucose and again, this is just a sample of blood glucose log, they all look this nice, right? Usually not. They're very hard to come by and when people do have them, they're generally a little bit sketchy. But when recommending self-monitoring the blood glucose, it's very important to look for values related to the therapy they just may have. So if you're looking at your basal insulin, you're focusing on your fasting plasma glucose. If you're looking at your lunchtime, you may want to focus on your before-lunch and your after-lunch blood glucose levels and then begin starting bolus therapy in the morning.

Whenever we move from augmentation with insulin to replacement, we end up having more monitoring to ensure their safety and that there's efficacy. And although we can't see the blood sugars throughout the day at this time with current glucometers, it creates problems if we want to get multiple blood sticks throughout the day, that people just don't like doing that. So one way to work on getting information is to check for a couple of different blood sugars throughout each day and look for patterns over time.

This is often difficult because people's lives and blood sugars are going to change day to day. And so what we often see is, often it's confusing, but occasionally, we'll see some patterns emerge at times when glucose levels are higher and when there may be risks of hypoglycemia.

On the next slide, and this might have a couple of clicks in it, Jan, to get images to show up. Short-acting insulins are preferred for managing glucose elevations related to meals. Ideal agents will begin to work rapidly with a short duration to mimic the normal pathophysiology of the body.

There are two classes of bolus insulin; short acting which is regular insulin and there's also rapid acting insulins which include Lispro, Aspart and Glulisine. You know, within regular insulin, there are two main brands; there's Novolin and Humulin. Both are equally efficacious and interchangeable. Novolin is on the IHS Core Formulary.

The discovery of insulin took place in the early 1900s when Dr. Banting, which should be the guy on the far left, who's a surgeon believed that the pancreas made insulin and that you could probably get it out of the pancreas if you took the pancreas out of the body. Although at that time it wasn't called insulin. There was a different word for it up until 1921. He proposed this idea to a guy named John Macleod at the University of Toronto who's in the picture next to him. After some discussion, Macleod gave him a lab to work in, 10 dogs and an assistant named Charles Best. He should be the guy right next to Macleod. They did some surgery on a dog and clamped his pancreas. Then they found out that whenever they did that, the dog developed what we know as diabetes. They then took some of the pancreas out, froze it and ground it up, then injected it back into the dog. And what they found was that the dog was doing better getting the taking injections. So they did a few more dog tests but they realized that they needed bigger pancreas for more testing. So they got a cow. So they did the testing with a cow and that all worked out great and they were ready to move on to human testing. But before injecting humans with cow pancreas, another guy, Bertram Collip was hired to purify the insulin.

So human testing began in 1922. The first patient was a 14-year-old boy named Leonard Thompson and that's him on the far right there. And his insulin administrations, you know, they really didn't know much about those things. They just gave him a couple of doses a day and he did much better. He was on the verge of death and he recovered and he led a productive life up until the age of 27 and he died of pneumonia.

In 1955 the insulin protein was sequenced and from this knowledge, scientists were able to recreate insulin rather than extract it from cows and pigs which often led to allergic reactions. The company called Genentech partnered with another company called Lilly and began mass production of the synthetic insulin that we are familiar with today in 1963. And in 1966, modifications to that protein were made and more rapid-acting insulins like Lispro as well as others were created. So we can see that the dawn of insulin has been very slow, but the progress that we've made in recent years has been very rapid in the options that we now have.

On the next slide, as we talk about regular insulin, I want to come back to the Humulin R U-100 vial and that's what you should be seeing on the screen now. The Humulin R U-500 contains 500 or five times more units of insulin than the usual U-100 insulin. And as we mentioned with the Glargine U300, U-500 also gives a little bit longer duration of action than regular insulin as well. The main reason for the higher concentration, this is to enable the appropriate amount of insulin to be delivered in one injection rather than multiple for people who need higher doses. Again, it's important to use caution when you have both insulins available to ensure you're using the right concentration.

On the next slide, we have a table of premixed insulins. Injections are not something that people look forward to or easily accept. It's hard to convince people to inject themselves one time a day, more difficult for two and as you move up into four, it gets pretty hard. But if we can provide adequate insulin coverage with fewer injections, people are often favorable to that approach. That's one of the reasons why twice daily injections with NPH and a fast-acting insulin are used. Premixed insulins can provide many patients with insulin coverage in fewer injections. On the downside, you can't modify the short-acting insulin without modifying the long-acting insulin as well. Premixed insulins are also useful for people who have difficulty managing their insulin or if you're just starting out with therapy and you're taking things slow.

On the next slide, what do you do with your medications when you start insulin? Well, when you're starting -- patients are starting off with basal insulin. They typically continue their medications as prescribed, no real change with oral meds. But when you begin to use bolus and basal insulin in your replacement, should you continue all of your oral meds or should you get rid of them?

On the next slide, there's no strict rules on what should be done and there have been a few studies to evaluate the benefits of continuing or discontinuing medications. Metformin is generally recommended to be continued because it's got lots of benefits. Sulfonylureas and meglitinides work to increase insulin production for the pancreas. If you don't think that the patient's pancreas is really producing insulin anymore, then it's very likely that sulfonylurea or meglitinide isn't doing much good. So there may be no benefit of continuing therapy with sulfonylureas or meglitinides at this time.

Thiazolidinediones have been used with and have been added to insulin therapy to reduce insulin resistance. In fact, some studies have shown that adding a thiazolidinedione will reduce the amount of insulin that a person needed to achieve their glycemic targets. On the other side, these medications may increase the risk of edema and weight gain. So, thiazolidinedione should be used with caution and you want to look at what your risks and your benefits are for your patient to determine whether you want to continue them or discontinue them.

Newer agents, such as SGLT2 inhibitors, the DPP-4 inhibitors, and GLP-1 agonists may be used with insulin. There are no contraindications against it and they may contribute to positive health outcomes. But the impact of adding these on to insulin or continuing them on with insulin is less clear.

The next slide, in recent days, very recent, this is a news article that was online I think three days ago. There have been concerns about reports of insulin costs skyrocketing and this is coming on the heels of the EpiPen price increases. In the private sector, the cost of rapid-acting insulins has more than doubled since 2008. And longer-acting insulins have been increasing as well. The next slide shows some price costs. In the IHS, the National Supply Service Center has a contract with Novo Nordisk and there's what's called option years that last until the mid-2020. That means our costs are going to stay pretty constant over the next couple of years.

The prices on the top chart are for the medications on the IHS Formulary and the bottom shows some of the costs of the medications that are not on the IHS Formulary. I just wanted to thank James Cummings from the National Supply Service Center for providing this pricing information. NPH, regular and 70-30 are approximately 54 cents per 100 units or one milliliter of insulin. That's about \$5.40 for a

vial. I don't have the actual cost for pens at this time but I've been told that the cost per milliliter is not much different. Aspart, for the rapid-acting insulin or the formulary, and both the vial and the pen is \$2.01 for 100 units so the pen has the same price as the vial. The combination of Aspart and NPH is also similar in price. Detemir is the once daily basal insulin that we have on the formulary and it goes for \$21.15 a vial or \$28.60 for an equivalent amount of insulin as a pen. Non-formulary insulins are more expensive but can still be purchased by your site if the insulin is necessary for patient care.

On the next slide, in the previous slide, I talked about the cost of insulin vials and also brought up the cost of insulin pens. Now, I'd like to talk a little bit about some of the reasons that you should consider insulin pens in your practice setting. There are many benefits to any insulin pens over insulin vials. They're much more convenient and they improve adherence to insulin therapy especially for people who are on a changing schedule or always on the go. One study found that patients continued to take their insulin more as it was prescribed if they were using a pen device compared to a vial and syringe. That's not everybody. Some patients will prefer using the vial and the syringe especially if they're very used to it. But for the most part, people tend to like the pen more. Pens are easier to use. You don't have to worry about drawing up the correct amount and it's easier to administer the correct dose. They also have inner shorter needles and may cause less pain. There's an improved acceptance of insulin therapy when pens are offered as a treatment option. It's easier for a patient to consider having a pen against their skin than a syringe needle and injecting it. Plus, it could be done more discreetly.

On the next slide, insulin pens are a good choice for people who have a hard time drawing up their dose, have poor eyesight and can't see if they drew up the right amount, if they have trypanophobia or the fear of needles, if there are small dosage requirements. So people who need small doses, there's generally smaller doses contained within each pen and if you're not using up your entire vial after 28 days, you're supposed to get rid of it. So if someone is using less than a full vial of insulin, it may be even cost beneficial to use a pen. They're good for people who wish to be discreet, who have a poor adherence to insulin syringes or may have erratic schedules and changing doses. An example is somebody who's counting carbohydrates and they go out to eat. The pen will let them decide what they're going to order, dial in the appropriate dose, and administer it just before their meal arrives.

On the next slide, the costs of formulary insulins are similar when purchased as vials and syringes. Today, more than ever, we have an opportunity to tailor insulin therapy to what the patient wants and what their needs are rather than being held back on what we can afford. Most insurance plans will cover insulin pen therapy the same as they will insulin vial and syringe. Some IHS programs have gone on to do some research and found that depending upon the pens that they're using, they may be able to get more back in reimbursement. One site reported that they used Humulin pens because the reimbursement for patients was greater. Sites have also reported that the reimbursement for pens has been easier to get than it has been for vial and syringe. So for many people, pens are a great option and if you haven't looked into that possibility of using them at your site, that's something you should consider.

The next slide, the insulin pen is pretty easy to use. There's a dial that twists to the correct number of units. The units appear in the easy-to-read window. The patient then sticks the pen into their desired location and presses the plunger. It may take 5 to 10 seconds for all the insulin to be injected so patients should be instructed to wait for about 10 seconds after they hit the plunger before they pull out the needle. As a short overview on insulin pens, in an old IHS Provider article from 2008, I think that from looking at this, the most interesting thing is how the price difference between the vial and the pen has really decreased over the past eight years.

The next slide, now I'm going to talk really briefly about some of the newer products and things that are coming out. The first is I want to talk a little bit about inhaled insulin. You may remember the drug Exubera, the inhaled insulin that was released by Pfizer but then withdrawn from the market after about a year due to poor sales. This was in part due to its awkward design, high cost and uncertainty of long

term side effects. On the bottom there, you can see some examples of people using Exubera except for that last one. That one's a mistake.

Now today, we have a new inhaled insulin. I'm on the next slide. The new inhaled insulin is called Afrezza. It uses what's called the Dreamboat delivery system and you can see a picture of it there. Afrezza delivers insulin from the lungs to the blood in 15 to 30 minutes, peaks quickly after just 12 to 15 minutes, and lasts for about three hours.

The next slide shows what the device looks like and what you do is you open it up, you put a cartridge of insulin in, close it, take off the mouthpiece and then inhale. So it's a much more convenient and easier to use device than the Exubera was. I think it is slide 42, a cartridge comes in different unit sizes. You're limited to certain units. You can't adjust unit by unit. So if somebody's taking 13 units, they can't take 13 units of Afrezza. They have to get to a close enough dose. That's based upon the different cartridges which are available. There are four-unit cartridges, eight-unit cartridges and twelve-unit cartridges. To get an appropriate dose, patients may have to take one or more inhalations.

As an example, if we have somebody who's taking 18 units of insulin by injection, and we go down the table there and we see that there's a range of 17 to 20, they'll take 20 units of Afrezza and to do that, they would do one puff of an eight-unit or green cartridge and one puff of a 12-unit yellow cartridge. The next slide, on the right-hand side you'll see a picture of the Afrezza packaging and on the left-hand side is an image showing when the stuff expires. Depending upon where you are in the packaging determines when everything is going to expire.

An unopened box or one of those plastic wrappers can be stored in a refrigerator until the expiration date that's written on the box. Once the package is opened, the blister packs, those are good in the fridge for about a month or they're good at room temperature for 10 days. The strips, the individual pieces that come off the blister card must be used within three days once opened and at room temperature. The strips don't need to be stored in the refrigerator. In fact, it's probably better once you're down to the strip level to keep them at a room temperature because you have to let those little cartridges to sit out for at least 10 minutes to get to room temperature before inhaling them. The inhaler is also disposable. The inhaler should be cleaned with a moist towel but that's about it. You don't want to submerge it or get it in soapy water. It's used for up to 15 days and then it gets replaced.

Next slide, inhaled insulin, Afrezza is not recommended for people who have diabetic ketoacidosis, people who have COPD or asthma and that's due to risks of bronchospasm, or people who smoke. And this includes people who quit within the last six months which are called cessation smokers. So in RPMS, we want to document smokers, as either they're a current smoker meaning they use it now. If the patient comes in and they quit, for the next six months, they're considered a cessation smoker and that's the time period when the person is very likely to relapse and go back to smoking. If they can get past the six months, then they're called a previous smoker. Non-smokers and previous smokers are able to use Afrezza.

The next slide goes into some of the other insulins that are in development. Basically the new products will have changes in their protein structure to make them act even faster than our rapid-acting insulins or they'll be combined with different chemicals and you can see on the bottom there hyaluronidase which is hyaluronic acid, nicotinamide, things that will kind of degrade the skin a little bit and allow the insulin to pass through it more quickly and into the bloodstream more quickly so that they act even more rapidly.

The next slide lists the Pegylated Lispro which is a basal insulin that's in development and they're pushing for even longer durations of action. In current testing, Pegylated Lispro goes for about 44 to 75 hours.

The next slide, if we go really into the future, we may see things like Smart Insulins. Smart Insulins are programmed to be glucose responsive so it may be possible that you don't even need a specific dose of insulin. You administer the Smart Insulins, the Smart Insulin determines what the glucose level is and how much activity is needed to compensate for that glucose level and delivers that functionality as it needs to. A little bit less in the future maybe, we may see the ability to administer insulin in different ways, an oral insulin spray or an oral gel capsule, both of those will be absorbed buccally and we won't be eating the insulin because of the protein, it degrades very rapidly, would break it down but if we can absorb it buccally in the skin, almost like snuff, how tobacco is absorbed. We can get fast reactions from insulin that way.

There's also different ways of looking to getting insulin through the skin more quickly. One is using what's called an insulin pad which will be a device that warms the skin in 10-minute intervals like an insulin patch except that it heats the skin up and as it heats the skin up, the skin gets warm enough that the insulin passes through continuously throughout the day. There's also thoughts of using intradermal insulin using microneedles which would put the insulin, instead of injecting into the subcutaneous tissue, would just inject and just under the dermis and it's believed that that would have an even faster action than putting it in subcutaneously.

So those are some of the things that may be coming out in the future but in the meantime we can go to the next slide that says, Insulin Basics. We should focus on what we have and look at the basics of that. We have insulin that's being injected subcutaneously and it's often stored in the refrigerator to prolong shelf life. We know that cold insulin is not comfortable when being injected so people need to be reminded just to warm it up to room temperature first. Insulins can be injected subcutaneously and patients may rotate sites but beware that changing locations may cause the onset and activity of insulin to differ. The fastest onset of insulin occurs whenever it's injected in the abdomen and the slower is in the butt. And so when we talk about rotating the sites it's always good to remind patients that we're not talking about going from the abdomen to the arm to the thigh but rather to go around don't inject in the same place in the abdomen, but go about one inch in between injections around the abdomen.

Atrophy and hypertrophy were more common with the cow and pig products. We don't see that very often but it may still occur especially in people who have been using insulin for a very long time, higher doses and injecting into the same space all the time. So again, the only thing we could do to prevent this is to encourage people to rotate the sites so they are not injecting in the same exact spot over and over.

Next slide has some -- there are some tips about insulin and the Joint Commission. Make sure that if you're a hospital that you have a double check system in place to ensure the appropriate insulin dose is being administered to the patient. There is a Joint Commission recommendation not to store insulin next to heparin just because the insulin and the heparin, if you look at the last part of those, the word, they look similar. It sounds like a silly mistake made but it has happened enough times that the Joint Commission highlights it as a recommendation. There is always the recommendation that we write out the word units when prescribing insulin and not abbreviate the U even if we're using an electronic system because someone could look at it, glance at it quickly and see the U as an O and make a mistake in the dosing.

The last slide I have here is just on some special situations. This is mainly a note that this presentation is obviously not a comprehensive presentation on insulin administration and dosing. There are many, many more things to consider such as the use of supplemental insulin for snacks, sick day management, carbohydrate counting, and insulin to carbohydrate ratios. These are all things that could be identified for future talks if there is interest on this topic. And so I'm just throwing some things out there that you may want to consider further for requesting in the future.

So with that, I'd like to thank you for your time. I hope that you got something out of today, something, anything at all and I welcome your feedback, the good, the bad and the ugly and your surveys.