

OPTN Pancreas Transplantation Committee Medical Urgency Workgroup

Meeting Summary

March 19, 2021

Conference Call

Antonio Di Carlo, MD, Chair

Introduction

The Pancreas Transplantation Committee Medical Urgency Workgroup (the Workgroup) met via Citrix GoToMeeting teleconference on 3/19/2021 to discuss the following agenda items:

1. Overview of Project & Recap of 1/29 Meeting
2. Review and Discussion: Medical Urgency Criteria
3. Risk Factors for Hospital Readmission in Patients with Diabetes
4. Next Steps

The following is a summary of the Workgroup's discussions.

1. Overview of Project & Recap of 1/29 Meeting

The Workgroup reviewed the goal of the Medical Urgency project, which is to evaluate and discuss criteria that should be considered medically urgent as it pertains to pancreas candidates. The following is the definition and goal of the medical urgency attribute in the pancreas continuous distribution model:

Medical Urgency: Amount of risk to a candidate's life or long term health without receiving an organ transplant

Goal of Medical Urgency: Prioritize sickest candidates first to reduce waiting list mortality

During the Workgroup's 1/29 meeting, the Workgroup added the following to their list of medical urgency criteria:

- Impaired Awareness of Hypoglycemia (IAH)

Summary of discussion:

There were no comments or questions.

2. Review and Discussion: Medical Urgency Criteria

The Workgroup reviewed the potential medical urgency criteria discussed during the Workgroup's previous call. The following were the suggested criteria:

- Hypoglycemic Unawareness
- Type I vs. Type II diabetes
- Pancreas Donor Risk Index (PDRI)
- Cardiac Autonomic Neuropathy
- Total duration of diabetes
- Pediatrics
- Accessibility to technology
- Diabetes ketoacidosis (DKA)

- Severe Hypoglycemic events
- Gastroparesis
- Impaired Awareness of Hypoglycemia (IAH)

The Workgroup received presentations from subject matter experts (SMEs) on what criteria the SMEs believed should be included in the medically urgent criteria.

Summary of discussion:

Type I versus (vs). Type II diabetes

A SME stated that Type I vs. Type II diabetes relates to residual beta cell function, which is critical when assessing potential candidates with Type II diabetes. The existing comorbidities and other options for management also need to be taken into consideration. The SME explained that, ultimately, when beta cell function reaches a level where it's no longer adequate, then insulin, either basal or basal-bolus, is needed. Patients with Type I have minimal if any residual beta cell function.

A SME mentioned that they would prioritize Type I diabetes over Type II diabetes; however, there should be a consideration for Type II diabetics that have documentation of low insulin secretion. The SME explained that, with Type II diabetes, there's a component of insulin resistance that ends up being more of an issue with many patients than insulin deficiency.

Cardiac Autonomic Neuropathy

A SME mentioned that cardiac autonomic neuropathy is related to hyperglycemic responsiveness or unawareness and can be corrected, to some extent, by adequate insulin secretion by either islets, pancreas, or kidney-pancreas transplants.

A SME stated that this impacts quality of life a lot, especially if the patient is having orthostatic symptoms and passing out because of drops in their blood pressure. The SME suggested placing this higher on the medical urgency list.

Total duration of diabetes

A SME stated that duration of diabetes is a complicated issue. For Type I, if a physician waits decades to list a patient, more comorbidities can develop, such as hypertension, renal disease, and retinopathy. This begs the question of whether it would be too late to address factors such as quality of list and outcomes successfully. The SME suggested that this attribute should not be rated very high on the list of medical urgency criteria.

Another SME pointed out that, while usually patients are going to have more complications the longer they have diabetes, they don't believe that this should be an absolute criteria. For example, the SME has encountered patients who have had diabetes for close to 60 years and had barely any complications – minimal retinopathy and a little bit of micro albumin. The SME emphasized that they don't think a patient like that, who has excellent genetics, needs to be prioritized over a patient who may have had diabetes less time but has a lot more complications.

Pediatrics

A SME stated that one-third of children now have Type II diabetes because of the obesity pandemic, but Type I is rarely indicated in children.

A SME mentioned that they agree with this being low on the list, unless there are some other overwhelming factors in terms of complications or quality of life issues related to diabetes.

The Chair inquired if there would be enough grounds to prioritize pediatric candidates if their complications are urgent enough that a center wants to list them. A SME stated that it would have to be a center wherein the capability, both surgically and medically, of dealing with those patients and extensive assessment and care really is in place in order to prioritize the pediatric candidate. The SME mentioned that listing a pediatric candidate is complex and that they would be hopeful that, at a sophisticated medical center, this child could be corrected to the extent that they wouldn't need to be listed.

Accessibility to technology

A SME inquired if accessibility to technology is in regards to access to insulin infusion pumps/ continuous glucose monitors (CGMs) or does it relate to regional success stories in pancreatic transplantation. The SME emphasized that individuals in a rural area who do not have access to a medical center nearby may have limited access to technology.

The Chair stated that in certain areas CGMs are not being prescribed and access to endocrinologists is becoming more limited. A SME stated that assigning medical urgency for this criteria should be a step-wise approach – if a patient did not have access to a CGM and isn't seeing an endocrinologist, then those would need to be offered to the patient before a transplant operation, which could potentially modify the quality of life and the expected mortality of the patient due to severe hypoglycemia. Historically, symptoms to hypoglycemia relate to two things: (1) rate of fall of glucose and (2) severity of hypoglycemia.

A SME mentioned that they would also put this criterion low on the list. While there may not be endocrinologists nearby, a certain amount of medical care can be provided online, which has been shown during COVID-19, and that could be a way to provide care to those patients. The SME noted that, if those patients don't have the technology to get online, then that's a different obstacle; however, that still shouldn't push them so far up the list. It was also explained that, with new technology, patients can be managed a lot better than they were 10-20 years ago. CGMs having alarms makes a huge difference for many patients in terms of how frequently they need glucagon to come back to consciousness.

Diabetes ketoacidosis (DKA)

A SME mentioned that "brittle" diabetes is a misnomer. There are patients that have many hospitalizations for DKA, but it's usually due to diabetes management. The SME emphasized the management of a patient's diabetes relies on very effective communication between the diabetologist and the patient, especially in relation to Type I diabetes.

A SME mentioned that some patients may have difficulty in managing their diabetes if they are being frequently admitted into the hospital, but often it's a matter of patient education. Some of these patients may have more psychiatric issues, which affect their ability to take care of themselves and take their insulin regularly. The SME suggested that patients should be prioritized if it can be shown that they have gotten the appropriate education, are working closely with endocrinology teams, and are still experiencing DKA.

Severe hypoglycemic events

A SME stated that severe hypoglycemic events is related to the "brittle" diabetes misnomer. Most patients with severe hypoglycemic events can be adequately managed with access to care, particularly by someone in the diabetes field.

A SME noted that this relates to hypoglycemic unawareness as well. If a patient gets a CGM and they continue to have issues then that might justify prioritizing them higher on the list; however, typically,

the frequency of these severe hypoglycemic events decreases dramatically once a patient gets on a CGM.

Gastroparesis

A SME stated that there's limited data and there's a doubtful benefit with including this, so they wouldn't rank gastroparesis high on the medically urgency list. There's difficulty when managing these patients medically.

A SME mentioned that this is clearly something that affects quality of life. There is some data indicating that a year after a patient with gastroparesis has had pancreas transplant, some of the gastroparesis symptoms improve. The SME suggested putting this higher on the list, partly because of how much it affects the quality of life for patients that have it. If there is data showing that gastroparesis will improve if a patient makes it a year after a pancreas transplant, then that would be a good use of the pancreas.

Impaired awareness of hypoglycemia (IAH)

SMEs agreed that this relates to severe hypoglycemic unawareness, severe hypoglycemic events, and possibly to cardiac autonomic neuropathy.

A member inquired if there's an easy definition to implement for IAH. A SME stated that defining this is sometimes problematic, but CGM is an important precursor to identifying IAH. People who typically have better glycemic control modify their ability to be alerted by hypoglycemia and that's often why they're on CGMs. It was explained that glucoses can be in the 55 to high 40s range and not be apparent, so the CGM is going to provide the data to document that fact that severe hypoglycemia is occurring and may not be recognized by the patient. The SME emphasized that this is technology dependent and it would not be a diagnosis that they would want to make without getting CGM data to confirm it.

Another SME stated that, for ease of implementation, the Workgroup could consider if the patient has symptoms when their blood sugar is less than 55 or 60 and, if the answer is no, then they probably have IAH for the purposes of these criteria. SMEs agreed with this. A SME stated that this could potentially be done with self-monitored blood glucoses captured by glucometers, ideally with objective downloads of the data, although a CGM would be better.

Hypoglycemic unawareness

A SME stated that this definitely impacts quality of life. It was explained that some patients don't hear alarms very well and still run into problems with hypoglycemic unawareness. The SME suggested that this should be higher on the list and, ideally, it could be defined by a CGM – the patient needs assistance and their glucose is below a certain level.

Other/Miscellaneous

A member stated that the challenge the Workgroup is going to have is creating a fair and easy system, so coordinators can easily check boxes instead of having to download a thousand glucoses from a CGM to get medical urgency prioritization.

The Chair inquired if there is a way that the Workgroup should be asking for insulin secretion to be measured since c-peptides can fluctuate from less than 1 to 6 in a Type II diabetic patient on different days. Should it be random mornings? Should the patient not have meals before? SMEs agreed the c-peptides are better measured in a stimulated environment – the setting of an oral glucose challenge or a mixed meal with a fair amount of carbohydrates. Another SME stated that a protocol for 1-2 hour Oral Glucose Tolerance Test to measure c-peptides could be used; however, fasting is a little risky because one can't predict what the glucose is going to be so it could be less informative.

A member inquired if there are cases of true insulin allergies and if it can be managed through an endocrinologist. A SME stated that most times when patients say they're allergic to the injectable insulin it is an additive within the insulin that the patient is allergic to. The SME explained that, typically, the patient is put on a different brand of insulin. However, there are protocols that are used during times when there are not as many insulins available for desensitizing patients.

Another SME stated that insulin allergies relate to impurities in the old insulins. The SME stated that patients on large amounts of insulin typically have some unusual syndrome of insulin resistance and there are many monogenic syndromes of severe insulin resistance that require more concentrated insulins, such as U300 and 500. The SME continued by mentioning that true insulin allergy would have to be extremely rare.

3. Risk Factors for Hospital Readmission in Patients with Diabetes

The Workgroup received a presentation from a SME regarding the complexity of the risk factors for readmission in patients with diabetes. It was explained that the main reasons for readmissions post-pancreas transplant were infection, surgical intervention, graft dysfunction, and vascular problems.

The following 5 themes were found to be associated with early readmission of diabetes management (DM) patients:

- Health system failure
- Poor health literacy
- Failure of expected protective factors
- Social determinants of health impeding care
- Loss of control over illness

Summary of discussion:

The Chair inquired if anemia and some irregularities and other markers could be grouped into chronic kidney disease and if diabetes with chronic kidney disease (CKD) is a high risk factor for readmission. A SME stated that CKD has been looked at as diagnosis, with just a diagnostic code, and it is associated with readmission risk; however, they are not sure if that's independent of the creatinine. The SME explained that not everyone with diabetic kidney disease has uncontrolled renal function when they come into the hospital, so the lab parameters (while correlated with diagnosis of CKD) will vary and can provide specific information for that particular hospitalization with a lab test that wouldn't necessarily be provided with just a diagnosis.

The Chair inquired about what macrovascular issues the SME was referring to in this presentation. SME stated that those are the standard macrovascular complications of diabetes – heart failure, coronary artery disease, peripheral vascular disease and stroke.

The Chair inquired if frequent readmission should be a consideration for increased risk of mortality in the Workgroup's medically urgent criteria. A SME questioned if all the urgency criteria are intended to be related to mortality. The Chair explained that the Workgroup wants to decrease mortality on the pancreas waitlist. A member explained that organ allocation systems are moving away from arbitrary judgements of wait time to which candidates are sickest on the list. It was mentioned that there's no such thing in the pancreas world and, right now, the Workgroup is trying to define this for pancreas alone candidates, but then there are also kidney-pancreas candidates who are generally more in need of transplantation than the patients with diabetes alone.

A SME stated that, typically, researchers look at either readmission or readmission and mortality; however, they aren't sure if readmission as a predictor for mortality has been looked at. The SME mentioned that they believed readmission could be a predictor.

The Chair inquired if there's any data the OPTN has that could be put into the SMEs calculator. The SME stated that the calculator could be applied to any patient as long as there's data, even if it's missing, to get a score and see what comes up in a population and cross reference it against the reality.

A member inquired about incorporating the frailty index into this conversation. It doesn't incorporate the distance from the hospital, but it has a role in predicting readmission rates as well as solid organ outcomes. The SME stated that there's a group in Boston that did a natural language processing study looking at language around frailty as predictors of readmission and came up with a score that identified frailty and determined it is a readmission risk predictor. The Chair stated that one of the challenges with frailty is that, as surgeons in non-transplant, frailty is used as a marker not to operate and, instead, find an alternative therapy.

4. Next Steps

The Workgroup reviewed the following timeline:

Phase 1: Evidence Gathering

- Compiling list of potential medical urgency criteria
- Gathering information from discussions with SMEs

Kidney and Pancreas Continuous Distribution concept paper: August 2021 Public Comment

Resume project after Board of Directors Meeting: December 2021

- Consider any additional feedback provided from concept paper
- Present project plan/timeline to Policy Oversight Committee (POC)

To coincide with the Kidney and Pancreas Continuous Distribution project, the Workgroup will pause the first phase of the project. This will allow for further feedback on the Continuous Distribution concept paper, which is scheduled to go out for public comment in August 2021. Once the feedback is received and reviewed, the Workgroup will resume the development of this project and prepare and outline to present to the POC.

There were no additional comments or questions. The meeting was adjourned.

Upcoming Meetings

- TBD

Attendance

- **Committee Members**
 - Antonio Di Carlo
 - Ken Bodziak
 - Maria Friday
 - Silke Niederhaus
 - Todd Pesavento
 - Wayne Tsuang
- **HRSA Representatives**
 - Raelene Skerda
- **SRTR Staff**
 - Bryn Thompson
 - Jon Miller
 - Nick Salkowski
 - Raja Kandawamy
- **UNOS Staff**
 - Joann White
 - Rebecca Brookman
 - Ross Walto
 - Nang Thu Thu Kyaw
- **Other Attendees**
 - Dan Rubin
 - Kristi Silver
 - Robert Eckel