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Islet Transplantation

An Evidence-Based Analysis

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Abbreviations/Acronyms

DM	Diabetes mellitus
HbA_{1c}	Glycosylated hemoglobin
IE	Islet equivalents
ITA	Islet cell transplantation alone
QoL	Quality of life

Glossary

Brittle diabetes	A term used when the blood glucose (sugar) level often swings quickly from high to low and low to high and is unstable.
C peptide	A protein that is attached to insulin produced in the body. When insulin is secreted by the pancreas, C peptide is released in the blood. C peptide levels can be used to assess beta cell function.
Diabetes mellitus	A disease characterized by a relative or absolute lack of insulin leading to uncontrolled carbohydrate metabolism.
Glucagon	A hormone secreted by the pancreas that stimulates increases in blood sugar levels in the blood (thus opposing the action of insulin)
HbA_{1c}	Glycosylated hemoglobin which provides a measurement of a patients average blood sugar level.
Insulin	A hormone that is secreted by the pancreas in response to high blood sugar levels.
Pancreatic islets	Cell clusters in the pancreas that form the endocrine part of the organ. Consist of at least 4 different types of cells: alpha cells (secrete glucagon); beta cells (most abundant and secrete insulin); delta cells (secrete somatostatin); and PP or F cells (secrete pancreatic polypeptide). Islets are also referred to as islets of Langerhans or isles of Langerhans.
Uremia	Abnormally high level of nitrogen-type wastes in the bloodstream, caused by conditions that reduce blood flow to the kidney.

EXECUTIVE SUMMARY

Objective

The Medical Advisory Secretariat undertook a review of the evidence on the effectiveness and cost-effectiveness of islet transplantation alone (ITA) in non-uremic patients with type 1 DM who have severe hypoglycemia and uncontrolled diabetes (brittle diabetics).

Results

- In a health technology assessment from Alberta, Guo et al. (2003) stated that limited evidence from the Edmonton series suggested that islet cell transplantation (ITA) (using the Edmonton Protocol) is effective in 1) controlling labile diabetes and 2) protecting against unrecognized hypoglycemia in highly selected patients in the short term. This conclusion by Guo et al. (2003) was based on the results of 11/17 insulin independent patients who were followed up for a median of 20.4 months in the trial by Ryan et al. (2002). In contrast, Paty et al. (2002) concluded that glucagon and epinephrine responses and hypoglycemic symptom recognition were not improved by islet transplantation in patients receiving the procedure in Edmonton, despite prolonged insulin independence and near-normal glycemic control. Paty et al. (2002) (a member of the Edmonton team) examined 7 ITA recipients, 7 type 1 DM patients (nonITA), and 7 nondiabetic control patients.
- The follow-up for most studies was short. It was suggested that the modifications to the conventional ITA approaches, including the steroid free immunosuppressive regimen, islet preparation in xenoproteins free media and transplantation of fresh islets from multiple donors were associated with improved success.
- The effects of ITA on beta cell function (secretion of insulin) look promising, however, the effects of ITA on pancreatic alpha cell function (secretion of counter-regulatory hormones such as glucagon and epinephrine) in long standing type 1 diabetes remain unclear.
- The most important barriers to more widespread islet transplantation using the Edmonton protocol are the availability of sufficient donor organs and the uncertainty of long term steroid free immunosuppressive therapy.
- Because the number of cadaveric pancreas donors is inadequate to the treat the increasing numbers of individuals on organ transplant waiting lists, isolated islet transplantation is unlikely to become practical for treatment of diabetes if each recipient requires islets from several (2-4) donors (Markmann et al., 2003). Therefore, it is important that the experience of the Edmonton investigators be validated by other centres not only in terms of effectiveness of the new immunosuppressive protocol, but also in the need for multiple transplants (Markmann et al., 2003).
- Preliminary results from a multinational trial indicate wide variation in the success of ITA between different sites. This raises concern about the reproducibility of the results.

Conclusion

- The current evidence on the use of ITA for non-uremic type 1 diabetic patients is limited since it is based on studies with weak methodological design (Level 4). The assessment of ITA is based on several small case series studies or small clinical studies studies (Ryan et al., 2002; Goss et al., 2002; Meyer et al., 1998; Paty et al., 2002). The results from these studies were mixed since the objectives and the protocols differed at each centre. In

particular, many jurisdictions have, to date, been unable to reproduce results achieved in Edmonton (success rate of 23% versus 90%) – this is the focus of an ongoing multicentre study.

- Ryan et al. (2002) reported that the median follow-up time for the 17 patients undergoing the Edmonton Protocol was 20.4 months from the first transplant. As of January, 2002, 11/17 patients remained insulin independent. Three of the 11 insulin independent patients had negative C-peptide secretion, indicative of impaired islet function.
- The effect of ITA on restoring hormonal responses to hypoglycemia is inconclusive.
- ITA in non-uremic type 1 diabetic patients with hypoglycemia unawareness or uncontrolled diabetes is an evolving procedure with promising preliminary, but inconclusive final results.

Objective

The Medical Advisory Secretariat (MAS) conducted a review of the effectiveness and cost-effectiveness of islet transplantation in non-uremic patients with type 1 diabetes mellitus (DM).

BACKGROUND

Clinical Indications

Diabetes mellitus (DM) is a chronic disorder identified by the presence of hyperglycemia (abnormally increased concentration of blood glucose) due to defective insulin secretion, insulin action or both (Meltzer et al., 1998). Type 1 (or juvenile) DM is mainly caused by a progressive destruction of insulin producing cells in the pancreatic islets, with absent or greatly reduced insulin secretion. In type 1 DM it is postulated that the insulin producing cells (also known as beta cells) are destroyed by an autoimmune process or by unknown causes. Type 1 DM patients usually develop diabetes in childhood or early adulthood and require insulin replacement therapy. The clinical symptoms of type 1 DM are not commonly detected until after the patients immune system has attacked and destroyed 90% or more of the total beta cells of the pancreas. Complications associated with type 1 diabetes include heart disease, stroke, hypertension, blindness, kidney disease, nervous system damage and amputations.

The current standard of care for type 1 DM includes insulin therapy, dietary restrictions and physical activities.

Diabetes is the third leading cause of death by disease in Ontario and Canada, after heart disease and cancer. Over two and a quarter million Canadians are estimated to have diabetes; 10% of the total cases are type 1 DM (Health Canada, 2003).

It is estimated that 20,000 new cases of DM are diagnosed annually in Ontario (MOHLTC, 2003). There are approximately 544,000 patients with DM currently living in Ontario (MOHLTC, 2003). Of these, approximately 55,000 are type 1 DM patients.

Chronic pancreatitis is a less common condition and is sometimes treated by removal of the pancreas (pancreatectomy). Although the true prevalence of chronic pancreatitis is not known, it is estimated to range between 0.04% and 5% in the normal healthy population (Tsirambidis et al., 2003). In developed countries, the disorder is related to alcohol abuse in approximately 60% to 70% of cases. Idiopathic pancreatitis, which accounts for 30% of all cases of chronic pancreatitis occurs in 2 distinct subgroups of patients: 1) young individuals aged 15-30 years, and 2) older individuals aged 50-70 years (Tsirambidis et al., 2003). A less common form, tropical pancreatitis, occurs in young children in areas of Africa and Asia. Chronic alcoholic pancreatitis is associated with a mortality rate of approximately 50% within 20 to 25 years. The prognosis for tropical pancreatitis and idiopathic pancreatitis is generally more favourable than for alcoholic pancreatitis.

Exogenous insulin injection frequently fails to achieve optimal glucose control, even when intensive regimens are used (Logdberg et al., 2003). In addition, intensive therapy using multiple daily insulin injections or insulin pump infusion with frequent monitoring of blood glucose, may lead to an increased incidence and severity of hypoglycemic episodes (Logdberg et al., 2003). Some patients have wide swings in blood glucose with episodes of hyper and hypoglycemia despite strict adherence to an exogenous insulin regimen. These patients are referred to as “brittle” diabetics and are at high risk for diabetic complications. Consequently, alternative methods have been investigated to ensure better glucose control.

Pancreatic Islets

A normal pancreas consists of approximately 1 million islets (Robertson, 2004). Islets, which are surrounded by pancreatic exocrine tissue, make up approximately 2-3% of the total pancreatic volume (Robertson, 2004). Islets have a portal circulation with blood flowing from beta to alpha to delta cells. The alpha, beta, and delta cells secrete glucagons, insulin and somatostatin respectively. Since normal islets produce the correct amount of insulin (Figure 1), islet transplantation may provide continuous better control of blood glucose than achieved by insulin injections, and this may also reduce complications from DM. Transplanted islets may provide benefits in several ways (Federlin and Pozza, 1999):

- Functioning beta cells (secrete insulin) lead to better control of blood glucose changes.
- Functioning alpha cells secrete glucagon when blood glucose decreases. This is especially important in patients who may still need some exogenous insulin after islet transplantation.

C-peptide is produced in pancreatic beta cells by the cleavage of proinsulin into insulin and C-peptide (Hardy et al., 2000). Measurement of C-peptide may be used to determine if a patient's hypoglycemia is due to an endogenous or exogenous cause. Also, the measurement of C-peptide is used for the assessment of beta cell function and permits estimation of remaining beta cell secretion of insulin (Hardy et al., 2000; Steffes et al., 2003). At present, islet graft survival is controlled by monitoring of 1) glycemia, 2) serum C-peptide (normal reference range 0.78-1.89 ng/mL), and 3) glycosylated hemoglobin (HbA1c) which provides a measurement of a patients average blood sugar level (Ritz-Laser et al., 2002).

Treatment

Transplantation of isolated pancreatic islets is a cellular therapy approach that uses infusions of isolated pancreatic islets from a cadaver (allogenic islets) or a patient's own pancreas (autologous islets). The islets can be placed in the liver (usually) or in the spleen. The islets lodge in the liver because they are too large to pass through the sinusoids (Robertson, 2000).

The pancreas with the donor islets is procured with the use of the same techniques that are used to procure a pancreas for whole-organ transplantation (Figure 2). Islets are separated from pancreatic exocrine tissue and purified. The final product is evaluated for purity and viability before it is transported for transplantation.

Autotransplantation of pancreatic islets is indicated secondary to total pancreatectomy. Autoislets are obtained from a living person who is not diabetic and not using immunosuppressive drugs, and are transplanted within approximately 2 hours (Robertson, 2001). Metabolic testing in autoislet recipients has provided valuable insights into what might be expected from alloislet transplantation in diabetic patients (Robertson, 2001).

Allotransplantation of cadaveric islets may be indicated in the following circumstances (Federlin and Pozza, 1999):

1. Previously transplanted kidney*.
2. End stage renal failure (simultaneous islet cell/kidney transplantation)*.
3. Lost function of a pancreatic organ graft.
4. Defect hypoglycemia counterregulation/life threatening hypoglycemia unawareness.
5. Autonomous cardiac neuropathy.
6. Significant clinical problems with insulin therapy (for example, brittle diabetes).

*When patients with diabetes undergo kidney transplantation alone, changes of early diabetic nephropathy usually recur in the transplanted kidney within 2 years, and progress to end-stage renal

disease (usually occurring in 10 years) (Rosenberg, 2000). Combined pancreas kidney transplantation protects the transplanted kidney, preventing recurrence of diabetic nephropathy (Rosenberg, 2000).

At present, there are no definitive inclusion and exclusion criteria for islet transplantation alone (ITA) in non-uremic (normal level of nitrogen-type wastes in the bloodstream, attributed to normal kidney function) patients with type 1 DM. However, Federlin and Pozza (1999) suggested the following contraindications to ITA:

Age <18 and >65 years.
Duration of diabetes <10 years.
Manifestation of diabetes after age 30
Residual C peptide secretion (stimulated C peptide 6 minutes after 1 mg glucagon i.v. ≥0.2 ng/mL)
Creatinine clearance <45 mL/min
Portal hypertension (increased pressure in blood vessels carrying blood to the liver)
Active or chronic infections as hepatitis C or B
Allergy against rabbit or horse serum
Active gastric or duodenal ulcer
Psychosis
Non compliance
Neoplasia (if not free from relapse >5 years)

Advantages to ITA include:

- Islets can be delivered by percutaneous catherterization of the portal vein, performed as a minimally invasive outpatient procedure under local anesthesia.
- Islets may be treated with immunosuppressive agents before injection to reduce immunogenicity.
- Avoidance of problems due to pancreas transplantation such as complications due to the exocrine pancreas and blood supply of whole organ pancreas grafts.

Until very recently, alloislet transplantation was combined with triple drug immunosuppression using prednisone, azathioprine and cyclosporin because it had proved successful for solid organ transplants (Robertson, 2001). However, one of the major issues that emerged in the 1990s was that the drugs used to immunosuppress patients could be toxic to isolated islets (Robertson et al., 2001; Berney et al., 2002; Federlin and Pozza, 1999).

The methods for ITA have changed over time. Most recipients need islet preparations isolated from more than one donor to provide a sufficient islet mass to obtain insulin independence. With most techniques, only 30%-50% of islets within a pancreas are isolated (Toso et al., 2002).

The Edmonton Protocol

Shapiro et al. (2000) developed a different approach for the ITA procedure known as the Edmonton protocol which has the following characteristics :

- Glucocorticoid free immunosuppression which may be less likely to cause diabetes after transplantation and is also less harmful to the kidneys.
- Isolation and purification of islets in xenoprotein (non-human)-free medium to avoid targeting by formed antibodies that lead to cell destruction.
- Short cold ischemic (storage) time. Cold storage of the donor pancreas for more than 12 hours reduces islet cell yields (White et al., 2001). The Edmonton protocol limits cold storage to less than 13 hours, inclusive of the islet cell isolation procedure (White et al., 2001).
- Transplantation of adequate number of viable islets. In the past, the threshold of 360,000 islets (6,000 [islets equivalent] IE/kg) which represented the approximate number of islets currently isolated from a pancreas was considered necessary for graft function. The Edmonton protocol extracts more islets, approximately 11,000 IE/kg, (almost double the

number that were previously used) from at least 2 pancreas donors and transplants the islets to a recipient several weeks apart.
- Selection of patients with life-threatening hypoglycemia and "brittle" diabetes. Patients do not have end-stage renal disease and no previous transplantations of kidney or other solid organs. Selection is based on recurrent severe hypoglycemia or metabolic instability and unresponsive to treatment with exogenous insulin.

Inclusion and exclusion criteria for the Edmonton Protocol are listed in the Appendix.

In recent years, there has been interest in the use of the in vitro generation of mature functional islets, even autologous islets, from pancreatic duct associated stem cells due to the shortage of human organ donors (Peck et al., 2001).

Groth et al. (1994) reported clinical experience of porcine islet xenotransplantation (use of animal islets) in 10 type 1 diabetic kidney transplant patients. Groth et al. (1994) concluded that porcine pancreatic endocrine tissue was able to survive in the human body. However, the implantation of xenogenic tissue has provoked ethical and epidemiological controversies (Bach et al., 1998). Specially bred pathogen free pig herds may reduce the concern of transmission of pig virus to humans (pig endogenous retrovirus infection) (Shapiro and Lakey, 2003). Subcutaneous delivery of pig islets in type 1 DM patients is currently undergoing clinical trial in Mexico (Valdes-Gomzalaez et al., 2002).

Alternative Technologies

Other possible treatments for patients with type 1 DM include multiple daily injections of insulin, continuous insulin infusion using an automatic pump implanted under the skin, or total pancreatic transplantation.

Historically, total pancreatic transplantation has been performed in conjunction with kidney transplantation, or with other organ transplantation (Peck et al., 2001). A major problem associated with total pancreatic transplants is the need for long-term immunosuppression. Since there is a limited supply of donor pancreases, candidates for this therapy have end-stage renal disease awaiting kidney transplant or have long standing type 1 DM and have failed insulin therapy because of poor compliance (Silverstein and Rosenbloom, 2000). The major argument against transplanting only the pancreas in non-uremic diabetic patients is that any improved quality of life is offset by the combined risks of immunosuppression and major surgery. In addition, there are substantial risks especially thrombosis of the graft's artery or vein, which results in a failure rate of 5-10% (Gruessner et al., 2000). Due to risks involved in vascularized pancreas transplantation, it is generally considered to be indicated for relatively few of the many patients with type 1 DM (Markmann et al., 2003).

There have been no randomized trials comparing pancreas transplants with conventional treatment with regard to development of later complications. However, limited data suggest that transplant is beneficial in this regard (Gruessner et al., 1997; Rosenberg, 2000; White et al., 2000).

Pancreas transplantation uses only one donated organ (Robertson, 2004).

Regulatory Status

Health Canada is developing a proposed new regulatory framework under the Food and Drugs Act for cells, tissues and organs, which will be based on National Safety Standards, currently under development by the Canadian Standards Association (Health Canada, 2003). Until the new regulatory framework is in place and the National Safety Standards are published, Health Canada recommends that establishments and individuals in Canada handling and/or processing human cells, tissues and organs adhere to basic standards of safety with respect to the manufacture and use of these products for transplantation (Health Canada, 2003). The directive applies to human cells, tissues and organs retrieved from a living or dead body and intended for transplantation, including islet cells and other cells derived from the pancreas (Health Canada, 2003).

Over the last 3 years, the US Food and Drug Administration (FDA) has seen a significant increase in investigational new drug (IND) applications for use in donor pancreas transplantation/ITA to treat type 1 DM (FDA, 2003). The FDA invited outside experts to discuss manufacturing, preclinical and clinical issues related to this topic at an advisory committee meeting in March 2000. Another meeting is scheduled for early October 2003 (FDA, 2003).

According to the FDA (2003), the clinical use of islets to treat type 1 DM meets the criteria for regulation as both a biologic product and a drug product. The FDA (2003) stated, "Therefore, clinical studies are needed for this experimental therapy in order to gather safety and effectiveness data in accordance with IND regulations set by FDA, and to ensure the safety and rights of patients in all phases of the investigation."

LITERATURE REVIEW ON EFFECTIVENESS

Objective

- To assess the effectiveness and cost-effectiveness of islet transplantation alone (ITA) in non-uremic patients with type 1 DM who have severe hypoglycemia and uncontrolled diabetes (brittle diabetics).

Methodology

Inclusion criteria:

- English language articles (1998-September 2003).
- Journal articles that report primary data on the effectiveness or cost effectiveness of obtained in a clinical setting, or analysis of primary data maintained in registries or databases.
- Study design and methods must be clearly described.
- Systematic reviews, randomized controlled trials (RCTs), non-randomized controlled trials and/or cohort studies, cost effectiveness studies.

Exclusion criteria

- Studies that are duplicate publications (superceded by another publication by the same investigator group, with the same objective and data).
- Non-English articles.
- Non-systematic reviews, letters and editorials.
- Animal and in-vitro studies.
- Case reports.

Patients

- Human non-uremic patients with type 1 DM who have severe hypoglycemia and/or uncontrolled diabetes and undergo ITA.

Literature Search

Cochrane database of systematic reviews
ACP Journal Club
DARE
INAHTA
Embase
Medline
Reference section from reviews and extracted articles

Outcomes of Interest

Insulin independence
Glycosylated hemoglobin values
Glucose levels
C peptide levels
Transplantation success
Adverse effects
Economics analysis data

Results of Literature Search

The Cochrane and INAHTA databases yielded 3 health technology assessments. A search of Medline and Embase 1998- September 2003 was conducted. This search produced 14 studies of which 2 met the inclusion criteria. The quality of the included articles is presented below.

Quality of Evidence

Study Design	Level of Evidence	Number of Eligible Studies
Large randomized controlled trial, systematic reviews of RCTs	1	
Large randomized controlled trial unpublished but reported to an international scientific meeting	1(g)	
Small randomized controlled trial	2	
Small randomized controlled trial unpublished but reported to an international scientific meeting	2(g)	
Nonrandomized study with contemporaneous controls	3a	
Nonrandomized study with historical controls	3b	
Nonrandomized study presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multi-site)	4b	
Case series (single site)	4c	1
Retrospective review, modeling	4d	
Case series presented at international conference	4(g)	1

g=grey literature

Assessment of Evidence

Reported Health Technology Assessments

A. Alberta Heritage Foundation for Medical Research [AHFMR] (Guo et al., April 2003)

The objectives of the AHFMR health technology assessment were to:

- Systematically review the medical literature on the efficacy/effectiveness and safety of ITA for non-uremic (no accumulation in the blood of nitrogen-bearing waste products that are usually excreted in the urine) type 1 DM patients who have severe hypoglycemia or uncontrolled diabetes despite compliance with an insulin regimen.
- Provide rational for determining the status of ITA for the specific subgroup of patients.

The use of islet cell transplantation combined with kidney transplantation for type 1 DM patients with end-stage renal disease was not addressed in the report. Additionally, the term ITA referred only to islet cell allotransplantation.

Methods

A comprehensive literature search was conducted by Guo et al. (2003) from 1992-December 2002. The first search was completed in August 2002 and the search was updated in December 2002.

Results

The following sections (A1-A6) are a summary of the results and discussion of the AHFMR report by Guo et al. (2003).

A-1) Efficacy of ITA

Islet transplantation has been mostly performed in combination with kidney transplantation for patients with type 1 diabetes with end stage renal failure. The patients required an immunosuppression regimen to prevent rejection of the transplanted kidney so that the islet graft would not present an additional risk (White et al., 2001; Oberholzer et al., 2001).

Guo et al. (2003) stated that according to the International Islet Transplant Registry, a total of 445 adult islet cell allotransplantations for patients with type 1 diabetes have been performed worldwide (mostly in North America and Europe) from 1974 to December 2000. The majority of transplantations were performed since 1990. Prior to 1990, the results of human islet transplantation were disappointing compared to whole pancreas transplantation. Of the 267 islet transplantations performed from 1990-1999, insulin independence after one year was achieved in only 8% of the patients. Some of the factors that may have contributed to poor long term function of the islets included: difficulties associated with the islet isolation technique; inadequate number of transplanted islets and the diabetigenic effects of the conventional immunosuppressive therapy. As a result, the approach adopted by the Edmonton team incorporated several new approaches to islet transplantation (Edmonton protocol).

No randomized controlled or other controlled clinical trials were conducted to compare the efficacy of ITA with insulin therapy or total pancreas transplantation for non-uremic type 1 DM patients with severe hypoglycemia or uncontrolled diabetes. All studies were case series or small clinical studies.

Several case series studies that reported islet transplantation combined with kidney transplantation for type 1 DM patients with end-stage renal failure were excluded from the

review since the patient populations involved in the studies were different from the patient group of interest.

Three islet transplantation centres in Canada, Germany, and the United States published their experiences with ITA for non-uremic type 1 diabetic patients with hypoglycemia unawareness or severe diabetic complications. In July 2000, Shapiro et al. reported the results of ITA using the Edmonton protocol in 7 non-uremic type 1 DM patients who had a history of severe hypoglycemia or uncontrolled diabetes despite compliance with an insulin regimen. All 7 patients were reported to have quickly attained sustained insulin independence after transplantation (median follow-up of 11.9 months, range 4.4-14.9 months).

Since the study by Shapiro et al. (2000) was published, several reports were published to update the data on the previous cases (Ryan et al., 2002) and to report the results on new cases (Ryan et al., 2001; Ryan et al., 2001; Shapiro et al., 2001). Only the study with the most recent results (Ryan et al., 2002) was assessed by Guo et al. (2003) in the AHFMR HTA.

Ryan et al. (2002) reported that as of January 1, 2002, 54 ITA procedures were performed on 30 patients and 17 of these patients completed the Edmonton protocol (Figure 3). Thirteen patients were excluded because of involvement in other protocols or were still undergoing the procedure. The median follow-up time for the 17 patients was 20.4 months (range 3.2-34.2 months) from the first transplant. Of 15 consecutive patients with at least 1 year follow-up after the initial transplant, 12 patients (80%) were insulin independent. As of January, 2002, 11/17 patients remained insulin independent. The follow-up data on 6 patients who are now more than 2 years post-transplant indicated that 4 of these patients remained off insulin. According to Ryan et al. (2002), the results suggested that long term insulin independence can be achieved.

In the 17 patients at median follow-up of 20.4 months from initial transplant, HbA_{1c} (glycosylated hemoglobin) levels decreased from pre-transplant values of $8.21 \pm 0.36\%$ to the most recent values of $6.08 \pm 0.77\%$ ($p<0.001$) (Ryan et al., 2002). A normal value for HbA_{1c} is <6.1%) (Ryan et al., 2002). Of the 11 patients who were off insulin as of January 1, 2002, HbA_{1c} levels decreased from pre-transplant $8.48 \pm 0.49\%$ to the most recent values of $5.8 \pm 0.13\%$ ($p<0.001$) at a median follow-up of 20.4 months (Ryan et al., 2002). These 11 patients had diabetes according to the American Diabetes Association criteria and 2 of the patients were on oral hypoglycemic agents because of increased glucose levels. In 8/11 patients, there were detectable levels of C peptide (a protein that is released into the blood when insulin is produced by the pancreas). Of the 6 patients who were back on insulin, 3 C peptide positive patients required a much lower daily insulin dose than their pre-transplant use of insulin (Ryan et al., 2002). Daily insulin doses required for the other 3 C peptide negative patients were not reported. Pre and post-transplant HbA_{1c} levels were not reported for the 6 patients who were back on insulin treatment. All the patients off insulin (n=11) had stable glucose values and did not have hypoglycemic episodes (Ryan et al., 2002).

Diabetic complications observed in the 17 patients included progression of retinopathy (3 patients required laser photocoagulation), rise in blood pressure post-transplant (10 patients), and rise of cholesterol (15 patients, in 4 patients cholesterol levels dropped again with diet therapy) (Ryan et al., 2002). No significant changes were observed in renal function or neuropathy.

In a personal correspondence in January 2003, Guo et al (2003) stated that according to Shapiro, 49 Canadian patients have now received ITA using the Edmonton Protocol at the University of Alberta and the 1 year insulin independence rate for completed transplants was

84%. However, the details of these 49 cases were not yet published apart from 30 of these patients reported by Ryan et al. (2002) and discussed above. The Edmonton protocol which has undergone a number of recent modifications (for example, 2 layer pancreas preservation, changes in islet cell culture, and use of other nonsteroidal immunosuppressant strategies) has been replicated in over 15 ITA centres involving over 160 patients worldwide (Shapiro, 2002), however, the results have not been published.

Goss et al. (2002) recently reported experience with ITA in 3 noneuremic type 1 diabetic patients in the United States. In an attempt to centralize the islet processing needed for islet transplantation and to avoid the development of another islet processing centre, Goss et al. (2002) assessed whether a collaborative islet transplant program between two geographically distant transplant centres could be established. Three consecutive patients underwent ITA in Houston. All islet cells were separated from pancreases procured in Houston and subsequently transported for isolation/purification to Miami (flight time approximately 2 hours and 10 minutes). After purification, the islets were transported back to Houston and transplanted.

Pancreatic islets were isolated using xenoprotein free media and an immunosuppressive regimen consisting of sirolimus, tarcrolimus, and daclizumab, similar to the Edmonton protocol.

Two patients received 2 transplants and the other patient received one. More than 10,000 IE/kg were given to each patient. Post transplant follow-up for the 3 patients was at 4, 3, and 0.5 months respectively. All 3 patients achieved insulin independence after their first pancreatic ITA. The mean glycosylated hemoglobin values were reduced after transplantation. Serum C peptide was not detectable in any of the patients before transplantation. After transplantation, all 3 patients consistently had a fasting C peptide level within the normal range. According to Goss et al. (2002), none of the 3 patients had an episode of hyperglycemia or hypoglycemia after transplantation. In addition, Goss et al. (2002) concluded that: 1) pancreatic islets remain viable after shipment to remote transplant sites; 2) pancreatic islet isolation techniques and experience can be concentrated at a small number of regional facilities that could supply islets to remote transplant centres; and 3) insulin independence via ITA can be achieved using a remote pancreatic islet isolation centre.

A-2) Hormonal Effects of ITA

Guo et al. (2003) identified two studies that specifically examined the effects of ITA on restoring hypoglycemia-induced hormonal counterregulation and hypoglycemia awareness in type 1 DM patients.

Meyer et al. (1998) investigated the secretory response of counter-regulatory hormones and hypoglycemic awareness before and after successful ITA in 3 German patients with chronic type 1 DM. All 3 patients received islets from a single donor pancreas. Immunosuppressive therapy was started 1 day before islet transplantation and included methylprednisolone, cyclosporine, and a specific antibody which was previously used in autoimmune diseases as a tolerance inducing drug (Meyer et al., 1998). Immunosuppressive drugs were stopped 4 weeks post transplantation to minimize any confounding effect. Insulin independence was achieved in 1 patient over 14 days and the two other patients required significantly less daily insulin after ITA. Islet transplants were rejected in all subjects approximately 2 months after termination of immunosuppressive therapy. There were no significant changes in HbA_{1c} levels post-transplantation. All 3 type 1 DM patients had multiple episodes of severe hypoglycemia in the previous year but none of the patients experienced such hypoglycemia at approximately 2 months after transplantation. Meyer et al. (1998) suggested that while ITA did not restore hypoglycemia induced glucagon secretion, ITA improved the responses of most counter-

regulatory hormones and hypoglycemic warning symptoms even in patients with chronic type 1 DM.

In a Canadian study, **Paty et al. (2002)** compared hormone responses and hypoglycemic symptom recognition in the first 7 insulin independent patients who received ITA using the Edmonton protocol (Shapiro et al., 2000), to 7 nontransplanted type 1 DM patients and to 7 nonDM control patients who were matched for age and weight with the islet transplant patients. The mean duration of insulin independence for all patients was 12.6±0.6 months from the time of the final islet infusion. None of the patients had an episode of hypoglycemia until plasma glucose level was <50 mg/dL. Glucagon responses of ITA recipients to hypoglycemia were significantly less than that observed in control subjects (incremental glucagon [mean±SE]: -12±12 versus 64±22 pg/ml, respectively, $p<0.05$) and not significantly different from that of nontransplanted type 1 DM patients (-17±10 pg/mL).

Epinephrine responses and symptom recognition were also not restored by ITA: (incremental epinephrine 195±128 [ITA recipients] versus 238±73 [type 1 DM patients] versus 633±139 pg/mL [nondiabetic control patients], $p<0.05$ versus control. Peak symptom scores were: 3.3±0.9 [ITA recipients] versus 3.1±1.1 [type 1 DM patients] versus 6.7±0.8 [nondiabetic control subjects].

Paty et al. (2002) concluded that glucagon and epinephrine responses and hypoglycemic symptom recognition were not improved by islet cell transplantation, despite prolonged insulin independence and near-normal glycemic control. Guo et al. (2003) stated that this result was contrary to the results reported by Meyer et al. (1998).

A-3) Safety of ITA

Ryan et al. (2002) reported details on the complications associated with ITA which included procedure related complications and complications from the immunosuppressive regimen. Goss et al. (2002) reported that there were no complications from the procedure or immunosuppression. Meyer et al. (1998) did not report or discuss any complications observed after ITA.

Complications reported by Ryan et al. (2002) are listed in Table 2, the most serious of which were moderate bleeding at the site of the transhepatic puncture and thrombosis of the portal vein.

A-4) Summary of Other HTA Reports Identified by Guo et al. (2003)

The literature search by Guo et al. (2003) also located two technology reports on pancreatic islet transplantation for patients with type 1 DM prepared by the Institute for Clinical Systems Improvement (ICSI, 2002) and ECRI (2000). The two reports were not considered to be systematic reviews by Guo et al. (2003), however the reasons for this were not stated. Guo et al. (2003) briefly summarized the two reports as follows:

> 1. ICSI
> According to ICSI, pancreatic islet transplantation appeared to be safe with low mortality and acceptably low morbidity (Guo et al., 2003). The number of treated patients was small, however, the efficacy of islet transplantation with respect to insulin independence, glycemic control, and serum C peptide levels improved in the past 2 years. The population of patients most appropriate for transplantation remains to be determined. ICSI suggested that at present due to difficulties with harvesting adequate numbers of islet cells and the need for evidence of effectiveness, islet transplantation is not a viable treatment option for most patients with type 1 DM.

2. ECRI

According to ECRI, no published guidelines or standards were identified on islet transplantation alone. ECRI concluded that islet transplantation rarely resulted in insulin independence for any length of time and it was rare for graft function to be maintained for ≥2 years. Partial function of transplanted islets appeared to be useful for reducing the amount of insulin needed daily for prevention of hypoglycemic episodes. The ECRI report was published in 2000 and therefore did not include information from the Edmonton case series.

A-5) Current Opinion on Islet Cell Transplantation and Regulatory Status

According to an expert from the International Islet Transplant Registry in Europe as well as the US, islet transplantation is still considered research as opposed to solid organ pancreas transplantation which is considered to be established clinical practice (Brendel, November 2001). During a personal communication between Guo et al. and Brendel in November 2002, islet transplantation alone was not yet seen as a "standard of medical care" among diabetologists and endocrinologists in Germany. It is considered a therapy with high potential for patients with diabetes with hypoglycemia unawareness or uncontrolled diabetes despite compliance with an insulin regimen.

In Germany, islet transplantation received funding support for several years as a therapeutic model. The funding was terminated in 1999 (Brendel, personal communication with Guo et al., November 2002). Islet transplantation is not covered by Medicare in the US.

A-6) Ongoing International Multicentre Clinical Trials

The Immune Tolerance Network (ITN) started a 2 year international multicentre trial at 10 centres (7 in North American and 3 in Europe) to confirm and extend the results of the Edmonton protocol in a total of 40 patients (4 patients per centre).

The ITN trial aims to standardize procedures of islet isolation and transplantation (Bluestone and Matthews, 2002). In December 2001, the first of the 40 patients in the ITN trial was transplanted in Edmonton (Bluestone and Matthews, 2002). After a personal communication with Shapiro in January 2003, Guo et al. (2003) stated that preliminary data indicated that the Edmonton protocol had been successfully replicated across the 9 centers involved in the ITN trial. The patients were insulin independent immediately after the transplant, and 20% of these patients achieved insulin independence with a single donor islet transplant.

In 2003 it was expected that all 40 patients will have received islet transplantation using the Edmonton protocol (Robertson, 2001).

B. National Institute for Clinical Excellence [NICE] (June, 2003)

NICE conducted a rapid review of islet transplantation for type 1diabetes or diabetes secondary to pancreatitis. The Advisory Committee at NICE made provisional recommendations about pancreatic islet transplantation. However, the document is not NICE's formal guidance on the procedure. The recommendations are provisional and may change after consultation. NICE stated that the target date for publication of guidance is September 24, 2003.

Results

The following sections (B1-B4) are a summary of the review by NICE (June, 2003).

One review was identified that examined islet transplantation in people with Type 1 diabetes (White et al., 2001).
No controlled studies were located.
No case series of islet transplantation in people with Type 1 diabetes was published after the search date of the systematic review which was in 2000 (White et al., 2001).

8 case series including 10 or more people having islet transplant following removal of the pancreas were found. NICE described the 3 largest studies (Table 3).

B-1) Efficacy

Most of the evidence available related to pancreatectomy. The rates of independence from injected insulin were not always reported. However, 2 case series reported rates of 51% and 59%.

The Specialist Advisors stated that if patients are able to establish normal glucose control after transplantation then the potential benefits are likely to be great. However, the identified studies did not compare blood glucose control or risks of diabetic complications for injected insulin versus islet transplant. There was also a lack of long term follow-up data.

B-2) Safety

All the studies reported deaths at follow-up. In one case series the mortality rate was reported as 11% at 7 years. A number of complications were also reported, including duodenal ischemia (rates in 2 case series of 6% and 13% respectively), and thrombosis in either the portal or splenic vein (2% and 8% respectively).

The Specialist Advisors all reported that there was a potential risk of thrombosis of the portal vein, as well as of bleeding from the liver at the time of transplantation. There was also concern about the serious side effects from the immunosuppressive drugs required after allogenic transplantation, including malignancy.

B-3) Other Comments

Most of the evidence related to pancreatectomy rather than to patients with type 1 diabetes. The identified studies did not compare blood sugar control or risks of diabetic complications with injected insulin versus islet transplant.

B-4) NICE Provisional Recommendation

1. Current evidence on the safety and efficacy of pancreatic islet transplantation does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. Clinicians wishing to undertake pancreatic islet transplantation should inform the clinical governance leads in their Trusts. They should ensure that patients offered the procedure understand the uncertainty about its safety and efficacy and that appropriate arrangements are in place for clinical audit and research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present.
2. The Advisory Committee also recommends that all cases are referred to the International Islet Transplant Registry (ITR) which is based in Germany.

C. Institute for Clinical Systems Improvement [ICSI] (January, 2002)

The following is the commentary by ICSI (2002) of islet transplantation.

With respect to pancreatic islet transplantation for patients with type 1 DM, the ICSI Technology Assessment Committee found:

1. Pancreatic islet transplantation appeared to be safe with low mortality and acceptably low morbidity.
2. Although the number of patients treated is small, recent reports suggest that the efficacy of islet transplantation with respect to insulin independence, glycemic control, and serum C peptide levels have improved in the past 2 years at certain centres. Islet allograft survival has increased from 35% to 60% or higher (values more similar to those observed following pancreas transplant). The improvement is attributed to changes in procedures for processing the islets, the number of islets transplanted, and the immunosuppressive regimens used. The reproducibility of these findings is currently being tested in multicentre studies).
3. To date, the longest reported post transplantation follow-up period in a published study is 24 months.
4. The population of patients most appropriate for transplantation remains to be determined. Due to the apparent low morbidity associated with islet transplantation, the risk/benefit analysis may include patients with less severe complications than those awaiting pancreas transplantation.
5. At present, due to difficulties with harvesting adequate numbers of islets and the need for evidence of the reproducibility (effectiveness) of the procedure, islet transplantation is not a viable treatment option for most patients with type 1 DM. No randomized controlled trials comparing islet transplants with conventional treatment have been completed or proposed.

Update to Health Technology Assessments

In the US, **Markmann et al. (2003)** examined the use of the Edmonton immunosuppressive regimen in 9 type 1 DM patients. Between February 2000 and December 2002, 144 human pancreases were processed for islets. Islet cells from 23 pancreases were isolated with the intent to transplant. Of these, 15 preparations were deemed suitable for transplantation and infused into nine patients.

To be accepted for islet transplantation patients had to have the following characteristics:

- Type 1 DM of at least 5 years duration.
- History of multiple episodes of dangerously severe hypoglycemic unawareness requiring hospitalization despite optimal management by an experienced diabetologist
- Undetectable C peptide levels measured 90 minutes after "mixed meal" stimulation by ingestion of 360 mL Boost (540 calories).

Patients were monitored with serial laboratory tests every 8 hours (x4) following the procedure, and blood glucose was determined hourly for the first 12 hours. A glucose monitoring schedule was performed daily for the first 3 months after transplant. At 3, 6, and 9 months post-transplant, the blood glucose level 1.5 hours after a Boost challenge was measured, as were serum C peptide levels before and after "mixed meal" ingestion.

Of the 9 patients transplanted, 7 patients completed the protocol that called for 2 islet transplants (unless one transplant resulted in normoglycemia). All 7 of these patients achieved insulin independence. One other patient recently transplanted was not normoglycemic and was awaiting re-transplantation (currently on one third of the pre-transplant insulin dose and free of hypoglycemic events). One patient was withdrawn from the study before receiving a second infusion.

Of the 7 patients who developed insulin independence, 5 required only a single infusion of islets and 2 gained insulin independence after a second infusion. Of the 5 preparations that rendered the patient insulin independent after a single infusion, 3 comprised islets from a single donor and 2 comprised islets combined from 2 donors.

Of the 7 patients who became insulin independent, 6 remained so. In one patient, partial graft failure occurred at 8 months, requiring resumption of insulin therapy. The patient currently requires half of the pre-transplant insulin dose. The patient demonstrated a gradual increase in fasting glucose levels before overt hyperglycemia. Whether graft dysfunction in this case resulted from graft rejection, autoimmune recurrence, or graft exhaustion is under study. The patient did not show serologic evidence of sensitization to donor antigens to date, however, this may be due to masking by the continued immunosuppression (Markmann et al., 2003).

One of the patients who became insulin independent following a single donor transplant developed mild fasting hyperglycemia 9 months post-transplant despite a C peptide level indicating stable islet function. This patient received a second infusion at 12.5 months with resumption of control.

An average of 8,246 IEq per kg per infusion was used. In 5 instances, a single infusion resulted in insulin independence. In these cases, the average total number of IEq infused was 9,282 IEq/kg recipient. In the 4 cases where a single infusion did not result in insulin independence, the average number of IEq's infused was 8,112 IEq/kg recipient. Two of these patients became

insulin independent following repeat single donor infusion and one patient awaits re-transplantation.

One patient who failed to achieve insulin independence following a single donor infusion of 9,700 Ieq/kg recipient was withdrawn form the study 3.5 months later (before re-transplantation) due to a non-healing traumatic foot wound. This patient was excluded from the survival analysis since the 2nd islet transplant was not possible.

No life threatening or otherwise serious complications occurred. A variety of minor complications were observed related either to the transplant procedure or the post-transplant medications. Development of mouth ulcerations was universal in the first 3 months. All ulcers responded spontaneously to dose reduction. Mild hematologic abnormalities were also commonly seen in the early post-transplant period. Abnormal liver function tests occurred in all patients post-transplantation but resolved spontaneously.

Unlike the Edmonton experience, however, in 5 cases success was achieved using a single infusion of islets, of which 3 preparations consisted of islets prepared from a single pancreas.

Kerr (2003) and Ault (2003) reported interim results of the ongoing multinational study of the Edmonton Protocol from the American Transplant Congress (ATC, Washington, DC, USA; May 30-June 4). A total of 49 transplants were performed in the first 36 patients enrolled at 9 of the international sites. The median follow-up time was 9.4 months.

To be eligible for the study, patients had to have type 1 DM with stable insulin requirements, a weight limit of 70 kg or less, creatinine clearance >80 mL/min, and no progressive diabetic complications. The primary endpoint of the trial is insulin independence. Secondary endpoints include metabolic parameters such as stable HbA_{1c}, glucose tolerance and stimulation tests.

To date, 52% of the patients who received any transplants are insulin independent, while 82.3% of those in whom transplants were completed are insulin independent. Some patients required 3 transplants.

Glucose control was abnormal in 92% of patients prior to islet transplantation. Glucose control was normal in 75% of patients after transplantation.

There have been no deaths in the study. There were 2 cases of severe neutropenia which were the two life threatening events to date, and 15 cases of severe adverse events, including bleeding at the percutaneous portal access site, transient elevation in liver function tests, mouth ulcerations, neutropenia, leukopenia, thrombocytopenia and hypercholesterolemia. All patients were C peptide negative prior to surgery and 94% were C peptide positive at the time of reporting.

Nineteen percent of patients received statin therapy for hyperlipidemia prior to transplantation and 39% began taking statins post-transplantation. The other 42% of patients remained statin free.

However, there was considerable variation in the success of ITA between the different multinational sites. At the Edmonton study centre, there was a 90% insulin free rate for patients who received islet cells. However, the rate was as low as 23% at other multinational centres. Shapiro suggested that the range reflected a learning curve and emphasized a need for training

and longer follow-up to define safety, quality of life issues, and the impact of possible secondary complications (Kerr, 2003).

Alejandro et al. (2003) stated that 13 of 15 patients in Miami who underwent ITA were initially insulin independent. However, there also seemed to be a partial loss of islet function or islet mass over time.

Discussion of Health Technology Assessments

AHFMR Guo et al, (2003)

Guo et al. (2003) stated that based on the limited evidence from clinical trials, ITA appears to be safe and effective in controlling labile diabetes and protecting against unrecognized hypoglycemia in highly selected type 1 diabetic patients. In a personal correspondence between Guo and Shapiro in January 2003, it was stated that the Edmonton protocol has been used in 49 non-uremic type 1 diabetic patients and 84% of these patients achieved insulin independence at 1 year of follow-up. No episode of hypoglycemia occurred after islet transplantation in any of the clinical studies (Ryan et al., 2002; Meyer et al., 1998; Goss et al., 2002). However, the follow-up for most studies was short. It has been suggested that the modifications to the conventional ITA approaches, including the steroid free immunosuppressive regimen, islet preparation in xenoprotein free media and transplantation of fresh islets from multiple donors were associated with improved rates.

The effects of ITA on beta cell function (secretion of insulin) look promising, however, the effects of ITA on pancreatic alpha cell function (secretion of counter-regulatory hormones such as glucagon and epinephrine) in long standing type 1 diabetes remain unclear. The Canadian study by Paty et al. (2002), which examined 7 patients in the Edmonton protocol series, suggested that ITA did not restore hypoglycemic hormonal counter-regulation or symptom recognition after insulin independence.

Meyer et al. (1998) in Germany assessed 3 patients before and after transplantations and determined that ITA did not restore hypoglycemia induced glucagon secretion, but it improved the response of most counter-regulatory hormones and hypoglycemic warning symptoms.

Guo et al. (2003) noted that there were major differences between the Canadian (Paty et al., 2002) and German study designs (Meyer et al., 1998):

1. The transplantation protocols and immunosuppressive regimens were different.
2. The immunosuppressive regimen was discontinued 4 weeks post transplantation in the German study.
3. The hormonal counter-regulatory responses were measured at different points of time in the 2 studies (2 months post transplantation in Meyer et al. (1998) and 1 month post transplantation in Paty et al. (2002).

The Edmonton protocol was designed to alleviate clinical problems encountered during transplantation. The dose of tacrolimus was lowered after kidney damage occurred in 2 recipients, and the dose of heparin was increased after portal venous thrombosis occurred in 2 patients (Ryan et al., 2002). The standard Edmonton protocol has recently undergone methodological changes including transplantation from a single donor, 2 layer pancreas preservation, changes in islet culture, the use of other nonsteroidal immunosuppressant strategies and preconditioning patients' immune systems (Shapiro, 2002a; Shapiro, 2002b). The advantages and disadvantages to each approach should be explored (Guo et al., 2003). For example, compared to single donor transplantation, transplantation from multiple donors may provide sufficient islets but may also cause transient increases in portal venous pressure (Casey et al., 2002). Patients who receive transplantation from multiple donors also develop a high level of antibodies which may make it more difficult to match cells or organs from other donors in the future (Shapiro, 2002b).

Guo et al. (2003) stated that the most important barriers to more widespread islet

transplantation using the Edmonton protocol are the availability of sufficient donor organs and the uncertainty of long term steroid free immunosuppressive therapy. Future challenges include (Guo et al., 2003):

Need for more trials.
Advances in single donor protocols.
Development of tolerance protocol (avoid immunosuppression).
Improvements in measures of islet mass/function to appropriately evaluate the efficacy/effectiveness of islet transplantation.
Development of effective markers of islet rejection to reverse rejection before critical function is lost.
Understanding the beneficial effects of islet transplantation on long term secondary complications of diabetes.

Since no data from controlled clinical trials were available at the time Guo et al. (2003) conducted the systematic review, Guo et al. concluded that evidence that can provide strong support of the use of ITA for a subgroup of type 1 patients is currently lacking.

Guo et al. (2003) concluded:

- Evidence on the use of ITA for non-uremic type 1 diabetic patients is limited since it is based on studies with weak methodological design. The assessment of efficacy and safety of ITA are based on several small case series or small clinical studies (Ryan et al., 2002; Goss et al., 2002; Meyer et al., 1998; Paty et al., 2002). The results from these studies were mixed since the objectives of their research and the protocols for the transplantation procedures were different at each centre even though the patients seemed to be clinically similar.
- The results regarding the effect of ITA on restoring hormonal responses to hypoglycemia are inconclusive at this time.
- The risks involved primarily related to the procedure itself and the immunosuppressive drugs. None of the serious surgical complications that may occur with whole pancreas transplantation were evident.
- Limited evidence from the Edmonton series suggested that ITA is effective in 1) controlling labile diabetes and 2) protecting against unrecognized hypoglycemia in highly selected patients in the short term. This conclusion by Guo et al. (2003) was based on the results of 11/17 insulin independent patients who were followed up for a median of 20.4 months in the trial by Ryan et al. (2002). In contrast, Paty et al. (2002) concluded that glucagon and epinephrine responses and hypoglycemic symptom recognition were not improved by islet transplantation in patients receiving the procedure in Edmonton, despite prolonged insulin independence and near-normal glycemic control.
- Limitations to the Edmonton series included:
  - The long-term effects of islet transplantation on metabolic control remain to be proven.
  - The overall long term effects of immunosuppressive regimen remain unknown.
  - There appears to be uncertainty about when to remove patients from immunosuppression therapy, particularly for patients who are insulin independent but with negative C peptide secretion.
  - Research is required to determine which monitoring tests correlate to glycemic control as a patient can be considered insulin independent but has severely impaired islet function as indicated by their C peptide secretion.
- ITA in non-uremic type 1 diabetic patients with hypoglycemia unawareness or uncontrolled diabetes is an evolving procedure with promising results but is not yet considered a "standard of care".
- The Immune Tolerance Network initiated an international multicentre clinical trial to replicate the Edmonton protocol. Data from the trial will help to determine the reproducibility of the benefits of ITA reported to date.

NICE (2003)

Overall, the review by NICE was weak. The methods for the NICE rapid review were not stated, the literature search cutoff dates were not reported, and inclusion/exclusion criteria were not stated. The study assessed by White et al. (2001) was not a systematic review and the methods within that paper were poorly reported. The preliminary review by NICE (2003) did not include studies that used the Edmonton protocol (for example Shapiro et al., 2000). It is unclear as to why papers that examined the Edmonton protocol were not included in the literature search.

ICSI (2002)

Overall conclusions were similar to those of Guo et al. (2003) and NICE (2003).

Markmann et al. (2003)

In the initial Edmonton reports, islets harvested from 16 donors were required to achieve insulin independence in 7 recipients (Shapiro et al., 2000). Markmann et al. (2003) cautioned that this may significantly underestimate the actual number of donors required per recipient, since it does not include those donor pancreases processed for transplantation but from which the preparation was not suitable for transplantation. Inclusion of these failed isolations may double the total number of donors procured per recipient. As such, the cost alone of multiple donors per recipient may impede widespread application of islet transplantation as an accepted therapy.

- Markmann et al. (2003) did not examine the response of counter-regulatory hormones and hypoglycemic awareness before and after ITA.
- Limitations for the study by Ryan et al. (2002) also apply to the study by Markmann et al. (2003).
- Insulin independence was achieved by a single islet transplant with islet cells isolated from one or two donors in pre-uremic diabetic recipients.
- Some patients required one transplant while the Edmonton group and others required multiple transplants. This may be due to the larger number of islets that were isolated from each donor pancreas than the Edmonton workers. In the Edmonton series, on average each infusion composed approximately 360,000 IEq. Markmann et al. (2003) averaged more than 540,000 IEq per infusion.
- A larger donor may have a pancreas that has a greater islet mass. A number of trends were revealed:
  - Recipients gaining insulin independence with a single infusion tended to weigh less, have lower BMIs, have a smaller daily insulin requirement ($p<0.05$), and required less insulin/kg.
  - Donors of successful single infusion preparations were larger, with a greater average BMI.

In a recent review of islet transplantation, Robertson (2004) discussed the following limitations to the procedure:

- Critics question the need for the purification step in the islet preparation process because it adds time, can cause the loss of 30-50% of islets and traumatizes the remaining islets that are harvested.
- It is unsure if the liver is the optimal site for islet infusion. Potential complications of an infusion into the liver include bleeding, portal venous thrombosis and portal hypertension. Anticoagulant agents are used to prevent clotting, however,

anticoagulation can promote bleeding at the sites of the percutaneous needle punctures. In addition, intrahepatic islets may be exposed to environmental toxins and potentially toxic prescribed medications absorbed from the gastrointestinal tract and delivered into the portal vein. Furthermore, intrahepatic islets are unable to release glucagon during hypoglycemia (Paty et al., 2002).

- The Edmonton trial design did not include a similar and concurrent control cohort. The observation period before transplantation was not as long or as intense as the observation period after transplantation. Therefore, extensive paired analysis of pre-transplantation and post-transplantation clinical data are not possible. It is unknown if 2 islet infusions a month apart are essential because recipients were not randomly assigned to receive either one infusion or two.
- The definition of success. The typical candidate has recurrent hypoglycemia with poor recognition of the resulting symptoms and abnormal glycosylated hemoglobin values. The use of a rigorous definition of success means recipients no longer use insulin, do not have hypoglycemia and poor recognition of symptoms and have normal glucose levels and glycosylated hemoglobin values for prolonged periods. The use of a more flexible definition means that the main problems that resulted in transplantation in the first place (frequent hypoglycemia with poor symptom recognition, poor quality of life and abnormal glycosylated hemoglobin values) have been solved. The more flexible view allows the use of oral hypoglycemic drugs and residual impaired glucose tolerance and is supported by some experts in the field (Luzi et al., 2001) but not all.
- Robertson (2004) suggested that the increase in quality of life, satisfaction with the procedure, and tolerance of adverse drug effects are likely to be greater among recipients of combined pancreas and kidney transplants than recipients of an islet transplant alone because the former group of patients is typically more ill to begin with. This outcome leads some clinicians to conclude that simultaneous kidney and islet transplantation or islet transplantation after kidney transplantation is the preferred approach, rather than the transplantation of islets in patients without any renal failure (Robertson, 2004).
- There are no data that allow firm conclusions to be drawn about who should receive this therapy (Robertson, 2004). Continuing improvements in the medical management of diabetes invalidate the use of data from historical controls (Robertson, 2004).
- Robertson (2004) suggested that if randomization is not possible, a case-control approach that includes patients who qualify for but decline to undergo the procedure could be used. Furthermore, subgroups should be stratified according to the secondary complications of diabetes and to whether islets are transplanted alone or in conjunction with a kidney.
- Demand for islet transplantation far exceeds the number of islets available.
- Robertson (2004) stated that the worldwide success rate of pancreas transplantation renders it the more effective procedure, especially since it uses only one donated organ.

United States Food and Drug Administration (2003)

In a summary of islet transplantation, the **US FDA (2003)** stated that although the results from clinical studies appear promising, there are significant issues that remain before the technique can be considered for widespread application. These include:

- **Limited Islet Supply**
  Based on the number of pancreas donors in the US each year, only a limited number are

suitable for transplant. The technique to isolate islets has not been perfected.

- **Toxicity of Immunosuppression**
- **Normal Blood Sugar Levels Not Achieved**
  Islet transplant patients appear to be able to have better control of their blood sugar levels compared to those who achieve it with insulin, diet, and exercise. However, only a small percentage of transplant patients achieve normal blood sugar levels.
- **Long-Term Safety**
  Gaining access to the portal vein of the liver to transplant islets is a difficult procedure and involves some risks. The immediate risks include portal vein thrombosis and bleeding. The long-term consequences are not known, but reports of hepatic steatosis have been documented. This happens when fat globules collect within the cells of the liver and cause the tissue to deteriorate and malfunction.
- **Duration of Islet Allograft Function**
  It is not known how long islets will function after transplantation, and whether patients need multiple transplants.
- **Effect on Diabetic Complications**
  Controversy remains regarding whether a transplant can stop or reverse secondary complications related to diabetes. It is also unclear whether transplantation will ultimately extend a patient's long-term survival rate.

ECONOMIC ANALYSIS

Literature Review

No formal economic analysis of islet transplantation was identified in the literature search.

Islet transplantation is currently performed within the setting of controlled research studies and the exact cost is unknown (ICSI, 2002). In addition to the costs of the transplantation procedure, there are costs associated with procuring the pancreas and isolating and purifying the islets. With the added costs, it was estimated by ICSI that the cost of islet transplantation is comparable to the cost of whole organ transplantation (ICSI, 2002).

In Alberta, the cost of each transplant is approximately $70,000 (CDN). However, most patients need two ITA procedures to increase their insulin levels. Therefore, the average cost of the procedure may be in the range of $140,000 (CDN).

OVERALL SUMMARY & CONCLUSION

- In a health technology assessment from Alberta, Guo et al. (2003) stated that limited evidence from the Edmonton series suggested that ITA is effective in 1) controlling labile diabetes and 2) protecting against unrecognized hypoglycemia in highly selected patients in the short term. This conclusion by Guo et al. (2003) was based on the results of 11/17 insulin independent patients who were followed up for a median of 20.4 months in the trial by Ryan et al. (2002). In contrast, Paty et al. (2002) concluded that glucagon and epinephrine responses and hypoglycemic symptom recognition were not improved by islet transplantation in patients receiving the procedure in Edmonton, despite prolonged insulin independence and near-normal glycemic control. Paty et al. (2002) (a member of the Edmonton team) examined 7 ITA recipients, 7 type 1 DM patients (nonITA), and 7 nondiabetic control patients.
- Conclusions are based on studies providing Level 4 evidence.
- The follow-up for most studies was short. It was suggested that the modifications to the conventional ITA approaches, including the steroid free immunosuppressive regimen, islet preparation in xenoproteins free media and transplantation of fresh islets from multiple donors were associated with the success.
- The effects of ITA on beta cell function (secretion of insulin) look promising, however, the effects of ITA on pancreatic alpha cell function (secretion of counter-regulatory hormones such as glucagon and epinephrine) in long standing type 1 diabetes remain unclear.
- The Edmonton protocol was designed to alleviate clinical problems encountered during transplantation.
  - The dose of tacrolimus was lowered after kidney damage occurred in 2 recipients, and the dose of heparin was increased after portal venous thrombosis occurred in 2 patients (Ryan et al., 2002).
  - Recent changes to the standard Edmonton protocol have included transplantation from a single donor, 2 layer pancreas preservation, changes in islet culture, the use of other nonsteroidal immunosuppressant strategies and preconditioning patients' immune systems.
  - The advantages and disadvantages to these approaches should be explored (Guo et al., 2003).
- Guo et al. (2003) stated that the most important barriers to more widespread islet transplantation using the Edmonton protocol are the availability of sufficient donor organs

and the uncertainty of long term steroid free immunosuppressive therapy. Future challenges include:

Need for more trials of islet transplantation.
Advances in single donor protocols.
Development of tolerance protocol to reduce therapeutic risk (avoid immunosuppression altogether).
Developments in alternative insulin producing sources.
Improvements in measures of islet mass/function to appropriately evaluate the efficacy/effectiveness of islet transplantation.
Development of effective markers of islet rejection to allow the possibility of reversing episodes of rejection before critical function losses.
Understanding of the beneficial effects of islet transplantation on long term secondary complications of diabetes.

- Because the number of cadaveric pancreas donors is inadequate to the treat the increasing numbers of individuals on organ transplant waiting lists, isolated islet transplantation is unlikely to become practical for treatment of diabetes if each recipient requires islets from several (2-4) donors (especially since whole pancreas transplantation requires only a single donor organ) (Markmann et al., 2003). Therefore, it is important that the experience of the Edmonton investigators be validated by other centres not only in terms of effectiveness of the new immunosuppressive protocol, but also in the need for multiple transplants (Markmann et al., 2003).
- Preliminary results from the multinational trial indicate wide variation in the success of ITA between different sites. This raises concern about the reproducibility of the results.

Conclusion

- The current evidence on the use of ITA for non-uremic type 1 diabetic patients is limited since it is based on studies with weak methodological design (Level 4). The assessment of ITA is based on several small case series studies or small clinical studies (Ryan et al., 2002; Goss et al., 2002; Meyer et al., 1998; Paty et al., 2002). The results from these studies were mixed since the objectives and the protocols for the transplantation procedures were different at each centre. In particular, many jurisdictions have, to date, been unable to reproduce results achieved in Edmonton (success rate of 23% versus 90%)– this is the focus of an ongoing multicentre study.
- Ryan et al. (2002) reported that the median follow-up time for the 17 patients undergoing the Edmonton Protocol was 20.4 months from the first transplant. As of January, 2002, 11/17 patients remained insulin independent. Three of the 11 insulin independent patients had negative C-peptide secretion, indicative of impaired islet cell function.
- The effect of ITA on restoring hormonal responses to hypoglycemia are inconclusive. Two small studies specifically examined the effects of ITA on restoring hypoglycemia induced hormonal counterregulation and hypoglycemia awareness in type 1 DM patients for 12 and 2 months respectively. Results from the two studies were contradictory. The larger study (Paty et al., 2002) examined 7 patients who received the ITA procedure in Edmonton compared to 7 nonITA type 1 DM patients compared to 7 nonDM control patients. Paty et al. (2002) concluded that glucagon and epinephrine responses and hypoglycemic symptom recognition were not improved by islet transplantation, despite prolonged insulin independence and near-normal glycemic control.
- ITA in non-uremic type 1 diabetic patients with hypoglycemia unawareness or uncontrolled diabetes is an evolving procedure with promising preliminary results, but inconclusive final results.
- There are significant methodological problems that need to be addressed and which are presumable responsible for non-reproducibility of ITA between centres. The results of the Immune Tolerance Network Study will be important in this regard.
- Limited islet supply could represent an important rate limiting step to uptake of this technology.

- Until more consistent data are available, this technology should be regarded as experimental.

Existing Guidelines Regarding the Utilization of the Technology

There are currently no specific clinical guidelines for ITA.

American Diabetes Association (2004)
The American Diabetes Association (2004) stated:

1. "Pancreas transplantation should be considered and acceptable therapeutic alternative to continued insulin therapy in diabetic patients with imminent or established end-stage renal disease who have had or plant to have a kidney transplant, because the successful addition of a pancreas does not jeopardize patient survival, may improve kidney survival and will restore normal glycemia. The pancreas transplant may be done simultaneous to, or subsequent to, a kidney transplant. Pancreas graft survival is better when done simultaneous to a kidney transplant."

2. "In the absence of indications for kidney transplantation, pancreas transplantation should only be considered a therapy in patients who exhibit these 3 criteria: 1) a history of frequent, acute, and severe metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention; 2) clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and 3) consistent failure of insulin-based management to prevent acute complications."

3. "Pancreatic islet transplants hold significant potential advantages over whole gland transplants. Islet transplantation is an experimental procedure, also requiring systemic immunosuppression and should be performed only within the setting of controlled research studies".

Canadian Diabetes Association Clinical Practice Guidelines (2001) [Yale et al., 2002]
Insulin therapy characterized by increased frequency of glucose monitoring, increase in the glucose targets, and multiple insulin injections with increased glucose targets is recommended to be used for individuals with hypoglycemia unawareness.

Neither pancreas transplantation nor islet transplantation were mentioned in these guidelines as treatment options for this group of patients. Guo et al. (2003) contacted experts at the Canadian Diabetes Association who failed to provide any comments on the roles of pancreas transplantation or islet transplantation in the management of type 1 diabetes with severe hypoglycemia and hypoglycemia unawareness.

At present, intensive insulin therapy with special caution should be considered the standard of care for this group of patients (Guo et al., 2003). Guo et al. (2003) stated that the problem with this strategy is that glycemic control will be compromised to reduce the risk of hypoglycemia and increase the possibility of long term diabetic complications.

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Appendix

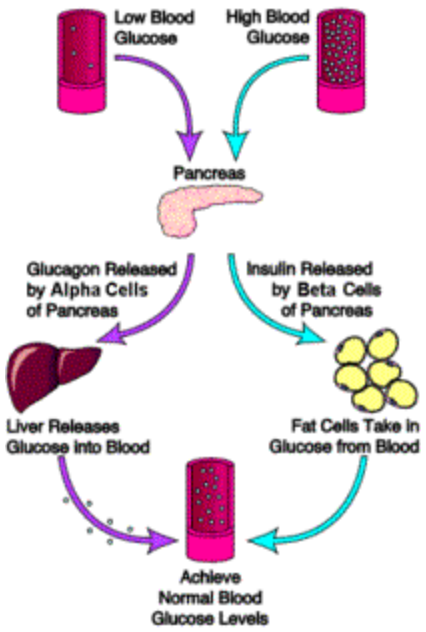

Figure 1. Role of Insulin and Glucagon. From: Pancreatic islet transplantation to treat type 1 diabetes. General information – September 10, 2003. Center for Biologics Evaluation and Research. US Food and Drug Administration. www.fda.gov/cber/genetherapy/pancislet.htm. Accessed September 16, 2003.

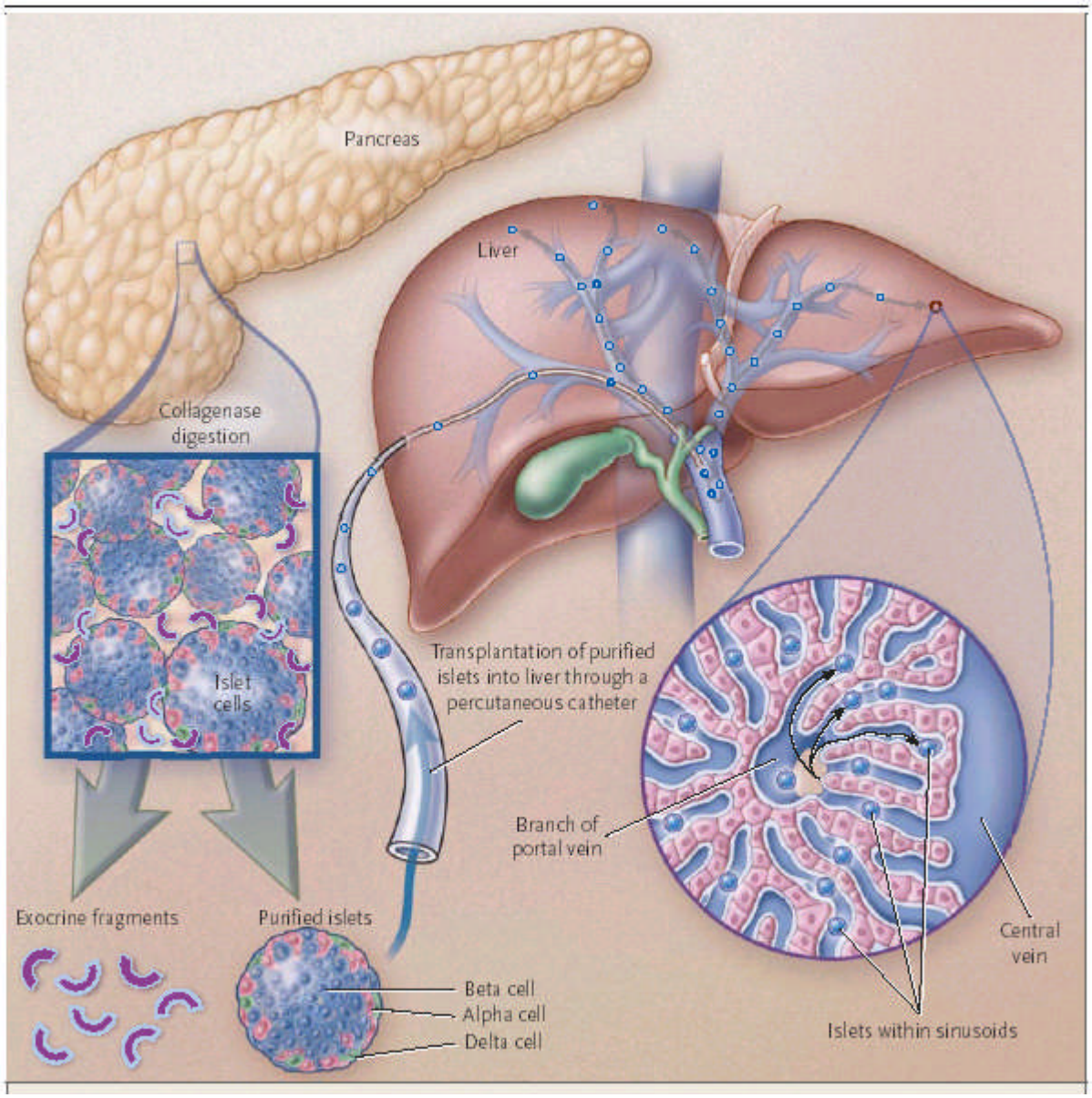

Figure 2. The process of islet transplantation. A pancreas is obtained from a donor. The pancreas is digested with collagenase to free the islets from surrounding exocrine tissue. The freed islets, containing mostly beta and alpha cells, are purified by density–gradient centrifugation to remove remaining exocrine cellular debris. The purified islets are infused into a catheter that has been placed percutaneously through the liver into the portal vein, whence they travel to the liver sinusoids. From Robertson, 2004.

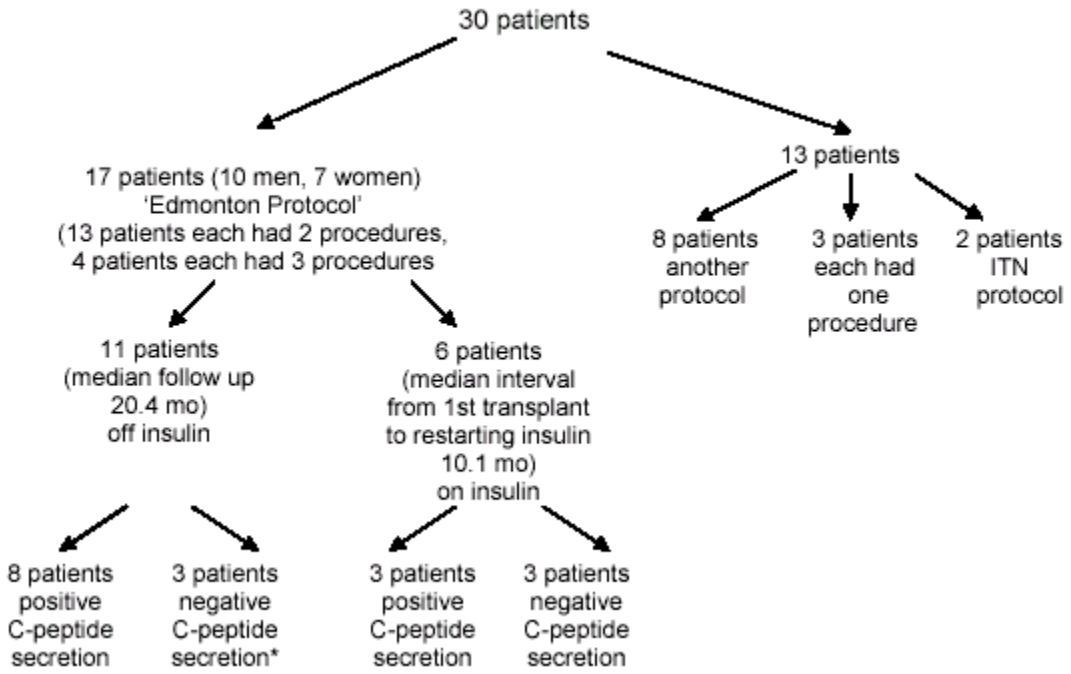

Figure 3. Followup of Edmonton case series. From Guo et al. (2003).

***Note:** Patients can be considered insulin independent but have severely impaired islet function.

Alberta Foundation for Diabetes Research
Clinical Islet Transplant Patient Selection Criteria for Assessment
From: http://www.afdr.ab.ca/trans_req.html.

The Clinical Islet Transplant Team would be pleased to consider Type 1 (C-peptide negative) diabetic individuals with the following indications for islet transplantation.

1. Severe hypoglycemic unawareness
As defined by at least two hypoglycemic reactions in the last 12 months that require outside help by someone other than the patient, and where the onset of hypoglycemia was not adequately felt by the patient.

OR

2. Brittle diabetes
As defined by:

- Metabolic instability sufficient to cause major disruption to the lifestyle or to endanger the life of the diabetic patient despite use of an optimal insulin regimen of glucose monitoring four times per day, and a TID/QID or CSII insulin regimen.

- Metabolic instability manifested by chaotic profiles of blood glucose as assessed by:
  - The number of hypoglycemic or ketoacidotic episodes (i.e. two episodes requiring hospital assistance for either hyper or hypoglycemia in the last 12 months).
  - Increased Mean Amplitude of Glycemic Excursion (>6.6mmol/l, where normal should be <3.5mmol/l).
- Disruption in lifestyle as assessed by the number of emergency admissions to hospital per year (2 or more), or the time absent from work or school (4 weeks or more), or unable to care for self or others in the household/home.

OR

3. Progressive secondary diabetic complications with the potential for reversal.
Despite an optimal insulin regime of glucose monitoring four times per day and a TID/QID/CSII insulin regime for more than six months:

- Microalbuminuria progressing despite being on an ACE inhibitor.
- Difficulties with peripheral or autonomic neuropathy.
- Proliferative retinopathy.

Contradictions to Clinical Islet Transplantation

1. Severe co-existing cardiac disease.
   - Recent MI (within the past 6 months)
   - Angio evidence of non-correctable CAD
   - Ejection fraction <40%
2. Active alcohol or substance abuse – includes cigarette smoking (must be abstinent for 6 months).
3. Major psychiatric illness.
4. History of non-compliance. If any question a compliance contract must be entered and compliance demonstrated for at least 3 months.
5. Active infection including hepatitis C, hepatitis B, HIV, or positive Mantoux test (unless previously immunized with BCG).
6. History of malignancy (unless disease free for at least 5 years).

7. Obesity (BMI >30).
8. C-peptide (i.e. ≥0.2ng/ml).
9. Inability to provide informed consent.
10. Age less than 18 or greater than 65 years.
11. Creatinine clearance < 45ml/min.

Table 1. Efficacy of ITA for non-uremic type 1 DM patients. From Guo et al., 2003.

Study/objective	Patient	Intervention	Outcome	
Ryan et al. 2002 Canada Report longer term outcomes of islet transplantation and delineate issues related to the procedure.	N=17 Type 1 non-uremic DM patients with severe hypoglycemia Duration of DM=mean 27.2±2.8 years Age=mean 39.7±2.0 years N=10 volunteers were studied as controls for metabolic tests.	ITA Number of donor pancreas used=2-4 Number of islets transplanted=mean 12,330±581 IE/kg Immunosuppression=sirolimus Tacrolimus Daclizumab Followup=median 20.4 months (range 3.2-34.2 months) from first transplant.	**Insulin independence** 80% insulin independence at 1 year after first transplantation. 4/6 patients were insulin independent after 2 years post transplantation. **HbA_{1c}** 8.48±0.49 (pre transplant) vs. 5.8±0.13 (most recent value post transplant), p<0.001) in 11 patients who were off insulin. **C Peptide** C peptide response improved after transplantation and stimulated C peptide values were equivalent to controls. Of the 11 patients off insulin, 8 had a detectable C peptide secretion. Fasting C peptide was maintained over prolonged follow-up. **Hypoglycemia** All patients off insulin had stable glucose values and did not have hypoglycemic reactions.	Prol be a acut and imm insu adeq glyc rema bene
Goss et al. 2002 USA To report transplantation experience with type 1 DM patients using pancreatic islets processed at an established remote pancreatic islet isolation centre.	N=3 Type 1 non-uremic DM patients with severe hypoglycemia and metabolic instability. C peptide not detected in any of the patients before transplantation. Duration of DM=at least 5 years.	ITA Number of donor pancreas used=1-2 Number of islets transplanted= Pt 1. 13,375 IEQ/kg Pt 2. 19,703 IEQ/kg Pt 3. 10,240 IEQ/kg Immunosuppression= Sirolimus Tacrolimus Daclizumab Follow-up= Pt 1 4 mos Pt 2 3 mos Pt 3 0.5 mos	**Insulin independence** All 3 patients attained sustained insulin independence after first transplantation. **HbA_{1c}** Pt 1: 8.7% (pre-transplant) vs. 5.7% (post-transplant) Pt 2: 9.1% (pre-transplant) vs. 5.9% (3 mos post transplant) Pt 3: data not available **C Peptide** Serum C peptide was not detectable in any of the 3 patients (<0.05 ng/mL) before transplantation. All 3 patients consistently had a fasting C peptide level >1.5 ng/mL (normal 0.09-1.9 ng/mL) after ITA **Hypoglycemia** None of the patients had an episode of hypoglycemia after ITA	Insu by p usin rem panc and at a
Meyer et al. 1998 Germany To test hypothesis that successful intraportal islet transplantation could improve hormonal glucose counterregulation and hypoglycemia awareness in patients with long standing type 1 DM	N=3 Type 1 non-uremic DM patients with severe hypoglycemia Duration of DM=20-34 years. N= 10 normal controls matched by age and body index	ITA Number of donor pancreas used=1 Number of islets transplanted= Pt 1. 440,000 IE Pt 2. 964,000 IE Pt 3. 565,000 IE Immunosuppression= Methypredinisolone Cyclosporine Monoclonal antiCD4 mice antibody All immunosuppressive drugs were stopped 4 wks after transplant Followup= Approximately 2 months	**Insulin independence** Achieved in 1 patient over 14 days and insulin requirement reduced in the other 2 patients after transplantation. Islet transplants were rejected 2 months after withdrawal from immunosuppressive therapy in all patients. **HbA_{1c}** No significant change occurred post transplant **C Peptide** Absent in all 3 pts before transplantation. 2-3 wks post transplantation basal plasma C peptide level averages 0.27, 0.65, and 0.41 nmol/L in 3 pts, respectively. Basal C peptide levels <0.16 nmol/L approximately 2 months after withdrawal from immunosuppressive therapy in all patients. **Hypoglycemia** No severe hypoglycemia occurred within 2 months post transplantation. **Hormonal response** No improvement in the glucagon response one month after successful transplantation. Glycemic thresholds and or peak incremental response to epinephrine, norepinephrine and cortisol improved in all patients post transplantation. All pts developed autonomic warning symptoms.	Intra not r gluc resp horm rege sym stan trans alter sele who hypo patie mon safe
Paty et al., 2002 Canada To determine whether glucagon and epinephrine responses and hypoglycemic symptom recognition are improved after successful islet transplantation.	N=7 (first 7 recipients in the Edmonton series as reported in Shapiro et al) Type 1 DM with hypoglycemia unawareness and severe metabolic instability. Duration of diabetes: mean 27+6 years N=7 controls with type 1 DM (matched by age and weight) N=7 normal controls (matched by age and weight).	ITA Number of donor pancreas : 2-4 Number of islets transplanted: 11,547±1,604 IE/kg Immunosuppression: Sirolimus Tacrolimus Daclizumab Followup: Mean duration of insulin independence for all patients was 12.6±0.6 months from the time of the final islet infusion.	**Insulin independence** Achieved in all 7 patients. Mean duration of insulin independence was 12.6±0.6 mos from the time of the final islet infusion. **HbA_{1c}** Data on HbA1c not available. No significant differences in the mean fasting and sequential 45 min glucose levels among the 3 groups. **C Peptide** No significant differences in the plasma C-peptide levels between islet transplant recipients and control subjects. **Hypoglycemia** None of the patients had an episode of hypoglycemia until plasma glucose level ≤50 mg/dL **Hormonal responses** No significant rise in the mean plasma glucagons level in transplanted group during the clamp. The mean incremental glucagon response (basal to 180 min) of the transplanted group was significantly less than that of	The prov inde glyc long hypo cour reco intra

			normal control group ($p<0.05$) and was not significantly different from that of the type 1 diabetic group. Overall no significant rise in plasma epinephrine. Mean incremental epinephrine response (basal to 180 min) of transplanted group was significantly less than that seen in the control group ($p<0.05$), and was not significantly different from that of patients with long standing type 1 diabetes.	

Table 2. Safety of Islet Transplantation. From: Guo et al. (2003).

Study	Procedure related complications	Immunosuppression related complications
Ryan et al. 2002 Followup: median 20.4 months (range 3.2-34.2) in 17 patients who completed the Edmonton Protocol.	Transient bradycardia n=2 Moderate bleeding at the site of the transhepatic puncture n=5 (4 patients required blood transfusion and one patient required transfusion and surgery) Thrombosis of aperipheral branch of the right portal vein n=2 Moderate abdominal pain n=12 Puncture of the gallbladder n=2 Abnormal liver function test (in 46% of cases, liver function test results rose to more than twice normal levels and returned to normal within a median time of 22 days post transplant)	Significant increase in serum creatinine (2 patients had elevated creatinine levels pre-transplant) Increase in urine protein n=4 Mild and superficial mouth ulcers n=15 Acne n=2 Arthralgias n=1 Rheumatoid arthritis n=1 Diarrhea n=10 Anemia n=8 Decrease in white blood cell counts (number of patients not reported)
Goss et al. 2002 Followup: 4, 3, and 0.5 months respectively.	No procedure related complications occurred.	No immunosuppression related complications occurred.
Meyer et al. Followup: approximately 2 months in 3 patients	Data not available	Data not available

Table 3. Summary of key efficacy and safety findings. From: NICE, 2003.

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key relia
White et al. (2000) Systematic review Search date: 2000 Identified 405 patients who received donor cell islet cell transplantation.	Overall rates of injected insulin independence not reported. In 267 patients with diabetes and renal failure independent of injected insulin for more than 7 days =12%.	Not reported	Search of Me Islet Transpla Methods repo Quality of ind systematicall
Wahoff et al. (1995) Case series Minnesota USA 1975-1995 48 patients who received transplants of their own islet cells after pancreatectomy; mean age 35 years (range 12-60) Median followup=5 years (range 1 month to 17 years)	Pain relief=83% Independent of injected insulin at 1 month=51% Independent of injected insulin at follow-up between 2 and 10 years=34%	Perioperative death=1 patient Duodenal ischemia=3 patients Abcess=2 patients Portal vein thrombosis on injection of islet cells=1 patient Splenic bleeding following injection of islet cells=2 patients	Uncontrolled Outcomes ap Followup long
Valente et al., 1986. Case series Genoa Italy 1978-1986. 27 patients who received transplants of their own islet cells after pancreatectomy; age range 35-57 years Followup =7 years.	Independent of injected insulin=16(59%) Diabetic=8(30%)	"no complications" Deaths at followup=3 (11%)	Uncontrolled Cases not de Followup long
White et al. (2001) Case series Leicester, UK 1994-1999 24 patients who received transplants of their own islet cells after pancreatectomy; median age =44 years. Followup 15 months to 5 years.	Independent of injected insulin=3 patients Still requiring opiate analgesia=23%	Duodenal ischemia=3 patients Splenic infarct=1 patient Partial portal vein thrombosis=1 patient Splenic vein thrombosis=1 patient Intraabdominal adhesions=6 patients Failure to relieve pain=4 patients Death within 30 days=1 patient	Uncontrolled Cases descri Outcome app Followup long

Table 4. Smaller case series for islet implantation. From NICE, 2003.

Reference	Number of study participants
Farney et al. (1991)	26 patients - likely to overlap with people in Wahoff et al. (1995)
Oberholzer et al. (2000)	13 patients who had pancreas removed
Sutherland et al. (1984)	13 patients
Morrow et al., (1984)	10 patients
Najarian et al. (1980)	10 patients