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ORIGINAL ARTICLE

First World Consensus Conference on pancreas transplantation: Part II – recommendations

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Abbreviations: AGREE II, appraisal of guidelines for research and evaluation II; BMI, body mass index; CDC, complement-dependent cytotoxicity; CMV, cytomegalovirus; CNI, calcineurin inhibitor; DBD, donation after brainstem death; DCD, donation after circulatory death; DSA, donor-specific antibody; GRADE, grading of recommendations, assessment, development and evaluations; HLA, human leukocyte antigens; HTK, histidine-tryptophan-ketoglutarate; IGL-1, Institut Georges Lopez-1; IPTR, International Pancreas Transplant Registry; m-TOR, mechanistic-target of rapamycin; OPTN, Organ Procurement and Transplantation Network; PAK, pancreas after kidney transplant; PRA, panel reactive antibody; PTA, pancreas transplant alone; SIGN, Scottish Intercollegiate Guidelines Network; SPK, simultaneous kidney and pancreas transplant; UNOS, United Network for Organ Sharing; UW, University of Wisconsin.

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The First World Consensus Conference on Pancreas Transplantation provided 49 jury deliberations regarding the impact of pancreas transplantation on the treatment of diabetic patients, and 110 experts' recommendations for the practice of pancreas transplantation. The main message from this consensus conference is that both simultaneous pancreas-kidney transplantation (SPK) and pancreas transplantation alone can improve long-term patient survival, and all types of pancreas transplantation dramatically improve the quality of life of recipients. Pancreas transplantation may also improve the course of chronic complications of diabetes, depending on their severity. Therefore, the advantages of pancreas transplantation appear to clearly surpass potential disadvantages. Pancreas after kidney transplantation increases the risk of mortality only in the early period after transplantation, but is associated with improved life expectancy thereafter. Additionally, preemptive SPK, when compared to SPK performed in patients undergoing dialysis, appears to be associated with improved outcomes. Time on dialysis has negative prognostic implications in SPK recipients. Increased long-term survival, improvement in the course of diabetic complications, and amelioration of quality of life justify preferential allocation of kidney grafts to SPK recipients. Audience discussions and live voting are available online at the following URL address: http://mediaeventi.unipi.it/category/1st-world-consensus-conference-of-pancreas-transplantation/246.

KEYWORDS
clinical research/practice, diabetes, pancreas/simultaneous pancreas-kidney transplantation, survey

1 | INTRODUCTION

Guidelines are available for transplantation of all solid organs but the pancreas and the intestine.[1–13] Unfortunately, pancreas transplantation is a relatively low volume but high complexity procedure that has never gained widespread acceptance. For instance, many of the medical protocols used in pancreas transplantation are borrowed from other types of transplantation, mostly from the kidney, and all immunosuppressive drugs are used off-label in pancreas transplantation.[14] In addition, because most pancreas transplants are performed as either simultaneous pancreas-kidney (SPK) or pancreas after kidney (PAK) transplants, the majority of recipients suffer from advanced diabetic nephropathy, a condition that has been associated with an increase in all-cause mortality due to higher incidence of micro- and macrovascular complications of diabetes.[15] Few patients are referred for pancreas transplant alone (PTA) at a stage when extrarenal diabetic complications might be reversible. Although many uremic patients can still receive a pancreas transplant in conjunction with a kidney transplant, the high prevalence and severity of associated chronic complications of diabetes cause these recipients to be less likely to experience stabilization or reversal of progressive diabetic complications.[16,17]

In recent years, there has been a decline in the number of pancreas transplants in the United States, Europe, and the United Kingdom.[18–20] Although the reasons for this decline are multifactorial, the lack of objective assessment of the impact of pancreas transplantation on the treatment of diabetic patients and absence of validated practice guidelines may be among the contributing factors. In selected patients, pancreas transplantation provides dramatic improvements in quality of life[21–35] and may prolong survival.[33–39] Additionally, some traditional deterrents have been minimized because pancreas transplantation currently requires the same immunosuppression as kidney transplantation[40] and surgical complications are observed at lower rates.[41]

We report herein the expert recommendations for the practice of pancreas transplantation developed during the First World Consensus Conference on Pancreas Transplantation held in Pisa, Italy, on October 17–19, 2019. We also report several additional deliberations on the impact of the different types of pancreas transplantation on the course of diabetes that were crafted by an independent jury following an exhaustive review and presentation of data from the literature and audience discussions with experts.

2 | SUMMARY OF METHODS

The methods used to achieve the consensus were presented in detail in a dedicated manuscript.[42]

Briefly, the steering committee defined 144 questions (grouped in 12 topics). The 12 topics were categorized into two key domains. The first domain (three topics—35 questions) included "nontechnical" issues related to the impact of SPK transplant, PAK transplant, and PTA on the management of patients with diabetes. The second domain (nine topics—109 questions) dealt with technical issues related to the practice of pancreas

transplantation. A systematic literature review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions for each topic and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[43,44] Quality of evidence was assessed using the SIGN (Scottish Intercollegiate Guidelines Network) methodology.[45] Questions in the first domain were assessed using the Zurich-Danish model[46] that charges an independent jury to draw the final deliberations. Questions in the second domain were assessed and approved by a panel of experts in pancreas transplantation and were validated by a distinct group of experts using the AGREE II instrument (Appraisal of Guidelines for Research and Evaluation II).[47] Jury deliberations and expert recommendations received a GRADE rating (Grading of Recommendations, Assessment, Development and Evaluations).[48] Consensus (agreement rate ≥85%) was reached by two online Delphi rounds and was finalized, after on-site discussions and live voting (Pisa, Italy, October 18 and 19, 2019).

Audience discussions and live voting are available online at the following URL address: http://mediaeventi.unipi.it/category/1st-world-consensus-conference-of-pancreas-transplantation/246

3 | DEFINITIONS

Sensitization (or sensitized patient) was defined as the presence of circulating antibodies directed against human leukocyte antigens (HLA).[49] High sensitization (or highly sensitized patients), was defined as a panel reactive antibody (PRA) >85%.[50]

Obesity was defined according to World Health Organization (i.e., body mass index [BMI] ≥30 kg/m^2).[51] Obesity classes (i.e., class I, class II, and class III) and ethnic variations that affect obesity definition were not considered due to lack of granular data in available literature.

Preemptive SPK transplantation was defined as the combined transplantation of a pancreas and a kidney in patients with stage 4/5 chronic kidney disease before they initiate dialysis.

4 | RESULTS

4.1 | Jury deliberations

The jury could not deliberate on two queries, due to lack of evidence, and released 49 deliberations. No deliberation was graded 1A. Twenty-three of 49 deliberations could not be graded. The remaining 26 deliberations were rated GRADE 2B (n = 22) and GRADE 2C (n = 4) (Figure 1A).

Jury deliberations are reported in Tables 1-3.

4.2 | Experts' recommendations

Experts released 110 recommendations. No recommendation was graded 1A. Fifty-one recommendations could not be graded. The remaining 59 recommendations were rated GRADE 1B (n = 13), GRADE 1C (n = 2), GRADE 2A (n = 2), GRADE 2B (N = 20), and GRADE 2C (n = 22) (Figure 1B).

Experts' recommendations are reported in Tables 4-12.

5 | DISCUSSION

This world consensus conference provides the first practice guidelines for pancreas transplantation. Islet cell transplantation, which is a further therapeutic option for beta-cell replacement in selected diabetic patients, was intentionally not addressed. Some of the recommendations provided for pancreas transplantation might also apply to islet cell transplantation, but this was not the aim of this consensus conference and no commitment exists for their use in this setting.

This consensus conference provided 49 jury deliberations and 110 expert recommendations. It is interesting to note that no statement achieved GRADE 1A, as no meta-analysis of prospective and randomized trials exists on discussed issues. Approximately 40% of approved statements could not be graded while an additional 10% resulted in extremely weak recommendations. This is probably the combined result of difficulties in designing and conducting clinical studies in the setting of a rarely performed procedure, lack of interest from stakeholders, paucity of investments from pharmaceutical companies in clinical trials, and the long period in which surgeons had to achieve clinical success rather than scientific evidence. On practical grounds, in pancreas transplantation, there are still many issues for which practice is not strongly supported by evidence, despite excellent clinical results.[21–39]

5.1 | Jury deliberations—impact of SPK

The jury deliberated that SPK transplantation improves both quality of life and long-term survival of patients with insulin-dependent diabetes in comparison to current medical treatments and other transplant options.[33,34,37,38,52–60] These deliberations were not based on a high level of evidence and applied more strictly to patients with type 1 diabetes. In patients with type 2 diabetes, it was not clear if SPK transplant conveyed a survival advantage over live donor renal transplantation alone, while it was deemed convenient over both dialysis and deceased donor kidney transplantation.

The association between SPK transplant and improved survival in type 1 diabetic recipients was reported several times.[33,34,37,38,52–59] The acknowledgment of this advantage by an independent jury prompts the transplant community to further pursue SPK transplantation, especially when a live kidney donor is not available.

The jury also provided deliberations regarding the value of SPK transplantation performed in preemptive recipients.[61–63] This is a key issue, considering donor shortage and the need to maintain a balance between equity and efficacy in graft allocation policy.[64,65] While preemptive SPK transplant seems to be an excellent option in

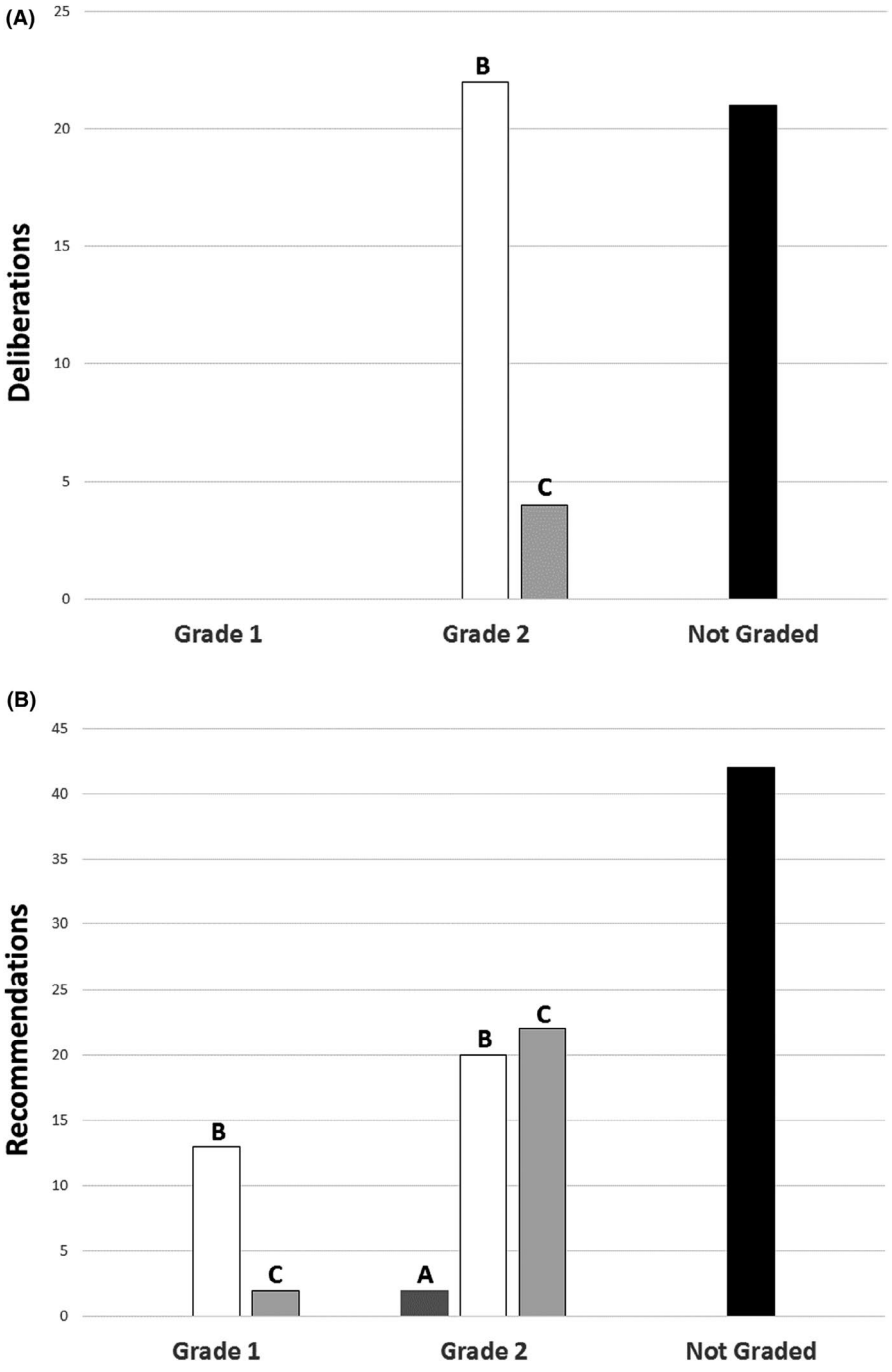

FIGURE 1 Level of evidence and strength of statements. (A) Jury deliberations; (B) expert recommendations.

the individual patient, sound evidence is still missing to demonstrate if and to which extent preemptive SPK transplantation could be convenient in the average SPK transplant recipient.

5.2 | Jury deliberations—impact of PAK

PAK was criticized due to possibly increased risks compared to continued insulin therapy. Indeed, in addition to the general concerns that apply to all types of pancreas transplantation, PAK transplant was associated with increased risk of renal graft loss.[66,67]

Jury deliberations indicate that PAK transplant increases the risk of mortality early after transplantation, but improves life expectancy thereafter. As already observed for the kidney,[68] higher early mortality is the consequence of the need for a major surgical procedure and administration of additional immunosuppression and should not discourage PAK transplantation. Indeed, after the early posttransplant period, the additional risk of mortality disappears while quality of life is greatly improved and renal graft function is better preserved. Considerations on quality of life and renal graft function apply well to patients with type 1 diabetes. In patient with type 2 diabetes, PAK transplant was deemed feasible but evidence on possible advantages was lacking.

TABLE 1 Impact of simultaneous pancreas-kidney (SPK) transplantation

Query	Deliberation	Grade
A.1 – *"In suitable recipients, does an SPK transplant increase life expectancy or improve quality of life?"*	**1. SPK transplantation improves quality of life and long-term survival compared to current medical treatment for people on the waitlist and compared to other transplant options**	**2B**
	2. The survival advantage with SPK transplantation is greater when a live donor kidney is not available or suitable	**2B**
	3. SPK transplantation improves quality of life and is not associated with an increased risk of premature loss of renal graft function	**2B**
A.2 – *"In suitable SPK recipients with type 1 diabetes does an SPK transplant improve life-expectancy or quality of life?"*	**1. In type 1 diabetes, SPK transplantation improves quality of life and long-term survival compared to current medical treatment for people on the waitlist and compared to other transplant options**	**2B**
	2. The survival advantage with SPK transplantation is greater when a live donor kidney is not available or suitable	**2B**
	3. SPK transplantation improves quality of life and is not associated with an increased risk of premature loss of renal graft function	**2B**
A.3 – *"In suitable SPK recipients with type 2 diabetes, does an SPK transplant improve life-expectancy or quality of life?"*	**1. In suitable type 2 diabetes recipients, SPK transplantation improves quality of life and improves survival compared to patients remaining on dialysis**	**NG**
	2. In type 2 diabetes, SPK transplantation improves survival compared to deceased donor kidney transplantation alone	**2B**
	3. In people with type 2 diabetes, there is insufficient evidence to determine whether survival is improved by SPK transplantation compared to living donor kidney transplant alone	**NG**
A.4 – *"In patients with type 1 diabetes and end stage-renal disease on dialysis, does an SPK transplant increase longevity or improve quality of life?"*	**In patients with type 1 diabetes and end-stage renal disease on dialysis, SPK transplantation both improves quality of life and increases longevity compared to current medical therapies**	**2B**
A.5 – *"In patients with type 1 diabetes and end-stage renal disease on dialysis, does an SPK transplant increase longevity or improve quality of life compared to live donor kidney transplantation?"*	**1. Live donor kidney transplantation alone is an alternative to SPK transplantation in case of anticipated long wait times and in people who do not qualify for dual transplantation**	**2C**
	2. Live donor kidney transplantation alone achieves survival similar to SPK transplantation in the medium term, but SPK transplantation has improved long-term survival	**2C**
A.6 – *"In patients with type 1 diabetes and end-stage renal disease on dialysis, does an SPK transplant increase longevity or improve quality of life compared to live donor kidney transplantation with islet cell transplantation?"*	**Because of lack of evidence, no conclusions can be drawn**	**-**
A.7 – *"In patients with type 1 diabetes and end-stage renal disease on dialysis, does an SPK transplant increase longevity or improve quality of life compared to deceased donor kidney transplantation?"*	**In selected patients, SPK transplantation improves long-term survival, kidney graft function, and quality of life compared to patients who receive deceased donor kidney transplantation alone**	**2C**
A.8 – *"In patients with type 1 diabetes and end-stage renal disease on dialysis, does an SPK transplant increase longevity or improve quality of life compared to deceased donor kidney transplantation with islet cell transplantation?"*	**Because of lack of evidence, no conclusions can be drawn**	**-**
A.9 – *"In preemptive SPK recipients with type 1 diabetes does an SPK transplant improve longevity or quality of life?"*	**There is indirect evidence that preemptive SPK transplantation improves longevity and quality of life in patients with type 1 diabetes**	**NG**
A.10 – *"In preemptive SPK recipients with type 1 diabetes does an SPK transplant improve longevity or quality of life compared to live donor kidney transplantation?"*	**Data are limited. Preemptive SPK transplantation and live donor kidney transplants both seem to provide excellent long-term outcomes in patients with type 1 diabetes**	**NG**

(Continues)

TABLE 1 (Continued)

Query	Deliberation	Grade
A.11 – *"In preemptive SPK recipients with type 1 diabetes does an SPK transplant improve longevity or quality of life compared to live donor kidney transplantation with islet cell transplantation?"*	**Because of lack of evidence, no conclusions can be drawn**	-
A.12 – *"In preemptive SPK recipients with type 1 diabetes does an SPK transplant improve longevity or quality of life compared to deceased donor kidney transplantation?"*	**Indirect evidence from deceased donor kidney transplant alone in patients with type 1 diabetes suggests that preemptive SPK transplantation is superior in terms of quality of life and longevity compared to deceased donor kidney transplantation alone**	**NG**
A.13 – *"In preemptive SPK recipients with type 1 diabetes does an SPK transplant improve longevity or quality of life compared to deceased donor kidney transplantation with islet cell transplantation?"*	**Because of lack of evidence, no conclusions can be drawn**	
A.14 – *"In patients with type 2 diabetes and end-stage renal disease on dialysis, does an SPK transplant improve quality of life or increase longevity?"*	**Indirect evidence from kidney transplant recipients with type 2 diabetes suggests that, in selected patients, SPK transplantantation could be associated with improved quality of life and increased longevity compared to remaining on dialysis**	**NG**
A.15 – *"In patients with type 2 diabetes and end-stage renal disease on dialysis, does an SPK transplant improve quality of life or increase longevity compared to live donor kidney transplantation?"*	**There is limited evidence. Indirect evidence suggests that in selected patients with type 2 diabetes on dialysis, the sustained normoglycemia after successful SPK transplantation offers additional advantages compared to live donor kidney transplantation alone**	**NG**
A.16 – *"In patients with type 2 diabetes and end-stage renal disease on dialysis, does an SPK transplant improve quality of life or increase longevity compared to deceased donor kidney transplantation?"*	**There is limited evidence. Indirect evidence suggests that in selected patients with type 2 diabetes on dialysis, the sustained normoglycemia after successful SPK transplantation offers additional advantages compared to deceased kidney donor transplantation alone**	**NG**
A.17 – *"In preemptive recipients with type 2 diabetes does an SPK transplant improve quality of life or increase longevity compared to current medical therapy?"*	**There are limited data. Indirect evidence from type 1 diabetes suggests that in selected patients with type 2 diabetes, preemptive SPK transplant improve quality of life and increase longevity compared to current medical therapy**	**NG**
A.18 – *"In preemptive recipients with type 2 diabetes does an SPK transplant improve quality of life or increase longevity compared to live donor kidney transplantation?"*	**There are limited data. It is not known whether preemptive SPK transplantation improves quality of life or increases longevity compared to live donor kidney transplantation in type 2 diabetes**	**NG**
A.19 – *"In preemptive recipients with type 2 diabetes does an SPK transplant improve quality of life or increase longevity compared to deceased donor kidney transplantation?"*	**There are limited data. It is not known whether preemptive SPK transplantation improves quality of life or increases longevity compared to deceased kidney donor transplantation in type 2 diabetes**	**NG**

Abbreviations: NG, not graded; SPK, simultaneous pancreas kidney.

5.3 | Jury deliberations—impact of PTA

Deliberations on PTA were truly important because they underscored the high value of this type of transplantation. Indeed, contrary to a landmark study,[69] the jury deliberated that PTA does not increase the long-term risk of death compared with people remaining on the waiting list. PTA might be actually associated with a long-term survival advantage in diabetic patients who have impaired hypoglycemia awareness. Although these deliberations are not based on new data,[27,39,70,71] they are key since they are provided by an independent jury and unambiguously debunk the myth of PTA recipients exposed to undue risks.

A further concern with PTA is the risk of accelerated loss of renal function.[73–75] The jury deliberated that impaired pretransplant renal function is a risk factor for accelerated end-stage renal failure after PTA, while an estimated glomerular filtration rate ≥60 ml/min/1.73 m^2 is sufficient to protect most recipients against this risk. The use of calcineurin inhibitors (CNIs) may contribute to a decline in renal function after PTA, while normalization of glucose levels could have beneficial effects on underlying diabetic nephropathy in the long term.[76,77] These additional and important data underscore the key role of accurate recipient selection for safe PTA and appropriate management of immunosuppression. Probably, patients with hypoglycemia unawareness should be referred for PTA before development of diabetic nephropathy.

The jury also deliberated that PTA improves quality of life, may stabilize/improve diabetic retinopathy (depending on severity of initial retinal damage), and may slow the progression of diabetic neuropathy.[32,78–80] No conclusion could be drawn regarding the effects of PTA on progression of cardiovascular disease. The positive effect of PTA on the course of microvascular complications of diabetes is

TABLE 2 Impact of pancreas after kidney (PAK) transplantation

Query	Deliberation	Grade
B.1 – *"In suitable PAK recipients, is PAK transplant associated with additional risks? What is the risk of death compared to current medical therapies?"*	**1. At 90 days, PAK transplantation is associated with an increased risk of mortality (compared to staying on the waitlist) which persists to 1 year**	**2B**
	2. After 1 year, PAK transplantation is associated with decreased mortality	**2B**
B.2 – *"In suitable PAK recipients with type 1 diabetes, does PAK transplant prolong life or improve quality of life compared to current diabetes therapy?"*	**1. Available evidence in patients with type 1 diabetes cannot determine whether PAK transplantation prolongs life expectancy**	**2B**
	2. PAK transplantation clearly improves quality of life due to superior renal graft survival and improved metabolic control	**2B**
B.3 – *"In suitable PAK recipients with type 1 diabetes who received a live donor kidney, does PAK transplant increase life expectancy or improve quality of life?"*	**1. Available evidence in patients with type 1 diabetes cannot determine whether PAK transplantation in live donor kidney recipients prolongs life expectancy**	**2B**
	2. PAK transplantation clearly improves quality of life due to superior renal graft survival and improves metabolic control compared to continued medical treatment of diabetes	**2B**
B.4 – *"In suitable PAK recipients with type 1 diabetes who received a deceased kidney transplant, does PAK transplant increase life expectancy or improve quality of life?"*	**1. Available evidence in patients with type 1 diabetes cannot determine whether PAK transplantation in deceased kidney transplant recipients prolongs life expectancy**	**NG**
	2. PAK transplantation clearly improves quality of life due to superior renal graft survival and improves metabolic control compared to continued medical treatment of diabetes	**NG**
B.5 – *"In suitable PAK recipients with type 2 diabetes does PAK transplant increase life expectancy or improve quality of life?"*	**Based on available evidence, PAK transplant in people with type 2 diabetes is feasible, but further data are required before conclusions on the impact of PAK transplant on life expectancy or quality of life can be made**	**NG**
B.6 – *"In suitable PAK recipients with type 2 diabetes does PAK transplant after a live donor kidney transplant increase life expectancy or improve quality of life?"*	**Based on available evidence, PAK transplant after a live donor kidney transplant in people with type 2 diabetes is feasible. Further data are required before conclusions on the impact on life expectancy or quality of life can be made**	**NG**
B.7 – *"In suitable PAK recipients with type 2 diabetes does PAK transplant after deceased donor kidney transplant increase life expectancy or improve quality of life?"*	**Based on available evidence, PAK transplant after a deceased donor kidney transplant in people with type 2 diabetes is feasible. Further data are required before conclusions on the impact on life expectancy or quality of life can be made**	**NG**

Abbreviations: NG, not graded; PAK, pancreas after kidney.

an important piece of information that sheds additional light on the role of PTA in the management of selected diabetic patients.

Overall, based on jury deliberations, PTA appears fully justified in patients with hypoglycemia unawareness and possibly in patients with other chronic complications of diabetes of mild/moderate severity. Regarding hypoglycemia unawareness, islet cell transplantation could be an alternative option, but this issue was not addressed in the consensus.

5.4 | Expert panel recommendations—activity volume and innovation

5.4.1 | Activity volume

For many surgical procedures, there is a clear relationship between volume of activity and outcomes.[81] In transplantation, volume-outcome relationship has been shown for the kidney,[82] liver,[83] heart,[84] and lung.[85]

In the United States, approximately 70% of transplant centers are low volume. Low volume programs (one to six pancreas transplants per year) may be associated with worse outcomes.[86] Volume-outcome relationship was confirmed in Europe,[16] by the Scientific Registry of Transplant Recipients,[17] and in few studies.[18,19] Based on these data, low volume seems to be associated with a higher risk for pancreas failure,[86] but there is no study specifically addressing the issue of minimum annual volume of pancreas transplant per center. Therefore, and considering that outcomes after pancreas transplantation are multifactorial and not just determined by surgery and/or care in the immediate post-transplant period, experts could not define a minimum annual volume but suggested that higher annual volume could be among the factors contributing to good outcomes.

No specific study addressed the impact of surgeon volume on outcomes of pancreas transplantation. As a consequence, no annual volume threshold exists. Evidence from other high complexity and relatively low volume procedures, such as pancreatoduodenectomy, suggests that higher volume surgeons perform better as compared to lower volume surgeons.[87] Hospital volume can mitigate the impact of low volume surgeons on outcomes,[88] and experienced surgeons have results similar to those achieved by high volume surgeons.[89] Experts

TABLE 3 Impact of pancreas transplantation alone (PTA)

Query	Deliberation	Grade
C.1 – *"In suitable recipients is PTA associated with an increased risk of death when compared to current medical therapies?"*	**1. PTA is not associated with an increased long-term risk of death compared with people remaining on the waiting list**	**2B**
	2. Indirect evidence suggests that PTA could be associated with a long-term survival advantage compared to people who have diabetes and impaired hypoglycemia awareness	**2B**
C.2 – *"In suitable PTA recipients, is PTA associated with an increased risk of earlier renal failure compared to current medical therapy?"*	**1. Renal failure has occurred in people receiving PTA who had significant pretransplant renal impairment**	**2B**
	2. Renal failure post-PTA is uncommon if pretransplant estimated glomerular filtration rate is ≥60 ml/min/1.73 m^2	**2B**
	3. In some people, there may be a decline in renal function after PTA with calcineurin inhibitor-based immunosuppression	**2B**
	4. By improving glucose levels, PTA could have beneficial effects on underlying diabetic nephropathy in the long term	**2B**
C.3 – *"In suitable PTA recipients, does PTA extend longevity or improve quality of life compared to current medical therapies?"*	**1. Patients with diabetes and impaired hypoglycemia awareness or diabetes and autonomic neuropathy have a high mortality risk and indirect evidence suggests that this group has improved longevity after PTA**	**NG**
	2. Overall PTA recipients have improved quality of life compared to patients remaining on the wait list	**NG**
C.4 – *"After the first post-transplant year, is PTA superior to current medical therapies for metabolic control?"*	**Successful PTA provides normal or near normal glucose levels and therefore is superior to current medical therapies for hypoglycemia and hyperglycemia**	**2B**
C.5 – *"Is PTA superior to current medical therapies in the course of chronic complications of diabetes?"*	**Indirect evidence suggests that successful PTA could improve the long-term course of most chronic diabetes complications**	**NG**
C.6 – *"Is PTA superior to current medical therapies in the course of diabetic retinopathy?"*	**Depending on initial severity of diabetic retinopathy, successful PTA may contribute to stabilization or improvement of diabetic retinopathy**	**2B**
C.7 – *"Is PTA superior to current medical therapies in the course of diabetic nephropathy?"*	**Depending on the severity of diabetic nephropathy, successful PTA may slow progression of diabetic nephropathy. These beneficial effects may be offset by calcineurin inhibitor-related nephrotoxicity**	**NG**
C.8 – *"Is PTA superior to current medical therapies in the course of diabetic neuropathy?"*	**Depending on severity of diabetic neuropathy, evidence suggests that successful PTA slows the progression of diabetic neuropathy when compared to current medical therapies**	**2C**
C.9 – *"Is PTA superior to current medical therapies in the course of cardiovascular disease?"*	**Insufficient evidence is available to determine whether PTA slows progression of cardiovascular disease**	**NG**

Abbreviations: NG, not graded; PTA, pancreas transplantation alone.

recommended that pancreas transplantation should not be performed occasionally by the individual surgeon and that younger surgeons should have received formal training and/or should operate under supervision.

5.4.2 | Innovation

Regarding innovation, two issues were assessed: live donor segmental pancreas transplantation and robotic pancreas transplantation.

Live donor segmental pancreas transplantation has been performed only in a few centers, for a total of approximately 200 procedures worldwide. Most of these transplants were done at a single institution, the University of Minnesota.[90,91] In general, segmental live donor pancreas transplantation is an option in sensitized recipients who have a suitable donor with a negative crossmatch. Due to the limited experience, donor risks cannot be precisely defined. Experience with the so called "Warshaw procedure,"[92] corresponding to a live donor segmental pancreatectomy performed in patients with benign or low-grade pancreatic tumors,[93] shows that this procedure is quite safe.[94] However, short- and long-term risks do exist. The most frequent early complications include splenic infarction (potentially requiring splenectomy), postoperative pancreatic fistula, and postoperative hemorrhage. Delayed complications/sequelae include gastric varices, hypersplenism, and diabetes. Sinistral portal hypertension was reported to have no clinical consequence in a large series of Warshaw procedures with long-term follow-up,[94] but a live donor of a segmental pancreatic graft did present with an upper gastrointestinal hemorrhage 25 years after surgery.[95] Splenectomy is curative in these patients, but massive gastrointestinal bleeding can be life-threatening. Therefore, experts recommended that live donor segmental pancreas transplantation could be carefully considered in sensitized recipients and in extremely well-selected pairs. They also recommended that the center be responsible to ensure quality of the procedure and careful lifelong follow-up of the donor.

The first robotic pancreas transplantation was performed in Pisa, Italy, on September 27, 2010 and the first three cases were reported

TABLE 4 Expert panel recommendations on activity volume and innovation in pancreas transplantation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
1.1 – *"What is the minimally acceptable annual volume of pancreas transplants per center?"*	**The outcome of pancreas transplantation is multifactorial. Higher annual volume is expected to be among the factors contributing to better outcome, but available data do not allow for a clear definition of a minimum annual volume, as this could also be influenced by several geographical variables as well as donor and recipient selection.**	**NG**	83%	97.3%	Investigate the impact of annual volume of pancreas transplants per center. Estimates should take into account the possible impact of concurrent volume of renal and hepatic transplantation.
1.2 – *"What is the minimally acceptable annual volume of pancreas transplants per surgeon?"*	**Pancreas transplantation should not be performed occasionally by the individual surgeon. Younger surgeons who are starting their practice are expected to have completed a formal training program in pancreas transplantation and/or act under the supervision of a proficient pancreas transplant surgeon.**	**NG**	96%	97.3%	Investigate volume-outcome relationship for individual surgeon. Investigate volume-outcome relationship based on overall surgeon experience vs. current annual volume.
1.3 – *"Is there a role for segmental live donor pancreas transplantation in non-immunized recipients?"*	**Live donor segmental pancreas transplantation could be an option even in nonimmunized patients in extremely well-selected pairs provided that the center is able to ensure quality of the procedure and careful lifelong follow-up of the donor.**	**NG**	68%	88.4%	None.
1.4 – *"Is there a role for segmental live donor pancreas transplantation in immunized recipients?"*	**Live donor segmental pancreas transplantation is an option in immunized patients in extremely well-selected pairs provided that the center is able to ensure quality of the procedure and careful lifelong follow-up of the donor.**	**NG**	70%	93.4%	None.
1.5 – *"What are the anticipated risks for the live donor?"*	**There is no enough specific evidence (i.e., direct evidence from live donors) to address this question, especially concerning the risks of simultaneous distal pancreatectomy and nephrectomy. There is a risk of early technical complications and a risk for delayed metabolic complications demanding for careful selection of donors and lifelong follow-up.**	**NG**	83%	88.4%	None.
1.6 – *"Is there evidence that minimally invasive pancreas transplantation increases the risk of the transplant procedure versus open pancreas transplantation?"*	**Robotic pancreas transplantation is feasible. Available data do not allow to draw a conclusion on safety, although there may be a potential benefit in obese recipients.**	**NG**	82%	94.1%	Establish a training path for safe implementation and diffusion of robotic pancreas transplantation. Report on additional cases.
1.7 – *"Is there evidence that minimally invasive pancreas transplantation is associated with worse long-term results versus open pancreas transplantation?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	97%	100%	Establish a training path for safe implementation and diffusion of robotic pancreas transplantation. Report on additional cases.
1.8 – *"Is there evidence of benefits from minimally invasive pancreas transplantation?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	79%	97.3%	Establish a training path for safe implementation and diffusion of robotic pancreas transplantation. Report on additional cases.
1.9 – *"Is there evidence that minimally invasive pancreas transplantation is more beneficial in obese versus lean pancreas transplant recipients"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	93%	97.3%	Establish a training path for safe implementation and diffusion of robotic pancreas transplantation. Report on additional cases.

Abbreviation: NG, not graded.

TABLE 5 Expert panel recommendations on pancreas donation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
2.1 – *"In the setting of DBD is age >40 years an absolute or relative contraindication to pancreas transplantation?"*	**In the setting of DBD, donor age >40 years should not be considered either an absolute or a relative contraindication to pancreas transplantation if the donor is otherwise suitable. Accumulation of risk factors and long ischemic times should be avoided.**	**1B**	90%	96.4%	Expand utilization of donors aged over 40 years and report on outcomes.
2.2 – *"In the setting of DBD is the use of pediatric donors an absolute or relative contraindication to pancreas transplantation?"*	**In the setting of DBD, pediatric pancreas donors should not be considered a contraindication to pancreas transplantation. Accumulation of risk factors and long ischemic times should be avoided.**	**2B**	82%	96.4%	Report outcomes of pancreas transplantation from donors of low body weight (<15 kg).
2.3 – *"In the setting of DBD is donor BMI >30 kg/m^2 a contraindication to pancreas transplantation?"*	**Properly selected donors with a BMI > 30 kg/m^2 can be used for pancreas transplantation. Accumulation of risk factors and long ischemic times should be avoided.**	**2B**	80%	93.2%	Report on multicenter experience with pancreas transplantation from donors with a BMI > 30 kg/m^2 compared to lower BMI donors. The ideal study should be prospective and should report on all pancreas offers with a focus on organ transplanted from donors with a BMI > 30 kg/m^2.
2.4 – *"Is DCD an absolute or relative contraindication to pancreas transplantation?"*	**Controlled DCD is not a contraindication to pancreas transplantation. Accumulation of risk factors and long ischemic times should be avoided.**	**2B**	85%	100%	Report on further series of pancreas transplantation from DCD.
2.5 – *"Is University of Wisconsin solution superior to Celsior solution for pancreas preservation?"*	**There is no evidence that the use of University of Wisconsin vs. the use of Celsior solutions results in improved pancreas transplantation outcomes when pancreas allografts are preserved for relatively short periods of time.**	**1B**	74%	85.7%	None.
2.6 – *"Is University of Wisconsin solution superior HTK solution for pancreas preservation?"*	**University of Wisconsin solution appears to be superior to HTK solution for pancreas preservation.**	**2B**	75%	93.2%	None.
2.7 – *"Is University of Wisconsin solution superior to IGL-1 solution for pancreas preservation?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	68%	100%	Publish retrospective series before planning for prospective and randomized comparisons.
2.8 – *"Are quick en-bloc techniques superior to conventional techniques for pancreas procurement?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	67%	96.4%	Report on outcomes of pancreas transplantation following quick en-bloc and conventional procurement techniques, after matching both donor and recipient population by propensity scores. Outcomes should include pancreas grafts discarded because of surgical injury.

(Continues)

TABLE 5 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
2.9 – *"Is the outcome of local versus imported grafts superior in pancreas transplantation?"*	**There is no evidence that imported pancreatic grafts have inferior transplant outcomes compared to local grafts. A proficient team should perform the donor procedure, and strategies should be developed to reduce cold preservation time of imported grafts.**	**2B**	84%	96.4%	Report on outcomes of pancreas transplantation from local vs. imported grafts while matching donor and recipient populations for known prognostic factors predicting early graft failure. Outcomes should include pancreas grafts discarded because of surgical injury and the experience of the recovery surgeon/team.
2.10 – *"For how long can pancreas grafts be ideally preserved?"*	**While minimization of ischemia times (less than 12 h) are associated with superior outcomes, results remain acceptable up to 24 h of preservation time. Beyond this time limit, pancreas transplantation can still be performed if the individual graft is believed to be particularly suitable for a given recipient.**	**1B**	78%	85.7%	None.
2.11 – *"Is machine perfusion of pancreas allografts feasible and associated with improved pancreas transplant outcomes?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	74%	96.4	Conduct further studies in preclinical models.

Abbreviations: DBD, donation after brainstem death; DCD, donation after circulatory death; HTK, Histidine-tryptophan-ketoglutarate; IGL-1, Institut Georges Lopez-1; NG, not graded.

in 2012.[96] Since then, only few additional cases (<20) were reported worldwide.[97,98] All procedures were successful, but the generalizability of these results remains to be established due to both selection biases and small sample size. The larger experience with robotic renal transplantation,[99,100] as well as with other complex intra-abdominal procedures requiring vascular anastomoses,[101,102] shows that robotic assistance permits pancreas transplantation. Justification for the pursuit of further experience with robotic pancreas transplantation includes the possibility of minimizing the incidence and severity of local complications, such as perigraft fluid collections and surgical site infections, and potentially expediting postoperative recovery. Based on this background, experts could only conclude that robotic pancreas transplantation is feasible.

5.5 | Expert panel recommendations—pancreas donation

5.5.1 | Donor characteristics

In general, the use of donors not fulfilling ideal criteria was considered acceptable provided that the accumulation of additional risk factors and long ischemic times was avoided. In detail, in the setting of donation after brainstem death (DBD), experts did not recommend against the use of donors aged >40 years,[103–108] pediatric donors,[109–113] and donors with a BMI > 30 kg/m^2.[114–116] In the discussion, experts underscored that the use of pediatric donors of low body weight (<15 kg) may increase the risk of technical failure, while a BMI < 35 kg/m^2 reduces the impact of obesity. In the setting of donation after circulatory death (DCD), the use of young controlled DCD donors was not considered a contraindication to pancreas transplantation, as evidence showed that when donor age is <40 years, results are good irrespective of donor source (i.e., DCD or DBD).[117–124]

5.5.2 | Preservation solutions

The comparative value of different preservation solutions was extensively debated due to concerns on outcomes with increasing preservation times. When grafts are preserved for <12 h, experts agreed that University of Wisconsin (UW) and Celsior solutions are equally safe and effective. This recommendation was mostly supported by two single center prospective and randomized studies.[125,126] On the contrary, UW was deemed to be superior to histidine-tryptophan-ketoglutarate (HTK) because of the description of higher rates of acute pancreatitis with HTK[127] and concerns on suitability of this preservation solution with increasing preservation times. However, in the discussion, experts acknowledged that HTK can also be employed if preservation time does not exceed 10 h and when using low perfusion volumes.[128–131] Finally, no conclusion could be drawn on Institut Georges Lopez-1 (IGL-1) solution, because of lack of a comparison group in available studies.[132–134]

TABLE 6 Expert panel recommendations on pancreas graft allocation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
3.1 – *"In SPK transplants, are the results of AB0-identical/-compatible transplantation superior to those of AB0 incompatible transplantation?"*	**Anecdotal experience shows that AB0-incompatible SPK transplantation can be performed safely. However, due to lack of supporting evidence, AB0-incompatible SPK transplantation should only be considered in selected circumstances and according to national allocation rules.**	**NG**	61%	94.2%	None.
3.2 – *"In solitary pancreas transplants are the results of AB0-identical/-compatible transplantation superior to those of AB0-incompatible transplantation?"*	**In the absence of evidence, AB0-incompatible solitary pancreas transplantation should not be performed.**	**NG**	60%	88.2%	None.
3.3 – *"In SPK transplants are the results of crossmatch negative transplants superior to those of crossmatch positive transplants?"*	**The results of crossmatch-negative SPK transplants are expected to be superior to those of crossmatch-positive transplants in terms of risk of recipients developing donor-specific antibody and higher rejection rates (including antibody-mediated rejection). SPK transplantation should not be performed in the presence of positive crossmatch.**	**NG**	87%	93.8	Report on the outcome of SPK transplants performed in the setting of T or B cell-positive crossmatch.
3.4 – *"In solitary pancreas transplants, are the results of crossmatch negative transplants superior to those of crossmatch positive transplants?"*	**The results of crossmatch-negative solitary pancreas transplants are expected to be superior to those of crossmatch-positive transplants in terms of risk of recipients developing donor-specific antibody and higher rejection rates (including antibody-mediated rejection). Solitary pancreas transplantation should not be performed in the presence of T cell and/or B cell CDC-positive crossmatch.**	**NG**	77%	87.5%	Report on the outcome of solitary transplants performed despite T or B cell-positive crossmatch.
3.5 – *"In SPK transplants, in the setting of a negative crossmatch, are the results of transplantation affected by the presence of DSA with MFI levels <3000?"*	**In the setting of limited evidence, presence of pretransplant DSA with an <3000 MFI level in patients with a negative T cell and B cell flow cytometric crossmatch could be considered for SPK transplantation as per center-specific policy.**	**NG**	65%	87.5%	Retrospective and prospective studies are needed.
3.6 – *"In SPK transplants, in the setting of a negative crossmatch, are the results of transplantation affected by the presence of DSA with MFI levels <5000?"*	**In the setting of a negative crossmatch, SPK transplantation could be considered, despite the presence of DSA with an MFI of <5000, as per center-specific policy.**	**NG**	60%	95.9%	Retrospective and prospective studies are needed.
3.7 – *"In solitary pancreas transplants, in the setting of a negative crossmatch, are the results of transplantation affected by the presence of DSA with MFI levels <3000?"*	**In the setting of extremely limited evidence, presence of pretransplant DSA with a low MFI level (<3000) in patients with a negative crossmatch could be considered for solitary pancreas transplantation as per center policy.**	**NG**	60%	90.6%	Retrospective and prospective studies are needed.
3.8 – *"In solitary pancreas transplants, in the setting of a negative crossmatch, are the results of transplantation affected by the presence of DSA with MFI levels <5000?"*	**Solitary pancreas transplantation could be considered in patients with a pretransplant DSA of intermediate (<5000) MFI level and a negative crossmatch, as per center-specific policy.**	**NG**	57%	93.8%	Retrospective and prospective studies are needed.

(Continues)

TABLE 6 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
3.9 – *"In SPK transplants are the results of transplantation improved by reduced HLA mismatching?"*	**The overall results of SPK transplantation are not improved by reduced HLA mismatching. However, there is a correlation between number of HLA mismatches and rate of acute rejection.**	**2C**	82%	100%	Prospective studies should investigate the relationships between HLA-matching, development of de novo DSA, and long-term SPK transplant immunologic outcomes.
3.10 – *"In solitary pancreas transplants, are the results of transplantation improved by reduced HLA mismatching?"*	**In solitary pancreas transplantation, reduced HLA-B and HLA-DR mismatch are associated with lower acute rejection rates, but not with improved overall pancreas allograft survival.**	**2C**	82%	93.8%	Further prospective and retrospective studies are recommended.
3.11 – *"Should kidneys be preferentially allocated to SPK recipients, when compared to recipients of kidney alone transplants?"*	**Kidneys of donors suitable for pancreas donation should be preferentially allocated to SPK transplant recipients because of the higher survival advantage in this patient population, of improved results with simultaneous vs. sequential transplantation, and of practical reasons concerning the organization of multi-organ procurement.**	**1B**	86%	100%	Provide additional analyses from registries to further evaluate the long-term survival benefits of SPK transplantation. Because most of the currently available data are provided by US centers (due to mandatory reporting to the UNOS/OPTN and the IPTR), data from non-US registry/collaborative studies should also be reported.
3.12 – *"Should kidneys be preferentially allocated to SPK recipients, when compared to recipients of kidney alone transplants with a PRA ≥ 80%?"*	**There is currently no evidence supporting priority for kidney allocation in the event of competition between HLA-highly sensitized recipients of kidney alone transplants and SPK transplant recipients. Allocation should be done according to national allocation policy.**	**NG**	85%	90.5%	Prospective and retrospective studies are strongly needed.
3.13 – *"Should kidneys be preferentially allocated to SPK recipients, when compared to recipients of other simultaneous transplants (i.e., liver-kidney, heart kidney, lung-kidney)?"*	**No evidence supports the priority for kidney allocation in the event of competition between recipients of SPK transplantation and recipients of other simultaneous transplants (i.e., liver-kidney, heart-kidney, and lung-kidney).**	**NG**	89%	90.5%	Prospective and retrospective studies are recommended.
3.14 – *"Are the results of SPK transplants in type 1 diabetic patients superior to the results of SPK transplants in type 2 diabetic patients so that a priority should be given to type 1 diabetics?"*	**There is no evidence to prioritize graft allocation for SPK transplantation to patients with type 1 vs. patients with type 2 diabetes.**	**2B**	90%	100%	Further prospective and retrospective studies are recommended. A clear definition of selection criteria for SPK transplantation in patients with type 2 diabetes is needed.
3.15 – *"Are the results of SPK transplants in patients aged ≤50 years superior to the results of SPK transplants in older patients so that a priority should be given to younger recipients?"*	**In selected patients, results of SPK transplantation are similar in younger and older recipients. There is no evidence to prioritize graft allocation based on recipient age.**	**2B**	90%	96.4%	Further prospective and retrospective (preferentially from large registries) studies are recommended to determine the benefit of SPK transplantation in older recipient categories.

Abbreviations: CDC, complement-dependent cytotoxicity; DSA, donor-specific antibody; HLA, human leukocyte antigen; IPTR, International Pancreas and Transplant Registry; MFI, mean fluorescent intensity; NG, not graded; PRA, panel reactive antibody; SPK, simultaneous pancreas kidney; UNOS/OPTN, United Network for Organ Sharing/Organ Procurement and Transplantation Network; US, United States.

TABLE 7 Expert panel recommendations on recipient selection for pancreas transplantation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
4.1 – *"Is there a higher risk of post-transplant renal failure in potential PTA recipients with normal (eGFR ≥90 ml/min/1.73 m^2) or mildly decreased (eGFR 60–89 ml/min/1.73 m^2) renal function and nephrotic syndrome when compared to recipients without nephrotic syndrome?"*	**In patients referred for PTA with normal or mildly decreased (eGFR 60–89 ml/min/1.73 m^2) renal function and nephrotic syndrome, the benefits of insulin independence should be balanced against the possible risk of accelerated renal failure.**	**NG**	70%	88.2%	Retrospective and prospective studies on PTA in patients with normal or mildly decreased renal function and nephrotic syndrome are very much needed.
4.2 – *"Is there a higher risk of post-transplant renal failure in potential PTA recipients with normal (eGFR ≥90 ml/min/1.73 m^2) or mildly decreased (eGFR 60–89 ml/min/1.73 m^2) renal function and proteinuria (without nephrotic syndrome) when compared to recipients without proteinuria?"*	**In PTA recipients, with normal or mildly decreased (eGFR 60–89 ml/min/1.73 m^2) renal function and proteinuria (without nephrotic syndrome), the benefits of insulin independence should be balanced against the potential risk of worsening of nephropathy.**	**2C**	74%	90.6%	Specific registry analysis and prospective studies are both needed to further clarify the possible increase in the risk of renal failure in PTA recipients with normal or mildly decreased renal function with proteinuria, but without nephrotic syndrome.
4.3 – *"Does PTA improve the course of chronic diabetic complications as compared to state-of-the-art medical therapies?"*	**Successful PTA is associated with an improved course of chronic complications of diabetes as compared to current therapies.**	**2C**	83%	90.6%	A prospective observational or randomized trial should probably be the next action to take.
4.4 – *"Are the results of PAK transplants performed in recipients with a creatinine clearance or eGFR ≤45 ml/min inferior to the results of PAK transplants performed in patients with higher creatinine clearance or eGFR levels?"*	**PAK transplantation in diabetic patients with a functioning kidney graft and a creatinine clearance or eGFR ≤ 45 ml/min could be performed after careful risk-benefit analysis in the individual patient. Immunosuppression should be optimized to protect renal function.**	**NG**	82%	90.6%	Ad hoc registry analysis as well as prospective studies are required to clarify if recipients with a creatinine clearance ≤45 ml/min are exposed to undue risk of renal graft failure when undergoing PAK transplant.
4.5 – *"Are the results of PAK transplants performed in recipients with a history of renal rejection inferior to the results of PAK transplants performed in patients without a history of renal rejection?"*	**Patients with history of renal allograft rejection should be selected very carefully for PAK transplantation. Optimal HLA matching and avoidance of donor-specific antibodies are both expected to mitigate the risk of post-PAK rejection.**	**NG**	84%	90.6%	Further retrospective and prospective observational studies are both needed.
4.6 – *"Are the results of PAK transplants performed within 6 months from renal transplantation inferior to the results of PAK transplants performed after this time interval?"*	**PAK transplantation performed within 6 months of renal transplantation is associated with similar outcomes when compared to PAK transplantation performed after this time point. PAK transplantation provides better results when performed within 1 year after kidney transplantation.**	**2C**	88%	96.4%	Further retrospective and prospective observational studies are both needed.
4.7 – *"Are the results of preemptive SPK transplants superior to those of SPK transplants performed in patients undergoing dialysis?"*	**Preemptive SPK transplant is associated with improved outcomes when compared to SPK transplant performed in patients undergoing dialysis.**	**2B**	98%	100%	Further studies should define the level of renal function at which SPK transplantation becomes preferred as compared to PTA.

(Continues)

TABLE 7 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
4.8 – *"Are the results of SPK transplants in obese patients inferior when compared to the results of SPK transplants in non-obese patients?"*	**Obese patients undergoing SPK transplant may face a higher rate of early complications when compared to nonobese recipients.**	2B	95%	91.4%	The value of bariatric procedures and/or minimally invasive transplantation in obese SPK candidates should be explored to improve the outcome of SPK transplantation in obese recipients.
4.9 – *"Are the results of SPK transplants in patients with a lower limb amputation inferior to the results of SPK transplants in patients without history of lower limb amputation?"*	**Pre-SPK transplant lower limb amputation, in the context of cardiovascular disease, may be a risk factor for inferior transplant results.**	2C	85%	94.3	None.
4.10 – *"Are the results of SPK transplants in patients with an history of coronary heart disease inferior to the results of SPK transplants in patients without an history of coronary heart disease?"*	**History of treated coronary heart disease is associated with an increased risk of post-SPK transplant cardiovascular events and inferior long-term results.**	2C	97%	94.3%	Report outcomes of SPK transplantation based on severity of coronary heart disease.

Abbreviations: eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; NG, not graded; PAK, pancreas after kidney; PTA, pancreas transplantation alone; SPK, simultaneous pancreas kidney.

5.5.3 | Procurement technique

Because of lack of comparative studies, experts could not decide about which procurement technique should be preferred (i.e., quick en-bloc or conventional technique). Reported results suggest that both techniques can be used based on individual preference and experience, with a preference for quick en-bloc techniques in hemodynamically unstable donors.[135–137]

5.5.4 | Local versus imported grafts

Imported grafts were not considered to be associated with inferior outcomes when compared to local grafts, provided that a proficient team performed the procurement and that cold preservation times were acceptably short.[138,139] The use of imported grafts increases costs and, despite efforts, is associated with longer preservation times that entail higher peak levels of pancreatic enzymes. Finally, results of available studies could have been influenced by several biases such as selective reporting (i.e., lack of intention-to-treat design), and use of different procurement techniques and preservation solutions.

5.5.5 | Preservation time

Ideally, pancreatic grafts should be preserved for <12 h.[140,141] Preservation times up to 24 h can still be accepted. Beyond this time limit, acceptance of a pancreatic graft for transplantation is based on individual circumstances, such as specific recipient needs. As for other recommendations, accumulation of risk factors should be avoided.

5.5.6 | Machine perfusion

No recommendation was drawn on the use of machine perfusion because of lack of clinical studies.[142–144]

5.6 | Expert panel recommendations—pancreas graft allocation

5.6.1 | AB0-incompatible pancreas transplantation

AB0-incompatible pancreas transplantation was not considered an option for standard recipients of both SPK and solitary pancreas transplantations. Concerns about AB0-incompatible SPK transplantation are justified by the extremely low number of reported cases[145,146] that include an episode of humoral rejection, eventually rescued with eculizumab,[145] and by the lack of comparisons with AB0-compatible SPK transplants. Concerns about AB0-incompatible solitary pancreas transplantations are strongly justified by the lack of reported cases. Therefore, AB0-incompatible

TABLE 8 Expert panel recommendations on surgical techniques for pancreas transplantation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
5.1 – *"Is pancreas transplantation with bladder drainage associated with more frequent surgical complications when compared to pancreas transplantation with enteric drainage?"*	**Bladder drainage of whole pancreaticoduodenal grafts is not associated with higher rates of immediate surgical complications when compared to enteric drainage of whole pancreaticoduodenal grafts. Bladder drainage, however, is associated with a higher rate of late reintervention, mostly required for enteric conversion of exocrine drainage.**	**2A**	96%	96.8%	None.
5.2 – *"Is pancreas transplantation with bladder drainage associated with more frequent urologic and metabolic complications when compared to pancreas transplantation with enteric drainage?"*	**Bladder drainage of whole pancreaticoduodenal grafts is associated with higher rates of urological and metabolic complications when compared to enteric drainage of whole pancreaticoduodenal grafts.**	**2C**	98%	100%	None.
5.3 – *"Is SPK transplant with bladder drainage associated with superior immunologic outcomes when compared to SPK transplants with enteric drainage?"*	**Bladder drainage of pancreas allografts at the time of SPK transplantation is not associated with superior immunologic outcomes when compared to enteric drainage.**	**2C**	100%	96.8%	None.
5.4 – *"Is solitary pancreas transplant with bladder drainage associated with superior immunologic outcomes when compared to pancreas transplant with enteric drainage?"*	**Solitary pancreas transplantation with bladder drainage is not associated with superior immunologic outcomes when compared to pancreas transplantation with enteric drainage.**	**2B**	95%	94.2%	None.
5.5 – *"Is pancreas transplantation with portal venous drainage associated with higher rates of surgical complications when compared to pancreas transplantation with systemic venous drainage?"*	**Pancreas transplantation with portal venous drainage is not associated with higher rates of surgical complications when compared to pancreas transplantation with systemic venous drainage.**	**1B**	93%	96.8%	None.
5.6 – *"Is pancreas transplantation with portal venous drainage superior to pancreas transplantation with systemic venous drainage, with respect to immunologic outcomes?"*	**Pancreas transplantation with portal venous drainage does not appear to be superior to pancreas transplantation with systemic venous drainage, with respect to immunologic outcomes.**	**2C**	99%	94.2%	Report immunologic outcomes of PTA with portal and systemic drainage.
5.7 – *"Is pancreas transplantation with portal venous drainage superior to pancreas transplantation with systemic venous drainage with respect to metabolic parameters?"*	**Portal venous drainage of pancreatic allografts does not clearly improve metabolic parameters when compared to systemic venous drainage.**	**1B**	95%	94.2%	None.
5.8 – *"Is duodeno-duodenal anastomosis associated with more frequent surgical complications when compared to duodeno-jejunal anastomosis?"*	**There is no clear evidence that duodeno-duodenostomy, when compared to duodeno-jejunostomy, increases the overall rate of surgical complications after pancreas transplantation. Further data are required to clarify the early risk profile of duodeno-duodenostomy vs. duodeno-jejunonostomy.**	**2C**	88%	90.6%	Design and conduct of prospective and randomized studies comparing safety of duodeno-duodenostomy vs. duodeno-jejunostomy.

(Continues)

TABLE 8 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
5.9 – *"Is duodeno-duodenal anastomosis associated with improved immunologic outcomes when compared to duodeno-jejunal anastomosis?"*	**Duodeno-duodenostomy does not appear to be associated with an immunologic advantage when compared to duodeno-jejunostomy.**	NG	93%	96.8%	Define the impact of endoscopic protocol duodenal and pancreatic biopsy in patients with duodeno-duodenal anastomosis on immunologic outcomes of pancreas transplantation.
5.10 – *"Is intraperitoneal pancreas placement associated with more frequent surgical complications when compared to retroperitoneal pancreas placement?"*	**In the setting of low-quality data, there is no evidence that intraperitoneal graft placement is associated with increased rates of surgical complications when compared to retroperitoneal graft placement.**	2C	73%	94.2%	Conduct registry analysis and/or collaborative studies to compare the outcomes of pancreas transplantation based on site of graft placement (i.e., intraperitoneal vs. retroperitoneal). Initiation of a prospective and randomized study could also be considered.
5.11 – *"Is graft accessibility for percutaneous biopsy improved by retroperitoneal versus intraperitoneal pancreas graft placement?"*	**Percutaneous biopsy of pancreas grafts placed in the retroperitoneum appears feasible, but there is no proof that graft accessibility is improved when compared to grafts placed intraperitoneally due to a lack of comparative studies.**	NG	91%	96.8%	Evaluate the rate of feasibility of percutaneous pancreas biopsy in pancreas allografts placed intra- and retroperitoneally.

Abbreviations: NG, not graded; SPK, simultaneous pancreas kidney.

pancreas transplantation should be considered investigational and should be performed only under urgent conditions or in clinical trials.

5.6.2 | Positive crossmatch

In general, a positive crossmatch contraindicates pancreas transplantation. Limited evidence shows that pretransplant B cell crossmatch positivity does not affect patient and pancreas graft survival, but is associated with higher rates of antibody-mediated rejection.[147,148] Few solitary pancreas transplants were performed despite a positive crossmatch with good outcomes.[149,150]

5.6.3 | Donor-specific antibodies

Detection of DSAs up to an MFI level <5000 may not be an absolute contraindication to pancreas transplantation if T and B cell crossmatch is negative. These recommendations are mostly supported by the lack of specific evidence showing the impact of pretransplant DSA on transplant outcomes. However, these recommendations may be subject to clinical and methodological limitations, as detection of de novo DSA was associated with worse outcomes,[150–154] and MFI values are method dependent and hence center specific.

5.6.4 | HLA mismatching

Reduced HLA mismatching was not specifically recommended in either SPK or solitary pancreas transplantation. These recommendations are supported by evidence showing that in either transplant categories, reduced HLA mismatching decreases the incidence of acute rejection episodes and detection of de novo DSA, but does not improve overall results.[155–159] Additionally, matching for some HLA alleles, such as DR3, is associated with increased risk of autoimmune recurrence of diabetes.[160]

5.6.5 | Preferential allocations of renal grafts

Renal grafts should be preferentially allocated to SPK recipients because of improved results with simultaneous vs. sequential transplantation, practical implications in organization of multi-organ procurement, and a more evident survival advantage of kidney transplantation in diabetic vs. nondiabetic patients.[33,34,37,53–61]

Preferential graft allocation to SPK could not be recommended in case of competition with highly sensitized recipients of a kidney alone transplantation with a negative crossmatch, because of lack of supporting evidence showing which transplant candidate could benefit most from that specific renal graft.[64]

Similarly, there is no evidence supporting priority for kidney allocation in the event of competition between recipients of SPK

TABLE 9 Expert panel recommendations on immunosuppression in pancreas transplantation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
6.1 – *"Is steroid usage versus steroid avoidance associated with improved immunologic outcomes?"*	**Available evidence does not demonstrate that steroid avoidance is associated with inferior immunologic outcomes when compared to a policy of steroid maintenance.**	**1B**	87%	96.7%	Retrospective and prospective studies to identify groups of patients who will better tolerate steroid avoidance.
6.2 – *"Is steroid usage versus early steroid withdrawal associated with improved immunologic outcomes?"*	**Available evidence does not demonstrate that early steroid withdrawal is associated with improved immunologic outcomes when compared to a policy of steroid maintenance.**	**1B**	87%	96.7%	Retrospective and prospective studies to identify groups of patients who will better tolerate early steroid withdrawal. Prospective studies comparing early steroid withdrawal with steroid avoidance should be performed.
6.3 – *"Is steroid withdrawal versus steroid maintenance associated with improved metabolic parameters?"*	**Steroid withdrawal, when maintained long term, seems to be associated with improved metabolic parameters.**	**1C**	81%	86.7%	Design and conduct prospective studies adequately powered to define the impact of steroid avoidance on metabolic parameters after pancreas transplantation in the setting of a homogenous recipient population and concurrent immunosuppression.
6.4 – *"Is early steroid withdrawal versus steroid maintenance associated with improved metabolic parameters?"*	**Early steroid withdrawal seems to be associated with improved metabolic parameters.**	**2C**	77%	90.4%	Design and conduct prospective studies adequately powered to define the impact of early steroid withdrawal on metabolic parameters after pancreas transplantation in the setting of a homogenous recipient population and concurrent immunosuppression.
6.5 – *"Is induction versus no induction therapy associated with improved immunologic outcomes?"*	**The use of induction therapy is associated with improved immunologic outcomes when compared to a policy of no induction therapy.**	**1B**	91%	100%	Additional studies are required to identify optimal induction therapy.
6.6 – *"Is induction versus no induction therapy associated with more early complications?"*	**Induction with depleting antibodies, when compared to no induction, is associated with increased rates and severity of early posttransplant infections that do not result in inferior clinical outcomes.**	**2B**	88%	93.3%	Additional studies are required to identify optimal induction therapy.
6.7 – *"Is induction versus no induction therapy associated with more oncologic complications?"*	**There is no clear evidence that current induction agents increase oncologic complications.**	**2B**	83%	86.7%	Retrospective studies, including registry analysis, should report on induction therapy and long-term oncologic complications in pancreas transplant recipients.
6.8 – *"Is induction therapy with depleting antibodies versus induction therapy with nondepleting antibodies associated with improved immunologic outcomes?"*	**In recipients at low immunologic risk (i.e., PRA <10%), there is no clear evidence that induction with depleting vs. nondepleting antibodies results in improved immunologic outcomes.**	**2C**	82%	86.7%	Design and conduct prospective and randomized trials, comparing policies of induction with depleting antibodies vs. policies of induction with nondepleting antibodies in the setting of "standardized" maintenance immunosuppression, after stratification of recipients based on immunologic risk according to current standards.
6.9 – *"Is induction therapy with depleting antibodies versus induction therapy with nondepleting antibodies associated with more early complications?"*	**Depleting antibodies are associated with increased rates of early complications that do not result in inferior patient and graft survival.**	**2B**	86%	90.4%	Further prospective randomized studies are required to identify optimal induction therapy and define the incidence and severity of early complications specifically caused by induction therapy.

(Continues)

TABLE 9 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
6.10 – *"Is induction therapy with depleting antibodies versus induction therapy with nondepleting antibodies associated with more oncologic complications?"*	**There is no evidence that induction with depleting antibodies vs. induction with nondepleting antibodies is associated with more oncologic complications.**	**2C**	83%	93.3%	Retrospective studies, including registry analysis, should report on long-term oncologic complications in pancreas transplant recipients.
6.11 – *"Is CNI-free immunosuppression associated with inferior immunologic outcomes in pancreas transplantation when compared to CNI-including immunosuppression?"*	**Current evidence suggests that CNI-free immunosuppression is associated with inferior immunologic outcomes.**	**NG**	85%	90.4%	Conduct multicenter and/or registry analyses to define recipient categories in which CNI-free could be safely implemented.
6.12 – *"Is CNI-free immunosuppression associated with reduced toxicity in pancreas transplantation when compared to CNI-including immunosuppression?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	80%	96.7%	Report on intention-to-treat studies describing the outcomes of long-term use of CNI-free protocols.
6.13 – *"Is tacrolimus superior to cyclosporine, with respect to immunologic outcomes, in SPK transplants?"*	**The use of tacrolimus is prevalent in pancreas transplantation as it achieves superior immunologic outcomes when compared to cyclosporine.**	**1C**	82%	90.5%	Tacrolimus has been established as the CNI of choice in pancreas transplantation. Future studies should focus on minimization strategies.
6.14 – *"Is tacrolimus superior to cyclosporine, with respect to immunologic outcomes, in solitary pancreas transplants?"*	**The use of tacrolimus is prevalent in solitary pancreas transplantation and is associated with excellent immunologic results. Despite lack of specific comparative studies, registry data and retrospective series show that tacrolimus achieves superior immunologic results.**	**2C**	83%	90.4%	Tacrolimus has been established as the CNI of choice in pancreas transplantation. Future studies should focus on minimization strategies, especially in patients with early renal dysfunction.
6.15 – *"Is once-a-day tacrolimus formulation superior to twice-a-day tacrolimus formulation in pancreas transplantation?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	79%	96.7%	Registry analysis and long-term data should be reported to establish long-term noninferiority of once-a-day vs. twice-a-day formulations of tacrolimus in SPK. Data on solitary pancreas transplants should also be provided.
6.16 – *"Is the use of mycophenolate formulations versus azathioprine associated with improved immunologic outcomes in pancreas transplantation?"*	**The use of mycophenolate formulations improves the immunologic outcomes of pancreas transplantation when compared to azathioprine.**	**1B**	90%	100%	None.
6.17 – *"Is the use of mycophenolate formulations versus azathioprine associated with more side effects in pancreas transplantation?"*	**Indirect evidence and retrospective data show that mycophenolate mofetil is associated with higher rates of gastrointestinal side effects than azathioprine.**	**NG**	68%	90.4%	None.

(Continues)

TABLE 9 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
6.18 – *"Is the use of m-TOR inhibitors versus mycophenolate formulations associated with improved immunologic outcomes in pancreas transplantation?"*	**In the setting of conflicting data, there is no clear evidence that the use of m-TOR inhibitors vs. mycophenolate formulations is associated with an immunologic advantage in pancreas transplantation.**	**NG**	71%	96.7%	The role of m-TOR inhibitors in pancreas transplantation should be further explored. Future studies should be designed taking into consideration that m-TOR inhibitors probably should not be used in the first few months after transplantation, because of the high incidence of surgical complications.
6.19 – *"Is the use of mycophenolate formulations versus m-TOR inhibitors associated with more side effects in pancreas transplantation?"*	**The use of m-TOR inhibitors vs. mycophenolate formulations as primary immunosuppressants in pancreas transplantation is associated with specific and less well-tolerated side effects.**	**1B**	82%	90.4%	The role of m-TOR inhibitors in pancreas transplantation should be further explored. Future studies should be designed taking into consideration that m-TOR inhibitors probably should not be used in the first few months after transplantation, because of the high incidence of surgical complications.
6.20 – *"Is m-TOR-based immunosuppression versus CNI-based immunosuppression associated with improved immunologic outcomes in pancreas transplantation?"*	**m-TOR-based immunosuppression is not associated with an immunologic advantage when compared to CNI-based immunosuppression in pancreas transplantation.**	**2C**	88%	90.4%	The role of m-TOR inhibitors in pancreas transplantation should be further explored. Future studies should be designed taking into consideration that m-TOR inhibitors probably should not be used in the first few months after transplantation, because of the high incidence of surgical complications.
6.21 – *"Is m-TOR-based immunosuppression versus CNI-based immunosuppression associated with more side effects in pancreas transplantation?"*	**Due to lack of data, this query cannot be answered at the present time.**	**NG**	77%	96.7%	The role of m-TOR inhibitors in pancreas transplantation should be further explored. Future studies should be designed taking into consideration that m-TOR inhibitors probably should not be used in the first few months after transplantation, because of the high incidence of surgical complications.
6.22 – *"Is m-TOR-based immunosuppression versus CNI-based immunosuppression associated with increased formation of donor specific antibodies in pancreas transplantation?"*	**Preliminary data suggest that the use of m-TOR-based immunosuppression vs. CNI-based immunosuppression could be associated with increased formation of donor-specific antibodies in pancreas transplantation.**	**2B**	85%	90.4%	The role of m-TOR inhibitors in pancreas transplantation should be further explored. Future studies should be designed taking into consideration that m-TOR inhibitors probably should not be used in the first few months after transplantation, because of the high incidence of surgical complications.
6.23 – *"Is delayed introduction of m-TOR inhibitor better tolerated than immediate m-TOR inhibitor introduction in pancreas transplantation?"*	**Delayed introduction of m-TOR inhibitors is better tolerated than immediate m-TOR inhibitor introduction in pancreas transplantation.**	**NG**	84%	96.7%	The role of m-TOR inhibitors in pancreas transplantation should be further explored. Future studies should be designed taking into consideration that m-TOR inhibitors probably should not be used in the first few months after transplantation, because of the high incidence of surgical complications.

Abbreviations: CNI, calcineurin inhibitor; m-TOR, mammalian target of rapamycin; NG, not graded; PRA, panel reactive antibody; SPK, simultaneous pancreas kidney.

TABLE 10 Expert panel recommendations on postoperative prophylaxis in pancreas transplantation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
7.1 – *"Does antithrombotic prophylaxis versus no prophylaxis reduce the rate of pancreas graft thrombosis in SPK transplants?"*	**Per protocol antithrombotic prophylaxis is suggested in SPK recipients as it may reduce the rate of pancreas graft loss due to vascular thrombosis**	**NG**	91%	98.8%	Plan prospective randomized comparisons between different protocols of antithrombotic prophylaxis after stratification of patients in risk categories for vascular (graft and/or deep vein) thrombosis.
7.2 – *"Does antithrombotic prophylaxis versus no prophylaxis reduce the rate of pancreas graft thrombosis in solitary pancreas transplantation?"*	**Per protocol antithrombotic prophylaxis is recommended in recipients of solitary pancreas transplants as it may reduce the rate of pancreas graft loss due to vascular thrombosis.**	**2C**	93%	98.8%	Plan prospective randomized comparisons between different protocols of antithrombotic prophylaxis after stratification of patients in risk categories for vascular (graft and/or deep vein) thrombosis.
7.3 – *"Does antithrombotic prophylaxis versus no prophylaxis reduce the rate of deep venous thrombosis and pulmonary embolism in SPK transplants?"*	**There is no evidence to support the use of per protocol antithrombotic prophylaxis in SPK recipients for the prevention of deep venous thrombosis and pulmonary embolism. However, considering that SPK recipients are at higher risk for deep venous thrombosis and pulmonary embolism, as well as of vascular thrombosis of the pancreas allograft, standard antithrombotic prophylaxis, based on local protocols, is recommended.**	**NG**	90%	100%	Report observational studies focusing on incidence and severity of deep venous thrombosis and pulmonary embolism in SPK and in solitary pancreas transplantation recipients.
7.4 – *"Does antithrombotic prophylaxis versus no prophylaxis reduce the rate of deep venous thrombosis and pulmonary embolism in solitary pancreas transplantation?"*	**Considering that recipients of solitary pancreas grafts recipients are at risk for deep venous thrombosis and pulmonary embolism, as well as of vascular thrombosis of the pancreas allograft, antithrombotic prophylaxis is recommended. Type and degree of antithrombotic prophylaxis can be trimmed based on local practice and recipient characteristics.**	**NG**	91%	100%	Report observational studies focusing on incidence and severity of deep venous thrombosis and pulmonary embolism in SPK and in solitary pancreas transplantation recipients.
7.5 – "*Is anticoagulation superior to antiaggregation/antiplatelet therapy in antithrombotic prophylaxis to prevent pancreas graft thrombosis in pancreas transplant recipients?"*	**Either anticoagulation or antiaggregation/antiplatelet therapy, or a combination thereof, can be used in pancreas transplant recipients to reduce the risk of pancreas graft thrombosis. There is no evidence on which strategy is preferred.**	**NG**	90%	96.4%	Report observational studies as well as comparative studies to study the benefits and risks of different therapies or combinations thereof.
7.6 – *"Does antiviral prophylaxis versus no prophylaxis reduce the incidence of CMV infection? in pancreas transplant recipients"*	**Antiviral prophylaxis is suggested in most pancreas transplant recipients. Type of drug as well as dose and duration of prophylaxis can be tailored based on donor/recipient matching for CMV serological status.**	**2B**	98%	98.8%	None.

(Continues)

TABLE 10 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
7.7 – "Is antiviral prophylaxis superior to preemptive therapy in reducing the rate of CMV infection in pancreas transplant recipients?"	**1. Anti-CMV prophylaxis is recommended in seronegative recipients receiving grafts from CMV seropositive donors.**	**2A**	94%	100%	Retrospective and randomized studies in seropositive patients receiving grafts from either seronegative or seropositive donors comparing CMV prophylaxis with preemptive therapy.
	2. In other donor/recipient pairs, there is no clear evidence of which strategy should be preferred. Per center-specific protocols may be applied according to specific guidelines.	**NG**	94%	100%	
7.8 – *"Does antimycotic prophylaxis versus no prophylaxis reduce the rate of fungal infections in pancreas transplant recipients?"*	**Antimycotic prophylaxis should be used as per center protocol to mitigate the risk of invasive fungal infections.**	**NG**	90%	100%	None.
7.9 – *"Does antimicrobial prophylaxis versus no prophylaxis reduce the rate of bacterial infections in pancreas transplant recipients?"*	**Antimicrobial prophylaxis, as per center protocol, is recommended in pancreas transplant recipients.**	**1B**	98%	100%	Observational and prospective studies focusing on specific antibiotic or combination of antibiotics.
7.10 – *"Does vaccination versus no vaccination reduce the rate of infections in pancreas transplant recipients?"*	**Evidence derived from transplantation of other solid organs supports vaccination according to general consensus guidelines.**	**NG**	94%	100%	Observational studies as well as comparative studies.

Abbreviations: CMV, cytomegalovirus; NG, not graded; SPK, simultaneous pancreas kidney.

transplantation and recipients of other simultaneous transplants (i.e., liver-kidney, heart-kidney, and lung-kidney).[65] Finally, there is also no evidence to prioritize graft allocation for SPK transplantation based on the type of diabetes (i.e., type 1 vs. type 2) or recipient age (< vs. >50 years).

5.7 | Expert panel recommendations—recipient selection

5.7.1 | Native renal function in PTA recipients

Baseline renal function is considered key to reduce the risk of accelerated graft loss in PTA recipients function.[73–75] In patients with normal (eGFR ≥ 90 ml/min/1.73 m^2) or mildly decreased (eGFR 60–89 ml/min/1.73 m^2) renal function and proteinuria (without nephrotic syndrome), experts recommended that the benefits of insulin independence should be balanced against the potential risk of worsening of nephropathy. Despite few studies have addressed this issue, this recipient population does not seem to be exposed to an undue risk of renal failure after PTA.[161–164] The same recommendation was released for patients with the same level of renal function and nephrotic syndrome. However, this recommendation could not be graded as it was supported only by anecdotal cases.[165]

5.7.2 | Impact of PTA on the course of chronic complications

In general, PTA improves the course of chronic complications of diabetes as compared to current medical therapies,[76,77,79,80,164,166,167] so that patients with evolving chronic complications could be considered for PTA before severe renal damage has occurred.

5.7.3 | Selection of PAK recipients

In potential PAK recipients, a creatinine clearance ≤45 ml/min was not considered an absolute contraindication to sequential pancreas transplantation. Few and conflicting data exist on the prognostic implication of pre-PAK creatinine clearance using 45 ml/min as a cutoff. In a retrospective and multicenter study, a pre-PAK eGFR ≤ 45 ml/min was associated with an increased probability of kidney graft failure.[66] On the other hand, in another retrospective study, eGFR significantly increased 3 months after grafting in patients with pretransplant eGFR ≤45 ml/min.[168]

In a retrospective and multicenter study reporting on PAK transplant, history of renal rejection was associated with increased risk of posttransplant mortality, renal graft failure, and pancreas graft failure.[66] However, experts did not recommend against PAK transplant in patients with history of renal allograft rejection, provided

TABLE 11 Expert panel recommendations on immunology in pancreas transplantation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
8.1 – *"Does surveillance evaluation of donor specific antibody levels improve the immunologic outcome of pancreas transplantation versus no protocol serology?"*	**De novo donor-specific antibodies are associated with increased rates of pancreas allograft rejection, potentially affecting survival. DSA monitoring after pancreas transplantation is advised.**	**2C**	94%	100%	Conduct prospective studies on the consequences of development of de novo DSA in pancreas transplantation.
8.2 – *"Does surveillance pancreas biopsy improve the immunologic outcome of pancreas transplantation versus no protocol biopsy in SPK transplants?"*	**Protocol biopsy of the kidney or pancreas graft in SPK transplantation may help in surveillance. Use of surveillance biopsy remains center specific.**	**NG**	84%	96.4%	Conduct prospective studies on protocol pancreas and kidney biopsy in SPK recipients.
8.3 – *"Does surveillance pancreas biopsy improve the immunologic outcome of pancreas transplantation versus no protocol biopsy in solitary pancreas transplants?"*	**Protocol biopsy in solitary pancreas transplants may help in graft surveillance. Use of surveillancebiopsy remains center specific. Combination with de novo donor-specific antibodies detection is advisable.**	**NG**	88%	98.8%	Conduct prospective studies on protocol pancreas biopsy in recipients of solitary pancreatic grafts.
8.4 – *"In SPK transplants, is a first rejection episode best treated with steroid pulses or T-cell depleting antibodies?"*	**Steroids can be used for clinically diagnosed rejection episodes or biopsy-proven grade 1 rejection. Higher biopsy grades require T-cell depleting antibodies. Treatment can be individualized based on clinical history and immunologic data.**	**2C**	81%	98.8%	Conduct prospective and randomized comparisons between different treatment strategies in recipients of SPK, with stratification of rejection severity based on histology scores.
8.5 – *"In solitary pancreas transplant recipients, is a first rejection episode best treated with steroid pulses or T-cell depleting antibodies?"*	**Steroids can be used for clinically diagnosed rejection episodes or biopsy-proven grade 1 rejection. Higher biopsy grades require T-cell depleting antibodies. Treatment can be individualized based on clinical history and immunologic data.**	**NG**	77%	98.8%	Conduct prospective and randomized comparisons between different treatment strategies in recipients of SPK, with stratification of rejection severity based on histology scores.
8.6 – *"In SPK transplants, is a second rejection episode best treated with steroid pulses or T-cell depleting antibodies?"*	**Treatment of second rejection episodes in SPK transplantation should be individualized based on clinical history, immunologic data, and/or biopsy results. In general, pancreas graft biopsy can add information. T-cell depleting antibodies should be used in most patients.**	**NG**	85%	100%	Conduct multicenter studies and/or registry analyses on treatment and outcome of second rejection episodes in SPK recipients.
8.7 – *"In solitary pancreas transplant recipients, is a second rejection episode best treated with steroid pulses or T-cell depleting antibodies?"*	**Treatment of second rejection episodes in solitary pancreas transplantation should be individualized based on clinical history, immunologic data, and/or biopsy results. In general pancreas graft biopsy can add information. T-cell depleting antibodies should be used in most patients.**	**NG**	86%	100%	Conduct multicenter studies and/or registry analyses on treatment and outcome of second rejection episodes in recipients of solitary pancreas transplants.
8.8 – *"What is the ideal treatment of antibody-mediated rejection in SPK transplants?"*	**Due to lack of specific data, treatment of antibody-mediated rejection in SPK transplantation follows the protocols established in kidney transplantation. Treatment can be individualized based on clinical history and immunologic data.**	**NG**	86%	100%	Conduct multicenter studies and/or registry analyses on treatment and outcome of antibody-mediated rejection in recipients of solitary pancreas transplants.

(Continues)

TABLE 11 (Continued)

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
8.9 – *"What is the ideal treatment of antibody-mediated rejection in solitary pancreas transplantation?"*	**Due to lack of specific data, treatment of antibody-mediated rejection in solitary pancreas transplantation follows the protocols established in kidney transplantation. Treatment can be individualized based on clinical history and immunologic data.**	NG	87%	100%	Conduct multicenter studies and/or registry analyses on treatment and outcome of antibody-mediated rejection in recipients of solitary pancreas transplants.
8.10 – *"Autoimmune recurrence. How patients should be surveilled?"*	**Autoantibodies related to autoimmune recurrence of type 1 diabetes can be assayed per protocol in patients with a functioning pancreas allografts. Pancreas allograft biopsy can be used to establish the diagnosis of autoimmune recurrence of diabetes in patients with rising antibodies and/or impaired pancreas allograft function (in the absence of other obvious reasons). The use of surveillance allograft biopsy in patients without laboratory and/or clinical suspicion of autoimmune recurrence can be performed per center-specific protocols.**	2C	83%	100%	Systematically investigate autoimmune reactivity in pancreas transplant recipients and report on incidence, severity, and treatment of autoimmune recurrence.

Abbreviations: DSA, donor-specific antibody; NG, not graded; SPK, simultaneous pancreas kidney.

that HLA matching is optimized and DSA are avoided, because of lack of clear evidence discouraging sequential pancreas transplantation in these recipients.

Regarding the timing of sequential pancreas transplantation, experts did not contraindicate early PAK transplant (i.e., <6 months from kidney transplant) and underscored that results are improved if PAK transplant is performed within 1 year after kidney transplantation.[66,169,170]

5.7.4 | Preemptive SPK

Experts acknowledged that preemptive SPK transplant is associated with improved outcomes when compared to SPK transplant performed in patients undergoing dialysis. Indeed, several retrospective studies, including registry analysis, show that preemptive SPK transplantation is associated with improved outcomes when compared to SPK transplantation performed in patients undergoing dialysis. Time on dialysis also has a negative prognostic impact in SPK recipients.[59,171–174]

5.7.5 | Other risk factors relevant to recipient selection

Obese patients may face a higher rate of early complications when compared to nonobese recipients[175–179] but obesity alone is not a contraindication to SPK transplant, considering that good results were reported.[116] Discussion highlighted also the importance of underweight (BMI < 18.5 kg/m^2), as a risk factor of long-term mortality.[116]

History of amputation and coronary heart disease were both considered risk factors for inferior results, but neither was deemed an absolute contraindication to SPK transplantation. Advanced atherosclerotic peripheral arterial disease, including the need for limb amputation in diabetic patients, is associated with increased mortality.[180] The association of advanced atherosclerotic peripheral arterial disease with end-stage renal failure increases the risk of mortality.[181] In general, pre-SPK limb amputation predicts inferior transplant outcomes as it portends higher cardiovascular risk.[182] Similarly, pretransplant history of coronary artery disease increases the risk of major adverse cardiovascular events after transplantation.[183,184] However, coronary artery disease is not a major risk factor for mortality if medically treated and revascularized according to standard guidelines.[185] Discussion highlighted the importance of assessment of coronary artery disease in all patients undergoing pancreas transplantation.

5.8 | Expert panel recommendations—surgical techniques

5.8.1 | Exocrine drainage

Several studies, including three with a prospective design, have compared bladder and enteric drainage of exocrine secretions in

TABLE 12 Expert panel recommendations on immunology in pancreas transplantation

Query	Recommendation	GRADE	Quality score	Agreement	Proposed action
9.1 – *"What are the effects of SPK transplants on retinopathy?"*	**Successful SPK transplantation may contribute to stabilization/improvement in diabetic retinopathy depending on retinopathy stage. Patients must be monitored closely by an ophthalmologist for progression in advanced retinopathy stages.**	**2B**	83%	97.2%	Prospective studies comparing SPK transplantation with standard medical diabetes therapies are highly advisable.
9.2 – *"What are the effects of SPK transplants on the development/occurrence of diabetic nephropathy in the kidney graft?"*	**Successful SPK transplantation prevents development/occurrence of diabetic nephropathy in the kidney graft.**	**2B**	82%	91.7%	Further studies are highly advisable aiming to compare kidney graft survival rates in SPK and live donor renal transplantation.
9.3 – *"What are the effects of SPK transplants on neuropathy?"*	**SPK transplantation has beneficial effects on mild to moderate neuropathy.**	**2B**	82	94.4%	Studies are needed on the impact of SPK transplantation on advanced neuropathy.
9.4 – *"What are the effects of SPK transplants on the cardiovascular system?"*	**SPK transplantation has beneficial effects on the cardiovascular system, including lower rate of cardiovascular death compared with either dialysis or kidney alone transplantation.**	**2B**	85%	94.4%	More prospective studies are advisable to confirm the positive impact of SPK transplantation at the cardiovascular level, in particular for peripheral arteries.
9.5 – *"What are the effects of SPK transplants on quality of life?"*	**Successful SPK transplantation is associated with improved quality of life.**	**1B**	79%	100%	None.
9.6 – "What are the effects of PTA on retinopathy?"	**Successful PTA contributes to stabilization/improvement in diabetic retinopathy.**	**2B**	79%	91.7%	Prospective studies comparing PTA with standard medical diabetes therapies highly advisable.
9.7 – "What are the effects of PTA on nephropathy?"	**Functioning PTA improves the evolution of diabetic nephropathy. These beneficial effects may be offset by CNI-related nephropathy.**	**NG**	82%	94.4%	More studies are needed to evaluate the role of associated albuminuria pre-PTA and to explore whether genetic factors play a role in affecting the course of native kidney function in PTA recipients.
9.8 – "What are the effects of PTA on neuropathy?"	**Evidence suggests that successful PTA improves the course of diabetic neuropathy.**	**2C**	81%	97.2%	Studies are urgently needed on the impact of PTA on somatic and autonomic diabetic neuropathy.
9.9 – "What are the effects of PTA on the cardiovascular system?"	**There is insufficient evidence available on the effects of PTA on the cardiovascular system.**	**NG**	73%	94.4%	Studies are urgently needed on the impact of PTA on the cardiovascular system.
9.10 – "What are the effects of PTA on quality of life?"	**Prospective studies are needed to assess the role of PTA on recipients' quality of life in comparison vs. pre-PTA.**	**NG**	78%	97.2%	Prospective studies are needed to assess the role of PTA on recipients' quality of life in comparison vs. pre-PTA.

Abbreviations: CNI, calcineurin inhibitor; NG, not graded; PTA, pancreas transplantation alone; SPK, simultaneous pancreas kidney.

pancreas transplantation. Bladder drainage, when compared to enteric drainage, does not increase immediate surgical complications but is associated with higher rates of late reintervention (mostly for enteric conversion).[186–206]

Only one study clearly showed a higher rate of surgical complications in bladder-drained transplants (41% vs. 26%; $p = .04$).[186] Need for enteric conversion was not considered a surgical complication in these studies, and was reported to occur in up to 20% of recipients.[190] Two recent long-term studies reported that >40% of patients with bladder drainage require enteric conversion at some point in time.[197,207] Additionally, bladder drainage increased the rate of metabolic and urologic complications,[188,198,208–216] and did not improve immunologic outcome of either SPK[187,190-192,196-198,205,206,208,214,217,218] or solitary pancreas transplantations.[70,171,219]

Duodeno-duodenostomy (vs. duodeno-jejunostomy) was not considered to clearly increase the overall rate of surgical complications after pancreas transplantation, despite higher rates of bleeding.[220–225] Additionally, duodeno-duodenostomy was not associated with improved immunologic outcomes, because of easier graft surveillance (endoscopic biopsy) with earlier diagnosis of rejection,[222–224] as reported in a study.[221] Indeed, duodenal biopsy alone may not be sufficient to rule out rejection, as suggested by both experimental[226] and clinical studies.[227,228]

5.8.2 | Venous drainage

No study demonstrated that portal venous drainage increases surgical risk[187,229–235] but, on the other hand, no study showed either an immunologic,[199,207,208,229,236] or a metabolic advantage.[233,234,237–244]

5.8.3 | Graft placement

Regarding final graft position, intraperitoneal graft placement (vs. retroperitoneal graft placement) was not associated with higher incidence of surgical complications because of lack of comparative studies.[224,225,245,246] The hypothesis that retroperitoneal graft placement facilitates percutaneous graft biopsy remains to be proven.

5.9 | Expert panel recommendations—immunosuppression

5.9.1 | Steroids

The use of steroids remains prevalent in maintenance protocols after pancreas transplantation.[40] Despite heterogeneity in background immunosuppressive regimens complicating interpretation of data, steroid avoidance is feasible in a good proportion of pancreas transplant recipients and does not result in inferior results when compared to steroid maintenance.[247–252] Early steroid withdrawal is also feasible.[253–258] Steroids avoidance, if maintained long term, is associated with improved metabolic profile.[257,259–262]

5.9.2 | Induction therapy

The use of induction therapy, typically in the form of depleting antibodies, is prevalent across all pancreas transplant categories.[40] Two randomized controlled trials showed that induction therapy is associated with improved immunologic outcomes when compared to a policy of no induction therapy.[263,264] However, there is no clear evidence that induction with depleting vs. nondepleting antibodies results in improved immunologic outcomes in patients at low immunologic risk (i.e., PRA < 10%).

Regarding safety, induction with depleting antibodies is associated with cytokine release syndrome requiring premedication and with an increased incidence of early posttransplant infections, in particular CMV viremia, when compared with a policy of use of nondepleting antibodies or no induction therapy.[40,263,265] Despite experience in renal transplantation showing that induction therapy with depleting antibodies is associated with increased rates of oncologic complications,[266] there is no clear evidence that this applies to recipients of pancreas transplantation.

In comparison to a policy of no induction, experts agreed that induction is associated with improved immunologic outcomes, and that induction with depleting antibodies is associated with increased rates and severity of early posttransplant infections (that do not result in inferior patient and graft survival) without evidence of increased risk of oncologic complications.

In comparison to a policy of induction with nondepleting antibodies in recipients at low immunologic risk (i.e., PRA < 10%), experts agreed that induction with depleting antibodies vs. induction with nondepleting antibodies does not improve immunologic outcomes and is associated with increased rates and severity of early posttransplant infections (that do not result in inferior patient and graft survival). However, there is no clear evidence that induction with depleting antibodies increases the risk of oncologic complications.

5.9.3 | CNI-free regimen

The main rationale for CNI-free immunosuppression is to avoid the side effects of CNI-based immunosuppression. However, long-term data on outcomes of patients maintained on CNI-free regimens after pancreas transplantation are lacking. Short-term data are sparse and suggest that this strategy is associated with inferior immunologic outcomes without a clear reduction in drug-related toxicity.[252,262]

Relatively more data are available for protocols of immunosuppression minimization and delayed withdrawal of CNI. In selected patients at low immunologic risk, these strategies may achieve immunologic results similar to CNI-based immunosuppression.[256,274,275,276] Results of a prospective and randomized trial

published after this Consensus Conference showed that CNI-free immunosuppression based on sirolimus achieved good patient and graft survival rates, but at the price of high drop-out rate (68%) and increased incidence of de novo DSA anti-class II HLA antigens at 12 months (19% vs. 2%). Additionally, due to high surgical complication rates, introduction of sirolimus was delayed until posttransplant month 3.[277] A phase 2 multicenter open-label randomized trial, that was also published after the Consensus Conference, compared the outcomes of SPK recipients treated with an immunosuppressive regimen including tacrolimus vs. a protocol using low-dose CNI plus costimulation blockade (belatacept) with intended CNI withdrawal. In both arms, patients received induction therapy with rabbit thymoglobulin, while steroids were rapidly withdrawn, and maintenance therapy included also mycophenolate sodium or mycophenolate mofetil. CNI withdrawal was associated with increased rates of pancreas rejection, despite similar rates of kidney rejection. The study was terminated after randomization of 43 of 60 planned patients. The authors concluded that costimulation blockade with belatacept did not provide sufficient immunosuppression to reliably prevent rejection of the pancreas in SPK transplants undergoing CNI withdrawal. Low-dose CNI used in conjunction with belatacept was sufficient to prevent rejection of both kidney and pancreas, while increasing the incidence of opportunistic infections.[278]

In comparison to CNI-based immunosuppression, experts agreed that CNI-free immunosuppression is associated with inferior immunologic outcomes without evidence of reduced drug-related toxicity.

5.9.4 | CNI-based regimen

The use of tacrolimus is prevalent in all categories of pancreas transplantation.[40] One multicenter, prospective, and randomized study showed that tacrolimus achieved superior immunologic results when compared to cyclosporine in SPK transplant recipients, although the high incidence of pancreas allograft thrombosis recorded in the cyclosporine arm may constitute a major bias of this study.[267] A single center, prospective, and randomized study did not confirm the superiority of tacrolimus over cyclosporine in SPK transplant recipients.[268] Basically, the introduction of tacrolimus corresponded to clinical success in solitary pancreas transplantation and comparison with historical series using cyclosporine showed improved results.[72,269]

Reported experience with the use of once-a-day tacrolimus formulation in pancreas transplantation is limited. Data are available only for SPK transplantation and show that once-a-day tacrolimus formulation is associated with excellent patient and graft survival, and that patients can be safely converted from standard tacrolimus to long-acting tacrolimus.[270–273]

In comparison with cyclosporine, experts agreed that the use of tacrolimus is prevalent in all pancreas transplant categories and is associated with superior immunologic outcomes. No conclusion could be drawn on the comparative efficacy of once-a-day vs. twice-a-day tacrolimus formulations due to lack of supporting data.

5.9.5 | Mycophenolate formulations

The use of mycophenolate formulations is clearly prevalent in pancreas transplantation.[40] A prospective, multicenter, randomized, open-label study comparing mycophenolate mofetil to azathioprine, in the setting of OKT3 induction and steroid/cyclosporine maintenance, did not demonstrate the superiority of mycophenolate mofetil in SPK transplantation.[279] An additional prospective and randomized study conducted at a single center showed that mycophenolate mofetil significantly decreased the incidence of biopsy-proven acute rejection in SPK transplantation.[280] A review showed that the use of mycophenolate mofetil in combination with a CNI and steroids, after induction treatment, was associated with a 40% reduction in the incidence of acute rejection at 1 year after pancreas transplantation.[281] Retrospective studies have shown that mycophenolate mofetil compared to azathioprine improves immunologic outcome of pancreas transplantation when used in combination with either tacrolimus or cyclosporine, but at the price of more gastrointestinal side effects that frequently require dose reduction.[269,282,283]

In comparison to azathioprine, experts agreed that mycophenolate formulations improve immunologic outcomes but are associated with more gastrointestinal side effects.

5.9.6 | m-TOR inhibitors

An analysis of all pancreas transplants included in the UNOS database from 1987 to 2016 showed that the use of m-TOR inhibitors when compared to immunosuppressive protocols without m-TOR inhibitors was associated with improved allograft survival and patient survival up to 10 years after transplantation.[284] However, there is no evidence that the use of m-TOR inhibitors improves immunologic outcomes of pancreas transplantation when compared to mycophenolate formulations. The results of a multicenter, prospective, and randomized study comparing sirolimus and mycophenolate mofetil in SPK recipients were never published. Preliminary data from this trial showed that sirolimus was potentially associated with improved immunologic outcomes[285] but at the price of a higher incidence of surgical complications (i.e., delayed wound healing, lymphocele, and incisional hernia) and hyperlipidemia.[286] Two retrospective studies showed that the results of sirolimus and mycophenolate mofetil were similar when used in combination with tacrolimus.[254,287] A single center, randomized, and prospective study with 10-year follow-up showed significantly better rates of rejection with sirolimus,[288] although allograft and patient survival rates were similar.

There are only few data on comparative efficacy of m-TOR-based immunosuppression vs. CNI-based immunosuppression in pancreas transplantation when these drugs are used as primary

immunosuppressants. In general, CNI-free immunosuppression in pancreas transplantation is associated with inferior immunologic outcomes.[251,266] In selected patients at low immunologic risk, m-TOR inhibitors may allow CNI minimization, while maintaining satisfactory immunologic results.[252,275,276] Data from a recently published prospective and randomized study showed that immediate use of sirolimus after SPK transplantation, in the context of CNI-free immunosuppression, is associated with an increased rate of surgical complications.[277] Additionally, the use of m-TOR inhibitors in the setting of CNI-free immunosuppression could increase the formation of DSA.[289] This issue is not fully addressed in the literature. Reported outcomes range from no effect,[290] to increased development on nondonor-specific HLA antibodies, with immediate evidence of worse graft outcome,[291] and to an increased incidence of de novo DSA anti-class II HLA agents at 1 year after transplantation.[277]

In comparison with mycophenolate formulations, and in the context of limited evidence, experts acknowledged that the use of m-TOR inhibitors is not clearly associated with an immunologic advantage. Additionally, when both drugs are used as primary immunosuppressants, experts agreed that the use of m-TOR inhibitors vs. mycophenolate formulations is associated with specific and less well-tolerated side effects.

In comparison with CNI-based immunosuppression, experts agreed that the use of m-TOR inhibitors is not associated with an immunologic advantage. Lack of specific evidence did not allow experts to define if m-TOR-based immunosuppression is associated with more side effects.

5.9.7 | Summary of immunosuppression

State of the art immunosuppressive regimen for all categories of pancreas transplantation consists in induction with depleting antibody and maintenance with tacrolimus, mycophenolate, and steroids. Early steroid withdrawal is feasible and may result in improved metabolic parameters in the long-term period.

The avoidance of CNI is associated with inferior immunologic outcomes without clear evidence of reduced toxicity. Concerns about early outcomes of CNI-free immunosuppression are an additional and major clinical issue.

Mycophenolate formulations improve immunologic outcomes when compared to azathioprine but are associated with high rates of gastrointestinal side effects.

m-TOR-based immunosuppression is not associated with an immunologic advantage when compared to CNI-based immunosuppression. The use of m-TOR inhibitors vs. mycophenolate formulations could be associated with improved immunologic outcomes but carry more side effects, especially if used as primary immunosuppressants. Immediate posttransplant use of m-TOR inhibitors is associated with high rates of surgical complications, making delayed introduction preferable. In the context of CNI-free regimens, m-TOR-based immunosuppression may increase the development of DSA.

5.10 | Expert panel recommendations—postoperative prophylaxis

5.10.1 | Antithrombotic prophylaxis

Vascular thrombosis is the leading cause of early graft loss in pancreas transplantation.[292] The high incidence of vascular thrombosis in pancreas grafts is explained by multiple factors such as the hypercoagulable state of diabetic patients,[292,293] increased donor age,[294] donor obesity,[292] cerebrovascular cause of donor death,[294] low microcirculatory blood flow of the pancreas allograft,[295] need for back table vascular reconstructions,[294] preservation injury,[292] long preservation times,[296] occurrence of graft pancreatitis,[292,294] endothelial damage promoted by high CNI levels,[293] and the disproportion in size between the large vascular pedicles and the small pancreatic branches following splenectomy and enterectomy.[292] Finally, vascular allograft thrombosis may also be caused, or promoted, by missed rejection.[297]

Experts recommended that per protocol antithrombotic prophylaxis should be given to all pancreas transplant recipients, although there is not enough evidence to define which prophylaxis protocol should be used.[293,298–305]

Regarding deep venous thrombosis, recipients of both SPK and solitary pancreas transplantation are at increased risk for deep venous thrombosis and pulmonary embolism. However, no study is available to compare a policy of no antithrombotic prophylaxis vs. a policy of per protocol antithrombotic prophylaxis in pancreas transplant recipients for the prevention of deep venous thrombosis and pulmonary embolism. There are also no studies comparing different anticoagulation prophylaxis protocols.[293,298–305] Experts did not recommend antithrombotic prophylaxis for the prevention of deep venous thrombosis in SPK recipients, due to lack of supporting evidence, while recommended antithrombotic prophylaxis in recipients of solitary pancreas transplants, taking into consideration also the higher risk of graft thrombosis in this recipient categories. Due to lack of evidence, decision on type and degree of antithrombotic prophylaxis could not be specified.

A further question was about the use of anticoagulation vs. anti-aggregation antiplatelet therapy. Many pancreas transplant recipients are already under chronic anti-aggregant therapy at the time of transplantation due to underlying cardiovascular disease or cardiovascular risk factors. Therefore, postoperative anticoagulant prophylaxis typically occurs in the setting of preexisting anti-aggregation. Because of lack of comparative studies, experts could not indicate a preference for a specific strategy.

5.10.2 | Antiviral prophylaxis

Recipients of pancreas transplantation are at high risk for virus activation or infection due to the frequent use of induction therapy with T-cell depleting antibodies, in particular when steroids are also used.[40] Most of the available literature focuses on cytomegalovirus

infection as infection with other viruses occurs less frequently. Published studies[251,263,306–312] and a Consensus Conference[313] on the management of cytomegalovirus in solid organ transplantation show that antiviral prophylaxis should be provided to pancreas transplant recipients. The type of antiviral drug, as well as duration of prophylaxis, can be tailored based on donor/recipient matching for cytomegalovirus serological status. When anti-cytomegalovirus medications are not administered, prophylaxis against herpes simplex virus and varicella-zoster virus should be considered.

Based on this background, experts recommended implementation of antiviral prophylaxis in most pancreas transplant recipients.

Regarding the use of prophylaxis or preemptive cytomegalovirus therapy, experts recommended prophylaxis in seronegative recipients receiving grafts from CMV-seropositive donors.[306,313] In other donor/recipient pairs, either strategies were considered acceptable.

5.10.3 | Antimycotic prophylaxis

Pancreas transplantation is associated with a risk of fungal infection. Fungal infections are associated with reduced patient and graft survival. Available literature does not provide clear evidence that fungal prophylaxis should be used in all pancreas transplant recipients. A selective policy of antifungal prophylaxis in patients at higher risk for invasive fungal infection is justified. Most centers use a protocolized short duration, systemic antifungal prophylaxis strategy.[312,314–321] Experts recommended the use of antimycotic prophylaxis, as per center protocol, to mitigate the risk of invasive fungal infections.

5.10.4 | Antimicrobial prophylaxis

Pancreas transplantation is associated with a high risk of bacterial infection. Antibacterial prophylaxis is largely prescribed following pancreas transplantation and is associated with a reduced incidence and severity of posttransplant bacterial infections. Debate remains concerning the ideal combination of antibiotics to use for prophylaxis as well as duration of prophylaxis.[322–328] Experts recommended the use of antimicrobial prophylaxis, as per center protocol.

5.10.5 | Vaccination

This consensus was held before the SARS-CoV-2 pandemic. Therefore, any recommendations on vaccination against SARS-CoV-2 have not been included.

While vaccination strategies have not been studied specifically in the setting of pancreas transplantation, evidence derived from experience in transplantation of other solid organs[329] supports a role for multiple vaccinations, based on individual needs, to reduce the incidence of late post-transplant infections. Therefore, experts recommended vaccinations in pancreas transplant recipients, based on general consensus guidelines.

5.11 | Expert panel recommendations—immunology

5.11.1 | DSA monitoring

The role of DSA is emerging as an important factor in immunological graft failure. Regarding a policy of per protocol evaluation of DSA, there is no specific study that has compared the immunologic outcome of pancreas transplant recipients with vs. without DSA monitoring. However, despite conflicting data,[154,330] several studies showed an association between de novo DSA and increased rate of rejection episodes/poorer graft survival in pancreas transplantation.[150–153] Experts recommended DSA monitoring after pancreas transplantation.

5.11.2 | Per protocol pancreas graft biopsy

There is no specific evidence supporting protocol biopsies in SPK transplant recipients, but in solitary pancreas grafts protocol biopsy improved immunologic outcomes.[331,332] Considering also that concordance between renal and pancreatic biopsy is not complete,[333–335] experts concluded that per protocol biopsy in SPK transplant recipients is center specific and may help in immunologic surveillance.

In solitary pancreas transplantation, few studies showed that protocol pancreas biopsy may improve immunologic outcome.[331,332] Pancreatic biopsy should be preferred over duodenal biopsy, when feasible, because concordance between pancreatic and duodenal biopsies is limited.[228] Experts concluded that use of protocol biopsy in solitary pancreas transplants is center specific. It may help in graft surveillance, especially if combined with DSA monitoring.

5.11.3 | Treatment of first rejection episodes

No prospective and randomized study has compared steroids vs. T-cell depleting antibody as a treatment of first rejection episodes in pancreas transplantation. Most authors treat first, or mild, rejection episodes with steroid pulses. Treatment with T cell depleting antibodies is typically reserved to patients with recurrent, or moderate/severe, rejection episodes.[333,336–339] A recent study found that outcome of first rejection episodes is not improved by administration of T-cell depleting antibodies when mild, but is improved when moderate or severe.[340] Experts recommended the use of steroids for treatment of clinically diagnosed rejection episodes or biopsy-proven grade 1 rejection. T-cell depleting antibodies can be used for higher rejection grades or based on clinical history and immunologic data.

5.11.4 | Treatment of second rejection episodes

There is basically no evidence in the literature supporting how a second rejection episode should be treated in recipients of solitary pancreas transplants. Experts recommended that treatment of second rejection episodes should be individualized. T-cell depleting antibodies should be used in most patients.

5.11.5 | Treatment of antibody-mediated rejection

The importance of antibody-mediated rejection in pancreas transplantation is becoming increasingly evident. However, the definition of antibody-mediated rejection has changed over time. Earlier studies defined antibody-mediated rejection as the combined presence of DSAs, graft dysfunction, and C4d positivity on histology slides.[341,342] These criteria were incorporated in the Banff schema for grading of pancreas allograft rejection published in 2008.[343] However, DSAs can be detected in the absence of rejection, graft dysfunction can occur without rejection and, as shown in kidney transplantation, C4d positivity may not be sufficient to establish a diagnosis of antibody-mediated rejection.[344] Updated Banff grading schema replaced graft dysfunction with histologic evidence of acute tissue injury.[344,345]

Currently available treatment strategies are basically derived from renal transplantation, and there are no comparative studies that specifically address the efficacy of these protocols in pancreas transplantation. Treatment options include the use of plasma exchange and intravenous immunoglobulins either alone[342,346] or in combination with rituximab.[341,347,349] A management algorithm was proposed by Redfield et al in 2015.[348]

Because of lack of specific data, experts could not draw a specific recommendation, and suggested that treatment of antibody-mediated rejection in pancreas transplantation can be individualized based on clinical history and immunologic data.

5.11.6 | Surveillance for autoimmune recurrence of diabetes

After the first description by Sutherland, Goetz, and Sibley in 1989,[350] autoimmune recurrence of diabetes is increasingly recognized as an important cause of graft loss. While the presence of autoantibodies before pancreas transplantation has no impact on graft outcome, major autoantibody changes (serum conversion, spreading from one to multiple autoantibodies, or titer increase) are predictive of subsequent loss of graft function.[160,351–353] More recently, the recurrence of autoreactive CD4 T cells has been described in both recipients' blood and pancreas grafts.[354] Monitoring of autoreactive CD4 T cells, in combination with autoantibodies and biopsies, was described in three SPK recipients with autoimmune recurrence.[355] Current status of autoimmune monitoring in pancreas transplantation is described in several reviews.[356,357]

Experts recommended per protocol assay of autoantibodies related to autoimmune recurrence of type 1 diabetes. In patients with rising antibodies and/or impaired pancreas allograft function (in the absence of other obvious reasons of graft injury), experts recommended also the use of pancreas allograft biopsy to establish the diagnosis of autoimmune recurrence of diabetes.

5.12 | Expert panel recommendations—follow-up

5.12.1 | Effects of pancreas transplantation on diabetic retinopathy

The impact of SPK transplantation on diabetic retinopathy is controversial.[78,358–363] In the most recent studies, diabetic retinopathy is stabilized/improved after successful SPK transplantation.[78,358,359] It should be noted that diabetic retinopathy is often severe in these patients, which makes reversal of the retinal damage unlikely. Results are better if accurate retinal examination is performed pre-SPK transplantation and appropriate ocular treatment ensured. Experts acknowledged that successful SPK transplantation may contribute to stabilization/improvement of diabetic retinopathy depending on retinopathy stage, and recommended that patients are monitored closely by an ophthalmologist for progression in advanced retinopathy stages.

Few studies have addressed the effects of PTA on retinopathy (including one in comparison with insulin therapy and one in comparison with failed PTA). Generally, successful PTA is associated with improved stabilization of advanced retinopathy and increased lesion reversal in nonproliferative retinopathy. One study reports the deceleration of retinal damage early after PTA, with potential stabilization over time.[26,78,80] Experts acknowledged that successful PTA contributes to stabilization/improvement of diabetic retinopathy.

5.12.2 | Effects of pancreas transplantation on diabetic nephropathy

Several studies have compared the effects of SPK transplantation on the survival of the transplanted kidney in comparison with the survival of renal alone grafts from deceased or living donors. The superiority of SPK vs. deceased donor renal transplantation is well established, whereas that vs. live donor renal transplantation is still uncertain. A few studies suggest that the function of the grafted kidney is better in SPK transplant than in recipients of live donor renal transplantation.[364–366] Experts acknowledged that successful SPK transplantation prevents development/occurrence of diabetic nephropathy in the kidney graft.

Several studies have evaluated the effects of PTA on the native kidneys, which can be damaged by immunosuppressive drug nephrotoxicity. Over the years, due to better titration of immunosuppression and selection of recipients, the rate of chronic kidney disease in PTA recipients has progressively diminished. Currently, the 10-year

cumulative incidence of post-PTA chronic kidney disease ranges from 10 to 30% when the pre-PTA eGFR is >60 ml/min/1.73 m^2, with some authors suggesting a threshold of eGFR pre-PTA of 70 ml/min/1.73 m^2. Less information is available on the role of associated albuminuria. Some data show that in patients with a functioning PTA and not evolving toward chronic kidney disease, the decrease in eGFR over time is similar to that observed in the general T1D population.[26,27,76] Experts acknowledged that functioning PTA improves the evolution of diabetic nephropathy, but underscored as these beneficial effects may be sometimes offset by CNI-related nephropathy.

5.12.3 | Effects of pancreas transplantation on diabetic neuropathy

Several studies, including prospective analyses, have evaluated the effects of SPK transplantation on somatic and autonomic neuropathy, also in comparison with kidney transplant alone and standard insulin therapy. Overall, evidence suggests that SPK transplantation improves symptoms of somatic neuropathy, parameters of peripheral nerve function, and autonomic nervous system cardiorespiratory tests, possibly also due to rescue from uremia. Insufficient data are available on the impact of SPK transplantation on advanced autonomic nervous system alterations, such as gastroparesis and neurogenic bladder.[79,367–372] Experts acknowledged that SPK transplantation has beneficial effects on mild to moderate neuropathy.

Scant information is available on the effects of PTA on diabetic neuropathy. Published data suggest some improvements in nerve conduction velocity, autonomic function, and epinephrine response.[28,166] Experts acknowledged that successful PTA may improve the course of diabetic neuropathy.

5.12.4 | Effects of pancreas transplantation on cardiovascular system

A few studies evaluated the effects of SPK transplantation on the cardiovascular system, also in comparison with kidney transplant alone. SPK transplantation has been reported to be associated with lower rate of cardiovascular death and reduced progression of carotid and lower limb arterial damage.[52,182,373–377] Experts acknowledged that SPK transplantation has beneficial effects on the cardiovascular system, including lower rate of cardiovascular death compared with either dialysis or kidney alone transplantation.

Limited data are available on the effects of PTA on the cardiovascular system, and mainly from a single group. PTA can lead to early and persistent reduction of a few cardiovascular risk factors (total and LDL cholesterol, blood pressure) and improved cardiac morphology and function (including diastolic parameters) as assessed by ultrasound evaluation.[29,167,375–377] Experts concluded that evidence available on the effects of PTA on the cardiovascular system is not sufficient to draw a final conclusion.

5.12.5 | Effects of pancreas transplantation on quality of life

Several studies have evaluated the effects of SPK transplantation on recipients' quality of life, mostly in comparison with kidney graft alone recipients or diabetic patients on dialysis. Consistently, successful grafting is associated with improved scores in multiple domains.[21–25] Experts acknowledged that successful SPK transplantation is associated with improved quality of life.

Little information is available on the effects of PTA on recipients' quality of life. Available data suggest enhanced quality of life after PTA.[30–32] Experts acknowledged that PTA improves recipient quality of life compared to patients on waiting list.

5.13 | Research agenda

Opportunities for research are presented as proposed actions for each recommendation in Tables 4-12. In general, the level of evidence was quite low demonstrating that well-designed studies as well as meta-analyses are greatly needed for many topics.

Additional studies are more urgently needed for volume-outcome relationship, pancreas allocation strategies, efficacy of IGL-1 solution (vs. UW solution), clinical role of machine perfusion, induction with depleting antibodies vs. induction without depleting antibodies in patients at low immunologic risk, pancreas transplantation in patients with type 2 diabetes, long-term results of preemptive SPK (vs. SPK in patients in dialysis), comparison of different anticoagulation prophylaxis regimens (including comparison between anticoagulation and anti-aggregation protocols), strategies for immunologic surveillance, treatment of rejection episodes (in particular, treatment of second rejection episodes and treatment of antibody-mediated rejections), effects of PTA on cardiovascular system, and effects of PTA on recipients' quality of life.

Multicenter studies are particularly needed.

5.14 | Limitations

As already reported while describing the methods of this consensus conference,[42] the main limitation of our collaborative effort was the need to review 50+ years of literature and consequently to extract data from several hundreds of articles. This extraordinary effort has intrinsic limitations and carries the risk of unintentional selection bias. Despite the creation of several dedicated teams for literature review, sharing and presentation of results of literature search, and online and in-person discussion of each statement, we acknowledge that some articles could have been missed. Additionally, Ovid/Medline was not included in the systematic reviews, and only data from full peer-reviewed manuscripts were considered. Consequently, we might have been missed additional information from these data sources.

Some of the data examined and discussed to reach the consensus may have been influenced by local practice as well as geographical and institutional variations. As most studies were provided by the United States and Europe, the applicability of these guidelines in other countries may require adaptations to local practice, legislative framework, organizational needs, epidemiology of organ donation, and other geographical/cultural variations.

Despite our effort to include all major transplant centers, and to specifically involve all physicians with known competence in pancreas transplantation, some prominent centers and influential colleagues may have not been invited or could not participate. However, having reached consensus among a large group of internationally recognized experts ensures balanced and competent assessment of available evidence.

5.15 | Conclusions

In conclusion, we have reported on 49 jury deliberations and 110 experts' recommendations, that we believe can be used to support and improve practice of pancreas transplantation worldwide. The main message from this consensus conference is that both SPK and PTA have the potential to improve patient survival in the long-term period, while all types of pancreas transplantation dramatically improve the quality of life of recipients. These advantages clearly appear to outweigh potential disadvantages, thus encouraging further implementation of pancreas transplantation.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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