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Success with Crossmatch Positive Pancreas Transplants

Rainer WG Gruessner*, Angelika C Gruessner

Professor of Surgery, State University of New York, USA

ABSTRACT

Crossmatch techniques have evolved over time from (cell-based) complement-dependent cytotoxicity to flow cytometry tests and, more recently, to virtual crossmatches. Since about 40% of all pancreas grafts in the United States are "imported" from a different UNOS region, virtual crossmatches have a clear advantage over cell-based crossmaches by lowering cold ischemia times and delayed graft function rates, both of which result in improved outcome. This review demonstrates that crossmatch positivity does not independently affect pancreas graft outcome, regardless of whether the crossmatch is T- or B-cell, current or historic. It also shows that hyperacute rejection is extremely rare in contrast to antibody-mediated rejection.

Keywords: Pancreas transplantation - Positive crossmatch

INTRODUCTION

Pancreas transplants across immunologic barriers are rare. In contrast to other solid organs, donor pancreases are not in short supply, nor are pancreas transplants considered lifesaving. For those reasons, there is in general no need to perform a pancreas transplant across a positive crossmatch. However, pancreas transplants across immunologic barriers have been performed when patients have received high-quality pancreas grafts without a final crossmatch pretransplant when the preservation time was long (>20 hours). In such cases, the crossmatch that was performed simultaneously with, or even after, the transplant came back positive after engraftment [1].

PANCREAS TRANSPLANTS AND CROSSMATCHING

Because the majority of pancreas transplants are performed in combination with a kidney from the same donor (simultaneous pancreas-kidney [SPK] category), the same antibody and crossmatch protocols are used as for kidney transplant alone (KTA) recipients.

The association between donor-reactive lymphocytic antibodies and hyperacute rejection was established in the mid-1960s [2-4]. Cell-based crossmatch testing was then primarily designed to detect anti-class-I antibodies, which were identified as the main cause of hyperacute rejection. It was also recognized that the development of antibodies was caused by a blood transfusion, pregnancy, or previous transplant and that sensitization was further caused by infections and autoimmune diseases. By the late 1960s, cell-based crossmatch testing was basically used by all

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***Corresponding Author**

Rainer WG Gruessner

Professor of Surgery, State University of New York, USA

Email: rainer.gruessner@downstate.edu

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laboratories for kidney transplants.

At the time, the complement-dependent cytotoxicity (CDC) test, a serologic microcytotoxicity assay, became the traditional (cell-based) crossmatch technique: Lysis of lymphocytes is caused by rabbit complement in the presence of antibodies to HLA antigens [5]. Purified donor T lymphocytes are used to detect class I antibodies in the CDC crossmatch. Purified donor B lymphocytes may be used to detect class I and II antibodies. Most centers perform kidney transplants primarily on the basis of the T-cell crossmatch result; a positive result usually precludes the transplant. In contrast, a positive B-cell crossmatch result is not considered an absolute contraindication to a kidney transplant. In fact, many centers during the time of CDC testing only did not routinely perform B-cell crossmatch testing because the relevance of class II antibodies was unclear [6].

Recognizing that the standard CDC test lacked sensitivity and early rejection episodes still occurred, even in the setting of a negative cross-match, a modified cytotoxicity assay was developed by adding a wash step to increase specificity and addition of an anti-human globulin (AHG) reagent to increase sensitivity [7,8]

An even more sensitive test is the flow cytometry (FC) crossmatch technique, which is able to detect even minute amounts of recipient antibodies on the surface of donor lymphocytes independent of complement binding [9,10] Despite its lack of specificity the cell-based flow cytometry crossmatch technique is used by most transplant centers; it is helpful for immunologically high-risk recipients (e.g., those undergoing a retransplant). As the sensitivity of the different crossmatch assays increases, the specificity decreases; the choice between tests that are too sensitive or not sensitive enough is up to the individual transplant center. Thus, immunogeneticists tend to favor one crossmatch technique and target cell combination over others based on their own data, experience and personal biases [11].

Another important factor for crossmatch testing is time. For deceased donor pancreas transplants, time is of the essence. Yet, in terms of time, there is no significant difference between serologic and molecular typing techniques: The CDC test can be performed in about 3 hours [2,4,12]; so can the polymerized chain reaction (PCR)-based typing method of allele-specific amplification through sequence-specific primers (PCR-SSP).

Because of prolonged cold ischemia time (CIT) with its associated adverse graft outcome, the "virtual crossmatch" (VXM) technique has been developed [13]. Single-antigen bead assays allow for detection of recipient donor-specific HLA antibodies, enabling prediction of compatibility (as in a cell-based crossmatch) through VXM [14]. Thus, VMX is also a "physical" crossmatch and compares anti-HLA antibodies of the recipient, as detected by Luminex technology, with the HLA of the donor. If there is a donor specific (DS)-antibody present this would represent a positive virtual crossmatch [13] The caveat is that this depends on the strength of the antibody as measured by the mean fluorescence intensity (MFI) rate; the HLA-lab/transplant program must compare the MFI values with their cell-based XM procedure.

Studies have demonstrated that VMX is associated with significantly shorter CIT, improved sharing of deceased donor organs, more efficient transplantation of highly sensitized patients, and high concordance with cell-based crossmatches [15-17].

An analysis of the first series of pancreas transplants across a positive crossmatch was done before VMX was available. Crossmatch testing at the time at the University of Minnesota included a screening (or preliminary) crossmatch and a final crossmatch. For the screening crossmatch, donor cells (peripheral blood lymphocytes, spleen or lymph node cells) were tested with the HLA antibody peak and the most recent serum samples from all ABO-compatible transplant candidates [18]. Serum samples from all patients on the waiting list were screened periodically (every 1 to 3 months) for antibodies against a lymphocyte panel, using either the CDC-AHG or enzyme-linked immunosorbent assay (ELISA) methods. Laboratories still need to screen for PRA regularly, in particular after immunizing events. A crossmatch is considered positive if either the peak or current serum samples give a positive result [6]. Once the sera of all eligible candidates were tested, the list of negative crossmatch candidates (to the deceased donor kidney graft) was ranked (in the United States according to the United Network for Organ Sharing [UNOS] point system). Then, a final crossmatch was carried out using donor cells and a fresh serum sample, obtained when the prospective recipient arrived at the hospital. However, delays were not uncommon: For locally procured organs, donor cells may have been available before the prospective recipient arrived at the hospital. For "imported" grafts (i.e., out of the transplant center's region), the prospective recipient's serum sample was only sometimes available before the donor cells arrived. The final (cell-based) crossmatch test still takes about 3 to 4 hours [18].

Historically, a kidney transplant was denied if any historic peak PRA sera gave a positive crossmatch, even if the current serum was crossmatch negative. This past-positive, current-negative crossmatch "no-transplant" rule was questioned in the early 1980s by some investigators who reported successful graft outcome in light of a past-positive crossmatch

[6,18]. However, this subject has remained controversial; both higher short- and long-term rates of graft loss from rejection have been reported [19]. Although an increasing number of kidney transplant centers before the introduction of VXM would have performed past-positive, current-negative crossmatch transplants, no uniform guidelines existed in regard to the pretransplant use of historic sera (>6 months) and post-transplant immunosuppression. Most centers, however, would avoid performing kidney transplants in the presence of specific antibodies (even if only identified in peak sera), in particular if the antibody is immunoglobulin G (IgG).

The willingness to perform a past-positive, current-negative crossmatch kidney transplant is highest in patients with high PRA levels, in particular those who have not lost their antibodies over time, or those for whom special protocols to reduce or eliminate such antibodies have failed [20]. Patients with >30% PRA levels belong to one of the largest growing groups on the kidney waiting list. Desensitization protocols include (1) antibody-removing techniques (e.g., plasmapheresis, immunoadsorption, IdeS [imlifidase]), (2) immunomodulatory strategies (e.g., use of pooled human immunoglobulin), (3) modified immunosuppressive therapy (e.g., induction therapy, cyclophosphamide), and (4) inhibition of antibody production and/or complement-system cascade (e.g., rituximab, bortezomib, eculizumab) [Table 1] [21-24]. Frequently, these different approaches are used in combination. Timing and order of administration of these treatment options are important. For example, the putative advantage of combining plasmapheresis and intravenous (IV) immunoglobulin is that plasmapheresis rapidly depletes donor-specific antibodies and IV immunoglobulin blocks the re-emergence of new antibodies.

Table 1: Desensitization modalities/ Treatment options for sensitized patients.

1.	Removal of antibody production (plasmapheresis, immunoadsorption)
2.	IVIG administration; imlifidase (cleaving IgG)
3.	Inhibition of antibody production (anti-CD20: rituximab or obintuzumab; proteasome inhibitor: bortezomib or carfilzomib)
4.	Inhibition of complement cascade (eculizumab [anti C5a]; C1-INH (C1 esterase inhibitor, inactivating C1r and C1s)
5.	Various antibodies (belatacept (CTLA4-Ig); tocilizumab [anti IL-6 receptor blocker]; belimumab [binding inhibitor of B-cell stimulator protein])
6.	Antibody induction therapy at transplant
7.	Splenectomy

Desensitization protocols have been used for both living and deceased donor recipients. The advantage of living donor transplants is that preemptive treatment protocols can be employed pretransplant [25]. until the crossmatch becomes negative, whereas for deceased donor transplants all therapy is usually initiated posttransplant [26].

A past-positive, current-negative crossmatch increases the chance for patients with high PRA levels to undergo a kidney transplant. But, a current-positive crossmatch, in standard clinical practice, means no kidney transplant. In contrast, a current-positive crossmatch has much less of an impact on graft outcome after a liver transplant [27]. Little information is available on the effect of a past-positive or a current-positive crossmatch on a pancreas transplant.

All protocols of cell-based crossmatches—unless prospectively done (i.e., before organ procurement)—add (substantially) to preservation time. Thus, cell-based crossmatch testing is not routine for liver, intestine, and non-sensitized heart or lung transplant recipients. The introduction of VXM may change the algorithm for highly sensitized extra-real organ transplants as well [28-30].

The pancreas (second only to the kidney) tolerates the longest preservation times (up to 30 hours), yet cell-based crossmatch testing is frequently not possible within the desired time frame.

Between 1/1/2014 and 12/31/2019), 56% of all solitary pancreas transplants (PAK, PTA) and 31% of combined pancreas and kidney (SPK) transplants were imported from out of state. The median preservation time for a local SPK was 9 hours (range: 0.5 to 36 hours) and for an imported SPK 11 hours (range: 1 to 32 hours). For solitary pancreas grafts (PAK, PTA), the median preservation time for a local graft was 7.8 hours (range: 0.1 to 27.5 hours) compared to 12.8 hours (range: 3.0 to 34.8 hours) for an imported pancreas graft (AC Gruessner, personal communication, November 2020).

For patients with documented 0% PRA levels, a pretransplant crossmatch test is usually not performed. This policy shortens preservation time, lowers the incidence of delayed graft function, and enhances cost efficiency. The policy of transplanting without a crossmatch, if the recipient's documented PRA level is 0% and if no interim

blood transfusions have been given, has also been applied to kidney transplants [6,31]. Key for safe implementation of such a policy is rigorous recording of potential allosensitizing events and comprehensive antibody screening [32]. As a result, many kidney transplant centers proceed to transplant without any additional laboratory-based HLA testing for patients who are well defined as HLA antibody negative. By using rapid HLA antibody tests (Luminex) at the time of donor organ offers, it is now possible to omit cell-based crossmatches even in many sensitized patients [33]. VXM may benefit sensitized patients in reducing CIT and the rate of delayed graft function. Yet, it carries risks such as missing clinically relevant non-HLA reactivity or allelic HLA antibody reactivity [33], although good correlation of VXM with all other crossmatch techniques specifically in the setting of high-resolution epitope analysis has been reported [34,35].

The use of VXM in pancreas transplantation was first studied by Eby et al. to investigate the utility and outcomes of VXM after transplantation of imported pancreases [36]. The authors acknowledge that imported pancreases are associated with increased CIT, limited utilization and less favorable outcomes and that flow cytometric crossmaching (FXM) further prolongs CIT. Three recipient groups of 153 pancreas transplants were studied: (1) imported VXM only, (2) imported VXM and FXM, (3) local VXM and FXM. There were no episodes of hyperacute rejection and only 1 episode of early antibody-mediated rejection in the imported VXM group. Death-censored graft survival, patient survival, and rejection rates were comparable among the recipient groups, but CIT was significantly lower in the VXM-only group. The authors concluded that VXM minimizes pancreas graft CIT without increasing rejection or adversely affecting graft survival, making it a viable approach to increase pancreas graft utilization across distant organ sharing regions.

Pancreas Transplants across a Positive Crossmatch: Literature Review

Very few studies on crossmatch positive pancreas transplants have been reported to the literature. In 1992, Peltenburg et al. reported on a pancreas-spleen allograft recipient with a positive T-cell crossmatch and accelerated acute rejection [37]. The patient had a 0% PRA level at 3 months pretransplant; the result of the pretransplant crossmatch test was not awaited, to shorten cold ischemia time. The spleen was irradiated ex vivo with 0.6 Gray. However, the patient became hyperglycemic on post-transplant day 2 and underwent splenectomy, because of rupture and hemorrhage, on posttransplant day 3. The pancreas was removed because of hemorrhagic infarction on post-transplant day 5. A massive lymphoplasmacellular infiltrate was noted: The retrospective crossmatch result was positive. Two factors may have contributed to graft failure: (1) no antibody induction therapy was given posttransplant and (2) simultaneous transplantation of the irradiated spleen may have contributed to accelerated acute rejection. The conversion from past-negative to current-positive crossmatch was caused by a transfusion of unfiltered packed cells within 3 months pretransplant [37].

The Minnesota study comprised the first large series of crossmatch positive pancreas transplants [1].

In order to limit preservation time to ≤ 30 hours, pancreas transplants were performed at University of Minnesota in consenting patients without a pretransplant crossmatch whenever the 30-hour preservation time limit would have been exceeded. The reason for cell-based crossmatch omission was the well documented fact that prolonged preservation time has an unfavorable effect on graft outcome after pancreas transplantation [38-40].

In the University of Minnesota series (October 1, 1987, through March 31, 2001), 5.5% (59/1076) of pancreas transplants were performed with a positive crossmatch [1]. Of these 59 recipients, 9 had a current T-cell-positive crossmatch, 15 a current B-cell-positive crossmatch, and 1 both a current T and B-cell-positive crossmatch. The remaining 34 recipients had a past T- or B-cell-positive crossmatch. For T-cell crossmatches, an AHG-augmented CDC test was used and for B-cell crossmatches an extended-incubation CDC test. Of note, IgM autoantibody levels were reduced by heat inactivation (63° for 10 minutes) before crossmatching, to avoid positive crossmatches due to IgM antibodies.

These 59 crossmatch-positive transplants were performed with either cyclosporine-based (1986 through 1994) or tacrolimus-based (1995 through 2001) immunosuppression for all three recipient categories (SPK, pancreas after kidney [PAK], and pancreas transplant alone [PTA]) and for both primary (47%) and retransplant (53%) recipients. In the 2001 cases only, all crossmatch-positive recipients received four doses of IVIG (0.5 g/kg) on posttransplant days 0, 2, 4, and 6; recipients with a current T-cell-positive crossmatch had four plasma exchanges, using fresh-frozen plasma (five to seven plasma volumes) before IV administration of Ig in hopes of both treatment modalities further reducing the risk of rejection [1].

For all three recipient categories, graft survival rates at 1- and 5-years posttransplant were similar for crossmatch-positive vs -negative recipients. There was a trend toward lower graft survival for recipients with (vs without) a positive T-cell crossmatch; this trend was not noted for recipients with (vs without) a positive B-cell crossmatch.

Of note, no grafts were lost to hyperacute rejection. The only graft lost to acute rejection was in a recipient with a historic peak past-positive B-cell crossmatch (who did not undergo antirejection treatment because of pulmonary infection). One might speculate that the surprising lack of impact of crossmatch positivity on graft outcome was due to aggressive induction therapy and/or the possibly oversensitive antiglobulin-enhanced crossmatch technique that was routinely used. In a multivariate analysis, only two variables had an impact on outcome: era, consistent with improved graft survival in the tacrolimus (vs cyclosporine) era, and transplant number, consistent with less favorable graft survival for a retransplant (vs a primary transplant) due to a higher technical complication rate. Recipients >45 years old and recipients with PRA levels > 15% did not have worse graft outcome.

The University of Minnesota results demonstrated that, as with kidney transplants, pancreas transplants can be successful with a past-positive crossmatch. But, even a current-positive crossmatch appeared to have little impact on pancreas graft survival. Based on this initial, relatively large experience, it was concluded that crossmatch positivity does not independently affect pancreas graft outcome, regardless of whether the crossmatch is T- or B-cell, current or historic [1].

Heilman et al. studied 72 consecutive SPK transplants of which 14 (study group) had positive crossmatches pretransplant (positive CDC-B cell and/or positive T or B crossmatches) [41]. The study group received induction with low-dose IVIG, rabbit-ATG (total dose 6mg/kg) or alemtuzumab (30mg single dose) and standard maintenance immunosuppression. Biopsy-proven acute rejection of the kidney occurred in 50% (7 patients) compared to only 10% in the control group. One patient in the study group experienced acute cellular rejection, the other 6 antibody-mediated rejection. Patient, pancreas and kidney graft was lower in the study group, but did not reach statistical significance. The authors concluded that SPK recipients with a positive crossmatch pretransplant have an increased risk of developing antibody-mediated rejection or that more intensive desensitization is needed (than what was used in their study protocol) [41].

Sammartino et al. reported on the first SPK transplant from a living donor (brother) against a positive crossmatch [42]. The recipient was highly sensitized with a PRA of 100% owing to previous pregnancies and blood transfusions. The authors used the same institutional protocol as for a crossmatch positive, highly sensitized living donor kidney transplant. The protocol consisted of 4 sessions of plasmapheresis on pre-transplant days 11, 7, 5, and 3, followed by infusion of IVIG 100mg/kg/dose after each plasmapheresis session. In addition, one dose of rituximab was given on pre-transplant day 7. After successful conversion to a negative crossmatch, the transplant procedures were carried out. Plasmapheresis and IVIG infusion were repeated on post-transplant days 0, 1, 3, 5, 7, 9; thymoglobulin (1.5mg/kg/dose x5) was given on those posttransplant days when plasmapheresis was not performed. The recipient was discharged with functioning grafts 8 days after the combined transplants and had no rejection episode at 9-month follow-up [42].

It has been postulated that early pancreas graft thrombosis beyond the immediate postoperative period is usually immunologically mediated [43]. Yadav et al. presented the case of a 34-year old PAK recipient with a weakly positive flow-cytometric crossmatch and without DSA. The pancreas graft thrombosed 6 weeks after the transplant procedure. The explant pathology showed changes consistent with severe acute antibody-mediated rejection and C4d deposition in the larger vessels. It remains unclear if the weakly positive crossmatch or some other inciting event (possibly the patient's early posttransplant pneumonia) caused the development of de-novo DSA and resulted in graft thrombosis [44].

Pancreas Transplants across a Positive Crossmatch: IPTR/UNOS Analysis

An analysis of the impact of a positive crossmatch on outcome after pancreas transplantation was performed after a new UNOS reporting format for crossmatch results was instituted on 4/1/2015.

Between 4/1/2015 and 12/31/2019, 4,172 pancreas transplants were reported to UNOS/OPTN. During that time period, a total of 85 positive T-cell crossmatches (2.0%) and 97 (2.3%) positive B-cell crossmatches were identified [45]. The overall positive crossmatch rate for pancreas transplants was only about 2%. The frequency of positive T- and B-cell crossmatches was slightly higher in female recipients and higher in pancreas retransplants compared to primary transplants. Tables 2 and 3 show the descriptive statistics by transplant category. There were no statistical differences in T- and B-cell positive crossmatches noted between the 3 transplant categories (SPK, PAK, PTA).

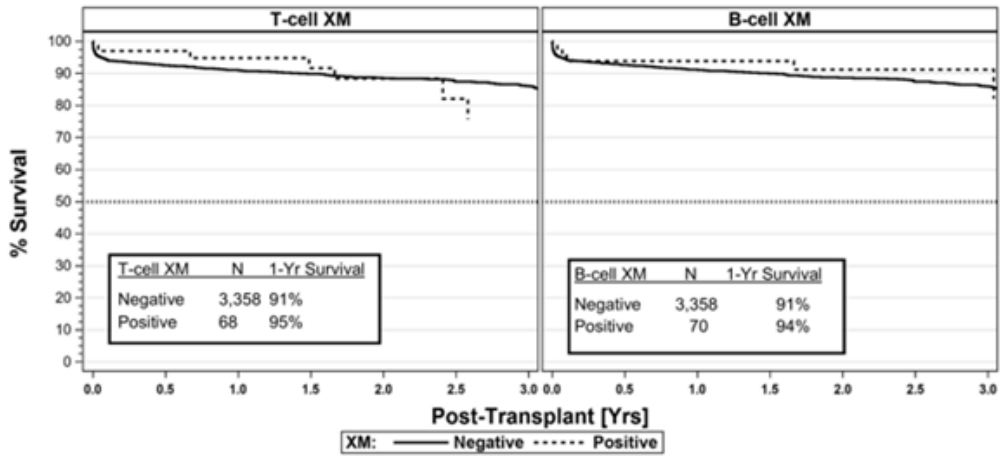
Table 2: Demographics for T-cell crossmatches of all pancreas transplants performed between 4/1/2015 and 12/31/2019.

	SPK		PAK		PTA		Total	
T-cell crossmatch	-	+	-	+	-	+	-	+
N (%)	3,519 (98)	70 (2)	310 (98)	6 (2)	258 (97)	9 (3)	4,087 (98)	85 (2)
Age [Yrs]	42.2±9.2	41.0±9.1	43.5±8.8	40.8±9.5	42.0±10.8	40.2±9.7	42.3±9.3	40.9±9.1
Female Gender (%)	1,322 (97)	35 (3)	139 (98)	3 (2)	149 (95)	8 (5)	1,610 (97)	46 (3)
Male Gender (%)	2,197 (98)	35 (2)	171 (98)	3 (2)	109 (99)	1 (1)	2,477 (98)	39 (2)
Primary Txs (%)	3,434 (98)	66 (2)	213 (98)	5 (2)	232 (97)	6 (3)	3879 (98)	77 (2)
Retransplants (%)	85 (96)	4 (4)	97 (99)	1 (1)	26 (90)	3 (10)	208 (96)	8 (4)

Table 3: Demographics for B-cell crossmatches of all pancreas transplants performed between 4/1/2015 and 12/31/2019.

	SPK		PAK		PTA		Total	
B-cell crossmatch	-	+	-	+	-	+	-	+
N (%)	3,486 (98)	72 (2)	302 (96)	13 (4)	254 (95)	12 (5)	4,042 (98)	97 (2)
Age [Yrs]	42.1±9.2	43.5±8.9	43.3±8.7	46.3±10.9	42.0±10.8	41.6±11.2	42.2±9.3	43.6±9.5
Female Gender (%)	1310 (97)	37 (3)	134 (94)	8 (6)	148 (95)	8 (5)	1592 (97)	53 (3)
Male Gender (%)	2176 98)	35 (2)	168 (97)	5 (3)	106 (96)	4 (4)	2450 (98)	44 (2)
Primary Txs (%)	3403 (98)	67 (2)	209 (96)	8 (4)	228 (96)	9 (5)	3840 (98)	84 (2)
Retransplants (%)	83 (94)	5 (6)	93 (95)	5 (5)	26 (90)	3 (10)	202 (94)	13 (6)

Figure: SPK primary pancreas graft survival by T- and B- cell crossmatch for pancreas transplants performed between 4/1/2015 and 12/31/2019.



Analyses of the impact of a positive crossmatch on outcome did not show any impact on pancreas graft function. Due to the very small number of positive crossmatches only the outcomes after SPK transplants are shown (Figure 1). Short- and long-term survival was excellent for pancreas transplants with T- and/or B-cell positive crossmatches. A positive crossmatch had no impact on the cause of pancreas graft failure. Of note, there was no graft failure due to hyperacute rejection reported over the time period of the study.

In summary, a positive crossmatch does not preclude good outcome after pancreas transplantation [46].

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