Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Infectious complications following 72 consecutive enteric-drained pancreas transplants

N. Berger,[1]* R. Wirmsberger,[1]* R. Kafka,[1] C. Margreiter,[1] C. Ebenbichler,[2] I. Stelzmueller,[1] R. Margreiter,[1] W. Steurer,[2] W. Mark[1] and H. Bonatti[1]

1 Department of General, Thoracic and Transplant Surgery, Innsbruck University Hospital, Innsbruck, Austria
2 Department of General Internal Medicine, Innsbruck University Hospital, Innsbruck, Austria

Keywords
enteric drainage, infection, pancreas transplantation.

Correspondence
Hugo Bonatti MD, PhD, Department of General Surgery, Innsbruck University Hospital, Anichstr. 35, A-6020 Innsbruck, Austria. Tel.: +43 512 504 22603; fax: +43 512 504 22605; e-mail: hugo.bonatti@uklibk.ac.at

*Both authors equally contributed to this paper.

Received: 1 July 2005
Revision requested: 26 July 2005
Accepted: 23 January 2006

doi:10.1111/j.1432-2277.2006.00293.x

Summary

New immunosuppressive protocols and advanced surgical technique resulted in an improved outcome of pancreatic transplantation (PTx) with infection remaining the most common complication. Seventy-two enteric-drained whole PTxs performed at the Innsbruck University Hospital between September 2002 and October 2004 were retrospectively analyzed. Prophylactic immunosuppression consisted of either the standard protocol consisting of single bolus antithymocyteglobuline (ATG) (Thymoglobulin, Sangstat or ATG Fresenius) induction (9 mg/kg), tacrolimus (TAC), mycophenylate mofetil (MMF) and steroids (38 patients) or a 4-day course of ATG (4 mg/kg) tacrolimus and steroids with MMF ($n = 19$), or Sirolimus ($n = 15$). Perioperative antimicrobial prophylaxis consisted of Piperacillin/Tazobactam (4.5 g q 8 h) in combination with ciprofloxacin (200 mg q 12 h) and fluconazole (400 mg daily). Ganciclovir was used for cytomegalovirus (CMV) prophylaxis if donor was positive and recipient-negative. Patient, pancreas, and kidney graft survival at 1 year were 97.2%, 88.8%, and 93%, respectively, with no difference between the groups. All retransplants ($n = 8$) and single transplants ($n = 8$) as well as all type II diabetics and nine of 11 patients older 55 years received standard immunosuppression (IS). The rejection rate was 14% and infection rate 46% with no difference in terms of incidence or type according to the three groups. Severe infectious complications included intra-abdominal infection ($n = 12$), wound infection ($n = 7$), sepsis ($n = 13$), respiratory tract infection ($n = 4$), urinary tract infection ($n = 12$), herpes simplex/human herpes virus 6 infection ($n = 5$), CMV infection/disease ($n = 7$), post-transplant lymphoproliferative disorder (PTLD, $n = 3$), invasive filamentous fungal infection ($n = 4$), Clostridial/Rotavirus colitis ($n = 1$), and endocarditis ($n = 1$). All four patients in this series died of infectious complications (invasive aspergillosis $n = 2$) (one with *Candida glabrata* superinfection), invasive zygomycosis ($n = 1$), PTLD ($n = 1$). Five grafts were lost (vascular thrombosis $n = 3$, pancreatitis $n = 1$, noncompliance $n = 1$). Infection represented the most frequent complication in this series and all four deaths were of infectious origin. Better prophylaxis and management of infections now should be the primary target to be addressed in the field of pancreas transplantation.

Introduction

Simultaneous pancreas kidney transplantation (SPK) has evolved as an effective treatment modality for patients with end stage nephropathy due to type I diabetes mellitus with a 1-year patient, pancreas, and kidney graft survival of 94%, 83%, and 90%, respectively [1–6]. This improvement in patient and graft survival has been

mainly achieved by a reduction in technical failures and more powerful immunosuppression with agents such as Tacrolimus and MMF [7]. Sirolimus recently was added to immunosuppressive protocols and has the advantage of not being nephrotoxic but at the same time can be associated with impaired wound healing due to its antiproliferative activity and can cause severe gastrointestinal side effects [8,9]. ATG induction has been reported in large series of all types of transplants to reduce immunological complications; however, these agents are associated with an increase in infectious complications. Some centers have used a single bolus induction with an increased dose instead of the conventional 4–6 days course [10,11].

Recently, for pancreas transplantation, the more physiologic enteric drainage (ED) has found acceptance by an increasing number of centers although it is associated with a high risk for intra-abdominal infections (IAI) [12–14]. A variety of factors influence the individual risk for infection following the pancreas transplantation such as pretransplant general condition, comorbidity, CMV match, graft function and quality, and level of immunosuppression among others [15].

In this retrospective analysis of 72 consecutive enteric/systemic-drained PTxs, infectious complications were recorded in detail. The impact of these infections on graft and patient survival was investigated. The influence of established risk factors for infection such as CMV match, patient age, presence of type II diabetes, rejection, and retransplantation together with the impact of different immunosuppressive protocols was studied.

Patient and methods

Donor and recipient demographics

Between September 2002 and October 2004, 71 consecutive patients ($n = 41$) with a median age of 42.9 (range 26.8–62.5) years underwent a total of 72 pancreas transplants at our center: in 64 cases together with a kidney from the same donor, which was placed retroperitoneally in the left iliac fossa (SPK). Seven patients received a pancreas graft sometime after kidney transplantation (PAK), and one patient a pancreas transplant alone. In eight instances, the pancreas transplant was a retransplant. Mean donor age was 28 (range 13–53) years. Mean cold ischemia time for the kidney transplants was 11.7 ± 3.3 h, and for the pancreas transplants 13.1±3.2 h. All pancreatic grafts were revascularized in an end-to-side fashion with the inferior vena cava and via a donor iliac Y-graft with the right common iliac artery. Exocrine drainage was completed as S/S duodeno-jejunostomy using a stapling device [16].

Immunosuppression

Three different protocols were used. In 38 patients (68%), a single shot ATG Fresenius at 9 mg/kg BW was given at begin of surgery. Another 34 patients received a 4-day course of ATG at a lower dosage: 4 mg/kg BW (Fresenius). One patient received basiliximab (Simulect®; Roche, Switzerland at a dose of 2 times 20 mg with an interval of 4 days) following a second pancreas retransplant. A rapid steroid tapering regimen was applied starting with 500 mg MP intraoperatively to reach a dose of 25 mg at the end of the first p.o. week and further reduction to a maintenance daily dose of 5 mg. In the vast majority of patients steroids were withdrawn within six months.

All patients received oral Tacrolimus (Tac) at 0.08 mg/kg/day b.i.d., starting 6 h after revascularization. The Tac dose was adjusted to achieve whole blood trough levels of 10–12 ng/ml for the first three months after transplantation, 8–10 ng/ml for 6–12 months and 6–8 ng/ml thereafter. MMF was given at a dose of 1 g b.i.d. orally and used in the 38 patients receiving single dose ATG and 15 patients receiving a four days ATG induction. All 19 patients who received Sirolimus with targeted trough levels of 6–10 ng/ml as initial immunosuppression in combination with Tac received four days ATG induction. Four patients were switched from Tac to CsA and another four from CsA to Tac.

Perioperative antimicrobial prophylaxis

Patients received Piperacillin/Tazobactam 3×4.5 g for 48–72 h as perioperative systemic antimicrobial prophylaxis. Ciprofloxacin was given at a dosage of 200 mg b.i.d. for 5 days and Fluconazol 400 mg q 24 h for 7 days. Prophylaxis for CMV infection was used in 13 patients (Ganciclovir 2×5 mg/kg/day for 10 days, followed by Valganciclovir 2×450 mg), who were CMV-negative and received a CMV-positive graft. All other patients were monitored on a weekly basis and treated pre-emptively if tested positive for CMV replication.

Microbiological monitoring

Maximum body temperature, graft function (urinary output, serum creatinine, blood glucose, amylase, and lipase), and white blood cell count and C-reactive protein were monitored on a daily basis.

Bacterial/fungal monitoring

For surveillance, specimens were taken from different body sites and fluids on a daily basis during intensive care unit (ICU) stay and thereafter thrice weekly. In pretransplant, a sample of preservation solution and the

donor ureter, as well as ascites and urine from the recipient, were taken. Post-transplant tips of removed urinary as well as intravascular catheters as well as tips of all intra-abdominal or intrathoracic drains were sent for microbiological investigation. Sputa, tracheal aspirations, alveolar lavages, aspiration fluids, wound swabs, cerebrospinal fluid, blood, and biopsies were sent whenever indicated. Blood cultures were taken in cases of fever (higher 38 °C): two to four consecutive samples within 4 h. In case of pulmonary infiltrate in all cases, CT-guided biopsy was carried out. Specimens were stained for fungal pathogens using Calcofluor White staining and cultured on selective media. In addition, samples were sent for pathology routine staining to exclude malignancy.

Viral monitoring

The donor CMV status was recorded from the report of the donor center and for the recipient on pretransplant serology. All patients underwent weekly testing using CMV polymerase chain reaction (PCR) (Amplicor®; Roche, Switzerland). An in-house Epstein-Barr virus (EBV) quantitative PCR was performed on request.

Data collection and statistical analysis

A database was created using MS excel 5.0. For each patient, an individual datasheet was completed that contained daily body temperature, laboratory results, immunosuppressive, and antimicrobial therapy as well as all results from microbiological investigations. Bacterial infection was assumed when a positive culture and clinical signs and/or laboratory parameters lead to antibiotic treatment. Positive surveillance cultures without clinical symptoms were considered colonization. Statistical analysis was carried out using MS excel and SPSS including chi-squared test and Kruskal–Wallis assay. Data are reported as median with minimum/maximum range, mean ± SD or 25%/75% quartile values. Patient survival was calculated from the date of transplantation until death, graft survival rates were censored for graft failure or patient death. Survival curves were generated using the Kaplan–Meier method. Groups were compared using the nonparametric Mann–Whitney *U*-test. A *P*-value <0.05 was considered statistically significant.

Results

Patient and graft survival

The median follow-up was 21 (range: 6–33) months. Demographic and clinical data according to the three immunosuppressive regimens are shown in Table 1. Overall 1- and 2-year actuarial patient survival was 97.2% and 94.9%, respectively. From the four deaths (3,6,8 and 9 months post-transplant), two occurred with functioning grafts, the other two patients lost renal graft function

Table 1. Demographic and clinical data according to applied immunosuppressive regimens; patients who received single shot ATG induction were significantly older and received grafts from older donors. All patients with type II DM and all patients undergoing single pancreatic transplantation (PTx) or rePTx received single shot ATG induction.

		single shot ATG, TAC, MMF	4 days ATG, TAC, MMF	4 days ATG, TAC, Sirolimus
n patients		37	15	19
n transplants		38	15	19
Immunosuppression				
ATG	Single shot: 9 mg/kg	4 days:4 mg/kg	4 days:4 mg/kg	
Steroides	1	1	1	
Tacrolimus	1	1	1	
MMF/Sirolimus	MMF	MMF	Sirolimus	
Demographic data				
Recipient age	46.7 (26.8–62.5)	39.0 (29.5–48.5)	43 (31.9–60.8)	$P = 0.036$
M/F	21/16	10/5	9/10	n.s
Donor age	33.5 (15.0–53.0)	23 (13.0–43.0)	27 (13.0–45.0)	$P = 0.06$, n.s.
Cold ischemia kidney	12 (6.0–18.3)	13.6 (6.9–21.6)	11.7 (6.5–18.4)	n.s
Cold ischemia pancreas	14.5 (8.9–19.9)	15.5 (9.3–19.0)	13.6 (8.9–20.6)	n.s
Type II DM	10	0	0	$P = 0.006$
Retransplants	8	0	0	$P = 0.018$
Single pancreas Tx	8	0	0	$P = 0.018$
Clinical data				
Death	2	0	2	n.s
Graft loss	5	0	1	n.s
Rejection rate	11%	27%	11%	n.s

prior to death. The causes of death were fungal infection in three cases and post-transplant lymphoproliferative disorder (PTLD) in the last case. The first patient died of invasive aspergillosis following his second pancreas retransplant. The second patient deceased from invasive zygomycosis following the infective endocarditis, which caused infective embolic graft arterial thrombosis in the renal graft. The third patient died of *Candida glabrata* and panresistant *Pseudomonas aeruginosa* pulmonary superinfection after successful treatment of pulmonary aspergillosis. The PTLD was EBV-associated, CD20-positive diffuse large B-cell lymphoma involving the lung and colon. The patient responded well to rituximab therapy but died of tumor lysis syndrome, sepsis, and multiorgan failure following the colonic perforation from a disintegrating lymphoma infiltrate.

Kidney 1- and 2-year survival was calculated to be 93.0% and 93.0%. Of the 64 transplanted kidneys, four grafts (6%) were lost. Two patients died with functioning graft, one kidney was lost due to septic arterial thrombosis deriving from infective endocarditis and another due to noncompliance.

Overall 1- and 2-year pancreas graft survival was 88.8% and 85.8%. Of the 72 pancreas grafts, 63 are currently functioning without exogenous insulin and normal HbA1c levels at a median follow-up of 21 (range: 6–33) months. Causes of the nine pancreas graft losses were irreversible rejection/dysfunction due to noncompliance ($n = 1$), IAI ($n = 1$), arterial thrombosis/infarction ($n = 3$), and death with functioning graft ($n = 4$).

Perioperative course

The median length of post-transplant hospitalization was 23 (range 14–114) days. During first hospitalization, a total of 10 rejection episodes in 10 patients (14%) were treated. In 12 instances out of 72 transplants, one or more relaparotomies for surgical complications were necessary within the first p.o. year. In one case, the pancreas graft was intraoperatively removed due to severe reperfusion injury and thrombosis, in another two cases the thrombosed pancreas graft was removed during relaparotomy and in one case the thrombosed and infected renal graft was removed during relaparotomy. The remaining relaparotomies were due to hemorrhage and evacuation of hematoma ($n = 4$) and IAI ($n = 4$).

Infectious complications

The spectrum of infectious complications according to the three immunosuppressive protocols is shown in Table 2. A total of 72 specimens from preservation solution were taken and 16 (22%) were contaminated. Isolated pathogens included *Enterococcus faecalis* ($n = 6$), Coagulase-negative

Table 2. Infectious complications following 72 pancreas transplants: summary and according to immunosuppressive regimen, all three cases of invasive aspergillosis were observed in patients with single bolus ATG, all three patients were elderly with underlying pulmonary diseases. Sepsis, intra-abdominal infection (IAI), and urinary tract infection were the most common infections. Ten of 12 IAIs were observed in the single bolus ATG group ($P = 0.02$): recipients of older donor grafts, patients with type II DM, and elderly individuals had the highest risk for IAI. All other common infections were equally distributed between the three groups.

	Total	Incidence*	1 day ATG, TAC, MMF	4 days ATG, TAC, MMF	4 days ATG, TAC, sirolimus (SIR)	
Viral infection						
CMV	7	9.9%	4	2	1	n.s.
Herpes simplex virus I/II (HSVI/II)	4	5.6%	1	2	1	
HHV6	1	1.4%	0	0	1	
Post-transplant lymphoproliferative disorder	3	4.2%	2	0	1	
Bacterial infection						
Wound infection	7	9.9%	4	1	2	n.s.
IAI	12	16.9%	10	1	1	$P = 0.02$
Urinary tract infection	12	16.9%	7	3	2	n.s.
Respiratory tract infection	4	5.6%	3	0	1	
Bloodstream infection	13	18.3%	8	3	2	n.s.
Endocarditis	1	1.4%	0	0	1	
Fungal infection						
Aspergillosis	3	4.2%	3	0	0	
Zygomycosis	1	1.4%	0	0	1	
Enteric infection						
Rotavirus/C.Difficile colitis	1	1.4%	0	0	1	

*Based on 71 patients.

staphylococci ($n = 4$), *P. aeruginosa* ($n = 3$), *Escherichia coli* ($n = 1$), *Proteus mirabilis* ($n = 1$), *Staphylococcus aureus* ($n = 1$), Candida ($n = 1$). In addition, 63 specimens of donor ureter were available for testing and only in four cases pathogens could be isolated (*Enterococcus fecalis* in three and *P. aeruginosa* in one case). Seventeen of 19 ascites specimens taken intraoperatively were sterile, coagulase-negative staphylococci were cultured from one specimen and *Enterobacter* sp. from another. A total of 52 of 54 urine specimens taken immediately pretransplant were sterile, the remaining two both grew *E. coli*.

Surgical infections

Wound infection rate was 9.7%. A total of 11 patients (16.7%) developed IAI with a median onset of 14 days (range 7–39) post-transplantation. One patient had two episodes.

The incidence of IAI was highest in the group receiving standard immunosuppression with 26% vs. 7% and 5% for the other two regimens ($P = 0.02$). Spectrum of bacterial pathogens is depicted in Table 3. Risk factors for IAI were older recipient, type II diabetes and donor age, the latter reaching statistical significance. IAI was successfully managed in all cases by antimicrobial therapy and intervention: percutaneous drainage ($n = 7$), a single laparotomy ($n = 4$), and multiple laparotomies ($n = 1$). No graft had to be removed due to IAI. However, in one case, the necrotic tail of the graft had to be resected. This patient later became insulin-dependent again due to fading graft function.

Nosocomial infections

Urinary tract infection was diagnosed in 12 patients (17%); four patients developed lower respiratory tract infection (6%). Thirteen patients (18%) developed blood-borne infection originating either from contaminated central venous lines or from IAI. The predominant organisms were coagulase-negative staphylococci.

Table 3. Spectrum of pathogens associated with IAI ($n = 12$).

Gram-positive cocci	
Coagulase-negative staphylococci	9
Streptococcus Milleri	3
Enterococcus fecalis	2
Enterococcus faecium	1
Gram-negative rods	
Escherichia coli	1
Klebsiella spp.	1
Enterobacter spp.	2
Nonfermentative bacilli	
Pseudomonas aeruginosa	1
Stenotrophomonas maltophila	1
Alcaligines xylooxidans	1
Anaerobes	
Bacteroides fragilis	2
Fungi	
Candida krusei	1

Opportunistic infections

Herpes simplex virus (HSV)-associated skin lesions were diagnosed in four patients; one patient developed HHV6-associated disease. Three patients presented with PTLD, one with a monoclonal B-cell lymphoma which led to death, the second with EBV-associated B-cell hyperplasia, which caused benign intrahepatic nodules and the third had mononucleosis-like syndrome. Tapering of immunosuppression in the last two patients led to complete disappearance of lesions and symptoms, respectively. Three patients developed early CMV infection, which in all cases was controlled by pre-emptive Ganciclovir. Another two patients developed early CMV disease, one biopsy-proven CMV esophagitis and another CMV syndrome. Both patients responded to Ganciclovir therapy. In two cases, CMV disease presented at a later stage (syndrome $n = 1$, duodenal ulcer $n = 1$), in both cases GCV therapy was successful. When looking at the CMV match in the patients who developed CMV infection and disease ($n = 7$), four had a CMV-mismatched transplant (donor positive/recipient negative), in the remaining three transplants donor and recipient were CMV sero-positive.

Fungal infections

Within this series, a total of five patients (six episodes) developed invasive fungal infections. Of those, three had apergillosis, one zygomycosis and the remaining was caused by yeast. Zygomycosis was the only fungal infection, which was diagnosed post-mortem. One patient was successfully treated for aspergillosis and developed later fatal superinfection of pulmonary caverns with *C. glabrata* and panresistant *P. aeruginosa* (Fig. 1). Another patient died of invasive aspergillosis following a second pancreas retransplant. In one patient, invasive aspergillosis was managed successfully with combination therapy including Caspofungin and Voriconazole. This combination also was successful in treating one case of IAI caused by *Candida krusei*.

Discussion

Since the introduction of the new immunosuppressive agents, Tacrolimus and MMF pancreas transplantation has become widely accepted as a life-saving procedure for patients with an end stage diabetic nephropathy. According to the International Pancreas Transplant Registry

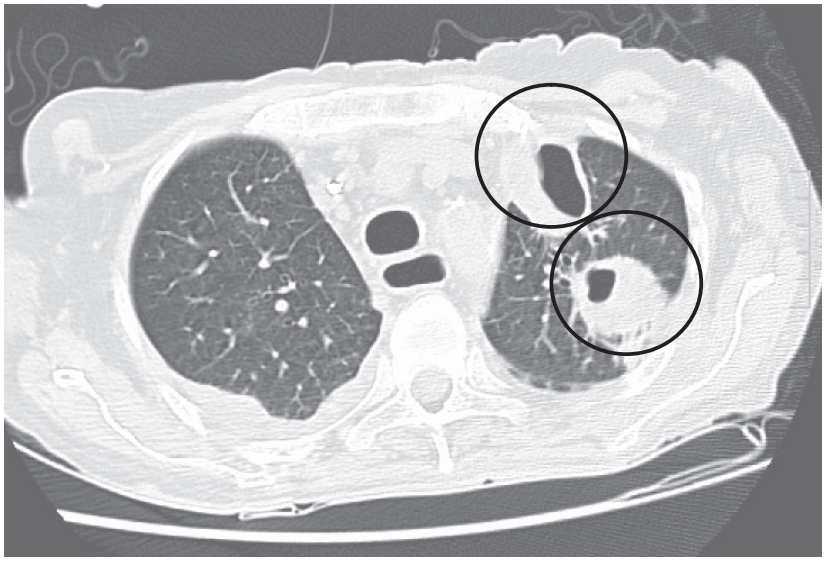

Figure 1 Large cavern associated with pulmonary aspergillosis; Superinfection with *Candida glabrata* and panresistant *Pseudomonas aeruginosa*.

report, recently the technical failure rates have exceeded the immunological failure rates [17]. According to the Collorative Transplant Study (CTS) Registry, ATG induction had no impact on graft survival after pancreas transplantation for the time period 1991–2000. Instead of a standard 3–10-day induction, we were using a single shot induction in 38 patients, the remaining received a 4-day course [10,11]. The addition of such a short course of ATG given at an increased dose was well tolerated by patients and was as effective as a 3-day course in terms of survival and prevention of rejection. In our series of 72 consecutive enteric-drained pancreas transplants, the 1-year patient, pancreas, and kidney graft survival was 97.2%, 88.8% and 93%, respectively. We did not find any difference in terms of graft or patient survival according to the use of the three immunosuppressive protocols.

Intra-abdominal infection accounted for high morbidity but only one graft loss. One graft was lost due to irreversible rejection of the pancreas in a patient who did not take the required immunosuppression. In three cases, vascular thrombosis occurred. In one case, this occurred intraoperatively and the pancreas was removed. The kidney functioned well and the patient subsequently underwent successful pancreas retransplantation. One patient received a pancreas alone and lost the graft due to venous thrombosis. We assume an immunological trigger as a second cross match performed at our own center turned out to be positive, whereas the pretransplant performed cross match at the donor center was negative. This patient had already lost two pancreas grafts previously due to rejection.

The overall rejection rate was 14% and there was no significant difference between the three groups. Rejection diagnosis was based on clinical signs and renal biopsy in all cases. All were successfully treated with bolused steroids. Rejection had no direct impact on graft survival as one acute antibody-mediated rejection was due to false-negative cross match and one immunological graft loss was due to noncompliance.

Infection remains the most common complication following the pancreas transplantation and prevention of fungal, viral, protozoal, and viral infection has become one of the most important factors contributing to the improved outcome [18,19]. Although many of these infections are well controlled due to rapid detection and highly active antimicrobials, some of them remain a challenge and serious risk for the patient. In pancreas recipients, postoperative infections are reported to occur in 50–100% [14,20]. Depending on the handling of the exocrine function (bladder versus ED) and other factors such as amount and type of immunosuppression, the number of rejection episodes not only the frequency of such infections but also the type differs substantially [12]. Bacterial infections, especially intra-abdominal sepsis, remain a significant source of morbidity during the immediate postoperative period [21]. Incidence of urinary tract infection (UTI) was profoundly reduced when compared with our historical group of 94 segmental pancreas transplants with bladder drainage performed between 1987 and 1995 with an incidence of UTI of 47% and pancreatic duct infection has disappeared completely [22]. When using a whole pancreatic graft including the duodenal segment with bladder drainage, even higher rates of UTI were reported. A shift from complications in the long term resulting from bladder drainage (i.e. metabolic acidosis, UTI, and graft duodenal ulcer and leaks) to early complications after ED (i.e. IAI and GI bleeding from the site of anastomosis) has been reported and can

be confirmed by our experience [12,23,24]. The rate of IAIs in our bladder-drained series was 9%, wound infection rate was 6%, sepsis rate was 10%, and the rate of pneumonia was 17%. The changes in terms of these infections must be seen in the light of changing surgical technique and the emergence of new immunosuppressive protocols. None of the three immunosuppressive regimes in this series was associated with an increased overall infection rate or a certain type of infection. Most likely, the previously reported differences have to be seen in the light of absence of intensified antimicrobial prophylaxis and the general lower level of prophylactic immunosuppression with an accepted higher rejection rate.

Viral infections have become less common after the universal use of CMV prophylaxis in high-risk patients. Pancreatic recipients are more frequently CMV-negative than recipients of other organs. This results in a high proportion of CMV mismatched transplants (25% in our series) [25,26]. On the other hand, using Gancyclovir prophylaxis for high-risk patients and a pre-emptive treatment strategy based on the CMV PCR for all other patients, CMV disease was observed in our series in only four patients. In our historical cohort, the CMV disease rate was 21%. Data, however, must be compared with caution as before 1995 only tests with low sensitivity such as the shell vial assay were available and were only carried out on request. The rate of HSV infection in this historical cohort was also higher with 28%.

Fungal infections, in particular mold infections, have become an increasing problem during the past decade. All three Aspergillus infections were observed in elderly patients. One of them had a second retransplant, another suffered from multiple other infections including CMV and bacterial pneumonia and the third had a complicated post-transplant course with neurological disorders and chronic obstructive pulmonary disease. In these elderly recipients, steroids might be withdrawn at an earlier stage or levels of Tacrolimus might be kept low.

Refinement of the surgical technique during organ retrieval, improvement in the antibiotic prophylaxis, and implantation using a stapling device for completion of the enteric anastomosis resulted in a reduction of IAIs when compared with an earlier series. Nevertheless, a total of 11 patients (16.7%) developed 12 episodes of IAI. The risk factors to develop IAI were advanced recipient age, advanced donor age, and type II DM, whereas in the group of retransplants surprisingly no increased risk for IAI could be found. We have previously reported that older donor age is a risk factor for IAI [8]. Possibly older recipients and those suffering from type II DM should receive a less aggressive immunosuppressive regimen as these patients were also found to have the highest risk for Aspergillus infection. In a cohort of 132 patients with 78% enteric-drained cases at the University of Pittsburgh, an overall postoperative infection rate of 38.6% was reported and serious infections occurring in 25.8% [24]. Severe early post-transplant IAI was reported in a significant risk factor for graft loss [12–14]. For antimicrobial prophylaxis, a combination of Piperacillin/Tacobactam, ciprofloxacin, and Fluconazol was used. In our series, Gram-positive cocci were found more frequently than Gram-negative rods, which might be due to the applied prophylactic regimen, with stronger activity against Gram-negative bacilli. The single case of Fluconazol resistant *C. krusei* IAI outlines the emergence of new pathogens in the setting of PTx. The threshold for relaparotomy after PTx should be low. An aggressive diagnostic approach as well as continuous microbiological monitoring is recommended to maximize the chance of graft rescue. Meticulous microbiological investigations are mandatory due to the diversity of isolated pathogens showing abnormal susceptibility in many cases. A moderate reduction of immunosuppression without immediate removal of the pancreatic graft seems to be justified [27]. With this strategy in patients with IAI, we were able to save all kidney grafts as well as the pancreatic graft in all but one case. Contamination of the graft must be considered as previously outlined, and the contamination rate of 22% for preservation solution is higher than in other types of allografts [28–30]. As the ureter specimen had a contamination rate of only 6%, the duodenal segment must be considered a potential source for pathogens even if the upper GI tract of the donor is rinsed through a nasogastric tube with polyvinyl-pyrolidone–iodine-containing solution and a stapler was used during procurement.

In summary, combined pancreas-kidney transplantation with systemic venous/enteric exocrine drainage can produce excellent results. The three applied regimens including either Tacrolimus/MMF or Tacrolimus/Sirolimus immunosuppression using a short course of high-dose ATG induction or 3-day standard dose ATG induction result in a low rate of immunological graft losses. However, there remains considerable surgical morbidity and significant morbidity and mortality from infectious complications. It is tempting to assume that still overimmunosuppression is a common occurrence. A more rapid steroid taper and lower Tacrolimus and Sirolimus levels and lower MMF dosage seem justified. For further cohorts, the decision which one of the agents should be reduced or even withdrawn must be guided by individual factors including presence of comorbidities and development of significant side effects. Currently, there seems no need to intensify immunosuppression but rather optimize the combination of the currently available agents according to the individual

requirements of each patient. Further improvements in pancreas preservation and better control of infectious complications and prevention of vascular thrombosis will be needed to improve outcome following the PTx [26,30–33].

References

1. Kaufman DB. Pancreas transplantation. In: Stuart FP, Abecassis MM, Kaufman DB, eds. *Organ Transplantation*. Texas: Landes Bioscience, 2000: 145.
2. Di Carlo A, Odorico JS, Leverson GE, *et al.* Long-term outcomes in simultaneous pancreas-kidney transplantation: lessons relearned. *Clin Transpl* 2003: 215.
3. Tyden G, Bolinder J, Solders G, *et al.* Improved survival in patients with insulin-dependent diabetes mellitus and end-stage diabetic nephropathy 10 years after combined pancreas and kidney transplantation. *Transplantation* 1999; **67**: 645.
4. Smets YF, Westendorp RG, van der Pijl JW, *et al.* Effect of simultaneous pancreas-kidney transplantation on mortality of patients with type-1 diabetes mellitus and end-stage renal failure. *Lancet* 1999; **353**: 1915.
5. Ojo AO, Meier-Kriesche HU, Hanson JA, *et al.* The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. *Transplantation* 2001; **71**: 82.
6. Becker BN, Brazy PC, Becker YT, *et al.* Simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic patients with end-stage renal disease. *Kidney Int* 2000; **57**: 2129.
7. Schulz T, Heimes M, Schindler A, Busing M. TAC/MMF/Pred/single shot ATG versus CsA/MMF/Pred single shot ATG after pancreas-/kidney transplantation (PNTX) – initial results of a prospective randomized study. *Langenbecks Arch Chir Suppl Kongressbd* 1998; **115**(Suppl. I): 141.
8. Steurer W, Bonatti H, Obrist P, *et al.* Incidence of intra-abdominal infection (Iai). In a consecutive series of 40 enteric drained pancreas transplants with Fk506 and Mmf immunosuppression. *Transplant int* 2000; **13** (Suppl. 1): 195.
9. Linhares MM, Gonzalez AM, Trivino T, *et al.* Simultaneous pancreas-kidney transplantation: infectious complications and microbiological aspects. *Transplant Proc* 2004; **36**: 980.
10. Bonatti H, Berger N, Kafka R, *et al.* Experience with ATG short course high dose induction therapy in a series of 112 enteric drained pancreatic transplants. *Ann Transplant* 2002; **7**: 22.
11. Yussim A, Shapira Z. Single-bolus high-dose ATG for prophylaxis of rejection in renal transplantation – a prospective, randomized study. *Transpl Int* 2000; **13** (Suppl. 1): S293.
12. Pirsch JD, Odorico JS, D'Alessandro AM, Knechtle SJ, Becker BN, Sollinger HW. Posttransplant infection in enteric versus bladder-drained simultaneous pancreas-kidney transplant recipients. *Transplantation* 1998; **66**: 1746.
13. Smets YF, van der Pijl JW, van Dissel JT, Ringers J, de Fijter JW, Lemkes HH. Infectious disease complications of simultaneous pancreas kidney transplantation. *Nephrol Dial Transplant* 1997; **12**: 764.
14. Lumbreras C, Fernandez I, Velosa J, Munn S, Sterioff S, Paya CV. Infectious complications following pancreatic transplantation: incidence, microbiological and clinical characteristics, and outcome. *Clin Infect Dis* 1995; **20**: 514.
15. Ronco C, Chiaramonte S, Remuzzi G, eds. *Kidney Transplantation: Strategies to Prevent Organ Rejection. Monitoring of Immunosuppressive Therapy in Renal Transplanted Patients*, Vol. 146. Karger: Contrib Nephrol. Basel, 2005.
16. Steurer W, Margreiter R, Königsrainer A. Surgical techniques of pancreas transplantation. *Acta Chirurgica Austriaca* 2001; **33**: S8.
17. Sutherland DER, Cecka M, Gruessner A. *Newsletter from the International Pancreas Transplant Registry*, 2001.
18. Vincenti F, Stock P. De novo use of sirolimus in immunosuppression regimens in kidney and kidney-pancreas transplantation at the University of California, San Francisco. *Transplant Proc* 2003; **35** (Suppl. 3): 183S.
19. Marty FM, Rubin RH. The prevention of infection post-transplant: the role of prophylaxis, preemptive and empiric therapy. *Transpl Int* 2006; **19**: 2.
20. Garbino J, Lorenzi P, Morel P, Romand JA. Kidney and pancreas transplantation: postoperative infectious complications. *Clin Microbiol Infect* 1999; **5**: 48.
21. Bonatti H, Königsrainer A, Allerberger F, Riedmann B, Margreiter R, Steurer W. How to treat graft infection after pancreas transplantation. *Transpl Proc* 1995; **27**: 3045.
22. Bonatti H, Steurer W, Konigsrainer A, Allerberger F, Margreiter R. Infection of the pancreatic duct following pancreas transplantation with bladder drainage. *J Chemother* 1995; **7**: 442.
23. Troppmann C, Gruessner AC, Dunn DL, Sutherland DE, Gruessner RW. Surgical complications requiring early relaparotomy after pancreas transplantation: a multivariate risk factor and economic impact analysis of the cyclosporine era. *Ann Surg* 1998; **227**: 255.
24. Kusne K, Chakrabarti P, Akhavan-Heidari M, Corry RJ. Association of bacterial and fungal infections with surgical complications in pancreas transplant recipients. *Transplantation* 1999; **67**: S174.
25. Jorgensen KA, Dieperink H, Kirkegaard P. Complications of immunosuppressive therapy in organ transplantation. *Ugeskr Laeger* 2003; **165**: 4727.
26. Hafiz MM, Poggioli R, Caulfield A, *et al.* Cytomegalovirus prevalence and transmission after islet allograft transplant in patients with type 1 diabetes mellitus. *Am J Transplant* 2004; **4**: 1697.

27. Stratta RJ, Gaber AO, Shokouh-Amiri MH, Reddy KS, Egidi MF, Grewal HP. Allograft pancreatectomy after pancreas transplantation with systemic-bladder versus portal-enteric drainage. *Clin Transplant* 1999; **13**: 465.
28. Wakelin SJ, Casey J, Robertson A, *et al*. The incidence and importance of bacterial contaminants of cadaveric renal perfusion fluid. *Transpl Int* 2005; **17**: 680.
29. Bucher P, Oberholzer J, Bosco D, *et al*. Microbial surveillance during human pancreatic islet isolation. *Transpl Int* 2005; **18**: 584.
30. Odorico JS, Heisey DM, Voss BJ, *et al*. Donor factors affecting outcome after pancreas transplantation. *Transpl Proc* 1998; **30**: 276.
31. Bindi ML, Biancofiore G, Meacci L, *et al*. Early morbidity after pancreas transplantation. *Transpl Int* 2005; **18**: 1356.
32. Stratta RJ, Lo A, Shokouh-Amiri MH, Egidi MF, Gaber LW, Gaber AO. Improving results in solitary pancreas transplantation with portal-enteric drainage, thymoglobin induction, and tacrolimus/mycophenolate mofetil-based immunosuppression. *Transpl Int* 2003; **16**: 154.
33. Friend PJ. Trends in organ preservation. *Transpl Int* 2003; **16**: 701.