Epidemiology, risk factors and impact on long-term pancreatic function of infection following pancreas-kidney transplantation

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Abstract

Limited information exists about epidemiology and risk factors of infection following pancreas-kidney transplantation and its impact on long-term pancreatic graft function. A retrospective chart review of episodes of severe infection in consecutive pancreas-kidney transplantations in a single institution was performed to assess the epidemiology, risk factors for infection and their impact on the development of pancreatic graft dysfunction. Ninety-four (81%) of 116 recipients (median follow-up of 1492 days; mean 1594) developed 248 episodes of severe infection. Bacterial infections were present in 208 episodes, with 12% of the isolates resistant to antibiotics used in prophylaxis. There were 40 episodes of fungal infection in 32 patients (28%) (mostly *Candida spp*), and CMV disease appeared in 20 patients (17%), of which 50% appeared after the third month following surgery. The multivariate analysis identified that surgical re-intervention and the use of steroid pulses were independently associated with the development of any infection. Additionally, pre-transplant evidence of peripheral artery disease, a longer cold ischaemia time and high transfusional requirements were associated with fungal infections. Cytomegalovirus (CMV) mismatch was independently related to CMV disease and female sex, and bladder drainage of the exocrine pancreas was associated with urinary tract infection. At the end of follow-up, 29 patients (25%) had developed severe pancreatic graft dysfunction, and fungal infection was independently associated with it. Our study identifies a subset of pancreas-kidney transplant recipients at a higher risk of developing severe infection. Fungal infection is an independent risk factor for the development of severe pancreatic graft dysfunction.

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Introduction

Combined pancreas and kidney transplantation (PKT) is now considered to be an accepted therapeutic option for patients with diabetes and end-stage renal failure [1,2]. The increasing success of pancreas transplantation is the result of better surgical techniques, immunosuppressive therapies, and the rational use of antimicrobials [3]. However, and despite such advances, infection remains a major cause of morbidity and mortality after PKT, increasing costs and having a negative impact on graft and patient survival [4–6].

In contrast to what occurs with other types of transplants, information regarding infectious complications following pancreas transplantation is scant and controversial. Most published studies have focused on specific types of infections or short-term infectious complications, but comprehensive reports involving enough recipients with an adequate follow-up are scarce [7]. As a consequence, there is not

an infection-related standard of care following pancreas transplantation, and important questions remain to be answered regarding the impact of infection on this type of transplant.

The aim of our study was to describe the epidemiology and microbiological characteristics of severe infections following PKT, as well as to analyse the risk factors associated with infection and its impact on long-term pancreatic graft function.

Material and Methods

Study population

We performed a retrospective chart review of the entire cohort of consecutive patients who underwent pancreatic transplantation in our institution from March 1995 to September 2008. We excluded patients who underwent pancreas transplantation as a part of a multivisceral transplant (with the exception of kidney transplants). All patients were followed-up to April 2010 or until they died or lost the pancreatic graft. The local ethical committee approved the study.

Variables related to donors and recipients were extensively reviewed. Recipient characteristics included: age, sex, type of diabetes, time from diabetes diagnosis, Charlson index [8], evidence of peripheral artery disease (PAD), type of pre-transplant dialysis, time on dialysis and previous transplant. Pre-transplantation variables included body mass index (BMI), biochemical and haematological data within 24 hours prior to transplant, including viral serologies, and crossmatching for HLA compatibility. Donor characteristics were also recorded, including age, sex, vasoactive drug requirements, BMI and CMV serostatus. Intraoperative factors included length of transplant surgery, cold and warm graft ischaemia time, blood product units given during surgery, and type of pancreatic exocrine drainage. Additionally, postoperative factors were analysed, including length of intensive care unit stay, vascular amine requirements, surgical re-intervention, immunosuppressive treatment, need for dialysis, acute or chronic rejection and length of hospital stay during the first hospitalization. The following outcomes were noted: duration of follow-up, pancreas graft survival, tumours and mortality at the end of follow-up. Data about microbiology, timing and site of each episode of infection were also collected.

Surgical technique

Pancreas transplantation was performed following standard techniques, as described previously [9]. Drainage of the exocrine pancreatic secretions was carried out using bladder drainage (mostly during the first years of the study) or enteric drainage.

Immunosuppression

Induction immunosuppression therapy included quadruple therapy with antithymocyte globulin (ATG) induction (1.5 mg/kg/day; range, 6–12 days), tacrolimus azathioprine or mycophenolate mofetil, and steroids. Those patients with allergic reactions to ATG received basiliximab. Acute rejection episodes were treated with steroid pulses.

Antimicrobial prophylaxis

Donor duodenal patches were irrigated with a solution including cefalotin and amphotericin B or fluconazole, as previously described [3]. All patients received perioperative antibacterial prophylaxis with vancomicin and ceftazidime for 3 days after transplantation and thereafter ciprofloxacin and fluconazole 100 mg/daily until discharge or for a maximum of 42 days [7]. Cotrimoxazole (800/160 mg) thrice weekly during the first 6 months was used in prophylaxis against *Pneumocystis jirovecii*. CMV prophylaxis changed over time. All patients received intravenous ganciclovir (5 mg/kg/24 IV, adjusted to renal function) while they were receiving ATG. Additionally, CMV-seropositive recipients received one of the following regimens: (i) no additional prophylaxis (from 1995 to April 1999); (ii) universal prophylaxis with oral ganciclovir or valganciclovir, adjusted to renal function for the first 12 weeks after transplantation (from May 1999 to September 2008, except from September 2002 to December 2004); or (iii) preemptive therapy (PT) guided by weekly pp65 antigenaemia (from September 2002 to December 2004). CMV-seronegative recipients who received a graft from a seropositive donor received prophylaxis with ganciclovir or valganciclovir during the first 12 weeks after transplantation [10].

Definitions

Severe infections were defined as those that needed systemic antibiotic therapy and required at least 24 hours of hospital admission. Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) criteria for infection definitions were used [11]. Asymptomatic bacteriuria and asymptomatic episodes of CMV viraemia were specifically excluded from the analysis. CMV disease required the presence of clinical symptoms with the demonstration of virus by means of virological or pathological methods [12]. A vascular surgeon, by means of Doppler studies, arteriography or computed tomography-guided angiography before transplantation, diagnosed peripheral artery disease. Severe pancreatic graft dysfunction was defined as the need for permanent insulin therapy at the end of the follow-up.