ORIGINAL ARTICLE

Bacterial infections as complications in patients within 3 months after simultaneous pancreas-kidney transplantation

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KEY WORDS

infectious complications, pancreas-kidney transplantation

ABSTRACT

INTRODUCTION Simultaneous pancreas-kidney transplantation (SPK) is associated with high risk of infectious complications.

OBJECTIVES The aim of the study was to evaluate the incidence of bacterial infections within 3 months after SPK transplantation.

PATIENTS AND METHODS 17 patients with type 1 diabetes at the age of 32–54 years (mean age 42.5 ±7.1) were retrospectively analyzed within 3 months after SPK.

RESULTS No septic complications were observed in 2 patients (12%). In the remaining 15 patients (88%), at least 1 (from 1 to 5, a total of 30) infection episode was observed during follow-up. The infections were located: only at the surgical site (1 patient – 6.7%), only in the urinary tract (6 patients – 40%), both at the surgical site and in the urinary tract (7 patients – 46.7%), at the surgical site and in blood (1 patient – 6.7%). 2 groups of microbes were predominant, namely enterococci represented by 1 species, *E. faecium* (13 isolates) and the so-called intestinal bacilli, *Enterobacteriaceae* (19 isolates). No methicillin resistant *Staphylococcus aureus* strains were isolated. *Candida* species fungi were isolated only 3 times.

CONCLUSIONS In our study only 2 types of infections were observed (urinary tract and surgical site infections) and each of them comprised nearly half of all the septic episodes recorded. Gram-negative bacilli were collected more often than Gram-positive cocci, both from the surgical site and urinary tract infections. All infections ended with full recovery.

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INTRODUCTION About 20 million people worldwide (about 150 thousand in Poland) suffer from type 1 diabetes. Despite continuous advances in diagnostic and treatment methods, type 1 diabetes continues to result in chronic renal diseases, vision loss, lower limb amputations and cardiovascular diseases in many patients.[1] The Diabetes Control and Complications Trial has confirmed that the development of chronic complications, which are the main cause of disabilities and premature deaths of patients with type 1 diabetes, can be prevented by intensive metabolic control which, however, leads to an increased incidence of hypoglycemia and increased body mass.[2]

Pancreas transplantation is a method of diabetes treatment which allows for restoration of endogenous insulin production and ensures normal glycemia without risk of hypoglycemia.[3] Pancreas was first transplanted in 1966 by Kelly and Lillehei who thus managed to achieve insulin

TABLE 1 Number of Human Leucocyte Antigen (HLA) mismatches in 17 recipients of simultaneous pancreas-kidney transplants

HLA – mismatch	Number of patients
1-2-2 (A1)	1
2-1-2 (B1)	1
1-1-2 (A1, B1)	1
0-2-2 (A1, A2)	1
2-2-1 (DR1)	1
2-2-0 (DR1, DR2)	1
2-1-1 (B2, DR2)	1
2-2-2	10

independence in a female patient only for 6 days. After that time, the transplant was rejected.[4] The introduction of new immunosuppressive drugs in the 1980s resulted in a significant improvement in results and an increase in the number of transplanted pancreata. Within the last 40 years, over 23 thousand of transplants were performed, including over 17 thousand in the USA. In Poland, kidney and pancreas have been transplanted in 157 patients since the year 2000.[5]

Pancreas transplantation is performed mainly in patients with type 1 diabetes, although there are published reports regarding successful transplants in patients with type 2 diabetes requiring insulin treatment and in patients after total pancreatectomy.[6,7]

The most common procedure is SPK transplantation recommended in patients with type 1 diabetes and chronic renal disease both before and after the initiation of renal replacement therapy. Pancreas transplantation is performed after a successful kidney transplantation (pancreas after kidney – PAK) in order to prevent progression of diabetic complications and recurrence of diabetic nephropathy in the transplanted kidney, while the pancreas transplant alone (PTA) is recommended mainly in cases of inability to control unstable diabetes, especially inability to prevent episodes of severe hypoglycemia.[3]

Recipient survival-related results of all types of pancreas transplant (SPK, PAK, PTA) are similar, at values >95% within the 1st year after the transplant. The transplanted pancreas survival times are also similar and equal 84%, 76% and 77% for SPK, PAK and PTA, respectively.[6]

Complications following a pancreas transplant occur in about 30–35% of patients. They include vascular thrombosis, inflammation with ischemia or organ transplant-related infections in the abdomen and pancreatic juice leakage at duodenoenterostomy or duodenocholecystomy sites.[8] About 62% of patients following duodenocholecystomy experience urinary tract infections owing to irritation of mucosal membranes by proteases. In case of duodenoenterostomy, the incidence of these infections is only 16%. The most commonly isolated microbes are *Escherichia coli*, *Enterococcus*, *Staphylococcus* and *Pseudomonas* species. These infections usually well respond to the treatments used. In case of recurrent infections, a conversion to duodenoenterostomy is required. The incidence rate of post-operational wound infections is increased in patients who had peritoneal dialyses performed prior to pancreas-kidney transplantation.[9]

Of significant importance is inadequate response to infection owing to neutrophil and macrophage function impairment and microangiopathy leading to tissue ischemia.[10]

The use of immunosuppression after a pancreas transplant increases the risk of infectious complications. Early infections may be associated with the activation of previously present, not identified inflammatory foci of e.g., tuberculosis or urinary tract infections, or with the postsurgical wound or vascular catheter insertion site.[11,12]

The purpose of this study was to evaluate the incidence of infectious complications within 3 months after SPK.

PATIENTS AND METHODS Bacterial infections occurring within 3 months after SPK in 17 patients – 6 females and 11 males – with type 1 diabetes, aged 32–54 years (mean age 42.5 ±7.1), performed between January and December 2006 were retrospectively analyzed. Duration of diabetes was 10–45 years (mean duration 28 ±8 years), 1 patient was in the pre-dialysis period while the others underwent renal replacement therapy (9 on hemodialysis, 7 on continuous ambulatory peritoneal dialysis) for 8–47 months (mean time 24 ±10.9 months). In all patients chronic diabetes complications of the kind of micro- and macroangiopathy and secondary hyperparathyroidism were detected. Glycated hemoglobin (HbA_{1c}) results were not evaluated since this parameter was considered unreliable in patients undergoing dialysis because of chronic kidney disease. However, when pancreas secretion was restored, which was confirmed by fasting concentrations of peptide C (7.1 ±3.3 ng/ml), the results of HbA_{1c} were 5.5 ±0.34%. Immunological matching of patients (in terms of human leukocyte antigen system) has been shown in TABLE 1. All patients received tacrolimus, mycophenolate mofetil and corticosteroids as immunosuppressive treatment after pancreas-kidney transplantation. Anti-thymocyte globulin was given as induction therapy at the dose of 1.5 mg/kg/24 h as an 8-hour infusion for 5 days. Tacrolimus 0.1 mg/24 h was administered orally or intravenously twice a day and the dosage was modified according to the desirable serum concentration. Mycophanolate mofetil at the dose of 2 g/24 h was given either *p.o.* or *i.v.* Initially, corticosteroids were given intravenously and then switched to oral medications; they were tapered and discontinued after 3 months.

RESULTS No septic complications were observed in 2 patients (12%). In the remaining 15 patients (88%), at least 1 (from 1 to 5, a total of 30) infection episode was observed within the observation

TABLE 2 Infectious complications episodes observed after simultaneous pancreas-kidney transplantation (number of patients, n = 17)

	Number of septic episodes in the weeks following transplantation											
	1	2	3	4	5	6	7	8	9	10	11	12
Urinary tract												
The 1st infection	2	4	2	1	–	2	1	–	–	–	–	1
The consecutive infections	–	–	–	–	–	–	1	1	–	–	1	–
Operational site												
The 1st infection	1	7	1	–	–	–	–	–	–	–	–	–
The consecutive infections	–	–	1	–	–	1	–	1	–	–	1	–
Bacteriemia	1	–	–	–	–	–	–	–	–	–	–	–

period (3 months after the procedure). The infections were located: only at the surgical site in 1 patient (6.7%), exclusively in the urinary tract in 6 patients (40%), both at the surgical site and in the urinary tract in 7 patients (46.7%), at the surgical site and in blood in 1 patient (6.7%). Infections of the surgical site and urinary tract occurred simultaneously only in 1 patient. In the remaining 6 patients, these infections occurred as separate episodes in time intervals from 2 days to >2 months.

Data presented in 1 show that the majority of urinary tract infections (70%) occurred within the first 3–4 weeks after transplantation. In the later period, occasional infections of different etiology were observed.

Surgical site infections emerged earlier (TABLE 2) – usually in the 2nd week after the surgery. In the same period (1st week) only blood infection occurred, and in the later period, occasional surgical site re-infections of different etiology were observed.

TABLE 3 presents data on microbial species isolated from all infections recorded. 24 positive urine cultures and 16 positive wound cultures were reported. As seen in the table, 2 groups of microbes were predominant: enterococci, represented by one species, *Enterococcus faecium* (13 isolates) and the so-called intestinal bacilli, *Enterobacteriaceae* (19 isolates). 3 strains of intestinal bacilli had a hospital-type resistance phenotype ESBL (+). No methicillin resistant *Staphylococcus* strains were isolated. *Candida* species fungi were isolated only 3 times. All infections ended with full recovery.

TABLE 3 Microorganisms isolated from infected sites (number of patients, n = 17)

Microorganisms	Wound	Urinary tract
Entrerobacteriaceae		
Escherichia coli	2	3
Klebsiella pneumoniae	3	3
Proteus mirabilis	1	1
Proteus vulgaris		1
Citrobacter freundii		1
Morganella morganii	1	
Klebsiella pneumoniae ESBL (+)		1
Enterobacter cloacae ESBL (+)		2
Total	7	12
Remaining microorganisms		
Enterococcus faecium	7	6
Acinetobacter baumanii	1	3
Pseudomonas aeruginosa		1
Candida tropicalis	1	1
Candida krusei		1
Total	9	12

DISCUSSION SPK is one of therapeutic options in advanced type 1 diabetes with nephropathy and end-stage renal insufficiency. However, it is unfortunately associated with high risk of infectious complications – higher than in case where only the kidney is transplanted.[13] This risk originates from both the primary disease and the course of the surgery and post-operational treatment.

Long-standing diabetes favors the development of infections not only in the result of vascular complications and trophic tissue lesions caused by autonomic neuropathy, but also in the result of an impaired phagocytic function of granulocytes. Glucose transformation in granulocytes is insulin-dependent and is inhibited in cases of insulin absence or deficiency which contributes to the impairment of the phagocytic function of granulocytes.[14]

The duration of SPK transplant procedure is very long, reaching up to 8 hours, significantly exceeding that of kidney transplant alone.[13] Exposition of operational area of that duration favors the development of surgical site infections.

Foley's catheter, central and peripheral punctures and respiratory support during the surgery may lead to urinary tract infections, bacteraemias and catheter-related sepses, and pneumonias, respectively.

The risk of infections in all above cases is increased by immunosuppression. To reduce adverse effects of immunosupression, the use of steroids has been limited and in recipients with normal function of the transplanted organ the medications have been withdrawn after 3 months from transplantation.[15]

If septic episodes occur in patients after the transplant, their number may vary from 1 to several episodes. It is difficult to compare the results published by different centers, both

because of different follow-ups and different result presentation methods. In our study, no deaths were observed within the 3-month follow-up; no septic complications occurred in 2 patients, while the remaining patients (88%) experienced 1 to 5 episodes of that kind which means 2.1 septic episodes per patient per 3-month follow-up. Other investigators, usually analyzing longer post-surgery periods, observed 2.1 episode per patient in a 39-month follow-up in 79% of recipients[16]; 2.9 episode per patient in a year in an observation period of 2.3 years on average, and as much as 4.8 episode per patient in the 1st year[17]; 3.4 episode per patient during follow-up of 40.1 months on average[13]; 1.6 episode per statistical patient during follow-up of up to 14 years, but with 24.5% mortality within 1 year following the transplant[18].

The highest incidence of septic episodes occurs in the early post-surgical period, mostly within the 1st month.[13,16,17] It was a similar case in our study since 60% of all septic episodes within the entire 3-month follow-up were observed within the 1st month.

The most common septic complications following pancreas-kidney transplant were urinary tract and surgical site infections. Depending on the reporting center, one or the other was predominant.[13,17,18] In our case, virtually only these 2 types of infections were observed, and each of them comprised nearly half of all recorded septic episodes. Gram-positive cocci (especially enterococci) were isolated more often (72%) than Gram-negative bacilli – 20%.[16] The latter were predominant in urinary tract infections but less common in surgical site infections.[17,18] It is valuable to observe that enterococci were relatively common in both types of infections. In our material, Gram-negative bacilli were collected more often than Gram-positive cocci, both from surgical site and urinary tract infections. The predominance of Gram-negative flora in the infections may be associated with mortality as high as 27%,[19] which was not observed in our study. All Gram-positive cocci isolates belonged to *Enterococcus faecium* species.

Sepsis occurred in patients after pancreas transplant with different incidence (6–25%) in various centers.[13,17,18,20,21] Etiology of sepsis as a consequence of pancreas transplant seem to be less dependent on the center and more on the starting point of the infection that gives rise to it. Thus, in 46 episodes of sepsis originating mostly from intra-abdominal infections, vascular lines and post-operational wounds, Gram-positive cocci comprised 77% of isolated strains and included coagulase-negative staphylococci – 43%, *Staphylococcus aureus* – 17%, and enterococci – 14%. Gram-negative bacilli comprised 18% of isolated strains. In these studies, sepsis significantly reduced the percentage of patients with 2-year transplant survival not affecting the survival of recipients themselves.[21] In other studies[17] where sepses originated from urinary tract infections, the predominant isolates were Gram-negative bacilli (69%), coagulase-negative staphylococci (19%) and enterococci (12%).

In our 2-month follow-up, only 1 episode of bacteremia (3% of all septic episodes) was observed. Of note, despite the reported septic episodes, no patient in our centre died within 1 year from the surgery. At various centers worldwide, the mortality ranged from 2%[17], through 2.8%[20], 12%[13], 18%[16], up to 24.5%.[18]

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