GASTROINTESTINAL COMPLICATIONS AFTER KIDNEY TRANSPLANTATION

Susanna Sarkio

Department of Transplantation and Liver Surgery

University of Helsinki

Helsinki, Finland

Academic Dissertation

To be presented with permission of the Medical Faculty of University of Helsinki
for public examination in the Richard Faltin auditorium,Surgical Hospital,
Helsinki University Central Hospital, in Kasarmikatu 11-13, Helsinki,
on April 21st, 2006, at 12 noon.

Helsinki 2006

Supervised by

Docent Leena Halme
Department of Transplantation and Liver Surgery
Helsinki University Central Hospital
Helsinki, Finland

Reviewed by

Docent Katri Kaukinen
University of Tampere
Tampere, Finland

and

Docent Pauli Puolakkainen
Department of Surgery
Helsinki University Central Hospital
Helsinki, Finland

Discussed with

Docent Heikki Saha
Department of Medicine
Tampere University Hospital
Tampere, Finland

ISBN 952-92-0028-5 (paperback)
ISBN 952-10-3005-4 (PDF)

Yliopistopaino 2006

To Rey

CONTENTS

ABBREVIATIONS

ASA	=	acetylsalicylic acid
AZA	=	azathioprine
BMI	=	body mass index
CagA	=	cytotoxic associated gene A
CAPD	=	continuous ambulatory peritoneal dialysis
CMV	=	cytomegalovirus
CsA	=	cyclosporine A
DGF	=	delayed graft function
DM	=	diabetes mellitus
EBV	=	Ebstein Barr virus
GI	=	gastrointestinal
HD	=	haemodialysis
HDL	=	high density lipoprotein
HIV	=	human immunodeficiency virus
HLA	=	human leukocyte antigen
H.pylori	=	Helicobacter pylori
HSV	=	herpes simplex virus
H2	=	histamine receptor 2
Ig	=	immunoglobulin
MP	=	methylprednisolone
MMF	=	mycophenolate mophetil
OKT3	=	monoclonal antibody muromonab CD3
OEGD	=	oesophagogastroduodenoscopy
PKD	=	polycystic kidney disease
PTLD	=	post transplant lymphoproliferative disorder
SLE	=	systemic lupus erythrematosus
US	=	ultrasound
VZV	=	varicella zoster virus

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in text by their Roman numerals I-V

I Sarkio S, Halme L, Kyllönen L, Salmela K. Severe gastrointestinal complications after 1515 adult kidney transplantations. Transplant Int 2004; 17: 505-510.

II Sarkio S, Rautelin H, Kyllönen L, Honkanen E, Salmela K, Halme L. Should *Helicobacter pylori* infection be treated before kidney transplantation? Nephrol Dial Transplant 2001; 16: 2053-2057.

III Sarkio S, Rautelin H, Halme L. The course of *Helicobacter pylori* infection in kidney transplantation patients. Scand J Gastroenterol 2003; 38: 20-26.

IV Sarkio S, Halme L, Arola J, Salmela K, Lautenschlager I. Gastroduodenal cytomegalovirus infection is common in kidney transplantation patients. Scand J Gastroenterol 2005; 40: 508-514.

V Sarkio S, Salmela K, Kyllönen L, Rosliakova M, Honkanen E, Halme L. Complications of gallstone disease in kidney transplantation patients. Submitted.

ABSTRACT

Aim: The aim of this study was to evaluate gastrointestinal (GI) complications after kidney transplantation in the Finnish population with a special focus in upper gastroduodenal ulcer development, gallstone disease and biliary complications, pancreatitis, colon perforations and GI malignancies.

Patients: The adult patients included in these studies underwent kidney transplantation at Helsinki University Central Hospital in Finland in 1990-2000.

Methods: Data on severe GI complications were collected from the Finnish Kidney Transplantation Registry and patient records. Questionnaires about upper gastroduodenal and gallstone complaints were sent to a subgroup of patients. *Helicobacter pylori* IgG and IgA antibodies were measured from 500 patients before kidney transplantation and after a median 6.8-year follow up, when also CagA antibodies were determined. For studies of gastroduodenal cytomegalovirus (CMV) infection oesophagogastroduodenoscopy (OEGD) with biopsies was performed on 46 kidney transplantation patients suffering from gastroduodenal symptoms and 43 dyspeptic controls. To determine the risk of gallstone formation after the transplantation ultrasound (US) examination of the gallbladder was performed on 304 patients after a median of 7.4 years post transplantation. In addition to this, data from these 304 patients were collected on serum lipids, body mass index (BMI) and the use of statin medication.

Results: The rate of severe GI complications was 147 (10%) after 1515 kidney transplantations, the complications occurring after a median time of 0.93 years. 6% of the complications were fatal. More than half of the complications occurred during the first post transplantation year, with the highest incidence in gastroduodenal ulcers and complications of the colon. Patients with GI complications were older and had more delayed graft function (DGF), and patients with polycystic kidney disease (PKD) had more GI complications than the other patients. *H.pylori* seropositivity rate was 31% in kidney transplantation patients, and this had no influence on graft or patient survival. 29% of the *H.pylori* seropositive patients seroreverted without eradication therapy. 74% of the kidney transplantation patients had CMV specific matrix protein pp65 or CMV

delayed early protein p52 positive findings in the gastroduodenal mucosa, and 53% of the pp65 or p52 positive patients had gastroduodenal erosions without *H.pylori* findings. After the transplantation 165 (11%) patients developed gallstones. A biliary complication, including 3 cases of biliary peritonitis and 1 fatal cholecystitis, developed in 15% of the patients with previous or present gallstones. 13 (0.9%) patients had pancreatitis, 3 (23%) of these were fatal. Colon perforations, 31% of them fatal, occurred in 16 (1%) patients. 13 (0.9%) developed a GI malignancy during the follow up.

Conclusions: Patients with gastroduodenal ulcers and colon complications were the biggest groups of GI complications after kidney transplantation. Most of the complications occurred early after transplantation. *H.pylori* has negligible influence on the outcome of kidney transplantation patients. On the other hand, CMV infection explains a part of the gastroduodenal lesions in kidney transplantation patients. In this patient group of kidney transplantation patients colon perforations are especially serious. High age, PKD and DGF are risk factors for GI complications in kidney transplantation patients.

INTRODUCTION

Kidney transplantation has been established as the most efficient treatment of end state renal disease with the advantage for the patient to live a nearly healthy life. It is also more cost-effective than dialysis if the kidney graft survives more than 1 to 3 years (Salonen et al. 2003, Gaston and Gitlin 2005). The first successful human kidney transplantation was performed between identical twins in 1954 (Merrill et al. 2001). In Finland the first kidney transplantation was performed in 1964. Since then the number of kidney transplantations has increased gradually. In 2005 166 adult kidney transplantations were performed in Finland. 5 of these transplants were from living donors and 161 were cadaveric kidney transplants. At the end of 2005 the total number of all Finnish kidney transplantations was 4919 (The Finnish Kidney Transplantation Registry).

Several factors, such as the cause of terminal uraemia, immunosuppressive medication and infections, can predispose kidney transplantation patients to the development of gastrointestinal (GI) problems. The diagnosis of severe GI complications can be delayed and treatment can be more complicated due to the use of immunosuppressive drugs (Stelzner et al. 1997).

Systemic lupus erythrematosus (SLE) and polycystic kidney disease (PKD) predispose patients independently to pancreatitis, diverticulosis and colon perforations (Padilla et al. 1994, Andreoni et al. 1999). Diabetes mellitus (DM) is known to predispose kidney transplantation patients to infectious GI complications (Logan et al. 2002). Gastric ulcer disease was a frequent and often fatal complication of kidney transplantation in the earlier years (Ahonen et al. 1977, Owens et al. 1977). The use of immunosuppressive medication also predisposes to the development of gallstones and pancreatitis (Frick et al. 1987, Fernandez-Cruz et al. 1989, Alberu et al. 2001).

Many opportunistic infections are common during immunosuppressive medication. Cytomegalovirus (CMV), which is considered to be the most important single post transplantation pathogen, can cause ulcerations, haemorrhage and perforations in the entire GI tract (Goodman et al. 1979, Goodgame 1993).

International recommendations for evaluating both the recipient and donor have been drawn to minimize the postoperative risks of kidney transplantation (EBPG 2000, Kasiske et al. 2001, EBPG 2002, Kälbe et al. 2005, Knoll et al. 2005). The pre transplantation work up in Finland includes abdominal ultrasound (US) screening and further examination of patients with GI complaints. The treatment of symptomatic colon diverticular disease and cholecystectomy in cases of gallstones have been among the requisites for acceptance to kidney transplantation.

The present study was carried out to examine the incidence and characteristics of severe post transplantation GI complications in Finnish kidney transplantation patients and to find out possible risk factors for these complications.

REVIEW OF THE LITERATURE

1.KIDNEY TRANSPLANTATION

1.1.General

Kidney transplantation is the only curative treatment for terminal uraemia. Primary renal diseases, congenital dysplasia of the urinary tract, as well as systemic diseases affecting kidneys, such as DM, SLE and amyloidosis, can lead to the development of end stage renal disease (Salmela et al. 1995).

The main indications for adult kidney transplantation in Finland in 2000-2003 were DM in 25%, PKD in 21%, glomerulonephritis in 21%, interstitial nephritis in 7% and congenital dysplasia of the urinary tract in 4% of the patients (Salmela et al. 2004).

Kidney transplantation is not suitable for all the patients with terminal uraemia. An absolute contraindication for kidney transplantation is an acute infection (Salmela et al. 1995, EBPG 2000). In patients with malignancy, at least a 2-year disease free time period before the transplantation, sometimes longer, is recommended depending on the type of cancer (EBPG 2000, Kälbe et al. 2005, Knoll et al. 2005). Relative contraindications consist of severe cerebral and cardiopulmonary circulatory disturbances, severe peripheral arterial disease, and severe psychiatric causes. HIV (human immunodeficiency virus), hepatitis B and C positivities are also considered to be relative contraindications (Kälbe et al. 2005). In contrast, old age is nowadays not considered to be a contraindication for kidney transplantation (Kälbe et al. 2005, Fijter and Persijn 2005).

The availability of donor organs sets limits to the number of kidney transplantations. In Finland, as well as in most of the other West European countries, the majority of the donated kidneys are from brain dead donors and only a few from living donors. In fact, Finland has the lowest number of living donors in the Nordic countries (Grunnet et al. 2001). Contraindications for kidney donation are chronic renal disease, a history of potentially metastasing malignancy, severe hypertension, sepsis, HIV positivity, hepatitis

B surface antigen positivity, hepatitis C, intravenous drug abuse, oliguric acute renal failure, and prolonged warm ischaemia (EBPG 2000, Kälbe et al. 2005).

Determination of ABO blood group and tissue typing with specific, serological or DNA based determinations of HLA (human leukocyte antigen) types are used to find the most suitable recipient-donor combinations. It is required in Finland that the recipient and donor share at least 2 HLA-AB and 1 HLA-DR alleles (Salmela et al. 1994, Kyllönen et al. 1999). Finally a cross-match test is performed between the recipient's blood and donor lymphocytes to avoid hyper acute rejection.

1.2. Operation technique

The surgical technique in adult kidney transplantation has changed only a little during the years (Koostra 1994). The donor kidney is transplanted extraperitoneally to the iliac fossa. The venous anastomosis is performed between the renal vein of the kidney and the recipient's external iliac vein end to side. The renal artery is connected with either internal iliac artery end to end or with external iliac artery end to side. The urether is anastomosed either to the recipient's urinary bladder or, when short or if the bladder is contracted, to the recipient's ipsilateral urether (Oliver 1995, Singer et al. 2005). Usually the recipient's own kidneys are not removed during the operation.

1.3. Immunosuppressive medication

After kidney transplantation patients need permanent immunosuppressive medication to prevent graft rejection and thereby loss of the graft. The mechanism of all the current immunosuppresive drugs is targeting T cell activation and cytokine production, clonal expansion or both. Figure 1 presents the targets of the immunosuppressants used in kidney transplantation (Denton et al. 1999).

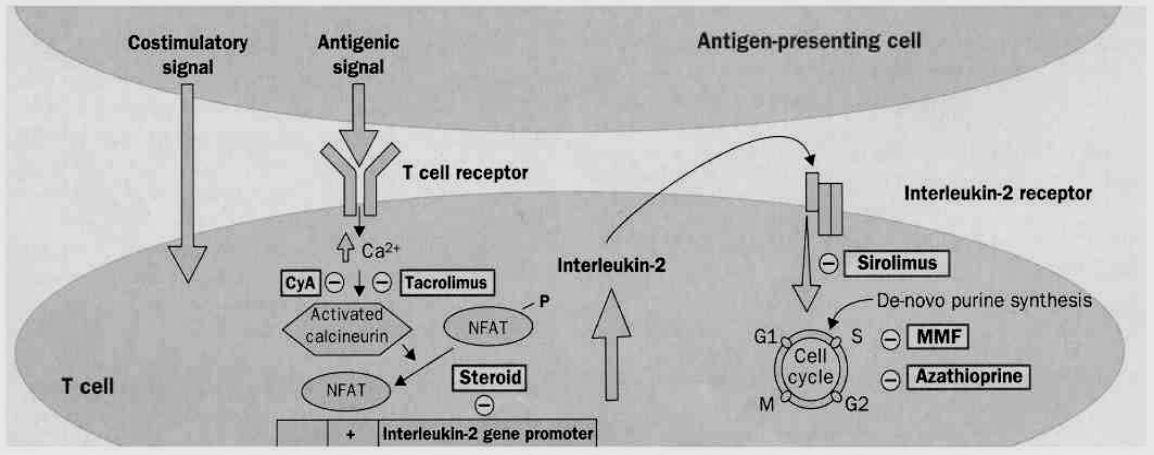

Figure 1. Targets for immunosuppressive agents (Reprinted from the Lancet 1999 Vol 353, Denton M, Magee C, Sayegh M. Immunosuppressive strategies in transplantation pp.1083-1091. Copyright with permission of Elsevier)

Calcineurin inhibitors

Calcineurin inhibitors are the cornerstones of modern immunosuppressive medication. The introduction of *cyclosporine A* (*CsA)* to clinical use during the early 1980's has dramatically improved the results of kidney transplantation. Since CsA was taken in use, acute rejection rate has fallen to 25% in Finland (Salmela and Kyllönen 1999, Kyllönen et al. 2000a). CsA is a small polypeptide of fungal origin that can form a complex with calcineurin inhibiting its normal function and thereby limiting cytokine production and T-cell proliferation. *Tacrolimus (FK 506)*, a newer product which is a macrolide antibiotic compound isolated from *streptomyces tsukubaensis*, has the same mechanism of action as CsA. Nephotoxicity is an important side effect of calcineurin inhibitors which limits their use (Danovitch 2005). Tacrolimus seems to be less nephrotoxic than CsA (Kälbe et al. 2005). Other side effects consist of effects on lipid profile, glucose intolerance, neurotoxic and cardiotoxic effects, thromboembolic complications and hyperuricaemia. Tacrolimus has been shown to be associated with DM in 20% as compared to 4% of CsA (Vincenti et al. 2002). Hypercholesterolemia, hypertriglyceridemia and effects such as acne, hirsutism and genital hyperplasia are more common with the use of CsA (Pirsch et al. 1997, Barry 1999).

Antiproliferative agents

Antiproliferative agents prevent the expansion of alloactivated T and B cells. *Azathioprine (AZA)* has been used since the 1960's in clinical transplantation. It is a purine analogue, an imidazole derivative of 6-mercaptopurine (Denton et al. 1999, Danovitch 2005). It inhibits purine nucleotide synthesis and interferes with the synthesis of DNA. It acts as a myelocyte suppressant and decreases the number of circulating monocytes. The most important side effect of AZA is bone marrow suppression. *Mycophenolate Mofetil (MMF)* is a prodrug, the active product of which is mycophenolic acid, a fermentation product of several *penicillum* species. It blocks the proliferation of T and B cells more specifically than AZA and inhibits antibody formation and generation of cytotoxic T cells in vitro (The tricontinental MMF renal transplantation study group 1996). Its use is limited by the many GI side-effects (Hardinger et al. 2004). *Sirolimus (rapamycin)* is a new potent immunosuppressive agent which acts by inhibiting T cell responses to cytokines. It inhibits intracellular signalling distal to the interleukin-2 receptor. Side effects consist of hyperlipidemia and thrombocytopenia (Murghia et al. 1996).

Corticosteroids

Corticosteroids have been used in transplantation since the early 1960's. They are non-specific anti-inflammatory agents and act by inhibiting cytokine production in T cells and macrophages. All stages of T-cell activation are inhibited. Corticosteroids can cause many side effects such as osteoporosis, cosmetic changes, impaired wound healing, impaired resistance to infection, cataract, hyperlipidemia, glucose intolerance and psychological effects (Danovitch 2005).

Antibodies

Anti T-cell preparations are used both in induction therapy in hyperimmunised patients and in steroid resistant rejections. *Antithymocyte globulin (ATG)* and *antilymphocyteglobulin (ALG)* bind themselves to multiple antigens on lymphoid cells. *Monoclonal antibody muromonab CD3* (*OKT3)* is a murine monoclonal antibody in wide

clinical use (Cosimi et al. 1981). It acts with the antigen recognition complex (CD3) on T cells. A feared side effect of its use is the toxic cytokine release syndrome. *Basiliximab* and *daclizumab* are new antibody preparations that act by blocking the interleukin-2 receptor expressed only by activated lymphocytes. Toxic cytokine release syndrome has not been reported in association with their use (Barry 1999).

Combination treatment

Because of the many side effects and different targets of inhibiting T cell activation, immunosuppressive agents are used in combination, usually as *triple therapy*, which includes CsA or tacrolimus combined with AZA or MMF and methylprednisolone (MP) (Denton 1999).

2. COMPLICATIONS OF KIDNEY TRANSPLANTATION

2.1. Technical postoperative complications

Wound infection occurs nowadays in less than 1% of the cases. This is so, because steroid doses are smaller than before and prophylactic antibiotics are used. Also recipient patients are in better general health condition than before (Beyga and Kahan 1998).

Postoperative bleeding usually occurs from the small vessels in the renal hilum that are not ligated during the operation. The bleeding can also arise from the vascular anastomoses when a myotic aneurysm or the graft itself ruptures (Beyga and Kahan 1998, Singer et al. 2005).

Graft thrombosis incidence varies from 0.5%-8% (Singer et al. 2005). It can be both of arterial or venous origin. Graft thrombosis usually occurs a few days after the transplantation. It is usually caused by poor surgical technique or acute rejection.

Renal artery stenosis occurs usually later, some weeks or months after the transplantation. The prevalence varies from 2%-10% (Beyga and Kahan 1998). The

stenosis can be in the end to end suture line or be pre- or post-anastomotic. It can be caused by rejection, arteriosclerosis, clamp injury, wrong suture technique, angulation of the vessel, and vessel size disproportion. The stenosis can usually be repaired with angioplasty and intra-arterial stents, and with this the recurrence rate has decreased to 10% (Bruno et al. 2003, Akbar et al. 2005). Introduction of the end to side anastomosis with aortic cuff to the recipients' external iliac artery has decreased the prevalence of renal artery stenosis.

Urological complications occur in 3%-20% of the patients after kidney transplantation (Pisani et al. 2005). In Finnish kidney transplantation patients the incidence has been 4.2% (Mäkisalo et al. 1997). The incidence of *urine leakage* can rise up to 10% (Beyga and Kahan 1998). It can be caused by slack urethral reimplantation or bladder closure or ishaemic urethral wall lesion. *Urethral obstruction* can be caused by a blood clot, urethral slough, technical problems in surgery, like malrotation or kinking of the anastomosis, and by compression from the outside by a lymphocele (Beyga and Kahan 1998).

Lymphoceles occur within weeks and the first months after the transplantation. They are caused by a leak from severed lymphatic vessels near the iliac vessels during the transplantation. The incidence of lymphocele formation varies between 1%-18% (Gruessner et al. 1995). Lymphoceles occur as an abdominal mass usually located medially to the transplanted kidney, between the graft and the bladder (Akbar et al. 2005). Lymphoceles can cause urethral obstruction and compress iliac veins leading to oedema of the leg and, in severe cases, even to deep vein thrombosis (Gruessner et al. 1995).

2.2. Rejections

The patient's immunosystem is activated after invasion of foreign material and both a non-specific inflammatory process and T-cell mediated antigen specific immune responses follow it. Rejection can be defined as an immune response against the graft, which without treatment leads to the destruction of the graft. There are three different types of rejection when classified according to the time of onset (Nast and Cohen 2005).

Hyperacute or accelerated rejection occurs if the recipient has previously been sensitised against the donor antigens and has circulating cytotoxic Ig (immunoglobulin) G anti-donor HLA or anti-AB (blood group) antibodies because of previous transplantations, blood transfusions or pregnancies. Hyperacute rejection usually occurs during the first hours after transplantation and leads to the loss of the graft. In most cases it can be avoided by the pre transplant cross-match test.

Acute rejection occurs usually during the first weeks or months after transplantation. If mild rejections are included, acute rejections occur in 40%-70% of the cases (Kälbe et al. 2005). It is a specific immunoresponse against the graft and its cells, and it manifests typically as asymptomatic elevation of serum creatinine. The diagnosis is confirmed with a doppler US and US guided biopsy which shows infiltrates of lymphocytes and oedema. Acute rejection usually responds well to high dose corticosteroid treatment, and it only slightly affects long-term graft survival (Kyllönen et al. 2000a).

Chronic rejection is defined as a gradual but progressive impairment of renal allograft function in the absence of other specific causes (Isoniemi 1994). It can occur at any time after the first post transplantation months. The pathogenesis is not well understood. It does not respond well to antirejection treatment and it usually leads to the loss of the graft.

2.3. Post transplantation infections

Immunosuppressive treatment predisposes transplantation patients to increased rates of normal and opportunistic, systemic and localized infections of viral, bacterial and fungal origin (Helderman and Goral 2002). Figure 2 presents the occurrence of common infections after transplantation (Fishman and Rubin 1998, American Society of Transplantation 2004, Kubak et al. 2005). The sources of infections occurring in the first weeks after kidney transplantation, such as pneumonia, urinary tract infections and wound infections, are similar to those that develop in nonimmunocompromised patients who have undergone surgery. Infections with opportunistic pathogens and cytomegalovirus usually develop 1 to 6 months after the transplantation, and infections that are common in the general population can be seen after 6 months (Akbar et al. 2005).

Cytomegalovirus (CMV) is considered to be the most common pathogen of organ transplantation occurring in 60%-70% of organ-transplanted population. CMV infection in a transplantation patient can be a primary CMV infection in a previously uninfected host, reinfection by the virus, or most commonly, reactivation of the latent virus (Goodgame 1993). CMV can affect many organs causing pneumonitis, hepatitis, pancreatitis, retinitis and thrombocytopenia or leucopenia (Shrestra et al. 1996, Griffiths et al. 2000, Sinha et al. 2003). CMV can cause ulcerations and haemorrhage in the whole GI tract (Goodgame 1993). CMV colitis can be the cause of colon perforation in transplantation patients (Goodman et al. 1979). The incidence of GI CMV disease is 10% in transplantation patients (Meng and Smith 1999), and CMV infection usually occurs during the first moths after transplantation (Shrestra et al. 1996). CMV is a risk factor for other infections both fungal and bacterial, and CMV infection is frequently found with the reactivation of the human herpesvirus 6 and 7 (Lautenschlager 2003) which are associated with graft rejection (Griffiths et al. 2000, American Society of Transplantation 2004).

Herpes simplex virus (HSV) is the second common viral agent causing clinical infection after transplantation. The latent virus is usually reactivated within the first 6 weeks after transplantation. It is known to affect many parts of the GI tract (Helderman and Goral 2002).

Varicella zoster virus (VZV) infection causes significant morbidity among solid organ transplant recipients. Its occurrence in kidney transplantation patients is 2%-10%. (Gourishankar et al. 2004, American Society of Transplantation 2004). In adults the infection is usually due to reactivation of the virus (American Society of Transplantation 2004)

Activated *Ebstein Barr virus (EBV)* is present in 20%-30% of transplant recipients receiving immunosuppressive therapy and in more than 80% of patients receiving antilymphocyte-antibody therapy (Fishman and Rubin 1998). The importance of EBV in transplantation is its role in the pathogenesis of post transplantation lymphoproliferative disorders (PTLDs). PTLD is usually a B-cell lymphoproliferative process. Its severity can vary from a benign process to a highly malignant polyclonal lymphoma (Fishman and Rubin 1998).

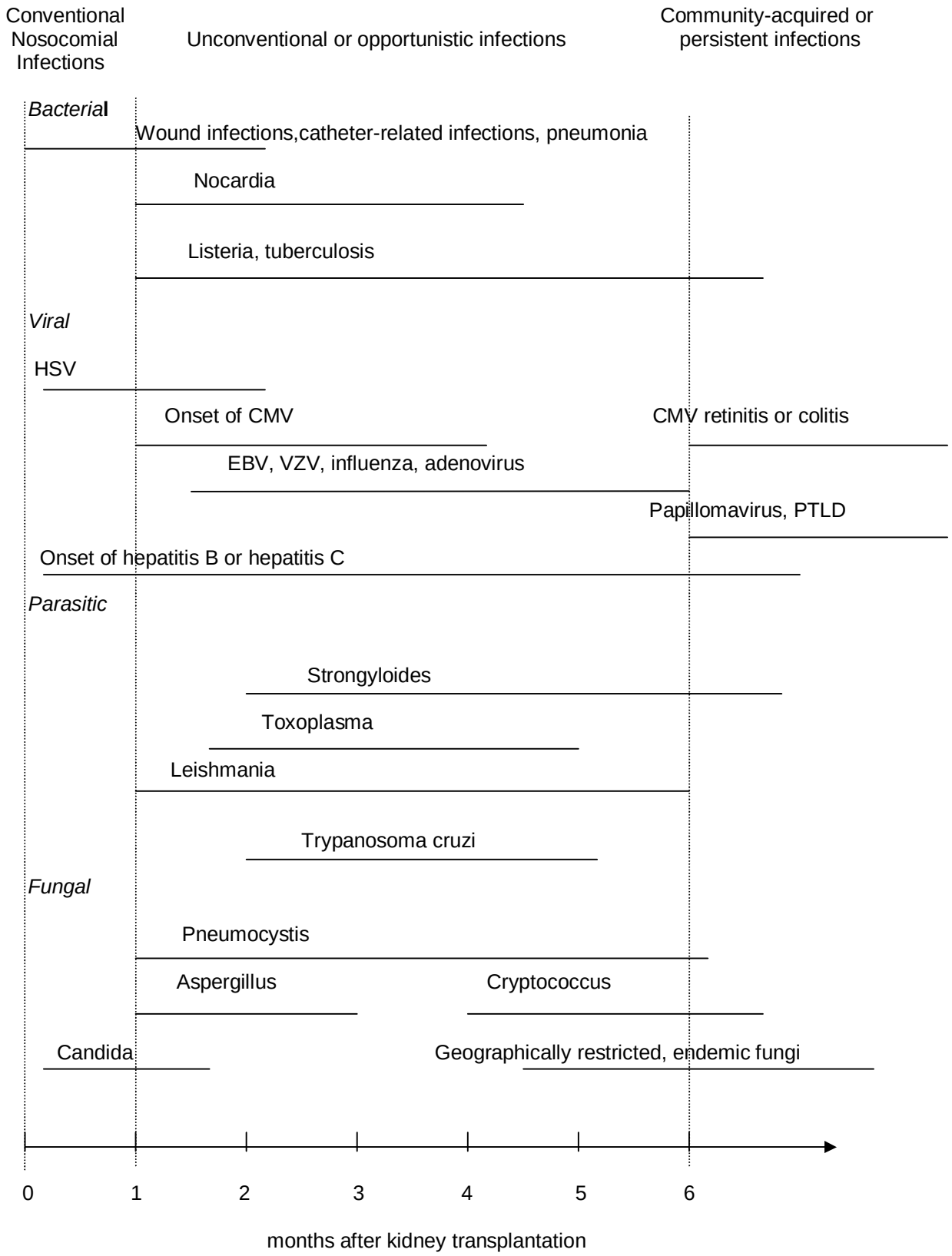

Figure 2. Usual occurrence of infections after transplantation

Fungal infections are the most fatal infections in immunosupressed patients (Meng and Smith 1999). *Candida albicans* is the most common fungal pathogen in this patient group and oesophagus the most common site of GI candida infection (Graham et al. 1995a, Helderman and Goral 2002, American Society of Transplantation 2004). Opportunistic fungal pathogens such as *aspergillus* and *pneumocystis carinii (pneumocystis jiroveci)* are also present post transplantation. The incidence of pneumocystis carinii pneumonia is 5%-15% after transplantation (American Society of Transplantation 2004). After introducing the prophylaxis of small dose sulphatrimethoprime (trimethoprime 80mg, sulfamethoxazole 400mg) pnemocystis carinii pneumonia has almost vanished. The prophylaxis has also reduced the risk of common respiratory pathogens and the risk of urinary infection in kidney transplantation patients (Fishman and Rubin 1998).

Bacterial pathogens in the early post transplantation period are similar to those of nonimmunosuppressed patients. Bacterial infections such as *listeria monocytogenes*, *yersinia enterocolica* and *clostridium difficile* can often be seen in transplantation patients with systemic CMV infection (Helderman and Goral 2002). Clostridium difficile infections have become more common in transplantation patients during recent years (Schaier et al. 2004).

2.4. Gastrointestinal complications

2.4.1. Gastroduodenal ulcer disease

In studies from the 1960's and 1970's, before the use of modern ulcer medication, the mortality because of ulcers in this patient group was over 40% due to massive haemorrhage and perforation. Even pre-kidney-transplant ulcer surgery was advocated in some centres (Owens et al. 1977, Ahonen et al. 1977). At present the incidence has declined mainly because of the screening of peptic ulcers pre transplant and because of the use of modern ulcer prophylaxis with histamine receptor 2 (H2) blockers or proton pump inhibitors (Ponticelli and Passerini 2005). Previously it was suggested that also dialysis treatment predisposed to the development of peptic ulcer and its complications

(Ala-Kaila 1987), but more recent studies do not support this (Kang 1993, Ponticelli and Passerini 2005).

The association of *Helicobacter pylori* infection with peptic ulcer disease is well known (NIH 1994). For duodenal ulcers it is almost 100% (Gisbert et al. 1999). The gene *cagA* that codes for the CagA protein is present in over 60% of the *H. pylori* strains in western countries (Atherton 1998, Gunn et al. 1998). In Finland that prevalence has varied between 71% and 79% (Oksanen et al. 2000, Rautelin et al. 2000). There is an association of more severe disease with CagA-positive strains with atrophy and higher incidence of duodenal ulcer (Atherton 1998, Navaglia et al. 1998). In the general population cagA-positive *H. pylori* infection seems to disappear more rapidly than the cagA-negative one (Perez-Perez et al 2002). In uraemic and kidney transplantation patients the seroprevalence of *H.pylori* does not differ from that of a normal population (Davenport et al. 1991, Gladziva et al. 1993, Özgur et al. 1997).

Viral organisms, like CMV and HSV, also cause ulcerations in the gastroduodenal tract (Goodgame 1993, Mosimann et al. 1994, Halme et al. 1998, Toljamo et al. 2002).

Development of peptic ulcer in kidney transplantation patients is multifactorial (Helderman and Goral 2002). In addition to the infectious agents, the stress of surgery, the use of non steroidal anti-inflammatory drugs, the use of steroids, AZA and MMF, and increased acid secretion during post transplantation dialysis have an influence on the formation of gastroduodenal ulcers (Steger et al. 1990). The association between corticosteroid treatment and ulcer development has been controversial, but recently the risk has been considered to increase only in patients with non-steroidal anti-inflammatory drug treatment, only used in low doses as thrombosis prophylaxis in kidney transplantation patients (Weil et al. 2000). Corticosteroids play a more important role in delaying the healing of the lesion after the use of non steroidal anti-inflammatory drugs than causing *de novo* ulceration (Piper et al. 1991). The incidence of severe gastroduodenal ulcers has diminished since CsA and effective ulcer prophylaxis with H2 blockers and proton pump inhibitors and new endoscopic techniques were taken in use (Benoit et al 1993, Troppmann et al 1995, Ponticelli and Passerini 2005). Steroid treatment can mask the symptoms and delay treatment. In Steger et al.'s material of kidney transplantation patients only 39% of the patients with post transplantation

gastroduodenal ulcers had symptoms, i.e. the number of ulcers in kidney transplantation patients is probably underestimated (Steger et al. 1990).

2.4.2. Gallstone disease and biliary complications

The aetiology of gallstone disease is multifactorial with predisposing factors, such as high age, female gender, family history of gallstone disease, obesity, rapid weight loss and diabetes mellitus. Also high serum triclycerides and low HDL (high density lipoprotein) levels appear to be risk factors for gallstone disease (Diehl 1991). In transplantation patients increased triglyceride and cholesterol levels are associated with the long term use of corticosteroids (Charco 2002, Kao et al. 2003). CsA, which is metabolised in liver, is lithogenic due to increased cholestasis and reduced bile flow (Lorber et al. 1987, Helderman and Goral 2002). Over 10% of the western population have gallstones (Diehl 1991, Juvonen 1994). The prevalence of pretransplant gallstone disease varies from 6.5% to 10.3% in kidney transplant recipients (Kao et al. 2003, Moray et al. 2003, Sianesi et al. 2005). After kidney transplantation the number of patients with newly diagnosed gallstones is 7.1%-17% (Graham et al. 1995, Greenstein et al. 1997). The prevalence of gallstone disease for pancreas and/or kidney transplantation patients is 16% when gallstones which are diagnosed both pre and post transplant are included (Kao et al. 2003). Kidney transplantation patients with DM are predisposed to the development of gallstones. The incidence of gallstone disease in kidney transplantation patients with DM was 27.3% compared to 12.2% in patients without DM (Lowell et al. 1993).

Studies of heart transplantation patients show that symptoms of gallstone disease develop in transplantation patients sooner than in the general population. The onset of symptoms is usually before the second year after transplantation (Milas et al. 1995). There is some controversy in studies about the morbidity and mortality of gallstone disease in kidney transplantation patients. Some studies show low incidence and morbidity of symptomatic gallstone disease (Greenstein et al. 1997, Melvin et al. 1998), but in one study the surgical morbidity occurred in 14% and mortality in 7% and kidney grafts were lost in 20% of the patients with symptomatic gallstones operated after the transplantation

(Graham 1995b). In the general population with gallstones complications of untreated gallstone disease like cholecystitis, cholangitis and biliary pancreatitis occur in 1%-2% annually (Friedman et al. 1989, Friedman 1993). The risk of gallstone complications in transplantation patients seems to be higher and the progression of symptoms more rapid (Kao et al. 2003, Sianesi et al. 2005). Because of immunosuppressive therapy the complications of gallstone disease are more severe and the diagnosis can be delayed.

2.4.3. Pancreatitis

Pancreatitis is an uncommon, but very serious and often fatal complication of kidney transplantation (Fernandez-Cruz et al. 1989, Slakey et al. 1997). The incidence of pancreatitis after kidney transplantation varies from 0.8%-11% (Frick et al. 1987, Fernandez- Cruz et al. 1989, Slakey et al. 1997, Adani and Baccarani 2005). Hyperparathyreoidism, hypercalcemia, the use of AZA and viral infections are considered to be specific aetiological factors of post transplantation pancreatitis (Mallory and Kern 1980, Frick et al. 1987, Fernandez-Cruz et al. 1989, Helderman and Goral 2002, Sinha et al. 2003). Frick et al. found a 5 times higher incidence of pancreatitis in kidney transplantation patients with hyperalcemia than in the general population (Frick et al. 1987). It has also been suggested that the use of corticosteroids can contribute to the development of pancreatitis post transplant, although the link has not been clearly shown (Mallory and Kern 1980, Fernandez-Cruz et al. 1989). As in general population acute pancreatitis can also develop in kidney transplantation patients due to alcohol use and biliary tract disease (Fernandez-Cruz et al. 1989).

2.4.4. Complications of the colon

Severe colon complications in kidney transplantation patients consist mainly of diverticulitis and CMV colitis (Goodman et al. 1979, Dominquez Fernandez et al. 1998). Nonobstructing colon dilatation is a more uncommon complication of kidney transplantation (Korneru et al. 1990). Perforation of the colon is the most feared

consequence of these complications, because the mortality rises to over 50% in this patient group (Benoit et al. 1993). A delay in the diagnosis in these patients is common, as the symptoms and signs are sparse and often masked by immunosuppression (Dominquez Fernandez et al. 1998). The incidence of colon perforations is 1%-2% in kidney transplantation patients (Church et a. 1986, Stelzner et al. 1997). Diverticulitis is its most common cause (Dominquez Fernandez et al. 1998, Remzi 2002). Other causes can be ischaemia or CMV colitis (Goodman et al. 1979, Remzi 2002).

Diverticulosis may occur in up to 50% of patients with uraemia (Stelzner et al. 1997). Patients with adult PKD have a higher incidence of colon diverticular disease than others (Scheff et al. 1980, Dominiquez Fernandez et al. 1998). Andreoni et al. showed also a higher perforation rate of 4.8% in this patient group (Andreoni et al. 1999). Lederman et al. found that 20% of patients with PKD had a history of acute diverticulitis compared to 3% of patients with other causes of terminal uraemia. Patients with PKD are also at a higher risk of diverticular complications after kidney transplantation than others (Lederman et al. 1998, Lederman et al. 2000). Stelzner at al. have found 2 different types of colon perforation in kidney transplantation patients. The first type which is usually due to diverticulitis or CMV colitis develops early after transplantation and is associated with high doses of immunosuppressive medication, particularly corticosteroids. The second type can occur years later and is caused by diverticulosis or malignancy (Stelzner et al. 1997).

2.4.5. Gastrointestinal malignancies

Long-term immunosuppression increases the risk of malignancies in kidney transplantation patients (London et al. 1995, Bustami et al. 2004). When GI malignancies are concerned, the risk of colon cancer is increased. In the material on transplantation patients by the University of Michigan the standardised incidence rate for colon cancer was significantly elevated being 2.5 (Feng et al. 2003). In a Finnish material on 2890 kidney transplantation patients the incidence of cancer was 16% after 15 years and 22% after 20 years; 39 (17%) of these 230 malignancies were of GI origin. The standardised

incidence rate for colon and small bowel carcinoma was significantly increased, the values being 11.8 and 3.9 respectively (Kyllönen et al. 2000b).

PTLDs are lymphoid tumours which can involve the GI tract in up to 10% of transplant recipients and usually occur early after transplantation (Helderman and Goral 2002). 1% of kidney transplantation patients develop PTLD (American Society of Transplantation 2004). It is usually a B cell lymphoproliferative process, the malignancy of which varies from a benign polyclonal process that can vanish after immunosuppressive therapy to a highly malignant monoclonal lymphoma that is resistant to all treatments (Fishman and Rubin 1998) The incidence depends on the organ transplanted, immunosuppression used and possible EBV and CMV infections (Muti et al. 2002). 90% of PTLDs are EBV positive (Gottschalk et al. 2005). Pediatric recipients have a 4-times higher risk to develop PTLD than adults, probably because they are often primarily EBV seronegative and receive a transplant from a seropositive donor (Schroff and Rees 2004). Also low grade gastric mucosa associated lymphoid tissue lymphomas (MALT lymphomas) associated with *H.pylori* infections have been documented in transplantation patients (Hsi et al. 2000, Aull et al. 2003).

AIMS OF THE STUDY

1. To examine the frequency and possible risk factors for post transplantation GI complications in Finnish kidney transplantation patients

2. To determine the role of *H. pylori* infection in upper GI complications in kidney transplantation patients and to find out the role of immunosuppressive medication in the course of *H. pylori* infection

3. To examine the characteristics of gastroduodenal CMV infection in kidney transplantation patients. To see how often the presence of CMV can be assessed in the gastroduodenal mucosa of kidney transplantation patients and to find out whether CMV infection can explain a part of the gastroduodenal complications

4. To examine the occurrence and characteristics of gallstone disease in kidney transplantation patients

PATIENTS AND METHODS

This study was carried out at the Department of Transplantation and Liver Surgery of Helsinki University Central Hospital. The study material consists of patients who received a kidney transplant in 1990-2000 at the Transplantation Unit. The Ethics committee of Helsinki University Central Hospital has approved all the studies.

1. KIDNEY TRANSPLANTATION PATIENTS

During 1990-2000 1608 adult patients (977 men, 631 women) underwent 1698 kidney transplantations. 86 of the patients received 2 and 2 patients 3 kidney grafts. 39 (2.3%) kidney transplants were from living donors. At the time of the transplantation the median age of the patients was 45.5 years (range 16.1-76.3 years). Before the transplantation all patients had been on maintenance dialysis, 907 (56%) on hemodialysis (HD) and 701 (44%) on peritoneal dialysis (CAPD). Figure 3 shows the distribution of the causes of uraemia in these patients. After the transplantation 95% of the patients received CsA and 4% tacrolimus based triple immunosuppression. The doses used were: AZA 2mg/kg/day, which was lowered to 1mg/kg/day during the first 2 post operative weeks; CsA 5mg/kg just before the transplant operation and postoperatively 10mg/kg/day, adjusting the dose with blood levels; tacrolimus 0.2mg/kg/day and lowering these doses during the 2 postoperative weeks, adjusting the dose with blood levels; and MP 1mg/kg/day lowering the dose to 0.25mg/kg/day during the 2 post operative weeks. Oral MP 3mg/kg/day for 5 days was used for episodes of acute rejection. Steroid resistant rejection episodes were treated with OKT3 5mg/day or ATG 1.5m/kg/day or plasmapheresis when vascular rejection had been detected in histology (Kyllönen 2000 a).

Just before the transplantation operation and 12 hours afterwards the patients received cephamandole 1g or cephuroxime 750mg intravenously for infection prophylaxis, and small-dose sulphatrimethoprime (trimethoprime 80mg and sulphamethoxazole 400mg) was used as *pneumocystis carinii* (*pneumocystis jiroveci*) prophylaxis twice a day 3 days a week for the first 3 months after the transplantation.

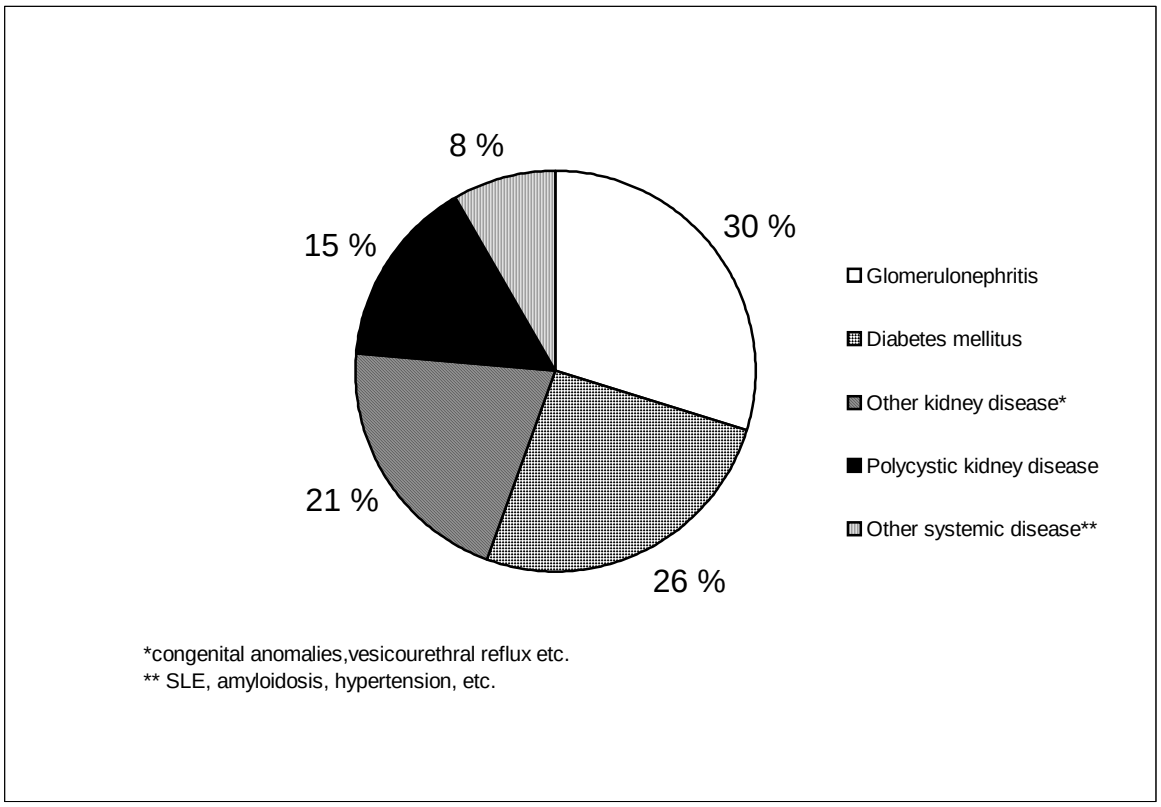

Figure 3. Causes of uraemia in study patients

Ranitidine 150mg/day or omeprazole 20mg/day was used at least in the first postoperative month as ulcer prophylaxis and acetylsalicylic acid (ASA) 50mg-100mg/day as thrombosis prophylaxis. In the beginning ganciclovir, from the year 1999 on valacyclovir and from the year 2002 on valgancyclovir was used for CMV prophylaxis in patients with donor positive and recipient negative combinations for 3 months.

The pre transplantation work up included abdominal US screening and further examination of patients with GI complaints. Cholecystectomy in cases of gallstones and colon resection for symptomatic diverticular disease were prerequisites for acceptance on the kidney waiting list.

Table 1 presents the patients in studies I-V.

2. METHODS

2.1. Data collection (studies I-V)

Clinical data of patients at the time they were accepted on the kidney waiting list, data of the post transplantation period at the hospital and follow up data sent regularly by the local nephrologists were retrospectively gathered from the original patient records and from the Finnish Kidney Transplantation Registry. To complete the information, questionnaires were sent to 428 patients about upper GI complaints, about how they were treated and examined (study II) and to 783 patients about diagnosed gallstones, cholecystectomies and possible gallstone complications, such as cholecystitis, choledocholithiasis, cholangitis and biliary pancreatitis (study V).

Gastroduodenal ulcers, severe GI infections and perforations, pancreatitis, cholecystitis and malignancies that were diagnosed by clinical, radiological or endoscopic methods were considered severe GI complications. Delayed graft function (DGF) was defined as serum creatinine concentration higher than 500μmol/l throughout the first post transplant week, or as the need for more than 1 dialysis session in the first week, or as oliguria of less than 1000ml/24h for more than 2 days (Kyllönen et al. 2000 a).

2.2. *Helicobacter pylori* analyses (studies II-III)

The IgG and IgA antibodies for *H. pylori* were measured from the pretransplant and follow-up samples by an in-house enzyme immunoassay (Kosunen et al. 1997, Oksanen et al. 1998). The cut off-titer was 700 for IgG and 70 for IgA. CagA antibodies (Study III) were determined from pre transplant serum samples from all 155 primary seropositive patients by a commercial immunoblot method (I.D.Blot *H.pylori* IgG, DPC, Los Angeles, CA, USA) according to the instructions of the manufacturer. Positive bands containing anti-CagA-antibody were estimated visually.

To confirm *H. pylori* status of the patients in study III, urea breath test was performed on 36 patients using ^{13}C labeled urea (Diabact UBT, Uppsala, Sweden) (Graham et al. 1987), and *H. pylori* stool antigen test (Premier platinum HpSA, Meridian Bioscience,

Cincinnati, USA) was performed on 2 of the patients. OEGD including biopsies was performed on 8 patients. *H. pylori* confirmation tests were performed on patients who were not receiving proton pump inhibitors, H2-blockers or antibiotics to avoid false negative results.

2.3. Cytomegalovirus analyses (study IV)

The CMV serostatus of all the kidney recipients and donors was determined prior to transplantation and that of 35 of the control patients at the time of OEGD. CMV viraemia was determined from blood by means of the CMV pp65 antigenemia test (The et al. 1995) using a monoclonal antibody against CMV pp65 antigens (Biotest Pharma, Frankfurt, Germany), when CMV infection was suspected, i.e. when patients had fever and/or their serum creatinine value was elevated without rejection. Biopsies from pathological findings, as well as biopsies from the second portion of the duodenum and from the antrum and corpus of the stomach, were taken for paraffin sections from the transplantation patients and controls. In addition to this, 2 biopsies from the second portion of the duodenum as well as 2 from the antrum of the stomach were taken for frozen sections. Routine histopathological examination included Haematoxylin and eosin, Alcian Blue PAS and Giemsa stainings. The histology of all biopsies was re-examined to score the inflammatory activity from 1 to 3 with the visual analogue scale according to the Sydney System (Dixon et al. 1996). CMV was demonstrated in frozen sections by immunoperoxidase staining using a monoclonal antibody against CMV specific antigen (pp65 matrix protein) (Halme et al. 2003). In studies later on a monoclonal antibody against the CMV delayed early protein (p52) (Dako A/S Glostrup Denmark), which detects the viral inclusions well, was used to demonstrate CMV in paraffin sections of the samples taken from the duodenum and antrum of the patients.

2.4. Ultrasound examination of the gallbladder and determination of lipid values (Study V)

Gallbladder US was performed in 2003-2004 to a subgroup of 304 of the 451 kidney transplantation patients from the Helsinki area still having a functioning graft and remaining in the follow up at the Division of Nephrology, Helsinki University Hospital. In addition to this, data on serum lipid values (total serum cholesterol, serum HDL and serum triclycerides), body mass index (BMI) and the use of statin medication at the time of transplantation and at the end of the follow up were collected from the patient records.

3. STATISTICAL ANALYSES

The parametric variables were compared using Student's T test (studies III-V) and nonparametric variables with Mann-Whitney U test (studies I and II). Fisher's exact test (studies I and III) or chi-square test (studies I-V) was used to compare proportions of patients between 2 groups.

Patient and graft survival in studies I and II was evaluated using the Kaplan Meier Life Table method and compared with the Log-rank test. Multivariate analysis in study I was performed with general regression model Statistica (Data analysis software system version 6 StatSoft. Inc 2003).

The data is expressed as median and range or mean and 95% confidence intervals. Significance was established at $p<0.05$.

RESULTS

1. GENERAL (Study I)

10% (147) of the 1445 kidney transplantation patients had a severe GI complication during the follow up in a median time of 0.93 years (range 2 days -11 years) after kidney transplantation. 15 (6%) of the GI complications were fatal. Patients with GI complications were older than patients without a complication at the time of transplantation (median 52.8 vs. 44.6 years, $p<0.01$). Patients with PKD were found to have GI complications significantly more often than patients with other causes of uraemia (14% vs. 8%, $p<0.05$).

75 (51%) of the verified GI complications in 70 patients occurred during the first postoperative year and the first year GI complication rate was 4.8% in the whole material. During the first year 60 (4.2%) patients died, 8 (0.6%) due to GI causes. 5-year patient survival rate in patients with a first year complication was 68% compared to 88% in patients with a later or no GI complication ($p<0.001$). Complications had no effect on the graft survival. DGF preceded a GI complication during the first year in 47% of the patients compared to 31% of the patients without a first year GI complication ($p<0.05$). The groups did not differ from each other with regards to rejection therapies or CMV infections. The 2 biggest groups of GI complications during the first year were gastroduodenal ulcers (44%) and colon complications (23%), including 2 gastroduodenal ulcer perforations and 12 perforations of the colon.

2. GASTRODUODENAL ULCER DISEASE (Studies I-IV)

2.1. The occurrence of gastroduodenal ulcers

During the 10-year follow up period 57 patients suffered from gastroduodenal ulcers with bleeding or perforation in 19 (33%) of them. The ulcers occurred in a median of 0.6 years (4 days - 11.2 years) after kidney transplantation. *H.pylori* infection was found in

gastroduodenal biopsies from 21% of the ulcer patients and CMV was detected from 7% of ulcer patients (Study I).

2.2. *Helicobacter pylori* (Studies II and III)

H. pylori seropositivity was found in 31% of a subgroup of 500 patients and the seropositivity increased with age. There was no difference in patient or graft survival between the seropositive and seronegative patient groups. During the first 3 months gastroduodenal ulcer was diagnosed in 1 seropositive and 5 seronegative patients. 3 of the ulcers were bleeding (Study II). In 4 patients with ulcers rejection therapy had been given before the detection of the ulcer and 1 of the seronegative patients had a concomitant CMV viraemia. Overall there were more ulcers in the *H.pylori* seropositive patient group than in the seronegative group (6% vs. 3%, N.S.).

92 of the 93 *H.pylori* seropositive patients had elevated IgG antibody titers, 73 had elevated IgA antibody titers, and in 1 patient only IgA titer was elevated. CagA antibodies were found in 83 (89%) primarily seropositive patients. The median decline in

IgG in the seropositive patients who had not received eradication therapy was from 3400 to 2000 ($p<0.01$) and the decline in median IgA titer from 170 to 110 (N.S.) during the median 6.8 year follow up. There was 1 patient with only IgA elevated the titer being 110. The IgA level remained unchanged during the follow-up, but the urea breath test was negative.

Spontaneous seroreversion of *H.pylori*, confirmed by 2 different tests occurred in 27 (29%) of the seropositive patients. All spontaneously eradicated patients received immunosuppressive treatment at least for 4 years. 22% of these patients received rejection treatment during the first 3 postoperative months compared to 15% of the other primarily seropositive patients. 8 of the spontaneously seroreverted patients had had a major infection that needed hospital care and intravenous antibiotics, while 11 of the remaining patients had only had a minor infection that needed short courses of antibiotics perorally. Because of the known interaction with CsA, none of these patients were treated with clarithromycin.

Table 1. Patients and main results of studies I-V

Study	Number of patients (transplantations)	Characteristics	Main results
I	1445 (1515)	Consecutive adult kidney transplantation patients transplanted in 1990-1999	● 147 (10%) GI complications occur, 75 (51%) during the first post transplantation year ● High age, DGF and polycystic kidney disease are risk factors for GI complications ● Gastroduodenal ulcers and colon complications are the biggest complication subgroups
II	500	Consecutive adult kidney transplantation patients transplanted in 1991-1994	● *H.pylori* seroprevalence is 31% ● *H. pylori* has no influence on patient or graft survival
III	93+88	*H.pylori* seropositive and seronegative patients from study II	● Spontaneous eradication of H. pylori occur in 27 (29%) of patients *
IV	46+43	Kidney transplantation patients transplanted in 1993-2003 and dyspeptic immuno-competent controls	● CMV positive cells are found in the gastroduodenal mucosa of 34 (74%) kidney transplantation patients and 17 (40%) controls ($p < 0.01$)
V	1608 (1698)	Consecutive adult kidney transplantation patients transplanted in 1990-2000	● 196 (12%) patients are diagnosed to have gallstones post transplant despite pre transplant screening ● Gallstone complications are found in 30 (15%) of the patients

* IgG decreased more than 70% or was less than 2000

2.3. CMV findings in the gastroduodenal mucosa (Study IV)

10 (22%) of the 46 transplantation patients studied (9 < 1 year and 1 > 1 year after transplantation) had macroscopical erosions with positive CMV pp65 or p52 findings in the gastric or duodenal mucosa. None of these patients had *H. pylori* in their biopsies but 5 (50%) revealed inclusions in the CMV p52 analysis. 1 *H. pylori* negative transplant patient with a positive CMV finding in the duodenal mucosa had a pyloric ulcer. Table 2 shows the findings of CMV pp65 or p52 in the gastric and duodenal mucosa. The histopathological findings in CMV positive samples were not specific but varied a lot and in general, they were scarce. There were, however, significantly increased amounts of inflammatory changes in the duodenal mucosa in CMV positive cases. In weakly positive cases histological changes were, if detected at all, mild and focal. Sometimes p52 immunostaining helped to find the inflammatory focus.

Table 2. CMV findings in the gastroduodenal mucosa of kidney transplantation patients and controls using a monoclonal antibody against the CMV pp65 antigens in frozen sections and a monoclonal antitibody against the CMV p52 antigens in paraffin sections. Positive cells / high power visual field was used as criterion of quantity in CMVpp65 test and inclusions found in CMVp52 test.

	Kidney transplantation patients			Controls
	All	< 1 year after transplantation	≥ 1 year after transplantation	
	n = 46	n = 27	n = 19	n = 43
Number of positive CMV pp65 or CMV p52 findings				
– Antrum:	14/46 (30%)	9/27 (33%)	5/19 (26%)	4/43 (9%)[1]
– Duodenum:	32/46 (70%)	17/27 (63%)	15/19 (79%)	15/43 (35%)[2]
– Antrum or duodenum	34/46 (74%)	19/27 (70%)	15/19 (79%)	17/43 (40%)[2]

[1] All kidney transplant patients vs. controls, $p < 0.05$
[2] All kidney transplant patients vs. controls, $p < 0.01$

3.GALLSTONE DISEASE AND BILIARY COMPLICATIONS (Study V)

Cholecystectomy because of gallstones had been performed on 71 (4%) of the 1608 patients before acceptance on the kidney transplantation waiting list. In a cross sectional study after a median 7.4-year follow up post transplantation an additional 196 (13%) patients (56% men) were diagnosed to have gallstones. In 165 (84%) of the patients the gallstones were not found before the transplantations, i.e. they were presumed to have developed after the transplantation.

After kidney transplantation 30 (15%, 70% of these men) patients with present or previous gallstones developed a biliary complication. Acalculous cholecystitis occurred in 4 patients. There was 1 fatal case of cholecystitis due to gallstones. 3 non-fatal gallbladder perforations, 1 without gallstones, were found. 17 of the patients with biliary complications required urgent operations.

In a subgroup of 304 (176, 58% of them men) kidney transplantation patients US screening of the gallbladder was performed after a median 7-year follow up. In this group 245 (81%) had no gallstones in the US, 31 (10%) patients had gallstones, and in 28 (9%) patients cholecystectomy had been performed earlier. Gallstones developed in 28 (10%) patients after transplantation.

Patients with a history of gallstone disease at the time of transplantation were significantly older than patients without pre transplant gallstone disease (52.3 vs. 44.2 years, $p<0.01$). Patients with gallstones after transplantation had gained most weight during the follow up. The increase in BMI was +2.0 in this group compared to +1.1 in patients without gallstones and +0.9 in patients with a history of pre transplant gallstones or cholecystectomy (N.S.) Lipid values did not differ between the groups. In the whole material 95% had CsA as the main immunosuppressive medication and in this subgroup CsA was the main immunosuppressive medication in all but one of the patients.

4. PANCREATITIS (Study I)

There were 13 cases of pancreatitis in a median 0.9 years (range 4 days - 6.2 years) after the transplantation. 3 of them were fatal. 2 of the fatal pancreatitis occurred during the

first postoperative year. Alcohol was the cause of 3 pancreatitis and gallstone disease of 1. In the others no specific aetiology in addition to immunosuppressive drugs could be found.

5. APPENDICITIS (Study I)

4 patients were diagnosed with appendicitis during the follow up. Of these 2 (50%) were perforated. Median time from the transplantation to the diagnosis was 0.7 years (range 109 days - 1.2 years).

6. COMPLICATIONS OF THE COLON (Study I)

Colon complications are presented in table 3. Half of the 16 colon perforations were caused by diverticulitis. The other colon perforations were caused by ishaemic colitis in 2, pseudo-obstruction in 2 and iatrogenic rectum perforation in 1 patient. In 3 patients no underlying cause of perforation could be found. 5 (31%) of the 16 colon perforations were fatal and 4 of them occurred during the first post transplantation year. High age and PKD were risk factors for colon complications. Patients with PKD as the cause of terminal uraemia had a higher incidence of diverticulitis than other patient groups ($p<0.01$).

Table 3. Complications of the colon in 1515 kidney transplantations of 1445 patients

Complication	n=31	Median time after transplantation (range)
Diverticulitis with perforation	8	1.7 months (4 days- 2.4 years)
Diverticulitis without perforation	12	19 months (2 days- 7.1 years)
Colitis with perforation	2	1.4 months (4 days-2.6 months)
Colitis without perforation	3	14.4 months (1.2 months- 4 years)
Other colon perforations	6	4.4 months (6 days-5.5 years)

7. GASTROINTESTINAL MALIGNANCIES (Study I)

13 (0.9%) of the patients developed a GI malignancy during the follow up, 2 of them during the first post operative year (table 4): A lymphoma of the jejunum developed to a male patient 7 months after the transplantation, and 1 female patient had a small sigmoid cancer (carcinoma in adenoma) 4.6 months after the transplantation. Median time to the development of GI malignancy was 3.3 years (range 138 days - 10.8 years) after kidney transplantation.

Summary of the results are presented in table 1.

Table 4. Gastrointestinal malignancies in 1515 kidney transplantations of 1445 patients

Malignancy	n=13	Years after transplantation median (range)
Pancreas cancer	2	4.5 (2.4-6.6)
Gastric cancer	3	2.1 (1.5- 5.1)
Carcinoid tumours	2	4.3 (3.3- 5.3)
Lymphoma	1	0.59
Cholangio cancer	1	8.1
Colon cancer	4	2.9 (0.39-10.8)

DISCUSSION

In this patient material of 1515 kidney transplantations during 1990-1999, which was screened before transplantation according to the recommendations of EBPG, the occurrence of serious GI complications was low as compared to earlier studies (10% vs. 8%-37%) (Meyers et al. 1978, Bardaxoglou et al. 1993, Benoit et al. 1993). 51% of all the GI complications and also more than half of the gastroduodenal ulcers and colon complications in this study were seen during the first post transplant year. This is probably due to the fact that high doses of immunosuppressive medication must be used during this early period.

Nowadays, when effective ulcer prophylaxis is used, the frequency of gastroduodenal ulcers has diminished in the general population as well as after kidney transplantation (Ohmann et al. 2005, Ponticelli and Passerini 2005, Smith and Stabile 2005). This can also be seen in the present study that includes only 4% of gastroduodenal ulcers. The figure is comparable with an earlier study consisting of patients from the 1980's and 1990's (Troppmann et al. 1995).

In study II the incidence of *H. pylori* seropositivity was 31%.The median age of the seropositive patients was significantly higher compared to that of the seronegative ones. These figures did not differ from another series in which the age-dependent occurence of *H. pylori* infection was described in a general Finnish population or from other reports of kidney transplantation patients (Davenport et al. 1991, Gladziwa et al. 1993, Kosunen et al 1997, Özgur et al. 1997). The number of new *H. pylori* infections decreases in developed countries, and consequently, the prevalence of the infection is higher in older age groups (Talley et al. 1993, Sipponen et al. 1996). *H. pylori* infection has negligible influence on the outcome of patients having undergone kidney transplantation. The frequency of gastroduodenal ulcers or ulcer bleedings within the first 3 post transplantation months did not increase among the *H.pylori* positive recipient group in study II. This is in accordance with an earlier finding that *H. pylori* infection does not account for the development of gastroduodenal ulcerative lesions in kidney allograft patients (Hruby et al. 1997). Furthermore, spontaneous eradication of *H. pylori* occurred

in 29% originally *H. pylori* seropositive kidney transplantation patients in study III after a median 6.8 year follow up, while in the general Finnish population only 4% of *H.pylori* seropositive patients have been found to serorevert (Kosunen et al. 1997). High degree of spontaneous seroreversion of *H.pylori* has also been reported in heart and liver transplantation patients (Dummer et al. 1995, Rudi et al. 1997). Low *H.pylori* IgG levels at the time of transplantation, long antibiotic treatment during the follow up and rejection treatments have been suggested to contribute to seroreversion (Dummer et al. 1995, Rudi et al. 1997). In addition to this, long-standing immunosuppression may be an important factor causing spontaneous eradication of *H. pylori* with reduced immune response to an ongoing mucosal *H.pylori* infection. This theory is, however, not supported by the findings that EBV titers have remained at the pre transplantation level while *H.pylori* antibodies have declined after the transplantation in heart transplantation patients (Dummer et al. 1995) and pneumococcal vaccination has resulted in antibody generation in kidney transplantation recipients (Arnold et al. 1985).

Other aetiologies than *H.pylori* for gastroduodenal ulcers are more probable in transplantation patients. According to the present data contributing factors could be low-dose ASA, preceding rejection therapy with high-dose corticosteroids and preceding CMV infection. Recently, the risk of corticosteroids causing ulcer was shown to increase only in those who concurrently received non-steroidal anti-inflammatory drugs (Weil et al. 2000). CMV, often activated by rejection therapy, causes also ulcerations in the gastroduodenal mucosa (Goodgame 1993, Halme et al. 1998). Based on these findings, the screening of *H. pylori* is not necessary before kidney transplantation.

In study IV, as well as in other studies, CMV was found in the gastroduodenal mucosa of transplantation patients (Hackman et al. 1994, Shrestra et al. 1996, Muir et al. 1998, Kaplan et al. 1999). Also other immunocompromised patients, especially HIV patients, have plenty of symptomatic GI CMV infections, predominantly colitis (Schwartz and Wilcox 1992, Baden and Maguire 2001). Interestingly CMV infected cells could also be found in the gastroduodenal mucosa in 40% of the control patients. There are reports of gastric or duodenal CMV infection also in immunocompetent patients (Cheung and Ng 1993, Novak et al. 1999, Maionara et al. 2003), though the relevance of this finding remains obscure. There are different methods to detect CMV infection of the gastroduodenal mucosa such as demonstration of early and late antigens, PCR

techniques, in situ DNA hybridisation and viral cultures (Hackman et al 1994, Muir et al 1998, Ljungman et al 2002). Study IV demonstrates that CMV pp65 and CMV p52 antigens are complementary to each other. According to the present study, as well as to an earlier study (Maionara et al 2003), demonstration of CMV p52 antigens proved useful in identifying inclusions and focal inflammatory areas in the gastroduodenal mucosa that had been overlooked in haematoxylin and eosin stained sections. Furthermore, if a kidney transplant patient has duodenitis, CMV infection should be strongly suspected, which another recent study also suggested (Telkes et al 2004). The possibility of CMV infection should also be searched in kidney transplantation patients with erosions in their gastroduodenal mucosa.

The prevalence of gallstone disease in solid organ transplantation candidates does not significantly differ from that of the general population. In studies about kidney or kidney and pancreas transplantation patients the prevalence has varied between 7%-17% (Graham et al. 1995b, Greenstein et al. 1997, Moray et al. 2003, Kao et al. 2003). The result of study V is in accordance with these observations. In the present study 95% of all the patients used CsA and practically all patients who developed gallstones after transplantation had CsA as the main immunosuppressive medication. The use of CsA has been associated with the formation of gallstones probably due to cholestasis and reduced bile flow (Helderman and Goral 2002). In the general population the rate of serious complications of gallstone disease is 1%-2% per year (Friedman 1993) In study V, as shown in other studies, the risk of gallstone complications in transplantation patients seems to be higher and the progression of symptoms more rapid (Kao et al. 2003, Sianesi et al. 2005). Because of immunosuppressive therapy the complications of gallstone disease can be more severe and the diagnosis delayed in transplantation patients. This emphasizes the importance of screening and treating also asymptomatic gallstones.

13 (0.9%) of the kidney transplantation patients in study I suffered from acute pancreatitis. This is in accordance with 0.8%-11% reported in the literature (Frick et al. 1987, Fernandez-Cruz et al. 1989, Slakey et al. 1997, Adani and Baccarani 2005). Pancreatitis is a severe complication of kidney transplantation with high mortality. In the present study the mortality was 23%. No specific aetiology could be found in 9 of the 13 pancreatitis. Moreover, most of the pancreatitis occurred early after the transplantation when the doses of immunosuppressive medication and the risk of opportunistic infections

such as CMV are at highest. Viral infections and immunosuppressive medication are suggested as aetiological factors in post tranplantation pancreatitis (Fernandez-Cruz et al. 1989, Sinha et al. 2003).

The occurrence of colon perforations was 1%, which is comparable with the earlier studies of kidney transplantation patients varying from 1%-2% (Church et al. 1986, Stelzner et al. 1997). Colon perforations proved to be very serious: 31% of the perforations were fatal. Most of the fatal perforations occurred during the first year after the transplantation. The diagnosis of colon perforations was often delayed because immunosuppressive drugs masked symptoms and affected the patients' responses to the septic condition. In this study, as well as in earlier reports, patients with PKD had significantly more often diverticulitis than patients with other causes of uraemia. (Scheff et al. 1980, Dominquez Fernandez et al. 1998, Andreoni et al. 1999). According to these findings the examination of the colon before transplantation is recommended.

Permanent immunosuppressive medication predisposes kidney transplantation patients to malignancies. Though most of these cancers are of cutaneous origin, the risk of colon cancer also rises (London et al. 1995, Bustami et al. 2004). It is important to screen pre-existing cancers before and after transplantation, as recommended by the EBPG expert group on renal transplantation (EBPG 2000, EBPG 2002). 2 of the malignancies in the present study were diagnosed during the first postoperative year; the PTLD lymphoma, first diagnosed as a MALT lymphoma, could probably be explained by high-dose immunosuppressive medication early after transplantation, and the small sigmoid carcinoma (carcinoma in adenoma) was probably missed in pre transplantation examinations. In study II 2 *H.pylori* seropositive patients and no seronegative ones suffered from gastroduodenal malignancies. There has been a lot of discussion of the role of *H. pylori* in the genesis of gastric carcinoma, and in 1994 *H.pylori* was classified as a group I carcinogen by the International Agency for Research on Cancer it being 1 of the co-factors involved in the development of neoplastic transformation of gastric mucosa (IARC 1994, Parsonnet et al. 1991, Kokkola et al. 1996). This justifies the treatment of known *H.pylori* infection before transplantation.

Kidney transplantation patients suffer from severe GI complications especially during the first post transplantation year but also later. Besides ordinary aetiologies also more rare aetiologies of GI complications should be suspected in this patient group.

CONCLUSIONS

On the basis of the present study the following conclusions can be drawn:

1. The frequency of severe GI complications in Finnish kidney transplantation patients is 10%. 51% of these complications occur during the first post transplant year. Especially serious complications in this patient group are GI perforations. High age, DGF and PKD increase the risk of GI complications.

2. *H. pylori* infection is common among kidney transplant patients, but it does not increase the risk of postoperative gastroduodenal complications nor does it affect graft or patient survival. Spontaneous eradication of *H. pylori* that is based on significant decrease of the IgG antibody titer is common occurring in 29% of kidney transplantation patients. Long-standing immunosuppressive medication may be the cause of spontaneous seroreversion.

3. CMV infected cells and inclusions are found in the gastroduodenal mucosa in 74% of kidney transplant patients. In kidney transplant patients CMV causes ulcerative gastroduodenitis, and this might explain some gastroduodenal symptoms.

4. Gallstone disease occurs in 12% of patients after kidney transplantation, which does not differ from a normal population. The complications of gallstone disease can be severe in kidney transplantation patients.

These results of kidney transplantation patients demonstrate the importance of meticulous pre transplant screening and post transplant follow up and treatment of GI disorders in at least elderly patients, patients with PKD and patients with DGF. Diagnosed *H.pylori* infection should be treated and gallstones should be screened and treated in kidney transplantation patients.

ACKNOWLEDGEMENTS

This work was carried out at the Department of Transplantation and Liver Surgery, Helsinki University Central Hospital in 1999-2006.

I wish to express my deepest gratitude to Professor Krister Höckerstedt, the head of the Department of Transplantation and Liver Surgery, for providing me with excellent research facilities. During the preparation of this thesis he had a positive and encouraging attitude towards my research work. He is an inspiring teacher and his work in the field of transplantation surgery is remarkable.

I owe my warmest appreciation to Docent Leena Halme, my supervisor. She introduced me to the field of research and came out with the topic of this thesis. I never stop admiring her enthusiasm in the scientific work. I thank her for her endless support and availability at any hours. I also enjoyed the several scientific sessions with food and wine at her house. Without her patient help this thesis would never have come to completion.

I am most grateful to Docent Kaija Salmela for her warm support and valuable advice during these years. I want to thank Docent Lauri Kyllönen especially for his irreplaceable help with the statistics in this work. I am also most thankful to my other co-authors Docent Johanna Arola, Docent Eero Honkanen, Docent Irmeli Lautenschlager, Docent Hilpi Rautelin, and Marina Rosliakova M.D. for their help and kind collaboration in these studies.

My sincerest thanks go Docent Katri Kaukinen and Docent Pauli Puolakkainen for their constructive criticism and valuable suggestions in reviewing this thesis.

The staff of the Transplantation Office is warmly thanked for their assistance. I am especially grateful to Mrs Hilkka Sokura for helping me with data collection. I also want to thank all my colleagues at the Department of Transplantation and Liver Surgery for their support.

I am most thankful to my colleagues and the staff at the Surgical Unit of Lohja Hospital. Without their flexibility and understanding it would have been impossible to complete this work.

I would like to thank all my friends for their help and care. Eeva Reissell M.D. and Erna Tapani M.D are especially thanked. I have had so much fun during our trips together to numerous places around the world. Erna's support during our trip to the Philippines was enormous. The long talks with Eeva have been most strength giving, not to mention the last-minute computer help.

My warmest thanks go to my sister Arla Maria Sarkio M.A. She has helped me irreplaceably by revising the English language of this thesis. Her support has been most valuable during these years.

I owe my dearest thanks to my parents Kirsti and Pertti Sarkio. They have supported me endlessly, and their love and belief in me has never failed. They have also helped me by taking care of Rey when this thesis has kept me busy.

This book is dedicated to my son Rey, the light of my life. He with his happy personality has taught me what is most important in life.

This work has been financially supported by the Finnish Kidney Foundation, the Research Funds of Orion Corporation, Biomedicum Helsinki Foundation, the Finnish Medical Society of Duodecim, Helsinki University Central Hospital Research Funds and the Finnish Society of Transplantation Surgery.

Helsinki, April 2006

Susanna Sarkio

REFERENCES

Adani G, Baccarani U. Acute pancreatitis after kidney transplantation. Am J Gastroenterol 2005; 100: 1620.

Ahonen J, Eklund B, Lindfors O, Kuhlbäck B, Lindström B: Peptic ulceration in kidney transplantation. Proc Eur Dial Transplant Assoc 1977; 14: 396-400.

American Society of Transplantation: Guidelines for the prevention and management of infectious complications of solid organ transplantation. Am J Transplant 2004; 4 (Suppl 10): 5-166.

Akbar S, Jafri Z, Amendola M, Madrazo B, Salem R, Bis K. Complications of renal transplantation. Radiographics 2005; 25: 1335-1356.

Ala-Kaila K. Upper Gastrointestinal findings in chronic renal failure. Scand J Gastroenterol 1987; 22: 372-376.

Alberu J, Gatica M, Cachafeiro-Vilar M, Robles-Diaz G, Bezaury P, Paz-Pinedo F, Vargas-Vorackova F. Asymptomatic gallstones and duration of cyclosporine use in kidney transplant recipients. Rev Invest Clin 2001; 53: 396-400.

Andreoni K, Pelletier R, Elkhammas E, Davies E, Bumgardner G, Henry M, Ferguson R. Increased incidence of gastrointestinal surgical complications in renal transplant recipients with polycystic kidney disease. Transplantation 1999; 67: 262-266.

Arnold W, Steele R, Rastogi S, Flanigan W: Response to pneumococcal vaccine in renal allograft recipients. Am J Nephrol 1985; 5: 30-34.

Atherton J. H.pylori virulence factors. British Med Bull 1998; 54: 105-120.

Aull M, Buell J, Peddi V, Trofe J, Beebe T, Hanaway J, Roy-Chaudhury P, Alloway R, First M, Woodle E. Maltoma: A Helicobacter pylori-associaed malignancy in transplant patients. Transplantation 2003; 27: 225-228.

Baden LR, Maguire JH. Gastrointestinal infections in the immunocompromised host. Infect Dis Clin North Am 2001; 13: 639-670.

Bardaxoglou E, Maddern G, Ruso L, Siriser F, Campion J, Pogamp P, Catheline J, Launois B. Gastrointestinal surgical emergencies following kidney transplantation. Transpl Int 1993; 6: 148-152.

Barry J. Renal transplantation. Curr Opin Urol 1999; 10: 121-127.

Benoit G, Moukarzel M, Verdelli G, Hiesse C, Buffet C, Bensadoun H, Charpentier B, Jardin A, Fries D. Gastrointestinal complications in renal transplantation. Transplant Int 1993; 6: 45-49.

Beyga Z, Kahan B. Surgical complications of kidney transplantation. J Nephrol 1998; 11: 137-145.

Bruno S, Remuzzi G, Ruggenenti P. Transplant renal artery stenosis. J Am Soc. Nephrol 2003; 15:134-141.

Bustami R, Akinloulu O, Wolfe R, Merion R, Bennett W, McDiarmic S, Leihtman A, Held P, Port F. Immunosupression and the risk of post-transplantation malignancy among cadaveric first kidney transplant recipients. Am J Transplant 2004; 4: 87-93.

Charco R, Dyslipidemia and long term immunosuppression. Transplant Proc 2002; 34: 124-126.

Cheung A, Ng I. Cytomegalovirus infection of gastrointestinal tract in non-AIDS patients. Am J Gastroenterol 1993; 88: 1882-1886.

Church J, Braun W, Norvick A, Fazio V, Steinmuller D. Perforation of the colon in renal homograft recipients. Ann Surg 1986; 203: 69-76.

Cosimi A, Burton R, Colvin R, Goldstein G, Delmonico F, La Quanglia M, Tolkoff-Rubin N, Rubin H, Herrin J, Russell P. Treatment of acute allograft rejection with OKT 3 monoclonal antibody. Transplantation 1981; 32: 535-539.

Danovitch G. Immunosuppressive protocols and medications for kidney transplantation. In handbook of kidney transplantation. Danovitch G. edit, Lippincott Williams & Wilkins 2005, Philadelphia, pp. 72-134.

Davenport A, Shallcross T, Crabtree J, Davison A, Will E, Heatley R. Prevalence of helicobacter pylori in patients with end-stage renal failure and renal transplant recipients Nephron 1991; 59: 597-601.

Denton M, Magee C, Sayegh M. Immunosuppressive strategies in transplantation. Lancet 1999; 353: 1083-1091.

Diehl A. Epidemiology and natural history of gallstone disease. Gastroenterol Clin North Am 1991; 20:1-19.

Dixon M, Genta R, Yardley J, Correa P. Classification and grading of gastritis: The updated Sydney System. Am J Surg Pathol 1996; 20: 1161-1181.

Dominquez Fernandez E, Albrecht K, Heeman U, Kohnle M, Erhard J, Stöblen F, Eigler F. Prevalence of diverticulosis and incidence of bowel perforation after kidney transplantation in patients with polycystic kidney disease. Transpl Int 1998; 11: 28-31.

Dummer J, Perez-Perez G, Breinig M, Lee A, Wolff S, Kormos R, Griffith B, Blaser M. Seroepidemiology of Helicobacter pylori infection in heart transplant recipients. Clin Infect Dis 1995; 21: 1303-1305.

The EBPG expert group on renal transplantation: European best practice guidelines for renal transplantation (part 1). Nephrol Dial Transplant 2000; 15 (suppl 7): 1-85.

The EBPG expert group on renal transplantation: European best practice guidelines for renal transplantation (part 2). Nephrol Dial Transplant 2002; 17 (Suppl 4) 1-67.

Feng S, Buell J, Chari R, Di Maio J, Hanto D. Tumours and transplantation: The 2003 third annual ASTS state of the art winter symposium. Am J Transplant 2003; 3: 1481-1487.

Fernandez-Cruz L, Targarona E, Cugat E, Alcaraz A, Oppenheimer F. Acute pancreatitis after renal transplantation. Br J Surg 1989; 76: 1132-1135.

Fijter J, Persijn G. Age, the riddle of renal transplantation. Nephrol Dial Transplant 2005; 20: 2307-2310.

Fishman J, Rubin R. Infection in organ-transplant recipients. N Engl J Med 1998; 338: 1741-1751.

Friedman G, Raviola C, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years follow-up in a health maintenance organization. J Chronic Dis 1989; 42: 127-136.

Friedman G. Natural history of asymptomatic and symptomatic gallstones. Am J Surg 1993; 165: 399-404.

Frick T, Fryd D, Sutherland D, Goodale R, Simmons R, Najarian J. Hypercalcemia associated with pancreatitis and hyperamylasemia in renal transplant recipients. Am J Surg 1987; 154: 487-489.

Gaston R, Gitlin M. Psychosocial and financial aspects of transplantation. In Handbook of kidney transplantation, Danovitch G. edit. Lippincott Williams & Wilkins 2005, Philadephia, pp.495-504.

Gisbert J, Blanco M, Mateos J, Fernández-Salazar L, Fernández-Bermejo M, Cantero J, Pajares J. H.pylori-negative duodenal ulcer prevalence and causes in 744 patients. Dig Dis Sci 1999; 44:2295-2301.

Gladziwa U, Haase G, Handt S, Riehl J, Wietholtz H, Dakshinamurty K, Glökner W, Siebert H. Prevalence of helicobacter pylori in patients with chronic renal failure. Nephrol Dial Transplant 1993; 8: 301-306.

Goodgame RW. Gastrointestinal Cytomegalovirus disease. Ann Intern Med 1993; 119: 924-935.

Goodman Z, Boitnott J, Yardlay J. Perforation of the colon associated with cytomegalovirus infection. Dig Dis Sci 1979; 24: 376-380.

Gottschalk S, Rooney C, Heslop H. Post-transplant lymphoproliferative disorders. Annu Rev Med 2005; 56: 29-44.

Gourishankar S, McDermid J, Jhangri J, Preiksatis J. Herpes Zoster infection following solid organ transplantation: Incidence, risk factors and outcomes in the current immunosuppressive era. Am J Transplant 2004; 4: 108-115.

Graham D, Klein P, Evans D Jr, Evans D, Alpert L, Opekun A, Boutton T. Campylobacter pylori detected noninvasively by the 13 urea breath test. Lancet 1987; 23 :1174-1177.

Graham S, Flowers J, Schweizer E, Bartlett S, Imbembo A. Opportunistic upper gastrointestinal infection in transplant recipients. Surg Endosc 1995; 9: 146-150. a

Graham S, Flowers J, Schweitzer E, Bartlett S, Imbembo A. The utility of prophylactic laparoscopic cholecystectomy in transplant candidates. Am J Surg 1995; 169: 44-48. b

Greenstein S, Katz S, Sun S, Glicklich D, Schechner R, Kutcher R, Tellis V. Prevalence of asymptomatic cholelithiasis and risk of acute cholecystitis after kidney transplantation. Transplantation 1997; 63: 1030-1032.

Griffiths P, Calrk D, Emery V. Betaherpesviruses in transplant recipients. J Antimicr Chemother 2000; 45: 29-34.

Gruessner R, Fasola C, Benedetti E, Foshager M, Gruessner A, Matas A, Najarian J, Goodale R. Laparoscopic drainage of lymphoceles after kidney transplantation: Indications and limitations. Surgery 1995; 117: 288-295.

Grunnet N, Ásmundsson P, Bentdal O, Madsen M, Pehrsson N, Salmela K, Tufveson G. Organ donation, allocation and transplantation in the Nordic countries: Scandiatransplant 1999. Transplant Proc 2001; 33: 2505-2510.

Gunn M, Stephens J, Stewart J, Rathbone B, West K: The significance of CagA and VacA subtypes of Helicobacter pylori in the pathogenesis of inflammation and peptic ulceration. J Clin Pathol 1998; 51: 761-764.

Hackman RC, Wolford JL, Gleaves CA, Myerson D, Beauchamp MD, Meyers JD, McDonald GB. Recognition and rapid diagnosis of upper gastrointestinal cytomegalovirus infection in marrow transplant recipients. Transplantation 1994; 57: 231-237.

Halme L, Höckerstedt K, Salmela K, Lautenschlager I. CMV infection detected in the upper gastrointestinal tract after liver transplantation. Transpl Int 1998; 11 (Suppl 1): 242-244.

Halme L, Höckerstedt K, Lautenschlager I. Cytomegalovirus infection and development of biliary complications after liver transplantation. Transplantation. 2003; 75: 1853-1858.

Hardinger K, Brennan D, Lowell J, Schnitzler M. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mophetil. Transpl Int 2004; 17: 609-616.

Helderman J, Goral S. Gastrointestinal complications of transplant immunosuppression. J Am Soc Nephrol 2002; 13: 277-287.

Hsi E, Singleton T, Swinnen L, Dunphy C, Alkan S. Mucosa associated lymphoid tissue lymphomas occurring in post transplantation patients. Am J Surg Pathol 2000; 24: 100-106.

Hruby Z, Myszka-Bijak K, Gosciniac G, Blaszuk J, Czyz W, Kowalski P, Falkiewicz P, Szymanska G, Przondo-Mordarska A. Helicobacter Pylori in kidney allograft recipients: High prevalence of colonization and low incidence of active inflammatory lesions. Nephron 1997; 75: 25-29.

IARC working group on the evaluation of the carcinogenic risks to humans. Schistosomes, liver flukes and Helicobacter Pylori. IARC: Lyon 1994; 61: 177-240.

Isoniemi H, Nurminen M, Tikkanen M, von Willebrandt E, Krogerus L, Ahonen J, Eklund B, Höckerstedt K, Salmela K, Häyry P. Risk factors predicting chronic rejection of renal allografts. Transplantation 1994; 57:68-72.

Juvonen T. Pathogenesis of gallstones. Scand J Gastroenterol 1994; 29:577-582.

Kang J. The gastrointestinal tract in uremia. Dig Dis Sci 1993; 38: 257-268.

Kao L, Kuhr C, Flum D. Should cholecystectomy be performed for asymptomatic cholelithiasis in transplant patients? J Am Coll Surg 2003; 197:302-312.

Kaplan B, Meier-Kriesche H, Jacobs M, Friedman G, Bonomi L, DeFranco P, Gelfand E, Mulgaonkar S. Prevalence of cytomegalovirus in the gastrointestinal tract of renal transplant recipients with persistent abdominal pain. Am J Kidney Dis 1999; 34: 65-68.

Kasiske B, Cangro C, Hariharan S, Hricik D, Kerman R, Roth D, Rush D, Varzquez M, Weir M. The evaluation of renal transplant candidates: Clinical practice guidelines. Am J Transplant 2001; 1 (Suppl2): 1-95.

Knoll G, Cocfield S, Blydt-Hansen T, Baran D, Kiberd B, Landsberg D, Rush D, Cole E. Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. CMAJ 2005; 173: 1-25.

Kokkola A, Valle J, Haapiainen R, Sipponen P, Kivilaakso E, Puolakkainen P. Helicobacter pylori infection in young patients with gastric carcinoma. Scand J Gastroenterol 1996; 31: 643-647.

Koostra G. Kidney transplantation. In Atlas of liver, pancreas and kidney transplantation. Kremer B, Broelsch C, Henne-Bruns D. Edit, Thieme 1994, New York, pp.128-149.

Korneru B, Selby D, O'Hair D, Tzakis G, Hakala T, Starzl E. Nonobstructing colonic dilatation and colon perforation following renal transplantation. Arch Surg 1990; 125: 610-613.

Kosunen T, Aromaa A, Knekt P, Salomaa A, Rautelin H, Lohi P, Heinonen O. Helicobacter antibodies in 1973 and 1994 in the adult population of Vammala, Finland. Epidemiol Infect 1997; 119: 29-34.

Kubak B, Maree C, Pegues D, Hwang A. Infections in kidney transplantation. In Handbook of kidney transplantation, Danovitch G. edit. Lippincott Williams & Willkins 2005, Philadelphia, pp.279-333.

Kyllönen L Salmela K, Eklund B, Halme L, Höckerstedt K, Isoniemi H, Mäkisalo H, Ahonen J. Long-term results of 1047 cadaveric kidney transplantations with special emphasis on initial graft function and rejection Transpl Int 2000; 13: 122-128. a

Kyllönen L, Salmela K, Pukkala E. Cancer incidence in a kidney-transplanted population. Transpl int 2000; 13(suppl 1): 394-398. b

Kyllönen L, Salmela K, Koskimies S. The clinical significance of conversion of complement-dependent cytotoxic T cell crossmatch test after renal transplantation. Transpl Int 1999; 12: 423-428.

Kälbe T, Lucan M, Nicita G, Sells R Burgos Revilla F, Wiesel M. Eau guidelines on renal transplantation. Eur Urol 2005; 47: 156-166.

Lautenschlager I. Cytomegalovirus and solid organ transplantation: an update. Curr Opin Org Transpl 2003; 8: 271-277.

Lederman E, Conti D, Lempert N, Singh T, Lee E. Complicated diverticulitis following renal transplantation. Dis Colon Rectum 1998; 41: 613-618.

Lederman E, McCoy G, Conti D, Lee E. Diverticulitis and polycystic kidney disease. Am Surg 2000; 66: 200-203.

Ljungman P, Griffiths P, Paya C. Definitions of cytomegaloviruus infection and disease in transplant recipients. CID 2002; 34: 1094-97.

Logan A, Morris-Stiff G, Bowrey D, Jurewicz W. Upper gastrointestinal complications after renal transplantation: a 3-yr sequential study. Clin Transplant 2002; 16: 163-167.

London N, Farmery S, Will E, Davison A, Lodge P. Risk of neoplasia in renal transplant patients. Lancet 1995; 346: 403-406.

Lorber M, Van Buren C, Flechner S, Williams C, Kahan B. Hepatobiliary and pancreatic complications of cyclosporine therapy in 466 renal transplant recipients. Transplantation 1987; 43: 35-40.

Lowell J, Stratta R, Taylor R, Bynon J, Larsen J, Nelson N. Cholelithiasis in pancreas and kidney transplant recipients. Surgery 1993; 114: 858-863.

Maiorana A, Baccarini P, Foroni M, Bellini N, Giusti F. Human cytomegalovirus infection of the gastrointestinal tract in apparently immunocompetent patients. Hum Pathol 2003; 34: 1331-1336.

Mallory A, Kern F. Drug-induced pancreatitis: A critical rewiev. Gastroenterology 1980; 78: 813-818.

Meng G, Smith P. Gastrointestinal infections of the immunocompromised host. Curr Opin Gastroenterol 1999; 15: 85-89.

Melvin W, Meier D, Elkhammas E, Bumgardner G, Davies E, Henry M, Pelletier R. Prophylactic cholecystectomy is not indicated following renal transplantation. Am J Surg 1998; 175: 317-319.

Merrill J, Murray J, Harrison J. Renal homotransplantation in identical twins. J Am Soc Nephrol 2001; 12: 201-204.

Meyers W, Harris N, Stein S, Brooks M, Jones R, Thompson W, Stickel D, Seigler H. Alimentary tract complications after renal transplantation. Ann Surg 1978; 4: 535-542.

Milas M, Ricketts R, Amerson R, Kanter K. Management of biliary tract stones in heart transplant patients. Ann Surg 1996; 223: 747-753.

Moray G, Basaran Ö, Karakayali H, Yagmurdus M, Bilgin N, Haberal M. Evaluation and treatment of biliary lithiasis in renal transplantation candidates. Transplant Proc 2003; 35: 2712-2713.

Mosimann F, Cuénoud P-F, Steinhäuslin F, Wauters J-P. Herpes Simplex esophagitis after renal transplantation. Transplant Int 1994; 7:79-82.

Muir S, Murray J, Farquharson M, Wheatley D, McPhaden A. Detection of cytomegalovirus in upper gastrointestinal biopsies from heart transplant recipients: comparison of light microscopy, immunocytochemistry, in situ hybridisation, and nested PCR. J Clin Pathol 1998; 51: 807-811.

Murghia M, Jordan S, Kahan B. The side effect profile of sirolimus: a phase I study in quiescent cyclosoprine-pednisolone treated renal transplantation patients. Kidney Int 1996; 49: 209-16.

Muti G, Cantoni S, Oreste P, Klersy C, Gini G, Rossi V, D'Avanso G, Comoll P, Baldanti F, Montillo M, Nosari A, Morra E. Post transplant lymphoproliferative

disorders: Improved outcome after clinico-pathologically tailored treatment. Haematologica 2002; 87: 67-77.

Mäkisalo H, Eklund B, Salmela K, Isoniemi H, Kyllönen L, Höckerstedt K, Halme L, Ahonen J. Urological complications after 2084 consecutive kidney transplantations. Transplant Proc 1997; 29: 152-153.

Navaglia F, Basso D, Piva M, Brogato L, Stefani A, Dal Bo N, Di Mario F, Rugge M, Plebani M. Helicobacter pylori cytotoxic genotype is associated with peptic ulcer and influences serology. Am J Gastroenterol 1998; 93: 227-230.

Nast C, Cohen A. Pathology of kidney transplantation. In Handbook of kidney transplantation. Danovitch G. edit, Lippincott Williams & Wilkins 2005, Philadelphia, pp.369-389.

NIH (The National Institutes of Health) Consensus Conference. Helicobacter pylori in peptic ulcer disease. JAMA 1994; 272: 65-69.

Novak T, Goddard M, Batteiger B, Cummings O. Evolution of acute cytomegalovirus gastritis to chronic gastrointestinal dysmotility in a nonimmunocompromised adult. Gastroenterology 1999; 116: 953-8.

Ohmann C, Imhof M, Ruppert C, Janzik U, Vogt C, Frieling T, Becker K, Neumann F, Faust S, Heiler K, Haas K, Jurisch R, Wenzel E-G, Norrman S, Bachmann O, Delgadillo J, Seidel F, Franke C, Lüthen R, Yang Q, Reinhold C. Time-trends in the epidemiology of peptic ulcer bleeding. Scand J Gastroenterol 2005; 40: 914-920.

Oksanen A, Veijola L, Sipponen P, Schauman K-O, Rautelin H: Evaluation of Pyloriset Screen, a rapid whole-blood diagnostic test for Helicobacter pylori infection. J Clin Microbiol 1998; 36: 955-957.

Oksanen A, Sipponen P, Karttunen R, Miettinen A, Veijola L, Sarna S, Rautelin H. Atrophic gastritis and Helicobacter pylori infection in outpatients referred for gastroscopy. Gut 2000; 46: 460-463.

Oliver J. Clinical indications, recipient evaluation, surgical considerations and the role of CT and MR in renal transplantation. Radiol Clin N Am 1995; 33: 435-446.

Owens M, Passaro E, Wilson S, Gordon H. Treatment of peptic ulcer disease in renal transplant patient. Ann Surg 1977; 186:17-21.

Padilla B, Pallak V, Pesce A, Kant S, Gilinsky N, Deddens J. Pancreatitis in patients with end stage renal disease. Medicine 1994; 73: 8-20.

Parsonnet J, Friedman G, Vandersteen D, Vogelman C, Orentreich N, Sibley R. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med 1991; 325: 1127-31.

Perez-Perez G, Salomaa A, Kosunen T, Daverman B, Rautelin H, Aromaa A, Knekt P, Blaser M. Evidence that cagA+ Helicobacter pylori strains are disappearing more rapidly than cagA- strains. Gut 2002; 50: 295-298.

Piper J, Ray W, Daugherty J, Griffin M. Corticosteroids use and peptic ulcer disease: Role of non steroidal anti-inflammatory drug therapy. Ann Intern Med 1991; 114: 735-740.

Pirch J, Miller J, Deierhoi M, Vincenti F, Filo R. A comparison of tacrolimus (FK506) and cyclosporine immunosuppression after cadaveric renal transplantation. Transplantation 1997: 63; 977-983.

Pisani F, Iaria G, D'Angelo M, Rascente M, Barletta A, Rizza V, Laurenzi C, Famulari A. Urologic complications in kidney transplantation . Transplant Proc 2005; 37: 2521-2522.

Ponticelli C, Passerini P. Gastrointestinal complications in renal transplant recipients. Transplant Int 2005; 18: 643-650.

Rautelin H, Oksanen A, Karttunen R, Seppälä K, Virtamo J, Aromaa A, Kosunen T. Association of CagA-positive infection with Helicobacter pylori antibodies of IgA class. Ann Med 2000; 32: 625-656.

Remzi F. Complications of organ transplantation. Transplant Proc 2002; 34: 2119-2121.

Rudi J, Engler S, Theilman L, Otto G, Stremmel W: Prevalence of serum antibodies to Helicobacter pylori and to CagA protein in liver transplant recipients. Am J Gastroenterol 1997; 92: 1492-1495.

Salmela K, Ahonen J, Kooststra G. Renal transplantation. In Atlas of clinical transplantation 1995, Harjula A, Höckerstedt K. edit. Recallmed Ltd, Jyväskylä, pp.68-79.

Salmela K, Kyllönen L. Renal transplantation in Helsinki: Influence on long-term survival of early posttransplant factors. In Clinical Transplants 1999, Terasaki, Cecka edit. UCLA Tissue typing laboratory, Los Angeles, pp. 173-179.

Salmela K, Höckerstedt K, Salminen U-S, Hämmäinen P. Elinsiirrot -käypää hoitoa jo 40 vuoden ajan. Duodecim 2004; 120: 67-76.

Salmela K, Kyllönen L, Eklund B, Isoniemi H, Holmberg C, Koskimies S, Höckerstedt K, Mäkisalo H, Leijala M, Ahonen J. Thirty years of renal transplantation in Helsinki. In Clinical Transplants 1994, Terasaki, Cecka edit, UCLA Tissue typing laboratory, Los Angeles, pp. 219-227.

Salonen T, Reina T, Oksa H, Sintonen H, Pasternack A. Cost analysis of renal replacement therapies in Finland. Am J Kidney Dis 2003; 42: 1228-1238.

Schaier M, Wendt C, Zeier M, Ritz E. Clostridium difficile diarrhoea in the immunosuppressed patient – update on prevention and management. 2004; 19: 2432-2436.

Scheff R, Zuckerman G, Harter H, Delmez J, Koehler R. Diverticular disease in patients with chronic renal failure due to polycystic kidney disease. Ann Int Med 1980; 92: 202-204.

Schwartz D, Wilcox C. Atypical cytomegalovirus inclusions in gastrointestinal biopsy specimens from patients with the acquired immunodeficiency syndrome. Human Pathol 1992; 23:1019-1026.

Shrestra B, Parton D, Gray A, Shepard D, Griffith D, Lord R, Salaman J, More R. Cytomegalovirus involving gastrointestinal tract in renal transplant recipients. Clin Transplant 1996; 10: 170-175.

Shroff R, Rees L. The post-transplant lymphoproliferative disorder- a literature review. Pediatr Nephrol 2004; 19: 369-377.

Sianesi M, Capocasale E, Ferreri G, Mazzoni M, Dalla Valle R, Busi N. The role of cholecystectomy in renal transplantation. Transplant Proc 2005; 37: 2129-2130.

Singer J, Gritsch H, Rosenthal J. The transplant operation and its surgical complications. In Handbook of kidney transplantation. Danovitch G. edit, Lippincott Williams & Wilkins 2005, Philadelphia, pp.193-211.

Sinha S, Jha R, Lahktakia S, Narayan G. Acute pancreatitis following kidney transplantation - role of viral infections. Clin Transplant 2003; 17: 32-36.

Sipponen P, Kosunen TU, Samloff IM, Heinonen OP, Siurala M. Rate of helicobacter pylori acquisition among Finnish adults. Scand J Gastroenterol 1996; 31: 229-232.

Slakey D, Johnson C, Cziperle D, Roza A, Wittmann D, Gray D, Roache J, Britton J, Morris P. Management of severe pancreatitis in renal transplant recipients. Ann Surg 1997; 29: 217-222.

Smith B, Stabile B. Emerging trends in peptic ulcer disease and damage control surgery in the *H. pylori* era. Am Surg 2005; 71: 797-801.

Stelzner M, Vlahakos D, Milford E, Tilney N. Colonic perforations after renal transplantation. J Am Coll Surg 1997; 184: 63-69.

Steger A, Timoney A, Griffen S, Salem R, Williams G. The influence of immunosuppression on peptic ulceration following renal transplantation and the role of endoscopy. Nephrol Dial Transplant 1990; 5: 289-292.

Talley N, Noak K. The worldwide prevalence of helicobacter pylori: Asymptomatic infection and clinical states associated with infection in adults. In Helicobacter Pylori Biology and clinical practice. Godwin, Worsley edit. Boza Rason CRC press Inc 1993, Florida, pp. 63-83.

Telkes P, Varga M, Sarvary E, Kovalszky I. Endoscopic diagnosis of cytomegalovirus infection of upper gastrointestinal tract in solid organ transplant recipients: Hungarian single-center experience. Clin Transplant 2004; 18: 580-584.

The T, van der Berg A, Harmsen M, van der Bij W, van Son W. The cytomegalovirus antigenemia assay; a plea for standardization. Scand J Infect Dis Suppl 1995; 99: 25-29.

The tricontinental mycophenolate mofetil renal transplantation study group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996; 7: 109-1037.

Toljamo K, Niemelä S, Karttunen T, Karttunen R, Karvonen A-L, Piiparinen H, Lehtola J. The role of Herpes simplex and Helicobacter pylori infection in the etiology of persistent or recurrent gastric erosions. Dig Dis Sci 2002; 47: 818-822.

Troppmann C, Paplois B, Chiou A, Benedetti E, Dunn D, Matas J, Najarian J, Gruessner R. Incidence, complications, treatment and outcome of ulcers of the upper gastrointestinal tract after renal transplantation during the cyclosporine era. J Am Coll Surg 1995; 180: 433-443.

Vincenti F, Jensik S, Filo R, Miller J, Pirch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: Evidence for improved allograft survival at five years. Transplantation 2002; 73:775-782.

Weil J, Langman MJS, Wainwright P. Lawson D, Rawlins M, Logan R, Brown T, Vessey M, Murphy M, Colin-Jones D. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut 2000; 46: 27-31.

Özgur O, Boyacioglu S, Özdogan M, Gur G, Telatar H, Haberal M. Helicobacter pylori infection in haemodialysis patients and renal transplant recipients. Nephrol Dial Transplant 1997; 12: 289-291.