ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2014 December 24; 4(4): 216-305

Published by Baishideng Publishing Group Inc

WJT World Journal of Transplantation

A peer-reviewed, online, open-access journal of transplantation

Editorial Board

2011-2015

The *World Journal of Transplantation* Editorial Board consists of 387 members, representing a team of worldwide experts in transplantation. They are from 43 countries, including Argentina (2), Australia (7), Austria (3), Belgium (4), Brazil (8), Bulgaria (1), Canada (15), China (32), Cuba (1), Czech Republic (1), Denmark (1), Finland (1), France (6), Georgia (1), Germany (14), Greece (6), Hungary (2), India (8), Iran (7), Israel (4), Italy (36), Japan (19), Jordan (1), Macedonia (1), Mexico (2), Morocco (1), Netherlands (5), Nigeria (1), Norway (1), Pakistan (1), Poland (2), Qatar (1), Saudi Arabia (4), Singapore (1), South Korea (17), Spain (9), Sweden (1), Switzerland (3), Thailand (2), Tunisia (1), Turkey (6), United Kingdom (17), and United States (131).

Poland

Piotr Czubkowski, *Warsaw*
Andrzej Zbigniew Rydzewski, *Warszawa*

Qatar

Moutaz Farouk Derbala, *Doha*

Saudi Arabia

Ali Al-Ahmari, *Riyadh*
Imran Khalid, *Jeddah*
Mohamed Mabed, *Jeddah*
Mohamed M Sayed-Ahmed, *Riyadh*

Singapore

Seng Hock Quak, *Singapore*

South Korea

Curie Ahn, *Seoul*
Jong Wook Chang, *Seoul*
Baik Hwan Cho, *Jeonju City*
Hyeon Joo Jeong, *Seoul*
Koo-Jeong Kang, *Daegu*
Chang Nyung Kim, *Yongin*
Gaab Soo Kim, *Seoul*
Kyung Mo Kim, *Seoul*
Yon Su Kim, *Seoul*
Jong Wook Lee, *Seoul*
Sang-Oh Lee, *Seoul*
Kyo-Cheol Mun, *Daegu*
Eun-Jee Oh, *Seoul*
Kwon Moo Park, *Daegu*
Chul Woo Yang, *Seoul*
Kun-Ho Yoon, *Seoul*
Seungkwon You, *Seoul*

Spain

Manuel Molina Arias, *Madrid*
Ruben Ciria, *Cordoba*
Luis Fontana, *Granada*
Maria Marco, *Barcelona*
Alberto Ortiz, *Madrid*
Julio Pascual, *Barcelona*
Carmen Peralta, *Barcelona*
Jose Antonio Pons, *Murcia*
Jesus Vaquero, *Madrid*

Sweden

Tobias Larsson, *Stockholm*

Switzerland

Andrea De Gottardi, *Berne*
Michela G Tempia-Caliera Schappi, *Geneva*
Christian Toso, *Geneva*

Thailand

Suradej Hongeng, *Bangkok*
Kittisupamongkol Weekitt, *Bangkok*

Tunisia

Kais Harzallah, *Tunis*

Turkey

Elvan Caglar Citak, *Mersin*
Emir Baki Denkbas, *Ankara*
İhsan Ergün, *Ankara*
Murat Kilic, *Izmir*
Oner Ozdemir, *Istanbul*
Baris D Yildiz, *Ankara*

United Kingdom

Jacob Attah Akoh, *Plymouth*
Atul Bagul, *Leicester*
Ricky Harminder Bhogal, *Birmingham*
Richard John Borrows, *Birmingham*
Eric Chemla, *London*
Sarah Anne Hosgood, *Leicester*
Stefan Georg Hűbscher, *Birmingham*
Alireza Hamidian Jahromi, *London*
Alan Jardine, *Glasgow*
Sanjeev Kanoria, *London*
Michel Modo, *London*
Paolo Muiesan, *Birmingham*
GH Neild, *London*
Magdi Shehata, *Leicester*
Afshin Tavakoli, *Manchester*
Alexander Woywodt, *Preston*
Qihe Xu, *London*

United States

Arshak R Alexanian, *Milwaukee*
Sharif Ali, *Detroit*
Jaime Aranda-Michel, *Jacksonville*
Robert Aris, *Chapel Hill*
Reto M Baertschiger, *Indianapolis*
David A Baran, *Newark*
Gerald Brandacher, *Baltimore*
Joseph F Buell, *New Orleans*
Herman S Cheung, *Coral Gables*
Gaetano Ciancio, *Miami*
Diane M Cibrik, *Ann Arbor*
Luca Cicalese, *Galveston*
Ari Cohen, *New Orleans*
David KC Cooper, *Pittsburgh*
Darshana Manji Dadhania, *New York*
Graciela De Boccardo, *New York*
Cataldo Doria, *Philadelphia*
Amrita Dosanjh, *San Diego*
Stavros G Drakos, *Salt Lake*
Sukru Emre, *New Haven*
Sherif S Farag, *Indianapolis*
Roberto J Firpi, *Gainesville*
Robert A Fisher, *Richmond*
Amy L Friedman, *Syracuse*
Tibor Fulop, *Jackson*
G Ian Gallicano, *Washington*
Wenda Gao, *Boston*
Roberto Gedaly, *Lexington*
W Scott Goebel, *Indianapolis*
Rujun Gong, *Providence*
Chad R Gordon, *Boston*
Angelika C Gruessner, *Tucson*
Gregg Allen Hadley, *Columbus*
Jeffrey B Halldorson, *Seattle*
Mehdi Hamadani, *Morgantown*
Karen Hardinger, *Kansas*
Imed Helal, *Aurora*
Allan Duane Hess, *Baltimore*
Ibtesam A Hilmi, *Pittsburgh*
Andres Jaramillo, *Itasca*
Randeep Kashyap, *Rochester*
Tatsuo Kawai, *Boston*
Ajai Khanna, *San Diego*
Dean Y Kim, *Detroit*
Katsuhiro Kita, *Galveston*
David J Kramer, *Jacksonville*
Jerzy W Kupiec-Weglinski, Los Angeles
Paul Y Kwo, *Indianapolis*
Victor E Laubach, *Charlottesville*
Techung Lee, *Buffalo*
Josh Levitsky, *Chicago*
Xian C Li, *Boston*
Suthat Liangpunsakul, *Indianapolis*
Seah H Lim, *Amarillo*
Ching-Shwun Lin, *San Francisco*
Julie Lin, *Boston*
Delong Liu, *Westchester*
Andrew Leon Lobashevsky, *Indianapolis*
Paul Allen Lucas, *Valhalla*
Xunrong Luo, *Chicago*
Didier A Mandelbrot, *Boston*
Martin J Mangino, *Richmond*
Richard S Mangus, *Indianapolis*
Ignazio R Marino, *Philadelphia*
Paulo Ney Aguiar Martins, *Boston*
Andrew Scott Mathis, *Long Branch*
James Michael Millis, *Chicago*
Tamir Miloh, *Phoenix*
Ayse Leyla Mindikoglu, *Baltimore*
Amr El-Husseini Mohamed, *Lexington*
Sandeep Mukherjee, *Omaha*
Yoko Mullen, *Duarte*
Raghavan Murugan, *Pittsburgh*
Tibor Nadasdy, *Columbus*
Atsunori Nakao, *Pittsburgh*
Singh Neeraj, *Columbus*
Justin H Nguyen, *Jackosnville*
Volker Nickeleit, *Chapel Hill*
Christopher Niyibizi, *Hershey*
Macaulay Onuigbo, *Eau Claire*
Jorge Alberto Ortiz, *Philadelphia*
Antonello Pileggi, *Miami*
Raymond M Planinsic, *Pittsburgh*
Qi Qian, *Rochester*
Rajalingam Raja, *Los Angeles*
Michael A Ramsay, *Dallas*
Raymund Rabe Razonable, *Rochester*
Mohammed S Razzaque, *Boston*
Pavan Reddy, *Ann Arbor*
Camillo Ricordi, *Miami*
Horacio L Rilo, *Tucson*
David Alan Rizzieri, *Durham*
Simon C Robson, *Boston*
Alvaro Rojas-Pena, *Ann Arbor*
Kenneth Rolston, *Houston*

WJT

World Journal of Transplantation

Contents

Quarterly Volume 4 Number 4 December 24, 2014

AIM AND SCOPE

World Journal of Transplantation (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJT covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation, and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, and xenotransplantation. The current columns of *WJT* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography.

AIM AND SCOPE

World Journal of Transplantation is now indexed in PubMed Central, PubMed, Digital Object Identifier.

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Quarterly

EDITOR-IN-CHIEF
Maurizio Salvadori, MD, Professor, Renal Unit, Careggi University Hospital, Viale Pieraccini 18, Florence 50139, Italy

EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Transplantation
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
December 24, 2014

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3230/g_info_20100722180909.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.216

World J Transplant 2014 December 24; 4(4): 216-221
ISSN 2220-3230 (online)

TOPIC HIGHLIGHT

Maurizio Salvadori, Professor, *Series Editor*

Pancreas transplantation in type Ⅱ diabetes mellitus

Phillip Weems, Matthew Cooper

Phillip Weems, Matthew Cooper, MedStar Georgetown Transplant Institute, Washington, DC 20007, United States
Author contributions: Weems P drafted the manuscript; Cooper M contributed with final review and editing as well as submission for peer review.
Correspondence to: Phillip Weems, MD, MedStar Georgetown Transplant Institute, 3800 Reservoir Road, NW 2 Main, Washington, DC 20007,
United States. weems.s.phillip@gunet.georgetown.edu
Telephone: +1-202-4440032 Fax: +1-202-4440899
Received: April 12, 2014 Revised: June 4, 2014
Accepted: July 15, 2014
Published online: December 24, 2014

Abstract

Although the diagnosis of type 2 diabetes mellitus was once considered a contraindication to simultaneous pancreas-kidney transplantation, a growing body of evidence has revealed that similar graft and patient survival can be achieved when compared to type 1 diabetes mellitus recipients. A cautious strategy regarding candidate selection may limit appropriate candidates from additional benefits in terms of quality of life and potential amelioration of secondary side effects of the disease process. Although our current understanding of the disease has changed, uniform listing characteristics to better define and study this population have limited available data and must be established.

Key words: Pancreas transplantation; Type 2 diabetes mellitus; Simultaneous pancreas-kidney transplantation

Core tip: Comparable outcomes have been achieved in simultaneous-pancreas kidney transplant among both type 1 diabetes mellitus and type 2 diabetes mellitus (DM2) recipients. Our current understanding of the pathogenesis of DM2 is in evolution and denial of simultaneous pancreas-kidney transplantation to appropriately screened DM2 recipients may limit access to a potential life-saving measure with beneficial quality of life improvements. Cautious utilization of DM2 listing criteria should be employed among all pancreas transplant centers in order to ensure optimum patient and graft survivals are achieved.

Weems P, Cooper M. Pancreas transplantation in type II diabetes mellitus. *World J Transplant* 2014; 4(4): 216-221 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/i4/216.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.216

INTRODUCTION

In October 1920, Dr. Frederick Banting approached Professor John Macleod with an idea that would result in one of the most significant discoveries of twentieth century medicine. Dr. Banting correctly theorized the presence of an "antidiabetic secretion" isolated from a surgically ligated pancreas. His proposed method for isolation and extraction was reluctantly rewarded with skepticism, an inadequate work space, ten canines to form an animal model, and the assistance of a young medical student, Charles Best. Banting and Best named the initial product of their extraction technique "isletin" and would use this substance to prove the endocrine function of the pancreas. Their impressive results were furthered with the addition of a talented biochemist, Bertram Collip, who was tasked with the purification of the insulin extract for testing in human subjects. In January 1922, a 14-year-old diabetic boy, Leonard Thompson, was chosen to be the first human to receive the team's purified insulin[1]. This landmark experiment led to the reversal of the young man's near-death condition and the effort was quickly expanded to other volunteer test subjects with equally positive results. The brilliant results of this team were rewarded with the Nobel Prize in Physiology and

Medicine in 1923[2].

The end of the twentieth century was greeted with the emergence of a new worldwide pandemic. It has been estimated that more than 340 million people are afflicted with diabetes worldwide, with 90% of cases manifesting as type 2 diabetes mellitus (DM2)[3,4]. In the United States alone, diabetes mellitus is the leading cause of end-stage renal disease (ESRD), accounting for 48215 new cases (44%) of renal failure in 2006; an incidence increasing at twice the rate of all other causes of ESRD[5]. The current United States renal transplant waiting list is compromised of > 40% of patients suffering from ESRD complications secondary to diabetes mellitus (DM).

With the discovery of insulin, diabetes was transformed from a rapidly fatal disease to a chronic condition with the emergence of noteworthy secondary conditions related to the primary disease process. Diabetes has been shown to vastly increase the risk of heart disease and stroke and is among the leading causes of chronic renal disease[6]. Diabetic retinopathy, a result of long-term accumulated damage to the small blood vessels of the retina, has been estimated to contribute to one percent of cases of blindness worldwide[7]. Diabetic neuropathy increases the risk of foot ulceration and, when found in conjunction with peripheral vascular disease, may lead to infectious limb complications and accelerated limb loss[6]. Since its proposal in the mid-twentieth century, the goals of pancreas transplantation have remained universal: to establish insulin independence and prevent/ameliorate the damaging secondary complications of the disease process.

PHENOTYPICAL ANALYSIS AND GENETICS OF DIABETES MELLITUS

Diabetes mellitus as a global disorder is characterized by hyperglycemia resulting from either an inadequate production or a decreased sensitivity to circulating insulin. Clinically, diabetes is broadly categorized as either type 1 (DM1) or DM2, depending on the genetic preponderance, age of onset, body habitus, inciting origin, and associated symptoms[8]. Traditionally, the DM2 phenotype is that of an older age and a larger body habitus with a lack of underlying autoimmunity prior to disease onset. In contrast, DM1 patients tend to present with an abrupt onset at an early age, possess a lean body habitus, and require immediate insulin therapy to reverse the consequences of the disease (Table 1).

As our knowledge regarding the pathophysiology of diabetes has further expanded, the distinction between these two seemingly separate disease processes has become decidedly less clear. The accelerator hypothesis of DM proposes a unique pathogenetic origin whereby excess body mass contributes to hyperglycemia resulting in increased insulin production to meet physiologic demands, the acceleration of β-cell apoptosis, and the induction of β-cell "immunogens" in a subset genetically predisposed to islet autoimmunity[9]. The accelerator hypothesis proposes an overlay rather than an overlap exists between the clinical manifestations of diabetes types with excess body mass central to the rising incidence of the disease worldwide[10].

Although the exact etiology of DM2 remains elusive, a series of common genetic variants, most of which (CDKAL1, CDKN2A, CDKN2, MTNR1B, TCF7L2, KCNJ11B) are associated with either reduced islet cell mass or reduced β-cell function, have been identified[11,12]. Recent studies have shown a similar frequency of DM2 risk genotypes for the transcription factor TCF7L2 in latent autoimmune (DM1) diabetic adults when compared to DM2[12]. The genomic identity of a similar pathologic predisposition further suggests that DM1 and DM2 are representative of the same disorder of insulin resistance, set against different phenotypic backgrounds.

EFFICACY OF PANCREAS TRANSPLANTATION IN DM2

Since the first reported successful pancreas transplant in 1966[13], more than 35000 pancreas transplantations have been reported to the International Pancreas Transplant Registry (IPTR). Of those, more than 24000 were reported from United States centers[14]. Traditionally, pancreas transplantation has been reserved for medically and surgically suitable candidates with DM1 suffering with ESRD (simultaneous kidney and pancreas, SPK), DM1 patients that have previously received a functioning renal graft (pancreas after kidney transplantation, PAK), or patients with brittle diabetes and hypoglycemic unawareness (pancreas transplant alone, PTA).

Although the diagnosis of DM2 was once considered a contraindication to pancreas transplantation, a growing body of evidence has revealed that favorable results can be achieved in selected candidates. Reluctance among some physician groups has favored denial to DM2 candidates secondary to a poorly understood mechanism by which transplanted pancreata may overcome the underlying pathophysiology of insulin resistance. In addition, elevated cardiovascular risks, an enlarged body habitus, an associated older age, and advanced secondary diabetic complications have been suggested as listing deterrents. This cautious judiciary strategy may account for the limited number of DM2 pancreas transplant recipients and small yet encouraging results reported for SPK transplants in DM2[15].

Light has reported a large retrospective series of SPK recipients with 20-year follow-up stratified according to detectable (> 0.8 ng/mL) *vs* undetectable (< 0.8 ng/mL) C-peptide values[16]. The patients with detectable C-peptide values were found to be older in age at the time of clinical diagnosis [24.2 years *vs* 15.4 years ($P < 0001$)], age of transplant [42.8 years *vs* 38.5 years ($P < 0001$)], and had a shorter duration of insulin dependence [19.1 years *vs* 23.1 years ($P < 0.012$)]. Study findings revealed increased graft survival with similar rates of glycemic control in detectable C-peptide patients when compared to non-detectable patients ($P = 0.064$). This finding was contrasted by increased

Table 1 Epidemiologic features differentiating type 1 from type 2 diabetes mellitus

Characteristic	Type 1 DM	Type 2 DM
Age (yr, at diagnosis)	< 25	> 25
Onset	Abrupt	Gradual
Body Habitus	Lean (weight < 105% of IBW)	Overweight/Obese (weight > 115% of IBW)
HLA-association	Yes	No
C-peptide	Undetectable	Detectable
Ketoacidosis	Yes	No
Immediate need for insulin	Yes	No

DM: Diabetes mellitus; IBW: Ideal body weight; HLA: Human leukocyte antigen.

patient survival discovered in the non-detectable C-peptide group ($P = 0.019$), hypothesized secondary to a younger age and fewer long-term secondary side effects associated within the undetectable C-peptide group. Light's findings caution the use of C-peptide to determine candidacy for pancreas transplantation and adds further controversy to the observed clinical overlap of the two disease phenotypes. In fact, of the study population, 17% of patients who were considered to have DM1 based upon standard clinical criteria (Table 1) were found to have elevated c-peptide values (≥ 0.8 ng/mL) while nearly 40% of patients considered having DM2 (where c-peptide should have been positive) had undetectable values[16].

Margreiter *et al*[17] conducted a single-center retrospective review analyzing twenty-one DM2 SPK recipients with comparisons to historical DM1 SPK and DM2 kidney transplant alone (KTA) controls. Actuarial pancreas graft survival for SPK recipients at 1- and 5-years post-transplant were calculated to be 92.6% and 80.7% respectively for the DM1 SPK group *vs* 81% and 75.9% respectively for the DM2 SPK group ($P = 0.19$). Kidney allograft survival at 5 years post-transplant was found to be 83.6% for DM1 SPK recipients, 80.4% for DM2 SPK recipients, and 52.7% for DM2 KTA recipients ($P < 0.001$). A multivariate analysis adjusting for potential confounders (donor/recipient age, presence of diabetic secondary complications, body mass index (BMI), wait list time, cold ischemic time, delayed graft function, and coronary risk factors) revealed no findings of statistical significance[17].

Several noteworthy registry-based studies have been conducted in order to further analyze clinical outcomes of SPK recipients among DM2 recipients. Sampaio *et al*[18] utilized the United Network for Organ Sharing (UNOS) database to compare outcomes of SPK transplants based upon recipient diabetes type. Of the 6756 SPK recipients transplanted between 2000 and 2007, 586 (8.6%) were reported as having type 2 diabetes. Rates of delayed graft function (11.7% *vs* 7.8%, $P < 0.001$) and kidney primary non-function (0.47% *vs* 1.03%, $P < 0.03$) were significantly more frequent in DM2 patients. Pancreas transplant complications were similar between groups and not statistically significant. Initial findings revealed inferior five-year overall and death-censored kidney graft survival in type 2 diabetics. However, after adjustment for recipient (age, race, body weight, dialysis time, and cardiovascular comorbidities), donor, and transplant immune characteristics, DM2 was not associated with increased risk of death or kidney or pancreas allograft failure when compared to DM1.

Wiseman utilized Scientific Registry of Transplant Recipients (SRTR) data to conduct a review of DM2 pancreas transplant recipients while utilizing a historical control population of selected DM2 transplant recipients (18-59 years of age, BMI from 18-30 kg/m^2) having received either a live donor kidney alone (LDKA) *vs* deceased donor kidney alone (DDKA)[19]. On adjusted analysis, patient and kidney graft survival rates were superior for LDKA *vs* SPK and DDKA. After 1-year post-transplant, patient and graft survival began to favor SPK when compared to DDKA (82.0% *vs* 75.5%; $P = 0.04$); a finding on multivariable analysis related to younger recipient and donor ages within this cohort. Surprisingly, 40% (269 out of 424 patients) of the SPK cohort were aged 50-59 years of age, and a significant percentage of these were older than age 55 years. Unadjusted pancreas allograft survival rates were 83.7% and 71% at 1- and 5-years, respectively, whereas death-censored pancreas graft survival rates were 87.7% at 1-year and 83.6% at 5-years[20]. These numbers are markedly similar to reported pancreas allograft survival rates within DM1 recipients and further reiterate the premise that excellent outcomes of SPK transplantation can be achieved regardless of recipient diabetes type.

CURRENT CONTROVERSIES IN PANCREAS TRANSPLANTATION AMONG TYPE 2 DIABETICS

In a review of > 35000 pancreas transplants reported to the International Pancreas Transplant Registry (IPTR), Gruessner *et al*[14] revealed an upward trend in the rate of pancreas transplantation performed upon DM2 candidates. Since 1994, diabetic type has been consistently reported within the registry with an overall rate of DM2 recipients increasing from 2% in 1995 to 7% in 2010 ($P < 0.0001$)[14]. Despite this upward trend, the rate of DM2 may in fact be lower (or higher) secondary to the absence of a unified and defined criteria by which transplant centers select DM2 candidates.

Although many defined criteria (age at diagnosis, BMI, family history, HLA association, detectable C-peptide) have been proposed to differentiate DM1 from DM2, no reliable and objective test(s) exist. In fact, as noted prior, several patients are found to categorically overlap. Fasting or stimulated C-peptide levels have long been used as a primary differentiating criterion to define DM1 *vs* DM2 transplant candidates[20-22]. As C-peptide is primarily metabolized in the kidney, levels in patients with ESRD can be disproportionately high and not representative of

Table 2 Proposed simultaneous pancreas-kidney type 2 diabetic selection criteria

Age < 55 yr
BMI < 30 kg/m^2
Insulin dependence
Total insulin requirements < 1 U/kg of IBW/d
Presence of renal failure (dialysis dependent or pre-dialysis advanced diabetic nephropathy with GFR ⩽ 20 mL/min per 1.73 m^2
Fasting c-peptide < 10 ng/mL
Low cardiac and vascular disease risk
History of medical and dietary compliance

IBW: Ideal body weight; GFR: Glomerular filtration rate.

the actual functioning β-cell mass. Wang *et al*[22] furthered this controversy by demonstrating that C-peptide levels, using ultrasensitive methods, may be detected in 10% of DM1 patients up to 30-years after disease onset. In addition, Singh confirmed that pre-transplant C-peptide levels had no influence on death-censored SPK survival rates for up to 3-years post-transplant. In this study, the selection criteria utilized to define their DM2 group included minimum insulin requirements of more than 5-years duration with daily requirements less than 1 U/kg per day, C-peptide levels ⩾ 1.8 ng/mL, BMI ⩽ 32 kg/m^2, and absence of advanced cardiovascular disease[23].

In order to properly evaluate and define selected DM2 candidates for SPK transplantation, universal listing criteria should be adopted. The definition of DM2 has been left to the discretion of the individual reporting centers and often does not account for variations in diabetes phenotype. Until recently, neither the UNOS database nor the SRTR required data regarding patient medication use, C-peptide values, or any other feature which may further confirm categorization of diabetes type. Others have proposed listing criteria to define the DM2 SPK populations. These have often been selected according to younger age, a relatively lean body habitus, and a limited advanced diabetic cardiovascular disease[16,23]. We propose the adoption of a defined list of selection criteria to better define potential DM2 recipients that may benefit from SPK transplantation and allow for closer population-based longitudinal studies (Table 2).

Contemporary management of DM2 patients has been profoundly influenced by the results of the United Kingdom Prospective Diabetes Study (UKPDS)[24-27]. The authors demonstrated a continuous relationship between euglycemia and microvascular complications, with a 35% reduction in risk for each 1% decrement in HbA1c. In most patients with DM2, a multimodal management scheme is employed to address the issue of euglycemia as well the long-term secondary influences on the disease. Central to this approach are dietary and lifestyle modifications, management of dyslipidemia and hypertension, and pharmacologic therapy with a goal of improved glycemic control.

Current available pharmacologic treatments are vast and include medications in the following drug classes: biguanides, sulfonylureas, meglitinide derivates, alpha-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, dipeptidy-l peptidase Ⅳ (DPP-4), selective sodium-glucose transporter-2 (SGLT-2) inhibitors, amylinomimetics, and insulin. With demonstrated treatment failure from any of the aforementioned combination of medical and/or lifestyle modifications, pancreas transplantation may provide the positive effects of normoglycemia in insulin requiring DM2 patients with end-stage renal disease.

In DM2 patients, peripheral insulin resistance, which is associated with relative insulin deficiency and insulin secretory defects, plays a central role[19]. It was once hypothesized that β-cells within the transplant would be subjected to overstimulation leading to "islet exhaustion" in a damaging cascade resulting in allograft failure. This has been disproved in a large, often cited longitudinal case series by Chakkera *et al*[21] and Light *et al*[28,29]. In fact, insulin secretion and sensitivity have been shown to improve long term after SPK in DM2 recipients[30].

Although a greater survival advantage at 5 years post-transplant has been reported for LDKA *vs* both SPK and DDKA in DM2 recipients[19], the quality of life benefits of euglycemia or the possible effects that euglycemia might have on the secondary complications of DM cannot be underestimated[31-33]. These added benefits have been shown to result in improved mental and physical health, disease perception, mobility, vitality, and patient satisfaction[31,32]. Whether the euglycemic effects of the added pancreas ultimately may lead to a survival advantage when compared to LDKA cannot be ruled out, as large retrospective analyses of DM1 SPK recipients have shown the added benefits of the additional pancreas over a kidney transplant alone become more evident over time[34,35].

Importantly, however, expansion of this transplantable cohort may decrease the number of donor pancreata available, further affecting a larger pool of DM1 SPK, PAK, and PTA recipients; a population whose survival benefits have been better defined[19,36]. In addition, the current UNOS algorithm awards priority to SPK recipients over all other forms of DDKA transplants within a given region. Coupled with judicious donor selection criteria at most centers and a relatively short simultaneous kidney-pancreas compared to deceased donor kidney waitlist, listing selected DM2 candidates for SPK may improve an individual's chance to obtain a quality organ transplant with less waiting time. In order to address this potential, UNOS policy has employed a 6-mo review process with proposed reduction in BMI eligibility criteria 2 kg/m^2 if more than 10% of the SPK waiting less is composed with DM2 candidates[19]. Cautious utilization of DM2 listing criteria should be employed among all pancreas transplant centers in order to ensure optimum patient and graft survivals are achieved. As the long-term outcomes of pancreas transplantation in DM2 candidates is not entirely known, SPK transplantation in this cohort should be limited to specialized and well experienced transplant centers to ensure the possibility of continued positive outcomes.

REFERENCES

1 **Banting FG**, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. 1922. *CMAJ* 1991; **145**: 1281-1286 [PMID: 1933711]

2 The Discovery of Insulin. Nobelprize.org. Nobel Media AB 2013, Web. 4 Mar 2014. Available from:URL: http://www.nobelprize.org/educational/medicine/insulin/discovery-insulin.html

3 **Danaei G**, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *Lancet* 2011; **378**: 31-40 [PMID: 21705069 DOI: 10.1016/S0140-6736(11)60679-X]

4 Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization, 1999 (WHO/NCD/NCS/99.2)

5 **Burrows NR**, Li Y, Geiss LS. Incidence of treatment for end-stage renal disease among individuals with diabetes in the U.S. continues to decline. *Diabetes Care* 2010; **33**: 73-77 [PMID: 20040673 DOI: 10.2337/dc09-0343]

6 **Morrish NJ**, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001; **44** Suppl 2: S14-S21 [PMID: 11587045 DOI: 10.1007/PL00002934]

7 Global data on visual impairments 2010. Geneva: World Health Organization, 2012

8 **Sener A**, Cooper M, Bartlett ST. Is there a role for pancreas transplantation in type 2 diabetes mellitus? *Transplantation* 2010; **90**: 121-123 [PMID: 20562677 DOI: 10.1097/TP.0b013e3181e5b7e6]

9 **Fourlanos S**, Harrison LC, Colman PG. The accelerator hypothesis and increasing incidence of type 1 diabetes. *Curr Opin Endocrinol Diabetes Obes* 2008; **15**: 321-325 [PMID: 18594271 DOI: 10.1097/MED.0b013e3283073a5a]

10 **Wilkin TJ**. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia* 2001; **44**: 914-922 [PMID: 11508279 DOI: 10.1007/s001250100548]

11 **Scalea JR**, Cooper M. Surgical strategies for type II diabetes. *Transplant Rev* (Orlando) 2012; **26**: 177-182 [PMID: 22115951 DOI: 10.1016/j.trre.2011.07.002]

12 **McCarthy MI**. Genomics, type 2 diabetes, and obesity. *N Engl J Med* 2010; **363**: 2339-2350 [PMID: 21142536 DOI: 10.1056/NEJMra0906948]

13 **Kelly WD**, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery* 1967; **61**: 827-837 [PMID: 5338113]

14 **Gruessner AC**. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 2011; **8**: 6-16 [PMID: 21720668 DOI: 10.1900/RDS.2011.8.6]

15 **Orlando G**, Stratta RJ, Light J. Pancreas transplantation for type 2 diabetes mellitus. *Curr Opin Organ Transplant* 2011; **16**: 110-115 [PMID: 21150617 DOI: 10.1097/MOT.0b013e3283424d1f]

16 **Light J**, Tucker M. Simultaneous pancreas kidney transplants in diabetic patients with end-stage renal disease: the 20-yr experience. *Clin Transplant* 2013; **27**: E256-E263 [PMID: 23480129]

17 **Margreiter C**, Resch T, Oberhuber R, Aigner F, Maier H, Sucher R, Schneeberger S, Ulmer H, Bösmüller C, Margreiter R, Pratschke J, Öllinger R. Combined pancreas-kidney transplantation for patients with end-stage nephropathy caused by type-2 diabetes mellitus. *Transplantation* 2013; **95**: 1030-1036 [PMID: 23407544 DOI: 10.1097/TP.0b013e3182861945]

18 **Sampaio MS**, Kuo HT, Bunnapradist S. Outcomes of simultaneous pancreas-kidney transplantation in type 2 diabetic recipients. *Clin J Am Soc Nephrol* 2011; **6**: 1198-1206 [PMID: 21441123 DOI: 10.2215/CJN.06860810]

19 **Wiseman AC**, Gralla J. Simultaneous pancreas kidney transplant versus other kidney transplant options in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2012; **7**: 656-664 [PMID: 22344508 DOI: 10.2215/CJN.08310811]

20 **Esmatjes E**, Fernández C, Rueda S, Nicolau J, Chiganer G, Ricart MJ, Junca E, Fernández-Cruz L. The utility of the C-peptide in the phenotyping of patients candidates for pancreas transplantation. *Clin Transplant* 2007; **21**: 358-362 [PMID: 17488385 DOI: 10.1111/j.1399-0012.2007.00649.x]

21 **Chakkera HA**, Bodner JK, Heilman RL, Mulligan DC, Moss AA, Mekeel KL, Mazur MJ, Hamawi K, Ray RM, Beck GL, Reddy KS. Outcomes after simultaneous pancreas and kidney transplantation and the discriminative ability of the C-peptide measurement pretransplant among type 1 and type 2 diabetes mellitus. *Transplant Proc* 2010; **42**: 2650-2652 [PMID: 20832562 DOI: 10.1016/j.transproceed.2010.04.065]

22 **Wang L**, Lovejoy NF, Faustman DL. Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. *Diabetes Care* 2012; **35**: 465-470 [PMID: 22355018 DOI: 10.2337/dc11-1236]

23 **Singh RP**, Rogers J, Farney AC, Hartmann EL, Reeves-Daniel A, Doares W, Ashcraft E, Adams PL, Stratta RJ. Do pretransplant C-peptide levels influence outcomes in simultaneous kidney-pancreas transplantation? *Transplant Proc* 2008; **40**: 510-512 [PMID: 18374116 DOI: 10.1016/j.transproceed.2008.01.048]

24 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 837-853 [PMID: 9742976 DOI: 10.1016/S0140-6736(98)07019-6]

25 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 854-865 [PMID: 9742977 DOI: 10.1016/S0140-6736(98)07037-80]

26 **United Kingdom Prospective Diabetes Study (UKPDS)**. 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 1995; **310**: 83-88 [PMID: 7833731 DOI: 10.1136/bmj.310.6972.83]

27 **Turner RC**, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; **281**: 2005-2012 [PMID: 10359389 DOI: 10.1001/jama.281.21.2005]

28 **Light JA**, Sasaki TM, Currier CB, Barhyte DY. Successful long-term kidney-pancreas transplants regardless of C-peptide status or race. *Transplantation* 2001; **71**: 152-154 [PMID: 11211183]

29 **Light JA**, Barhyte DY. Simultaneous pancreas-kidney transplants in type I and type II diabetic patients with end-stage renal disease: similar 10-year outcomes. *Transplant Proc* 2005; **37**: 1283-1284 [PMID: 15848696 DOI: 10.1016/j.transproced.2004.12.215]

30 **Pox C**, Ritzel R, Büsing M, Meier JJ, Klempnauer J, Schmiegel W, Nauck MA. Combined pancreas and kidney transplantation in a lean type 2 diabetic patient. Effects on insulin secretion and sensitivity. *Exp Clin Endocrinol Diabetes* 2002; **110**: 420-424 [PMID: 12518254 DOI: 10.1055/s-2002-36429]

31 **Smith GC**, Trauer T, Kerr PG, Chadban SJ. Prospective quality-of-life monitoring of simultaneous pancreas and kidney transplant recipients using the 36-item short form health survey. *Am J Kidney Dis* 2010; **55**: 698-707 [PMID: 20176426 DOI: 10.1053/j.ajkd.2009.12.025]

32 **Isla Pera P**, Moncho Vasallo J, Torras Rabasa A, Oppenheimer Salinas F, Fernández Cruz Pérez L, Ricart Brulles MJ. Quality of life in simultaneous pancreas-kidney transplant recipients. *Clin Transplant* 2009; **23**: 600-605 [PMID: 19674015 DOI: 10.1111/j.1399-0012.2009.01054.x]
33 **Gremizzi C**, Vergani A, Paloschi V, Secchi A. Impact of pancreas transplantation on type 1 diabetes-related complications. *Curr Opin Organ Transplant* 2010; **15**: 119-123 [PMID: 20010104 DOI: 10.1097/MOT.0b013e32833552bc]
34 **Morath C**, Zeier M, Döhler B, Schmidt J, Nawroth PP, Opelz G. Metabolic control improves long-term renal allograft and patient survival in type 1 diabetes. *J Am Soc Nephrol* 2008; **19**: 1557-1563 [PMID: 18495965 DOI: 10.1681/ASN.2007070804]
35 **Morath C**, Zeier M, Döhler B, Schmidt J, Nawroth PP, Schwenger V, Opelz G. Transplantation of the type 1 diabetic patient: the long-term benefit of a functioning pancreas allograft. *Clin J Am Soc Nephrol* 2010; **5**: 549-552 [PMID: 20093348 DOI: 10.2215/CJN.03720609]
36 **Sollinger HW**, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg* 2009; **250**: 618-630 [PMID: 19730242 DOI: 10.1097/SLA.0b013e3181b76d2b]

P- Reviewer: Fourtounas C, Fujino Y, Sakata N **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.222

World J Transplant 2014 December 24; 4(4): 222-228
ISSN 2220-3230 (online)

TOPIC HIGHLIGHT

Maurizio Salvadori, Professor, *Series Editor*

Challenges in pediatric renal transplantation

Licia Peruzzi, Alessandro Amore, Rosanna Coppo

Licia Peruzzi, Alessandro Amore, Rosanna Coppo, University-Hospital Health Agency Città della Salute e della Scienza di Torino, Nephrology, Dialysis and Transplantation Unit, Regina Margherita University Children's Hospital, 10126 Turin, Italy
Author contributions: Peruzzi L, Amore A and Coppo R equally reviewed the references, discussed the topic and wrote the paper.
Correspondence to: Licia Peruzzi, MD, PhD, University-Hospital Health Agency Città della Salute e della Scienza di Torino, Nephrology, Dialysis and Transplantation Unit, Regina Margherita University Children's Hospital, Piazza Polonia 94, 10126 Turin, Italy. licia.peruzzi@unito.it
Telephone: +39-1-13131761 Fax: +39-1-16635543
Received: September 4, 2014 Revised: November 20, 2014
Accepted: December 3, 2014
Published online: December 24, 2014

Abstract

Transplantation in children is the best option to treat renal failure. Over the last 25 years the improvements in therapy have dramatically reduced the risk of early acute rejection and graft loss, however the long term results in terms of graft survival and morbidity still require search for new immunosuppressive regimens. Tolerance of the graft and minimization of side effects are the challenges for improving the outcome of children with a grafted kidney. Notwithstanding the difficulties in settling in children large multicenter trials to derive statistically useful data, many important contributions in the last years brought important modifications in the immunosuppressive therapy, including minimization protocols of steroids and calcineurin inhibitors and new induction drugs. New methods for diagnosis of anti HLA antibodies and some new protocols to improve both chance and outcome of transplantation in immunized subjects represent area of ongoing research of extreme interest for children.

Key words: Kidney transplantation; Children; Immunosuppressive therapy; Acute humoral rejection; Desensitization

Core tip: Several novelties in the immunosuppressive treatment regimens in kidney transplantation in children are becoming available, with the aim of reducing the long terms side effects, particularly growth retardation, infections and malignancies, as well as improving the long term survival of the graft through a better treatment of chronic rejection. Moreover new induction drugs and specific protocols addressed to sensitized subjects may widen the possibility to receive a graft even for highly immunized children. These innovative aspects of therapy in kidney transplantation in children are reviewed.

Peruzzi L, Amore A, Coppo R. Challenges in pediatric renal transplantation. *World J Transplant* 2014; 4(4): 222-228 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/i4/222.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.222

INTRODUCTION

In children and adolescents affected by chronic renal failure the treatment of choice is kidney transplant. Transplantation indeed, is advocated even before dialysis as the best option to treat the metabolic, psychological and familiar derangement induced by renal failure.

Over the last 25 years remarkable improvements have been reached not only in terms of graft and patient survival[1,2] but also for comorbidities and full rehabilitation[3]. However the optimal immunosuppressive and supportive treatments assuring long term and high quality survival have not been standardized yet.

The immunosuppressive regimens adopted in the last 25 years have dramatically reduced the risk of acute rejection and graft loss within the first months after transplant but concerning the long term results the rate of graft loss is still high, particularly in patients receiving a transplant as small children and facing adolescence with an aged graft. They are bearing the cumulative risks of prolonged therapies,

malignancies, infections and cardio vascular diseases. Cardiovascular risk is one of the most important aspects clarified in recent years as conditioning patient survival and requiring a proactive and systemic preventive approach since the early phases of renal failure[4].

While primary non function and delayed graft function reduction have allowed progressive improvements of short term allograft survival, data on the long run are still not fully satisfactory. Optimal management of chronic allograft nephropathy remains one of the critical challenges to improve long-term kidney transplant outcomes in children. Both immunologic and non immunologic factors are involved in the pathogenesis of chronic allograft nephropathy, often in a subclinical way, and great efforts are frequently required for prompt diagnosis and appropriate treatment. The search for non invasive markers of immunological damage has not produced so far predictive and satisfactory tools to avoid the graft biopsy and protocol biopsies often are advocated also in children for better follow up[2].

The utopistic search for an ideal immunosuppressive regimen able to allow tolerance of the graft and the minimization of the side effects due to over-or under-immunosuppression in children match with the difficulties in settling multicenter trials with sufficiently large number of enrolled patients to derive statistically useful data.

However, several pivotal studies have consistently improved the perspective outcome of children with a grafted kidney, assessing new challenging frontiers in this delicate area.

STEROID MINIMIZATION, EARLY INTERRUPTION AND AVOIDANCE IN PAEDIATRIC KIDNEY TRANSPLANTATION

For more than 40 years steroid therapy has been a cornerstone of immunosuppressive therapy in renal transplantation. Despite their effectiveness, steroids are associated with severe well known side effects including glucose intolerance, diabetes, hypertension, hyperlipidemia, cataract formation, osteoporosis, fractures, mood and cosmetic changes. In children, steroid therapy has the additional very important drawback of marked growth retardation. Because of these side effects, many efforts have been made on trying to withdraw, minimize or avoid steroid therapy in paediatric renal transplantation.

The early attempts of steroid withdrawal after kidney transplantation in children were performed in the late eighties (1987-1990). However the high rate of acute rejections observed suggested the need of steroids for maintenance therapy in paediatric patients.

The introduction of new powerful immunosuppressive agents and new effective induction therapy led to the development in the last years of new trials aimed at steroid early withdrawal or avoidance in children.

One of the first report was the randomized controlled trial (RCT) from Benfield *et al*[5], who used anti CD25 monoclonal Ab (basiliximab), sirolimus, calcineurin inhibitors (CNIs) and steroids for 6 mo. Before randomization a renal biopsy was performed in each case. Fifty nine of the 132 enrolled children were randomized to maintain 0.15 mg/kg per day of prednisone while the remaining 73 children to steroid withdrawal. There was a trend ($P < 0.06$) of increased frequency of acute rejection in the steroid-free group, and moreover, after three years follow-up, frequency of graft loss or death in the steroid-free group became statistically significant ($P < 0.002$). The study started in 2001 but was discontinued in 2004 because of an unanticipated high risk of post-transplant lymphoproliferative disorders (PTLD). In the steroid-free group, 106/107 children treated for > 6 mo had at least one adverse event during the first 6 mo and most worrying, 10 children developed PTLD. From this study it was concluded that in children it is possible to withdraw or avoid steroids if other immunosuppressive agents are given in large doses; however high immunosuppression carries an increased risk of PTLD, which was considered unacceptable.

More satisfying data came from the TWIST RCT led by Grenda *et al*[6] in Europe aimed at investigating the effect of steroid withdrawal on children's growth. All 220 children were treated with daclizumab 1 mg/kg at transplantation and at day 14, tacrolimus (TAC) 0.3 mg/kg per day (target through levels 10-20 ng/mL on days 0-21; 5-15 ng/mL on days 22-186) in combination with mycofenolate mofetil (MMF) 1200 mg/m^2 per day for 2 wk, followed by 600 mg/m^2 per day. In addition to these drugs, children were randomized to (1) arm with steroid withdrawal, assuming methylprednisolone (MP) 300-600 mg/m^2, with daily reduction (60, 40, 30, 20 mg/m^2) and discontinuation at day 5; and (2) arm with steroids: MP 300-600 mg/m^2 and 40 mg/m^2 days 2-7, reduced from day 43 to 183 at discretion of investigators.

The primary end point was fully achieved in pre-pubertal children, who showed a significant benefit from steroid early discontinuation in modification of height standard deviation score. In the latter group, the absolute change in mean height at 6 mo was significantly better. The estimated rate of children free from biopsy proven acute rejection at protocol biopsy performed after 6 mo was 89% *vs* 92%, thus not proving any statistical difference between children with or without steroid discontinuation. Outcome of rejection, as well as graft and patients' survival were similar in the two groups. However, the follow-up was very short, being six months only.

There was a need for longer follow-up, provided by the Stanford University group, which has been the leader in trying the steroid minimization strategy. Sarwal *et al*[7] addressed to complete steroid avoidance in a multicenter RCT with three years of follow-up. The protocol was based on a common treatment with TAC 0.15 mg/kg per day (12-14 ng/mL day 0-7; 10-12 ng/mL from 2nd wk; 4-6 ng/mL at 1 year and 3-5 ng/mL after 1th year) in association with MMF: 1200 mg/m^2 per day for 2 d, than 600-900 mg/m^2 per day. Children were randomized

in two arms, including: (1) Steroid free arm, daclizumab 2 mg/kg pre transplant, at weeks 2, 4, 6, 8, 11 and months 4, 5, 6; (2) Steroid based arm, daclizumab 1 mg/kg pre transplantation, at weeks 2, 4, 6, 8. Moreover, prednisone was given, MP 10 mg/kg perioperatively, followed by 2 mg/kg and 0.5, 0.3, 0.2, 0.1, 0.15, 0.1 mg/kg per day at the end of weeks 1, 2, 4, 6, 16. The dose of 0.1 mg/kg was achieved no later than six months post transplantation.

After three years of follow-up no significant difference in estimated glomerular filtration rate was found between the two groups as well as in protocol biopsies at 6, 12 and 24 mo, despite some borderline changes were slightly more frequent in the steroid-free group. This observation induced further subanalysis on subclinical inflammation and chronic renal graft injury in children who underwent this NIH organized RCT[8]. No difference between steroid and steroid free regimens was found as far as T mediated rejection or T mediated borderline changes were concerned. There was a significant increase in blood pressure in children on steroids in comparison to those without it as well as an increase in cholesterol. Changes in height-Z score from baseline tended to be different in the two groups over the first months after transplantation (as observed in TWIST RCT) but this effect was lost after one year of transplantation. From this RCT it was concluded that three year follow up of steroid free regimen in unsensitized recipients at first transplantation with double dose of daclizumab in comparison to children on steroids was safe and did not increase the frequency of PTLD. However, no significant difference was observed in linear growth at three years even though at 6 mo there was a better growth in the steroid free group. In this study 13% of children had a failure to maintain steroid-free regimen and had a worse prognosis compared to those who maintained the steroid-free protocol, mostly due to difficulty to control acute rejection or to recurrence of original glomerulonephritis.

A recent systematic review by Pascual *et al*[9] including children and adults, concluded that the issue of steroid withdrawal is still controversial. After analysis of 9 RCT and 1934 subjects investigated, death and graft loss were similar in steroid avoidance and control patients, with no differences between CsA and TAC studies. After steroid avoidance, acute rejection was more frequent than conventional steroid use in CsA trials but not when TAC was used. Steroid avoidance was associated with less frequent new-onset diabetes mellitus, but this decrease was only evident with CsA, whereas this difference was not significant analyzing TAC studies. Despite this trend, the corresponding interaction tests were not statistically significant for acute rejection and new-onset diabetes mellitus, respectively.

The conclusions from this meta-analysis were that steroid avoidance or early withdrawal within the first two weeks is safe in kidney transplant recipients receiving induction with anti-interleukin-2 receptor antibodies or thymoglobulin and a drug regimen based on calcineurin inhibitor and MMF. However, the real benefits remain unclear.

CALCINEURIN INHIBITORS–FREE PROTOCOLS IN PAEDIATRIC RENAL TRANSPLANTATION

CNI carry relevant side effects, including hirsutism, hypertension, diabetes, seizures and renal toxicity which contributes to long term graft loss. Hence the search for CNI free protocols is one of the frontiers for renal transplantation in children. The Renal transplantation Center in Atlanta reported a five-year experience using sirolimus (SRL)-based, CNI-free immunosuppression in pediatric renal transplantation[10]. A cohort of low-risk renal pediatric transplant recipients was switched from TAC to SRL. All children received basiliximab induction and TAC, MMF, and prednisone. Conversion was pursued in cases at first transplant without history of nephrotic syndrome and without histologic evidence for acute rejection at three months after transplantation. Fifty-one children were converted from TAC to SRL. SRL was discontinued in 11 cases over the first year because of adverse events, particularly in 20% of the cases for aphtous ulcers. The remaining 40 children had 91% graft survival at five years. Acute rejection was detected in 13% of patients during the first year after conversion. BK viremia was detected in 20% and proteinuria in 7%. This study concluded that SRL-based immunosuppression associated with a CNI-free regimen can be successful in selected lower-risk patients, though the side effects are relevant.

A very relevant issue in children transplantation is growth since height is compromised by previous long term-uremia, dialysis treatment, and children undergoing renal transplantation have to face the need of steroids after transplant, which further limits the possibility of attaining a satisfactory final height. A report from Heidelberg Group has recently investigated the growth in pediatric kidney transplant recipients on an everolimus *vs* an MMF-based steroid-free immunosuppressive regimen[11]. Indeed some concerns were raised about the possible interference of mammalian target of rapamycin inhibitors (mTORi) in pediatric transplant recipients with bone growth by inhibition of growth factor signaling and growth plate chondrocyte proliferation. The study focused on longitudinal growth over 2 years in steroid-free pediatric kidney transplant recipients. Fourteen children on a steroid-free maintenance immunosuppressive regimen with low-dose everolimus (EVR) associated with low-dose CsA were compared to 14 children on steroid-free protocol and standard MMF regimen in conjunction with a standard CNI dose. No difference in change in height standard deviation score was detected between EVR and MMF groups. Similarly, the percentage of prepubertal patients experiencing catch-up growth, was similar in children in the two protocols. The Authors concluded that low-dose EVR does not have a negative impact on growth in pediatric renal transplant recipients.

A recently proposed drug for CNI free protocol is belatacept (which differs from abatacept only for two amino

acids), a fusion protein constituted by the Fc fragment of human IgG1 linked to the extracellular domain of CTLA-4, which is crucial for T-cell costimulation. In pediatric kidney transplantation belatacept is a promising agent for allowing steroid-free and CNI free immunosuppression. In a recent report[12] in living donor kidney transplant belatacept was used monthly in association with daily sirolimus. Belatacept and sirolimus effectively prevented kidney allograft rejection without CNIs or steroids when used following alemtuzumab induction. The effect of a similar protocol in children is under investigation.

NEW INDUCTION PROTOCOLS FOR RENAL TRANSPLANTATION IN CHILDREN

Alemtuzumab (Campath-1H) a humanized monoclonal antibody directed against CD52, is a new interesting option for induction with good results also in children[13,14]. Alemtuzumab recognizes CD52, a glycoprotein expressed on T and B lymphocytes, monocytes and natural killer cells[15,16]. This drug is the most efficient presently available lymphocyte-depleting agents, inducing, after a single administration, a prompt and prolonged depletion of circulating lymphocytes. Alemtuzumab was used since 1998[17] with the interesting result of allowing a low-dose CsA monotherapy. Recent RCT in adults have shown lower frequency of acute rejection in comparison to basiliximab in patients non at high immunological risk[18,19]. In children the first relevant experience was from Kidney Transplantation Center in Moskow, as Kaabak *et al*[20] reported, in living related pediatric renal transplants. The rationale was to eradicate peripheral lymphomonocytes and induce donor- specific tolerance, by infusing two doses of 30 mg alemtuzumab, one 12-29 d prior to transplantation and the other at surgery. They reported a large experience on 101 living-donor kidney transplantations in pediatric recipients. The maintenance immunosuppression included low doses CNI and MMF. The mean follow-up was 3 years. Graft survival was 96% at one year and 89% at three years. Acute rejection was detected at protocol biopsies in 26% of children at one year and in 35% at two years, while no rejection was detected thereafter. The conclusion from this study were that alemtuzumab pretreatment before living related kidney transplantation is a good option allowing a reduction in usual doses of CNI and obtaining satisfactory middle-term results.

A subsequent study performed by the Portland Group of pediatric kidney transplantation[21] investigated the effects of alemtuzumab, 0.5 mg/kg for a maximum of 30 mg, in 25 children undergoing cadaveric kidney transplantation, in whom the drug was given after anesthesia, before kidney transplantation. MP was given 10 mg/kg peri-operatively and before revascularization. Children received steroid therapy for other four days. TAC as monotherapy was initiated at day 1 (target through levels of 8-10 ng/mL over 6 mo, then 6-8 ng/mL). MMF was added only in cases of high immunological risk or prolonged delayed graft function. Over a mean follow-up of two years, TAC monotherapy was maintained in 48% of children, and steroids were avoided in 80%. The actuarial survival rate at 3 years was 100%. Acute rejection rate was 12% within the first year and 16% in the following two years. The frequency of BK or CMV infection was 16%. The Authors concluded that alemtuzumab induction with TAC monotherapy is a good option for children with low immunological risk ensuring excellent short and medium-term follow-up outcome.

A recent report provided interesting results of 7 years follow-up in children treated with alemtuzumab and corticosteroid minimization after cadaveric renal transplantation[22]. The maintenance therapy was a steroid-free regimen with TAC and MMF immunosuppression. All children had immediate graft function and graft survival was excellent (95%). No patient had cytomegalovirus infection, PTLD or polyoma BK nephropathy. The conclusion of this study was that steroid avoidance provided a good outcome with adequate immunosuppression after single-dose alemtuzumab with maintenance therapy with TAC and low-dose MMF.

DESENSITIZATION PROTOCOLS IN CHILDREN

Over the last years a growing interest has been focused on donor-specific antibodies (DSA Ab) for a previously unsuspected role in graft function and survival[23]. Acute antibody-mediated graft rejection is a problem involving children as well as adults, but even more relevant is becoming the role of DSA Ab as one of the mayor causes of graft loss[24]. Children candidates to a kidney transplant, particularly after a first failed graft, more often than in the past present with antibodies against HLA antigens, often at high titres, raising the problem of the risk of hyperacute or acute humoral rejections and reducing the chances of being transplanted[25,26]. The new flow cytometry based techniques used to investigate the presence of anti HLA antibodies have a much higher sensitivity than complement dependent cytotoxicity assays and are able to reveal panels of antibodies whose capacity to bind complement and induce antibody mediated lysis of target cells is not ascertained. For some years the true role of these low titres antibodies has not been clearly defined: hyperacute rejection is not common but either acute rejection and a chronic damage induced by these antibodies has been demonstrated[23,24].

Sensitization may occur after blood transfusion with red blood cells not appropriately washed or filtered, however the main origin of sensitization is a previous transplant. Proteins as well as stem cells of donor origin have been demonstrated to be persistently present even after removal of the graft, being able to maintain the persistence of immunological stimulus[25]. De novo antibodies, mostly directed against HLA, have been detected in a United States multicenter report in up to 24% of children with renal transplant. Six percent of these antibodies were DSA

Ab and 6% anti MHC class 1 related chain A (MICA), and were equally found either on steroid-free or steroid-based regimens[25]. The presence of anti HLA and anti MICA Ab was significantly associated with acute and chronic rejection with faster graft loss. Similar results were reported by a single center Italian study[26] in 82 children who underwent kidney transplantation, without prior DSA Ab: 23% of this cohort developed after 4 years of follow-up de novo DSA Ab, mostly directed against HLA-DQ antigens. A significant correlation was found between DSA Ab and chronic antibody-mediated rejection. The conclusion of both studies[25,26] were that children developing DSA Ab are at risk of graft dysfunction and that there is the need of developing new strategies to prevent antibody mediated graft damage and progression to graft failure.

In candidates to a kidney transplant persistent large panel of antibodies against HLA and PRA > 50% require a desensitization approach for increasing the chance of receiving a graft. Several protocols have been proposed also in children aiming at reducing the antibody titres. The desensitizing protocols include removal of DSA by high-dose *i.v.* immunoglobulins administration (IVIg), plasmapheresis, immunoadsorption, or a combination of the two approaches. In the attempt of reducing recurrence of DSA Ab, rituximab has been introduced in the last years. In some cases immunosuppression with alkylating agents is also considered[23]. The major drawbacks of these protocols are the risk of infections and the rebound of antibodies allowing a short window interval time for receiving a transplant, requiring repeated desensitization if a suitable donor is not found. In pediatric age, due to low numbers of desensitized patients there is a lack of large studies.

Most protocols are based on intravenous immunoglobulins which in children have been reported to be effective even when used alone in significantly reducing PRA. Al-Uzri *et al*[27] showed that weekly infusion for three consecutive weeks every 12 wk of high-dose (500 mg/kg) Immunoglobulins reduced PRA to zero, and the effect lasted for over three years. Tyan reported a case where IVIG were successfully used to reduce PRA from 95% to 15% and allow retransplant in a 13 years old boy[28].

In adults Immunoglobulin infusion alone have not produced satisfactory results, hence different protocols of combination treatment with other drugs or procedures have been tried and adopted also in children. The combination of rituximab with plasmapheresis was able to maintain over longer time the immunoglobulin depleting effect of plasmapheresis maintaining the lowering effect so as to allow the use of this protocol also in deceased-donor transplant. Rituximab cannot by itself reduce anti HLA antibody level, but can prevent clonal B cells expansion and consequently DSA production. The advantage of rituximab (1 g/1.73 m^2) for children is the wide experience in pediatric nephrotic syndrome which reported low incidence of infections and of major complications and effects lasting sometimes even one year, avoiding the need for vascular access and repeated procedures, like in the case of plasmapheresis. Rituximab was given in some protocols after plasmapheresis[29].

Billing *et al*[30] treated children with active chronic DSA Ab rejection with 4 weekly doses of 1 g/kg IVIg followed by one single dose of rituximab (375 mg/m^2). They reported a significantly lower loss of GFR over 6 mo of treatment in 4/6 cases. These results were confirmed in a larger trial enrolling 20 children followed over 2 years, with a response rate (evaluated as reduction of GFR loss) in 70% of the patients. Meanwhile, there was a reduction of 60% of antibodies against both HLA class I and Class II[31].

Another drug used to successfully prevent or reduce DSA Ab is MMF (390 to 500 mg/m^2 per day), which gave satisfactory results in a 4-year-old child[32].

New treatments, like Eculizumab which is a complement inhibitor directed against terminal complement protein C5, and the proteasome inhibitor Bortezomib, are theoretically useful to block the final effects of preformed anti HLA antibodies and their noxious effect, but still not yet experienced in sensitized children. A recent retrospective study reported 4 cases of children with grafted kidneys who were treated with bortezomib for high levels of DSA and acute antibody mediated rejection[33]. Children received four doses of bortezomib 1.3 mg/m^2 at day 1, 4, 8 and 11. All of them were treated with various drug combinations, including rituximab, methylprednisolone, plasmapheresis or IVIg. The conclusion from this limited series were that bortezomib therapy is an effective and safe methods for a rapid reduction in DSA levels, although its effectiveness from the clinical point of view was not clearly defined in this preliminary experience in children.

CONCLUSION

In agreement with a recent systematic review performed by the Cochrane group[34] to highlight the current trends in immunosuppression in pediatric renal transplantation, when we focus on challenging new frontiers for these children, we still face an uncertain horizon. Newly proposed drugs, including belatacept and alemtuzumab, carry serious side-effects, and interleukin-2 receptor antagonists remain the safest and effective agents for pediatric kidney transplantation. The new steroid-free regimens can improve growth and not hamper graft survival over a short follow-up, however, long-term outcome remains to be determined. mTOR inhibitors, sirolimus and everolimus, are a promising option for primary immunosuppression as CNI sparing agents, however beneficial results on long term graft survival are still to be proven. Desensitization protocols are being performed, but benefits and harms are still to be analyzed and long-term graft survival analysis studies are needed.

In spite of these apparently non optimistic considerations, the improvement of the short and long term results of kidney transplantation in children have been so impressive over the last decades, that we optimistically think that the new frontiers presently representing a challenge will be achieved in a few years as consistent point for further improving the

outcome of kidney transplanted children.

REFERENCES

1 **Patel UD**. Outcomes after pediatric kidney transplantation improving: how can we do even better? *Pediatrics* 2014; **133**: 734-735 [PMID: 24616364 DOI: 10.1542/peds.2014-0124]
2 **Van Arendonk KJ**, Boyarsky BJ, Orandi BJ, James NT, Smith JM, Colombani PM, Segev DL. National trends over 25 years in pediatric kidney transplant outcomes. *Pediatrics* 2014; **133**: 594-601 [PMID: 24616363 DOI: 10.1542/peds.2013-2775]
3 **Ellis EN**, Martz K, Talley L, Ilyas M, Pennington KL, Blaszak RT. Factors related to long-term renal transplant function in children. *Pediatr Nephrol* 2008; **23**: 1149-1155 [PMID: 18301925 DOI: 10.1007/s00467-008-0779-0]
4 **Kaidar M**, Berant M, Krauze I, Cleper R, Mor E, Bar-Nathan N, Davidovits M. Cardiovascular risk factors in children after kidney transplantation--from short-term to long-term follow-up. *Pediatr Transplant* 2014; **18**: 23-28 [PMID: 24134654 DOI: 10.1111/petr.12174]
5 **Benfield MR**, Bartosh S, Ikle D, Warshaw B, Bridges N, Morrison Y, Harmon W. A randomized double-blind, placebo controlled trial of steroid withdrawal after pediatric renal transplantation. *Am J Transplant* 2010; **10**: 81-88 [PMID: 19663893 DOI: 10.1111/j.1600-6143.2009.02767.x]
6 **Grenda R**, Webb NJ. Steroid minimization in pediatric renal transplantation: Early withdrawal or avoidance? *Pediatr Transplant* 2010; **14**: 961-967 [PMID: 20874824 DOI: 10.1111/j.1399-3046.2010.01403.x]
7 **Sarwal MM**, Ettenger RB, Dharnidharka V, Benfield M, Mathias R, Portale A, McDonald R, Harmon W, Kershaw D, Vehaskari VM, Kamil E, Baluarte HJ, Warady B, Tang L, Liu J, Li L, Naesens M, Sigdel T, Waskerwitz J, Salvatierra O. Complete steroid avoidance is effective and safe in children with renal transplants: a multicenter randomized trial with three-year follow-up. *Am J Transplant* 2012; **12**: 2719-2729 [PMID: 22694755 DOI: 10.1111/j.1600-6143.2012.04145.x]
8 **Naesens M**, Salvatierra O, Benfield M, Ettenger RB, Dharnidharka V, Harmon W, Mathias R, Sarwal MM. Subclinical inflammation and chronic renal allograft injury in a randomized trial on steroid avoidance in pediatric kidney transplantation. *Am J Transplant* 2012; **12**: 2730-2743 [PMID: 22694733 DOI: 10.1111/j.1600-6143.2012.04144.x]
9 **Pascual J**, Royuela A, Galeano C, Crespo M, Zamora J. Very early steroid withdrawal or complete avoidance for kidney transplant recipients: a systematic review. *Nephrol Dial Transplant* 2012; **27**: 825-832 [PMID: 21785040 DOI: 10.1093/ndt/gfr374]
10 **Hymes LC**, Warshaw BL. Five-year experience using sirolimus-based, calcineurin inhibitor-free immunosuppression in pediatric renal transplantation. *Pediatr Transplant* 2011; **15**: 437-441 [PMID: 21338459 DOI: 10.1111/j.1399-3046.2011.01477.x]
11 **Billing H**, Burmeister G, Plotnicki L, Ahlenstiel T, Fichtner A, Sander A, Höcker B, Tönshoff B, Pape L. Longitudinal growth on an everolimus- versus an MMF-based steroid-free immunosuppressive regimen in paediatric renal transplant recipients. *Transpl Int* 2013; **26**: 903-909 [PMID: 23865768 DOI: 10.1111/tri.12148]
12 **Kirk AD**, Guasch A, Xu H, Cheeseman J, Mead SI, Ghali A, Mehta AK, Wu D, Gebel H, Bray R, Horan J, Kean LS, Larsen CP, Pearson TC. Renal transplantation using belatacept without maintenance steroids or calcineurin inhibitors. *Am J Transplant* 2014; **14**: 1142-1151 [PMID: 24684552 DOI: 10.1111/ajt.12712]
13 **Li L**, Chaudhuri A, Chen A, Zhao X, Bezchinsky M, Concepcion W, Salvatierra O, Sarwal MM. Efficacy and safety of thymoglobulin induction as an alternative approach for steroid-free maintenance immunosuppression in pediatric renal transplantation. *Transplantation* 2010; **90**: 1516-1520 [PMID: 20935596 DOI: 10.1097/TP.0b013e3181fc8937]
14 **De Serres SA**, Mfarrej BG, Magee CN, Benitez F, Ashoor I, Sayegh MH, Harmon WE, Najafian N. Immune profile of pediatric renal transplant recipients following alemtuzumab induction. *J Am Soc Nephrol* 2012; **23**: 174-182 [PMID: 22052056 DOI: 10.1681/ASN.2011040360]
15 **Ratzinger G**, Reagan JL, Heller G, Busam KJ, Young JW. Differential CD52 expression by distinct myeloid dendritic cell subsets: implications for alemtuzumab activity at the level of antigen presentation in allogeneic graft-host interactions in transplantation. *Blood* 2003; **101**: 1422-1429 [PMID: 12393688 DOI: 10.1182/blood-2002-04-1093]
16 **Kirk AD**, Hale DA, Mannon RB, Kleiner DE, Hoffmann SC, Kampen RL, Cendales LK, Tadaki DK, Harlan DM, Swanson SJ. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). *Transplantation* 2003; **76**: 120-129 [PMID: 12865797 DOI: 10.1097/01.TP.0000071362.99021.D9]
17 **Calne R**, Friend P, Moffatt S, Bradley A, Hale G, Firth J, Bradley J, Smith K, Waldmann H. Prope tolerance, perioperative campath 1H, and low-dose cyclosporin monotherapy in renal allograft recipients. *Lancet* 1998; **351**: 1701-1702 [PMID: 9734890 DOI: 10.1016/S0140-6736(05)77739-4]
18 **Study T**, Group C. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. *Lancet* 2014; **6736**: 1-7 [PMID: 25078310 DOI: 10.1016/S0140-6736(14)61095-3]
19 **Kuypers DRJ.** Alemtuzumab induction therapy in kidney transplantation. *Lancet* 2014; 6736: 10-11 [PMID: 25078307 DOI: 10.1016/S0140-6736(14)61174-0]
20 **Kaabak MM**, Babenko NN, Samsonov DV, Sandrikov VA, Maschan AA, Zokoev AK. Alemtuzumab induction in pediatric kidney transplantation. *Pediatr Transplant* 2013; **17**: 168-178 [PMID: 23442101 DOI: 10.1111/petr.12048]
21 **Sung J**, Barry JM, Jenkins R, Rozansky D, Iragorri S, Conlin M, Al-Uzri A. Alemtuzumab induction with tacrolimus monotherapy in 25 pediatric renal transplant recipients. *Pediatr Transplant* 2013; **17**: 718-725 [PMID: 24164824 DOI: 10.1111/petr.12159]
22 **Supe-Markovina K**, Melquist JJ, Connolly D, DiCarlo HN, Waltzer WC, Fine RN, Darras FS. Alemtuzumab with corticosteroid minimization for pediatric deceased donor renal transplantation: a seven-yr experience. *Pediatr Transplant* 2014; **18**: 363-368 [PMID: 24712738 DOI: 10.1111/petr.12253]
23 **Salvadori M**, Bertoni E. Impact of donor-specific antibodies on the outcomes of kidney graft: Pathophysiology, clinical, therapy. *World J Transplant* 2014; **4**: 1-17 [PMID: 24669363 DOI: 10.5500/wjt.v4.i1.1]
24 **Pape L,** Becker JU, Immenschuh S, Ahlenstiel T. Acute and chronic antibody-mediated rejection in pediatric kidney transplantation. *Pediatr Nephrol* 2014 [PMID: 24865478 DOI: 10.1007/s00467-014-2851-2]
25 **Chaudhuri A**, Ozawa M, Everly MJ, Ettenger R, Dharnidharka V, Benfield M, Mathias R, Portale A, McDonald R, Harmon W, Kershaw D, Vehaskari VM, Kamil E, Baluarte HJ, Warady B, Li L, Sigdel TK, Hsieh SC, Dai H, Naesens M, Waskerwitz J, Salvatierra O, Terasaki PI, Sarwal MM. The clinical impact of humoral immunity in pediatric renal transplantation. *J Am Soc Nephrol* 2013; **24**: 655-664 [PMID: 23449533 DOI: 10.1681/ASN.2012070663]
26 **Ginevri F**, Nocera A, Comoli P, Innocente A, Cioni M, Parodi A, Fontana I, Magnasco A, Nocco A, Tagliamacco A, Sementa A, Ceriolo P, Ghio L, Zecca M, Cardillo M, Garibotto G, Ghiggeri GM, Poli F. Posttransplant de novo donor-specific hla antibodies identify pediatric kidney recipients at risk for late antibody-mediated rejection. *Am J Transplant* 2012; **12**: 3355-3362 [PMID: 22959074 DOI: 10.1111/j.1600-6143.2012.04251.x]
27 **Al-Uzri AY**, Seltz B, Yorgin PD, Spier CM, Andreoni K.

Successful renal transplant outcome after intravenous gamma-globulin treatment of a highly sensitized pediatric recipient. *Pediatr Transplant* 2002; **6**: 161-165 [PMID: 12000474 DOI: 10.1034/j.1399-3046.2002.01055.x]

28 **Tyan DB**, Li VA, Czer L, Trento A, Jordan SC. Intravenous immunoglobulin suppression of HLA alloantibody in highly sensitized transplant candidates and transplantation with a histoincompatible organ. *Transplantation* 1994; **57**: 553-562 [PMID: 8116041]

29 **Jackson AM**, Kraus ES, Orandi BJ, Segev DL, Montgomery RA, Zachary AA. A closer look at rituximab induction on HLA antibody rebound following HLA-incompatible kidney transplantation. *Kidney Int* 2014 Jul 23; Epub ahead of print [PMID: 25054778 DOI: 10.1038/ki.2014.261]

30 **Billing H**, Rieger S, Ovens J, Süsal C, Melk A, Waldherr R, Opelz G, Tönshoff B. Successful treatment of chronic antibody-mediated rejection with IVIG and rituximab in pediatric renal transplant recipients. *Transplantation* 2008; **86**: 1214-1221 [PMID: 19005402 DOI: 10.1097/TP.0b013e3181880b35]

31 **Billing H**, Rieger S, Süsal C, Waldherr R, Opelz G, Wühl E, Tönshoff B. IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2-year follow-up. *Transpl Int* 2012; **25**: 1165-1173 [PMID: 22897111 DOI: 10.1111/j.1432-2277.2012.01544.x]

32 **Wong H**, Laberge R, Harvey E, Filler G. Preventing sensitization with mycophenolate mofetil in a pediatric kidney recipient. *Pediatr Transplant* 2006; **10**: 367-370 [PMID: 16677363 DOI: 10.1111/j.1399-3046.2005.00469.x]

33 **Nguyen S**, Gallay B, Butani L. Efficacy of bortezomib for reducing donor-specific antibodies in children and adolescents on a steroid minimization regimen. *Pediatr Transplant* 2014; **18**: 463-468 [PMID: 24814755 DOI: 10.1111/petr.12274]

34 **Kim S**, Webster AC, Craig JC. Current trends in immunosuppression following organ transplantation in children. *Curr Opin Organ Transplant* 2013 [PMID: 23995377 DOI: 10.1097/MOT.0b013e3283651b35]

P- Reviewer: Garcia-Roca R, Trimarchi H **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.229

World J Transplant 2014 December 24; 4(4): 229-242
ISSN 2220-3230 (online)

TOPIC HIGHLIGHT

Maurizio Salvadori, Professor, *Series Editor*

Female gender in the setting of liver transplantation

Kryssia Isabel Rodríguez-Castro, Eleonora De Martin, Martina Gambato, Silvia Lazzaro, Erica Villa, Patrizia Burra

Kryssia Isabel Rodríguez-Castro, Eleonora De Martin, Martina Gambato, Silvia Lazzaro, Patrizia Burra, Multivisceral Transplant Unit, Deparment of Surgery, Oncology and Gastroenterology, Padua University Hospital, 35128 Padua, Italy
Erica Villa, Department of Gastroenterology, Azienda Ospedaliero-Universitaria and University of Modena and Reggio Emilia, 41124 Modena, Italy
Author contributions: Rodríguez-Castro KI contributed to the conception, design, and performance of the research, drafting of the manuscript, approval of the final version; De Martin E contributed to the conception, design, and performance of the research, drafting of the manuscript, approval of the final version; Gambato M contributed to the critical revision of the manuscript, approval of the final version; Lazzaro S critically revised the manuscript, approval of the final version; Villa E contributed to the conception and design of the research, critical revision of the manuscript, approval of the final version; Burra P contributed to the conception and design of the research, critical revision of the manuscript, approval of the final version.
Correspondence to: Patrizia Burra, Professor, MD, PhD, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Via Giustiniani 2, 35128 Padua, Italy. burra@unipd.it
Telephone: +39-49-8212892 Fax: +39-49-8218727
Received: April 8, 2014 Revised: May 27, 2014
Accepted: July 15, 2014
Published online: December 24, 2014

Abstract

The evolution of liver diseases to end-stage liver disease or to acute hepatic failure, the evaluation process for liver transplantation, the organ allocation decision-making, as well as the post-transplant outcomes are different between female and male genders. Women's access to liver transplantation is hampered by the use of model for end-stage liver disease (MELD) score, in which creatinine values exert a systematic bias against women due to their lower values even in the presence of variable degrees of renal dysfunction. Furthermore, even when correcting MELD score for gender-appropriate creatinine determination, a quantifiable uneven access to transplant prevails, demonstrating that other factors are also involved. While some of the differences can be explained from the epidemiological point of view, hormonal status plays an important role. Moreover, the pre-menopausal and post-menopausal stages imply profound differences in a woman's physiology, including not only the passage from the fertile age to the non-fertile stage, but also the loss of estrogens and their potentially protective role in delaying liver fibrosis progression, amongst others. With menopause, the tendency to gain weight may contribute to the development of or worsening of pre-existing metabolic syndrome. As an increasing number of patients are transplanted for non-alcoholic steatohepatitis, and as the average age at transplant increases, clinicians must be prepared for the management of this particular condition, especially in post-menopausal women, who are at particular risk of developing metabolic complications after menopause.

Key words: Liver transplantation; Female gender; Estrogens; Model for end-stage liver disease score; Creatinine; Gender donor-recipient match

Core tip: Gender differences play an important role in liver diseases, their evolution and outcome, and in liver transplantation, not only in terms of access to this resource, but also in terms of graft survival, metabolic aspects, and quality of life after liver transplantation. Not only gender differences, are important, however, but clearly the different hormonal status throughout a woman's lifetime determines many aspects not only regarding fertility and sexual issues such as pregnancy, but also metabolic complications. Notwithstanding this, decision-making algorithms regarding indications, risk factors, and outcomes after transplant do not yet incorporate many of these concepts that affect the clinical practice.

Rodríguez-Castro KI, De Martin E, Gambato M, Lazzaro S, Villa E, Burra P. Female gender in the setting of liver transplantation. *World J Transplant* 2014; 4(4): 229-242 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/i4/229.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.229

INTRODUCTION

It is ever clearer that gender differences play an important role in liver diseases, their evolution and outcome, and in liver transplantation (LT), not only in terms of access to this resource, but also in terms of graft survival, metabolic aspects, and quality of life after LT. Nevertheless, proposed measures for correcting the systematic bias disadvantaging women's access to LT, and the gender variable itself, are not yet fully incorporated into decision-making algorithms regarding evaluation of indications, risk factors, and outcomes in LT. The present review, therefore aims at highlighting gender differences in diseases that lead to LT, access to LT, and outcomes after transplant.

GENDER DISPARITY IN ACCESS TO LT

Sociodemographic determinants

Access to a life-saving resource such as LT has unfortunately been hampered for ethnic minorities, women, and patients of low socioeconomic status or inadequate insurance coverage; in a study analyzing health care inequities that prevent patients with end-stage liver disease from being evaluated and waitlisted for LT, patients were less likely to undergo evaluation, waitlisting and transplantation if they were women, black and lacked commercial insurance ($P <$ 0.001 each)[1].

This disparity of access to LT probably owes to several factors, including body and organ size considerations, differences in the etiology of the underlying liver disease, and limits of the model for end-stage liver disease (MELD) score, especially regarding creatinine levels[2].

MELD, MELD-related issues and non-MELD determinants of access to LT

In the pre-MELD era, a study from the Organ Procurement and Transplantation Network (OPNT) showed that female sex was significantly correlated with longer stay on the liver transplant waiting list and also with the risk of dying before LT[3]. Unequal access to LT for women was unfortunately perpetuated upon implementation of the MELD score for organ allocation, however. In a study based on UNOS data comparing pre- and post-MELD cohorts, women were more likely than men to die or become too sick for LT post-MELD [23.7% *vs* 21.4%; odds ratio (OR) = 1.30; $P =$ 0.003] *vs* pre-MELD (22.4% *vs* 21.9%; OR = 1.08; $P = 0.37$). Similarly, women were less likely than men to receive a liver transplant within 3 years both pre-MELD (64.8% *vs* 67.6%; OR = 0.80; $P = 0.002$) and post-MELD (39.9% *vs* 48.7%; OR = 0.70; $P < 0.001$)[4]. Actually, organ allocation based on MELD sore has further increased gender disparity, as waiting list mortality risk has risen, particularly for MELD scores > 15[5]. In fact, female gender, together with primary non-function, fulminant hepatic failure, blood group O, CTP ⩾ 11 and MELD score ⩾ 20 have been found to be predictors of waiting list mortality[6].

A systematic bias against women, resulting in part from the use of creatinine as a measure of renal function, has been identified in MELD-based liver allocation. Women's lesser body (and muscular) mass determines lower creatinine levels, one of the most important determinants of MELD score; due to the employment of creatinine instead of weight-adjusted glomerular filtration rate (GFR), the degree of renal dysfunction is likely in women is likely underestimated. Thus, MELD scores will be lower in women than in men with the same degree of renal compromise, which inevitably leads to a decreased access for women to LT[2]. Moreover, attempts at correcting creatinine-induced MELD bias against women by including estimated GFR have not improved discrimination for 3-mo mortality after enrolment for LT[7]. Likewise, the accuracy of MELD score in predicting 3- and 6-mo mortality in female LT candidates did not improve with the employment of the Modification of Diet in Renal Disease formula[8]. Providing that renal function assessment was adequately corrected for gender, a negative bias against women would still remain, since women are more likely than men to suffer from autoimmune liver diseases, including primary biliary cirrhosis, which are less likely than hepatitis C (HCV) to lead to kidney dysfunction and higher MELD scores[2].

Moreover, aside from the inaccuracy of MELD score in terms of renal dysfunction assessment in female patients, it is well known that patients with certain pathological conditions are poorly served by this score, including refractory ascites, refractory encephalopathy, recurrent cholangitis, and intractable pruritus in cholestatic diseases[9], the latter of which encompass mainly women[10-12]. Nevertheless, some of these conditions constitute symptom-based MELD exceptions and are awarded extra MELD points[13].

On the other hand, standard exclusions to MELD, which are more regularly applied, include the presence of hepatocellular carcinoma (HCC)[14-18], which is more common in men, further increasing the disparity of access to LT. After the implementation of the Milan Criteria[14], the number of LTs for HCC has increased worldwide and currently in Europe about 27% of all LT patients have HCC with countries peaking over 40%[19]. While exception points have greatly improved access to transplantation for HCC patients[20], recent studies suggest that the current point scheme inadvertently prioritizes HCC over patients without HCC diagnosis (non-HCC) by overestimating the presumed risk of tumor progression[21,22]. Even more vexing is the observation that even for equal MELD scores, women are at a disadvantage with respect to men in terms to LT access, suggesting that other factors must play a role in the gender disparity documented for LT rates[7,23].

GENDER DIFFERENCES IN INDICATIONS FOR LT

According to the OPTN records for LT performed in the US

between January 1, 1988 until December 31, 2013[24], a search for gender by diagnosis outlines several significant gender differences: significantly more women than men underwent LT for Wilson disease (410/47608 *vs* 326/78534, $P < 0.0001$), primary biliary cirrhosis (4796/47608 *vs* 809/78534, $P < 0.0001$), drug-induced acute hepatic necrosis (748/47608 *vs* 295/78534, $P < 0.0001$), Budd Chiari syndrome 441/47608 *vs* 233/78534), autoimmune cirrhosis 3025/47608 *vs* 959/78534, $P < 0.0001$), cryptogenic cirrhosis (4245/47608 *vs* 5009/78534, $P < 0.0001$), and non-alcoholic steatohepatitis (NASH) (1673/47608 *vs* 1875/78534, $P < 0.0001$).

On the contrary, significantly more men underwent LT for alcoholic cirrhosis (11195/78534 *vs* 3227/47608, $P < 0.0001$), alcoholic cirrhosis with HCV (4938/78534 *vs* 888/47608, $P < 0.0001$), HCC (2768/78534 *vs* 899/47608, $P < 0.0001$), HCC and cirrhosis (77555/78534 *vs* 2099/47608, $P < 0.0001$), HBsAg + Hepatitis B (2778/78534 *vs* 651/47608, $P < 0.0001$), and HCV (18187/78534 *vs* 8135/47608, $P < 0.0001$)[24].

Viral hepatitis

Several studies have demonstrated a differential effect of gender on the outcomes of patients infected with HCV, showing that in female patients, the natural history of HCV virus infection tends to be characterized by slower rates of progression to advanced liver disease, with better response rates to antiviral therapy[25-28]. Moreover, overall lower death rates for HCV-related liver disease as well as lower rates of HCC are observed in female patients[29].

Regarding menopausal course of HCV-related liver disease, however, recent studies have reported that the reduced estrogen levels that characterize this state may determine the accelerated progression to fibrosis and higher rates of no response to antiviral therapy observed in this subpopulation, especially in genotype 1 HCV-infected patients[30-32]; a statistically significant increase of tumor necrosis factor-α and interleukin-6 occur in menopause, and these proinflammatory cytokines have been associated to increased resistance to interferon-based therapy[33]. A higher SVR rate with Peg-IFNα-2b plus ribavirin *vs* IFNα-2a plus ribavirin has been documented in menopausal women, which likely corresponds the former's pharmacokinetic properties that allow the drug to reach visceral fat and oppose the increased cytokine production and enhanced inflammatory status in menopause[34].

Regarding hepatitis B (HBV), although significantly more men than women are transplanted for chronic HBV, LT for fulminant HBV is significantly more frequent in women[35]. As well, hepatitis E virus (HEV) is unfortunately associated with disproportionately high rates of fulminant hepatitis in pregnant women, particularly during the third trimester, with case-fatality rates in epidemics ranging from 0.2%-4% in the general population, *vs* 10%-25% in the pregnant population[36-38], possibly reflecting hormonal changes that increase susceptibility to a more aggressive course[39].

Non-alcoholic steatohepatitis

NASH has increased in frequency as indication for LT[40-42], and is bound to become one of the principal indications in many Western countries, with the increasing worldwide prevalence of this entity[43], and with the advent of new-acting direct antiviral agents, which will probably contribute to decreasing the percentage of HCV patients who necessitate LT.

In a study analyzing characteristics of patients referred for LT evaluation due to NASH ($n = 71$) from 1998 to 2008, and compared to the non-NASH possible candidates ($n = 472$)[44], it was found that patients with NASH were older (58.7 years *vs* 52.5 years, $P < 0.0001$) and more likely of female gender (50.7% *vs* 32.1%, $P = 0.003$). As expected, NASH patients were more likely to suffer from diabetes, hypertension, obesity, and cardiac disease ($P < 0.05$). Moreover, for paired MELD scores, NASH was associated with similar bilirubin levels (2.34 mg/dL *vs* 3.16 mg/dL; $P = 0.11$), but significantly increased creatinine values (1.26 mg/dL *vs* 0.98 mg/dL; $P = 0.0018$) and lower international normalized ratio (INR) values (1.14 *vs* 1.27; $P = 0.04$), in contrast with LT candidates without NASH, respectively. This suggests that NASH is associated with renal dysfunction, which is translated into greater priority, as established by the MELD calculus.

Thus, MELD score in this setting might not truly reflect liver dysfunction, but could be more directly related to features of the metabolic syndrome, including microvascular renal damage associated with diabetes and hypertension. Therefore, the disadvantage posed to women by creatinine's weight in the MELD calculus formula might be outweighed in the future, with increasing number of patients being transplanted for NASH, most of them being of female gender. However, the present state of the matter is yet far from this scenario, as only 5%-8% of LT are currently performed for this indication, and the time needed for MELD's disparity to be counterbalanced by this theoretical female gender benefit is expectedly long[2].

Putting together all these data is especially concerning, since women are generally more likely to have GFR < 60 mL/min per 1.73 m^2 previous to LT with respect to men, and the presence of this factor (OR = 3.28, $P \leqslant 0.001$), aside from female gender (OR = 2.96, $P < 0.001$) and age (OR = 1.09, $P < 0.001$), has been demonstrated to be independently predictive of stage ⩾ 3 chronic kidney disease (CKD) at 1 year post-LT[45]. In addition, this same study demonstrated that female gender (OR = 2.52, $P = 0.004$), age (OR = 1.05, $P = 0.003$) and NASH (OR = 2.95, $P = 0.039$) were independently predictive of ⩾ stage 3 CKD at 5 years post-LT.

Considering, that NASH LT recipients are more frequently women, that women's renal dysfunction is not adequately accounted for by creatinine measurement and thus not well served by MELD score, together with the fact that women are more likely to have compromised renal function prior to transplant, and that this variable predicts advanced CKD after LT, it becomes clear that this population stands a particular risk and should be addressed more carefully.

Autoimmune hepatitis

Differences in sex-hormone (estrogen and androgen) modulation of the immune system may be responsible

for gender variations observed in autoimmune disorders; women have a significantly higher number of CD4+T lymphocytes and a higher CD4+/CD8+ ratio than men[46], secretion of interferon-γ (IFN-γ) and interleukin 10 (IL-10) are enhanced after the addition of estrogen in T-cell clones isolated from women[47], while androgens have been demonstrated to inhibit the secretion of IFN-γ, IL-4, and IL-5 in murine T cells[48].

Autoimmune hepatitis, characterized by progressive inflammatory destruction of the liver parenchyma associated with the presence of circulating autoantibodies, hypergammaglobulinemia and interface hepatitis on liver biopsy, is strongly preponderant in females (female/male ratio is 3.6/1)[49]. Although corticosteroid treatment tends to achieve transaminase normalization more frequently in female patients[50], women appear to have worse long-term survival than men[51].

Primary biliary cirrhosis

Primary biliary cirrhosis, a chronic cholestatic liver disease characterized by immune-mediated inflammatory destruction of the small intrahepatic bile ducts and fibrosis, affects predominantly women with respect to men, with incidence rates ranging from 3:1 to 22:1, with an average incidence rate in women of 10:1[52]. Gender differences also characterize the evolution of the disease: diagnosis of PBC is usually established at a younger age in women (51 years in women *vs* 62 years in men)[53]. Women are more likely to be symptomatic, and experience pruritus as a single symptom more often than males, while jaundice, jaundice with pruritus, and upper gastrointestinal bleeding are more frequently manifested in men[54]. Some symptoms such as severe daytime somnolence and depressive symptoms seem to affect men and women in an equal proportion, while autonomic symptoms seem to be more severe in women[55,56]. The presence of concomitant autoimmune disorders such as Sicca syndrome, overlap syndrome, and autoimmune hepatitis, also determining a more aggressive course and generally poorer response to therapy, is more frequent in women, especially in those of Hispanic origin, as has been recently demonstrated in a US cross-sectional study[57]. Development of hepatocellular carcinoma, however, seems to be more frequent in men[58]. Although PBC entails a high risk of postmenopausal osteoporosis, it seems to be more associated with the severity of chronic liver disease, rather than specifically the PBC etiology[59], and a recent Cochrane database systematic review reported that in female patients with cirrhosis, hormone replacement had no effect on all-cause mortality, fractures, liver-related mortality, liver transplantation, liver-related morbidity, serum bilirubin concentration nor lumbar spine bone mineral density. On the contrary, hormone replacement significantly increased the frequency of adverse events[60].

Wilson disease

Although this autosomic recessive disorder characterized by a wide spectrum of clinical manifestations should theoretically be present in females and males in equal proportion[61], a slight female predominance has been reported[62] partly reflecting the variable penetrance of genetic mutations that cause this disease. More significantly, however, neurological symptoms have been more frequently associated with female gender ($P = 0.051$) and with an acute, often fulminant course upon presentation when there is hepatic involvement ($P = 0.046$)[63]. In a French study analyzing medical records of 121 patients who underwent LT for Wilson Disease, male gender, pre-transplant renal insufficiency, non-elective procedure, and neurological indication for LT were significantly associated with poorer survival rate ($P = 0.04$) at univariate analysis. However, none of these factors remained statistically significant on multivariate analysis[64].

Alcohol

Alcohol has been demonstrated to exert a more deleterious effect in women and female animal models with respect to males[65], which can partly be explained by lower levels of gastric alcohol dehydrogenase in females, resulting in lower alcohol threshold for women[66]. Moreover, acute liver injury develops more rapidly and more extensively in women than in men even for a smaller quantity consumed[67]. Ethanol has been demonstrated to increase TNF-α mRNA expression and cause more severe acute liver injury in females[68]. Interestingly, estrogens have a major influence on Kupffer cell reactivity and proinflammatory cytokine production, and this could constitute a major determinant of women's increased risk of alcohol-induced liver disease[69].

Drug-induced liver injury and gender

Different patterns of drug-induced liver damage between males and females have been recognized both in humans[70] as well as in animal models[71]. It has been reported that overall, women have a 1.5- to 1.7-fold greater risk of developing adverse drug reactions than men[72], and a prospective, multicenter study based on intensive pharmacovigilance confirmed a higher risk of acute adverse drug reactions in women *vs* men[73]. Excluding behavioural or dosing differences, there are three main hypotheses regarding the mechanisms behind these differences, including: (1) different pharmacokinetics between females and males; (2) gender-specific hormonal effects or interaction with signalling molecules that may affect drug safety; and (3) differences in aberrant immune response that targets the liver following drug exposure that can result in adverse drug reactions[70]. Gender-based differences that may have an impact on drug pharmacokinetics and subsequent toxicity include differences in gastrointestinal blood flow, gastric acid secretion, relative amount of circulating drug-binding proteins, relative proportions of muscular and adipose tissue, renal blood flow, gender-specific expression of cytochrome P450 (CYP450) isozymes, as well as physiologic and hormonal changes during the menstrual cycle, during pregnancy and after menopause[74].

A study based on World Health Organization-endorsed VigiBase™, the largest and most comprehensive database

on global "Individual Case Safety Reports", analyzed gender and age differences in reporting of drug-induced hepatic failure for a 10-year period (2000-2009). From a total of 6370 reports from 38 countries, and excluding missing gender data in 379 cases, females accounted for 54.03% of cases. The largest proportion of hepatic failure cases corresponded to patients younger than 55 years (42.57%), with a female predominance (56.81%), whereas gender was almost evenly distributed in the group above 55 years of age. Regarding drug types, there was a significant female preponderance in hepatic failure associated with analgesics, antiepileptics, anti-inflammatory and antirrheumatic agents, antidiabetics, and antibacterials for systemic use, whereas males were significantly overrepresented in hepatic failure cases associated with antivirals[75].

Female gender is more frequently associated with paracetamol overdose, which fortunately only in a fraction of patients leads to acute liver injury and acute liver failure; in a study from Iceland analyzing 1913 drug-related poisoning episodes, of which 352 involved paracetamol overdoses, the female/male ratio was 3.0, and the principal age group was 16-25 years. However, amongst those who required hospitalization, 16% were accidental overdoses and there were no gender differences[76].

HCC

In spite of the striking preponderance of male sex amongst patients with HCC, probably estrogens play a very important role in liver carcinogenesis[77] and wild-type vs variant estrogen receptors in the liver accurately predict survival in patients with HCC[78]. If transplant centers maintain the adopted trend of allocating nearly 17%-40% of organs to patients who have HCC[19,79], women, whom are listed for LT less frequently for this indication, will have a reduced access to LT with respect to men, since while men will have theoretically 100% of organs available, women will have to "compete" against men for the remaining organs allocated to non-HCC indications for LT.

Notwithstanding the fact that HCC affects men more frequently, and that previous database studies had found gender disparities favouring men in rates of LT in cohorts of HCC patients only, a recent retrospective US database analysis spanning 10 years and over 40000 patients[80] demonstrated that women with HCC present less often with decompensated liver disease (OR = 0.79, $P < 0.001$), and are more likely to receive invasive HCC treatment, with significantly higher rates of resection across different ethnicities and diagnoses (OR = 1.34 and 1.44, $P < 0.001$). In this study, univariate analysis showed that although women have lower unadjusted rates of LT, disparity resolves after controlling for other clinical and demographic factors[80].

ISSUES OF SIZE AND GENDER IN DONOR-RECIPIENT MATCHING

Liver donor size mismatch has been proposed as partially accountable for the disparity between LT rates between male and female patients[2]. A large study based on the OPTN demonstrated that, controlling for region and blood type, women were 25% less likely to undergo LT in a given month in comparison with men ($P < 0.001$). Including gender within the model increased the OR for this variable to 0.84. Of this 25%, 9% was found to be attributable to MELD score. Stemming from this study, an additional 3% increase in the OR for gender (0.87, $P < 0.001$) is imputable to estimated liver volume (mean estimated liver volume was significantly lower for female patients than for male patients on the LT waiting list, $P < 0.001$), therefore partly explaining gender disparity in LT rates[81]. Henceforth, even after accounting for MELD score and estimated liver size, approximately half of the 25% gender disparity remains unexplained.

In fact, other relevant factors related to survival on the waiting list for LT, such as the metabolic and nutritional status, are not accounted for by the MELD score. Notwithstanding the fact that in general women are characterized by less muscle mass than men, this difference is furthermore often not evaluated nor compensated for with adequate formulas[82]. The standardized triceps skinfold thickness and mid-arm muscular circumference determinations, which are more adequate for evaluation of nutritional status than body mass index in patients with ascites, were found to be lower in female patients[83]. Moreover, in a recent study analyzing pretransplant muscle mass on more than 300 LT recipients, of whom 68% could have been defined as cachectic, in female patients, muscle mass predicted intensive care unit stay, total length of stay, and days of intubation, but did not predict survival after LT (mean follow-up of 2.8 years)[84].

The impact of gender mismatch between donors and recipients on the outcome of LT is still a matter of debate, and may differ amongst deceased-donor LT (DDLT), living-donor LT (LDLT), and pediatric LDLT. Lehner *et al*[85] reported that gender mismatch does not play a role in the outcome of LT. On the contrary, some studies have reported on the negative impact of gender mismatch on graft failure, specifically regarding male recipients who receive grafts from female donors in DDLT[86-89]. Furthermore, a recently published prospective study analyzing outcomes of 1042 LT recipients demonstrated that graft survival in patients who received an organ matched for their gender was better than those receiving a gender mismatch ($P = 0.047$), and the worst combination was female-to-male LT ($P < 0.001$)[90].

Regarding LDLT, a male recipient receiving a graft from a female donor was shown to be an independent risk factor for recipient mortality in adults[91], while in pediatric LDLT, an interesting finding has been that recipients of maternal grafts have reportedly lower rates of graft failure and refractory rejection in contrast with recipients of paternal grafts[92]. In the specific setting of HCV infection, no difference has been observed in terms of graft nor patient survival according to donor-recipient gender matching[93].

Being smaller, female patients have a limited access to the pool of available organs, and may have to wait longer for organs of an appropriate size, since livers from

pediatric donors are preferentially allocated to children awaiting LT. Further increasing this disparity is the fact that a small organ may be adequate for a large individual, but the contrary is not always possible[2].

Interestingly, a Japanese study analyzing 114 LDLT using parental grafts performed for recipients with biliary atresia demonstrated that gender mismatch alone was an independent risk factor for acute cellular rejection (P = 0.012), and paternal grafts with gender mismatch were associated with a higher incidence of acute cellular rejection with respect to maternal grafts with gender match (P = 0.002)[94]. The authors infer that maternal antigens may have an important clinical impact on graft tolerance in LDLT, which is in line with what was first hypothesized by Starzl *et al*[95] regarding induction of tolerance by microchimerism, and what has been demonstrated regarding non-inherited maternal antigens and maternal microchimerism in blood and various organs[96,97]. Exposure to maternal antigens, in fact, may have tolerogenic effects on offspring, resulting in acceptance or rejection of allografts expressing the maternal antigens[98], although a functional linkage between microchimerism and tolerance has been difficult to establish[99,100].

Another factor that might play a relevant role in gender-matching is the different hormonal array regarding estrogens (and their receptors). Female-to-female matched LT have been associated with a decreased risk of graft failure with respect to male-male matched transplants, but only for non-HCV female recipients[86]. In animal models, a greater degree of hepatic lactic acidosis during warm ischemia has been demonstrated to occur in females with respect to males[101], which may provide a potential metabolic explanation for the worse outcome in recipients of female donors. However, the matter entails complex aspects that have not yet been fully understood, and this is reflected by the disparity in reports on the role of estrogens in ischemia-reperfusion[102-105]. Apparently, females are more susceptible to hepatic reperfusion injury, but experimental data in the mouse model have shown that estrogens actually reduce ischemia/reperfusion damage[106]. The mechanisms for sex differences in the liver's metabolic response to ischemia do seem, however, to be estrogen-mediated, even in the presence of male hormones[107].

However, again, not all of these differences may be attributable to hormone status solely, but may actually represent an immunological basis. Late-presenting nonanastomotic biliary strictures after LT have been reported to occur more frequently in female-male gender donor-recipient matches, as well as in patients transplanted for primary sclerosing cholangitis, and in patients in whom Roux-en-Y bile duct reconstructions were performed[108], and while ischemia and preservation factors seem to play a preponderant role in early-presenting non-anastomotic biliary strictures, immunological factors are the predominant factor in late-presenting non-anastomotic biliary structures. Interestingly, the fact that immunological processes are implied, does not rule out the fact that still poorly understood linkages between hormones, hormonal receptor, and immunological mechanisms exist.

OUTCOMES AFTER LIVER TRANSPLANTATION IN FEMALE RECIPIENTS

Overall outcomes after LT, especially in the long-term, are reportedly better in women[24] with respect to men. A 20-year follow-up study of 313 LT recipients revealed that, together with primary indication (P < 0.001), age (P < 0.001), impaired renal function at 6 mo (P < 0.001) and retransplantation (P = 0.034), gender (P = 0.017) had a significant impact on patient survival[109]. The reported protective effect of female gender in the development of metabolic complications related to hyperglycemia[109] has been confirmed in other series as well; a study based on the OPTN/United Network Sharing (UNOS) database including 19582 DDLT non-diabetic recipients (in whom the incidence of new-onset diabetes after transplantation (NODAT) has been established to be greater with respect to LDLT recipients), demonstrated that male sex was a predictor for NODAT, while this was not the case for LDLT recipients[110].

After LT, de novo NASH or non-alcoholic fatty liver disease (NAFLD) reportedly develop in 20% and 10% of cases, respectively[92], while approximately 50% of patients transplanted for NASH will experience recurrence[90], with 5% to 10% of patients progressing to cirrhosis[91]. Importantly, menopausal status, which is associated with weight gain and increased central fat mass[111], constitutes a risk factor for developing NASH and metabolic syndrome; in a long-term observational study spanning 12 years, metabolic syndrome was a significant risk factor for mortality in postmenopausal women compared to men and premenopausal women[93].

Regarding renal function, as mentioned above, in a recent study, female gender was found to be an independent and significant predictor of advanced stages of CKD at 1 year post-LT (OR = 2.96, P < 0.001) and at 5 years post-LT (OR = 2.52, P = 0.004)[45], and results from the MOST study had revealed that 1-year GFR is significantly affected both by HCV infection and recipient female gender (P < 0.01 for both)[112].

The impact of gender on outcomes after LT varies according to the indication for LT. Along with recurrent HCC (P < 0.001) and retransplantation (P = 0.01), female gender (P = 0.002) has been significantly associated with worse survival after LT for Hepatitis B, as shown in a multicener US study pooling 738 LT recipients[113]. Concerning HCV, post-LT recurrence is nearly universal[114-116], and female gender has been described as a risk factor for severe HCV recurrence and graft lost after LT, and the risk increases with increasing donor age[86,117,118]. The important fibrosis suppression effect of estrogens demonstrated experimentally in animal models[119,120] is reflected in the clinically slower fibrosis progression observed in women with respect to men in chronic HCV[121,122]. However, most LT female recipients are post-menopausal, and the lower estrogenic levels associated with this state have been clinically associated with higher degrees of fibrosis[30,123]. Although in immune-

competent HCV-infected women menopause is per se frequently associated with steatosis, which is an important cofactor for disease progression[118,124], another hypothesis is that women who require LT are the ones with genetic, virological and immunological factors that determine a more severe course of HCV-related disease, leading to LT, which in turn progresses more rapidly after LT[117]. Moreover, female gender has been shown to be an independent negative prognostic factor for the outcome of HCV antiviral therapy after LT[125]. Although male and female patients did not differ in HCV viral load, histology, or rate of diabetes at baseline, SVR was significantly lower in females than in males (29.5% *vs* 42.1%; $P = 0.03$). Partly explaining this unfavorable response rate, the authors found that compliance to therapy was also significantly lower in women with respect to men (43.4% *vs* 23.8%; $P = 0.001$), and that anemia was the main reason for lower adherence. On multivariate analysis, female gender ($P < 0.04$), early virological response ($P < 0.0001$), and adherence to therapy ($P < 0.0001$) were independent predictors for SVR[126].

SPECIAL ISSUES REGARDING LIVER TRANSPLANTATION AND GENDER

Bone metabolism

Immunosuppressive medication is a major contributor to osteoporosis in the post transplant period[127,128], and post-menopausal women are at higher risk for developing osteoporosis compared to women in the fertile age, as a consequence of decreased serum estrogen levels[129]. The predominant deleterious effects of steroids on bone metabolism include reduced bone formation by decreasing osteoblast replication and differentiation, and increased apoptosis[130,131]. Among calcineurin inhibitors, cyclosporine has increase bone turnover[132], whereas tacrolimus may cause less bone loss[133,134]. A prospective study evaluated 23 women who underwent LT, of whom 13% were peri-menopausal and 56.5% were post-menopausal, finding that in peri- and post-menopausal women, an inferior bone mass was observed in 81.2% of patients: of whom 50% diagnosed with having low bone mass and 31.2% with osteoporosis. Moreover, the postmenopausal stage was significantly associated with a decreased bone mass ($P < 0.0001$)[135].

Risk of de novo malignancy

Aside from the risks concerning bone disease, immunosuppression increases the probability of de novo tumors[136-138]; in a multicentric Italian study showed that the risk for some types of tumors was particularly and significantly higher in women, specifically carcinomas of tongue, all tumors of the oral cavity, and head/neck cancers[139]. In contrast, a smaller study analyzing predictors of de novo malignancies in 534 LT recipients, did not find gender to play a role[140].

Sexual life, fertility and pregnancy

Reproductive function is often severely compromised in women with advanced liver disease, and is frequently characterized by menstrual irregularity, amenorrhea, and infertility in nearly half of patients[141,142]. Etiologies of chronic liver disease which more frequently affect female patients, such as autoimmune hepatitis, may worsen during the course of pregnancy, as most diseases of autoimmune origin, with flares of disease activity reported in 7%-21% and 11%-86% of women during the gestational period and during the post-partum period, respectively[141,143-146]. Although maternal outcomes are generally favorable, pregnancy has been reportedly the trigger for hepatic decompensation (leading to LT in some cases) and maternal death (including liver-related death), with fetal outcomes which are lower than those of the general population, but comparable to those of other autoimmune diseases[141,143-147]. In the study by Westbrook and collaborators[147], of 81 pregnancies in 53 autoimmune hepatitis patients, 41% took place in the context of cirrhosis, and live birth rate was significantly lower within this category. Furthermore, a serious maternal adverse event (death or need for LT) during or within 12-mo of delivery, or hepatic decompensation during or within 3-mo of delivery, occurred with 9 pregnancies (11%) and was more common in women with cirrhosis ($P = 0.028$), and patients who experienced a flare in association with pregnancy were more likely to develop hepatic decompensation ($P = 0.01$)[147]. As flares are more frequent in patients who are not on therapy or who have had a disease flare in the year prior to conception and, pre-conception counselling and adequate gestational management are paramount.

In general, an elevated percentage of women are sexually active after LT[148,149]. Approximately 70% of transplant recipients in a study from Brazil were reportedly sexually active after a median of 36 mo after successful LT[150], whereas decreased libido and difficulty to reach orgasm with intercourse has been described in 26% of female LT recipients[151]. Successful LT restores menstrual function in 97% of female patients, as well as childbearing potential[152-154]. In general, LT leads to partial or complete normalization of both levels of sex hormones and sexual function within several months of LT[155], with nearly 48% of women in their fertile age experiencing regular menses, 26% irregular bleeding, and 26% amenorrhea[153], while more than 60% of peri-menopausal women reportedly experience a higher frequency of menstrual pattern disorders[156]. In the United States only, approximately 14000 women of childbearing age are currently LT recipients, and another 500 women will undergo LT annually[24]. The optimal timing of conception is still a matter of debate, but waiting at least 1 year after LT is generally recommended[157]. Regarding immunosuppression, calcineurin inhibitors and steroids can be used safely, while azathioprine and mycophenolate mofetil have been associated with increased toxic effects[158]. Pregnancy outcomes after LT are acceptable in terms of the health of the mother and of the newborn[159], and reportedly better in comparison to those obtained after kidney transplantation, with significantly lower rates of hypertension, preeclampsia, preterm

Table 1 Key points

Several factors contribute to the unequal access to liver transplantation that penalizes women, including inadequacy of MELD score in accounting for renal dysfunction in females, the limitation of MELD score in reflecting the actual severity of liver disease and associated complications in certain clinical conditions that are more frequent in women, and the centers' increasing prevalence of policies that favor transplantation for hepatocellular carcinoma, which is more frequent in males
Different etiologies of liver disease follow a characteristic pattern of gender-related frequency, natural evolution, and response to treatment, partly owing to socioepidemiological factors as well as to phenotypical differences regarding enzymatic activity and hormonal status
Within the female population, a clear difference exists between the pre- and the post-menopausal stages, and after this turning point, the protective effect of estrogens on slowing fibrosis progression, amongst others, is lost, causing an acceleration of hepatic injury, a detrimental response to therapy, and the potential establishment of a new set of complications associated with altered fat and bone metabolism
Although long-term overall outcomes after liver transplantation are better in women, certain conditions such as renal dysfunction, hepatocellular carcinoma as an indication for transplant and recurrent hepatitis C infection are associated with worse prognosis in women with respect to men
In spite fertility and sexual activity may be curbed in advanced cirrhosis, there are numerous reports of unaffected pregnancies in this stage, while successful liver transplantation restores fertility and sexual activity in most patients, with pregnancy outcomes which are reportedly better in comparison to those obtained after kidney transplantation

MELD: Model for end-stage liver disease.

deliveries, and birth of neonates small for their gestational age[160].

In a study from Vienna assessing 39 deliveries and 40 live births[161], the mean time from organ transplantation to delivery was 67.6 ± 47.2 mo. A meta-analysis on 450 pregnancies in 306 LT recipients showed that although the rates of pre-eclampsia (21.9%), caesarean section delivery (44.6%), and preterm delivery (39.4%) were higher than the rates for the US general population (3.8%, 31.9%, and 12.5%, respectively), the post-LT live birth rate (76.9%) was higher than the live birth rate for the US general population (66.7%), and the post-LT miscarriage rate (15.6%) was lower than the miscarriage rate for the general population (17.1%)[162].

Quality of life after liver transplantation

In a German cross-sectional, single-center study evaluating the quality of life in 281 LT recipients[163], similar results were observed between male and female subjects, whereas in another study analyzing gender differences after HCV-related LT, however, it emerged that male subjects score significantly higher on physical role functioning and physical activity compared with females, whereas women had reportedly better quality of life compared to males with regard to the emotional state and mental health 1-year after LT[164].

CONCLUSION

Important gender differences exist regarding etiologies of liver disease, severity of the course of these diseases, and on outcomes after LT. Unfortunately, access to LT is still governed by an imperfect allocation system, currently based on MELD score, which includes systematic biases against women, and is also hampered by factors that are not adequately taken into account by MELD score, doubly penalizing female gender. A delayed access to LT wait-listing and subsequently to LT due to renal dysfunction underestimation, is a determinant factor that has an impact on post-transplant renal function as well. Being generally smaller than men, organ allocation decisions generally favor children as recipients of small organs, and men as recipients of large organs, conditioning a longer waiting time for an organ in adult women.

Throughout a women's life, profound hormonal changes also determine the natural course of diseases; while estrogens may protect against inflammation and fibrosis during the fertile age, the post status takes a high toll on disease progression both before and after LT, and may be further complicated by obesity, NASH, NAFLD, and other components of the metabolic syndrome. The above are summarized in Table 1 (Key points). It is therefore ever clearer that special attention should be paid to the integral management of women during the different life periods, and with respect to special situations regarding natural evolution and risk factors for liver disease, as well as to those affecting post-transplant outcome.

ACKNOWLEDGMENTS

The authors would like to acknowledge all members of Women in Hepatology Group: Erica Villa, Modena, Italy (Chair); Anna Alisi, Rome, Italy; Clara Balsano, Rome, Italy; Veronica Bernabucci, Modena, Italy; Annalisa Berselli, Modena, Italy; Annalisa Berzigotti, Barcelona, Spain/ Bologna, Italy; Elena Bertolini, Modena Italy; Maurizia Brunetto, Pisa Italy; Elisabetta Bugianesi, Turin, Italy; Patrizia Burra, Padua, Italy; Vincenza Calvaruso, Palermo Italy; Elisabetta Cariani, Modena Italy; Alessia Ciancio, Turin, Italy; Barbara Coco, Pisa, Italy; Isabelle Colle, Bruxelles, Belgium; Eleonora De Martin, Padua, Italy; Mariagrazia Del Buono, Modena, Italy; Giovanna Fattovich, Verona, Italy; Annarosa Floreani, Padua, Italy; Guadalupe Garcia-Tsao, New Haven, United States; Chantal Housset, Paris, France; Aimilia Karampatou, Modena, Italy; Barbara Lei, Modena, Italy; Anna Licata, Palermo, Italy; Alessandra Mangia, San Giovanni Rotondo, Italy; Maria Luz Martinez-Chantar, Bilbao, Spain; Filomena Morisco, Naples, Italy; Paola Nasta, Brescia, Italy; Tomris Ozben, Antalya, Turkey; Teresa Pollicino, Messina, Italy; Maria Laura Ponti, Cagliari, Italy; Patrizia Pontisso, Padua, Italy; Helen Reeves, Newcasatle, United Kingdom; Maria Rendina, Bari, Italy;

Kryssia I Rodríguez-Castro, Padua, Italy; Caterina Sagnelli, Salerno, Italy; Teresa Santantonio, Foggia, Italy; Giada Sebastiani, Venice, Italy; Antonella Smedile, Turin, Italy; Gloria Taliani, Rome, Italy; Carmen Vandelli, Modena, Italy; Ranka Vukotic, Modena, Italy; Anna Linda Zignego, Florence, Italy.

REFERENCES

1 **Bryce CL**, Angus DC, Arnold RM, Chang CC, Farrell MH, Manzarbeitia C, Marino IR, Roberts MS. Sociodemographic differences in early access to liver transplantation services. *Am J Transplant* 2009; **9**: 2092-2101 [PMID: 19645706 DOI: 10.1111/j.1600-6143.2009.02737.x]

2 **Axelrod DA**, Pomfret EA. Race and sex disparities in liver transplantation: progress toward achieving equal access? *JAMA* 2008; **300**: 2425-2426 [PMID: 19033595 DOI: 10.1001/jama.2008.732]

3 **Klassen AC**, Klassen DK, Brookmeyer R, Frank RG, Marconi K. Factors influencing waiting time and successful receipt of cadaveric liver transplant in the United States, 1990 to 1992. *Med Care* 1998; **36**: 281-294 [PMID: 9520954]

4 **Moylan CA**, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. *JAMA* 2008; **300**: 2371-2378 [PMID: 19033587 DOI: 10.1001/jama.2008.720]

5 **Mathur AK**, Schaubel DE, Gong Q, Guidinger MK, Merion RM. Sex-based disparities in liver transplant rates in the United States. *Am J Transplant* 2011; **11**: 1435-1443 [PMID: 21718440 DOI: 10.1111/j.1600-6143.2011.03498.x]

6 **Fink MA**, Berry SR, Gow PJ, Angus PW, Wang BZ, Muralidharan V, Christophi C, Jones RM. Risk factors for liver transplantation waiting list mortality. *J Gastroenterol Hepatol* 2007; **22**: 119-124 [PMID: 17201891 DOI: 10.1111/j.1440-1746.2006.04422.x]

7 **Myers RP**, Shaheen AA, Aspinall AI, Quinn RR, Burak KW. Gender, renal function, and outcomes on the liver transplant waiting list: assessment of revised MELD including estimated glomerular filtration rate. *J Hepatol* 2011; **54**: 462-470 [PMID: 21109324 DOI: 10.1016/j.jhep.2010.07.015]

8 **Mariante-Neto G**, Marroni CP, Fleck Junior AM, Marroni CA, Zanotelli ML, Cantisani G, Brandão AB. Impact of creatinine values on MELD scores in male and female candidates for liver transplantation. *Ann Hepatol* 2013; **12**: 434-439 [PMID: 23619260]

9 **Wiesner RH**. Patient selection in an era of donor liver shortage: current US policy. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 24-30 [PMID: 16265097 DOI: 10.1038/ncpgasthep0070]

10 **Leuschner U**. Primary biliary cirrhosis--presentation and diagnosis. *Clin Liver Dis* 2003; **7**: 741-758 [PMID: 14594129]

11 **Mela M**, Mancuso A, Burroughs AK. Review article: pruritus in cholestatic and other liver diseases. *Aliment Pharmacol Ther* 2003; **17**: 857-870 [PMID: 12656688]

12 **Levy C**, Lindor KD. Management of Primary Biliary Cirrhosis. *Curr Treat Options Gastroenterol* 2003; **6**: 493-498 [PMID: 14585238]

13 **Freeman RB**, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl* 2002; **8**: 851-858 [PMID: 12200791 DOI: 10.1053/jlts.2002.35927]

14 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

15 **Figueras J**, Jaurrieta E, Valls C, Ramos E, Serrano T, Rafecas A, Fabregat J, Torras J. Resection or transplantation for hepatocellular carcinoma in cirrhotic patients: outcomes based on indicated treatment strategy. *J Am Coll Surg* 2000; **190**: 580-587 [PMID: 10801025]

16 **Pomfret EA**, Washburn K, Wald C, Nalesnik MA, Douglas D, Russo M, Roberts J, Reich DJ, Schwartz ME, Mieles L, Lee FT, Florman S, Yao F, Harper A, Edwards E, Freeman R, Lake J. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. *Liver Transpl* 2010; **16**: 262-278 [PMID: 20209641 DOI: 10.1002/lt.21999]

17 **Llovet JM**, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; **30**: 1434-1440 [PMID: 10573522 DOI: 10.1002/hep.510300629]

18 **Liver allocation policy.** Last accessed March 2014. Available from: URL: http: //optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/ policy_8.pdf. 2012

19 **Adam R**, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012; **57**: 675-688 [PMID: 22609307 DOI: 10.1016/j.jhep.2012.04.015]

20 **Sharma P**, Balan V, Hernandez JL, Harper AM, Edwards EB, Rodriguez-Luna H, Byrne T, Vargas HE, Mulligan D, Rakela J, Wiesner RH. Liver transplantation for hepatocellular carcinoma: the MELD impact. *Liver Transpl* 2004; **10**: 36-41 [PMID: 14755775 DOI: 10.1002/lt.20012]

21 **Washburn K**, Edwards E, Harper A, Freeman R. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. *Am J Transplant* 2010; **10**: 1643-1648 [PMID: 20486906 DOI: 10.1111/j.1600-6143.2010.03127.x]

22 **Volk ML**. Unfair priority for HCC: A problem whose ideal solution remains unsolved. *Am J Transplant* 2010; **10**: 1507-1508 [PMID: 20642675 DOI: 10.1111/j.1600-6143.2010.03154.x]

23 **Mindikoglu AL**, Regev A, Seliger SL, Magder LS. Gender disparity in liver transplant waiting-list mortality: the importance of kidney function. *Liver Transpl* 2010; **16**: 1147-1157 [PMID: 20879013 DOI: 10.1002/lt.22121]

24 **Liver transplantation between 1988 and 2013 in the United States.** Last accessed February 2014. Available from: URL: http: //optn.transplan.hrsa.gov/latestData/rptData.asp

25 **Barrett S**, Goh J, Coughlan B, Ryan E, Stewart S, Cockram A, O'Keane JC, Crowe J. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: spontaneous viral clearance and chronic HCV infection. *Gut* 2001; **49**: 423-430 [PMID: 11511566]

26 **Pagliaro L**, Peri V, Linea C, Cammà C, Giunta M, Magrin S. Natural history of chronic hepatitis C. *Ital J Gastroenterol Hepatol* 1999; **31**: 28-44 [PMID: 10091101]

27 **Burra P**, De Martin E, Gitto S, Villa E. Influence of age and gender before and after liver transplantation. *Liver Transpl* 2013; **19**: 122-134 [PMID: 23172830 DOI: 10.1002/lt.23574]

28 **De Martin E**, Rodriguez-Castro K, Gambato M, Villa E, Burra P. (2014) Women after Liver Transplantation. *Organs, Tissues and Cells* 2014; In press

29 **Leone N**, Rizzetto M. Natural history of hepatitis C virus infection: from chronic hepatitis to cirrhosis, to hepatocellular carcinoma. *Minerva Gastroenterol Dietol* 2005; **51**: 31-46 [PMID: 15756144]

30 **Di Martino V**, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, Moussalli J, Thabut D, Buffet C, Poynard T. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. *Hepatology* 2004; **40**: 1426-1433 [PMID: 15565616 DOI: 10.1002/hep.20463]

31 **Villa E**, Karampatou A, Cammà C, Di Leo A, Luongo M, Ferrari A, Petta S, Losi L, Taliani G, Trande P, Lei B, Graziosi A, Bernabucci V, Critelli R, Pazienza P, Rendina M, Antonelli

A, Francavilla A. Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. *Gastroenterology* 2011; **140**: 818-829 [PMID: 21167831 DOI: 10.1053/j.gastro.2010.12.027]
32 **Villa E**, Vukotic R, Cammà C, Petta S, Di Leo A, Gitto S, Turola E, Karampatou A, Losi L, Bernabucci V, Cenci A, Tagliavini S, Baraldi E, De Maria N, Gelmini R, Bertolini E, Rendina M, Francavilla A. Reproductive status is associated with the severity of fibrosis in women with hepatitis C. *PLoS One* 2012; **7**: e44624 [PMID: 22970270 DOI: 10.1371/journal.pone.0044624]
33 **Neuman MG**, Benhamou JP, Malkiewicz IM, Akremi R, Shear NH, Asselah T, Ibrahim A, Boyer N, Martinot-Peignoux M, Jacobson-Brown P, Katz GG, Le Breton V, Le Guludec G, Suneja A, Marcellin P. Cytokines as predictors for sustained response and as markers for immunomodulation in patients with chronic hepatitis C. *Clin Biochem* 2001; **34**: 173-182 [PMID: 11408014]
34 **Villa E**, Cammà C, Di Leo A, Karampatou A, Enea M, Gitto S, Bernabucci V, Losi L, De Maria N, Lei B, Ferrari A, Vukotic R, Vignoli P, Rendina M, Francavilla A. Peginterferon-A_2B plus ribavirin is more effective than peginterferon-A_2A plus ribavirin in menopausal women with chronic hepatitis C. *J Viral Hepat* 2012; **19**: 640-649 [PMID: 22863268 DOI: 10.1111/j.1365-2893.2012.01593.x]
35 **Rifai K**, Hadem J, Wiegand J, Potthoff A, Pischke S, Klempnauer J, Strassburg C, Wedemeyer H, Manns MP, Tillmann HL. Gender differences in patient receiving liver transplantation for viral hepatitis. *Z Gastroenterol* 2012; **50**: 760-765 [PMID: 22895904 DOI: 10.1055/s-0031-1281631]
36 **Khuroo MS**, Teli MR, Skidmore S, Sofi MA, Khuroo MI. Incidence and severity of viral hepatitis in pregnancy. *Am J Med* 1981; **70**: 252-255 [PMID: 6781338]
37 **Ramalingaswami V**, Purcell RH. Waterborne non-A, non-B hepatitis. *Lancet* 1988; **1**: 571-573 [PMID: 2894501]
38 **Tsega E**, Krawczynski K, Hansson BG, Nordenfelt E. Hepatitis E virus infection in pregnancy in Ethiopia. *Ethiop Med J* 1993; **31**: 173-181 [PMID: 8404882]
39 **Mateos Lindemann ML**, Morales JG, Fernández-Barredo S, Domínguez MR, García de la Hoz F, Halfon P, Pérez Gracia MT. Fulminant hepatitis E in a woman taking oral contraceptive medication. *Am J Trop Med Hyg* 2010; **82**: 12-15 [PMID: 20064988 DOI: 10.4269/ajtmh.2010.09-0436]
40 **United Network for Organ Sharing**. Last accessed February 2014. Available from: URL: http: //optn.transplant.hrsa.gov/latestData/rptData.asp.2014
41 **European Liver Transplant Registry.** Last accessed February 2014. Available from: URL: http: //www.eltr.org/spip.php?article161
42 **Charlton M**. Nonalcoholic fatty liver disease: a review of current understanding and future impact. *Clin Gastroenterol Hepatol* 2004; **2**: 1048-1058 [PMID: 15625647]
43 **Loomba R**, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 686-690 [PMID: 24042449 DOI: 10.1038/nrgastro.2013.171]
44 **Park CW**, Tsai NT, Wong LL. Implications of worse renal dysfunction and medical comorbidities in patients with NASH undergoing liver transplant evaluation: impact on MELD and more. *Clin Transplant* 2011; **25**: E606-E611 [PMID: 21958082 DOI: 10.1111/j.1399-0012.2011.01497.x]
45 **Fussner LA,** Charlton MR, Heimbach JK, Fan C, Dierkhising R, Coss E, Watt KD. The impact of gender and NASH on chronic kidney disease before and after liver transplantation. *Liver Int* 2013; **34**: 1259-1266 [PMID: 24262002]
46 **Amadori A**, Zamarchi R, De Silvestro G, Forza G, Cavatton G, Danieli GA, Clementi M, Chieco-Bianchi L. Genetic control of the CD4/CD8 T-cell ratio in humans. *Nat Med* 1995; **1**: 1279-1283 [PMID: 7489409]
47 **Gilmore W**, Weiner LP, Correale J. Effect of estradiol on cytokine secretion by proteolipid protein-specific T cell clones isolated from multiple sclerosis patients and normal control subjects. *J Immunol* 1997; **158**: 446-451 [PMID: 8977221]
48 **Araneo BA**, Dowell T, Diegel M, Daynes RA. Dihydrotestosterone exerts a depressive influence on the production of interleukin-4 (IL-4), IL-5, and gamma-interferon, but not IL-2 by activated murine T cells. *Blood* 1991; **78**: 688-699 [PMID: 1830499]
49 **Manns MP**, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; **51**: 2193-2213 [PMID: 20513004 DOI: 10.1002/hep.23584]
50 **Miyake Y**, Iwasaki Y, Sakaguchi K, Shiratori Y. Clinical features of Japanese male patients with type 1 autoimmune hepatitis. *Aliment Pharmacol Ther* 2006; **24**: 519-523 [PMID: 16886918 DOI: 10.1111/j.1365-2036.2006.03013.x]
51 **Al-Chalabi T**, Underhill JA, Portmann BC, McFarlane IG, Heneghan MA. Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis. *J Hepatol* 2008; **48**: 140-147 [PMID: 18023911 DOI: 10.1016/j.jhep.2007.08.013]
52 **Nalbandian G**, Van de Water J, Gish R, Manns M, Coppel RL, Rudich SM, Prindiville T, Gershwin ME. Is there a serological difference between men and women with primary biliary cirrhosis? *Am J Gastroenterol* 1999; **94**: 2482-2486 [PMID: 10484012 DOI: 10.1111/j.1572-0241.1999.01380.x]
53 **Kim WR**, Lindor KD, Locke GR, Therneau TM, Homburger HA, Batts KP, Yawn BP, Petz JL, Melton LJ, Dickson ER. Epidemiology and natural history of primary biliary cirrhosis in a US community. *Gastroenterology* 2000; **119**: 1631-1636 [PMID: 11113084]
54 **Rubel LR**, Rabin L, Seeff LB, Licht H, Cuccherini BA. Does primary biliary cirrhosis in men differ from primary biliary cirrhosis in women? *Hepatology* 1984; **4**: 671-677 [PMID: 6745856]
55 **Newton JL**, Davidson A, Kerr S, Bhala N, Pairman J, Burt J, Jones DE. Autonomic dysfunction in primary biliary cirrhosis correlates with fatigue severity. *Eur J Gastroenterol Hepatol* 2007; **19**: 125-132 [PMID: 17272997 DOI: 10.1097/01.meg.0000252629.96043.67]
56 **Newton JL**, Hudson M, Tachtatzis P, Sutcliffe K, Pairman J, Burt JA, Jones DE. Population prevalence and symptom associations of autonomic dysfunction in primary biliary cirrhosis. *Hepatology* 2007; **45**: 1496-1505 [PMID: 17538969 DOI: 10.1002/hep.21609]
57 **Levy C**, Naik J, Giordano C, Mandalia A, O'Brien C, Bhamidimarri KR, Schiff ER, Martin P. Hispanics with primary biliary cirrhosis are more likely to have features of autoimmune hepatitis and reduced response to ursodeoxycholic acid than non-Hispanics. *Clin Gastroenterol Hepatol* 2014; **12**: 1398-1405 [PMID: 24361417 DOI: 10.1016/j.cgh.2013.12.010]
58 **Lucey MR**, Neuberger JM, Williams R. Primary biliary cirrhosis in men. *Gut* 1986; **27**: 1373-1376 [PMID: 3792920]
59 **Floreani A**, Mega A, Camozzi V, Baldo V, Plebani M, Burra P, Luisetto G. Is osteoporosis a peculiar association with primary biliary cirrhosis? *World J Gastroenterol* 2005; **11**: 5347-5350 [PMID: 16149144]
60 **Rudic JS**, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Hormone replacement for osteoporosis in women with primary biliary cirrhosis. *Cochrane Database Syst Rev* 2011; (**12**): CD009146 [PMID: 22161447 DOI: 10.1002/14651858.CD009146.pub2]
61 **Scheinberg IH**. Wilson's disease. *J Rheumatol Suppl* 1981; **7**: 90-93 [PMID: 6939890]
62 **Rodrigo Agudo JL**, Valdés Mas M, Vargas Acosta AM, Ortiz Sánchez ML, Gil del Castillo ML, Carballo Alvarez LF, Pons Miñano JA. [Clinical presentation, diagnosis, and long-term outcome of 29 patients with Wilson's disease]. *Rev Esp Enferm Dig* 2008; **100**: 456-461 [PMID: 18942896]
63 **Bruha R**, Marecek Z, Pospisilova L, Nevsimalova S, Vitek L, Martasek P, Nevoral J, Petrtyl J, Urbanek P, Jiraskova A, Ferenci P. Long-term follow-up of Wilson disease: natural history, treatment, mutations analysis and phenotypic correlation. *Liver Int* 2011; **31**: 83-91 [PMID: 20958917 DOI: 10.1111/j.1478-3231.2010.02354.x]

64 **Guillaud O**, Dumortier J, Sobesky R, Debray D, Wolf P, Vanlemmens C, Durand F, Calmus Y, Duvoux C, Dharancy S, Kamar N, Boudjema K, Bernard PH, Pageaux GP, Salamé E, Gugenheim J, Lachaux A, Habes D, Radenne S, Hardwigsen J, Chazouillères O, Trocello JM, Woimant F, Ichai P, Branchereau S, Soubrane O, Castaing D, Jacquemin E, Samuel D, Duclos-Vallée JC. Long term results of liver transplantation for Wilson's disease: experience in France. *J Hepatol* 2014; **60**: 579-589 [PMID: 24211743 DOI: 10.1016/j.jhep.2013.10.025]

65 **Meier Y**, Cavallaro M, Roos M, Pauli-Magnus C, Folkers G, Meier PJ, Fattinger K. Incidence of drug-induced liver injury in medical inpatients. *Eur J Clin Pharmacol* 2005; **61**: 135-143 [PMID: 15726344 DOI: 10.1007/s00228-004-0888-z]

66 **Soldin OP**, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2009; **48**: 143-157 [PMID: 19385708 DOI: 10.2165/00003088-200948030-00001]

67 **Thurman RG**. Sex-related liver injury due to alcohol involves activation of Kupffer cells by endotoxin. *Can J Gastroenterol* 2000; **14** Suppl D: 129D-135D [PMID: 11110625]

68 **Kono H**, Wheeler MD, Rusyn I, Lin M, Seabra V, Rivera CA, Bradford BU, Forman DT, Thurman RG. Gender differences in early alcohol-induced liver injury: role of CD14, NF-kappaB, and TNF-alpha. *Am J Physiol Gastrointest Liver Physiol* 2000; **278**: G652-G661 [PMID: 10762620]

69 **Müller C**. Liver, alcohol and gender. *Wien Med Wochenschr* 2006; **156**: 523-526 [PMID: 17103288 DOI: 10.1007/s10354-006-0348-8]

70 **Amacher DE.** Female gender as a susceptibility factor for drug-induced liver injury. *Hum Exp Toxicol* 2013; **33**: 928-939 [PMID: 24299907 DOI: 10.1177/0960327113512860]

71 **Sheng Y**, Liang Q, Deng Z, Ji L, Wang Z. Acetaminophen induced gender-dependent liver injury and the involvement of GCL and GPx. *Drug Discov Ther* 2013; **7**: 78-83 [PMID: 23715506]

72 **Rademaker M**. Do women have more adverse drug reactions? *Am J Clin Dermatol* 2001; **2**: 349-351 [PMID: 11770389]

73 **Zopf Y**, Rabe C, Neubert A, Gassmann KG, Rascher W, Hahn EG, Brune K, Dormann H. Women encounter ADRs more often than do men. *Eur J Clin Pharmacol* 2008; **64**: 999-1004 [PMID: 18604529 DOI: 10.1007/s00228-008-0494-6]

74 **Fletcher CV**, Acosta EP, Strykowski JM. Gender differences in human pharmacokinetics and pharmacodynamics. *J Adolesc Health* 1994; **15**: 619-629 [PMID: 7696281]

75 **Petronijevic M**, Ilic K. Associations of gender and age with the reporting of drug-induced hepatic failure: data from the VigiBase™. *J Clin Pharmacol* 2013; **53**: 435-443 [PMID: 23440959 DOI: 10.1002/jcph.3]

76 **Kjartansdottir I**, Bergmann OM, Arnadottir RS, Björnsson ES. Paracetamol intoxications: a retrospective population-based study in Iceland. *Scand J Gastroenterol* 2012; **47**: 1344-1352 [PMID: 22827594 DOI: 10.3109/00365521.2012.703236]

77 **Villa E**. Role of estrogen in liver cancer. *Womens Health* (Lond Engl) 2008; **4**: 41-50 [PMID: 19072450 DOI: 10.2217/17455057.4.1.41]

78 **Villa E**, Moles A, Ferretti I, Buttafoco P, Grottola A, Del Buono M, De Santis M, Manenti F. Natural history of inoperable hepatocellular carcinoma: estrogen receptors' status in the tumor is the strongest prognostic factor for survival. *Hepatology* 2000; **32**: 233-238 [PMID: 10915729 DOI: 10.1053/jhep.2000.9603]

79 **Liver transplantation for hepatocellular carcinoma**. Last accessed March 2014. Available from: URL: http: //optn.transplant.hrsa.gov/latestData/ rptData.asp

80 **Cauble S**, Abbas A, Balart L, Bazzano L, Medvedev S, Shores N. United States women receive more curative treatment for hepatocellular carcinoma than men. *Dig Dis Sci* 2013; **58**: 2817-2825 [PMID: 23812858 DOI: 10.1007/s10620-013-2731-9]

81 **Mindikoglu AL**, Emre SH, Magder LS. Impact of estimated liver volume and liver weight on gender disparity in liver transplantation. *Liver Transpl* 2013; **19**: 89-95 [PMID: 23008117 DOI: 10.1002/lt.23553]

82 **Yoshizumi T**, Shirabe K, Nakagawara H, Ikegami T, Harimoto N, Toshima T, Yamashita Y, Ikeda T, Soejima Y, Maehara Y. Skeletal muscle area correlates with body surface area in healthy adults. *Hepatol Res* 2014; **44**: 313-318 [PMID: 23607375 DOI: 10.1111/hepr.12119]

83 **Campillo B**, Paillaud E, Uzan I, Merlier I, Abdellaoui M, Perennec J, Louarn F, Bories PN. Value of body mass index in the detection of severe malnutrition: influence of the pathology and changes in anthropometric parameters. *Clin Nutr* 2004; **23**: 551-559 [PMID: 15297091 DOI: 10.1016/j.clnu.2003.10.003]

84 **DiMartini A**, Cruz RJ, Dew MA, Myaskovsky L, Goodpaster B, Fox K, Kim KH, Fontes P. Muscle mass predicts outcomes following liver transplantation. *Liver Transpl* 2013; **19**: 1172-1180 [PMID: 23960026 DOI: 10.1002/lt.23724]

85 **Lehner F**, Becker T, Klempnauer J, Borlak J. Gender-incompatible liver transplantation is not a risk factor for patient survival. *Liver Int* 2009; **29**: 196-202 [PMID: 18673439 DOI: 10.1111/j.1478-3231.2008.01827.x]

86 **Lai JC**, Feng S, Roberts JP, Terrault NA. Gender differences in liver donor quality are predictive of graft loss. *Am J Transplant* 2011; **11**: 296-302 [PMID: 21219572 DOI: 10.1111/j.1600-6143.2010.03385.x]

87 **Rustgi VK**, Marino G, Halpern MT, Johnson LB, Umana WO, Tolleris C. Role of gender and race mismatch and graft failure in patients undergoing liver transplantation. *Liver Transpl* 2002; **8**: 514-518 [PMID: 12037781 DOI: 10.1053/jlts.2002.33457]

88 **Francavilla R**, Hadzic N, Heaton ND, Rela M, Baker AJ, Dhawan A, Mieli-Vergani G. Gender matching and outcome after pediatric liver transplantation. *Transplantation* 1998; **66**: 602-605 [PMID: 9753339]

89 **Brooks BK**, Levy MF, Jennings LW, Abbasoglu O, Vodapally M, Goldstein RM, Husberg BS, Gonwa TA, Klintmalm GB. Influence of donor and recipient gender on the outcome of liver transplantation. *Transplantation* 1996; **62**: 1784-1787 [PMID: 8990363]

90 **Croome KP**, Segal D, Hernandez-Alejandro R, Adams PC, Thomson A, Chandok N. Female donor to male recipient gender discordance results in inferior graft survival: a prospective study of 1,042 liver transplants. *J Hepatobiliary Pancreat Sci* 2014; **21**: 269-274 [PMID: 24123790 DOI: 10.1002/jhbp.40]

91 **Yoshizumi T**, Shirabe K, Taketomi A, Uchiyama H, Harada N, Ijichi H, Yoshimatsu M, Ikegami T, Soejima Y, Maehara Y. Risk factors that increase mortality after living donor liver transplantation. *Transplantation* 2012; **93**: 93-98 [PMID: 22203391 DOI: 10.1097/TP.0b013e318238dacd]

92 **Nijagal A**, Fleck S, Hills NK, Feng S, Tang Q, Kang SM, Rosenthal P, MacKenzie TC. Decreased risk of graft failure with maternal liver transplantation in patients with biliary atresia. *Am J Transplant* 2012; **12**: 409-419 [PMID: 22221561 DOI: 10.1111/j.1600-6143.2011.03895.x]

93 **Grąt M**, Kornasiewicz O, Lewandowski Z, Ligocka J, Grąt K, Wronka KM, Zieniewicz K, Krawczyk M. Post-transplant outcomes of patients with and without hepatitis C virus infection according to donor age and gender matching. *Ann Transplant* 2013; **18**: 705-715 [PMID: 24361968 DOI: 10.12659/AOT.889537]

94 **Sanada Y**, Kawano Y, Miki A, Aida J, Nakamura K, Shimomura N, Ishikawa N, Arai T, Hirata Y, Yamada N, Okada N, Wakiya T, Ihara Y, Urahashi T, Yasuda Y, Takubo K, Mizuta K. Maternal grafts protect daughter recipients from acute cellular rejection after pediatric living donor liver transplantation for biliary atresia. *Transpl Int* 2014; **27**: 383-390 [PMID: 24472036 DOI: 10.1111/tri.12273]

95 **Starzl TE**, Demetris AJ, Trucco M, Ramos H, Zeevi A, Rudert WA, Kocova M, Ricordi C, Ildstad S, Murase N. Systemic chimerism in human female recipients of male livers. *Lancet* 1992; **340**: 876-877 [PMID: 1357298]

96 **Loubière LS**, Lambert NC, Flinn LJ, Erickson TD, Yan Z,

Guthrie KA, Vickers KT, Nelson JL. Maternal microchimerism in healthy adults in lymphocytes, monocyte/macrophages and NK cells. *Lab Invest* 2006; **86**: 1185-1192 [PMID: 16969370 DOI: 10.1038/labinvest.3700471]

97 **Maloney S**, Smith A, Furst DE, Myerson D, Rupert K, Evans PC, Nelson JL. Microchimerism of maternal origin persists into adult life. *J Clin Invest* 1999; **104**: 41-47 [PMID: 10393697 DOI: 10.1172/JCI6611]

98 **Dutta P**, Burlingham WJ. Microchimerism: tolerance vs. sensitization. *Curr Opin Organ Transplant* 2011; **16**: 359-365 [PMID: 21666480 DOI: 10.1097/MOT.0b013e3283484b57]

99 **Bonilla WV**, Geuking MB, Aichele P, Ludewig B, Hengartner H, Zinkernagel RM. Microchimerism maintains deletion of the donor cell-specific CD8+ T cell repertoire. *J Clin Invest* 2006; **116**: 156-162 [PMID: 16395404 DOI: 10.1172/JCI26565]

100 **Burlingham WJ**, Grailer AP, Fechner JH, Kusaka S, Trucco M, Kocova M, Belzer FO, Sollinger HW. Microchimerism linked to cytotoxic T lymphocyte functional unresponsiveness (clonal anergy) in a tolerant renal transplant recipient. *Transplantation* 1995; **59**: 1147-1155 [PMID: 7732562]

101 **Wittnich C**, Belanger MP, Askin N, Boscarino C, Wallen WJ. Lower liver transplant success in females: gender differences in metabolic response to global ischemia. *Transplant Proc* 2004; **36**: 1485-1488 [PMID: 15251365 DOI: 10.1016/j.transproceed.2004.05.055]

102 **Jin B**, Liu CZ, Hu SY, Wang TT, Wang L, Jiang XS, Frezza EE. Influence of estrogen and androgen on the outcome of liver transplantation. *Hepatogastroenterology* 2008; **55**: 207-211 [PMID: 18507108]

103 **Vilatoba M**, Eckstein C, Bilbao G, Frennete L, Eckhoff DE, Contreras JL. 17beta-estradiol differentially activates mitogen-activated protein-kinases and improves survival following reperfusion injury of reduced-size liver in mice. *Transplant Proc* 2005; **37**: 399-403 [PMID: 15808658 DOI: 10.1016/j.transproceed.2004.12.053]

104 **Shen SQ**, Zhang Y, Xiong CL. The protective effects of 17beta-estradiol on hepatic ischemia-reperfusion injury in rat model, associated with regulation of heat-shock protein expression. *J Surg Res* 2007; **140**: 67-76 [PMID: 17336333 DOI: 10.1016/j.jss.2006.10.022]

105 **Harada H**, Pavlick KP, Hines IN, Hoffman JM, Bharwani S, Gray L, Wolf RE, Grisham MB. Selected contribution: Effects of gender on reduced-size liver ischemia and reperfusion injury. *J Appl Physiol* (1985) 2001; **91**: 2816-2822 [PMID: 11717250]

106 **Eckhoff DE**, Bilbao G, Frenette L, Thompson JA, Contreras JL. 17-Beta-estradiol protects the liver against warm ischemia/reperfusion injury and is associated with increased serum nitric oxide and decreased tumor necrosis factor-alpha. *Surgery* 2002; **132**: 302-309 [PMID: 12219027]

107 **Soric S**, Belanger MP, Askin N, Wittnich C. Impact of female sex hormones on liver tissue lactic acidosis during ischemia. *Transplantation* 2007; **84**: 763-770 [PMID: 17893610 DOI: 10.1097/01.tp.0000280542.61123.ec]

108 **Buis CI**, Verdonk RC, Van der Jagt EJ, van der Hilst CS, Slooff MJ, Haagsma EB, Porte RJ. Nonanastomotic biliary strictures after liver transplantation, part 1: Radiological features and risk factors for early vs. late presentation. *Liver Transpl* 2007; **13**: 708-718 [PMID: 17457932 DOI: 10.1002/lt.21166]

109 **Schoening WN**, Buescher N, Rademacher S, Andreou A, Kuehn S, Neuhaus R, Guckelberger O, Puhl G, Seehofer D, Neuhaus P. Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. *Am J Transplant* 2013; **13**: 2384-2394 [PMID: 23915357 DOI: 10.1111/ajt.12384]

110 **Yadav AD**, Chang YH, Aqel BA, Byrne TJ, Chakkera HA, Douglas DD, Mulligan DC, Rakela J, Vargas HE, Carey EJ. New Onset Diabetes Mellitus in Living Donor versus Deceased Donor Liver Transplant Recipients: Analysis of the UNOS/OPTN Database. *J Transplant* 2013; **2013**: 269096 [PMID: 24205434 DOI: 10.1155/2013/269096]

111 **Polotsky HN**, Polotsky AJ. Metabolic implications of menopause. *Semin Reprod Med* 2010; **28**: 426-434 [PMID: 20865657 DOI: 10.1055/s-0030-1262902]

112 **Burra P**, Senzolo M, Masier A, Prestele H, Jones R, Samuel D, Villamil F. Factors influencing renal function after liver transplantation. Results from the MOST, an international observational study. *Dig Liver Dis* 2009; **41**: 350-356 [PMID: 19046932 DOI: 10.1016/j.dld.2008.09.018]

113 **Campsen J**, Zimmerman M, Trotter J, Hong J, Freise C, Brown RS, Cameron A, Ghobrial M, Kam I, Busuttil R, Saab S, Holt C, Emond JC, Stiles JB, Lukose T, Chang MS, Klintmalm G. Multicenter review of liver transplant for hepatitis B-related liver disease: disparities in gender and ethnicity. *Clin Transplant* 2013; **27**: 829-837 [PMID: 24033475 DOI: 10.1111/ctr.12224]

114 **Ponziani FR**, Viganò R, Iemmolo RM, Donato MF, Rendina M, Toniutto P, Pasulo L, Morelli MC, Burra P, Miglioresi L, Merli M, Di Paolo D, Fagiuoli S, Gasbarrini A, Pompili M, Belli L, Gerunda GE, Marino M, Montalti R, Di Benedetto F, De Ruvo N, Rigamonti C, Colombo M, Rossi G, Di Leo A, Lupo L, Memeo V, Bringiotti R, Zappimbulso M, Bitetto D, Vero V, Colpani M, Fornasiere E, Pinna AD, Morelli MC, Bertuzzo V, De Martin E, Senzolo M, Ettorre GM, Visco-Comandini U, Antonucci G, Angelico M, Tisone G, Giannelli V, Giusto M. Long-term maintenance of sustained virological response in liver transplant recipients treated for recurrent hepatitis C. *Dig Liver Dis* 2014; **46**: 440-445 [PMID: 24635906 DOI: 10.1016/j.dld.2014.01.157]

115 **De Martin E**, Senzolo M, Gambato M, Germani G, Vitale A, Russo FR, Burra P. Fibrosis progression and the pros and cons of antiviral therapy for hepatitis C virus recurrence after liver transplantation: a review. *Transplant Proc* 2010; **42**: 2223-2225 [PMID: 20692449 DOI: 10.1016/j.transproceed.2010.05.035]

116 **De Martin E**, Senzolo M, Boninsegna S, Guido M, Masier A, Germani G, Tomat S, Brolese A, Neri D, Cillo U, Gambato M, Russo FP, Farinati F, Burra P. HCV histological recurrence and survival following liver transplantation in patients with and without hepatocellular carcinoma. *Transplant Proc* 2008; **40**: 1974-1975 [PMID: 18675104 DOI: 10.1016/j. transproceed.2008.05.040]

117 **Lai JC**, Verna EC, Brown RS, O'Leary JG, Trotter JF, Forman LM, Duman JD, Foster RG, Stravitz RT, Terrault NA. Hepatitis C virus-infected women have a higher risk of advanced fibrosis and graft loss after liver transplantation than men. *Hepatology* 2011; **54**: 418-424 [PMID: 21538434 DOI: 10.1002/hep.24390]

118 **Belli LS**, Burroughs AK, Burra P, Alberti AB, Samonakis D, Cammà C, De Carlis L, Minola E, Quaglia A, Zavaglia C, Vangeli M, Patch D, Dhillon A, Cillo U, Guido M, Fagiuoli S, Giacomoni A, Slim OA, Airoldi A, Boninsegna S, Davidson BR, Rolles K, Pinzello G. Liver transplantation for HCV cirrhosis: improved survival in recent years and increased severity of recurrent disease in female recipients: results of a long term retrospective study. *Liver Transpl* 2007; **13**: 733-740 [PMID: 17370330 DOI: 10.1002/lt.21093]

119 **Shimizu I**, Mizobuchi Y, Yasuda M, Shiba M, Ma YR, Horie T, Liu F, Ito S. Inhibitory effect of oestradiol on activation of rat hepatic stellate cells in vivo and in vitro. *Gut* 1999; **44**: 127-136 [PMID: 9862839]

120 **Yasuda M**, Shimizu I, Shiba M, Ito S. Suppressive effects of estradiol on dimethylnitrosamine-induced fibrosis of the liver in rats. *Hepatology* 1999; **29**: 719-727 [PMID: 10051473 DOI: 10.1002/hep.510290307]

121 **Poynard T**, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; **349**: 825-832 [PMID: 9121257]

122 **Deuffic-Burban S**, Poynard T, Valleron AJ. Quantification of fibrosis progression in patients with chronic hepatitis C using a Markov model. *J Viral Hepat* 2002; **9**: 114-122 [PMID:

11876793]
123 **Codes L**, Asselah T, Cazals-Hatem D, Tubach F, Vidaud D, Paraná R, Bedossa P, Valla D, Marcellin P. Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormone replacement therapy. *Gut* 2007; **56**: 390-395 [PMID: 17005762 DOI: 10.1136/gut.2006.101931]
124 **Burra P**. Liver abnormalities and endocrine diseases. *Best Pract Res Clin Gastroenterol* 2013; **27**: 553-563 [PMID: 24090942 DOI: 10.1016/j.bpg.2013.06.014]
125 **Giannelli V**, Giusto M, Farcomeni A, Ponziani FR, Pompili M, Viganò R, Iemmolo RM, Donato MF, Rendina M, Toniutto P, Pasulo L, Morelli MC, De Martin E, Miglioresi L, Di Paolo D, Fagiuoli S, Merli M. Treatment of hepatitis C recurrence is less successful in female than in male liver transplant recipients. *Transpl Int* 2012; **25**: 448-454 [PMID: 22353419 DOI: 10.1111/j.1432-2277.2012.01440.x]
126 Abstracts of the 2011 Joint International Congress of ILTS (International Liver Transplantation Society), ELITA (European Liver and Intestine Transplant Association), and LICAGE (Liver Intensive Care Group of Europe). June 22-25, 2011. Valencia, Spain. *Liver Transpl* 2011; **17** Suppl 1: S79-324 [PMID: 21618695]
127 **Ebeling PR**. Approach to the patient with transplantation-related bone loss. *J Clin Endocrinol Metab* 2009; **94**: 1483-1490 [PMID: 19420272 DOI: 10.1210/jc.2009-0205]
128 **Kulak CA**, Borba VZ, Kulak J, Custódio MR. Osteoporosis after transplantation. *Curr Osteoporos Rep* 2012; **10**: 48-55 [PMID: 22167576 DOI: 10.1007/s11914-011-0083-y]
129 **Melton LJ**. How many women have osteoporosis now? *J Bone Miner Res* 1995; **10**: 175-177 [PMID: 7754796 DOI: 10.1002/jbmr.5650100202]
130 **Defranco DJ**, Lian JB, Glowacki J. Differential effects of glucocorticoid on recruitment and activity of osteoclasts induced by normal and osteocalcin-deficient bone implanted in rats. *Endocrinology* 1992; **131**: 114-121 [PMID: 1611989 DOI: 10.1210/endo.131.1.1611989]
131 **Canalis E**, Delany AM. Mechanisms of glucocorticoid action in bone. *Ann N Y Acad Sci* 2002; **966**: 73-81 [PMID: 12114261]
132 **Epstein S**. Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. *J Bone Miner Res* 1996; **11**: 1-7 [PMID: 8770690 DOI: 10.1002/jbmr.5650110102]
133 **Goffin E**, Devogelaer JP, Depresseux G, Squifflet JP, Pirson Y. Osteoporosis after organ transplantation. *Lancet* 2001; **357**: 1623 [PMID: 11386322]
134 **Monegal A**, Navasa M, Guañabens N, Peris P, Pons F, Martínez de Osaba MJ, Rimola A, Rodés J, Muñoz-Gómez J. Bone mass and mineral metabolism in liver transplant patients treated with FK506 or cyclosporine A. *Calcif Tissue Int* 2001; **68**: 83-86 [PMID: 11310351]
135 **Baccaro LF**, Boin IF, Pedro AO, Costa-Paiva L, Leal AL, Ramos CD, Pinto-Neto AM. Decrease in bone mass in women after liver transplantation: associated factors. *Transplant Proc* 2011; **43**: 1351-1356 [PMID: 21620127 DOI: 10.1016/j.transproceed.2011.02.027]
136 **Baccarani U**, Piselli P, Serraino D, Adani GL, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, De Paoli A, Cimaglia C, Bresadola V, Toniutto P, Risaliti A, Cillo U, Bresadola F, Burra P. Comparison of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. *Dig Liver Dis* 2010; **42**: 55-60 [PMID: 19497797 DOI: 10.1016/j.dld.2009.04.017]
137 **Baccarani U**, Adani GL, Serraino D, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, Piselli P, De Paoli A, Bresadola V, Risaliti A, Toniutto P, Cillo U, Bresadola F, Burra P. De novo tumors are a major cause of late mortality after orthotopic liver transplantation. *Transplant Proc* 2009; **41**: 1303-1305 [PMID: 19460546 DOI: 10.1016/j.transproceed.2009.03.079]
138 **Serraino D**, Piselli P, Busnach G, Burra P, Citterio F, Arbustini E, Baccarani U, De Juli E, Pozzetto U, Bellelli S, Polesel J, Pradier C, Dal Maso L, Angeletti C, Carrieri MP, Rezza G, Franceschi S. Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. *Eur J Cancer* 2007; **43**: 2117-2123 [PMID: 17764927 DOI: 10.1016/j.ejca.2007.07.015]
139 **Ettorre GM**, Piselli P, Galatioto L, Rendina M, Nudo F, Sforza D, Miglioresi L, Fantola G, Cimaglia C, Vennarecci G, Vizzini GB, Di Leo A, Rossi M, Tisone G, Zamboni F, Santoro R, Agresta A, Puro V, Serraino D. De novo malignancies following liver transplantation: results from a multicentric study in central and southern Italy, 1990-2008. *Transplant Proc* 2013; **45**: 2729-2732 [PMID: 24034034 DOI: 10.1016/j.transproceed.2013.07.050]
140 **Chatrath H**, Berman K, Vuppalanchi R, Slaven J, Kwo P, Tector AJ, Chalasani N, Ghabril M. De novo malignancy post-liver transplantation: a single center, population controlled study. *Clin Transplant* 2013; **27**: 582-590 [PMID: 23808800 DOI: 10.1111/ctr.12171]
141 **Heneghan MA**, Selzner M, Yoshida EM, Mullhaupt B. Pregnancy and sexual function in liver transplantation. *J Hepatol* 2008; **49**: 507-519 [PMID: 18715668 DOI: 10.1016/j.jhep.2008.07.011]
142 **Christopher V**, Al-Chalabi T, Richardson PD, Muiesan P, Rela M, Heaton ND, O'Grady JG, Heneghan MA. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. *Liver Transpl* 2006; **12**: 1138-1143 [PMID: 16799943 DOI: 10.1002/lt.20810]
143 **Terrabuio DR**, Abrantes-Lemos CP, Carrilho FJ, Cançado EL. Follow-up of pregnant women with autoimmune hepatitis: the disease behavior along with maternal and fetal outcomes. *J Clin Gastroenterol* 2009; **43**: 350-356 [PMID: 19077726 DOI: 10.1097/MCG.0b013e318176b8c5]
144 **Penney GC**, Mair G, Pearson DW. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* 2003; **110**: 315-318 [PMID: 12628275]
145 **Schramm C**, Herkel J, Beuers U, Kanzler S, Galle PR, Lohse AW. Pregnancy in autoimmune hepatitis: outcome and risk factors. *Am J Gastroenterol* 2006; **101**: 556-560 [PMID: 16464221 DOI: 10.1111/j.1572-0241.2006.00479.x]
146 **Buchel E**, Van Steenbergen W, Nevens F, Fevery J. Improvement of autoimmune hepatitis during pregnancy followed by flare-up after delivery. *Am J Gastroenterol* 2002; **97**: 3160-3165 [PMID: 12492204 DOI: 10.1111/j.1572-0241.2002.07124.x]
147 **Westbrook RH**, Yeoman AD, Kriese S, Heneghan MA. Outcomes of pregnancy in women with autoimmune hepatitis. *J Autoimmun* 2012; **38**: J239-J244 [PMID: 22261501 DOI: 10.1016/j.jaut.2011.12.002]
148 **Park ES**, Villanueva CA, Viers BR, Siref AB, Feloney MP. Assessment of sexual dysfunction and sexually related personal distress in patients who have undergone orthotopic liver transplantation for end-stage liver disease. *J Sex Med* 2011; **8**: 2292-2298 [PMID: 21492399 DOI: 10.1111/j.1743-6109.2011.02264.x]
149 **Burra P**, Germani G, Masier A, De Martin E, Gambato M, Salonia A, Bo P, Vitale A, Cillo U, Russo FP, Senzolo M. Sexual dysfunction in chronic liver disease: is liver transplantation an effective cure? *Transplantation* 2010; **89**: 1425-1429 [PMID: 20463637 DOI: 10.1097/TP.0b013e3181e1f1f6]
150 **Parolin MB**, Rabinovitch I, Urbanetz AA, Scheidemantel C, Cat ML, Coelho JC. Impact of successful liver transplantation on reproductive function and sexuality in women with advanced liver disease. *Transplant Proc* 2004; **36**: 943-944 [PMID: 15194326 DOI: 10.1016/j.transproceed.2004.03.124]
151 **Ho JK**, Ko HH, Schaeffer DF, Erb SR, Wong C, Buczkowski AK, Scudamore CH, Yoshida EM. Sexual health after orthotopic liver transplantation. *Liver Transpl* 2006; **12**: 1478-1484 [PMID: 16741905 DOI: 10.1002/lt.20831]
152 **Cundy TF**, O'Grady JG, Williams R. Recovery of menstruation and pregnancy after liver transplantation. *Gut* 1990; **31**: 337-338 [PMID: 2323601]
153 **Mass K**, Quint EH, Punch MR, Merion RM. Gynecological and

reproductive function after liver transplantation. *Transplantation* 1996; **62**: 476-479 [PMID: 8781613]
154 **Jabiry-Zieniewicz Z**, Cyganek A, Luterek K, Bobrowska K, Kamiński P, Ziółkowski J, Zieniewicz K, Krawczyk M. Pregnancy and delivery after liver transplantation. *Transplant Proc* 2005; **37**: 1197-1200 [PMID: 15848667 DOI: 10.1016/j.transproceed.2005.01.011]
155 **Burra P**. Sexual dysfunction after liver transplantation. *Liver Transpl* 2009; **15** Suppl 2: S50-S56 [PMID: 19876949 DOI: 10.1002/lt.21899]
156 **Jabiry-Zieniewicz Z**, Kaminski P, Bobrowska K, Pietrzak B, Wielgos M, Smoter P, Zieniewicz K, Krawczyk M. Menstrual function in female liver transplant recipients of reproductive age. *Transplant Proc* 2009; **41**: 1735-1739 [PMID: 19545718 DOI: 10.1016/j.transproceed.2009.03.073]
157 **Murthy SK**, Heathcote EJ, Nguyen GC. Impact of cirrhosis and liver transplant on maternal health during labor and delivery. *Clin Gastroenterol Hepatol* 2009; **7**: 1367-1372, 1372.e1 [PMID: 19686866 DOI: 10.1016/j.cgh.2009.08.008]
158 **Kim HW**, Seok HJ, Kim TH, Han DJ, Yang WS, Park SK. The experience of pregnancy after renal transplantation: pregnancies even within postoperative 1 year may be tolerable. *Transplantation* 2008; **85**: 1412-1419 [PMID: 18497680 DOI: 10.1097/TP.0b013e318170f8ed]
159 **Gerlei Z**, Wettstein D, Rigó J, Asztalos L, Langer RM. Childbirth after organ transplantation in Hungary. *Transplant Proc* 2011; **43**: 1223-1224 [PMID: 21620095 DOI: 10.1016/j.transproceed.2011.03.087]
160 **Wielgos M**, Szpotanska-Sikorska M, Mazanowska N, Bomba-Opon D, Kociszewska-Najman B, Jabiry-Zieniewicz Z, Cyganek A, Kaminski P, Pietrzak B. Pregnancy risk in female kidney and liver recipients: a retrospective comparative study. *J Matern Fetal Neonatal Med* 2012; **25**: 1090-1095 [PMID: 21919553 DOI: 10.3109/14767058.2011.622010]
161 **Jabiry-Zieniewicz Z**, Szpotanska-Sikorska M, Pietrzak B, Kociszewska-Najman B, Foroncewicz B, Mucha K, Zieniewicz K, Krawczyk M, Wielgos M. Pregnancy outcomes among female recipients after liver transplantation: further experience. *Transplant Proc* 2011; **43**: 3043-3047 [PMID: 21996220 DOI: 10.1016/j.transproceed.2011.08.070]
162 **Deshpande NA**, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Cameron AM, Singer AL, Dagher NN, Segev DL. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. *Liver Transpl* 2012; **18**: 621-629 [PMID: 22344967 DOI: 10.1002/lt.23416]
163 **Zahn A**, Seubert L, Jünger J, Schellberg D, Weiss KH, Schemmer P, Stremmel W, Sauer P, Gotthardt DN. Factors influencing long-term quality of life and depression in German liver transplant recipients: a single-centre cross-sectional study. *Ann Transplant* 2013; **18**: 327-335 [PMID: 23817439 DOI: 10.12659/AOT.883962]
164 **Bianco T**, Cillo U, Amodio P, Zanus G, Salari A, Neri D, Bombonato G, Schiff S, Baggio G, Ronco C, Brocca A, Soni S, Minazzato L. Gender differences in the quality of life of patients with liver cirrhosis related to hepatitis C after liver transplantation. *Blood Purif* 2013; **36**: 231-236 [PMID: 24496196 DOI: 10.1159/000356362]

P- Reviewer: Silva R, Xia VW **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.243

World J Transplant 2014 December 24; 4(4): 243-266
ISSN 2220-3230 (online)

TOPIC HIGHLIGHT

Maurizio Salvadori, Professor, *Series Editor*

What's new in clinical solid organ transplantation by 2013

Maurizio Salvadori, Elisabetta Bertoni

Maurizio Salvadori, Elisabetta Bertoni, Department of Transplantation, Careggi University Hospital, 50139 Florence, Italy
Author contributions: Salvadori M and Bertoni E contributed equally to conceivement, finding materials, writing and reviewing this paper.
Correspondence to: Maurizio Salvadori, MD, Professor of Nephrology, Deparment of Transplantation, Careggi University Hospital, viale Pieraccini 18, 50139 Florence, Italy. maurizio.salvadori1@gmail.com
Telephone: +39-05-5597151 Fax: +39-05-5597151
Received: May 22, 2014 Revised: July 11, 2014
Accepted: July 27, 2014
Published online: December 24, 2014

Abstract

Innovative and exciting advances in the clinical science in solid organ transplantation continuously realize as the results of studies, clinical trials, international conferences, consensus conferences, new technologies and discoveries. This review will address to the full spectrum of news in transplantation, that verified by 2013. The key areas covered are the transplantation activity, with particular regards to the donors, the news for solid organs such as kidney, pancreas, liver, heart and lung, the news in immunosuppressive therapies, the news in the field of tolerance and some of the main complications following transplantation as infections and cancers. The period of time covered by the study starts from the international meetings held in 2012, whose results were published in 2013, up to the 2013 meetings, conferences and consensus published in the first months of 2014. In particular for every organ, the trends in numbers and survival have been reviewed as well as the most relevant problems such as organ preservation, ischemia reperfusion injuries, and rejections with particular regards to the antibody mediated rejection that involves all solid organs. The new drugs and strategies applied in organ transplantation have been divided into new way of using old drugs or strategies and drugs new not yet on the market, but on phase Ⅰ to Ⅲ of clinical studies and trials.

Key words: News in transplantation, kidney transplantation, pancreas transplantation, liver transplantation; Heart transplantation; Lung transplantation; New immunosuppressant; Tolerance

Core tip: Basic and clinical science in solid organ transplantation are continuously evolving. In this review we outlined the most important innovative findings recently discovered. The period of time chosen was 2013, but attention has been paid to the outstanding conferences held in 2012, but published in 2013, as well as to the conferences and meetings held in 2013 but published in 2014. We are aware that when this study will be published, new interesting and relevant findings will have been discovered. The science is flowing continuously, nevertheless analyzing in depth a short period of time can give useful information to the readers.

Salvadori M, Bertoni E. What's new in clinical solid organ transplantation by 2013. *World J Transplant* 2014; 4(4): 243-266 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/i4/243.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.243

INTRODUCTION

Innovative and exciting advances in the clinical science in organ transplantation continuously realize as the results of studies, clinical trials, international conferences, consensus conferences, new technologies and discoveries. This review will address to the full spectrum of the news in transplantation, that verified by 2013 and the key areas covered for every organ as the organ transplant activity,

the organ survival rates, the organ preservation and allocation, the new immunosuppressive regimens, the new immunological findings and the most important complications following organ transplantation.

The organ procurement transplant network/scientific report transplant recipients (OPTN/SRTR), the most wide and extensive registry on transplantation, by the end of 2013 published the complete data[1] concerning organ transplantation for 2012 and allowed for several considerations on the transplant activity. In particular, in the 2013 report, for the first time, OPTN/SRTR has undertaken to publish the worldwide transplant rates as part of its annual data report[2].

This report found that the transplant counts and rates vary among the countries around the world for different reasons: (1) Differences in the rates of end-organ disease. Country to country variability in the underlying incidence of end-organ disease can be expected to affect the organ transplant rate. However other factors undoubtedly play a role in determining the transplant rates. For example the incidence of end stage renal disease (ESRD) in Norway in 2009 was one third of the incidence in the United States. Nevertheless, in 2010, the rates of kidney transplant were similar in Norway and the United States, probably due to the very high activity related to living donor that characterizes the Norway; (2) Socioeconomic factors. There is a strong correlation between the Human Development Index (HDI) and the rate of deceased and living donor kidney transplants among the world health organization member states[3]. Similarly, the rates of liver transplant are lower in the countries with lower HDIs; (3) Cultural differences. An example is Japan that has a very high HDI, but lower rate of kidney transplants; and (4) Thoroughness of the transplant reporting, that varies by country.

Worldwide, use of living kidney donors varies widely, from less than 10% to more than 75% The rates of liver transplant have increased by more than 10% in several countries and declined in very few countries. In the past 5 years, the lung transplant rates have remained stable. The heart transplant rates changed little in the majority of countries.

NEW INSIGHTS FOR DONORS

In 2012 the number of deaths eligible for organ recovery for transplantation was lower than 2011 and 2010[4]. Similarly the mean number of organs transplanted per donor in United States in 2012 was 3.02, lower than in 2011 and 2010. Numbers of hearts and lungs procured for transplant but not used are smaller than the numbers of kidneys, pancreas and livers because the former organs are recovered only after the acceptance by the transplant center.

Data from OPTN/SRTR show that the number of Standard Criteria Donors (SCD) have remained about the same in United States and Europe, but there has been a dramatic increase in older donors and organs classified as donation after cardiac death. Overall, among deceased donors there is an organ donor shift[5]. Indeed, the percentage of all donors who are SCD is on the decline and there is an increase in Expanded Criteria Donors (ECD).

This shift could impact on the outcomes and more research is necessary to improve the quality of organ used for transplant and to optimize the use of a further expanded donor pool.

A wide, retrospective study from Heaphy *et al*[6] confirms this issue, as the donor quality has significant interactions by race, primary diagnosis and age. Another study[7] suggests that the judicious use of ECD kidneys may be an appropriate strategy to expand the donor pool minimizing the effects upon the outcomes.

Improving the organ cold storage by machine perfusion (MP) has been proposed to improve the solid organ outcomes. Especially in liver[8], heart and lung transplantation[9], the MP seems to be a promising tool to improve post-operative outcome, but a general evidence-based recommendation for or against on application of MP, cannot be given due to the lack of highest level of clinical evidence.

In addition to the above mentioned shift among deceased donors, recently, at least in United States, a decline in living kidney donation rate has been observed. This decline is about 13% per year and is more pronounced among blacks, men, younger adults, siblings and parents[10]. This fact warrants an action by transplant centers and national governments, also because another wide study[11] documented that the public is supportive of the living donation and in favor of protecting the health and safety of living donors.

A barrier to solid organ transplantation is often represented by the pre-transplant presence of donor specific antigens (DSAs) in the recipient sera. This fact is well known for the kidneys but has clinical relevance also for liver, heart and lung transplantation[12].

In such condition, for deceased donor kidney donation, the technique of acceptable human leukocyte antigen (HLA) mismatches has shown its efficacy. Two 2013 large studies proved its transnational efficacy[13,14].

In the case of the living kidney donation the presence of preformed antibodies may represent a relevant barrier to transplantation. In kidney transplantation, this barrier may be overcome by the network called kidney paired donation (KPD). Originally conceived as simple two-way reciprocal exchange between AB0 incompatible, KPD has evolved to include complex, multicenter, discontinuous chains, with transcontinental transport of kidneys. To date the majority of the researches performed on KPD has involved computer generated mathematical optimization algorithms. Several 2013 papers confirm the effectiveness of such network[15-17].

NEW INSIGHTS FOR KIDNEY

Main kidney related issues considered in 2013 publications have been: the kidney and recipient graft survivals, the impact and consequences of ischemia-reperfusion injury, the antibody mediated rejection (ABMR) and the new

techniques involved in rejection diagnosis.

Transplant activity and kidney graft survival

According OPTN/SRTR data, the shortage of kidneys for transplant remains a major problem for patients with ESRD. The number of candidates on the waiting list continues to increase, while the organ donation numbers remain flat[18]. Many kidneys recovered for transplant are then discarded for organ related problems and the discard rate is increasing. Living donation rates have been unchanged for the past decade. For both living and deceased donor recipients, the early post-transplant results have shown ongoing improvement.

For the first time, the graft survival rates have been systematically compared between Europe and United States. Utilizing data from OPTN/SRTR for United States and data from the Collaborative Transplant Study for Europe, the 1, 5 and 10-year graft survival rates have been compared among Europeans and White, African and Hispanic Americans[19]. While the 1-year graft survival rate was similar, the 5 and 10-year graft survival rates were considerably higher for Europe than for any of the three United States populations. Differences increased beyond three to four years after transplantation and these differences are not explained by differences in baseline patient characteristics. Studies are needed to identify factors contributing to the observed graft survival differences. Previous studies have documented that the limitations in access to immunosuppressive medications[20,21] and related compliance[22] are important determinants of long-term graft failure. Indeed, in the past the extension of immunosuppressive coverage in the US has shown to effectively reduce the income-related disparities in graft survival[23]. An United States study in 2013 examined the impact of Community risk factors on the kidney transplant outcomes[24]. The study documented that community risks are powerful factors associated with processes of care; and represent important considerations for developing effective interventions.

Ischemia-reperfusion injury

The Food and Drug Administration (FDA) held an open public workshop in September 2011 to discuss the current state of science related to the effects of ischemic reperfusion injury (IRI) on the outcomes in kidney transplantations. The summary of the workshop has been published in 2013[25]. The conclusions were that IRI impacts on graft survival and a better understanding of the underlying mechanisms is needed. Medical products to impact on IRI are urgently needed, but their development relies on both clinical and non-clinical researches. Also qualification of biomarkers is essential to elucidate the mechanisms[26].

Necroptosis in immunity and IRI have been principally studied in 2013[27-30]. Pathways of regulated necrosis (RN), an alternative to apoptosis have been recently described. The best studied RN pathway, the necroptosis, is triggered by perturbation of caspase-8-mediated apoptosis. In this condition the necroptosome is assembled and quickly leads to the necrotic-type cell death, release of the cell death-associated molecular patterns and severe organ damage. Interference with necroptosis (*e.g.*, by necrostatin) is more likely to be of clinical benefit in situations in which the reperfusion damage can be anticipated as solid organ transplantation.

Antibody-mediated rejection

Recent studies indicate that ABMR is among the most important barriers to improving long term outcomes principally in kidney transplantation, but in other solid organs as well[31].

Additionally new knowledge in ABMR pathophysiology, classification, diagnostic techniques and therapeutic approaches has merged. While the new therapeutic approaches will be described in the therapy chapter, the other issues will be treated in this paragraph.

A relevant and new finding is that not only the donor specific antibodies anti HLA (DSAs-HLA) are involved in ABMR. The antibodies against other molecules[32,33] and also polyreactive antibodies directed against apoptotic cells may cause ABMR[34].

The antibodies cause graft damage by endothelial cell injury mediated by the activation of complement. C4d is a split product of C4 activation and is often present on endothelial cells in ABMR. Sis *et al*[35] described that 60% of kidneys with high endothelial activation and injury transcripts (ENDATs) and chronic ABMR were C4d negative. A recent microarray study from Sellarés *et al*[36] concluded that changes in ABMR-associated gene expression correlates with the presence of capillary lesions or of DSAs and may predict graft failure independently of C4d staining. Taken together these observations point to the low sensitivity of C4d for the diagnosis of ABMR and support the addition of novel biomarkers of capillary inflammation and endothelial injury, including natural killer cells and macrophages, for the diagnosis algorithm of ABMR[37,38]. This recommendation was officially incorporated into the new Banff 2013 diagnostic criteria for ABMR[39].

The 12th Banff conference on allograft pathology was held in Comandatuba, Brazil in August 2013. The conference led to the following conclusions in the field of ABMR in renal allograft: (1) For acute/active ABMR the following three features must be present for diagnosis, not colon histological evidence of acute tissue injury, evidence of current/recent antibody interaction with vascular endothelium, serologic evidence of DSAs; (2) For chronic/active ABMR the following three features must be present for diagnosis, morphologic evidence of chronic tissue injury, evidence of current/recent antibody interaction with vascular endothelium, serologic evidence of DSAs; and (3) C4d staining without rejection (often accommodation), must include: linear C4d staining in peritubular capillaries, no morphologic lesions by light microscopy and electronic microscopy, no acute cell-mediated rejection.

New techniques involved in rejection diagnosis

Bachelet *et al*[40] with a seminal work demonstrated that DSAs detection in kidney allograft biopsy eluates is a

feasible method to predict the graft outcomes. Indeed, patients with intragraft DSAs displayed more severe ABMR pathology and worse outcome than patients with only DSAs in the serum. According to this work the intragraft DSA detection is a new test to dichotomize HLA antibodies into high and low injurious activity[41].

There are no doubts on the unmet medical need for improvement of diagnostic of renal injury to allow a more personalized therapeutic approach. Therefore, it is believed that the opportunity lies in new technologies such as molecular analysis, as messenger RNA (mRNA) and micro RNA expression from biopsies or even from blood or urine samples[42].

Two reports from the group of Edmonton in 2013 reported the results of molecular analyses of renal allograft biopsies[43,44]. The first report aimed to develop a diagnostic test for the T and B cell-mediated rejection by bootstrapping from the pathology.

The main messages of this paper were: (1) A molecular scoring was developed for diagnosis of rejection; (2) A molecular classification is based on selected genes related to immune cells and their activation products; and (3) The study confirmed certain disagreements among pathologists in applying the golden standard histopathology. In two other studies[45,46] the scoring assessed by the microarray test was validated by the INTERCOM study.

These papers revealed that a previously identified "acute kidney injury signal" early after transplantation was also present in the late kidney biopsies related to late T cell and ABMR, but not to fibrosis.

The multicenter Clinical Trials in Organ Transplantation 04 (CTOT-04) study was designed to investigate whether the urinary-cell mRNA levels encoding immune system proteins implicated in transplant rejection are diagnostic of acute rejection[47]. By logistic regression the authors correlated a three-gene signature of CD3ε mRNA, IP-10 mRNA, and 18S rRNA levels in urinary cells with allograft rejection. This study offers new insight into the possible use of non-invasive diagnostic and prognostic markers for the acute cellular rejection in kidney allograft.

NEW INSIGHTS FOR PANCREAS AND ISLET TRANSPLANTATION

Transplant activity and graft survival

Pancreas and islet cell transplantation (ICTx) confirmed to be the best treatment for diabetes mellitus type I (T1DM). According the OPTN/SRTR data, the number of pancreas transplants has decreased over the past years, most notably the numbers of pancreas after kidney (PAK) and pancreas transplant alone (PTA)[48]. Deceased donor pancreas donation rates have been declining since 2005 and the donation rate remains low. The outcomes of pancreas graft are better for simultaneous pancreas-kidney (SPK) transplantation. The challenges of pancreas transplant are reflected in the high rate of re-hospitalization, most occurring within the first six month post-transplant.

Very recent data[49] confirm the excellent long-term prognosis of SPK transplantation principally in recipients with functioning graft 1-year after transplantation. Patients who receive PTA or PAK grafts have shorter long-term graft survival[50]. Multiple strategies are aimed to be applied to improve immunologic surveillance and to obtain an early diagnosis of the graft rejection in patients receiving PTA.

An interesting study[51] documented an improved patient survival rate for recipients with diabetic end-stage renal disease receiving SPK than that receiving kidney transplant alone (KTA). ICTx remains a hot topic. The collaborative islet transplant registry investigators[52] presented the results of 752 islet allograft recipients with optimal and improving insulin independence rate at 3 years.

Pancreas transplantation for type 2 diabetes mellitus

SPK is widely accepted as an optimal therapeutic option for patients with T1DM and end-stage renal disease, but the indication for patients with type 2 diabetes mellitus (T2DM) is still controversially discussed. Indeed, there is continued uncertainty as to whether to T2DM patients are appropriate pancreas transplant candidates. In an editorial of 2012 Cohen *et al*[53] reviewed the most recent experience with pancreas transplantation in T2DM.

Gruessner *et al*[54] summarized the united network for organ sharing (UNOS) and International Pancreas Transplant Registry and reported no differences in the outcomes of patients with T2DM *vs* T1DM. Orlando *et al*[55] also found equivalent outcomes, regardless of whether the patients were classified as having T1DM or T2DM. Sampaio *et al*[56] reviewing the UNOS database, reported similar results even if T2DM represented only from 4.1% to 7.4% of diabetic patients transplanted.

More recently, Margreiter *et al*[57] reported the outcomes of 21 T2DM recipients receiving SPK and 32 T2DM receiving KTA. Patient and kidney graft survival rates were significantly lower for patients with KTA. The multivariate analysis adjusted for donor and recipient age, body mass index and coronary risk factors, showed that the differences did not remain statistically significant. The authors concluded that, according to the selection criteria proposed by other groups[58], selecting T2DM with an acceptable coronary risk profile and ageing not more than 55 years, is useful to identify those patients that may have a benefit from SPK.

ABMR in pancreas transplantation

ABMR is a recently identified entity. In a recent published paper[59], risk factors for pancreas ABMR were PTA and race mismatch. The diagnosis should be actively sought using C4d staining and DSAs levels in patients with graft dysfunction.

Preliminary studies have been presented at the already mentioned 2013 Banff conference[39]. These studies described the potential association of rejection-related vascular lesions with ABMR. Other studies demonstrated that immunostaining can enhance the understanding of pancreas T cell mediated rejection and ABMR even if the

accurate grade and type of rejection rests principally on the systematic evaluation of morphological features on routinely stained sections[60].

Islet transplantation

ICTx is a modality to treat selected diabetic patients. The "Edmonton Protocol" became a milestone by reporting sustained C-peptide production and high rates of insulin-independence after transplant in T1DM[61].

Long-term analysis of these results indicates that insulin-independence was not durable and most patients returned to moderate amounts of insulin approximately 5-years post-infusion[62]. The causes for this islet graft dysfunction are not completely understood, but are likely associated to several factors as the immune rejection, the autoimmunity or the chronic exposure to diabetogenic immunosuppressant[63].

In the last years relevant progress has occurred testing new immunosuppressant, testing novel devices to provide islets with a safer environments, as well as new transplant sites to overcome the limitations inherent to the current intraportal access[64-68]. The autoimmunity is a limiting factor to the success of ICTx. In a recent study Takita *et al*[69]. documented an early loss of transplanted allergenic islets despite T cell depletion induction. The authors concluded that the T cell depletion with anti-inflammatory regimen can enhance engraftment and survival; however, autoimmune recurrence by islet auto antibodies, principally GAD65 may limit the results.

The revascularization of transplanted pancreatic islets and the role of the transplantation site is another important issue[70]. Indeed, pancreatic islets are highly vascularized, which is important for their ability to secrete insulin in response to changes in blood glucose. The islet isolation process interrupts the connections between the islet vasculature and the systemic circulation. As the revascularization of the ICTx is not immediate, allocating cells in proximity to a good vascular supply is essential. A recent study proved the impaired revascularization of pancreatic islets into the liver[71]. In addition, the portal vein after islets injection undergoes instant blood-mediated inflammatory rejection (IBMIR) which results in an early inflammatory reaction. Therefore, it is essential to avoid this by either identifying a transplant site with minimal interaction with blood or by protecting the vascular grafts from IBMIR[70].

Among other sites, recent studies documented good results with omentum and muscle. The peritoneum offers an unlimited space for transplanted islets and is an attractive site for concurrent use of encapsulated device to protect the islets. A recent study[72] suggests the potential for longevity of islets allocated in the peritoneal cavity. Muscle-skeletal sites offer several advantages. They are easy to access, offer substantial space in which to transplant cells and are highly vascularized making them a very useful area. In a recent study, mice islets were successfully transplanted intramuscularly and the authors concluded that the early hypoxia after transplantation could be overcome by co-implantation of polymerized hemoglobin[73].

Finally, the islet encapsulation has been the issue of a very recent review[74]. Islet encapsulation allows the protection of this tissue without the use of toxic medications and expanding the donor pool to include animal sources. Before the use of this therapy, there are still issues that need to be resolved as the materials to be used, the shapes and sizes of the capsules and the aspects of bioengineering.

NEW INSIGHTS FOR LIVER

Transplant activity and liver graft survival

According the OPTN/SRTR data, in United States the number of adults who registered on the liver transplant waiting list decreased for the first time since 2002. However, the median waiting time for active wait-listed adult candidates increased, as did the number of candidates removed from the list because they were too sick to undergo transplant[75]. Graft survival continues to improve, especially for donation after circulatory death livers.

Since the first liver transplantation, short-term survival has improved rapidly; however, long-term attrition rates have not changed similarly[76]. In 2013 the first publication of European single-center 20-year survival data have been published[77]. The 20-year patient and graft survival rate of 313 patients has been reported. The 20-year patient and graft survival rates were respectively 52.5% and 46.6%. These results were better than two other single center long-term survivals[78,79] and also than the 20-year survival published by the European Liver Transplant Registry[80].

Impaired renal function and re-transplantation had significant impact on patient survival and recurrent diseases. Infections and *de novo* malignancies were the main cause of death. Much work is needed to combat recurrent disease and side effects of immunosuppressants.

The Japanese Liver Transplantation Society analyzed the outcomes of 2224 pediatric patients who underwent living donor liver transplantation[81]. No donor mortality related to transplant has been reported and the 10 and 20-year patient survival rates were 82.8% and 79.6%, respectively.

Primary disease impacts on the outcomes of liver transplantation (LTx). A recent analysis of OPTN/SRTR[82] documented an optimal short and long-term survival of LTx for primary biliary cirrhosis; similar good outcomes were reported for primary sclerosing cholangitis, non-alcoholic steatohepatitis and for hepatitis B virus (HBV). The worst results (HR = 1.5-2.4) were reported for hepatitis C virus (HCV) and hepatocellular carcinoma.

More than one-third of listed potential liver recipients in many western and some Asian countries are infected with the HCV. Recurrence of infection with HCV after LTx is associated with accelerated graft loss and diminished patient survival[83]. Until recently, HCV treatment has been limited to the use of pegylated interferon alpha (Peg IFN) plus ribavirin. In 2012 two direct acting anti-viral drugs, boceprevir and telaprevir were licensed by FDA for the treatment of chronic genotype 1 HCV[84,85]. The use of protease inhibitors (PI) based triple anti HCV

therapy in LTx recipients, is complicated by the known pharmacokinetic effect of the PI on cytochrome P450[86]. Nevertheless, promising small series of HCV recipients treated by PI based triple therapy have been reported[87]. Future approaches rely on the possible use of prophylactic neutralizing monoclonal antibodies to HCV[88].

Ischemia reperfusion injury

IRI is a major cause of morbidity and mortality in LTx. After a transient ischemia, the restoration of blood flow is necessary to restore cellular function, but paradoxically the reperfusion can initiate a cascade of pathways that causes further cellular injury after prolonged ischemia[89].

The lack of oxygen in hepatocytes during ischemia causes adenosine 3 phosphate depletion and alterations in H^+, Na^+ and Ca^{2+} homeostasis that activate hydrolytic enzymes and impair the volume regulation, leading to the swelling of sinusoidal endothelial cells and Kupffer cells (KCs). This fact together with the imbalance between nitric oxide and endothelin production, contributes to the narrowing of the sinusoidal lumen and thus to microcirculatory dysfunction. The activation of KCs releases reactive oxygen species (ROS) and proinflammatory cytokines (TNF alpha and IL 1). Cytokines and chemokines promote neutrophil activation and subsequent release of ROS and proteases. In addition, IL 1 and TNF alpha activate CD4 T-lymphocytes which produce granulocyte-macrophage colony-stimulating factor, IFN gamma and TNF beta. Platelet-activating factor can prime neutrophils for superoxide generation[90].

Several studies in 2013 evaluated different molecules in attempt to attenuate the damage induced by IRI. The most important studies in this field have been extensively reviewed in the work of Akhtar *et al*[91]. Attempt to protect IRI may involve several strategies and several pathways[92-95]. This issue will be described in the therapy chapter.

DSA and acute and chronic liver rejection

The issue of the impact of preformed DSAs on LTx has been a matter of discussion. Early clinical experience showed no differences in patient or graft survival rate[96-98] and DSAs were thought to be an integral part of tolerance development. Later studies documented that patients transplanted with a positive cross-match had an increased risk of early graft loss[99-101]. However, since consistent results are lacking, practice has not changed. In 2013, a study from Kaneku *et al*[102], documented that patients with LTx developing de novo DSAs after transplantation, had significantly lower patient and graft survival rates.

The 2013 Banff conference[39] stated that currently, recognized acute ABMR, occurs in small percentage of sensitized patients and that DSAs can be associated with more progressive fibrosis and an indolent progressive perivascular and subsinusoidal fibrosis. The conference concludes that high titer IgG3 recipients more often show adverse consequences, whereas exclusively not IgG3/IgG1 DSAs appear in some operationally tolerant recipients weaned from immunosuppression.

New tools for rejection diagnosis

Current liver biopsy is the most frequent used technique to evaluate allograft status and is the gold standard for the diagnosis of the acute rejection after orthotopic liver transplantation (OLT). As already described for the kidney, plasma microRNA is now revealing to be a potential biomarker for acute rejection after OLT[103,104].

NEW INSIGHTS FOR HEART

Figures, characteristics and trends for heart transplantation

According to the OPTN/SRTR data, in United States the number of heart transplants performed annually continues to increase gradually, and the number of adult candidates on the waiting list increased by 25% from 2004 to 2012[105]. Heart transplantation (HTx) appears to be more expensive than ventricular assist devices for managing the end-stage heart failure, but is more effective and likely more cost-effective.

By the end of 2013 the data of the Registry of the International Society for Heart and Lung Transplantation (ISHLT) have been published[106]. Cardiomiopathy in recent years has been the leading cause for HTx, followed by coronary artery disease (CAD). This trend has been particularly higher in Europe and the rest of the world than United States, reaching percentage of 57%-60%. Both recipient and donor age statistically increased, as well as the percentage of patients with pre-transplant panel reactive antibodies in the sera > 10%.

In the recent years a highly significant number of patients bridged to transplantation with mechanical circulatory support (MCS) have been registered. Nevertheless, should be outlined that a better survival rate has been reported for patients not on mechanical support prior transplantation.

A progressive and significant increase of Kaplan Meier survival by ERA was reported except for the last two years. Congenital diseases as primary disease attained the best survival rate while re-transplants attained the worst. Importantly long-term freedom from cardiac allograft vasculopathy (CAV) was higher by ERA and by female gender. The causes of death were stable in the last year with prevalence of graft failure, followed by infections.

In 2013, the ISHLT Registry focused a peculiar study on the relevance of age. Interestingly in the recent years, the graft survival rate was not statistically influenced by recipient age, except 18-39 years compared to 60-69 years. On the contrary donor age had significant impact on the graft survival. CAD was the leading cause of HTx for patients aged 60-69 years (53%).

In the recent years an increase of both donor and recipient age has been registered. The most striking variation for elder patients has been observed as the percentage of patients bridged with MCS. By 2012 almost 40% of patients ageing 60-69 years were on MCS prior to transplantation, while only 15% of patients had similar support by 2006. Leading causes of death for patients ageing 60-69 years were graft failure and infections. The elder patients had also more

malignancies and after 10 years only 50% of patients were free from malignancies.

Mechanical circulatory support

As aforementioned in recent years we observed an impressive advance in MCS devices and, overall, newer MCS devices are smaller and more reliable than the first generation of technological devices. Increasing number of reports conclude that in some cases of heart failure, the devices may be used not only as bridges to transplantation, but also as destination therapies[107]. A new device, the Heart Ware Ventricular Assist System is a miniaturized implantable continuous flow blood pump and in 332 patients in a pivotal bridge to transplant demonstrated a high 180-d survival rate[108]. This and other mechanical supports were examined in a recent paper[109] which led to the conclusion that patients with mechanical support, despite being older and less favorable recipients, spent more time in status 1A and had greater waitlist survival.

In a systematic review, Sutcliffe *et al*[110] tried to evaluate the clinical effectiveness and cost effectiveness of last generation MCS as either bridge to transplant (BTT) or alternative to transplant (ATT). The authors concluded that MCS as BTT compared with medical management are effective but with higher cost-effectiveness ratio. MCS as ATT have a reduced cost, but cause reduced quality of life. Considering the wide use of MCS, with the intent to regularize its use, in 2013 ISHLT published the Guidelines for the use of MCS[111].

Prediction of mortality and cardiac allocation score

As a consequence of the aforementioned variables impacting on heart graft survival, several attempts have been made to evaluate the mortality prediction after heart transplantation. In 2013 the Index for Mortality Prediction after Cardiac Transplantation (IMPACT) score was validated using international data[112]. This study validated the use of the IMPACT score as a predictor of short- and long-term mortality after orthotopic heart transplantation.

Other scoring modalities, in addition to the IMPACT score, are the Heart Failure Survival Score, the Seattle Heart Failure Model and the Interagency Registry for Mechanically Assisted Circulatory Support. All these scores were evaluated in a Eurotransplant pilot study for predicting waiting list mortality among heart transplant candidates and among transplanted patients[113]. In non MCS patients all the scores provide accurate risk stratification. The authors conclude that further studies are needed to reveal whether these models should be considered the basis for a new heart allocation policy.

ABMR in heart transplantation

Previous studies have documented that the presence of de novo donor HLA specific antibodies after HTx is an independent predictor of poor survival[114]. Similarly the detection of Luminex positive DSA in pre-transplant serum is a negative predictor of mortality[115] and also IgM non HLA antibodies have been identified as a risk for early allograft failure[116].

Nevertheless in the last Banff Conference[39] it was observed that lacking of search for DSAs or C4d staining are limiting factors to identify ABMR in heart transplantation. While biopsies positive for C4d and C3d are strongly associated with DSAs and allograft dysfunction and represent true ABMR, biopsies only positive for C4d are mostly subclinical. On a morphologic basis, is not possible to designate the latter as accommodation *vs* subclinical ABMR. Moreover there is also uncertainty about the management of subclinical ABMR. To this end the American Heart Association will be publishing a scientific statement evaluating clinical and pathological evidence regarding ABMR.

The ISHLT working formulation for the standardization of nomenclature of ABMR in heart transplantation has published a consensus paper by the end of 2013[117]. As ISHLT itself recognizes is hard to date to make a definitive statement on this issue and there remain numerous challenges and unresolved clinical, immunologic and pathologic questions. Moreover, there is no hard evidence of a direct causality between ABMR and CAV, neither any systematic study of antibody-dependent cellular cytotoxicity as an alternative mechanism linking antibodies to CAV[39].

Chronic cardiac allograft rejection: new insights

Several papers in 2013 have treated new findings on chronic cardiac allograft rejection. A review by Costello *et al*[118] recognized that chronic rejection in the form of CAV is one of the major factors that affect the long-term graft and patient survival. Whereas multiple factors (hyperlipidemia, cytomegalovirus, baseline coronary artery disease) contribute to the development of CAV, immunologic mechanisms play the prevalent role.

Using the intravascular ultrasound (IVUS) to evaluate intimal thickening, some recent studies have validated the use of everolimus (EVR) with reduced-dose cyclosporine (CsA)[119,120]. These studies documented a similar efficacy of EVR with reduced-dose CsA to Mycophenolate Mofetil (MMF) with standard-dose CsA and a reduced intimal proliferation at 12 mo in *de novo* heart transplant recipients. However, these studies have been criticized[121] both because IVUS was made only in a subgroup of patients and because IVUS was performed only at 1 year post-transplant.

Finally, the technique of optical coherence tomography has been proposed to evaluate cardiac allograft vasculopathy[122]. This is a new technique to assess early morphologic changes, but its clinical predictive value remains to be determined.

NEW INSIGHTS FOR LUNG

Figures, characteristics and trends for lung transplantation

In United States lung transplants are increasingly used as treatment for the end-stage lung diseases. Lungs are allocated to adult and adolescent transplant candidates on the basis of age, geography, blood type compatibility and

the Lung Allocation Score (LAS)[123]. The overall median waiting time in 2012 was 4 mo, and 65.3% of candidates underwent transplant within 1-year of listing. Both graft and patient survival rates have continued to improve; survival rates for recipients aged 6-11 years are better than those of younger recipients. Similarly as for the heart by the end of 2013 the data of the ISHLT Registry have been published also for the lung[124].

Obstructive pulmonary diseases (COPD), interstitial pulmonary fibrosis (IPF) and cystic fibrosis (CF) are among the most common causes of LuTx. COPD represents one of the most common indications for LuTx and accounts for one/third of all the procedures[125]. Worldwide a recent analysis of all the recipients reported that 23% had IPF and 3% pulmonary artery hypertension[126]. LuTx has become an excellent treatment option for patients with CF and bronchiectasis. In these patients survival is more favorable than that seen in patients with COPD and IPF[127].

In recent years there has been a significant increase of recipient's age (24% ageing 60-65). As a consequence there was an increase of patients transplanted for COPD, for IPF and for re-transplantation. Though the patients with COPD, IPF and re-transplant have the worst survival, an increase of Kaplan Meier survival by ERA was registered. Recently has been reported an increase of bilateral/double LuTx with respect to single LuTx for all the primary diseases. As double LuTx is associated with an improved graft survival rate for any disease, this could be the cause for the improved survival rate observed in recent years.

Among the side consequences of lung transplantation, both a reduction in renal dysfunction and an increase of hyperlipidemia and diabetes has been registered and probably this fact is related to modification in the dose and type of immunosuppressant[124].

Donor selection and extended criteria donors

The scarcity of suitable donor organs limits lung transplantation[128]. To overcome this problem, recently there was an increased interest towards an expanded donor pool associated with the techniques aimed to evaluate an improve donor lungs as the availability of *ex vivo* lung perfusion (EVLP). The utilization rate of these lungs changed from less than 15% to 50%. It is now quite clear that many of the historical factors used to define a lung as "Extended" do not actually produces significantly worse outcomes.

In a review of the UNOS database[129], the outcomes after LuTx using donors aged 55 to 64 years, were similar to those observed with standard donors. In this review only the donors aged more than 65 years were associated with the decreased intermediate-term survival. In Eurotransplant in 2013 the Hannover center reported its results utilizing lungs turned down for donor-related medical reasons by 3 centers. The authors obtained excellent graft survival similar to the standard lungs and concluded that the rescue allocation donor lungs may be used safely and therefore salvaged for the donor pool[130].

New findings on recipients and LAS

The relevance of size-matching has been evaluated in an extensive study based on evidence-based reviews[131]. Unfortunately the authors conclude that the evidence base that informs the decisions regarding lung size mismatching is limited and composed primarily of small studies with heterogeneous groups of patients.

Currently data are lacking to give the surgeons robust guidelines to conduct decision making for size matching of donors and recipients. Among the pre-transplant variables that affect the survival after LuTx, markers of nutritional status are associated with poorer recipient survival. A recent paper[132] examined several variables associated with the nutrition, including body mass index, body surface area, albumin levels, total proteins and immunoglobulins. Although no nutritional variables were found to be associated with major post-operative complications or infections, a low serum albumin (< 3 mg/dL) was associated with increased risk of death. Even if the results of this study differ slightly from others studies[133]; the body of literature to date suggests that the nutritional status may affect post-transplant outcomes.

The LAS was developed in 2005 to reduce the mortality on the waiting list, to prioritize candidates basing on urgency, to minimize the role of geography and to maximize the transplant benefit. In prioritizing patients with the most urgent status, a new controversy has come into the forefront: whether or not the increased number of critically ill recipients maximizes the transplant benefit. Despite the controversy, the LAS system is an improvement compared with the traditional first-come, first-served system and it has been adopted by UNOS and Eurotransplant[134]. A recent review of the UNOS data[135] concluded that social disparities in lung transplantation have decreased with the implementation of LAS; however, gender disparities (in favor of men) may have actually increased in the LAS ERA.

Primary graft dysfunction, ABMR and chronic allograft dysfunction

Primary graft dysfunction (PGD) is a syndrome encompassing a spectrum of mild to severe lung injury that occurs within the 72 h after LuTx. In addition, PGD has a significant impact on the short and long-term outcomes[136].

The pathogenesis of PGD is complex and influenced by donor, recipient, technical factors and by different combinations of all the above. PGD is driven by an inflammatory response as well as by immunological (both innate and cell mediated) processes[137]. Several strategies have been investigated to prevent and treat PGD[138]. These strategies will be discussed in the therapy chapter.

Allograft rejection is a major cause of a limited survival rate in LuTx. Moreover, the acute rejection represents the principal risk factor for chronic rejection[139]. Acute cellular rejection (ACR) is defined as a perivascular or peribronchiolar lymphocytic infiltrates primarily diagnosed by bronchoscopic transbronchial biopsies[140]. ACR involves several T-cell subtypes and several cytokines.

Data suggest a correlation between acute rejection and effector memory T cells in LuTx and the measurement of peripheral blood CD8+ effector memory T-cells before

LuTx may define the patients at high risk for ACR[141].

The study of Krustrup *et al*[142] documented the association between the distribution of Tregs in the transbronchial biopsies and the level of FoxP3 mRNA in the bronchoalveolar lung fluid (BALF). This indicates that Tregs may play a role in the cellular processes that affect ACR and that looking for FoxP3 mRNA in BALF is a reliable non-invasive method for evaluating the number of Tregs in lung tissue.

Higher values of CXCL10 (IP-10) in BALF are associated with ACR in LuTx suggesting a potential mechanistic role in the pathogenesis of ACR[143]. These results suggest that therapeutic strategies to inhibit CXCL10 (IP-10) and/or its cognate receptor (CXCR3) warrant investigations to prevent and/or treat the ACR in LuTx.

Some retrospective studies conducted and published in 2013 highlighted the relevance of ABMR in LuTx. In one study[144] a clear association between DSAs, ABMR, ACR, bronchiolitis obliterans syndrome (BOS) has been documented. Another study[145] identified ABMR in 21 recipients basing on the presence of HLA-DSAs, the histological evidence of acute lung injury, C4d deposition and clinical allograft dysfunction. In this study the majority of patients who recovered from ABMR, developed chronic lung allograft dysfunction (CLAD) during the follow-up.

Due to the relevance of the syndrome, the Pathology Council of the ISHLT elaborated the Consensus points for pathologic diagnosis of pulmonary ABMR[146]. The conclusions were: (1) The diagnosis of pulmonary ABMR requires a multidisciplinary approach that includes the presence of clinical allograft dysfunction, circulating DSAs and pathologic findings; (2) The histopathology findings in ABMR are non-specific patterns of injury that can be seen also in disorders such as severe ACR, infection, graft preservation injury and drug reaction; and (3) Positive capillary C4d staining should be always reported.

The last Banff conference[39] reviewed the Pathology Council survey and added that the early detection of DSAs following LuTx and the systematic monitoring with sensitive solid-phase platforms are recommended[147]. The overall conclusions revealed that to date survival is poor after ABMR but may improve with the rapid clearance of the antibodies[145].

Important unanswered questions include: (1) How to grade graft dysfunction; (2) What constitutes a significant mean fluorescent intensity of DSAs; (3) How to manage the patient in whom there is discordance between the criteria enumerated; and (4) What's about the non-HLA targets, principally because, according many authors, the BOS is the result of humoral response against non-HLA molecules[148].

CLAD continues to be the major limitation to long-term survival[149]. Its pathogenesis is complex and involves both alloimmune and non-alloimmune pathways. In particular, acute damage to the allograft, including episodes of acute rejection, PGD, cytomegalovirus (CMV), pneumonitis, gastro esophageal reflux and early and late new-onset diffuse alveolar damage have all been shown to increase the risk of CLAD[150].

BOS, characterized by obstructive physiologic changes, is the conventional form of CLAD. Increasing evidence, however suggests that CLAD is a heterogeneous condition and that BOS is not the only form of CLAD. While BOS itself has been recently redefined as neutrophilic reversible allograft dysfunction (NRAD)[151], Sato *et al*[152,153] recently identified a type of CLAD who showed restrictive physiology and peripheral lung fibrosis and named this condition "restrictive allograft syndrome" (RAS). The prognosis of RAS is poor and more severe than that of NRAD.

As already mentioned the pathogenesis is multi-factorial and recently has been documented that acute rejection, lymphocytic bronchiolitis, colonization with Pseudomonas, infection and BALF eosinophilia and neutrophilia are risk factors for both RAS and NRAD[154]. Moreover, immunologic factors as complement activation[155] and the defensins have been implicated in the pathogenesis of CLAD[156].

NEW INSIGHTS ON IMMUNOSUPPRESSIVE THERAPIES IN SOLID ORGAN TRANSPLANTATION

This chapter may be divided into two paragraphs: (1) Old drugs recently revised and used in new strategies; and (2) New drugs recently introduced on the market or still waiting for their approval.

Old drugs recently revised and used in new strategies

The concept that the chronic loose of renal function after kidney transplantation (KTx) should be ascribed to chronic renal calcineurine inhibitors (CNIs) nephrotoxicity, led to a number of trials attempting to avoid or withdraw CNIs from the maintenance immunosuppression therapy.

With the exception of few trials all these attempts documented that to date is not yet the time to give up with CNIs[157]. Moreover, in 2013 a meta-analysis[158] has not documented a favorable effect of CNIs reduction on kidney function in HTx.

Many trials of CNIs reduction have been made thanks to the use of mammalian target of rapamycin inhibitors (mTORIs), a class of drugs devoid of CNIs side-effects. Overall an analysis of 139370 United States kidney transplant recipients documented that the complete substitution of CNIs with mTORIs was associated to a greater risk of allograft failure and death[159].

The use of mTORIs in LTx led to contradictory results. In a phase Ⅱ prospective randomized trial[160] the use of sirolimus with reduced dose of tacrolimus (TAC) in the de novo liver transplant recipients was associated with higher rates of graft loss, deaths and sepsis when compared to the use of the conventional dose of TAC.

In the recent H2304 trial[161,162] liver transplant patients randomized to EVR with TAC elimination showed strikingly good renal function at 2-year post-transplant, but this treatment group was terminated due to a higher rate of acute rejections. However, there was no significant

difference between the EVR and reduced TAC *vs* TAC control group[163]. The study Preservation of Renal function in liver Transplant recipients with Certican Therapy (PROTECT)[164] documented that an EVR-based CNI-free immunosuppression is feasible following LTx and the patients benefit from sustained preservation of renal function when compared to patients on CNIs, for at least three years.

The discrepancies between the results of H2304 and PROTECT studies could be explained by the use of Il-2 receptor antibody only in the latter study and in the abrupt TAC withdrawal in the former.

The contradictions in the use of mTORIs in LTx have been examined in an editorial of Levitsky *et al*[165]. Probably like any other drug with a narrow therapeutic window, mTORIs must be used in the right amount, right time period and right patient. Right amount is without a loading dose and targeting moderate trough levels. Right time is neither too early nor too late after LTx. The right patient is the one who is at high risk to develop nephrotoxicity.

Several studies document the attenuation of cardiac allograft vasculopathy by mTORIs. A study from Matsuo *et al*[166] documented the usefulness of sirolimus in the case of early initiation. As aforementioned, the recent most important contributions in this field are the Eisen *et al*[119] and Kobashigawa *et al*[120] studies.

They documented the efficacy of EVR with reduced-dose CsA, similar to MMF + standard dose CsA. Patients treated by EVR had reduced intima proliferation. Recently the use of mTORIs in the treatment of lung transplant recipients is an area of active investigation[167,168]. Newer researches involving the use mTORIs or antimetabolites have been made in the treatment and prevention of BOS[169,170]. In a recent review[171], Borro highlights that one of the advantages in LuTx is the administration of the treatments *via* the inhalator route.

A randomized, prospective study of inhalator CsA *vs* placebo documented significant improvements concerning survival and BOS free interval[172]. Inhalator corticosteroids have been suggested in the lymphocytic bronchiolitis, based on the possible reduction of the airway inflammatory markers[173].

Immune modulating and beneficial effect in LuTx have been documented for the statins and Azithromycin. Concerning statins, some groups have considered adding such treatment on a systematic basis in the patients with suspected or confirmed BOS[174]. Principally in patients with an increased bronchoalveolar lavage neutrophilia, azithromycin could prevent BOS, most likely through its interactions with the innate immune system[175].

The finding of the relevance of DSAs in determining ABMR and reduced graft function for any transplanted organ led to search for new strategies in organ immunosupppression. A systematic review[176] on the induction therapy in HTx concluded that acute rejection might be reduced by IL-2R antibodies compared with no induction and by the antithymocyte globulin (ATG) compared with IL-2R antibodies. Similarly, the depleting antibody induction has become the mainstay of immunosuppression in pancreas TX[177].

In KTx the use of ATG is associated with a significant reduction of DSAs and ABMR[178]. The Alemtuzumab induction therapy obtains similarly good results in a systematic review[179]. Further induction trials in the attempt to prevent ABMR with rituximab are ongoing, including the Rituximab Induction in Renal Tx (ReMIND) trial (Clinical-Trials.gov No. NCT01095172)[180,181]. No result has been obtained with Rituximab in the treatment of ABMR as reported from a phase Ⅲ multicenter, randomized, placebo-controlled trial (RITUX ERAH)[182].

New drugs recently introduced in the market or still waiting for approval

Prevention and treatment of ABMR: Eculizumab, the humanized anti C5 antibody is among the new drugs recently used in the prevention of the ABMR in KTx. Its efficacy was recently assessed in one study[183]. There is an ongoing, multicenter, international, randomized trial testing the role of eculizumab that may clarify its utility (NCT00670774)[184].

Limited clinical trial evidence suggests that the proteasome inhibitor Bortezomib may be useful to treat the ABMR following KTx[185]. Agents targeting the B activating factors belonging to the TNF Family (BAFF) pathway which co-stimulates B cell survival and expansion are also in the clinical development as atacicept and belimumab[186].

A further possibility in the field of ABMR is complement inhibition by C1-esterase inhibitors. A trial studying the safety and tolerability of the C1 inhibitor therapy in the prevention of the acute rejection is now ongoing (Clinical Trials gov NCT01134510).

New drugs in KTx: Belatacept, a fusion receptor protein that blocks the co-stimulation pathway CD80/CD86-CD28, was recently approved for the prevention of acute rejection in KTx. In 2013 two papers reported the results at 5 years of immunosuppression with belatacept + MMF and steroids respect to standard CsA maintenance immunosuppression[187,188]. Continued treatment with belatacept was associated with a consistent safety profile and sustained improvement in renal function *vs* CsA overtime.

In a smaller study Kirk *et al*[189] documented the feasibility of an immunosuppressive therapy in KTx with belatacept only, without maintenance steroids or CNIs after alemtuzumab induction. Another co-stimulation pathway is the CD40/CD40L pathway. Humanized anti CD40 antibodies prevented the acute rejection and prolonged the renal graft in non-human primates. In addition, these anti-CD40 antibodies appear safe and effective as maintenance immunosuppressive therapies[190,191]. To date 5 monoclonal antibodies directed against CD40 have been studied for different diseases including KTx (ClinicalTrials.gov NCT01780844).

Alefacept is a recombinant LFA3/IgG1 fusion protein that reduces the number of memory T cells. After its

successful use in psoriasis, a recent study evaluated the efficacy of alefacept when combined with TAC, MMF and steroids in renal transplant patients[192]. Six-month efficacy, safety and tolerability were similar to control group, but the trial was too short to draw conclusions.

Janus kinase (JAKs), are a cytoplasmic tyrosine kinases that participate in the signaling of a broad range of cell surface receptors. JAK3 inhibition by tofacitinib in KTx trials in humans[193,194] have demonstrated tofacitinib to be non inferior to CsA for rejection rates and graft survival, however there was a trend towards more infections.

Sotrastaurin (AEB071) is a small molecular weight immunosuppressant that blocks the early T cell activation through selective inhibition of protein kinase C, crucial for IL-2 and interferon gamma production. In a phase II trial[195] sotrastaurin at a dose of at least 200 mg/d + reduced TAC had comparable efficacy to mycophenolic acid (MPA) in prevention of rejection. In another phase II study[196] sotrastaurin + everolimus compared to CsA + EVR had higher efficacy rates failure.

New drugs in pancreas Tx and ICTx: In pancreas Tx, after induction therapy the most widely used maintenance protocols are based on TAC and MMF with steroid withdrawal[197]. Considering the recent documented negative impact of DSAs on pancreas Tx, whether promising novel agents such as sotrastaurin, tofacitinib, belatacept, bortezomib or eculizumab will prove to be beneficial for pancreas Tx requires further investigations.

A long-term insulin-independence after ICTx was documented in 10 patients adding efalizumab or belatacept to the standard immunosuppression[64]. In another study[65] efalizumab was compared to belatacept and has been documented that efalizumab increases percentages of the circulating Tregs and profoundly suppresses T-cell reactivity, thus promoting the transplantation tolerance.

Combining anti-inflammatory biologics to maintenance immunosuppression has led to improved success rate. Naziruddin *et al*[66], adding etanercept (TNF alpha antagonist) to immunosuppression obtained protection from inflammatory reaction during the peritransplant period. The same authors obtained an even better protection adding Anakinra (IL-1 beta blocker) to Etanercept[66]. Another group obtained excellent results adding Reparixin (CXCL8 inhibitor) to the immunosuppressive therapy[67,68].

The stabilization of Glucagon-Like-Peptide-1 (GLP-1) by inhibiting Dipeptidyl Peptidase IV by sitagliptin increases beta cell mass by modulating vascularization[198]. To date two official trials are ongoing on the effect of sitagliptin (NCT00853944 and NCT01186562).

New drugs in LTx: In liver transplantation new drugs have been principally used to protect the IRI. Attempt to protect the IRI may involve several strategies and several pathways[92-95]. Elias-Miro *et al*[92] evaluated antioxidant strategies to reduce the oxidative stress. The positive Pentoxifylline effect seems to be related to the inhibition of TNF alpha according Genoves *et al*[93].

Tiriveedhi *et al*[94] found a protective effect of Bortezomib on IRI. This proteosoma inhibitor effectively attenuates the IRI by inhibiting the matrix metalloproteinase and the chitinase 3-like 1 (YLK-40) both involved in the extracellular matrix deposition and fibrosis principally in steatotic livers. The complement pathway is also involved in the IRI and a recent and promising study in the mice[95] documented that the C1-esterase inhibitor administration attenuates the liver injury compared to controls.

New drugs in LuTx: New drugs in the field of LuTx are represented by pirfenidone and the C1 esterase inhibitor. Pirfenidone, a small synthetic non peptide molecule demonstrated a potent antifibrotic effect by inhibiting the transforming growth factor beta (TGF beta) and TNF alpha, important mediators of fibrosis and inflammation. Its usefulness has been principally suggested in the lung transplant patients with RAS[199].

Over the last few years, the development of innovative techniques such as EVLP or the refinement in the artificial support methods as Extracorporeal Membrane Oxygenations also contributed to treat and redefine the outcomes of patients with PGD. A very recent study by Sommer *et al*[138] reported a trial with C1-esterase- inhibitor in patients affected by severe PGD. The one year survival was significantly higher than that of not treated patients.

NEW INSIGHTS ON TRANSPLANT TOLERANCE

One of the hallmarks of the adaptive immune system is its ability to recognize a vast number of different antigens. This ability is a consequence of the large lymphocyte repertoire, in which each cell has a different antigen receptor generated by the process of somatic recombination. This process is able to produce an estimate of 10^{15} different lymphocyte clones, each with a different antigen receptor that can hypothetically recognize any naturally occurring structure[200]. Since the somatic recombination is a random process, it generates T cell clones that can recognize self-structures or self-peptides (auto antigens). The mechanism used by the immune system in order to avoid a possible harmful immune response against an individual's own cells and tissues, is known as the immune tolerance and can be classified into central and peripheral tolerance.

Immune tolerance in transplantation is defined as a specific absence of a destructive immune response to a transplanted tissue without immunosuppression. Operative criteria are the complete withdrawal of immunosuppression followed by no evidence for rejection for the transplanted organ for over one year. In humans is characterized by specific *in vitro* non-responsiveness to the donor.

Induction of tolerance differs according the transplanted organ. Indeed, although up to 20% of liver transplant recipients may be successfully withdrawn from immunosuppression[201]; operational tolerance to renal allograft appears to be much

less frequent. In a recent review, Ruiz *et al*[202] reviewed the new strategies to induce the long-term acceptance to organ transplantation. These include: (1) Mixed chimerism as a strategy to induce allograft tolerance; (2) Dendritic cells and Regulatory Macrophages; (3) Exosomes and Phagosomes as tools for alloantigen delivery; (4) Apoptotic cells; (5) Regulatory T cells; and (6) Mesenchimal Stromal/Stem cells.

In the recent American Society of Transplantation (AST) Cutting Edge of Transplantation meeting, held in Arizona (US) February 13th-15th 2014, the best approaches to induce renal allograft tolerance have been reviewed. They are principally two: (1) Tolerance through induction of durable chimerism. In HLA disparate patients the protocols to date principally used are the Massachusetts General Hospital and the Northwestern University protocols; and (2) Immunomodulation through use of donor hematopoietic stem cells, as the Northwestern University protocol.

Mixed chimerism is defined as the coexistence of donor and recipient hematopoietic cells after allogeneic bone marrow transplantation (BMT). To be considered mixed chimerism, donor cells in the blood must represent more than 1% of the total cells. To induce a state of mixed chimerism, it is necessary to perform a conditioning treatment in order to allow the donor bone marrow acceptance. Currently used mixed chimerism protocols induce robust donor-specific tolerance and allow long-term acceptance of fully mismatched skin grafts in murine models[203].

Recently Kawai *et al*[204] reported the results of a study of combined kidney and bone marrow transplantation without maintenance immunosuppression. The conditioning regimen consisted in cyclophosphamide, thymic irradiation, antiCD20 monoclonal antibody and an 8 to 14 mo course of CNIs.

The major problems encountered with these protocols have been "the engraftment syndrome" which causes transient renal dysfunction[205] and the occurrence of low levels of DSAs after discontinuation of immunosuppression. To overcome the engraftment syndrome, the authors have considered the use of low-dose total-body irradiation rather than cyclophosfamide as preconditioning treatment. DSAs occurrence caused an increase of anti CD20 administration.

As myeloablative conditioning is not ethically accepted due to the high risk involved in this type of conditioning, non myeloablative conditioning has emerged as an alternative to induce tolerance through mixed chimerism. Using a simultaneous bone marrow and kidney transplantation and a preconditioning protocol consisting in the co-stimulatory blockade with anti CD154 antibody, Kawai *et al*[206] and Wekerle *et al*[207] achieved the establishment of mixed chimerism in non-human primates. Later on, Kawai *et al*[208] reported tolerance induction using pharmacological immunosuppression and thymic irradiation. The main obstacle remains the presence of the memory T cells that can cross-react with alloantigens[209].

Other immunomodulatory cells with a high potential in future therapies in transplantation are hematopoietic mesenchimal stem cells (MSCs). It is well known that bone-marrow derived MSCs have the capacity to migrate to inflammatory sites and regulate the function of most immune cells through direct contact and/or by cytokine secretion[210].

Leventhal *et al*[211] developed an approach using a bioengineered mobilized cellular product enriched for hematopoietic stem cells (HSC) and tolerogenic CD8 positive/T cell receptor (TCR)$^-$ graft facilitating cells (FCs), combined with non-myeloablative conditioning. This allows the engraftment, a durable chimerism, and the tolerance induction in highly mismatched related and unrelated donor-recipient pairs.

The same author[212] reported in 2013 an intermediate-term follow up of this phase Ⅱ trial. All 20 patients demonstrated donor specific hypo-responsiveness and were weaned from full-dose immunosuppression. Complete immunosuppression withdrawal at 1 year was successful with durable chimerism in the majority of patients. No graft *vs* host disease or engraftment syndrome has been reported. In all the cited studies a predictive biomarker for success *vs* failure in weaning immunosuppression has not been reliably identified and validated so as to be used as a tool to discontinue immunosuppression.

Leventhal *et al*[213] documented that durable chimerism predicts the outcome. Moreover, the immune/inflammatory gene expression in the peripheral blood and urine were differentially down regulated between tolerant and non tolerant recipients. As aforementioned memory T cells (Tm) represent a major barrier for immunosuppression and tolerance induction after solid organ transplantation. Taking into consideration the critical role of the intrinsic apoptosis pathway in the generation and maintenance of Tm, Cippà *et al*[214] developed a new concept to deplete alloreactive Tm by targeting B Cell Lymphoma-2 (Bcl-2) proteins. The small-molecule Bcl-2/Bcl-XL inhibit ABT-737 efficiently induced apoptosis in alloreactive Tm *in vitro* and *in vivo* and prolonged skin graft survival in sensitized mice. Since Bcl-2 inhibitors yielded encouraging safety results in cancer trials, this novel approach might represent a substantial advance to prevent the allograft rejection and induce tolerance in sensitized recipients.

The mechanisms above mentioned to induce tolerance are almost the same for the liver, even if the liver has particular tolerogenic properties that allow its being spontaneously acceptable in some animal species. The liver structure is considered to favor a tolerogenic environment. Indeed several studies demonstrated that the liver capacity to induce tolerance partly results from the in situ T-cell activation. The hepatocytes, as non-professional antigen presenting cells (APCs), may play key roles in regulating the immune responses and facilitating tolerance induction[215]. Warren *et al*[216] documented that the intrahepatic lymphocytes and the circulating naïve CD8+ cells could interact with the hepatocytes by means of cytoplasmic extensions capable of going through the liver sinusoidal endothelial cells fenestrations. This local activation of T cells by the hepatocytes provides the latter with a significant role as APCs and induces tolerance development in the liver[217]. The peripheral tolerance

mechanisms also play a role in liver graft spontaneous tolerance. As for kidney, also for the liver the most significant mechanism in the tolerance induction is the chimerism[218]. In humans BMT-induced mixed chimerism has been shown to confer the acceptance of donor liver allograft without long-term immunosuppression. However, recipients must be able to withstand the conditioning regimens that allow donor stem cell to engraft.

NEW INSIGHTS ON MAJOR COMPLICATIONS IN TRANSPLANTED PATIENTS: INFECTIONS AND CANCERS

Infections

Infections post solid organ transplantation (SOT) is one of the more important complications. In 2013 many papers have been published on this topic. Among these, the most relevant, in our opinion are: (1) The publication of the third Edition of the American Society of Transplantation on Infectious Disease Guidelines[219]; (2) the publication of the Public Health Service (PHS) Guidelines for Preventing Transmission of Human Immunodeficiency Virus (HIV), HBV and HCV through organ transplantation[220]; (3) the International Consensus Guidelines on the Management of CMV in SOT[221]; and (4) an overview on CMV and the Herpes Viruses in transplantation[222].

Two main factors increase the risk for transplanted patients for infections following transplantation: (1) Risk related to the continuous expanding pool of marginal donors; and (2) Risk related to the requirement to increase immune suppression to treat rejection after SOT. In particular the use of antilymphocyte preparations and many of an increasing diverse list of biologic agents have been associated with an enhanced risk of infection[223].

Overall the risk factors that predisposes to infections in the recipients of SOT may be categorized as being present before transplant within the recipient and those secondary to intraoperative and post-transplant events[224]. Organ transplant recipients are at risk of acquiring pathogens from donors with active or latent infections at the time of the procurement. Examples of pathogens associated with expected donor-derived infections include CMV, Epstein Barr Virus and Toxoplasma. Of greater concern is the development of unexpected donor-derived infections from a growing number of pathogens, including Mycobacterium tubercolosis, Histoplasma, West Nile virus, HBV, HCV and HIV.

Although OPTN policy requires that all potential deceased organ donors are screened for HIV, HBV and HCV by serology, no current policy requires the use of nuclear molecular acid testing (NAT) for donor screening. In 2013 an electronic survey was sent to 58 Organ Procurement Organizations (OPOs) in the United States to assess the current screening practices[225]. All OPOs performed the required serology screening, even if only 52% performed NAT for HIV and HCV. Moreover, respect to a previous survey made in 2008[226], the number of OPOs performing NAT has increased and more OPOs are now testing all donors.

In 2013 the PHS published new Guidelines for reducing HIV, HBV and HCV transmission through organ transplantation[220]. These Guidelines superseded the 1994 PHS Guidelines[227]. Most significant changes are: (1) Expanding the Guideline to include HBV and HCV in addition to HIV; (2) Using factors known to be associated with an increased likelihood of recent HIV, HBV or HCV infection; and (3) Limiting the focus to organs and blood vessel conduit recovered for organ transplantation because the FDA implemented more comprehensive regulations for human cell and tissue products[228].

These guidelines include 34 recommendations on risk assessment of living and deceased donors; informed consent discussion with transplant candidates; testing of recipients' pre and post transplant, collection and/or storage of donor and recipient specimens and tracking and reporting of HIV, HBV and HCV.

Studies on specific pathogens

The human BK polyomavirus is the major cause of polyomavirus-associated nephropathy (PyVAN). Because effective antiviral therapies are lacking, screening kidney transplant patients for BKV replication in urine and blood has become the key recommendation to guide the reduction of immunosuppression in patients with BKV viremia. Retransplantation after PyVAN is largely successful, but requires close monitoring for recurrent BK viremia[229].

Sood *et al*[230] evaluated the relationship of pre-transplantation BK virus-specific donor and recipient serostatus to post-transplant BKV infection. Overall infection was highest in the D+R-group and lowest in the D-R-group. BKV serostatus may be used to risk stratify patients for post-transplantation infection.

CMV remains one of the most common complications affecting SOT, with significant morbidity and occasional mortality. In addition to the direct effects of CMV infection and disease, there are indirect effects, both general and transplant specific, which may significantly impact the outcomes.

An international panel of experts was convened by late 2012 to revise and expand evidence and expert opinion-based consensus guidelines. The reports of such recommendations have been published in 2013[221]. Viral culture of blood or urine has a very limited role for the diagnosis of the disease. Histology/immune-histochemistry is the preferred method for diagnosis of tissue-invasive disease. Quantitative nucleic acid amplification testing (QNAT) is preferred for diagnosis, decision regarding pre-emptive therapy and monitoring response to therapy. If QNAT is not available, antigenemia is an acceptable alternative.

Both universal prophylaxis and pre-emptive strategies are viable approaches for the prevention of CMV disease. For D+R- the use of either prophylaxis or pre-emptive therapy after kidney and liver transplant are recommended. For

D+R- the use of prophylaxis over pre-emptive therapy after heart and lung Tx is recommended. When a pre-emptive therapy strategy is used, it is recommended that the centers develop and validate their local protocol[231]. For non-severe CMV disease, Valganciclovir or intravenous Ganciclovir are recommended as first line treatment, while dose reduction of immunosuppressive therapy should be considered in severe CMV disease.

CMV vaccines are in preclinical, phase I and phase Ⅱ trials[232,233]. The primary goal of a CMV vaccine should be to prevent or to modulate CMV replication and/or CMV disease. Herpes viruses infect most animal species. Infections due to the eight human herpes viruses (HHV) are exacerbated by immunosuppression in SOT. The special features of the herpes virus life cycle include the ability to establish latent, non-productive infection and the life-long capacity for reactivation to productive lytic infection. Interactions between the latent virus and the immune system determine the frequency and severity of symptomatic infection. In an overview Fishmann[222] reports how the immunologic and cellular effects of herpes virus infections contribute to risk for the opportunistic infections and the graft reactions. Among the most important advances in transplantation are laboratory assays for the diagnosis and monitoring of herpes virus infections and antiviral agents with improved efficacy in the prophylaxis and therapy.

HCV infection is common in SOT recipients and is a significant cause of morbidity and mortality after transplantation. The severity of HCV infection in liver transplantation has been already discussed in the liver chapter. Carbone *et al*[234] reviewed the extent of the problem in donors, kidney, heart and lung transplant candidates.

In HCV-infected kidney allograft recipient, the progression of fibrosis should be evaluated serially. Transplantation of kidneys from HCV positive donors should be restricted to HCV positive recipients. HCV antiviral therapy should be considered for all HCV-RNA positive kidney transplant candidates. The impact of HCV infection on survival in heart and lung transplantation is unclear but even assuming a worse survival in those receiving HCV-infected organs, it has not been evaluated whether they do better or worse than those remaining on the waiting list.

Cancers

Malignancies after SOT are divided into three chapters: donor transmission of cancer, recipients with prior cancer and general epidemiology of cancers after SOT.

Donor transmission of cancers: Xiao *et al*[235] reviewed all case reports, case series and registry studies that described the outcomes of the kidney transplant recipients with donor cancer transmission published up to December 2012. The most common transmitted cancer types were renal cancer, followed by melanoma, lymphoma and lung cancer. Overall the risk of donor transmission of cancer appears low, but there is a high likelihood of reporting bias. The findings of this review support the current recommendation for rejecting organs from donors with a previous history of melanoma and lung cancer, but suggest that the use of donor kidneys with a history of small, incidental renal cell cancer may be reasonable.

At the 2013 American Transplant Congress (ATC), Desai *et al*[236] analyzed data from 30000 recipients of SOT from more than 14000 donors in the National Transplant Registry (NTR) in the United Kingdom to determine whether the risk of cancer transmission from organ donors could be eliminated.They found a very low rate of donor-origin cancer: only 0.6%. The risk of cancer transmission cannot be eliminated because the presence of cancer was not known at donation. This finding is useful to obtain an informed consent for prospective recipients, but in transplants other than kidney and pancreas, the benefits should be planned against the risk of remaining on the waiting list.

In another study the same group looked at donor transmission in a different way, linking donor data to the cancer registries, to determine the risk for donor transmission to the recipients analyzing more than 17000 donors[237,238]. More than 200 (about 1.5%) had a cancer history. Although 61 of these donors were at high risk for transmission, none transmitted their cancer to any of the recipients. These data raise the question about whether we are being too strict and losing potential donors. To put this in context, the death rate on the waiting list is 5% to 15% per year compared with this very low rate of donor transmission of cancer.

At 2013 ATC, Engels *et al*[239,240] analyzed data from the SOT registry in the United States to link donor organs to 15 cancer registries. They concluded that recipients of donors with the cancer did not have significantly increased incidence of cancer compared with the recipients whose donors did not have cancer.

Risk of recurrence of preexisting cancer in organ recipients: Again Desai *et al*[241] analyzed data from NTR in United Kingdom on the issue of the recurrence of a preexisting cancer in an organ transplant recipient. They identified 64 (1.32%) recipients with a history of cancer diagnosed before organ transplantation.

Five recipients developed cancer recurrence and the rate of recurrence within 10 years was 11.9%. This study is interesting because data on this topic are sparse, and it's increasingly become a problem for nephrologists as the ESRD population ages and the burden of co morbidity in KTx candidates is increasing. Although this is a small cohort, the data are useful because this is one of the only contemporary studies of cancer recurrence risk in SOT recipients.

De novo post-transplant malignancies

De novo post-transplant malignancies (PTM) are a serious complication post-transplantation. In an analysis of the US National Transplant Data, Sampaio *et al*[242] analyzed 200000 recipients of kidney, liver, heart and lung. The PTM incidence was 8.03, 11, 14.4 and 19.8 in KTx, LTx, HTx and LuTx respectively. The PTM recipients were older,

mostly white and males in all SOTs.

A cohort study was conducted in Australia using population based, liver and cardiothoracic registries[243]. During a median 5-year follow-up, the risk of any cancer in the liver and cardiothoracic recipients, was significantly elevated compared to the general population (Standardized Incidence Ratio = 2.62). An excess risk was observed for 16 cancer types, predominantly cancers with a viral etiology. The adjusted HR for any cancer in all recipients was higher in heart compared to liver (HR = 1.29). Understanding the factors responsible for the higher cancer incidence in cardiothoracic compared to liver recipients has the potential to lead to targeted cancer prevention strategies in this high risk population.

Two interesting presentations at the ATC 2013 focused the association between the development of a skin cancer and the subsequent development of a solid organ tumor. Cho *et al*[244] analyzed data from OPTN/UNOS database and compared the incidence of solid tumors in organ recipients with and without melanoma skin cancer (NMSC). Developing a skin cancer was a risk factor for developing a solid tumor: 9.4% in those who developed a skin cancer *vs* 3.3% in those who did not.

A very similar study was conducted in Australia. McDonald *et al*[245] analyzed the data from Australia and New Zealand Dialysis and Transplantation (ANZDATA). They found that having a NMSC increased the risk of other cancers by 1.2%. These studies are interesting because skin cancers may be a useful tool to identify people at higher risk for developing other cancers.

The International Transplant Skin Cancer Collaborative (ITSCC) and its European counterpart: Skin Cancer in Organ Transplant Patients Europe (SCOPE) held by the end of 2012 a joint meeting that has been recently published[246].

The cutaneous squamous cell carcinoma (CSCC) incidence has been previously ascribed to immunosuppressive therapies. The decreased immunosurveillance by innate and adapted immune cells has been investigated and the specific role of macrophages. The direct effect of immune suppression on keratinocyte development has been postulated as well. Because of the need of CSCC epidemiology studies, was outlined an international collaboration between ITSCC and SCOPE to prospectively study CSCC in transplant patient.

CONCLUSION

In few fields of human medical knowledge, the science is so rapidly evolving as in organ transplantation. In this review the principal news that occurred by 2013 are described. By, because some news refers to meeting, consensus conference or guidelines held in the late 2012 but published in 2013; others on the contrary were held in 2013, but published in the first months of 2014.

In these conclusions we highlight several points, which in our opinion represent new frontiers in transplantation. While the donor pool is not as large as it would be necessary, the donor shift towards the so called ECD realize new problems in the organ allocations and in the organ preservation, Relevant news has been found in the field of antibody mediated rejection, both acute and chronic. This kind of rejection involves any solid organ, even if the majority of studies have been done in the kidneys. A new Banff conference has been held in 2013 and new classifications have been made whenever possible.

The ischemia reperfusion injury concerns also any organ. In this field the majority of researches have been made in liver transplantation. The innate immunity is involved and new drugs have been found or are on clinical trials. Pancreas transplantation is now a therapeutic option also for T2DM, even if a limiting factor is the shortage of pancreas available. Islet cell transplantation is improving with new techniques for implantation and for microencapsulation.

Heart transplantation has now optimal graft survival rate and also the MCS is evolving so to represent an alternative to transplantation in addition to bridge to transplantation. New strategies for primary graft dysfunction in lung transplantation have been found as well as a better understanding of the different types of chronic allograft dysfunction. New drugs appear at the horizon, principally for kidney transplantation. In particular, drugs targeting the B cells and the complement pathway are interesting, considering the relevance of ABMR. Other drugs for different organs such as liver, pancreatic islet and lung are being studied in clinical trials. Anti-inflammatory drugs enhance the effect of the immunosuppressant drugs.

The knowledge on tolerance is improving either applying bone marrow cells or mesenchimal stem cells. The infections and the cancers remain among the principal drawbacks in transplantation and several meetings and conferences have been held principally to elaborate guidelines to check and control HCV, HIV, CMV and others HHV.

The need to realize international registries for an improved knowledge of cancer epidemiology has been stressed by several authors. Finally a point of weakness in the field of transplantation is the differences that exist among the countries in the world. The different transplant rate depends also by the fact that in several countries peoples do not reach end stage disease. This probably represents the hardest frontier to be afforded.

REFERENCES

1 OPTN/SRTR 2012 Annual Data Report Introduction. *Am J Transplant* 2014; **14** Suppl 1: 8-10 [DOI: 10.1111/ajt.12578]

2 **Kasiske BL**, Skeans MA, Leighton TR, Ghimire V, Leppke SN, Israni AK. OPTN/SRTR 2011 Annual Data Report: international data. *Am J Transplant* 2013; **13** Suppl 1: 199-225 [PMID: 23237702 DOI: 10.1111/ajt.12026]

3 **Garcia GG**, Harden P, Chapman J. The global role of kidney transplantation. *Lancet* 2012; **379**: e36-e38 [PMID: 22405254 DOI: 10.1016/S0140-6736(12)60202-5]

4 **Israni AK**, Zaun D, Rosendale JD, Snyder JJ, Kasiske BL. OPTN/SRTR 2012 Annual Data Report: deceased organ donation. *Am J Transplant* 2014; **14** Suppl 1: 167-183 [PMID: 24373172 DOI: 10.1111/ajt.12585]

5 **Pondrom S**. Fewer living: a decline in living donors may be due to multiple factors. *Am J Transplant* 2014; **14**: 245-246

[PMID: 24472188 DOI: 10.1111/ajt.12657]
6 **Heaphy EL**, Goldfarb DA, Poggio ED, Buccini LD, Flechner SM, Schold JD. The impact of deceased donor kidney risk significantly varies by recipient characteristics. *Am J Transplant* 2013; **13**: 1001-1011 [PMID: 23406350 DOI: 10.1111/ajt.12154]
7 **Singh SK**, Kim SJ. Does expanded criteria donor status modify the outcomes of kidney transplantation from donors after cardiac death? *Am J Transplant* 2013; **13**: 329-336 [PMID: 23136921 DOI: 10.1111/j.1600-6143.2012.04311.x]
8 **Matsuno N**, Kobayashi E. Challenges in machine perfusion preservation for liver grafts from donation after circulatory death. *Transplant Res* 2013; **2**: 19 [PMID: 24283383 DOI: 10.1186/2047-1440-2-19]
9 **Bruns H**, Schemmer P. Machine perfusion in solid organ transplantation: where is the benefit? *Langenbecks Arch Surg* 2014; **399**: 421-427 [PMID: 24429900 DOI: 10.1007/s00423-014-1161-2]
10 **Rodrigue JR**, Schold JD, Mandelbrot DA. The decline in living kidney donation in the United States: random variation or cause for concern? *Transplantation* 2013; **96**: 767-773 [PMID: 23759882 DOI: 10.1097/TP.0b013e318298fa61]
11 **Tong A**, Chapman JR, Wong G, Josephson MA, Craig JC. Public awareness and attitudes to living organ donation: systematic review and integrative synthesis. *Transplantation* 2013; **96**: 429-437 [PMID: 23677051 DOI: 10.1097/TP.0b013e31829282ac]
12 **Campbell P**. Clinical relevance of human leukocyte antigen antibodies in liver, heart, lung and intestine transplantation. *Curr Opin Organ Transplant* 2013; **18**: 463-469 [PMID: 23838652 DOI: 10.1097/MOT.0b013e3283636c71]
13 **Süsal C**, Roelen DL, Fischer G, Campos EF, Gerbase-DeLima M, Hönger G, Schaub S, Lachmann N, Martorell J, Claas F. Algorithms for the determination of unacceptable HLA antigen mismatches in kidney transplant recipients. *Tissue Antigens* 2013; **82**: 83-92 [PMID: 23718733 DOI: 10.1111/tan.12137]
14 **Böhmig GA**, Fidler S, Christiansen FT, Fischer G, Ferrari P. Transnational validation of the Australian algorithm for virtual crossmatch allocation in kidney paired donation. *Hum Immunol* 2013; **74**: 500-505 [PMID: 23380140 DOI: 10.1016/j.humimm.2013.01.029]
15 **Blumberg JM**, Gritsch HA, Reed EF, Cecka JM, Lipshutz GS, Danovitch GM, McGuire S, Gjertson DW, Veale JL. Kidney paired donation in the presence of donor-specific antibodies. *Kidney Int* 2013; **84**: 1009-1016 [PMID: 23715120 DOI: 10.1038/ki.2013.206]
16 **Garonzik-Wang JM**, Sullivan B, Hiller JM, Cass V, Tchervenkow J, Feldman L, Baran D, Chaudhury P, Cantarovich M, Segev DL, Montgomery RA. International kidney paired donation. *Transplantation* 2013; **96**: e55-e56 [PMID: 24100847 DOI: 10.1097/TP.0b013e3182a68879]
17 **Sharif A**. Unspecified kidney donation--a review of principles, practice and potential. *Transplantation* 2013; **95**: 1425-1430 [PMID: 23778567 DOI: 10.1097/TP.0b013e31829282eb]
18 **Matas AJ**, Smith JM, Skeans MA, Thompson B, Gustafson SK, Schnitzler MA, Stewart DE, Cherikh WS, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2012 Annual Data Report: kidney. *Am J Transplant* 2014; **14** Suppl 1: 11-44 [PMID: 24373166 DOI: 10.1111/ajt.12579]
19 **Gondos A**, Döhler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. *Transplantation* 2013; **95**: 267-274 [PMID: 23060279 DOI: 10.1097/TP.0b013e3182708ea8]
20 **Willoughby LM**, Fukami S, Bunnapradist S, Gavard JA, Lentine KL, Hardinger KL, Burroughs TE, Takemoto SK, Schnitzler MA. Health insurance considerations for adolescent transplant recipients as they transition to adulthood. *Pediatr Transplant* 2007; **11**: 127-131 [PMID: 17300489 DOI: 10.1111/j.1399-3046.2006.00639.x]
21 **Kennedy J**, Erb C. Prescription noncompliance due to cost among adults with disabilities in the United States. *Am J Public Health* 2002; **92**: 1120-1124 [PMID: 12084695]
22 **Butler JA**, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation* 2004; **77**: 769-776 [PMID: 15021846]
23 **Woodward RS**, Page TF, Soares R, Schnitzler MA, Lentine KL, Brennan DC. Income-related disparities in kidney transplant graft failures are eliminated by Medicare's immunosuppression coverage. *Am J Transplant* 2008; **8**: 2636-2646 [PMID: 19032227 DOI: 10.1111/j.1600-6143.2008.02422.x]
24 **Schold JD**, Heaphy EL, Buccini LD, Poggio ED, Srinivas TR, Goldfarb DA, Flechner SM, Rodrigue JR, Thornton JD, Sehgal AR. Prominent impact of community risk factors on kidney transplant candidate processes and outcomes. *Am J Transplant* 2013; **13**: 2374-2383 [PMID: 24034708 DOI: 10.1111/ajt.12349]
25 **Cavaillé-Coll M**, Bala S, Velidedeoglu E, Hernandez A, Archdeacon P, Gonzalez G, Neuland C, Meyer J, Albrecht R. Summary of FDA workshop on ischemia reperfusion injury in kidney transplantation. *Am J Transplant* 2013; **13**: 1134-1148 [PMID: 23566221 DOI: 10.1111/ajt.12210]
26 **Pepe MS**, Etzioni R, Feng Z, Potter JD, Thompson ML, Thornquist M, Winget M, Yasui Y. Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst* 2001; **93**: 1054-1061 [PMID: 11459866]
27 **Linkermann A**, Hackl MJ, Kunzendorf U, Walczak H, Krautwald S, Jevnikar AM. Necroptosis in immunity and ischemia-reperfusion injury. *Am J Transplant* 2013; **13**: 2797-2804 [PMID: 24103029 DOI: 10.1111/ajt.12448]
28 **Lau A**, Wang S, Jiang J, Haig A, Pavlosky A, Linkermann A, Zhang ZX, Jevnikar AM. RIPK3-mediated necroptosis promotes donor kidney inflammatory injury and reduces allograft survival. *Am J Transplant* 2013; **13**: 2805-2818 [PMID: 24103001 DOI: 10.1111/ajt.12447]
29 **Mannon RB**. Necroptosis in solid organ transplantation: a missing link to immune activation? *Am J Transplant* 2013; **13**: 2785-2786 [PMID: 24103049 DOI: 10.1111/ajt.12450]
30 **Shuh M**, Bohorquez H, Loss GE, Cohen AJ. Tumor Necrosis Factor-α: Life and Death of Hepatocytes During Liver Ischemia/Reperfusion Injury. *Ochsner J* 2013; **13**: 119-130 [PMID: 23531747]
31 **Djamali A**, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M. Diagnosis and management of antibody-mediated rejection: current status and novel approaches. *Am J Transplant* 2014; **14**: 255-271 [PMID: 24401076 DOI: 10.1111/ajt.12589]
32 **Taniguchi M**, Rebellato LM, Cai J, Hopfield J, Briley KP, Haisch CE, Catrou PG, Bolin P, Parker K, Kendrick WT, Kendrick SA, Harland RC, Terasaki PI. Higher risk of kidney graft failure in the presence of anti-angiotensin II type-1 receptor antibodies. *Am J Transplant* 2013; **13**: 2577-2589 [PMID: 23941128 DOI: 10.1111/ajt.12395]
33 **Giral M**, Foucher Y, Dufay A, Van Huyen JP, Renaudin K, Moreau A, Philippe A, Hegner B, Dechend R, Heidecke H, Brouard S, Cesbron A, Castagnet S, Devys A, Soulillou JP, Dragun D. Pretransplant sensitization against angiotensin II type 1 receptor is a risk factor for acute rejection and graft loss. *Am J Transplant* 2013; **13**: 2567-2576 [PMID: 23919486 DOI: 10.1111/ajt.12397]
34 **Porcheray F**, Fraser JW, Gao B, McColl A, DeVito J, Dargon I, Helou Y, Wong W, Girouard TC, Saidman SL, Colvin RB, Palmisano A, Maggiore U, Vaglio A, Smith RN, Zorn E. Polyreactive antibodies developing amidst humoral rejection of human kidney grafts bind apoptotic cells and activate complement. *Am J Transplant* 2013; **13**: 2590-2600 [PMID: 23919437 DOI: 10.1111/ajt.12394]
35 **Sis B**, Jhangri GS, Bunnag S, Allanach K, Kaplan B, Halloran PF. Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. *Am J Transplant* 2009; **9**: 2312-2323 [PMID:

19681822 DOI: 10.1111/j.1600-6143.2009.02761.x]
36 **Sellarés J**, Reeve J, Loupy A, Mengel M, Sis B, Skene A, de Freitas DG, Kreepala C, Hidalgo LG, Famulski KS, Halloran PF. Molecular diagnosis of antibody-mediated rejection in human kidney transplants. *Am J Transplant* 2013; **13**: 971-983 [PMID: 23414212 DOI: 10.1111/ajt.12150]
37 **Moreau A**, Varey E, Anegon I, Cuturi MC. Effector mechanisms of rejection. *Cold Spring Harb Perspect Med* 2013; **3**: [PMID: 24186491 DOI: 10.1101/cshperspect.a015461]
38 **Krneta T**, Gillgrass A, Ashkar AA. The influence of macrophages and the tumor microenvironment on natural killer cells. *Curr Mol Med* 2013; **13**: 68-79 [PMID: 22834841 DOI: 10.2174/1566524011307010068]
39 **Haas M**, Sis B, Racusen LC, Solez K, Glotz D, Colvin RB, Castro MC, David DS, David-Neto E, Bagnasco SM, Cendales LC, Cornell LD, Demetris AJ, Drachenberg CB, Farver CF, Farris AB, Gibson IW, Kraus E, Liapis H, Loupy A, Nickeleit V, Randhawa P, Rodriguez ER, Rush D, Smith RN, Tan CD, Wallace WD, Mengel M. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant* 2014; **14**: 272-283 [PMID: 24472190 DOI: 10.1111/ajt.12590]
40 **Bachelet T**, Couzi L, Lepreux S, Legeret M, Pariscoat G, Guidicelli G, Merville P, Taupin JL. Kidney intragraft donor-specific antibodies as determinant of antibody-mediated lesions and poor graft outcome. *Am J Transplant* 2013; **13**: 2855-2864 [PMID: 24102857 DOI: 10.1111/ajt.12438]
41 **Sis B**. Intragraft donor-specific antibody detection: a new test to dichotomize HLA alloantibodies into high and low injurious activity. *Am J Transplant* 2013; **13**: 2787-2789 [PMID: 24102879 DOI: 10.1111/ajt.12440]
42 **Volk HD**, Sawitzki B, Reinke P. Molecular analysis of renal allograft biopsies--more than a nice toy for researchers? *Am J Transplant* 2013; **13**: 539-540 [PMID: 23437880 DOI: 10.1111/ajt.12081]
43 **Reeve J**, Sellarés J, Mengel M, Sis B, Skene A, Hidalgo L, de Freitas DG, Famulski KS, Halloran PF. Molecular diagnosis of T cell-mediated rejection in human kidney transplant biopsies. *Am J Transplant* 2013; **13**: 645-655 [PMID: 23356949 DOI: 10.1111/ajt.12079]
44 **Famulski KS**, Reeve J, de Freitas DG, Kreepala C, Chang J, Halloran PF. Kidney transplants with progressing chronic diseases express high levels of acute kidney injury transcripts. *Am J Transplant* 2013; **13**: 634-644 [PMID: 23356967 DOI: 10.1111/ajt.12080]
45 **Halloran PF**, Pereira AB, Chang J, Matas A, Picton M, De Freitas D, Bromberg J, Serón D, Sellarés J, Einecke G, Reeve J. Microarray diagnosis of antibody-mediated rejection in kidney transplant biopsies: an international prospective study (INTERCOM). *Am J Transplant* 2013; **13**: 2865-2874 [PMID: 24119109 DOI: 10.1111/ajt.12465]
46 **Halloran PF**, Pereira AB, Chang J, Matas A, Picton M, De Freitas D, Bromberg J, Serón D, Sellarés J, Einecke G, Reeve J. Potential impact of microarray diagnosis of T cell-mediated rejection in kidney transplants: The INTERCOM study. *Am J Transplant* 2013; **13**: 2352-2363 [PMID: 23915426 DOI: 10.1111/ajt.12387]
47 **Suthanthiran M**, Schwartz JE, Ding R, Abecassis M, Dadhania D, Samstein B, Knechtle SJ, Friedewald J, Becker YT, Sharma VK, Williams NM, Chang CS, Hoang C, Muthukumar T, August P, Keslar KS, Fairchild RL, Hricik DE, Heeger PS, Han L, Liu J, Riggs M, Ikle DN, Bridges ND, Shaked A. Urinary-cell mRNA profile and acute cellular rejection in kidney allografts. *N Engl J Med* 2013; **369**: 20-31 [PMID: 23822777 DOI: 10.1056/NEJMoa1215555]
48 **Israni AK**, Skeans MA, Gustafson SK, Schnitzler MA, Wainright JL, Carrico RJ, Tyler KH, Kades LA, Kandaswamy R, Snyder JJ, Kasiske BL. OPTN/SRTR 2012 Annual Data Report: pancreas. *Am J Transplant* 2014; **14** Suppl 1: 45-68 [PMID: 24373167 DOI: 10.1111/ajt.12580]
49 **Schulz T**, Pries A, Caliebe A, Kapischke M. Long-term survival after simultaneous pancreas-kidney transplantation with primary function of at least one year--a single-center experience. *Ann Transplant* 2014; **19**: 106-111 [PMID: 24576894 DOI: 10.12659/AOT.889715]
50 **Montiel-Casado MC**, Pérez-Daga JA, Aranda-Narváez JM, Fernández-Burgos I, Sánchez-Pérez B, León-Díaz FJ, Cabello-Díaz M, Rodríguez-Burgos D, Hernández-Marrero D, Santoyo-Santoyo J. Pancreas graft survival in simultaneous pancreas-kidney versus pancreas-after-kidney and pancreas alone transplantations: a single institution experience. *Transplant Proc* 2013; **45**: 3609-3611 [PMID: 24314973 DOI: 10.1016/j.transproceed.2013.10.019]
51 **Lindahl JP**, Hartmann A, Horneland R, Holdaas H, Reisæter AV, Midtvedt K, Leivestad T, Oyen O, Jenssen T. Improved patient survival with simultaneous pancreas and kidney transplantation in recipients with diabetic end-stage renal disease. *Diabetologia* 2013; **56**: 1364-1371 [PMID: 23549518 DOI: 10.1007/s00125-013-2888-y]
52 CITR Investigators 2011 Update from the Collaborative Islet Transplant Registry. *Am J Transplant* 2012; **12** (Suppl 3): S161 [DOI: 10.1111/j. 1600-6143.2012.04112.x]
53 **Cohen DJ**, Ratner LE. Type 2 diabetes: the best transplant option is still uncertain. *Clin J Am Soc Nephrol* 2012; **7**: 530-532 [PMID: 22442186 DOI: 10.2215/CJN.02120212]
54 **Gruessner AC**, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. *Clin Transplant* 2005; **19**: 433-455 [PMID: 16008587 DOI: 10.1111/j.1399-0012.2005.00378.x]
55 **Orlando G**, Stratta RJ, Light J. Pancreas transplantation for type 2 diabetes mellitus. *Curr Opin Organ Transplant* 2011; **16**: 110-115 [PMID: 21150617 DOI: 10.1097/MOT.0b013e3283424d1f]
56 **Sampaio MS**, Kuo HT, Bunnapradist S. Outcomes of simultaneous pancreas-kidney transplantation in type 2 diabetic recipients. *Clin J Am Soc Nephrol* 2011; **6**: 1198-1206 [PMID: 21441123 DOI: 10.2215/CJN.06860810]
57 **Margreiter C**, Resch T, Oberhuber R, Aigner F, Maier H, Sucher R, Schneeberger S, Ulmer H, Bösmüller C, Margreiter R, Pratschke J, Öllinger R. Combined pancreas-kidney transplantation for patients with end-stage nephropathy caused by type-2 diabetes mellitus. *Transplantation* 2013; **95**: 1030-1036 [PMID: 23407544 DOI: 10.1097/TP.0b013e3182861945]
58 **Sener A**, Cooper M, Bartlett ST. Is there a role for pancreas transplantation in type 2 diabetes mellitus? *Transplantation* 2010; **90**: 121-123 [PMID: 20562677 DOI: 10.1097/TP.0b013e3181e5b7e6]
59 **Niederhaus SV**, Leverson GE, Lorentzen DF, Robillard DJ, Sollinger HW, Pirsch JD, Torrealba JR, Odorico JS. Acute cellular and antibody-mediated rejection of the pancreas allograft: incidence, risk factors and outcomes. *Am J Transplant* 2013; **13**: 2945-2955 [PMID: 24102905 DOI: 10.1111/ajt.12443]
60 **Drachenberg CB**, Torrealba JR, Nankivell BJ, Rangel EB, Bajema IM, Kim DU, Arend L, Bracamonte ER, Bromberg JS, Bruijn JA, Cantarovich D, Chapman JR, Farris AB, Gaber L, Goldberg JC, Haririan A, Honsová E, Iskandar SS, Klassen DK, Kraus E, Lower F, Odorico J, Olson JL, Mittalhenkle A, Munivenkatappa R, Paraskevas S, Papadimitriou JC, Randhawa P, Reinholt FP, Renaudin K, Revelo P, Ruiz P, Samaniego MD, Shapiro R, Stratta RJ, Sutherland DE, Troxell ML, Voska L, Seshan SV, Racusen LC, Bartlett ST. Guidelines for the diagnosis of antibody-mediated rejection in pancreas allografts-updated Banff grading schema. *Am J Transplant* 2011; **11**: 1792-1802 [PMID: 21812920 DOI: 10.1111/j.1600-6143.2011.03670.x]
61 **Shapiro AM**, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl*

J Med 2000; **343**: 230-238 [PMID: 10911004 DOI: 10.1056/NEJM200007273430401]
62 **Jahansouz C,** Jahansouz C, Kumer SC, Brayman KL. Evolution of β-Cell Replacement Therapy in Diabetes Mellitus: Islet Cell Transplantation. *J Transplant* 2011 [DOI: 10.1155/2011/247959]
63 **Pepper AR**, Gala-Lopez B, Ziff O, Shapiro AJ. Current status of clinical islet transplantation. *World J Transplant* 2013; **3**: 48-53 [PMID: 24392308 DOI: 10.5500/wjt.v3.i4.48]
64 **Masharani U,** Moassesfar S, Frassetto L, Szot G, Tavakol M, McElroy J, Ramos M, Johnson K, Stock PG, Posselt A. Long Term Insulin Independence After Islet Transplant Alone (ITA) and Pancreas Transplant Alone (PTA) in Patients with Type 1 Diabetes (T1D) – A Single Institution Experience. *Transplantation* 2013; **96**: 6S, S44
65 **Tang Q,** Posselt A, Szot GL, Melli K, Pauli M, Frasetto L, Masharani U, Fong L, Stock PG. Immunological Impact of Efalizumab Versus Belatacept in Islet Transplantation. *Transplantation* 2013; **96**: 6S, 115
66 **Naziruddin B,** Takita M, Kunnathodi F, Shahbazov R, Kanak M, Lawrence M, Onaca N, Levy M. Early Treatment with Etanercept and Anakinra Prevents Islet Graft Damage in Clinical Islet Auto-transplantation. *Transplantation* 2013; **96**: 6S, 5
67 **Maffi P,** Daffonchio L, Ruffini PA, Allegretti M, Citro A, Magistretti P, Melzi R, Mercalli A, Nano R, Sordi V, Secchi A, Piemonti L. Islet Allotransplantation in Type 1 Diabetes: Phase 2 Pilot Study with CXCL8 Inhibitor (reparixin). *Transplantation* 2013; **96**: 6S, 4
68 **Citro A**, Cantarelli E, Maffi P, Nano R, Melzi R, Mercalli A, Dugnani E, Sordi V, Magistretti P, Daffonchio L, Ruffini PA, Allegretti M, Secchi A, Bonifacio E, Piemonti L. CXCR1/2 inhibition enhances pancreatic islet survival after transplantation. *J Clin Invest* 2012; **122**: 3647-3651 [PMID: 22996693 DOI: 10.1172/JCI63089]
69 **Takita M,** Shahabazov R, Kunnathodi F, Mueller C, Kurup P, Kanak M, Lawrence M, Onaca N, Ueno H, Naziruddin B, Levy M. Early Loss of Transplanted Allogeneic Islets Despite T-Cell Depleting Induction: The Role of Autoimmunity in Clinical Islet Transplantation. *Transplantation* 2013; **96**: 6S, 121
70 **Pepper AR,** Gala-Lopez B, Ziff O, Shapiro AM. Revascularization of transplanted pancreatic islets and role of the transplantation site. *Clin Dev Immunol* 2013 [DOI: 10.1155/2013/352315]
71 **Henriksnäs J**, Lau J, Zang G, Berggren PO, Köhler M, Carlsson PO. Markedly decreased blood perfusion of pancreatic islets transplanted intraportally into the liver: disruption of islet integrity necessary for islet revascularization. *Diabetes* 2012; **61**: 665-673 [PMID: 22315321 DOI: 10.2337/db10-0895]
72 **Bellin M,** Hering B, Balamurugan AN, Parazzoli S, Oseid E, Dunn T, Beilman G, Sutherland D, Robertson RP. Alpha Cells in Intraperitoneal, but not Intra-hepatic, Auto-islet Transplants Function Normally During Hypoglycemia in Humans After Total Pancreatectomy and Islet Auto-transplantation. *Transplantation* 2013; **96**: 6S, 7
73 **Espes D,** Lau J, Quach M, Palmer AF, Carisson PO. Hypoxia in Islets After Intramuscular Transplantation can be Overcome by Co-Implantation of Polymerized Hemoglobin. *Transplantation* 2013; **96**: 6S, 44
74 **Buder B**, Alexander M, Krishnan R, Chapman DW, Lakey JR. Encapsulated islet transplantation: strategies and clinical trials. *Immune Netw* 2013; **13**: 235-239 [PMID: 24385941 DOI: 10.4110/in.2013.13.6.235]
75 **Kim WR**, Smith JM, Skeans MA, Schladt DP, Schnitzler MA, Edwards EB, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2012 Annual Data Report: liver. *Am J Transplant* 2014; **14** Suppl 1: 69-96 [PMID: 24373168 DOI: 10.1111/ajt.12581]
76 **Lodhi SA**, Lamb KE, Meier-Kriesche HU. Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. *Am J Transplant* 2011; **11**: 1226-1235 [PMID: 21564524 DOI: 10.1111/j.1600-6143.2011.03539.x]
77 **Schoening WN**, Buescher N, Rademacher S, Andreou A, Kuehn S, Neuhaus R, Guckelberger O, Puhl G, Seehofer D, Neuhaus P. Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. *Am J Transplant* 2013; **13**: 2384-2394 [PMID: 23915357 DOI: 10.1111/ajt.12384]
78 **Jain A**, Singhal A, Fontes P, Mazariegos G, DeVera ME, Cacciarelli T, Lopez RC, Sindhi R, Humar A, Marsh JW. One thousand consecutive primary liver transplants under tacrolimus immunosuppression: a 17- to 20-year longitudinal follow-up. *Transplantation* 2011; **91**: 1025-1030 [PMID: 21378604 DOI: 10.1097/TP.0b013e3182129215]
79 **Duffy JP**, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, Venick RS, Feist S, Goldstein L, Saab S, Hiatt JR, Busuttil RW. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Ann Surg* 2010; **252**: 652-661 [PMID: 20881772 DOI: 10.1097/SLA.0b013e3181f5f23a]
80 **Adam R**, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012; **57**: 675-688 [PMID: 22609307 DOI: 10.1016/j.jhep.2012.04.015]
81 **Kasahara M**, Umeshita K, Inomata Y, Uemoto S. Long-term outcomes of pediatric living donor liver transplantation in Japan: an analysis of more than 2200 cases listed in the registry of the Japanese Liver Transplantation Society. *Am J Transplant* 2013; **13**: 1830-1839 [PMID: 23711238 DOI: 10.1111/ajt.12276]
82 **Singal AK**, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; **95**: 755-760 [PMID: 23370710 DOI: 10.1097/TP.0b013e31827afb3a]
83 **Burton JR**, Everson GT. Management of the transplant recipient with chronic hepatitis C. *Clin Liver Dis* 2013; **17**: 73-91 [PMID: 23177284 DOI: 10.1016/j.cld.2012.09.013]
84 **Jacobson IM**, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405-2416 [PMID: 21696307 DOI: 10.1056/NEJMoa1012912]
85 **Poordad F**, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]
86 **Garg V**, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. *Hepatology* 2011; **54**: 20-27 [PMID: 21618566 DOI: 10.1002/hep.24443]
87 **Croagh CM**, Lubel J. Advances in the management of hepatitis C. *Intern Med J* 2013; **43**: 1265-1271 [PMID: 24330361 DOI: 10.1111/imj.12304]
88 **Sautto GA**, Diotti RA, Clementi M. New therapeutic options for HCV infection in the monoclonal antibody era. *New Microbiol* 2012; **35**: 387-397 [PMID: 23109006]
89 **Datta G**, Fuller BJ, Davidson BR. Molecular mechanisms of liver ischemia reperfusion injury: insights from transgenic knockout models. *World J Gastroenterol* 2013; **19**: 1683-1698 [PMID: 23555157 DOI: 10.3748/wjg.v19.i11.1683]
90 **Mendes-Braz M,** Elias-Miró M, Jiménez-Castro, MB, Casillas-Ramírez A, Ramalho FS, Peralta C. The current state of knowledge of hepatic ischemia-reperfusion injury based on

its study in experimental models. *J Biomed Biotechnol* 2012; [DOI: 10.1155/2012/298657]
91 **Akhtar MZ**, Henderson T, Sutherland A, Vogel T, Friend PJ. Novel approaches to preventing ischemia-reperfusion injury during liver transplantation. *Transplant Proc* 2013; **45**: 2083-2092 [PMID: 23953517 DOI: 10.1016/j.transproceed.2013.04.004]
92 **Elias-Miró M**, Jiménez-Castro MB, Rodés J, Peralta C. Current knowledge on oxidative stress in hepatic ischemia/reperfusion. *Free Radic Res* 2013; **47**: 555-568 [PMID: 23738581 DOI: 10.3109/10715762.2013.811721]
93 **Genovés P**, García D, Cejalvo D, Martin A, Zaragoza C, Toledo AH, Toledo-Pereyra LH, Lloris-Carsi JM. Pentoxifylline in liver ischemia and reperfusion. *J Invest Surg* 2014; **27**: 114-124 [PMID: 24143911 DOI: 10.3109/08941939.2013.835454]
94 **Tiriveedhi V**, Upadhya GA, Busch RA, Gunter KL, Dines JN, Knolhoff BL, Jia J, Sarma NJ, Ramachandran S, Anderson CD, Mohanakumar T, Chapman WC. Protective role of bortezomib in steatotic liver ischemia/reperfusion injury through abrogation of MMP activation and YKL-40 expression. *Transpl Immunol* 2014; **30**: 93-98 [PMID: 24380732 DOI: 10.1016/j.trim.2013.12.003]
95 **Saidi RF**, Rajeshkumar B, Shariftabrizi A, Dresser K, Walter O. Human C1 inhibitor attenuates liver ischemia-reperfusion injury and promotes liver regeneration. *J Surg Res* 2014; **187**: 660-666 [PMID: 24433870 DOI: 10.1016/j.jss.2013.09.009]
96 **Iwatsuki S**, Rabin BS, Shaw BW, Starzl TE. Liver transplantation against T cell-positive warm crossmatches. *Transplant Proc* 1984; **16**: 1427-1429 [PMID: 6390842]
97 **Gordon RD**, Fung JJ, Markus B, Fox I, Iwatsuki S, Esquivel CO, Tzakis A, Todo S, Starzl TE. The antibody crossmatch in liver transplantation. *Surgery* 1986; **100**: 705-715 [PMID: 3532391]
98 **Ruiz R**, Tomiyama K, Campsen J, Goldstein RM, Levy MF, McKenna GJ, Onaca N, Susskind B, Tillery GW, Klintmalm GB. Implications of a positive crossmatch in liver transplantation: a 20-year review. *Liver Transpl* 2012; **18**: 455-460 [PMID: 22139972 DOI: 10.1002/lt.22474]
99 **Takaya S**, Bronsther O, Iwaki Y, Nakamura K, Abu-Elmagd K, Yagihashi A, Demetris AJ, Kobayashi M, Todo S, Tzakis AG. The adverse impact on liver transplantation of using positive cytotoxic crossmatch donors. *Transplantation* 1992; **53**: 400-406 [PMID: 1371195]
100 **Ogura K**, Koyama H, Takemoto S, Terasaki PI, Busuttil RW. Significance of a positive crossmatch on outcome in human liver transplantation. *Transplant Proc* 1992; **24**: 1465 [PMID: 1496620]
101 **O'Leary JG**, Kaneku H, Demetris AJ, Marr JD, Shiller SM, Susskind BM, Tillery GW, Terasaki PI, Klintmalm GB. Antibody-mediated rejection as a contributor to previously unexplained early liver allograft loss. *Liver Transpl* 2014; **20**: 218-227 [PMID: 24382837 DOI: 10.1002/lt.23788]
102 **Kaneku H**, O'Leary JG, Banuelos N, Jennings LW, Susskind BM, Klintmalm GB, Terasaki PI. De novo donor-specific HLA antibodies decrease patient and graft survival in liver transplant recipients. *Am J Transplant* 2013; **13**: 1541-1548 [PMID: 23721554 DOI: 10.1111/ajt.12212]
103 **Hu J**, Wang Z, Tan CJ, Liao BY, Zhang X, Xu M, Dai Z, Qiu SJ, Huang XW, Sun J, Sun QM, He YF, Song K, Pan Q, Wu Y, Fan J, Zhou J. Plasma microRNA, a potential biomarker for acute rejection after liver transplantation. *Transplantation* 2013; **95**: 991-999 [PMID: 23466638 DOI: 10.1097/TP.0b013e31828618d8]
104 **Wei L**, Gong X, Martinez OM, Krams SM. Differential expression and functions of microRNAs in liver transplantation and potential use as non-invasive biomarkers. *Transpl Immunol* 2013; **29**: 123-129 [PMID: 24001411 DOI: 10.1016/j.trim.2013.08.005]
105 **Colvin-Adams M**, Smith JM, Heubner BM, Skeans MA, Edwards LB, Waller C, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2011 Annual Data Report: heart. *Am J Transplant* 2013; **13** Suppl 1: 119-148 [PMID: 23237699 DOI: 10.1111/ajt.12023]
106 **Lund LH**, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, Dobbels F, Kirk R, Rahmel AO, Yusen RD, Stehlik J. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report--2013; focus theme: age. *J Heart Lung Transplant* 2013; **32**: 951-964 [PMID: 24054804 DOI: 10.1016/j.healun.2013.08.006]
107 **Pondrom S**. Heart failure options broaden. *Am J Transplant* 2013; **13**: 827-828 [PMID: 23551626 DOI: 10.1111/ajt.12231]
108 **Slaughter MS**, Pagani FD, McGee EC, Birks EJ, Cotts WG, Gregoric I, Howard Frazier O, Icenogle T, Najjar SS, Boyce SW, Acker MA, John R, Hathaway DR, Najarian KB, Aaronson KD. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. *J Heart Lung Transplant* 2013; **32**: 675-683 [PMID: 23796152 DOI: 10.1016/j.healun.2013.04.004]
109 **Taghavi S**, Jayarajan SN, Komaroff E, Mangi AA. Continuous flow left ventricular assist device technology has influenced wait times and affected donor allocation in cardiac transplantation. *J Thorac Cardiovasc Surg* 2014; **147**: 1966-1971, 1971.e1 [PMID: 24613158 DOI: 10.1016/j.jtcvs.2014.02.001]
110 **Sutcliffe P**, Connock M, Pulikottil-Jacob R, Kandala NB, Suri G, Gurung T, Grove A, Shyangdan D, Briscoe S, Maheswaran H, Clarke A. Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model. *Health Technol Assess* 2013; **17**: 1-499, v-vi [PMID: 24280231 DOI: 10.3310/hta17530]
111 **Feldman D**, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant* 2013; **32**: 157-187 [PMID: 23352391 DOI: 10.1016/j.healun.2012.09.013]
112 **Kilic A**, Allen JG, Weiss ES. Validation of the United States-derived Index for Mortality Prediction After Cardiac Transplantation (IMPACT) using international registry data. *J Heart Lung Transplant* 2013; **32**: 492-498 [PMID: 23474362 DOI: 10.1016/j.healun.2013.02.001]
113 **Smits JM**, de Vries E, De Pauw M, Zuckermann A, Rahmel A, Meiser B, Laufer G, Reichenspurner H, Strueber M. Is it time for a cardiac allocation score? First results from the Eurotransplant pilot study on a survival benefit-based heart allocation. *J Heart Lung Transplant* 2013; **32**: 873-880 [PMID: 23628111 DOI: 10.1016/j.healun.2013.03.015]
114 **Smith JD**, Banner NR, Hamour IM, Ozawa M, Goh A, Robinson D, Terasaki PI, Rose ML. De novo donor HLA-specific antibodies after heart transplantation are an independent predictor of poor patient survival. *Am J Transplant* 2011; **11**: 312-319 [PMID: 21219570 DOI: 10.1111/j.1600-6143.2010.03383.x]
115 **Smith JD**, Hamour IM, Banner NR, Rose ML. C4d fixing, luminex binding antibodies - a new tool for prediction of graft failure after heart transplantation. *Am J Transplant* 2007; **7**: 2809-2815 [PMID: 17908268 DOI: 10.1111/j.1600-6143.2007.01991.x]
116 **Smith JD**, Hamour IM, Burke MM, Mahesh B, Stanford RE, Haj-Yahia S, Robinson DR, Kaul P, Yacoub MH, Banner NR, Rose ML. A reevaluation of the role of IgM Non-HLA antibodies in cardiac transplantation. *Transplantation* 2009; **87**: 864-871 [PMID: 19300190 DOI: 10.1097/TP.0b013e31819a65fa]
117 **Berry GJ**, Burke MM, Andersen C, Bruneval P, Fedrigo M, Fishbein MC, Goddard M, Hammond EH, Leone O, Marboe C, Miller D, Neil D, Rassl D, Revelo MP, Rice A, Rene Rodriguez E, Stewart S, Tan CD, Winters GL, West L, Mehra

MR, Angelini A. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. *J Heart Lung Transplant* 2013; **32**: 1147-1162 [PMID: 24263017 DOI: 10.1016/j.healun.2013.08.011]

118 **Costello JP**, Mohanakumar T, Nath DS. Mechanisms of chronic cardiac allograft rejection. *Tex Heart Inst J* 2013; **40**: 395-399 [PMID: 24082367]

119 **Eisen HJ**, Kobashigawa J, Starling RC, Pauly DF, Kfoury A, Ross H, Wang SS, Cantin B, Van Bakel A, Ewald G, Hirt S, Lehmkuhl H, Keogh A, Rinaldi M, Potena L, Zuckermann A, Dong G, Cornu-Artis C, Lopez P. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. *Am J Transplant* 2013; **13**: 1203-1216 [PMID: 23433101 DOI: 10.1111/ajt.12181]

120 **Kobashigawa JA**, Pauly DF, Starling RC, Eisen H, Ross H, Wang SS, Cantin B, Hill JA, Lopez P, Dong G, Nicholls SJ. Cardiac allograft vasculopathy by intravascular ultrasound in heart transplant patients: substudy from the Everolimus versus mycophenolate mofetil randomized, multicenter trial. *JACC Heart Fail* 2013; **1**: 389-399 [PMID: 24621971 DOI: 10.1016/j.jchf.2013.07.002]

121 **Mehra MR**. Advancing immunosuppression in heart transplantation: "one step forward, two steps back. *Am J Transplant* 2013; **13**: 1119-1120 [PMID: 23621159 DOI: 10.1111/ajt.12177]

122 **Khandhar SJ**, Yamamoto H, Teuteberg JJ, Shullo MA, Bezerra HG, Costa MA, Selzer F, Lee JS, Marroquin OC, McNamara DM, Mulukutla SR, Toma C. Optical coherence tomography for characterization of cardiac allograft vasculopathy after heart transplantation (OCTCAV study). *J Heart Lung Transplant* 2013; **32**: 596-602 [PMID: 23499356 DOI: 10.1016/j.healun.2013.02.005]

123 **Valapour M**, Skeans MA, Heubner BM, Smith JM, Schnitzler MA, Hertz MI, Edwards LB, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2012 Annual Data Report: lung. *Am J Transplant* 2014; **14** Suppl 1: 139-165 [PMID: 24373171 DOI: 10.1111/ajt.12584]

124 **Yusen RD**, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Lund LH, Rahmel AO, Stehlik J. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report--2013; focus theme: age. *J Heart Lung Transplant* 2013; **32**: 965-978 [PMID: 24054805 DOI: 10.1016/j.healun.2013.08.007]

125 **Shah RJ**, Kotloff RM. Lung transplantation for obstructive lung diseases. *Semin Respir Crit Care Med* 2013; **34**: 288-296 [PMID: 23821504 DOI: 10.1055/s-0033-1348468]

126 **Gottlieb J**. Lung transplantation for interstitial lung diseases and pulmonary hypertension. *Semin Respir Crit Care Med* 2013; **34**: 281-287 [PMID: 23821503 DOI: 10.1055/s-0033-1348462]

127 **Corris PA**. Lung transplantation for cystic fibrosis and bronchiectasis. *Semin Respir Crit Care Med* 2013; **34**: 297-304 [PMID: 23821505 DOI: 10.1055/s-0033-1348469]

128 **Snell GI**, Paraskeva M, Westall GP. Donor selection and management. *Semin Respir Crit Care Med* 2013; **34**: 361-370 [PMID: 23821510 DOI: 10.1055/s-0033-1348464]

129 **Bittle GJ**, Sanchez PG, Kon ZN, Claire Watkins A, Rajagopal K, Pierson RN, Gammie JS, Griffith BP. The use of lung donors older than 55 years: a review of the United Network of Organ Sharing database. *J Heart Lung Transplant* 2013; **32**: 760-768 [PMID: 23664760 DOI: 10.1016/j.healun.2013.04.012]

130 **Sommer W**, Kühn C, Tudorache I, Avsar M, Gottlieb J, Boethig D, Haverich A, Warnecke G. Extended criteria donor lungs and clinical outcome: results of an alternative allocation algorithm. *J Heart Lung Transplant* 2013; **32**: 1065-1072 [PMID: 23953918 DOI: 10.1016/j.healun.2013.06.021]

131 **Barnard JB**, Davies O, Curry P, Catarino P, Dunning J, Jenkins D, Sudarshan C, Nair S, Tsui S, Parmar J. Size matching in lung transplantation: an evidence-based review. *J Heart Lung Transplant* 2013; **32**: 849-860 [PMID: 23953814 DOI: 10.1016/j.healun.2013.07.002]

132 **Chamogeorgakis T**, Mason DP, Murthy SC, Thuita L, Raymond DP, Pettersson GB, Blackstone EH. Impact of nutritional state on lung transplant outcomes. *J Heart Lung Transplant* 2013; **32**: 693-700 [PMID: 23664761 DOI: 10.1016/j.healun.2013.04.005]

133 **Shah P**, Orens JB. Impact of nutritional state on lung transplant outcomes: the weight of the evidence. *J Heart Lung Transplant* 2013; **32**: 755-756 [PMID: 23856213 DOI: 10.1016/j.healun.2013.06.001]

134 **McShane PJ**, Garrity ER. Impact of the lung allocation score. *Semin Respir Crit Care Med* 2013; **34**: 275-280 [PMID: 23821502 DOI: 10.1055/s-0033-1348461]

135 **Wille KM**, Harrington KF, deAndrade JA, Vishin S, Oster RA, Kaslow RA. Disparities in lung transplantation before and after introduction of the lung allocation score. *J Heart Lung Transplant* 2013; **32**: 684-692 [PMID: 23582477 DOI: 10.1016/j.healun.2013.03.005]

136 **Suzuki Y**, Cantu E, Christie JD. Primary graft dysfunction. *Semin Respir Crit Care Med* 2013; **34**: 305-319 [PMID: 23821506 DOI: 10.1055/s-0033-1348474]

137 **Bertani A**. Overcoming primary graft dysfunction after lung transplantation: are we finding our way there? *Transplantation* 2014; **97**: 1100-1101 [PMID: 24573115]

138 **Sommer W**, Tudorache I, Kühn C, Avsar M, Salman J, Ius F, Gras C, Weber P, Welte T, Gottlieb J, Haverich A, Warnecke G. C1-esterase-inhibitor for primary graft dysfunction in lung transplantation. *Transplantation* 2014; **97**: 1185-1191 [PMID: 24573112 DOI: 10.1097/TP.0000000000000034]

139 **McManigle W**, Pavlisko EN, Martinu T. Acute cellular and antibody-mediated allograft rejection. *Semin Respir Crit Care Med* 2013; **34**: 320-335 [PMID: 23821507 DOI: 10.1055/s-0033-1348471]

140 **Glanville AR**. The role of surveillance bronchoscopy post-lung transplantation. *Semin Respir Crit Care Med* 2013; **34**: 414-420 [PMID: 23821514 DOI: 10.1055/s-0033-1348466]

141 **San Segundo D**, Ballesteros MÁ, Naranjo S, Zurbano F, Miñambres E, López-Hoyos M. Increased numbers of circulating CD8 effector memory T cells before transplantation enhance the risk of acute rejection in lung transplant recipients. *PLoS One* 2013; **8**: e80601 [PMID: 24236187 DOI: 10.1371/journal.pone.0080601]

142 **Krustrup D**, Madsen CB, Iversen M, Engelholm L, Ryder LP, Andersen CB. The number of regulatory T cells in transbronchial lung allograft biopsies is related to FoxP3 mRNA levels in bronchoalveolar lavage fluid and to the degree of acute cellular rejection. *Transpl Immunol* 2013; **29**: 71-75 [PMID: 23969200 DOI: 10.1016/j.trim.2013.08.002]

143 **Husain S**, Resende MR, Rajwans N, Zamel R, Pilewski JM, Crespo MM, Singer LG, McCurry KR, Kolls JK, Keshavjee S, Liles WC. Elevated CXCL10 (IP-10) in bronchoalveolar lavage fluid is associated with acute cellular rejection after human lung transplantation. *Transplantation* 2014; **97**: 90-97 [PMID: 24025324 DOI: 10.1097/TP.0b013e3182a6ee0a]

144 **Lobo LJ**, Aris RM, Schmitz J, Neuringer IP. Donor-specific antibodies are associated with antibody-mediated rejection, acute cellular rejection, bronchiolitis obliterans syndrome, and cystic fibrosis after lung transplantation. *J Heart Lung Transplant* 2013; **32**: 70-77 [PMID: 23260706 DOI: 10.1016/j.healun.2012.10.007]

145 **Witt CA**, Gaut JP, Yusen RD, Byers DE, Iuppa JA, Bennett Bain K, Alexander Patterson G, Mohanakumar T, Trulock EP, Hachem RR. Acute antibody-mediated rejection after lung transplantation. *J Heart Lung Transplant* 2013; **32**: 1034-1040 [PMID: 23953920 DOI: 10.1016/j.healun.2013.07.004]

146 **Berry G**, Burke M, Andersen C, Angelini A, Bruneval P, Calabrese F, Fishbein MC, Goddard M, Leone O, Maleszewski J, Marboe C, Miller D, Neil D, Padera R, Rassl D, Revello

M, Rice A, Stewart S, Yousem SA. Pathology of pulmonary antibody-mediated rejection: 2012 update from the Pathology Council of the ISHLT. *J Heart Lung Transplant* 2013; **32**: 14-21 [PMID: 23260701 DOI: 10.1016/j.healun.2012.11.005]

147 **Snyder LD**, Wang Z, Chen DF, Reinsmoen NL, Finlen-Copeland CA, Davis WA, Zaas DW, Palmer SM. Implications for human leukocyte antigen antibodies after lung transplantation: a 10-year experience in 441 patients. *Chest* 2013; **144**: 226-233 [PMID: 23328795 DOI: 10.1378/chest.12-0587]

148 **Glanville AR**. Antibody-mediated rejection in lung transplantation: turning myth into reality. *J Heart Lung Transplant* 2013; **32**: 12-13 [PMID: 23260700 DOI: 10.1016/j.healun.2012.11.015]

149 **Weigt SS**, DerHovanessian A, Wallace WD, Lynch JP, Belperio JA. Bronchiolitis obliterans syndrome: the Achilles' heel of lung transplantation. *Semin Respir Crit Care Med* 2013; **34**: 336-351 [PMID: 23821508 DOI: 10.1055/s-0033-1348467]

150 **Saito T**, Takahashi H, Kaneda H, Binnie M, Azad S, Sato M, Waddell TK, Cypel M, Liu M, Keshavjee S. Impact of cytokine expression in the pre-implanted donor lung on the development of chronic lung allograft dysfunction subtypes. *Am J Transplant* 2013; **13**: 3192-3201 [PMID: 24164971 DOI: 10.1111/ajt.12492]

151 **Verleden SE**, Vandermeulen E, Ruttens D, Vos R, Vaneylen A, Dupont LJ, Van Raemdonck DE, Vanaudenaerde BM, Verleden GM. Neutrophilic reversible allograft dysfunction (NRAD) and restrictive allograft syndrome (RAS). *Semin Respir Crit Care Med* 2013; **34**: 352-360 [PMID: 23821509 DOI: 10.1055/s-0033-1348463]

152 **Sato M**, Ohmori-Matsuda K, Saito T, Matsuda Y, Hwang DM, Waddell TK, Singer LG, Keshavjee S. Time-dependent changes in the risk of death in pure bronchiolitis obliterans syndrome (BOS). *J Heart Lung Transplant* 2013; **32**: 484-491 [PMID: 23433813 DOI: 10.1016/j.healun.2013.01.1054]

153 **Sato M**, Hwang DM, Waddell TK, Singer LG, Keshavjee S. Progression pattern of restrictive allograft syndrome after lung transplantation. *J Heart Lung Transplant* 2013; **32**: 23-30 [PMID: 23260703 DOI: 10.1016/j.healun.2012.09.026]

154 **Verleden SE**, Ruttens D, Vandermeulen E, Vaneylen A, Dupont LJ, Van Raemdonck DE, Verleden GM, Vanaudenaerde BM, Vos R. Bronchiolitis obliterans syndrome and restrictive allograft syndrome: do risk factors differ? *Transplantation* 2013; **95**: 1167-1172 [PMID: 23425818 DOI: 10.1097/TP.0b013e318286e076]

155 **Suzuki H**, Lasbury ME, Fan L, Vittal R, Mickler EA, Benson HL, Shilling R, Wu Q, Weber DJ, Wagner SR, Lasaro M, Devore D, Wang Y, Sandusky GE, Lipking K, Pandya P, Reynolds J, Love R, Wozniak T, Gu H, Brown KM, Wilkes DS. Role of complement activation in obliterative bronchiolitis post-lung transplantation. *J Immunol* 2013; **191**: 4431-4439 [PMID: 24043901 DOI: 10.4049/jimmunol.1202242]

156 **Tiriveedhi V**, Banan B, Deepti S, Nataraju A, Hachem R, Trulock E, Alexander PG, Thalachallour M. Role of defensins in the pathogenesis of chronic lung allograft rejection. *Hum Immunol* 2014; **75**: 370-377 [PMID: 24380698 DOI: 10.1016/j.humimm.2013.12.014]

157 **Salvadori M**, Bertoni E. Is it time to give up with calcineurin inhibitors in kidney transplantation? *World J Transplant* 2013; **3**: 7-25 [PMID: 24175203 DOI: 10.5500/wjt.v3.i2.7]

158 **Cornu C**, Dufays C, Gaillard S, Gueyffier F, Redonnet M, Sebbag L, Roussoulières A, Gleissner CA, Groetzner J, Lehmkuhl HB, Potena L, Gullestad L, Cantarovich M, Boissonnat P. Impact of the reduction of calcineurin inhibitors on renal function in heart transplant patients: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2014; **78**: 24-32 [PMID: 24251918 DOI: 10.1111/bcp.12289]

159 **Isakova T**, Xie H, Messinger S, Cortazar F, Scialla JJ, Guerra G, Contreras G, Roth D, Burke GW, Molnar MZ, Mucsi I, Wolf M. Inhibitors of mTOR and risks of allograft failure and mortality in kidney transplantation. *Am J Transplant* 2013; **13**: 100-110 [PMID: 23025566 DOI: 10.1111/j.1600-6143.2012.04281.x]

160 **Asrani SK**, Wiesner RH, Trotter JF, Klintmalm G, Katz E, Maller E, Roberts J, Kneteman N, Teperman L, Fung JJ, Millis JM. De novo sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: the 2000-2003 phase II prospective randomized trial. *Am J Transplant* 2014; **14**: 356-366 [PMID: 24456026 DOI: 10.1111/ajt.12543]

161 **Saliba F**, De Simone P, Nevens F, De Carlis L, Metselaar HJ, Beckebaum S, Jonas S, Sudan D, Fischer L, Duvoux C, Chavin KD, Koneru B, Huang MA, Chapman WC, Foltys D, Dong G, Lopez PM, Fung J, Junge G. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. *Am J Transplant* 2013; **13**: 1734-1745 [PMID: 23714399 DOI: 10.1111/ajt.12280]

162 **Junge G**, Dumortier T, Schwende H, Fung J. mTOR inhibition in liver transplantation: how to dose for effective/safe CNI reduction? *Transplant Proc* 2013; **45**: 1979-1980 [PMID: 23769088 DOI: 10.1016/j.transproceed.2013.02.102]

163 **Bhat M**, Charlton M. Preserving flow in liver transplant recipients: mTOR inhibitors everolimus and sirolimus are not peas from a pod. *Am J Transplant* 2013; **13**: 1633-1635 [PMID: 23802724 DOI: 10.1111/ajt.12290]

164 **Sterneck M**, Kaiser GM, Heyne N, Richter N, Rauchfuss F, Pascher A, Schemmer P, Fischer L, Klein CG, Nadalin S, Lehner F, Settmacher U, Neuhaus P, Gotthardt D, Loss M, Ladenburger S, Paulus EM, Mertens M, Schlitt HJ. Everolimus and early calcineurin inhibitor withdrawal: 3-year results from a randomized trial in liver transplantation. *Am J Transplant* 2014; **14**: 701-710 [PMID: 24502384 DOI: 10.1111/ajt.12615]

165 **Levitsky J**, Feng S. Sirolimus and mTOR inhibitors in liver transplantation: the wheel has come full circle. *Am J Transplant* 2014; **14**: 249-250 [PMID: 24620373 DOI: 10.1111/ajt.12545]

166 **Matsuo Y**, Cassar A, Yoshino S, Flammer AJ, Li J, Gulati R, Topilsky Y, Raichlin E, Lennon RJ, Lerman LO, Rihal CS, Kushwaha SS, Lerman A. Attenuation of cardiac allograft vasculopathy by sirolimus: Relationship to time interval after heart transplantation. *J Heart Lung Transplant* 2013; **32**: 784-791 [PMID: 23856215 DOI: 10.1016/j.healun.2013.05.015]

167 **Witt CA**, Hachem RR. Immunosuppression: what's standard and what's new? *Semin Respir Crit Care Med* 2013; **34**: 405-413 [PMID: 23821513 DOI: 10.1055/s-0033-1348465]

168 **Gurk-Turner C**, Manitpisitkul W, Cooper M. A comprehensive review of everolimus clinical reports: a new mammalian target of rapamycin inhibitor. *Transplantation* 2012; **94**: 659-668 [PMID: 22986894 DOI: 10.1097/TP.0b013e31825b411c]

169 **Da Dalt L**, Bressan S, Martinolli F, Perilongo G, Baraldi E. Treatment of bronchiolitis: state of the art. *Early Hum Dev* 2013; **89** Suppl 1: S31-S36 [PMID: 23809346 DOI: 10.1016/S0378-3782(13)70011-2]

170 **Sacher VY**, Fertel D, Srivastava K, Panos A, Nguyen D, Baxter T, Shafazand S, Pham SM. Effects of prophylactic use of sirolimus on bronchiolitis obliterans syndrome development in lung transplant recipients. *Ann Thorac Surg* 2014; **97**: 268-274 [PMID: 24119986 DOI: 10.1016/j.athoracsur.2013.07.072]

171 **Borro JM**. Advances in immunosuppression after lung transplantation. *Med Intensiva* 2013; **37**: 44-49 [PMID: 22854620 DOI: 10.1016/j.medin.2012.05.011]

172 **Iacono AT**, Johnson BA, Grgurich WF, Youssef JG, Corcoran TE, Seiler DA, Dauber JH, Smaldone GC, Zeevi A, Yousem SA, Fung JJ, Burckart GJ, McCurry KR, Griffith BP. A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med* 2006; **354**: 141-150 [PMID: 16407509 DOI: 10.1056/NEJMoa043204]

173 **Whitford H**, Walters EH, Levvey B, Kotsimbos T, Orsida B, Ward C, Pais M, Reid S, Williams T, Snell G. Addition of inhaled corticosteroids to systemic immunosuppression after lung transplantation: a double-blind, placebo-controlled trial. *Transplantation* 2002; **73**: 1793-1799 [PMID: 12085003]

174 **Johnson BA**, Iacono AT, Zeevi A, McCurry KR, Duncan SR. Statin use is associated with improved function and survival of lung allografts. *Am J Respir Crit Care Med* 2003; **167**: 1271-1278 [PMID: 12615629 DOI: 10.1164/rccm.200205-410OC]

175 **Vos R**, Vanaudenaerde BM, Verleden SE, Ruttens D, Vaneylen A, Van Raemdonck DE, Dupont LJ, Verleden GM. Anti-inflammatory and immunomodulatory properties of azithromycin involved in treatment and prevention of chronic lung allograft rejection. *Transplantation* 2012; **94**: 101-109 [PMID: 22461039 DOI: 10.1097/TP.0b013e31824db9da]

176 **Penninga L**, Møller CH, Gustafsson F, Gluud C, Steinbrüchel DA. Immunosuppressive T-cell antibody induction for heart transplant recipients. *Cochrane Database Syst Rev* 2013; **12**: CD008842 [PMID: 24297433 DOI: 10.1002/14651858.CD008842]

177 **Stratta RJ**, Farney AC, Rogers J, Orlando G. Immunosuppression for pancreas transplantation with an emphasis on antibody induction strategies: review and perspective. *Expert Rev Clin Immunol* 2014; **10**: 117-132 [PMID: 24236648 DOI: 10.1586/1744666X.2014.853616]

178 **Mako M,** Hager D, Muth B, Kaufman D, Ellis T, Djamali A. Thymoglobulin is associated with a significant reduction in de novo donor-specific antibodies and antibody mediated rejection in moderately sensitized renal transplant recipients. *Am J Transplant* 2013; **13**: S113

179 **Morgan RD**, O'Callaghan JM, Knight SR, Morris PJ. Alemtuzumab induction therapy in kidney transplantation: a systematic review and meta-analysis. *Transplantation* 2012; **93**: 1179-1188 [PMID: 22660659 DOI: 10.1097/TP.0b013e318257ad41]

180 **Barnett AN**, Hadjianastassiou VG, Mamode N. Rituximab in renal transplantation. *Transpl Int* 2013; **26**: 563-575 [PMID: 23414100 DOI: 10.1111/tri.12072]

181 **Kohei N**, Hirai T, Omoto K, Ishida H, Tanabe K. Chronic antibody-mediated rejection is reduced by targeting B-cell immunity during an introductory period. *Am J Transplant* 2012; **12**: 469-476 [PMID: 22054413 DOI: 10.1111/j.1600-6143.2011.03830.x]

182 **Sautenet B,** Blancho G, Buchler M. One year results of the effects of rituximab on acute humoral rejection in renal transplantation: RITUX ERAH, a multicenter randomized placebo controlled trial. *Am J Transplant* 2013; **13**: S112

183 **Stegall MD**, Diwan T, Raghavaiah S, Cornell LD, Burns J, Dean PG, Cosio FG, Gandhi MJ, Kremers W, Gloor JM. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. *Am J Transplant* 2011; **11**: 2405-2413 [PMID: 21942930 DOI: 10.1111/j.1600-6143.2011.03757.x]

184 A service of the U.S. National Institutes of Health. Cited: 2013-06-03. Available from: URL: http: //www.clinicaltrials.gov/

185 **Fehr T**, Gaspert A. Antibody-mediated kidney allograft rejection: therapeutic options and their experimental rationale. *Transpl Int* 2012; **25**: 623-632 [PMID: 22394269 DOI: 10.1111/j.1432-2277.2012.01453.x]

186 **Page EK**, Dar WA, Knechtle SJ. Biologics in organ transplantation. *Transpl Int* 2012; **25**: 707-719 [PMID: 22420711 DOI: 10.1111/j.1432-2277.2012.01456.x]

187 **Charpentier B**, Medina Pestana JO, Del C Rial M, Rostaing L, Grinyó J, Vanrenterghem Y, Matas A, Zhang R, Mühlbacher F, Pupim L, Florman S. Long-term exposure to belatacept in recipients of extended criteria donor kidneys. *Am J Transplant* 2013; **13**: 2884-2891 [PMID: 24103072 DOI: 10.1111/ajt.12459]

188 **Rostaing L**, Vincenti F, Grinyó J, Rice KM, Bresnahan B, Steinberg S, Gang S, Gaite LE, Moal MC, Mondragón-Ramirez GA, Kothari J, Pupim L, Larsen CP. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. *Am J Transplant* 2013; **13**: 2875-2883 [PMID: 24047110 DOI: 10.1111/ajt.12460]

189 **Kirk AD**, Guasch A, Xu H, Cheeseman J, Mead SI, Ghali A, Mehta AK, Wu D, Gebel H, Bray R, Horan J, Kean LS, Larsen CP, Pearson TC. Renal transplantation using belatacept without maintenance steroids or calcineurin inhibitors. *Am J Transplant* 2014; **14**: 1142-1151 [PMID: 24684552 DOI: 10.1111/ajt.12712]

190 **Goldwater R**, Keirns J, Blahunka P, First R, Sawamoto T, Zhang W, Kowalski D, Kaibara A, Holman J. A phase 1, randomized ascending single-dose study of antagonist anti-human CD40 ASKP1240 in healthy subjects. *Am J Transplant* 2013; **13**: 1040-1046 [PMID: 23356210 DOI: 10.1111/ajt.12082]

191 **Watanabe M**, Yamashita K, Suzuki T, Kamachi H, Kuraya D, Koshizuka Y, Ogura M, Yoshida T, Aoyagi T, Fukumori D, Shimamura T, Okimura K, Maeta K, Miura T, Sakai F, Todo S. ASKP1240, a fully human anti-CD40 monoclonal antibody, prolongs pancreatic islet allograft survival in nonhuman primates. *Am J Transplant* 2013; **13**: 1976-1988 [PMID: 23841873 DOI: 10.1111/ajt.12330]

192 **Rostaing L**, Charpentier B, Glyda M, Rigotti P, Hettich F, Franks B, Houbiers JG, First R, Holman JM. Alefacept combined with tacrolimus, mycophenolate mofetil and steroids in de novo kidney transplantation: a randomized controlled trial. *Am J Transplant* 2013; **13**: 1724-1733 [PMID: 23730730 DOI: 10.1111/ajt.12303]

193 **Vincenti F**, Tedesco Silva H, Busque S, O'Connell P, Friedewald J, Cibrik D, Budde K, Yoshida A, Cohney S, Weimar W, Kim YS, Lawendy N, Lan SP, Kudlacz E, Krishnaswami S, Chan G. Randomized phase 2b trial of tofacitinib (CP-690,550) in de novo kidney transplant patients: efficacy, renal function and safety at 1 year. *Am J Transplant* 2012; **12**: 2446-2456 [PMID: 22682022 DOI: 10.1111/j.1600-6143.2012.04127.x]

194 **Wojciechowski D**, Vincenti F. Tofacitinib in kidney transplantation. *Expert Opin Investig Drugs* 2013; **22**: 1193-1199 [PMID: 23841583 DOI: 10.1517/13543784.2013.811231]

195 **Russ GR**, Tedesco-Silva H, Kuypers DR, Cohney S, Langer RM, Witzke O, Eris J, Sommerer C, von Zur-Mühlen B, Woodle ES, Gill J, Ng J, Klupp J, Chodoff L, Budde K. Efficacy of sotrastaurin plus tacrolimus after de novo kidney transplantation: randomized, phase II trial results. *Am J Transplant* 2013; **13**: 1746-1756 [PMID: 23668931 DOI: 10.1111/ajt.12251]

196 **Tedesco-Silva H**, Kho MM, Hartmann A, Vitko S, Russ G, Rostaing L, Budde K, Campistol JM, Eris J, Krishnan I, Gopalakrishnan U, Klupp J. Sotrastaurin in calcineurin inhibitor-free regimen using everolimus in de novo kidney transplant recipients. *Am J Transplant* 2013; **13**: 1757-1768 [PMID: 23659755 DOI: 10.1111/ajt.12255]

197 **Kimelman M**, Brandacher G. Trends in immunosuppression after pancreas transplantation: what is in the pipeline? *Curr Opin Organ Transplant* 2013; **18**: 76-82 [PMID: 23254700 DOI: 10.1097/MOT.0b013e32835c6eda]

198 **Samikannu B**, Chen C, Lingwal N, Padmasekar M, Engel FB, Linn T. Dipeptidyl peptidase IV inhibition activates CREB and improves islet vascularization through VEGF-A/VEGFR-2 signaling pathway. *PLoS One* 2013; **8**: e82639 [PMID: 24349326 DOI: 10.1371/journal.pone.0082639]

199 **Vos R**, Verleden SE, Ruttens D, Vandermeulen E, Yserbyt J, Dupont LJ, Van Raemdonck DE, De Raedt N, Gheysens O, De Jong PA, Verleden GM, Vanaudenaerde BM. Pirfenidone: a potential new therapy for restrictive allograft syndrome? *Am J Transplant* 2013; **13**: 3035-3040 [PMID: 24102752 DOI: 10.1111/ajt.12474]

200 **Bonarius HP**, Baas F, Remmerswaal EB, van Lier RA, ten Berge IJ, Tak PP, de Vries N. Monitoring the T-cell receptor repertoire at single-clone resolution. *PLoS One* 2006; **1**: e55 [PMID: 17183685 DOI: 10.1371/journal.pone.0000055]

201 **Levitsky J**. Operational tolerance: past lessons and future prospects. *Liver Transpl* 2011; **17**: 222-232 [PMID: 21384504 DOI: 10.1002/lt.22265]

202 **Ruiz P**, Maldonado P, Hidalgo Y, Gleisner A, Sauma D, Silva C, Saez JJ, Nuñez S, Rosemblatt M, Bono MR. Transplant tolerance: new insights and strategies for long-term allograft acceptance. *Clin Dev Immunol* 2013; **2013**: 210506 [PMID: 23762087 DOI: 10.1155/2013/210506]

203 **Sachs DH**, Sykes M, Kawai T, Cosimi AB. Immunointervention for the induction of transplantation tolerance through mixed chimerism. *Semin Immunol* 2011; **23**: 165-173 [PMID: 21839648 DOI: 10.1016/j.smim.2011.07.001]

204 **Kawai T**, Sachs DH, Sykes M, Cosimi AB. HLA-mismatched renal transplantation without maintenance immunosuppression. *N Engl J Med* 2013; **368**: 1850-1852 [PMID: 23656665 DOI: 10.1056/NEJMc1213779]

205 **Farris AB**, Taheri D, Kawai T, Fazlollahi L, Wong W, Tolkoff-Rubin N, Spitzer TR, Iafrate AJ, Preffer FI, Locascio SA, Sprangers B, Saidman S, Smith RN, Cosimi AB, Sykes M, Sachs DH, Colvin RB. Acute renal endothelial injury during marrow recovery in a cohort of combined kidney and bone marrow allografts. *Am J Transplant* 2011; **11**: 1464-1477 [PMID: 21668634 DOI: 10.1111/j.1600-6143.2011.03572.x]

206 **Kawai T**, Sogawa H, Boskovic S, Abrahamian G, Smith RN, Wee SL, Andrews D, Nadazdin O, Koyama I, Sykes M, Winn HJ, Colvin RB, Sachs DH, Cosimi AB. CD154 blockade for induction of mixed chimerism and prolonged renal allograft survival in nonhuman primates. *Am J Transplant* 2004; **4**: 1391-1398 [PMID: 15307826 DOI: 10.1111/j.1600-6143.2004.00523.x]

207 **Wekerle T**, Kurtz J, Ito H, Ronquillo JV, Dong V, Zhao G, Shaffer J, Sayegh MH, Sykes M. Allogeneic bone marrow transplantation with co-stimulatory blockade induces macrochimerism and tolerance without cytoreductive host treatment. *Nat Med* 2000; **6**: 464-469 [PMID: 10742157 DOI: 10.1038/74731]

208 **Kawai T**, Cosimi AB, Spitzer TR, Tolkoff-Rubin N, Suthanthiran M, Saidman SL, Shaffer J, Preffer FI, Ding R, Sharma V, Fishman JA, Dey B, Ko DS, Hertl M, Goes NB, Wong W, Williams WW, Colvin RB, Sykes M, Sachs DH. HLA-mismatched renal transplantation without maintenance immunosuppression. *N Engl J Med* 2008; **358**: 353-361 [PMID: 18216355 DOI: 10.1056/NEJMoa071074]

209 **Adams AB**, Williams MA, Jones TR, Shirasugi N, Durham MM, Kaech SM, Wherry EJ, Onami T, Lanier JG, Kokko KE, Pearson TC, Ahmed R, Larsen CP. Heterologous immunity provides a potent barrier to transplantation tolerance. *J Clin Invest* 2003; **111**: 1887-1895 [PMID: 12813024 DOI: 10.1172/JCI200317477]

210 **Casiraghi F**, Perico N, Remuzzi G. Mesenchymal stromal cells to promote solid organ transplantation tolerance. *Curr Opin Organ Transplant* 2013; **18**: 51-58 [PMID: 23254705 DOI: 10.1097/MOT.0b013e32835c5016]

211 **Leventhal J**, Abecassis M, Miller J, Gallon L, Ravindra K, Tollerud DJ, King B, Elliott MJ, Herzig G, Herzig R, Ildstad ST. Chimerism and tolerance without GVHD or engraftment syndrome in HLA-mismatched combined kidney and hematopoietic stem cell transplantation. *Sci Transl Med* 2012; **4**: 124ra28 [PMID: 22399264 DOI: 10.1126/scitranslmed.3003509]

212 **Leventhal J**, Abecassis M, Miller J, Gallon L, Tollerud D, Elliott MJ, Bozulic LD, Houston C, Sustento-Reodica N, Ildstad ST. Tolerance induction in HLA disparate living donor kidney transplantation by donor stem cell infusion: durable chimerism predicts outcome. *Transplantation* 2013; **95**: 169-176 [PMID: 23222893 DOI: 10.1097/TP.0b013e3182782fc1]

213 **Leventhal JR**, Mathew JM, Salomon DR, Kurian SM, Suthanthiran M, Tambur A, Friedewald J, Gallon L, Charette J, Levitsky J, Kanwar Y, Abecassis M, Miller J. Genomic biomarkers correlate with HLA-identical renal transplant tolerance. *J Am Soc Nephrol* 2013; **24**: 1376-1385 [PMID: 23787913 DOI: 10.1681/ASN.2013010068]

214 **Cippà PE**, Gabriel SS, Kraus AK, Chen J, Wekerle T, Guimezanes A, Wüthrich RP, Fehr T. Bcl-2 inhibition to overcome memory cell barriers in transplantation. *Am J Transplant* 2014; **14**: 333-342 [PMID: 24472193 DOI: 10.1111/ajt.12554]

215 **Lau AH**, de Creus A, Lu L, Thomson AW. Liver tolerance mediated by antigen presenting cells: fact or fiction? *Gut* 2003; **52**: 1075-1078 [PMID: 12865260]

216 **Warren A**, Le Couteur DG, Fraser R, Bowen DG, McCaughan GW, Bertolino P. T lymphocytes interact with hepatocytes through fenestrations in murine liver sinusoidal endothelial cells. *Hepatology* 2006; **44**: 1182-1190 [PMID: 17058232 DOI: 10.1002/hep.21378]

217 **McAvoy EF**, Kubes P. Holey endothelium: gateways for naïve T cell activation. *Hepatology* 2006; **44**: 1083-1085 [PMID: 17058224 DOI: 10.1002/hep.21421]

218 **Wu SL**, Pan CE. Tolerance and chimerism and allogeneic bone marrow/stem cell transplantation in liver transplantation. *World J Gastroenterol* 2013; **19**: 5981-5987 [PMID: 24106398 DOI: 10.3748/wjg.v19.i36.5981]

219 **Blumberg EA,** Danziger-Isakov L, Kumar D, Michaels MG, Razonable RR. The American Society of Transplantation Infectious Diseases Guidelines. 3rd ed. *Am J Transplant* 2013; **13**, S 4: 1-371 [DOI: 10.1111/ajt.12129]

220 **Seem DL**, Lee I, Umscheid CA, Kuehnert MJ. Excerpt from PHS guideline for reducing HIV, HBV and HCV transmission through organ transplantation. *Am J Transplant* 2013; **13**: 1953-1962 [PMID: 23890284 DOI: 10.1111/ajt.12386]

221 **Kotton CN**, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, Humar A. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013; **96**: 333-360 [PMID: 23896556 DOI: 10.1097/TP.0b013e31829df29d]

222 **Fishman JA**. Overview: cytomegalovirus and the herpesviruses in transplantation. *Am J Transplant* 2013; **13** Suppl 3: 1-8; quiz 8 [PMID: 23347210 DOI: 10.1111/ajt.12002]

223 **Humar A**, Michaels M. American Society of Transplantation recommendations for screening, monitoring and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation. *Am J Transplant* 2006; **6**: 262-274 [PMID: 16426310 DOI: 10.1111/j.1600-6143.2005.01207.x]

224 **Green M**. Introduction: Infections in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 3-8 [PMID: 23464993 DOI: 10.1111/ajt.12093]

225 **Theodoropoulos N**, Jaramillo A, Ladner DP, Ison MG. Deceased organ donor screening for HIV, hepatitis B, and hepatitis C viruses: a survey of organ procurement organization practices. *Am J Transplant* 2013; **13**: 2186-2190 [PMID: 23711196 DOI: 10.1111/ajt.12260]

226 **Orlowski J,** Alexander C, Ison M, Rosendale J, Chabalewski F. NAT Survey Workgroup, Richmond, VA. Nucleic Acid Testing (NAT) for HIV, HBV, and HCV: Current Practices of 58 US Organ Procurement Organizations (OPOs). *Am J Transplant* 2009; **9**: S2 197 [DOI: 10.1111/j.1600-6143.2009.02658.x]

227 **Rogers MF,** Simonds RJ, Lawton KE, Moseley RR, Jones WK. Guidelines for preventing transmission of human immunodeficiency virus through transplantation of human tissue and organs. *MMWR Recomm Rep* 1994; **43**: 1-17

228 Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products. Available from: URL: http: //www.fda.gov/downloads/Biologics Blood Vaccines/Guidance ComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf

229 **Hirsch HH**, Randhawa P. BK polyomavirus in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 179-188 [PMID: 23465010 DOI: 10.1111/ajt.12110]

230 **Sood P**, Senanayake S, Sujeet K, Medipalli R, Van-Why SK, Cronin DC, Johnson CP, Hariharan S. Donor and recipient BKV-specific IgG antibody and posttransplantation BKV infection: a prospective single-center study. *Transplantation* 2013; **95**: 896-902

[PMID: 23511214 DOI: 10.1097/TP.0b013e318282ba83]
231 **Greiner M**, Cusini A, Ruesch M, Schiesser M, Ledergerber B, Fehr T, Mueller NJ. A stringent preemptive protocol reduces cytomegalovirus disease in the first 6 months after kidney transplantation. *Infection* 2012; **40**: 669-675 [PMID: 23015480 DOI: 10.1007/s15010-012-0343-5]
232 **Griffiths PD**, Stanton A, McCarrell E, Smith C, Osman M, Harber M, Davenport A, Jones G, Wheeler DC, O'Beirne J, Thorburn D, Patch D, Atkinson CE, Pichon S, Sweny P, Lanzman M, Woodford E, Rothwell E, Old N, Kinyanjui R, Haque T, Atabani S, Luck S, Prideaux S, Milne RS, Emery VC, Burroughs AK. Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial. *Lancet* 2011; **377**: 1256-1263 [PMID: 21481708 DOI: 10.1016/S0140-6736(11)60136-0]
233 **Kharfan-Dabaja MA**, Boeckh M, Wilck MB, Langston AA, Chu AH, Wloch MK, Guterwill DF, Smith LR, Rolland AP, Kenney RT. A novel therapeutic cytomegalovirus DNA vaccine in allogeneic haemopoietic stem-cell transplantation: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis* 2012; **12**: 290-299 [PMID: 22237175 DOI: 10.1016/S1473-3099(11)70344-9]
234 **Carbone M**, Mutimer D, Neuberger J. Hepatitis C virus and nonliver solid organ transplantation. *Transplantation* 2013; **95**: 779-786 [PMID: 23172130 DOI: 10.1097/TP.0b013e318273fec4]
235 **Xiao D**, Craig JC, Chapman JR, Dominguez-Gil B, Tong A, Wong G. Donor cancer transmission in kidney transplantation: a systematic review. *Am J Transplant* 2013; **13**: 2645-2652 [PMID: 24034231 DOI: 10.1111/ajt.12430]
236 **Desai R**, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Cancer transmission from organ donors-unavoidable but low risk. *Transplantation* 2012; **94**: 1200-1207 [PMID: 23269448 DOI: 10.1097/TP.0b013e318272df41]
237 **Desai R,** Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Death on waiting-list and risk of transmission of cancer: where is the right balance? *Am J Transplant* 2013; **13** (suppl 5): S140
238 **Desai R**, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. *Br J Surg* 2014; **101**: 768-774 [PMID: 24771410 DOI: 10.1002/bjs.9460]
239 **Engels E.** Risk for transmission of cancer from solid organ donors in the United States. *Am J Transplant* 2013; **13** (suppl 5): S536
240 **Engels EA**, Castenson D, Pfeiffer RM, Kahn A, Pawlish K, Goodman MT, Nalesnik MA, Israni AK, Snyder J, Kasiske B. Cancers among US organ donors: a comparison of transplant and cancer registry diagnoses. *Am J Transplant* 2014; **14**: 1376-1382 [PMID: 24712385 DOI: 10.1111/ajt.12683]
241 **Desai R,** Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Risk of recurrence of preexisting cancer in organ recipients. *Am J Transplant* 2013; **13** (suppl 5): S98
242 **Sampaio MS**, Cho YW, Qazi Y, Bunnapradist S, Hutchinson IV, Shah T. Posttransplant malignancies in solid organ adult recipients: an analysis of the U.S. National Transplant Database. *Transplantation* 2012; **94**: 990-998 [PMID: 23085553 DOI: 10.1097/TP.0b013e318270bc7b]
243 **Na R**, Grulich AE, Meagher NS, McCaughan GW, Keogh AM, Vajdic CM. Comparison of de novo cancer incidence in Australian liver, heart and lung transplant recipients. *Am J Transplant* 2013; **13**: 174-183 [PMID: 23094788 DOI: 10.1111/j.1600-6143.2012.04302.x]
244 **Cho Y,** Sampaio M, Shah T, Qazi Y, Fong T, Hutchinson IV. Association between de novo post-transplant nonmelanoma skin cancer and solid tumor after organ transplantation – an analysis of OPTN/UNOS data. *Am J Transplant* 2013; **13** (suppl 5): S536
245 **McDonald S,** Carroll R. The occurrence of non-melanoma skin cancer predicts risk of subsequent solid organ cancer. *Am J Transplant* 2013; **13** (suppl 5): S97
246 **Hanlon A**, Colegio OR. The cutting edge of skin cancer in transplant recipients: scientific retreat of international transplant Skin Cancer Collaborative and Skin Cancer in Organ Transplant Patients Europe. *Am J Transplant* 2014; **14**: 1012-1015 [PMID: 24612476 DOI: 10.1111/ajt12681]

P- Reviewer: Furka A, Gong JP, Sipos F, Wang GY
S- Editor: Wen LL **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.267

World J Transplant 2014 December 24; 4(4): 267-275
ISSN 2220-3230 (online)

TOPIC HIGHLIGHT

Maurizio Salvadori, Professor, *Series Editor*

Psychopathological aspects of kidney transplantation: Efficacy of a multidisciplinary team

Concetta De Pasquale, Massimiliano Veroux, Luisa Indelicato, Nunzia Sinagra, Alessia Giaquinta, Michele Fornaro, Pierfrancesco Veroux, Maria L Pistorio

Concetta De Pasquale, Massimiliano Veroux, Luisa Indelicato, Nunzia Sinagra, Alessia Giaquinta, Pierfrancesco Veroux, Maria L Pistorio, Vascular Surgery and Organ Transplant Unit, Department of Surgery, Transplantation and Advanced Technologies, University Hospital of Catania, 95124 Catania, Italy
Michele Fornaro, Department of Formative Sciences, University of Catania, 95124 Catania, Italy
Author contributions: De Pasquale C, Veroux M, Indelicato L, Sinagra N, Giaquinta A, Fornaro M, Veroux P and Pistorio ML all contributed to this paper.
Correspondence to: Massimiliano Veroux, MD, PhD, Vascular Surgery and Organ Transplant Unit, Department of Surgery, Transplantation and Advanced Technologies, University Hospital of Catania, Via S. Sofia, 86-95123 Catania, Italy. veroux@unict.it
Telephone: +39-95-3782384 Fax: +39-95-3782948
Received: March 14, 2014 Revised: May 2, 2014
Accepted: May 29, 2014
Published online: December 24, 2014

Abstract

Renal transplantation is a well established treatment for end-stage renal disease, allowing most patients to return to a satisfactory quality of life. Studies have identified many problems that may affect adaptation to the transplanted condition and post-operative compliance. The psychological implications of transplantation have important consequences even on strictly physical aspects. Organ transplantation is very challenging for the patient and acts as an intense stressor stimulus to which the patient reacts with neurotransmitter and endocrine-metabolic changes. Transplantation can result in a psychosomatic crisis that requires the patient to mobilize all bio-psycho-social resources during the process of adaptation to the new foreign organ which may result in an alteration in self-representation and identity, with possible psychopathologic repercussions. These reactions are feasible in mental disorders, *e.g.*, post-traumatic stress disorder, adjustment disorder, and psychosomatic disorders. In organ transplantation, the fruitful collaboration between professionals with diverse scientific expertise, calls for both a guarantee for mental health and greater effectiveness in challenging treatments for a viable association between patients, family members and doctors. Integrated and multidisciplinary care should include uniform criteria and procedures for standard assessments, for patient autonomy, adherence to therapy, new coping strategies and the adoption of more appropriate lifestyles.

Key words: Psychiatric consultation; Psychological care; Kidney transplantation; Therapeutic compliance; Social and family support

Core tip: Kidney transplantation is now an established clinical technique, although the emotional experiences and the psychological and psychopathological complications related to organ donation and transplantation should not be underestimated. Following transplantation, problems related to the physical integration of a foreign body can arise. On the one hand, the "Life-Extending" process creates a kind of symbolic rebirth with euphoric aspects, and on the other hand, the patient can develop a kind of emotional vulnerability with body image and self-representation disorders, or paranoid reactions to a panic crisis due to the presence of a foreign object (transplanted organ). In fact, the transplanted patient may experience a reactive psychopathologic process (depression, anxiety, dissociative disorder) both due to transplanted organ acceptance difficulties and immunosuppressive therapy complications. The study of psychological aspects and their evaluation using a multidisciplinary approach are important to avoid issues not adequately recognized, which can undermine the transplant success, and/or lead to psychological

distress and psychological suffering in the patient. Transplanted patient re-employment and social and family reintegration requires psychotherapeutic support to implement new coping strategies.

De Pasquale C, Veroux M, Indelicato L, Sinagra N, Giaquinta A, Fornaro M, Veroux P, Pistorio ML. Psychopathological aspects of kidney transplantation: Efficacy of a multidisciplinary team. *World J Transplant* 2014; 4(4): 267-275 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/i4/267.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.267

INTRODUCTION

Renal transplantation is a well-established treatment for end-stage renal disease, allowing most patients to return to a satisfactory quality of life. Advances in medical science and technology in this field are impressive. However, there are still some difficulties that limit the number of transplants performed and the positive outcomes of the interventions. In addition to the insufficient number of donated organs from deceased and living donors, a major difficulty is the result of transplant course management often exclusively medical-surgical, ignoring the close interaction between mind and body.

In recent years there has been a gradual increase in integration between medical and psychological disciplines and psychological support to patients at all stages of the transplantation and to the donor's family, which is now a fairly well-established method of intervention[1-6]. In the case of deceased organ donation, the medical-surgical process is conditioned by the death of another human being, and this raises biological, moral, religious, psychological and social questions.

On the one hand, the donation and removal of organs bring out strong feelings in the relatives of donors, such as demoralization, loneliness, pain and anguish. On the other hand, the person receiving the transplant has feelings of hope, joy, desire for life and rebirth. The inability to mourn and to accept the loss in donor relatives (usually mothers) may result in the so-called "syndrome of the hound". This is a state of mental suffering that involves some people who remain in a state of denial and in mourning, and who show an irresistible desire to know the identity of the transplanted person[7].

In the case of a living donor, the family takes on the responsibility of donation. Feelings of guilt, any need of repair and symbiotic relationships between family members are sometimes reasons that prevent the specialist from granting suitability for transplantation. Psychotherapy has a very important function as it helps the patient to deal with reality, giving a different meaning to the motivations that lead to transplantation.

With regard to the psychological aspects of the recipient with chronic kidney disease, kidney transplantation, although it represents for many patients the "liberation" from the restrictions imposed by the "dialysis addiction", it can also arouse doubts, anxiety and distress which can become, in the post-operative period, fear of infections, worries of rejection and of the unpredictable outcome. In fact, transplant patients can develop emotional distress and affective disorders, such as anxiety and depression, associated with a compromised quality of life[8-12].

Transplantation can also result in a psychosomatic crisis that requires the patient to mobilize all their bio-psycho-social resources during the process of adaptation to the new foreign organ which may result in an alteration in self-representation and identity, with possible psychopathologic repercussions[13-15].

This article will review relevant research on the psychopathological aspects of kidney transplantation. The topics analyzed include body image, personality, post-transplant psychopathological risk, and therapeutic compliance.

BODY IMAGE IN KIDNEY TRANSPLANTATION

The human being has a mental representation of one's body. This, as only a small part is innate, is something that is formed in early childhood, which can change during a person's lifetime and varies in health and disease. The body, therefore, is also a mentally complex construct.

In Schilder's theory (1935), organic disease is a factor of fundamental importance in the evolution and organization of our body schema. Disease in an organ can facilitate a "psychosomatic crisis", a crisis in which the somatic and the psychic aspects are of equal importance, and influence each other[16,17].

In transplantation, if surgery rapidly restores the anatomical and physiological function, cognitive and emotional integration is required: "psychic transplantation[10,18-20].

In this context, the contributions from psychosomatic aspects refer to the complex task of mind reconstruction which the transplanted subject must perform in their own image. This is a difficult process of reconstruction, which allows the acceptance and psychic integration of the new organ[21-23].

During the course of transplantation, the wholeness and unity of the body image is broken. This "Life-Extending" process can develop a kind of emotional vulnerability with body image and self-representation disorders, or paranoid reactions to a panic crisis due to the presence of a foreign object (transplanted organ). This reconstruction process is long and difficult and requires psychic integration of the transplanted organ. According to Castelnuovo-Tedesco (1981), during the organ integration process there are three stages: (1) phase of the foreign body, in which the transplanted organ as foreign can cause persecutory anxieties, or on the contrary idealization; (2) phase of partial incorporation, in which the patient begins to integrate the organ; and (3) phase of total incorporation, in which the organ is acquired automatically, therefore, spontaneous consciousness of the same is absent[18]. Therefore, following

transplantation the "foreign" organ is integrated leading to good harmonization of body image in the recipient[24-26].

PERSONALITY AND RECIPIENT EMOTIONAL PATTERNS

The affective profile in transplanted patients should be more extensively examined to review all aspects of their mental and emotional assessment, as the emotional pattern constitutes a critical clinical feature of these patients[27]. Receiving an organ requires the death of the donor, or at best, living donor surgery, and even if voluntary, this may be the cause of guilt fantasies expressed by transplant subjects[28,29].

Another important aspect to be taken into consideration concerns the psychological attitudes in the stages preceding the transplant, as the patient may have "unrealistic expectations" that will be an obstacle in dealing with transplant procedures and consequences[30-32].

Equally disappointing may be the "traumatic" discovery that the transplant did not provide a good "restitutio ad integrum", with the onset of depressive dynamics and difficulties in accepting the therapeutic post-transplant program[33-37].

This lack of motivation must be identified and possibly corrected before transplantation, as it can lead to rejection resulting in a waste of resources and equipment. If the patient is motivated and understands all the implications of kidney disease in the terminal phase of uremia, the patient feels a responsibility to himself, his family and hopes to improve, following transplantation, his quality of life and his own mental and physical balance[38-42].

De Pasquale *et al*[23] explored personality characteristics in patients undergoing renal transplantation and confirmed the hypothesis that transplantation can pose a potential risk to the patient's psychological balance. The analyzed psychological variables showed a "hysterical personality" characterized by immaturity and self-centeredness, impulsive behavior, dependency, inferiority feelings, hypercontrol and superficial interpersonal relationships. This mental condition is well established in transplanted subjects who tend to be egocentric, dependent on caregivers and focus only on their own needs and the new physical condition, thus changing relationship quality, emotions and self-esteem.

In determining hysterical phenomenology, congenital factors as well as acquired factors related to the environment, suffering, stress and electrolyte changes (K/Ca) are important[43]. Organ transplantation is very challenging in patients and acts as an intense stressor stimulus to which the patient reacts with neurotransmitter and endocrine-metabolic changes. These reactions can result in mental disorders, *e.g.*, post-traumatic stress disorder, adjustment disorder, and psychosomatic disorders.

Pistorio *et al*[30] investigated other personality traits which may emerge in transplant patients and found borderline personality and obsessive-compulsive personality, which are traits negatively correlated with good quality of life. They concluded that it is important to identify patients who have shown pathologic personality traits in order to provide adequate psychologic-psychiatric support and follow-up.

LIVING KIDNEY TRANSPLANTATION

Kidney donation from a living donor is the best solution for end-stage renal failure, both in terms of cost-effectiveness and quality of life, and has many advantages compared with cadaveric transplantation. However, medical practice has long been questioned on ethical, legal and psychological aspects related to living donation.

In this regard, it is important to remember altruistic or "Samaritan" organ donation, only allowed for kidney donation, which follows the National Bioethics Committee of April 23, 2010 and Board of Health of May 4, 2010 guidelines, in compliance with the law n. 458/67 and its implementing regulation n. 116 of April 16, 2010. The Samaritan donor's clinical suitability evaluation follows the same procedures as recommended for standard living donation. Personality dimensions are an essential prerequisite for suitability assessment in transplantation[44,45].

Both recipient and donor affective disorders diagnosed by diagnostic and statistical manual of mental disorders IV TR Axis I personality disorders, substance or benzodiazepine addiction and cognitive deficits should be excluded to avoid psychological and psychiatric post-donation complications[46,47].

Studies have identified many issues which may affect adaptation to the transplanted condition and post-operative compliance[21,48].

The decision to choose living donor transplantation is determined by a particular condition characterized by strong mental and emotional distress in the patient and his family, compounded by the fact that the donor is almost always a family member. Living kidney transplantation creates a particular donor-recipient relationship, characterized by mutual emotional support, which is useful in dealing with this delicate situation[49].

Several authors point out that the reasons for living donation seem to be linked to the suffering of their relative due to progressive renal failure, dialysis and its side effects and long waiting times for deceased donor transplant. Attention should also be paid to the indirect benefits that donation brings to the donor in terms of improvements in self-esteem and self-image.

It is necessary to explore the development of motivation for living donation in order to achieve and maintain a harmonious relationship with the recipient, while respecting their individuality.

In the intra-family selection process for donor identification, the donor is most often the mother enforcing the "maternal privilege" of being the only one eligible for donation[50-52].

In identifying the donor it is necessary to assess the risks of an "impulsive" or poorly cognitively and affectively processed decision, caused by excessive "moral obligation" feelings, "hypomania" and "megalomania" aspects[31,53,54].

Several studies have shown the presence of reluctance on the part of the sick person to accept the donation from a relative. The reasons for this reluctance are different and vary

from one individual to another, and transplant failure can result in intense guilt feelings in the recipient[28,55-57].

With regard to the couple (donor-recipient), some studies have reported an improvement in this relationship, while others have defined it as stable[58-62].

According to a study conducted in 2006 in The Netherlands, the main factor leading to the increase in the number of consents in favor of living donation was being properly informed about the surgical procedures and any risks to themselves and to the donor through specific interviews and questionnaires[63,64].

The risk of problems in recipient sexual identity may occur in people who show sexual identity problems or in adolescents. In these cases, kidney adaptation and integration processes may be more difficult if the donor is of the opposite sex[65].

Therefore, the psychological coping process involved in living kidney donation demands a reconstitution of the body self[66].

De Pasquale *et al*[31] (2013) analyzed living kidney donor personality by examining a sample of 18 living kidney donors using the Millon Clinical Multiaxial Inventory-Ⅲ; they found the presence of narcissistic, histrionic and obsessive-compulsive personality traits in living kidney donors.

POST-TRANSPLANT PSYCHOPATHOLOGICAL RISK

The emotional impact of transplantation can be a traumatic event that interrupts the sense of continuity and personal integrity, eliciting strong emotions.

The experience of negative and disorganized contents makes the person unable to cope with the stressors, including hospitalization, surgery, and invasive treatments, which can be encoded in a distorted way and experienced as terrifying perceptions[67,68].

The threat to the "physical integrity" can then turn into a threat to the "mind integrity", giving rise to psychopathological reactions of different nature and gravity[69-72].

Several international studies showed physical functions and overall post-transplant quality of life improvement: uremic symptoms, sleep disturbances and appetite disorders disappeared, and hematocrit and hemoglobin levels increased significantly, as well as improvements in cognitive function[73-80]. However, despite these improvements and a reduction in total symptom distress, many studies also found a risk of psychopathological and psychosocial malaise[75,81-83].

In the period immediately following surgery, the patient may present a confusional psychosis with anxiety, restlessness, confusion, agitation, hallucinations, confabulation and emotional lability. The frequency of this confusional psychosis varies (20%-40%) and the use of steroids may prolong the psychotic state resulting in "steroid psychosis" with the prevalence of paranoid and hallucination reactions[65].

In the subsequent post-transplant period, liberation feelings, intense emotionalism, euphoria and a sense of rebirth may be prevalent. This phase, which is defined as the "honeymoon", also presents negative symptoms including rejection fear, post-transplant complications, existential uncertainty and gratitude feelings, but also guilt feelings towards the donor[84,85].

In the case where "healing" expectations are amplified, both for a lack of information and for a state of post-operative euphoria, anxious-depressive states may be present in the post-transplant phase[86,87].

The hospital discharge, return to the family and social context require an adaptation process lasting 6 mo to a year, the "life by sick" and dependence on others waiver. The perception of loss of support from physicians can make readjustment to the outside world difficult for transplant patients. This experience is more noticeable in people with a weak perception of their personal abilities and autonomy, for example, after a long period of dialysis[88].

The acceptance of transplant status change is often difficult for family members who have had to redefine roles within the family and recognize the effective autonomy skills of their relative. The process is complex and can present moments of opposition to change, with a need to recover the pre-transplant relations system[44].

The state of post-transplant well-being may be hindered by the following factors: (1) late shock effects/surgery stress (6 mo-1 year), which can lead to cognitive disorders, insomnia, anxiety and depression; (2) anti-rejection therapy side effects: tremors and ataxia due to cyclosporine, changes in body image; (3) anxiety for regular medical checks; (4) emotional crises for complications or rejection episodes with fear, anguish, dejection and anger; and (5) organic or psychological sexual dysfunction[23,65,87-89]. In summary, for better post-transplant rehabilitation and given the obvious risks of psychopathology, the development of interdisciplinary interventions such as socio-medical and psychotherapeutic programs, without which adaptation after transplantation may be difficult and with inevitable repercussions on quality of life[90].

THE ROLE OF A MULTIDISCIPLINARY TEAM ON ADHERENCE IN KIDNEY TRANSPLANTATION

Transplantation results in a significant improvement in expectations and quality of life, even if possible adaptation difficulties may be present such as psychopathological disorders, problems with compliance and adherence to treatment protocols. Such non-adherence seems to predict morbidity and mortality[91-93].

After transplantation, regular immunosuppressive drug administration is crucial, and even small deviations from the prescribed regimen are associated with an increased risk of rejection. The eventual resumption of dialysis replacement therapy after transplantation affects not only patient physical function, but especially his personal, daily and social life. Strong feelings of discomfort, especially

in females, with a "resignation to a life of eternal sick", a reduction in self-esteem due to the change in their role in the family have been reported in the literature[94-101].

A strong concern for the future of himself and of his family prevails, in addition to a strong psychological stress condition that leads to anger and depression. The sense of self-efficacy, coping with the disease and self-monitoring, fosters respect for prescriptions. Patients with a higher self-efficacy show a greater ability to self-manage their own health, with better physical health, a satisfactory quality of life and a decreased risk of complications[95,102-109]. Other studies have shown a positive correlation between self-efficacy and several indicators of health: better control of diabetes, fewer depressive symptoms, lower use of health care institutions and long-term adherence to prescribed drug therapy[110-113]. The beneficial effect of exercise on allograft function and its positive correlation with better health and quality of life were also demonstrated.

Another problem observed concerning psychiatric disorders prior to transplantation is related to non-optimal post-transplant therapeutic compliance[114-120]. Depression pre-or post-transplantation is associated with an increased risk of non-adherence to medical prescriptions, as well as high levels of anxiety and hostility and the presence of unstable personality traits. An excessive perception of "restored health" can lead to promiscuity, abuse of various substances and non-adherence to prescribed treatment in transplant patients, which has a significant impact on post-transplant recovery[65,121,122].

The perceived consequences of living with a chronic medical condition (such as a renal transplant) likely affect adherence and psychological outcomes. Among investigations in adults with a chronic illness, more severe perceived consequences have been found to be associated with greater use of avoidance coping strategies, denial, and behavioral disengagement[123-125]. Medication non-adherence is a common problem in organ transplantation patients with severe consequences for the patients' health[126].

A better understanding of the perceived adversity associated with different aspects of living with a chronic illness may clarify possible interventions to improve illness outcomes. According to recent literature, patients who receive a protocol of psychological support before transplantation and during post-transplant follow-up, this leads to improved treatment compliance and quality of life with modifications related to the physical, emotional and psychological aspects[127]. In this context, consultation and liaison psychiatry has played, and continues to play, a role in stimulating research and fostering the integration between psychiatry and other medical and surgical disciplines.

In a hospital environment, there is a growing need for liaison between operators, and doctors and nurses from different specialties. More use should be made of the Consultation-Liaison Psychiatry facilities, particularly where there is a strong emotional impact on the relationship between operator and patient, such as the intensive care unit, *etc*., where psychiatrists and psychologists should encourage the involvement of the various stakeholders in patient management, and encourage the exchange of knowledge and experience in appropriate and useful liaison activities to prevent burn-out[128].

It is also necessary to include discussions on clinical cases as part of the multidisciplinary team and to promote training sessions and supervision, which are useful in planning cognitive and psychosocial rehabilitation, and psychotherapy both for the patient and his family.

Assessment of quality of life is one of the key indicators for monitoring coping strategies acquired by the transplanted patient and/or the donor-recipient pair. In fact, although it constitutes a subjective variable, quality of life constantly changes in relation to the short- and long-term therapeutic results, and with recipient and donor expectations[119,129,130].

Integrated and multidisciplinary care should also include uniform criteria and procedures for standard assessments, patient autonomy studies, adherence to therapy, new coping strategies and the adoption of more appropriate lifestyles. Only through a "working network" is it possible to monitor the re-employment, family and social reintegration of transplant patients, as health is the result of a number of social, environmental, psychological, economic and genetic determinants[1,48].

REFERENCES

1 **House R**, Trzepacz PT, Thompson TL. Psychiatric consultation to organ transplant services. In: Tasman A; Goldfinger SM, Kaufman CA, editors. Review of psychiatry volume 9. Washington, DC: American Psychiatric Press, 1990: 515-535

2 **Klapheke MM**. The role of the psychiatrist in organ transplantation. *Bull Menninger Clin* 1999; **63**: 13-39

3 **Levenson JL**, Olbrisch ME. Psychosocial screening and selection of candidates for organ transplantation. In: Trzepacz P, DiMartini A, editors. The Transplant Patient: biological, psychiatric and ethical issues in organ transplantation. UK: Cambridge University Press, 2000: 21-41 [DOI: 10.1017/CBO9780511544385.003]

4 **Olbrisch ME**, Benedict SM, Ashe K, Levenson JL. Psychological assessment and care of organ transplant patients. *J Consult Clin Psychol* 2002; **70**: 771-783 [PMID: 12090382 DOI: 10.1037/0022-006X.70.3.771]

5 **Schweitzer J**, Seidel-Wiesel M, Verres R, Wiesel M. Psychological consultation before living kidney donation: finding out and handling problem cases. *Transplantation* 2003; **76**: 1464-1470 [PMID: 14657687 DOI: 10.1097/01.TP.0000084320.57817.32]

6 **López-Navas A**, Ríos A, Riquelme A, Martínez-Alarcón L, Pons JA, Miras M, Sanmartín A, Febrero B, Ramírez P, Parrilla P. Psychological care: social and family support for patients awaiting a liver transplant. *Transplant Proc* 2011; **43**: 701-704 [PMID: 21486578 DOI: 10.1016/j.transproceed.2011.01.095]

7 **Lovera G,** Basile A, Bertolotti M, Comazzi AM, Clerici CA, Gandione M, Mazzoldi M, Rupolo G, Feltrin A, Ponton P. Psychological assistance in organ transplantation. *Ann Ist Super Sanità* 2000; **36**: 225-246 [PMID: 11213654]

8 **De Vito Dabbs A**, Dew MA, Stilley CS, Manzetti J, Zullo T, McCurry KR, Kormos RL, Iacono A. Psychosocial vulnerability, physical symptoms and physical impairment after lung and heart-lung transplantation. *J Heart Lung*

Transplant 2003; **22**: 1268-1275 [PMID: 14585388 DOI: 10.1016/S1053-2498(02)01227-5]
9 **Surman OS**. Psychiatric aspects of liver transplantation. *Psychosomatics* 1994; **35**: 297-307 [PMID: 8036258 DOI: 10.1016/S0033-3182(94)71777-1]
10 **Dew MA**, Roth LH, Schulberg HC, Simmons RG, Kormos RL, Trzepacz PT, Griffith BP. Prevalence and predictors of depression and anxiety-related disorders during the year after heart transplantation. *Gen Hosp Psychiatry* 1996; **18**: 48S-61S [PMID: 8937923 DOI: 10.1016/S0163-8343(96)00077-1]
11 **Dew MA**, Kormos RL, DiMartini AF, Switzer GE, Schulberg HC, Roth LH, Griffith BP. Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. *Psychosomatics* 2001; **42**: 300-313 [PMID: 11496019 DOI: 10.1176/appi.psy.42.4.300]
12 **Erim Y**, Beckmann M, Valentin-Gamazo C, Malago M, Frilling A, Schlaak JF, Gerken G, Broelsch CE, Senf W. Quality of life and psychiatric complications after adult living donor liver transplantation. *Liver Transpl* 2006; **12**: 1782-1790 [PMID: 17133566 DOI: 10.1002/lt.20907]
13 **Dew MA**. Behavioral factors in heart transplantation: Quality of life and medical compliance. *J APPL BIOBEHAV RES* 1999; **2**: 28-54 [DOI: 10.1111/j.1751-9861.1994.tb00037.x]
14 **Dew MA**, Switzer GE, DiMartini AF, Matukaitis J, Fitzgerald MG, Kormos RL. Psychosocial assessments and outcomes in organ transplantation. *Prog Transplant* 2000; **10**: 239-259; quiz 260-261 [PMID: 11232552]
15 **Griva K**, Ziegelmann JP, Thompson D, Jayasena D, Davenport A, Harrison M, Newman SP. Quality of life and emotional responses in cadaver and living related renal transplant recipients. *Nephrol Dial Transplant* 2002; **17**: 2204-2211 [PMID: 12454234 DOI: 10.1093/ndt/17.12.2204]
16 **Schilder P**. The Image and Appearance of the Human Body: Studies in the Constructive Energies of the Psyche. Madison: International Universities Press, 1950
17 **Chiesa S**. Il trapianto d'organo: crisi e adattamento psicologico. *Psichiatria e Medicina* 1989; **10**: 15-21
18 **Castelnuovo-Tedesco P**. Transplantation: psychological implications of changes in body image. In Levy Psychonephrology, Psychological factors in hemodialysis and transplantation. New York: Plenum Press, 1981
19 **Castelnuovo-Tedesco P**. Organ transplant, body image, psychosis. *Psychoanal Q* 1973; **42**: 349-363 [PMID: 4579589]
20 **Fukunishi I**, Sugawara Y, Takayama T, Makuuchi M, Kawarasaki H, Kita Y, Aikawa A, Hasegawa A. Psychiatric problems in living-related transplantation (II): the association between paradoxical psychiatric syndrome and guilt feelings in adult recipients after living donor liver transplantation. *Transplant Proc* 2002; **34**: 2632-2633 [PMID: 12431555 DOI: 10.1016/S0041-1345(02)03455-3]
21 **Rupolo G**, Poznanski C. Psicologia e psichiatria del trapianto d'organi. Masson: Elsevier, 1999: 1-188
22 **Lefebvre P**, Crombez JC, LeBeuf J. Psychological dimension and psychopathological potential of acquiring a kidney. *Can Psychiatr Assoc J* 1973; **18**: 495-500 [PMID: 4128311]
23 **De Pasquale C**, Pistorio ML, Sorbello M, Parrinello L, Corona D, Gagliano M, Giuffrida G, Giaquinta A, Sinagra N, Zerbo D, Veroux P, Veroux M. Body image in kidney transplantation. *Transplant Proc* 2010; **42**: 1123-1126 [PMID: 20534240 DOI: 10.1016/j.transproceed.2010.03.071]
24 **Lastrico A**, Politi PL, Barale F. Sul vissuto del trapianto cardiaco. *Minerva Psichiatr* 1994; **35**: 139-145 [PMID: 7968410]
25 **Bertini M**. Problemi psicologici nei cosiddetti procedimenti 'life extending'. In: AAVV Rigetto psicologico di protesi, innesti, trapianti e plastiche. Roma: Istituto Italiano di Medice Sociale, 1972
26 **Plassman R**. Organ worlds: outline of an analytical psychology of the body. *Psychoanalitic Inquiry* 1998; **18**: 344-367 [DOI: 10.1080/07351699809534197]
27 **Chisholm MA**. Identification of medication-adherence barriers and strategies to increase adherence in recipients of renal transplants. *Manag Care Interface* 2004; **17**: 44-48 [PMID: 15521285]
28 **Kranenburg L**, Zuidema W, Weimar W, Ijzermans J, Passchier J, Hilhorst M, Busschbach J. Postmortal or living related donor: preferences of kidney patients. *Transpl Int* 2005; **18**: 519-523 [PMID: 15819799 DOI: 10.1111/j.1432-2277.2005.00081.x]
29 **Martínez-Alarcón L**, Ríos A, Conesa C, Ramírez P. Postmortal or living related donor: preferences of kidney patients. *Transpl Int* 2006; **19**: 598-599; author reply 600 [PMID: 16764640 DOI: 10.1111/j.1432-2277.2006.00290.x]
30 **Pistorio ML**, Veroux M, Corona D, Sinagra N, Giaquinta A, Zerbo D, Giacchi F, Gagliano M, Tallarita T, Veroux P, De Pasquale C. The study of personality in renal transplant patients: possible predictor of an adequate social adaptation? *Transplant Proc* 2013; **45**: 2657-2659 [PMID: 24034016 DOI: 10.1016/j.transproceed.2013.07.003]
31 **De Pasquale C**, Veroux M, Corona D, Sinagra N, Giaquinta A, Zerbo D, Cimino S, Gagliano M, Giuffrida G, Veroux P, Pistorio ML. The concept of self and emotional involvement in living kidney donation: a psychometric investigation. *Transplant Proc* 2013; **45**: 2604-2606 [PMID: 24034001 DOI: 10.1016/j.transproceed.2013.08.00]
32 **Morris PL**, Jones B. Transplantation versus dialysis: a study of quality of life. *Transplant Proc* 1988; **20**: 23-26 [PMID: 3278459]
33 **Kerr S**, Johnson E, Pandian K, Gillingham K, Matas A. Psychological impact of a failed kidney transplant. *Transplant Proc* 1997; **29**: 1573 [PMID: 9123430 DOI: 10.1016/S0041-1345(96)00680]
34 **Fauci AS**, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. *Ann Intern Med* 1976; **84**: 304-315 [PMID: 769625 DOI: 10.7326/0003-4819-84-3-304]
35 **Strauss B**, Thormann T, Strenge H, Biernath E, Foerst U, Stauch C, Torp U, Bernhard A, Speidel H. Psychosocial, neuropsychological and neurological status in a sample of heart transplant recipients. *Qual Life Res* 1992; **1**: 119-128 [PMID: 1301119 DOI: 10.1007/BF00439719]
36 **Deshields TL**, McDonough EM, Mannen RK, Miller LW. Psychological and cognitive status before and after heart transplantation. *Gen Hosp Psychiatry* 1996; **18**: 62S-69S [PMID: 8937924 DOI: 10.1016/S0163-8343(96)00078-3]
37 **Chisholm MA**, Mulloy LL, Jagadeesan M, DiPiro JT. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications. *Clin Transplant* 2001; **15**: 330-336 [PMID: 11678959 DOI: 10.1034/j.1399-0012.2001.150505.x]
38 **Kizilisik AT**, Shokouh-Amiri MH, Tombazzi CR, Desmukh S, Grewal HP, Vera SR, Gaber AO. Psychiatric complications after liver transplantation. *Transplant Proc* 2001; **33**: 3697 [PMID: 11750575 DOI: 10.1016/S0041-1345(01)02508-8]
39 **Köllner V**, Schade I, Maulhardt T, Maercker A, Joraschky P, Gulielmos V. Posttraumatic stress disorder and quality of life after heart or lung transplantation. *Transplant Proc* 2002; **34**: 2192-2193 [PMID: 12270360 DOI: 10.1016/S0041-1345(02)03198-6]
40 **Favaro A**, Gerosa G, Caforio AL, Volpe B, Rupolo G, Zarneri D, Boscolo S, Pavan C, Tenconi E, d'Agostino C, Moz M, Torregrossa G, Feltrin G, Gambino A, Santonastaso P. Posttraumatic stress disorder and depression in heart transplantation recipients: the relationship with outcome and adherence to medical treatment. *Gen Hosp Psychiatry* 2011; **33**: 1-7 [PMID: 21353121 DOI: 10.1016/j.genhosppsych.2010.10.001]
41 **Depasquale C**, Pistorio ML, Corona D, Mistretta A, Zerbo D, Sinagra N, Giaquinta A, Tallarita T, Esker B, Mociskyte D, Leonardi A, Gula R, Veroux P, Veroux M. Correlational study between psychic symptoms and quality of life among hemodialysis patients older than 55 years of age. *Transplant Proc* 2012; **44**: 1876-1878 [PMID: 22974860 DOI: 10.1016/j.transproceed.2012.06.015]
42 **Waterman AD**, Robbins ML, Paiva AL, Peipert JD, Davis LA,

Hyland SS, Schenk EA, Baldwin KA, Amoyal NR. Measuring kidney patients' motivation to pursue living donor kidney transplant: Development of Stage of Change, Decisional Balance and Self-Efficacy measures. *J Health Psychol* 2013 Oct 22; Epub ahead of print [PMID: 24155194]

43 **Halligan PW**, David AS, eds. Conversion Hysteria: Towards a Cognitive Neuropsychological Account. *Psychology* (Press Hove) 1999 [DOI: 10.1093/brain/124.1.232]

44 **Fidel Kinori SG**, Alcántara Tadeo A, Castan Campanera E, Costa Requena G, Diez Quevedo C, Lligoña Garreta A, Lopez Lazcano A, Martínez Del Pozo M, Rangil Muñoz T, Peri Nogués JM; en nombre del Grupo de Trabajo de evaluación psiquiátrica y psicológica de la Organización Catalana de Trasplantes. Unified Protocol for psychiatric and psychological assessment of candidates for transplantation of organs and tissues, PSI-CAT. *Rev Psiquiatr Salud Ment* 2014 Apr 6; Epub ahead of print [PMID: 24717548]

45 **Anand-Kumar V**, Kung M, Painter L, Broadbent E. Impact of organ transplantation in heart, lung and liver recipients: assessment of positive life changes. *Psychol Health* 2014; **29**: 687-697 [PMID: 24460459 DOI: 10.1080/08870446.2014.882922]

46 **Cramond WA**, Knight PR, Lawrence JR, Higgins BA, Court JH, MacNamara FM, Clarkson AR, Miller CD. Psychological aspects of the management of chronic renal failure. *Br Med J* 1968; **1**: 539-543 [PMID: 4868553 DOI: 10.1136/bmj.1.5591.539]

47 **American psychiatric Association**. Diagnostic and Statistical manual of Mental Disorders. 4th ed. Washington, DC: America Psychiatric Association, 1994: Text Revision, 2000

48 **Levenson JL**, Olbrisch ME. Psychosocial evaluation of organ transplant candidates. A comparative survey of process, criteria, and outcomes in heart, liver, and kidney transplantation. *Psychosomatics* 1993; **34**: 314-323 [PMID: 8351306 DOI: 10.1016/S0033-3182(93)71865-4]

49 **Franklin PM**, Crombie AK. Live related renal transplantation: psychological, social, and cultural issues. *Transplantation* 2003; **76**: 1247-1252 [PMID: 14578766 DOI: 10.1097/01.TP.0000087833.48999.3D]

50 **Binet I**, Bock AH, Vogelbach P, Gasser T, Kiss A, Brunner F, Thiel G. Outcome in emotionally related living kidney donor transplantation. *Nephrol Dial Transplant* 1997; **12**: 1940-1948 [PMID: 9306347 DOI: 10.1093/ndt/12.9.1940]

51 **Pradel FG**, Mullins CD, Bartlett ST. Exploring donors' and recipients' attitudes about living donor kidney transplantation. *Prog Transplant* 2003; **13**: 203-210 [PMID: 14558635]

52 **Sajjad I**, Baines LS, Salifu M, Jindal RM. The dynamics of recipient-donor relationships in living kidney transplantation. *Am J Kidney Dis* 2007; **50**: 834-854 [PMID: 17954298 DOI: 10.1053/j.ajkd.2007.07.029]

53 **Heinrich TW**, Marcangelo M. Psychiatric issues in solid organ transplantation. *Harv Rev Psychiatry* 2009; **17**: 398-406 [PMID: 19968454 DOI: 10.3109/10673220903463259]

54 **Trzcinska M**, Włodarczyk Z. Psychological Aspects of Kidney Transplantation. *UROL NEPHRO* 2011 [DOI: 10.5772/16725]

55 **Waterman AD**, Stanley SL, Covelli T, Hazel E, Hong BA, Brennan DC. Living donation decision making: recipients' concerns and educational needs. *Prog Transplant* 2006; **16**: 17-23 [PMID: 16676669]

56 **Murray LR**, Conrad NE, Bayley EW. Perceptions of kidney transplant by persons with end stage renal disease. *ANNA J* 1999; **26**: 479-483; discussion 484 [PMID: 10776075]

57 **de Groot IB**, Schipper K, van Dijk S, van der Boog PJ, Stiggelbout AM, Baranski AG, Marang-van de Mheen PJ. Decision making around living and deceased donor kidney transplantation: a qualitative study exploring the importance of expected relationship changes. *BMC Nephrol* 2012; **13**: 103 [PMID: 22958636 DOI: 10.1186/1471-2369-13-103]

58 **Clemens KK**, Thiessen-Philbrook H, Parikh CR, Yang RC, Karley ML, Boudville N, Ramesh Prasad GV, Garg AX. Psychosocial health of living kidney donors: a systematic review. *Am J Transplant* 2006; **6**: 2965-2977 [PMID: 17294524 DOI: 10.1111/j.1600-6143.2006.01567.x]

59 **Andersen MH**, Bruserud F, Mathisen L, Wahl AK, Hanestad BR, Fosse E. Follow-up interviews of 12 living kidney donors one yr after open donor nephrectomy. *Clin Transplant* 2007; **21**: 702-709 [PMID: 17988262 DOI: 10.1111/j.1399-0012.2007.00726.x]

60 **Neuhaus TJ**, Wartmann M, Weber M, Landolt MA, Laube GF, Kemper MJ. Psychosocial impact of living-related kidney transplantation on donors and partners. *Pediatr Nephrol* 2005; **20**: 205-209 [PMID: 15627165]

61 **Duque JL**, Loughlin KR, Kumar S. Morbidity of flank incision for renal donors. *Urology* 1999; **54**: 796-801 [PMID: 10565736 DOI: 10.1016/S0090-4295(99)00274-5]

62 **Giessing M**, Reuter S, Schönberger B, Deger S, Tuerk I, Hirte I, Budde K, Fritsche L, Morgera S, Neumayer HH, Loening SA. Quality of life of living kidney donors in Germany: a survey with the Validated Short Form-36 and Giessen Subjective Complaints List-24 questionnaires. *Transplantation* 2004; **78**: 864-872 [PMID: 15385806 DOI: 10.1097/01.TP.0000133307.00604.86]

63 **Kranenburg L**, Zuidema W, Weimar W, IJzermans J, Passchier J, Hilhorst M, Busschbach J. Postmortal or living related donor: preferences of kidney patients. Authors' reply. *Transplant Int* 2006; **19**: 600 [DOI: 10.1111/j.1432-2277.2006.00305.x]

64 **Klapheke MM**. The role of the psychiatrist in organ transplantation. *Bull Menninger Clin* 1999; **63**: 13-39 [PMID: 10028744 DOI: 10.1002/1098]

65 **Ilić S**, Avramović M. Psychological aspects of living donor kidney transplantation. *Med Biol* 2002; **9**: 195-200

66 **Kumnig M**, Beck T, Höfer S, König P, Schneeberger S, Weißenbacher A, Bunzel B, Schüßler G, Rumpold G. Preoperative evaluation of the body concept of donors and recipients of living kidney donations. *Z Psychosom Med Psychother* 2013; **59**: 3-12 [PMID: 23467994]

67 **Cotugno A**. Trauma, attaccamento e sviluppo psicologico della personalità. *Psicobiettivo* 1999; **19:** 15-26

68 **Costantini E**, Monticelli F. Catastrofe e emozione veemente. *Psicobiettivo* 1999; **19**: 3

69 **Stukas AA**, Dew MA, Switzer GE, DiMartini A, Kormos RL, Griffith BP. PTSD in heart transplant recipients and their primary family caregivers. *Psychosomatics* 1999; **40**: 212-221 [PMID: 10341533 DOI: 10.1016/S0033-3182(99)71237-5]

70 **Manne S**, DuHamel K, Nereo N, Ostroff J, Parsons S, Martini R, Williams S, Mee L, Sexson S, Wu L, Difede J, Redd WH. Predictors of PTSD in mothers of children undergoing bone marrow transplantation: the role of cognitive and social processes. *J Pediatr Psychol* 2002; **27**: 607-617 [PMID: 12228332 DOI: 10.1093/jpepsy/27.7.607]

71 **Stuber ML**, Shemesh E. Post-traumatic stress response to life-threatening illnesses in children and their parents. *Child Adolesc Psychiatr Clin N Am* 2006; **15**: 597-609 [PMID: 16797441 DOI: 10.1016/j.chc.2006.02.006]

72 **Gattinara P**, Andovini C, Costantini E, Morganti G, Onofri A. I trapianti d'organo nella prospettiva cognitivo-evoluzionistica. *Psicobiettivo* 2005; **XXV**: 18-20 [DOI: 10.1400/64499]

73 **Johnson JP**, McCauley CR, Copley JB. The quality of life of hemodialysis and transplant patients. *Kidney Int* 1982; **22**: 286-291 [PMID: 6757524 DOI: 10.1038/ki.1982.167]

74 **Christensen AJ**, Holman JM, Turner CW. A prospective study of quality of life in end stage renal disease: effects of cadaveric renal transplantation. *Clin Transplant* 1991; **5**: 40-47

75 **Witzke O**, Becker G, Franke G, Binek M, Philipp T, Heemann U. Kidney transplantation improves quality of life. *Transplant Proc* 1997; **29**: 1569-1570 [PMID: 9123428 DOI: 10.1016/S0041-1345(96)00678-1]

76 **Tsuji-Hayashi Y**, Fukuhara S, Green J, Takai I, Shinzato T, Uchida K, Oshima S, Yamazaki C, Maeda K. Health-related quality of life among renal-transplant recipients in Japan. *Transplantation* 1999; **68**: 1331-1335 [PMID: 10573072 DOI: 10.0041-1337/99/6809-1331/0]

77 **Mingardi G**. Quality of life and end stage renal disease

therapeutic programs. DIA-QOL Group. Dialysis quality of life. *Int J Artif Organs* 1998; **21**: 741-747 [PMID: 9894753]
78 **Bakewell AB**, Higgins RM, Edmunds ME. Does ethnicity influence perceived quality of life of patients on dialysis and following renal transplant? *Nephrol Dial Transplant* 2001; **16**: 1395-1401 [PMID: 11427631 DOI: 10.1093/ndt/16.7.1395]
79 **van der Mei SF**, Groothoff JW, van Sonderen EL, van den Heuvel WJ, de Jong PE, van Son WJ. Clinical factors influencing participation in society after successful kidney transplantation. *Transplantation* 2006; **82**: 80-85 [PMID: 16861945 DOI: 10.1097/01.tp.0000225768.56981.aa]
80 **Kramer L**, Madl C, Stockenhuber F, Yeganehfar W, Eisenhuber E, Derfler K, Lenz K, Schneider B, Grimm G. Beneficial effect of renal transplantation on cognitive brain function. *Kidney Int* 1996; **49**: 833-838 [PMID: 8648927 DOI: 10.1038/ki.1996.115]
81 **Min SK**, Kim KH, Shin JH, Han JO, Lee KY, Kang WR. Psychiatric aspects of hemodialysis and kidney transplantation. *Yonsei Med J* 1984; **25**: 122-132 [PMID: 6400060]
82 **Grady KL**, Jalowiec A, White-Williams C. Improvement in quality of life in patients with heart failure who undergo transplantation. *J Heart Lung Transplant* 1996; **15**: 749-757 [PMID: 8878757]
83 **Chilcot J**, Spencer BW, Maple H, Mamode N. Depression and kidney transplantation. *Transplantation* 2014; **97**: 717-721 [PMID: 24342977 DOI: 10.1097/01.TP.0000438212.72960.ae]
84 **Surman OS**. Psychiatric aspects of organ transplantation. *Am J Psychiatry* 1989; **146**: 972-982 [PMID: 2665527]
85 **Christopherson LK**. Cardiac transplantation: a psychological perspective. *Circulation* 1987; **75**: 57-62 [DOI: 10.1161/01.CIR.75.1.57]
86 **Fukunishi I**, Hasegawa A, Ohara T, Aikawa A, Hatanaka A, Suzuki J, Kikuchi M, Amagasaki K. Kidney transplantation and liaison psychiatry, part I: anxiety before, and the prevalence rate of psychiatric disorders before and after, transplantation. *Psychiatry Clin Neurosci* 1997; **51**: 301-304 [PMID: 9413877]
87 **Kalman TP**, Wilson PG, Kalman CM. Psychiatric morbidity in long-term renal transplant recipients and patients undergoing hemodialysis. A comparative study. *JAMA* 1983; **250**: 55-58 [PMID: 6343654 DOI: 10.1001/jama.1983.03340010037025]
88 **Cavallero P**, Ferrari MG, Verbena V, Mosca F. Vicinanza e risorse nelle persone sottoposte a trapianto d'organo e loro familiari. *Psychofenia* 2007; X: 17 [DOI: 10.1285/i17201632vXn17p71]
89 **Rupolo G**, Bertolini C. Modalità di coping nei pazienti sottoposti a trapianto d'organo. Riv. *Psichiatria* 1996; **3**: 94-102
90 **Lovera G**, Basile A, Bertolotti M, Comazzi AM, Clerici CA, Gandione M, Mazzoldi M, Rupolo G, Feltrin A, Ponton P. [Psychological assistance in organ transplantation]. *Ann Ist Super Sanita* 2000; **36**: 225-246 [PMID: 11213654]
91 **Chisholm MA**, Lance CE, Mulloy LL. Patient factors associated with adherence to immunosuppressant therapy in renal transplant recipients. *Am J Health Syst Pharm* 2005; **62**: 1775-1781 [PMID: 16120736 DOI: 10.2146/ajhp040541]
92 **Chisholm-Burns MA**, Spivey CA, Wilks SE. Social support and immunosuppressant therapy adherence among adult renal transplant recipients. *Clin Transplant* 2010; **24**: 312-320 [PMID: 19694770 DOI: 10.1111/j.1399-0012.2009.01060.x]
93 **Burra P**, Germani G, Gnoato F, Lazzaro S, Russo FP, Cillo U, Senzolo M. Adherence in liver transplant recipients. *Liver Transpl* 2011; **17**: 760-770 [PMID: 21384527 DOI: 10.1002/lt.22294]
94 **Hawkins DW**, Fiedler FP, Douglas HL, Eschbach RC. Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients. *Am J Hosp Pharm* 1979; **36**: 1321-1325 [PMID: 507073]
95 **De Geest S**, Borgermans L, Gemoets H, Abraham I, Vlaminck H, Evers G, Vanrenterghem Y. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. *Transplantation* 1995; **59**: 340-347 [PMID: 7871562 DOI: 10.1097/00007890-199502000-00006]
96 **De Geest S**, Abraham I, Moons P, Vandeputte M, Van Cleemput J, Evers G, Daenen W, Vanhaecke J. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant* 1998; **17**: 854-863 [PMID: 9773856]
97 **De Geest S**, Abraham I, Dunbar-Jacob J, Vanhaecke J. Behavioral strategies for long-term survival of transplant recipients. In: Metry, J.; Meyer, U., editors. Drug Regimen Compliance: Issues in Clinical Trials and Patient Management. Chichester NY: John Wiley & Sons, 1999: 163-180 [DOI: 10.1002/047084633X.ch12]
98 **Desmyttere A**, Dobbels F, Cleemput I, De Geest S. Noncompliance with immunosuppressive regimen in organ transplantation: is it worth worrying about? *Acta Gastroenterol Belg* 2005; **68**: 347-352 [PMID: 16268422]
99 **Rao PS**, Schaubel DE, Jia X, Li S, Port FK, Saran R. Survival on dialysis post-kidney transplant failure: results from the Scientific Registry of Transplant Recipients. *Am J Kidney Dis* 2007; **49**: 294-300 [PMID: 17261432 DOI: 10.1053/j.ajkd.2006.11.022]
100 **Takemoto SK**, Pinsky BW, Schnitzler MA, Lentine KL, Willoughby LM, Burroughs TE, Bunnapradist S. A retrospective analysis of immunosuppression compliance, dose reduction and discontinuation in kidney transplant recipients. *Am J Transplant* 2007; **7**: 2704-2711 [PMID: 17868065 DOI: 10.1111/j.1600-6143.2007.01966.x]
101 **Mennilli S**, Vosolo MN, Di Liberato L, Bonomini M. Quando il trapianto renale fallisce: necessità di pianificazione di un percorso assistenziale al paziente che riprende il trattamento sostitutivo dialitico. *Giornale di Tecniche Nefrologiche & Dialitiche Wichting Editore* 2010; **22**: 17-21 [DOI: 10.5301/GTND.2012.10129]
102 **Tsay SL**, Healstead M. Self-care self-efficacy, depression, and quality of life among patients receiving hemodialysis in Taiwan. *Int J Nurs Stud* 2002; **39**: 245-251 [PMID: 11864647 DOI: 10.1016/S0020-7489(01)00030-X]
103 **Weng LC**, Dai YT, Huang HL, Chiang YJ. Self-efficacy, self-care behaviours and quality of life of kidney transplant recipients. *J Adv Nurs* 2010; **66**: 828-838 [PMID: 20423370 DOI: 10.1111/j.1365-2648.2009.05243.x]
104 **Maeda U**, Shen BJ, Schwarz ER, Farrell KA, Mallon S. Self-efficacy mediates the associations of social support and depression with treatment adherence in heart failure patients. *Int J Behav Med* 2013; **20**: 88-96 [PMID: 22212607 DOI: 10.1007/s12529-011-9215-0]
105 **Gaines JM**, Talbot LA, Metter EJ. The relationship of arthritis self-efficacy to functional performance in older men and women with osteoarthritis of the knee. *Geriatr Nurs* 2002; **23**: 167-170 [PMID: 12075283 DOI: 10.1067/mgn.2002.125420]
106 **Bodenheimer T**, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *JAMA* 2002; **288**: 2469-2475 [PMID: 12435261 DOI: 10.1001/jama.288.19.2469]
107 **Linnell K**. Chronic disease self-management: one successful program. *Nurs Econ* 2005; **23**: 189-191; 196-198 [PMID: 16189984]
108 **Christensen AJ**, Ehlers SL, Raichle KA, Bertolatus JA, Lawton WJ. Predicting change in depression following renal transplantation: effect of patient coping preferences. *Health Psychol* 2000; **19**: 348-353 [PMID: 10907653 DOI: 10.1037/0278-6133.19.4.348]
109 **Baines LS**, Joseph JT, Jindal RM. Compliance and late acute rejection after kidney transplantation: a psycho-medical perspective. *Clin Transplant* 2002; **16**: 69-73 [PMID: 11982618 DOI: 10.1034/j.1399-0012.2002.00111.x]
110 **Ikeda K**, Aoki H, Saito K, Muramatsu Y, Suzuki T. Associations of blood glucose control with self-efficacy and rated anxiety/depression in type II diabetes mellitus patients. *Psychol Rep* 2003; **92**: 540-544 [PMID: 12785638]
111 **Weng LC**, Dai YT, Wang YW, Huang HL, Chiang YJ. Effects of self-efficacy, self-care behaviours on depressive symptom of Taiwanese kidney transplant recipients. *J Clin*

Nurs 2008; **17**: 1786-1794 [PMID: 18266845 DOI: 10.1111/j.1365-2702.2007.02035.x]
112 **Mancusi F**. Le risorse di fronteggiamento dell'insufficienza renale cronica: una ricerca sperimentale in un centro di dialisi. *Psychomed* 2011; **6**: 61-65
113 **Lorig KR**, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract* 2001; **4**: 256-262 [PMID: 11769298]
114 **Painter PL**, Hector L, Ray K, Lynes L, Paul SM, Dodd M, Tomlanovich SL, Ascher NL. Effects of exercise training on coronary heart disease risk factors in renal transplant recipients. *Am J Kidney Dis* 2003; **42**: 362-369 [PMID: 12900820 DOI: 10.1016/S0272-6386(03)00673-5]
115 **van den Berg-Emons RJ**, van Ginneken BT, Nooijen CF, Metselaar HJ, Tilanus HW, Kazemier G, Stam HJ. Fatigue after liver transplantation: effects of a rehabilitation program including exercise training and physical activity counseling. *Phys Ther* 2014; **94**: 857-865 [PMID: 24557657]
116 **Shirali AC**, Bia MJ. Management of cardiovascular disease after kidney transplantation. *Clin J Am Soc Nephrol* 2008 [DOI: 10.2215CJN.05081107]
117 **Mosconi G**, Panicali L, Corsini S. Physical activity in solid organ transplant recipients. *Transplant Int* 2009; **22**: 175-176
118 **McAuley E**. The role of efficacy cognitions in the prediction of exercise behavior in middle-aged adults. *J Behav Med* 1992; **15**: 65-88 [PMID: 1583674]
119 **Denhaerynck K**, Dobbels F, Steiger J, De Geest S. Quality of life after kidney transplantation. In Veroux M, Veroux P: Kidney Transplantation: challenging the future, United Arab Emirates. Bentham: Bentham Publisher, 2012: 71-84
120 **Shapiro PA**, Williams DL, Foray AT, Gelman IS, Wukich N, Sciacca R. Psychosocial evaluation and prediction of compliance problems and morbidity after heart transplantation. *Transplantation* 1995; **60**: 1462-1466 [PMID: 8545875]
121 **Cukor D**, Newville H, Jindal R. Depression and immunosuppressive medication adherence in kidney transplant patients. *Gen Hosp Psychiatry* 2008; **30**: 386-387 [PMID: 18585547 DOI: 10.1016/j.genhosppsych.2007.12.003]
122 **Dew MA**, Roth LH, Thompson ME, Kormos RL, Griffith BP. Medical compliance and its predictors in the first year after heart transplantation. *J Heart Lung Transplant* 1996; **15**: 631-645 [PMID: 8794030]
123 **Kemp S**, Morley S, Anderson E. Coping with epilepsy: do illness representations play a role? *Br J Clin Psychol* 1999; **38** (Pt 1): 43-58 [PMID: 10212736 DOI: 10.1348/014466599162656]
124 **Morris R**, Petrie K, Weinman J. Functioning in chronic fatigue syndrome: do illness perceptions play a regulatory role? *BJHP* 1996; **1**: 15-25 [DOI: 10.1111/j.2044-8287.1996.tb00488.x]
125 **Hagger MS**, Orbell S. A meta-analytic review of the common-sense model of illness representation. *Psychol Health* 2003; **18**: 141-184 [DOI: 10.1080/0887044031000813 21]
126 **Zelikovsky N**, Schast AP. Eliciting accurate reports of adherence in a clinical interview: development of the Medical Adherence Measure. *Pediatr Nurs* 2008; **34**: 141-146 [PMID: 18543839]
127 **De Pasquale C**, Pistorio ML, Veroux P, Giuffrida G, Sinagra N, Ekser B, Zerbo D, Corona D, Giaquinta A, Veroux M. Quality of life in kidney transplantation from marginal donors. *Transplant Proc* 2011; **43**: 1045-1047 [PMID: 21620049 DOI: 10.1016/j.transproceed.2011.01.156]
128 **Roussel MG**, Gorham N, Wilson L, Mangi AA. Improving recovery time following heart transplantation: the role of the multidisciplinary health care team. *J Multidiscip Healthc* 2013; **6**: 293-302 [PMID: 24009423]
129 **Comazzi AM.** Indagine psicologica sulla disponibilità alla donazione d organi per trapianti. Min. *Psich Psicol* 1974; 15: 27-31
130 **Comazzi AM**, Clerici CA, Facchetti E, Pizzi C, Scalamogna M, Sirchia G. Psychological support for donor families in the North Italy Transplant Program (NITp). VA: American Psychiatric Press, 1990: 515-535

P- Reviewer: Lopez-Jornet P, Markic D **S- Editor**: Ji FF
L- Editor: Webster JR **E- Editor:** Wu HL

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.276

World J Transplant 2014 December 24; 4(4): 276-293
ISSN 2220-3230 (online)

REVIEW

Diagnosis and management of coronary allograft vasculopathy in children and adolescents

Nathalie Dedieu, Gerald Greil, James Wong, Matthew Fenton, Michael Burch, Tarique Hussain

Nathalie Dedieu, Matthew Fenton, Michael Burch, Great Ormond Street Hospital for Children NHS Foundation Trust, WC1 3JH London, United Kingdom
Nathalie Dedieu, Gerald Greil, James Wong, Tarique Hussain, King's College London, Division of Imaging Sciences and Biomedical Engineering, St Thomas Hospital, SE1 7EH London, United Kingdom
Author contributions: All authors contributed to the paper.
Correspondence to: Nathalie Dedieu, MD, King's College London, Division of Imaging Sciences and Biomedical Engineering, St Thomas Hospital, Westminster Bridge Road, 4th Floor Lambeth wing, SE1 7EH London, United Kingdom. nathaliededieu@hotmail.com
Telephone: +44-20-71889617 Fax: +44-20-71885442
Received: June 9, 2014 Revised: August 12, 2014
Accepted: September 16, 2014
Published online: December 24, 2014

Abstract

Coronary allograft vasculopathy remains one of the leading causes of death beyond the first year post transplant. As a result of denervation following transplantation, patients lack ischaemic symptoms and presentation is often late when the graft is already compromised. Current diagnostic tools are rather invasive, or in case of angiography, significantly lack sensitivity. Therefore a non-invasive tool that could allow early diagnosis would be invaluable.This paper review the disease form its different diagnosis techniques,including new and less invasive diagnostic tools to its pharmacological management and possible treatments.

Key words: Cardiac transplantation; Allograft vasculopathy; Paediatrics; Diagnosis; Management which reflect the content of the study

Core tip: Coronary allograft vasculopathy remains the leading cause of great loss in children after the first year post transplant. This paper offers a state of the art review of the disease from diagnosis including most recent and less invasive tools to management.

Dedieu N, Greil G, Wong J, Fenton M, Burch M, Hussain T. Diagnosis and management of coronary allograft vasculopathy in children and adolescents. *World J Transplant* 2014; 4(4): 276-293 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/i4/276.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.276

DEFINITION AND PHYSIOPATHOLOGY

In children, coronary allograft vasculopathy (CAV) remains the main limiting survival factor after heart transplantation and the major cause of mortality after the first year post transplant leading ultimately to graft loss[1,2].

One elegant etiological description of CAV is that of "immunologic mechanisms operating in a milieu of non-immunologic risk factors"[3]. The process is believed to start off as a response to endothelial injury in the graft, originated by a complex interaction of multiple donor and recipient factors. The resulting endothelial dysfunction, leads to altered endothelial permeability and subsequent intimal hyperplasia as a consequence of the vascular remodeling originated by the inflammatory response. The immunologic events constitute the original trigger and non-inflammatory events such as cytomegalovirus infection, ischemic time (reperfusion injury), increased donor age and classical cardiovascular risk factors (*i.e.,* diabetes, dyslipidemias, smoking and hypertension), perpetuate the inflammatory response and increase the endothelial injury[4].

Typical lesions (Figures 1 and 2) consist of diffuse intimal proliferation leading to the development of luminal stenosis and small vessels occlusion which then limits blood supply to the graft causing chronic vascular injury and ultimately myocardial ischemia[5]. The lesions develop earlier and quicker than atherosclerotic lesions.

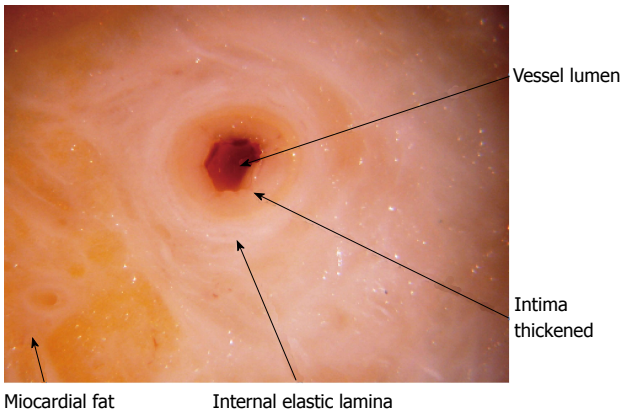

Figure 1 Stenotic coronary artery macroscopic aspect in post mortem study of explanted heart.

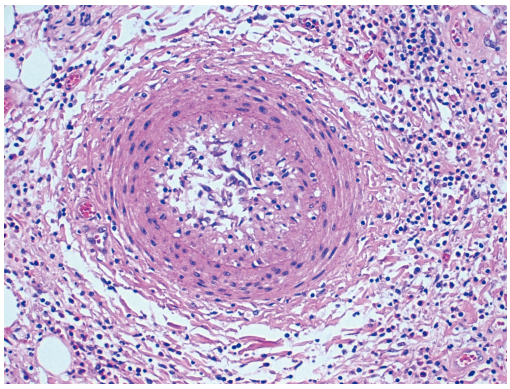

Figure 2 Histopathologic example of stenotic microvasculopathy: Medial thickening and endothelial swelling with evidence of luminal stenosis (hematoxylin-eosin stain).

In addition, progression is often silent due to the lack of ischemic symptoms from the denervated heart and often, the first clinical manifestation is an adverse cardiac event[6].

The real incidence of CAV among the pediatric population remains unknown, with a reported incidence varying between studies from 3% to 43%[7]. According to an angiographic multicenter study, the incidence of CAV would be 2%, 9% and 17% at 1, 3 and 5 years[1]. Looking at the incidence reported in studies that use intravascular ultrasound (IVUS), this is even higher, with 75% incidence of detectable intimal thickening at 5 years, with half of these representing at least mild disease[8]. The most current angiographic data estimates the incidence of CAV in the pediatric cohort of 13% at 5 years, 25% at 10 years and 54% at 15 years[9].

According to the ISHLT registry, using angiographic definitions, 65% of recipients are free of CAV at 10 years, but after a diagnosis of CAV, the 2-year graft survival rate is less than 50%[2].

Age at transplantation has a strong influence on survival with a 74% 8-year freedom of CAV in younger recipients compared to 56% in recipients older than 10 years[10].

As CAV lesions are preceded by endothelial dysfunction, it is essential to identify and characterize this as early as possible for targeted therapy and ultimately to improve patient survival.

DIAGNOSIS

The diagnosis of CAV is challenging. As a result of the denervation inherent to heart transplantation, patients fail to display classical clinical warning signs of angina[11]. The ability of early diagnosis is essential but unfortunately, the majority of the diagnostic techniques lack sensitivity or are rather invasive. A reliable and repeatable non-invasive method that detects CAV and its functional significance would have a huge impact on the follow up of heart transplant recipients. However, sensitivity and specificity of the currently available non-invasive tests remain limited.

Screening protocols vary among centers and the majority of units use a combination of diagnostic modalities, depending mainly on local preferences and expertise.

Angiography

For many years, until the introduction of IVUS, this has been the cornerstone of CAV diagnosis[12,13]. Despite its relatively low sensitivity[14,15] and resulting delay in diagnosis, coronary angiography remains the most widely used diagnostic technique for CAV in the majority of transplant centers.

Angiography is known to underestimate the disease[16]. Adults series display a low sensitivity and negative predictive value. St Goar *et al*[14] found that 50% of patients with normal angiographies had moderate to severe intima thickening on IVUS. In a series by Tuzcu *et al*[17] the sensitivity of angiography for CAV detection (defined by maximal intimal thickness > 0.5 mm) was 43%, specificity was however high with 95%.

Similarly in a most recent paper, Gregory *et al*[18], using the same definition, showed a sensitivity even lower of 11% with a negative predictive value of 57%. Defining CAV as mean intimal thickness > 0.3 mm, Störk *et al*[19] found a sensitivity of 44% and a negative predictive value of 28% when compared to the IVUS data.

Its main limitation arises from the fact that it assesses the vessel lumen. The contrast fills the patent lumen without direct visualisation of the vessel wall. By the time a filling defect appears and there is significant stenosis, the graft is already compromised. CAV tends to be diffuse and concentric affecting large and medium size vessels as well as the microvasculature[14,20]. Typically there is initial vessel expansion: as the intima thickens, the external elastic membrane expands preserving initially the lumen area (Glagov-type positive remodeling)[21-24]. This explains why the coronary angiography result can be normal in the presence of significant disease demonstrated by IVUS. Nevertheless, angiography is inexpensive, readily available across centers and findings have proven prognostic implications regarding graft survival and adverse cardiac events[25,26].

One of the largest experiences in pediatric patients has been published by Pahl *et al*[1] in 2005 and included

Table 1 ISHLT consensus grading for coronary allograft vasculopathy (Mehra *et al*[13] 2010)

Grade	
0 (Not significant)	No detectable angiographic lesion
I (Mild)	Angiographic LM < 50% stenosis, or primary vessel with maximal lesion of < 70%, or any branch stenosis of < 70% (including diffuse narrowing)
II (Moderate)	Angiographic LM 50%-69% stenosis, a single primary vessel ⩾ 70% stenosis, or isolated branch stenosis of ≥ 70%in branches of 2 systems
III (Severe)	Angiographic LM ⩾ 70%, or 2 or more primary vessels ⩾ 70% stenosis, or isolated branch stenosis of ⩾ 70% in all 3 systems, or mild/moderate angiographic disease with LVEF < 45% or evidence of significant restrictive physiology (*i.e.*, symptomatic heart failure with echocardiographic E to A velocity ratio > 2 (> 1.5 in children), shortened isovolumetric relaxation time (< 60 ms), shortened deceleration time (< 150 ms), or restrictive hemodynamic values (Right Atrial Pressure > 12 mmHg, Pulmonary Capillary Wedge Pressure > 25 mmHg, Cardiac Index < 2l min/m^2)

LM: Left main.

Table 2 Stanford score (severity based on the localization of the most severe disease

Grade	Severity	Intimal thickness
I	Minimal	< 0.3 mm and < 180 degrees
II	Mild	< 0.3 mm and > 180 degrees
II	Moderate	0.3-0.5 mm OR 0.5-1 mm and < 180 degrees
IV	Severe	> 1 mm OR 0.5-1 mm and > 180 degrees

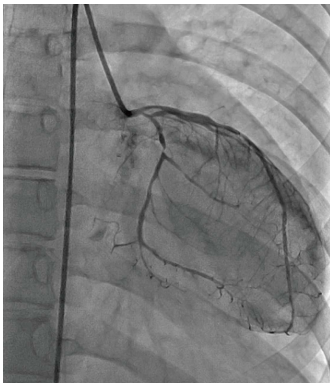

Figure 3 Left coronary angiography showing severe epicardial disease with multiple stenosis in left anterior descending artery and left circumflex artery.

multicenter data proceeding from the Pediatric Heart Transplant Study database. Two thousand and forty-nine angiograms from 751 patients were analysed. The incidence of angiographic abnormalities at 5 years was 17%. However, moderate-to-severe disease occurred in only 6% at 5 years[1]. The use of IVUS in children is limited and they showed a sensitivity of angiography to detect CAV when compared to IVUS data between 18% and 30%[8,27].

In 2010, the ISHLT published new guidelines for CAV including a new classification (Table 1) in view to provide a more refined definition and prognostic value[13]. Figures 3 and 4 showed angiography of two grats with severe disease.

IVUS

IVUS is more sensitive than angiography for early CAV detection and allows delineation of the vessel wall as well as measurement of intimal thickness[14]. Even if it might provide an oversimplified picture of the disease process, the intimal thickening measured *via* IVUS remains the most sensitive diagnostic modality available[13].

As mentioned above, Glagov-type positive remodeling occurs in response to the vessel wall disease. This serves to maintain initial lumen patency and the angiographic appearance of the vessel can therefore be normal despite significant CAV. This is particularly significant in the first year post transplantation. Later on in the disease process, constrictive negative remodeling of the vessel will occur and lead to the stenosis of the vessel[23].

IVUS parameters reported in the literature include: intimal thickness, mean intimal index (ratio of the mean intimal area to the sum of the mean intimal and luminal areas), total atheroma volume and percentage of atheroma volume. In 1995, the Rickenbacher *et al*[28] demonstrated that, in an adult cohort, moderate to severe intimal thickening diagnosed by IVUS was predictive of the future development of angiographically detectable disease (Table 2). This article describes CAV as being present when maximal intimal thickness is ⩾ 0.3 mm. A further finding was that maximal intimal thickness (MIT) ⩾ 0.3 at 1 year was associated with a 4 year survival of 73% compared to 96% within the group of MIT < 0.3 mm[28]. Two more recent studies published in 2005[17,29] reported that a change of MIT ⩾ 0.5 mm over the first year post-transplant was an independent predictor for subsequent angiographic development of CAV; for myocardial infarction and for all-cause death at 5-years post-transplant. Patients with a change in MIT > 0.5 mm had a 5-year incidence of 21% for death or graft loss, 46% for all major adverse events and 65% for the development of subsequent angiographic disease compared to 6%, 17% and 35% respectively for patients without a 0.5 mm change[29].

Interestingly, however, intimal proliferation evaluated in IVUS does not always correlate with microvascular or small artery disease in biopsies specimens[13,30]. Looking specifically at Pediatric data, IVUS has not shown yet

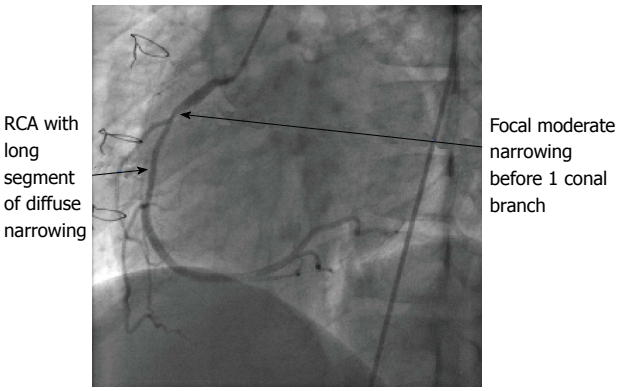

Figure 4 RCA angiography.

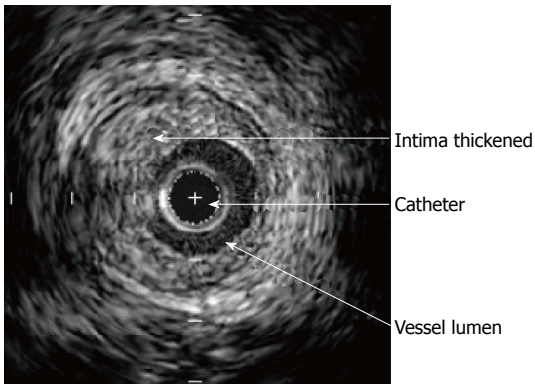

Figure 5 Intravascular ultrasound still frame showing severe intimal thickening (Stanford grade IV).

impact on prognosis[27] and this probably relates to the limited number of studies, each with differing analysis methodology.

According to published data, sensitivity increases with the number of vessels imaged[31]. However, our experience in children suggests that this is not the case and multi-vessel imaging increases risk without substantially altering sensitivity. Therefore, in our usual practice, we only image the left main and proximal left anterior descending. We use automatic pullback to enhance consistent sampling and identification of branch vessels that are used as landmarks in order to be able to compare serial investigations. We analyze 30 cross-section images taken at 1.5 mm intervals and identified (as mentioned above) by branch points. Additionally, image analysis is performed during mid-diastolic rest period for consistency. In addition to maximal intimal thickness, mean intimal thickness, and mean intimal index, Stanford grading score (Table 2) and percentage of atheroma are recorded. We also use a semi-automatic interactive edge detection software (QIVUS) to improve reproducibility of measurements[32] (Figure 5).

Unfortunately, IVUS remains rather unused in clinical routine: the higher cost and potential morbidity added to the requirement of a trained operator, limits its use currently. This is particularly true in the pediatric population, where the size of the patient is an additional limitation. Nicolas *et al*[27], have reported feasibility in patients $\geqslant$ 10 kg but in our institution, we normally do not proceed in patients under 10 years of age[8,27].

Echocardiography

The usefulness and accuracy of several echocardiographic techniques, as diagnostic methods for CAV have been explored. Published data have shown disparate results but more recent reports involving dobutamine stress echocardiography have demonstrated greater prognostic value[33-40].

Dobutamine stress echocardiography (DSE) allows assessment of wall motion, inducible ischemia and viability. Nevertheless, the sensitivity, specificity positive predictive value and negative predictive value vary significantly among these studies. Despite these limitations, Spes *et al*[35] noted, in an adult cohort, that in patients with abnormal DSE, 90% had significant CAV by IVUS, but only 49% by angiography again demonstrating the relative insensitivity of angiography. Furthermore, they showed that a normal pharmacological stress echocardiography after heart transplantation has a high negative predictive value for any major adverse cardiovascular event. This suggests that if a strict DSE protocol is followed, a selective invasive angiography/IVUS policy may be adopted[34,35,37,38,41]. This was corroborated in a Pediatric cohort by Pahl *et al*[39]. Some authors have pointed out that endothelial dysfunction might be the cause of abnormal wall motion detected by DSE and normal angiography[42].

In children, the variability when compared to angiography, is even higher than that showed in adult series. Sensitivity rates vary between 35% and 71%, specificity between 80% and 94%, positive predictive value between 45% and 91% and negative predictive value between 81% and 92%[37,43,44]. If reliability within a given department is established, then it certainly appears to be an attractive option for children due to its non-invasive nature. However, it does require a good set up, effective sedation, expertise in images acquisition, expertise in interpretation and a standardised, reproducible protocol.

Sensitivity and specificity of stress echocardiography techniques can be improved by quantitative analysis using strain imaging. This modality can quantify regions of wall motion abnormality, (*i.e.*, a reduction in peak systolic strain % will be seen in LV segments associated with inducible ischemia and accurate measurements of time to peak strain may also give information on regional wall motion abnormalities). Eroglu *et al*[40], showed that, in adults, the accuracy of DSE can be improved using strain analysis (Figure 6).

Combined use of contrast-enhanced echocardiography with adenosine mediated hyperemia in order to assess coronary flow reserve has shown encouraging results in adults. Tona *et al*[45] demonstrated feasibility and prognostic value of coronary flow reserve measured by contrast enhanced echocardiography with good correlation with major acute cardiac events. Severe Coronary Flow Reserve (CFR) alteration was shown to precede acute cardiac event

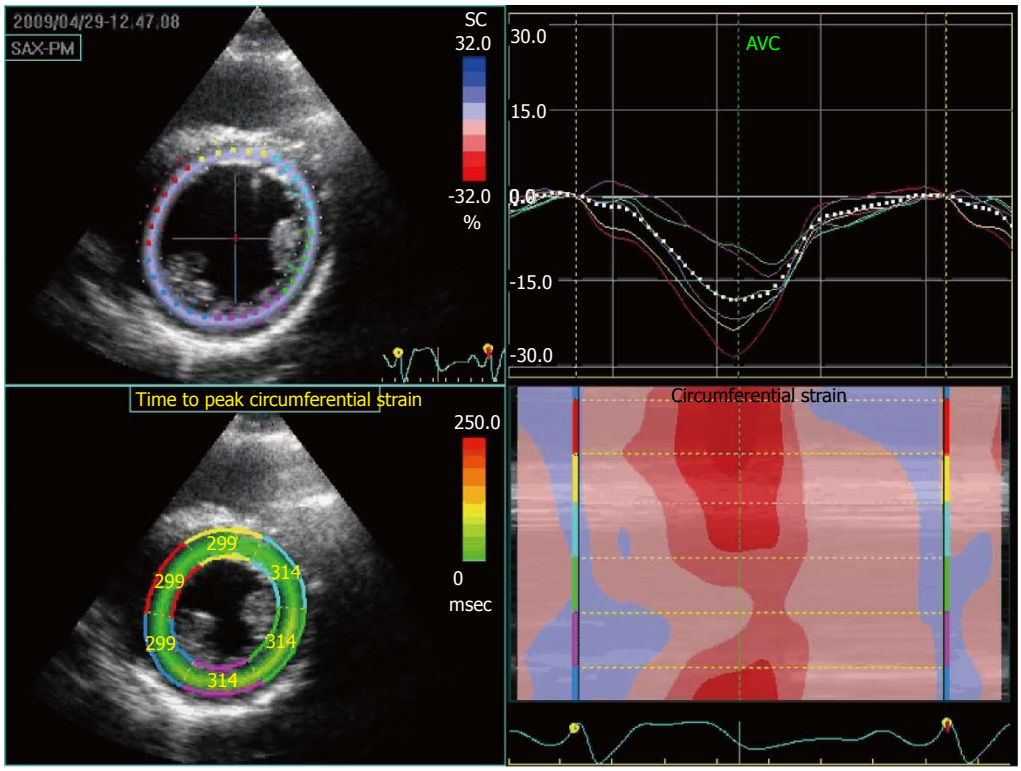

Figure 6 Speckle-tracking echocardiographic analysis of myocardial deformation showing circumferential strain in a patient with coronary allograft vasculopathy. On the top right image we can appreciate the dyssinchrony (later contraction compared to the rest of the segments) and lower contractility of the green and purple segment corresponding to LCX territory. On the bottom right figure, we can appreciate how the same green and purple segments have significant lower contractility than the others (red corresponds to the maximum contractility and blue to the absence of it). The left superior panel shows the color coding for each of the segments. The left inferior panel shows the time interval between beginning of QRS and maximal strain value.

onset. On a more recent study, the same group, showed high sensitivity and specificity for this technique in the detection of significant CAV (defined by Media Intimal Thickness > 0.5 in IVUS)[46]. Although these results are really encouraging, more studies are needed to establish the reproducibility. Interestingly, a separate small study in adults showed that transesophageal echocardiographic measurement of CFR impairment could identify CAV but it did not allow grading of severity[47]. However, this approach will be more difficult to implement in children, owing to difficulty in imaging due to the small size of the coronary arteries and the need for sedation in many patients.

The application of tissue Doppler techniques to the transplant population is also worth mentioning. Dandel *et al*[48,49] showed the utility of power Doppler TDI for the diagnosis of CAV in adults. Systolic Tissue Doppler Imaging (TDI) parameters at basal lateral LV wall level showed the highest diagnostic accuracy. Peak systolic motion velocity (Sm) and time to peak systole (TSm) differed significantly between patients with and without CAV as identified by IVUS. Furthermore, with Sm > 11 cm/s and TSm > 110 cm/s^2, angiographic disease can be excluded and, in the absence of any rejection, an Sm < 10 cm/s has a positive predictive value of over 97% for CAV (as detected by IVUS or angiography)[48,49]. The main limitations for the widespread use of this technique arise from the inter-observer and inter-departmental variability. These techniques have been applied to adult cohorts mainly and the available literature in the pediatric population is still very limited. One small retrospective study has shown that tricuspid annulus velocity was the best predictor of graft failure in pre-terminal patients. However, conventional echocardiographic parameters such as increase in tricuspid regurgitation severity and a reduction in left ventricular ejection fraction were also associated with increased mortality[50]. However, another recent study in a pediatric cohort showed poor correlation between TDI and hemodynamics parameters[51], highlighting the need for further confirmatory studies in children.

Exercise stress echocardiography (ESE) in adult patients was initially found to have unacceptably low sensitivity for the detection of CAV[33,52]. However, Chen *et al*[53] showed recently a sensitivity higher than 88% with almost 92% specificity in detecting significant epicardial angiographic CAD among pediatric heart transplant recipients. The positive predictive value of ESE was 72.7%, and the negative predictive value was 97.1%[53]. These results need wider confirmation prior to consideration as a screening tool.

Invasive coronary hemodynamics

CAV is a complex and diffuse process that leads to concentric luminal stenosis and occlusion of epicardial large and medium sized vessels. It also affects the intramyocardial microvasculature. Microvascular disease is present in heart transplant recipients early after transplant, even in

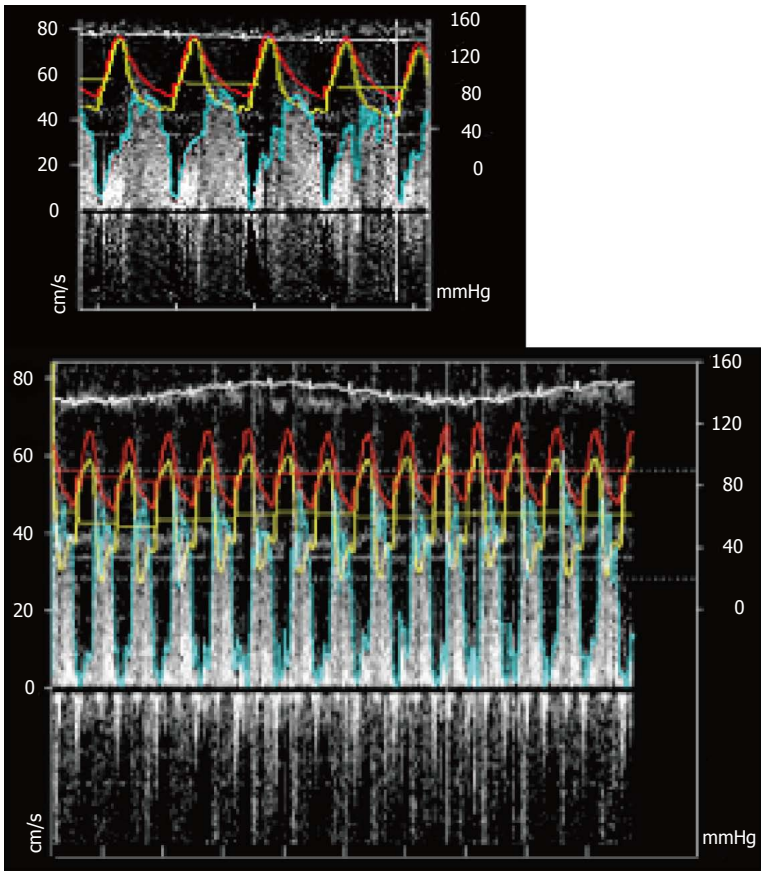

Figure 7 (A) Resting pressure and flow recording (Red: Aortic pressure; Yellow: Distal coronary pressure; Blue: Pulse wave Doppler envelope) and (B) during hyperemia note that the aortic pressure has decrease as well as the distal coronary pressure. FFR: Ratio of the mean distal coronary pressure at a point past the stenosis the aortic pressure during maximal hyperemia; CFR: Ratio of hyperemic blood flow to resting myocardial blood flow.

asymptomatic patients[20,54] and it is known to be associated with CAV, ischemia and death.

Fractional flow reserve (FFR) is defined as the ratio of maximum flow in the presence of a stenosis to normal maximum flow. It is a lesion-specific index of stenosis severity that can be calculated by simultaneous measurement of mean arterial, distal coronary, and central venous pressure, during pharmacological vasodilation. FFR is a well established tool to assess hemodynamic significance of coronary focal stenosis and has been recommended since 2010 by European Society of Cardiology for the physiological assessment of moderate coronary stenosis when functional information is lacking[55] in atherosclerotic disease.

In such cases, pressure gradients and FFR are recorded throughout the length of the artery through a pull back of the wire during maximum pharmacologically-induced hyperemia.

The Combowire® XT also allows simultaneous measurement of flow and pressure and FFR simultaneously to the coronary flow reserve (CFR) (Figure 7).

In transplanted patients, the exact value of FFR to determine epicardial disease is difficult to establish and results have been inconsistent between series[56,57]. In a publication by Hirohata *et al*[20], FFR improved as the microvascular disease deteriorated and therefore, due to the particular interaction between microvascular and epicardial disease that occurs in CAV, FFR might not be the best reflection of epicardial affectation in this situation.

CFR reflects the ability of the myocardium to increase blood flow in response to maximal exercise or stress. It is expressed by the ratio of the myocardial blood flow at peak stress, or maximal vasodilatation, to the flow at rest. Decrease in CFR, after Adenosine administration to achieve maximum vasodilation, in the absence of significant epicardial stenosis (normal fractional flow reserve) indicates microvascular dysfunction[58]. If the significance of decreased CFR is well established in the atherosclerotic population[59,60]. Although theoretically more important for CAV, the exact significance of CFR measurement remains to be determined. Using acetylcholine-mediated, endothelium-dependent, coronary vasodilatation measurement of CFR, Hollenberg *et al*[61] showed that endothelial microvascular dysfunction was more common in the group suffering adverse outcomes (death or angiographic evidence of CAV) than in those without adverse outcome. However, published data are not consistent between studies. Kübrich *et al*[62], in a larger cohort, found no correlation between epicardial and microvascular disease and found that, whilst microvascular dysfunction demonstrated by CFR was a predictor of outcome (death or adverse cardiovascular event) in the univariate analysis, it did not predict outcome in the multivariate analysis.

The pediatric population offers very limited data for CFR. In a small cohort, a decrease in CFR correlated with microvasculopathy seen in endomyocardial biopsy specimens[63]. The invasive nature of Doppler wire flow measurements to determine CFR makes it an unattractive tool for children.

Several groups have presented data of CFR quantified

by CMRI of the coronary sinus showing good correlation with PET or flow phantoms[64-66]. More recently, Ishida *et al*[67] presented data on CFR as independent predictor of MACE in patients with known or suspected CAD. Kennedy *et al*[68] have translated this idea into the transplant population: they found that CFR determination by Cardiac Magnetic Resonance Imaging (CMRI) in the coronary sinus, was significantly decreased inpatients with severe CAV and therefore, it may be a useful tool in non-invasively evaluating coronary allograft vasculopathy in heart transplant recipients.

Single photon emission computed tomography

Single photon emission computed tomography (SPECT) is a useful clinical tool for myocardial perfusion imaging to detect and risk-stratify of coronary atherosclerotic disease for management guidance[69]. Either exercise or pharmacological stress can be employed and, most commonly, one of theTc-99m-labeled tracers is used. Numerous studies in adult population with coronary atherosclerotic disease have assessed the relative accuracies of stress imaging using nuclear cardiology techniques: for stress SPECT, sensitivity is around 87% with a specificity of 73% (compared to coronary angiography)[70]. Recently, it has been recognized that some patients with non-critical coronary artery stenosis can have abnormal stress perfusion imaging. This is due to microvascular and endothelial dysfunction causing abnormal flow reserve[71].

When applied to CAV, SPECT has a high negative predictive value in adults[72-77]. When using Dobutamine stress and 99m technetium tetrofosmin, abnormal perfusion is associated to a risk ratio of 3.5 in predicting cardiac death[78-80]. A reversible perfusion defect on stress SPECT is an independent predictor of mortality or graft loss[72,81-83] and it seems that stress SPECT at one year post transplantation could be an earlier prognostic indicator[84].

In Pediatrics, the experience with SPECT is largely anecdotal. The small size of the heart might be a limiting technical factor and the radiation related to the technique itself makes it a rather unattractive diagnostic tool.

Positron emission tomography

Positron emission tomography (PET) has established itself as the gold standard for noninvasive assessment of myocardial perfusion measuring myocardial blood flow at rest and during stress. As well as myocardial perfusion reserve, perfusion of the epicardial arteries and the microvasculature can be determined[85,86]. In patients after heart transplantation, myocardial perfusion reserve measured with PET has been performed in a few studies[87-89]. Wu *et al*[88] found good correlation between IVUS and myocardial perfusion reserve even in the absence of angiographic lesions. Published data is very limited even in adults, related to the limited availability of the technique and the expertise required.

Multidetector computed tomography

In the atherosclerotic population, multidetector computed tomography (MDCT) has shown high sensitivity and specificity in the diagnosis of angiographic coronary arteriopathy and characterization of the stenotic disease[90]. Recent studies also indicate that detection and characterization of the plaque is possible although challenging[91,92] increasing potential value as a diagnostic tool.

The literature provides some data regarding the heart transplant population: Sigurdsson *et al*[93] used a 16-detector MDCT to identify coronary stenosis and compared to angiographic disease (defined by luminal stenosis > 95%). Sensitivity, specificity, positive and negative predictive values were 86%, 99%, 81% and 99% respectively, unfortunately only a few subgroup of patients underwent IVUS.

Gregory *et al*[18], on the other hand, did use IVUS to compare 64-slice MDCT results in 20 patients at 1 year post-transplant. They defined CAV as maximal intimal thickness > 0.5 mm and found that MDCT has a sensitivity of 70% and a specificity of 92% with a positive predictive value of 89% and negative predictive value of 77%. However, in this study, slightly less than 20% of coronary segments (mainly distal) could not been analysed due to poor image quality (probably in relation with elevated heart rate)[18].

Recent studies showed that dual source MDCT allows good image quality of vessel lumen[94,95] and, when validated against IVUS, high diagnostic accuracy[96]. A small study, just under 20 patients, demonstrated that MDCT, using 64-slices, was superior to angiography for the identification of non-obstructive vessel wall disease. However, they did not use IVUS for comparison[94]. Schepis *et al*[96] compared 64 channels dual source MDCT with IVUS to look at vessel wall thickness. Defining CAV as intimal thickness > 0.5 mm on IVUS they established sensitivity, specificity, negative predictive value and positive predictive value of MDCT of 85%, 84%, 76% and 91% respectively.

Therefore, MDCT appears to be a useful tool for CAV screening. Although not as sensitive as IVUS, it is non-invasive and clearly superior to angiography. However, the elevated heart rate post-transplantation, especially in pediatric patients, compromises image quality and the need for potentially nephro-toxic contrast agent adds concern for heart transplant recipients, for whom renal impairment is a frequent comorbidity[97,98].

There is preliminary data available in children using MDCT compared to angiography and IVUS to identify coronary luminal stenosis, although the size of the series was very small[99] and results would require further studies to be validated.

Again, the implied repeated radiation dosage makes it a less attractive screening option in children.

Optical coherence tomography

Optical coherence tomography (OCT) is an intravascular high resolution imaging modality that measures reflected light waves intensity and converts these into a high resolution tomographic image[100]. In CAD patients, OCT has been used to characterize plaque composition and differentiate between intimal hyperplasia, fibrous plaque, lipid-rich plaque or calcifications[101,102] (Figure 8).

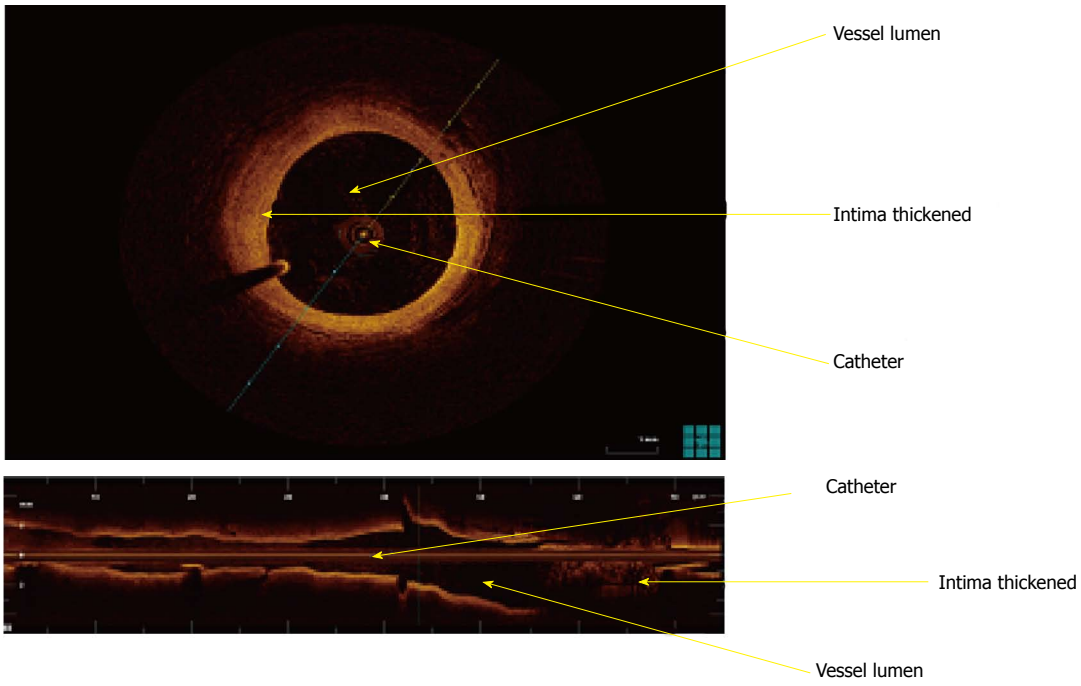

Figure 8 Optical coherence tomography images showing intima hyperplasia. The superior image shows a transverse cut of the coronary. On the inferior part of the image, longitudinal cut.

Recent studies have evaluated the use of OCT in heart transplant recipients with promising results. The OCTAV study demonstrated, in 15 patients early post-transplant (with no angiographic evidence of CAV), that early quantification of intima-media ratio and characterization of the plaque is possible. There was no IVUS performed for comparison[103]. Garrido *et al*[104] compared OCT to IVUS in 21 patients, later post-transplant, and not only found good correlation with IVUS but also postulated that OCT offers better plaque characterization and less inter-observer variability.

Cassar *et al*[105] compared OCT to IVUS and angiography in 53 patients, showing that OCT was superior to angiography but not to IVUS. IVUS and OCT were strongly correlated with 100% agreement.

Further prospective and larger studies are needed to define the exact role of OCT in the diagnosis of CAV and, more importantly, to define its prognostic implications.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMRI) coronary angiography in the context of CAD has proved its capacity to detect atherosclerotic plaque and proximal to mid-coronary artery stenoses[106-108]. Uribe *et al*[109] have demonstrated the feasibility and accuracy of MR coronary angiography in the detection of coronary anomalies in children, despite elevated heart rates with whole heart dual phase cardiac imaging[109,110]. Greil *et al*[111], have also previously shown the utility of coronary magnetic resonance angiography (CMRA) in patients with Kawasaki disease.

These studies undoubtedly open the door for the application of CMRA in CAV including in pediatric cohorts. Unfortunately, when compared to MDCT, CMRA does not seem to be as sensitive or robust in the detection of coronary stenoses, although limited studies have been done. CMRI offers several advantages: it provides functional information on myocardial characterization and contractility as well as wall motion performance; it allows quantitative measurements of ventricular volumes and it is radiation-free, which is especially valuable in a population already exposed to repeated X-ray angiography.

In conventional atherosclerosis, perfusion imaging has shown to be effective in detecting myocardial ischemia and to assess microvascular dysfunction as it detects downstream microvacular blood flow within the myocardium. The MR-IMPACT study demonstrated that CMRI is superior to SPECT in identifying perfusion defects within the myocardium for atherosclerotic patients[112]. Perfusion stress with adenosine also provides prognostic data: a normal CMR stress perfusion scan showed 99% event free survival at 3 years[113].

The use of adenosine for myocardium stress perfusion after heart transplantation has not been widely reported. Nevertheless, Muehling *et al*[114] showed a reduced myocardial perfusion reserve in patients with CAV with good correlation between MRI and invasive measurements. Unfortunately, microvascular disease in this study could not be assessed. They also demonstrated that patients with CAV have a reduced myocardial perfusion even during rest conditions[114].

In regards to CMR tissue characterization, Steen *et al*[115] showed that more than 80% of patients with severe angiographic CAV had a late gadolinium enhancement pattern suggesting subendocardial infarction with a distribution consistent with the angiographic pattern. Furthermore, he was able to identify silent myocardial

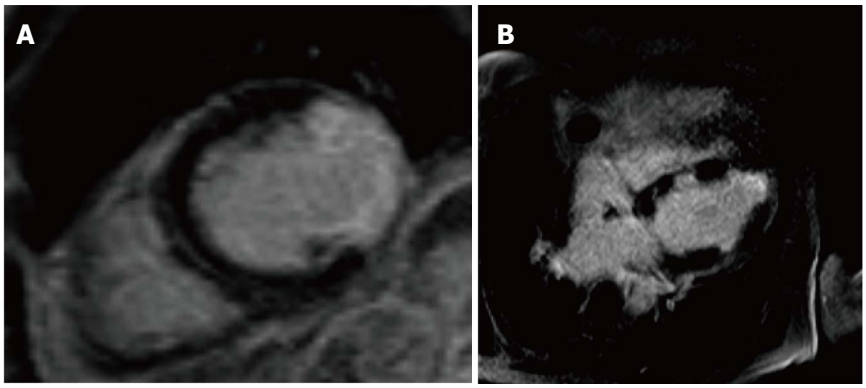

Figure 9 Late gadolinium enhancement scar imaging. A: Typical infarct pattern Late enhancement with > 75% transmurality; B: Atypical pattern with diffuse pattern of late enhancement.

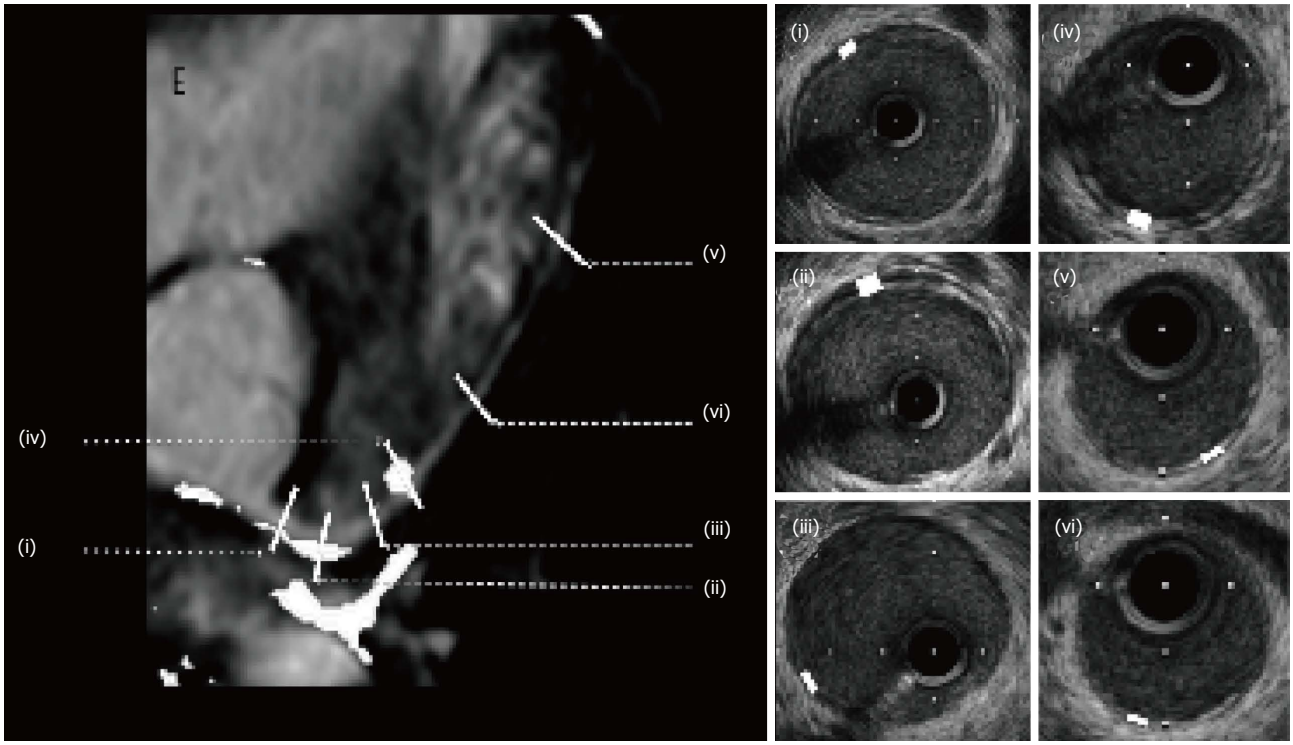

Figure 10 Late gadolinium enhancement in the coronary vessel wall showing corresponding positions for intravascular ultrasound: Illustrates intimal thickening corresponding to enhancement on overlay picture on the left.

infraction in otherwise apparently event-free patients (Figure 9). In a more recent publication, the same group looked at infarct-atypical myocardial involvement that they were not able to correlate with coronary angiographic pattern in the prior study. According to their findings, within the 4 different patterns of infarct-atypical LGE-CMR, only the diffuse form was significantly higher patients early post transplantation, but they could not establish a definite reason for the findings[116].

Hussain *et al*[117], have taken this technique further showing that high resolution late gadolinium enhancement (LGE) can be used to show vessel wall disease in CAV with good correlation with IVUS Figure 10. LGE scores correlated well with the maximal intimal thickness and mean intimal index [Pearson coefficient 0.80 ($P < 0.001$) and 0.92 ($P < 0.001$), respectively]. An enhancement diameter > 7.5 mm gave promising sensitivity and specificity values of 86% and 93%, respectively, for the detection of significant CAV.

A recently published paper, evaluated in 48 transplanted patients both epicardial and microvacular disease concomitantly. The patients underwent coronary angiography, invasive coronary physiological assessment, IVUS and multi-parametric cardiac MRI that includes, tissue characterization, perfusion analysis and tissue tagging. They found that cardiac MRI-based myocardial perfusion reserve was independently predictive of both epicardial and microvacular components of CAV and furthermore that diagnostic performance was significantly higher than angiography[118].

More studies are needed to establish CMRI as a reliable non-invasive tool for CAV diagnostic but certainly the latest

data are encouraging and more work needs to be achieved in this direction.

PREVENTION AND TREATMENT

Rapid progression of CAV within the first year post transplant is a strong indicator of severe CAV, graft loss and mortality[17]. Therefore, prophylactic strategies are paramount and must been introduced early to improve long-term outcomes and prognosis.

Similar to native coronary disease, primary prevention includes control of traditional cardiovascular risk factors such as hypertension, smoking, diabetes and hyperlipidemia. This can be challenging, as many of these factors are also side effects of the immunosuppressive therapy. Tobacco should be avoided and care should be taken to avoid passive smoking in children. Modifications of specific risk factors related to the transplant include prevention and aggressive treatment in case of cytomegalovirus (CMV) sero-conversion[118]. In addition, it is essential to treat any episode of rejection early and aggressively.

Psychological care

Psychological support is crucial in transplanted children and their families throughout all the transplant journey: Leaving with a reduced life expectancy when compared to peers is often complicated and despite good quality of life can be a source of distress for the recipients. In the context of CAV psychological support is especially important: Prevention is paramount; and, if it is essential to treat aggressively any rejection episode, it is also vital for the patients to be compliant with the antirejection therapy. However, it is well known that often therapy compliance declines in adolescence and case of sudden death have been reported related to antirejection treatment discontinuation. In these patients psychological support is essential to ensure therapy obeisance. In cases of advanced CAV the ineluctability of the graft loss and its implication lead to severe depression and negation that also frequently required psychological input.

Statins

Most transplant protocols nowadays include statin, independently of the lipid level. Several studies have highlighted their benefits beyond lipid lowering effects[119-121]; including reduced incidence of severe rejection episodes, reduced CAV progression and improved long term survival[122-124]. Consensus guidelines unequivocally recommend statin therapy[125].

CMV

CMV infection results in acceleration of CAV as the result of the host immune response. Aggressive treatment with ganciclovir reduces progression of CAV[126] and the lack of prophylaxis is associated with increased lumen loss[127]. Our institution, as with most of the transplant centers, uses acyclovir for CMV prophylaxis during the first 3 mo post-transplantation.

Vasodilators

A few reports indicate a potential role for vasodilators in preventing and slowing CAV progression. Calcium channels blockers and ACE inhibitors have been reported in the literature to be beneficial but large prospective trials are needed to determine their exact role[128-130]. Most transplant institutions use both of these to treat hypertension, which develops frequently as side effect of calcineurin inhibitors therapy.

Immunosuppression

Most of the data are from adult studies with limited evidence in the pediatric population.

Calcineurin inhibitors

Tacrolimus not only offers better protection against acute rejection compared to cyclosporine[131-133], but it is also superior against CAV[134]. Moreover, Petrakopoulou *et al*[135] showed that tacrolimus is better than cyclosporine in the prevention of microvascular endothelial dysfunction.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) has demonstrated superiority to azathioprine in mortality and graft loss[136]. In the re-analysis of the same study, it also showed less intimal thickening and wider lumen area[137]. Finally, Kaczmarek *et al*[138], in 2006 demonstrated that MMF decreased CAV incidence.

Proliferation signal inhibitors

Contrary to Calcineurin Inhibitors (CNIs) that blocks T-cell activation and proliferation by suppressing lymphokines production, proliferation signal inhibitors (PSIs) inhibit Tcell and B cell proliferation by impairing their response to growth promoting lymphokines[139]. In addition, PSIs have also a significant cytostatic effect on the immune system[134,140]. In 2003, Eisen *et al*[141] published the first data in favor of PSIs, using everolimus de novo after heart transplantation. They showed preservation of the coronary lumen at 1 year with significant lower incidence of CAV in the everolimus group compared to the aziathropine group. A sub-study published in 2007 confirmed the results at 24 mo[142] and the same group has also shown reduced incidence of cardiovascular events in the everolimus group[143]. Nevertheless, despite the promising results of these studies, all of them compared PSIs to Azathioprine, which is not used as first line therapy anymore and known to be associated to higher rate of rejection than newer immunosuppressive agents. The results of an eagerly awaited clinical trial comparing everolimus de novo to cyclosporine has been recently published showing marked improvement in renal function at 12 mo in the everolimus group without increased of adverse events as well as demonstrated, *via* IVUS, significantly reduced CAV progression at 12 mo in the everolimus group[144].

Mancini *et al*[145], in a randomized study reported that sirolimus (as a secondary immunosuppressant) slows progression of CAV and reduces the incidence of clinically significant events, such as death or graft failure. Keogh *et al*[146], using randomized de novo treatment between

sirolimus or azathioprine reported significantly reduced progression in intimal and medial proliferation at 6 mo post-transplant and a reduction in the number of acute rejection episodes of around 50%. The effect was sustained at 2 years post transplant using IVUS to quantify vessel wall proliferation.

Although a combined regime CNIs + PSIs appears to be attractive in preventing and slowing CAV, serious concerns with this regimen should be raised regarding nephrotoxicity. PSIs have shown in several studies to increase side effects of CNIs, especially for nephropathy[147-151].

Raichlin *et al*[152] have published encouraging data with sirolimus-based immunosuppression, and even postulated that a CNI free regimen would be safe, well tolerated and associated with less CAV progression, coronary events and graft failure, when initiated beyond the first year (and within the first 2 years).

In a more recent study, the same group showed that early conversion to sirolimus attenuated plaque progression, improved overall survival, and increased freedom from cardiac events. However, the retrospective nature of the design and the differences in criteria for the therapy changes, make the results less generalizable[153]. Moreover, a recent study reported that late conversion to PSIs is associated with necrotic plaque core and calcification of the plaque[154].

Hence, safety of early CNI withdrawal with PSI conversion remains uncertain, especially in the first year post-transplant with concerns also raised about acute rejection. Therefore, many continue to recommend against withdrawal of CNIs during the first 12 mo post transplantation[155].

Side effects from PSIs are not infrequent: anemia, dyslipidemia, increased incidence of bacterial infections, peripheral oedema, pericardial or pleural effusion, pneumonitis and delayed wound closure. They seem to be dose-related and reversed by discontinuation of the drug, although most can be controlled with dose adjustments[155].

PSIs have also been attributed with a reduction in CMV infections and an inhibition of Epstein-Barr virus-infected tumorigenic cell lines[156-158]. In the Pediatric population, PSI use is still limited to a rescue therapy for post-transplant complications such as CAV or renal impairment secondary to therapy.

Coronary revascularization

In contrast to native coronary disease, CAV is progressive and revascularization procedures are only palliative with no survival benefit[159,160]. Moreover, the concentric, diffuse and distal nature of CAV precludes the majority of patients for revascularization procedures.

Percutaneous interventions

Percutaneous intervention in transplanted patients are characterized by good short term results but high restenosis rates[160-165].

Unfortunately, stents do not offer better long-term results with a late re-stenosis rate around 70%. Drug eluting stents appear to have slightly better results with less restenosis[57,166]. However, only the minority of CAV lesions are amenable for percutaneous revascularization as outlined above and stent angioplasty might only be an option in selected patients.

Bypass grafting

Surgical revascularization is associated with a very high mortality (up to 40%)[162,167,168] and limited success. Indication is then reserved to highly selected patients.

Re-transplantation

Re-transplantation is the only definitive treatment for CAV. Unfortunately it is associated with lower survival than with the primary graft[169] (relative risk for 10 years mortality according to ISHLT 2012 data is 1.56) and the probability of CAV recurrence is higher (50% at 3 years)[167,170].

The scarcity of donors, and prior antigen sensitization means that, in practice, re-transplantation occurs infrequently.

CONCLUSION

Despite a wide range of new diagnostic techniques, angiography remains, to date, the most commonly used diagnostic tool for CAV. Not only is it invasive, costly and radiation-prone but it also fails to identify the disease in its early phase. IVUS is the most sensitive technique but requires trained operators and it is, again, an invasive technique requiring ionizing radiation.

Overall, the available published evidence support a role for MDCT or DSE as non-invasive screening test to reduce the number of invasive angiograms (and IVUS). However, an accurate and reproducible non-invasive diagnostic tool is yet to be widely established. CMR offers anatomical, histological and physiological assessments and, in the future, it could be valuable in the detection and grading of CAV.

Early detection is paramount but remains challenging. It may allow us to identify those requiring modification in immunosuppression, such as early introduction of PSIs for those with more aggressive CAV.

Unfortunately CAV remains the primary cause of graft failure after the first year post-transplantation and the only definitive treatment is re-transplantation.

REFERENCES

1 **Pahl E**, Naftel DC, Kuhn MA, Shaddy RE, Morrow WR, Canter CE, Kirklin J. The impact and outcome of transplant coronary artery disease in a pediatric population: a 9-year multi-institutional study. *J Heart Lung Transplant* 2005; **24**: 645-651 [PMID: 15949722 DOI: 10.1016/j.healun.2004.03.021]

2 **Kirk R**, Edwards LB, Kucheryavaya AY, Aurora P, Christie JD, Dobbels F, Rahmel AO, Stehlik J, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: thirteenth official pediatric heart transplantation report--2010. *J Heart Lung Transplant* 2010; **29**: 1119-1128 [PMID: 20870166 DOI: 10.1016/j.healun.2010.08.009]

3 **Rahmani M**, Cruz RP, Granville DJ, McManus BM. Allograft vasculopathy versus atherosclerosis. *Circ Res* 2006; **99**: 801-815 [PMID: 17038650 DOI: 10.1161/01.RES.0000246086.93555.f3]

4 **Colvin-Adams M**, Harcourt N, Duprez D. Endothelial dysfunction and cardiac allograft vasculopathy. *J Cardiovasc Transl Res* 2013; **6**: 263-277 [PMID: 23135991 DOI: 10.1007/s12265-012-9414-3]

5 **Valantine H**. Cardiac allograft vasculopathy after heart transplantation: risk factors and management. *J Heart Lung Transplant* 2004; **23**: S187-S193 [PMID: 15093804 DOI: 10.1016/j.healun.2004.03.009]

6 **Raichlin ER**, McConnell JP, Lerman A, Kremers WK, Edwards BS, Kushwaha SS, Clavell AL, Rodeheffer RJ, Frantz RP. Systemic inflammation and metabolic syndrome in cardiac allograft vasculopathy. *J Heart Lung Transplant* 2007; **26**: 826-833 [PMID: 17692787 DOI: 10.1016/j.healun.2007.05.008]

7 **Conway J**, Dipchand AI. Heart transplantation in children. *Pediatr Clin North Am* 2010; **57**: 353-373, table of contents [PMID: 20371041 DOI: 10.1016/j.pcl.2010.01.009]

8 **Dent CL**, Canter CE, Hirsch R, Balzer DT. Transplant coronary artery disease in pediatric heart transplant recipients. *J Heart Lung Transplant* 2000; **19**: 240-248 [PMID: 10713248]

9 **Kobayashi D**, Du W, L'ecuyer TJ. Predictors of cardiac allograft vasculopathy in pediatric heart transplant recipients. *Pediatr Transplant* 2013; **17**: 436-440 [PMID: 23714284 DOI: 10.1111/petr.12095]

10 **Kirk R**, Edwards LB, Aurora P, Taylor DO, Christie JD, Dobbels F, Kucheryavaya AY, Rahmel AO, Stehlik J, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: Twelfth Official Pediatric Heart Transplantation Report-2009. *J Heart Lung Transplant* 2009; **28**: 993-1006 [PMID: 19782282 DOI: 10.1016/j.healun.2009.08.008]

11 **Gao SZ**, Schroeder JS, Hunt SA, Billingham ME, Valantine HA, Stinson EB. Acute myocardial infarction in cardiac transplant recipients. *Am J Cardiol* 1989; **64**: 1093-1097 [PMID: 2816760]

12 **Schmauss D**, Weis M. Cardiac allograft vasculopathy: recent developments. *Circulation* 2008; **117**: 2131-2141 [PMID: 18427143 DOI: 10.1161/CIRCULATIONAHA.107.711911]

13 **Mehra MR**, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, Madsen J, Parameshwar J, Starling RC, Uber PA. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant* 2010; **29**: 717-727 [PMID: 20620917 DOI: 10.1016/j.healun.2010.05.017]

14 **St Goar FG**, Pinto FJ, Alderman EL, Valantine HA, Schroeder JS, Gao SZ, Stinson EB, Popp RL. Intracoronary ultrasound in cardiac transplant recipients. In vivo evidence of "angiographically silent" intimal thickening. *Circulation* 1992; **85**: 979-987 [PMID: 1537134 DOI: 10.1161/01.CIR.85.3.979]

15 **O'Neill BJ**, Pflugfelder PW, Singh NR, Menkis AH, McKenzie FN, Kostuk WJ. Frequency of angiographic detection and quantitative assessment of coronary arterial disease one and three years after cardiac transplantation. *Am J Cardiol* 1989; **63**: 1221-1226 [PMID: 2653018]

16 **Johnson DE**, Alderman EL, Schroeder JS, Gao SZ, Hunt S, DeCampli WM, Stinson E, Billingham M. Transplant coronary artery disease: histopathologic correlations with angiographic morphology. *J Am Coll Cardiol* 1991; **17**: 449-457 [PMID: 1991903]

17 **Tuzcu EM**, Kapadia SR, Sachar R, Ziada KM, Crowe TD, Feng J, Magyar WA, Hobbs RE, Starling RC, Young JB, McCarthy P, Nissen SE. Intravascular ultrasound evidence of angiographically silent progression in coronary atherosclerosis predicts long-term morbidity and mortality after cardiac transplantation. *J Am Coll Cardiol* 2005; **45**: 1538-1542 [PMID: 15862431 DOI: 10.1016/j.jacc.2004.12.076]

18 **Gregory SA**, Ferencik M, Achenbach S, Yeh RW, Hoffmann U, Inglessis I, Cury RC, Nieman K, McNulty IA, Laffan JA, Pomerantsev EV, Brady TJ, Semigran MJ, Jang IK. Comparison of sixty-four-slice multidetector computed tomographic coronary angiography to coronary angiography with intravascular ultrasound for the detection of transplant vasculopathy. *Am J Cardiol* 2006; **98**: 877-884 [PMID: 16996866 DOI: 10.1016/j.amjcard.2006.04.027]

19 **Störk S**, Behr TM, Birk M, Uberfuhr P, Klauss V, Spes CH, Angermann CE. Assessment of cardiac allograft vasculopathy late after heart transplantation: when is coronary angiography necessary? *J Heart Lung Transplant* 2006; **25**: 1103-1108 [PMID: 16962473 DOI: 10.1016/j.healun.2006.05.009]

20 **Hirohata A**, Nakamura M, Waseda K, Honda Y, Lee DP, Vagelos RH, Hunt SA, Valantine HA, Yock PG, Fitzgerald PJ, Yeung AC, Fearon WF. Changes in coronary anatomy and physiology after heart transplantation. *Am J Cardiol* 2007; **99**: 1603-1607 [PMID: 17531589 DOI: 10.1016/j.amjcard.2007.01.039]

21 **Glagov S**, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987; **316**: 1371-1375 [PMID: 3574413 DOI: 10.1056/NEJM198705283162204]

22 **Tsutsui H**, Schoenhagen P, Ziada KM, Crowe TD, Klingensmith JD, Vince DG, Bott-Silverman C, Starling R, Hobbs RE, Young J, Nissen SE, Tuzcu EM. Early constriction or expansion of the external elastic membrane area determines the late remodeling response and cumulative lumen loss in transplant vasculopathy: an intravascular ultrasound study with 4-year follow-up. *J Heart Lung Transplant* 2003; **22**: 519-525 [PMID: 12742413]

23 **Tsutsui H**, Ziada KM, Schoenhagen P, Iyisoy A, Magyar WA, Crowe TD, Klingensmith JD, Vince DG, Rincon G, Hobbs RE, Yamagishi M, Nissen SE, Tuzcu EM. Lumen loss in transplant coronary artery disease is a biphasic process involving early intimal thickening and late constrictive remodeling: results from a 5-year serial intravascular ultrasound study. *Circulation* 2001; **104**: 653-657 [PMID: 11489770 DOI: 10.1161/hc3101.093867]

24 **Wong C**, Ganz P, Miller L, Kobashigawa J, Schwarzkopf A, Valantine von Kaeper H, Wilensky R, Ventura H, Yeung AC. Role of vascular remodeling in the pathogenesis of early transplant coronary artery disease: a multicenter prospective intravascular ultrasound study. *J Heart Lung Transplant* 2001; **20**: 385-392 [PMID: 11295575]

25 **Costanzo MR**, Naftel DC, Pritzker MR, Heilman JK, Boehmer JP, Brozena SC, Dec GW, Ventura HO, Kirklin JK, Bourge RC, Miller LW. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. *J Heart Lung Transplant* 1998; **17**: 744-753 [PMID: 9730422]

26 **Barbir M**, Lazem F, Banner N, Mitchell A, Yacoub M. The prognostic significance of non-invasive cardiac tests in heart transplant recipients. *Eur Heart J* 1997; **18**: 692-696 [PMID: 9129903]

27 **Nicolas RT**, Kort HW, Balzer DT, Trinkaus K, Dent CL, Hirsch R, Canter CE. Surveillance for transplant coronary artery disease in infant, child and adolescent heart transplant recipients: an intravascular ultrasound study. *J Heart Lung Transplant* 2006; **25**: 921-927 [PMID: 16890112 DOI: 10.1016/j.healun.2006.03.022]

28 **Rickenbacher PR**, Pinto FJ, Lewis NP, Hunt SA, Alderman EL, Schroeder JS, Stinson EB, Brown BW, Valantine HA. Prognostic importance of intimal thickness as measured by intracoronary ultrasound after cardiac transplantation. *Circulation* 1995; **92**: 3445-3452 [PMID: 8521566]

29 **Kobashigawa JA**, Tobis JM, Starling RC, Tuzcu EM, Smith AL, Valantine HA, Yeung AC, Mehra MR, Anzai H, Oeser BT, Abeywickrama KH, Murphy J, Cretin N. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. *J Am Coll Cardiol* 2005; **45**: 1532-1537 [PMID: 15862430 DOI: 10.1016/j.jacc.2005.02.035]

30 **Clausell N**, Butany J, Molossi S, Lonn E, Gladstone P, Rabinovitch M, Daly PA. Abnormalities in intramyocardial arteries detected in cardiac transplant biopsy specimens and

lack of correlation with abnormal intracoronary ultrasound or endothelial dysfunction in large epicardial coronary arteries. *J Am Coll Cardiol* 1995; **26**: 110-119 [PMID: 7541058]

31 **Kapadia SR**, Ziada KM, L'Allier PL, Crowe TD, Rincon G, Hobbs RE, Bott-Silverman C, Young JB, Nissen SE, Tuzcu EM. Intravascular ultrasound imaging after cardiac transplantation: advantage of multi-vessel imaging. *J Heart Lung Transplant* 2000; **19**: 167-172 [PMID: 10703693]

32 **Koning G**, Dijkstra J, von Birgelen C, Tuinenburg JC, Brunette J, Tardif JC, Oemrawsingh PW, Sieling C, Melsa S, Reiber JH. Advanced contour detection for three-dimensional intracoronary ultrasound: a validation--in vitro and in vivo. *Int J Cardiovasc Imaging* 2002; **18**: 235-248 [PMID: 12123316]

33 **Smart FW**, Ballantyne CM, Cocanougher B, Farmer JA, Sekela ME, Noon GP, Young JB. Insensitivity of noninvasive tests to detect coronary artery vasculopathy after heart transplant. *Am J Cardiol* 1991; **67**: 243-247 [PMID: 1990786]

34 **Derumeaux G**, Redonnet M, Soyer R, Cribier A, Letac B. Assessment of the progression of cardiac allograft vasculopathy by dobutamine stress echocardiography. *J Heart Lung Transplant* 1998; **17**: 259-267 [PMID: 9563602]

35 **Spes CH**, Klauss V, Mudra H, Schnaack SD, Tammen AR, Rieber J, Siebert U, Henneke KH, Uberfuhr P, Reichart B, Theisen K, Angermann CE. Diagnostic and prognostic value of serial dobutamine stress echocardiography for noninvasive assessment of cardiac allograft vasculopathy: a comparison with coronary angiography and intravascular ultrasound. *Circulation* 1999; **100**: 509-515 [PMID: 10430765]

36 **Bacal F**, Moreira L, Souza G, Rodrigues AC, Fiorelli A, Stolf N, Bocchi E, Bellotti G, Ramires JA. Dobutamine stress echocardiography predicts cardiac events or death in asymptomatic patients long-term after heart transplantation: 4-year prospective evaluation. *J Heart Lung Transplant* 2004; **23**: 1238-1244 [PMID: 15539121 DOI: 10.1016/j.healun.2003.09.007]

37 **Larsen RL**, Applegate PM, Dyar DA, Ribeiro PA, Fritzsche SD, Mulla NF, Shirali GS, Kuhn MA, Chinnock RE, Shah PM. Dobutamine stress echocardiography for assessing coronary artery disease after transplantation in children. *J Am Coll Cardiol* 1998; **32**: 515-520 [PMID: 9708485]

38 **Lewis JF**, Selman SB, Murphy JD, Mills RM, Geiser EA, Conti CR. Dobutamine echocardiography for prediction of ischemic events in heart transplant recipients. *J Heart Lung Transplant* 1997; **16**: 390-393 [PMID: 9154948]

39 **Pahl E**, Crawford SE, Swenson JM, Duffy CE, Fricker FJ, Backer CL, Mavroudis C, Chaudhry FA. Dobutamine stress echocardiography: experience in pediatric heart transplant recipients. *J Heart Lung Transplant* 1999; **18**: 725-732 [PMID: 10452350]

40 **Eroglu E**, D'hooge J, Sutherland GR, Marciniak A, Thijs D, Droogne W, Herbots L, Van Cleemput J, Claus P, Bijnens B, Vanhaecke J, Rademakers F. Quantitative dobutamine stress echocardiography for the early detection of cardiac allograft vasculopathy in heart transplant recipients. *Heart* 2008; **94**: e3 [PMID: 17916666 DOI: 10.1136/hrt.2007.119693]

41 **Akosah KO**, McDaniel S, Hanrahan JS, Mohanty PK. Dobutamine stress echocardiography early after heart transplantation predicts development of allograft coronary artery disease and outcome. *J Am Coll Cardiol* 1998; **31**: 1607-1614 [PMID: 9626841]

42 **Jackson PA**, Akosah KO, Kirchberg DJ, Mohanty PK, Minisi AJ. Relationship between dobutamine-induced regional wall motion abnormalities and coronary flow reserve in heart transplant patients without angiographic coronary artery disease. *J Heart Lung Transplant* 2002; **21**: 1080-1089 [PMID: 12398873]

43 **Dipchand AI**, Bharat W, Manlhiot C, Safi M, Lobach NE, McCrindle BW. A prospective study of dobutamine stress echocardiography for the assessment of cardiac allograft vasculopathy in pediatric heart transplant recipients. *Pediatr Transplant* 2008; **12**: 570-576 [PMID: 18363614 DOI: 10.1111/j.1399-3046.2007.00861.x]

44 **Di Filippo S**, Semiond B, Roriz R, Sassolas F, Raboisson MJ, Bozio A. Non-invasive detection of coronary artery disease by dobutamine-stress echocardiography in children after heart transplantation. *J Heart Lung Transplant* 2003; **22**: 876-882 [PMID: 12909467 DOI: 10.1016/S1053-2498(02)00664-2]

45 **Tona F**, Caforio AL, Montisci R, Angelini A, Ruscazio M, Gambino A, Ramondo A, Thiene G, Gerosa G, Iliceto S. Coronary flow reserve by contrast-enhanced echocardiography: a new noninvasive diagnostic tool for cardiac allograft vasculopathy. *Am J Transplant* 2006; **6**: 998-1003 [PMID: 16611336 DOI: 10.1111/j.1600-6143.2006.01298.x]

46 **Tona F**, Osto E, Tarantini G, Gambino A, Cavallin F, Feltrin G, Montisci R, Caforio AL, Gerosa G, Iliceto S. Coronary flow reserve by transthoracic echocardiography predicts epicardial intimal thickening in cardiac allograft vasculopathy. *Am J Transplant* 2010; **10**: 1668-1676 [PMID: 20642688 DOI: 10.1111/j.1600-6143.2010.03160.x]

47 **Rodrigues AC**, Frimm Cde C, Bacal F, Andreolli V, Tsutsui JM, Bocchi EA, Mathias W, Lage SG. Coronary flow reserve impairment predicts cardiac events in heart transplant patients with preserved left ventricular function. *Int J Cardiol* 2005; **103**: 201-206 [PMID: 16080981 DOI: 10.1016/j.ijcard.2004.12.017]

48 **Dandel M**, Hummel M, Müller J, Wellnhofer E, Meyer R, Solowjowa N, Ewert R, Hetzer R. Reliability of tissue Doppler wall motion monitoring after heart transplantation for replacement of invasive routine screenings by optimally timed cardiac biopsies and catheterizations. *Circulation* 2001; **104**: I184-I191 [PMID: 11568053]

49 **Dandel M**, Wellnhofer E, Hummel M, Meyer R, Lehmkuhl H, Hetzer R. Early detection of left ventricular dysfunction related to transplant coronary artery disease. *J Heart Lung Transplant* 2003; **22**: 1353-1364 [PMID: 14672750 DOI: 10.1016/S1053-2498(03)00055-X]

50 **Fyfe DA**, Ketchum D, Lewis R, Sabatier J, Kanter K, Mahle W, Vincent R. Tissue Doppler imaging detects severely abnormal myocardial velocities that identify children with pre-terminal cardiac graft failure after heart transplantation. *J Heart Lung Transplant* 2006; **25**: 510-517 [PMID: 16678028 DOI: 10.1016/j.healun.2005.11.453]

51 **Savage A**, Hlavacek A, Ringewald J, Shirali G. Evaluation of the myocardial performance index and tissue doppler imaging by comparison to near-simultaneous catheter measurements in pediatric cardiac transplant patients. *J Heart Lung Transplant* 2010; **29**: 853-858 [PMID: 20471861 DOI: 10.1016/j.healun.2010.03.014]

52 **Collings CA**, Pinto FJ, Valantine HA, Popylisen S, Puryear JV, Schnittger I. Exercise echocardiography in heart transplant recipients: a comparison with angiography and intracoronary ultrasonography. *J Heart Lung Transplant* 1994; **13**: 604-613 [PMID: 7947876]

53 **Chen MH**, Abernathey E, Lunze F, Colan SD, O'Neill S, Bergersen L, Geva T, Blume ED. Utility of exercise stress echocardiography in pediatric cardiac transplant recipients: a single-center experience. *J Heart Lung Transplant* 2012; **31**: 517-523 [PMID: 22301421 DOI: 10.1016/j.healun.2011.12.014]

54 **Hollenberg SM**, Klein LW, Parrillo JE, Scherer M, Burns D, Tamburro P, Oberoi M, Johnson MR, Costanzo MR. Coronary endothelial dysfunction after heart transplantation predicts allograft vasculopathy and cardiac death. *Circulation* 2001; **104**: 3091-3096 [PMID: 11748106]

55 **Wijns W**, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J* 2010; **31**: 2501-2555 [PMID: 20802248 DOI: 10.1093/eurheartj/ehq277]

56 **Fearon WF**, Hirohata A, Nakamura M, Luikart H, Lee DP, Vagelos RH, Hunt SA, Valantine HA, Fitzgerald PJ, Yock PG, Yeung AC. Discordant changes in epicardial and microvascular

coronary physiology after cardiac transplantation: Physiologic Investigation for Transplant Arteriopathy II (PITA II) study. *J Heart Lung Transplant* 2006; **25**: 765-771 [PMID: 16818118 DOI: 10.1016/j.healun.2006.03.003]

57 **Lee CM**, Wu YW, Jui HY, Yen RF, Tzen KY, Chou NK, Wang SS. Intravascular ultrasound correlates with coronary flow reserve and predicts the survival in angiographically normal cardiac transplant recipients. *Cardiology* 2008; **109**: 93-98 [PMID: 17664873 DOI: 10.1159/000105548]

58 **Fearon WF**, Nakamura M, Lee DP, Rezaee M, Vagelos RH, Hunt SA, Fitzgerald PJ, Yock PG, Yeung AC. Simultaneous assessment of fractional and coronary flow reserves in cardiac transplant recipients: Physiologic Investigation for Transplant Arteriopathy (PITA Study). *Circulation* 2003; **108**: 1605-1610 [PMID: 12963639 DOI: 10.1161/01.CIR.0000091116.84926.6F]

59 **Suwaidi JA**, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000; **101**: 948-954 [PMID: 10704159]

60 **Schächinger V**, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; **101**: 1899-1906 [PMID: 10779454]

61 **Hollenberg SM**, Klein LW, Parrillo JE, Scherer M, Burns D, Tamburro P, Bromet D, Satran A, Costanzo MR. Changes in coronary endothelial function predict progression of allograft vasculopathy after heart transplantation. *J Heart Lung Transplant* 2004; **23**: 265-271 [PMID: 15019634 DOI: 10.1016/S1053-2498(03)00150-5]

62 **Kübrich M**, Petrakopoulou P, Kofler S, Nickel T, Kaczmarek I, Meiser BM, Reichart B, von Scheidt W, Weis M. Impact of coronary endothelial dysfunction on adverse long-term outcome after heart transplantation. *Transplantation* 2008; **85**: 1580-1587 [PMID: 18551063 DOI: 10.1097/TP.0b013e318170b4cd]

63 **Schubert S**, Abdul-Khaliq H, Wellnhofer E, Hiemann NE, Ewert P, Lehmkuhl HB, Meyer R, Miera O, Peters B, Hetzer R, Berger F. Coronary flow reserve measurement detects transplant coronary artery disease in pediatric heart transplant patients. *J Heart Lung Transplant* 2008; **27**: 514-521 [PMID: 18442717 DOI: 10.1016/j.healun.2008.02.005]

64 **van Rossum AC**, Visser FC, Hofman MB, Galjee MA, Westerhof N, Valk J. Global left ventricular perfusion: noninvasive measurement with cine MR imaging and phase velocity mapping of coronary venous outflow. *Radiology* 1992; **182**: 685-691 [PMID: 1535881]

65 **Koskenvuo JW**, Sakuma H, Niemi P, Toikka JO, Knuuti J, Laine H, Komu M, Kormano M, Saraste M, Hartiala JJ. Global myocardial blood flow and global flow reserve measurements by MRI and PET are comparable. *J Magn Reson Imaging* 2001; **13**: 361-366 [PMID: 11241807]

66 **Schwitter J**, DeMarco T, Kneifel S, von Schulthess GK, Jörg MC, Arheden H, Rühm S, Stumpe K, Buck A, Parmley WW, Lüscher TF, Higgins CB. Magnetic resonance-based assessment of global coronary flow and flow reserve and its relation to left ventricular functional parameters: a comparison with positron emission tomography. *Circulation* 2000; **101**: 2696-2702 [PMID: 10851206]

67 **Ishida M**, Ito T, Shiraishi Y, Kitagawa K, Dohi K, Nakajima H, Ito M, Sakuma H. Impaired coronary flow reserve determined by MR measurement of coronary sinus flow predicts adverse outcome in patients with known or suspected coronary artery disease. *J Cardiovasc Magn Reson* 2013; **15** (Suppl 1): O91 [DOI: 10.1186/1532-429X-15-S1-O91]

68 **Kennedy K**, Dick A, Drangova M, Raval A, Mahoney C, Karlik S, Pflugfelder PW. Magnetic resonance measurements of coronary flow reserve in heart transplant recipients: an exploratory study of the relationship to coronary angiographic findings. *J Cardiovasc Magn Reson* 2007; **9**: 701-707 [PMID: 17578727 DOI: 10.1080/10976640701198980]

69 **Shaw LJ**, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*2008; **117**: 1283-1291 [PMID: 18268144 DOI: 10.1161/CIRCULATIONAHA.107.743963]

70 **Klocke FJ**, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 2003; **108**: 1404-1418 [PMID: 12975245 DOI: 10.1161/01.CIR.0000080946.42225.4D]

71 **Camici PG**, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007; **356**: 830-840 [PMID: 17314342 DOI: 10.1056/NEJMra061889]

72 **Wu YW**, Yen RF, Lee CM, Ho YL, Chou NK, Wang SS, Huang PJ. Diagnostic and prognostic value of dobutamine thallium-201 single-photon emission computed tomography after heart transplantation. *J Heart Lung Transplant* 2005; **24**: 544-550 [PMID: 15896751 DOI: 10.1016/j.healun.2003.12.004]

73 **Carlsen J**, Toft JC, Mortensen SA, Arendrup H, Aldershvile J, Hesse B. Myocardial perfusion scintigraphy as a screening method for significant coronary artery stenosis in cardiac transplant recipients. *J Heart Lung Transplant* 2000; **19**: 873-878 [PMID: 11008077]

74 **Ciliberto GR**, Mangiavacchi M, Banfi F, Massa D, Danzi G, Cataldo G, Cipriani M, Piccalò G, Dabalà A, Gronda E. Coronary artery disease after heart transplantation: non-invasive evaluation with exercise thallium scintigraphy. *Eur Heart J* 1993; **14**: 226-229 [PMID: 8449198]

75 **Rodney RA**, Johnson LL, Blood DK, Barr ML. Myocardial perfusion scintigraphy in heart transplant recipients with and without allograft atherosclerosis: a comparison of thallium-201 and technetium 99m sestamibi. *J Heart Lung Transplant* 1994; **13**: 173-180 [PMID: 8031797]

76 **Howarth DM**, Forstrom LA, Samudrala V, Sinak LJ, McGregor CG, Rodeheffer RJ. Evaluation of 201Tl SPET myocardial perfusion imaging in the detection of coronary artery disease after orthotopic heart transplantation. *Nucl Med Commun* 1996; **17**: 105-113 [PMID: 8778633]

77 **Ambrosi P**, Habib G, Kreitman B, Metras D, Riberi A, Faugère G, Bernard P, Luccioni R. Thallium perfusion and myocardial hypertrophy in transplanted heart recipients with normal or near-normal coronary arteriograms. *Eur Heart J* 1994; **15**: 1119-1123 [PMID: 7988605]

78 **Elhendy A**, Sozzi FB, van Domburg RT, Vantrimpont P, Valkema R, Krenning EP, Roelandt JR, Maat LP, Balk AH. Accuracy of dobutamine tetrofosmin myocardial perfusion imaging for the noninvasive diagnosis of transplant coronary artery stenosis. *J Heart Lung Transplant* 2000; **19**: 360-366 [PMID: 10775817]

79 **Verhoeven PP**, Lee FA, Ramahi TM, Franco KL, Mendes de Leon C, Amatruda J, Gorham NA, Mattera JA, Wackers FJ. Prognostic value of noninvasive testing one year after orthotopic cardiac transplantation. *J Am Coll Cardiol* 1996; **28**: 183-189 [PMID: 8752812]

80 **Elhendy A**, van Domburg RT, Vantrimpont P, Poldermans D, Bax JJ, van Gelder T, Baan CC, Schinkel A, Roelandt JR, Balk AH. Prediction of mortality in heart transplant recipients

by stress technetium-99m tetrofosmin myocardial perfusion imaging. *Am J Cardiol* 2002; **89**: 964-968 [PMID: 11950436]
81 **Ciliberto GR**, Ruffini L, Mangiavacchi M, Parolini M, Sara R, Massa D, De Maria R, Gronda E, Vitali E, Parodi O. Resting echocardiography and quantitative dipyridamole technetium-99m sestamibi tomography in the identification of cardiac allograft vasculopathy and the prediction of long-term prognosis after heart transplantation. *Eur Heart J* 2001; **22**: 964-971 [PMID: 11428820 DOI: 10.1053/euhj.2000.2422]
82 **Hacker M**, Tausig A, Romüller B, Hoyer X, Klauss V, Stempfle U, Reichart B, Hahn K, Tiling R. Dobutamine myocardial scintigraphy for the prediction of cardiac events after heart transplantation. *Nucl Med Commun* 2005; **26**: 607-612 [PMID: 15942481]
83 **Manrique A**, Bernard M, Hitzel A, Bubenheim M, Tron C, Agostini D, Cribier A, Véra P, Bessou JP, Redonnet M. Diagnostic and prognostic value of myocardial perfusion gated SPECT in orthotopic heart transplant recipients. *J Nucl Cardiol* 2010; **17**: 197-206 [PMID: 20151240 DOI: 10.1007/s12350-009-9166-x]
84 **Lenihan DJ**, Rosenbaum AF, Burwinkel P, Tseng CY, Bhat G, Wagoner L, Walsh RA, Gerson MC. Prediction of human transplantation arteriopathy and coronary events with lung/heart count ratios during intravenous dipyridamole thallium-201 imaging. *Am Heart J* 1999; **137**: 942-948 [PMID: 10220645]
85 **Bengel FM**, Higuchi T, Javadi MS, Lautamäki R. Cardiac positron emission tomography. *J Am Coll Cardiol* 2009; **54**: 1-15 [PMID: 19555834 DOI: 10.1016/j.jacc.2009.02.065]
86 **Uren NG**, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med* 1994; **330**: 1782-1788 [PMID: 8190154 DOI: 10.1056/NEJM199406233302503]
87 **Allen-Auerbach M**, Schöder H, Johnson J, Kofoed K, Einhorn K, Phelps ME, Kobashigawa J, Czernin J. Relationship between coronary function by positron emission tomography and temporal changes in morphology by intravascular ultrasound (IVUS) in transplant recipients. *J Heart Lung Transplant* 1999; **18**: 211-219 [PMID: 10328146]
88 **Wu YW**, Chen YH, Wang SS, Jui HY, Yen RF, Tzen KY, Chen MF, Lee CM. PET assessment of myocardial perfusion reserve inversely correlates with intravascular ultrasound findings in angiographically normal cardiac transplant recipients. *J Nucl Med* 2010; **51**: 906-912 [PMID: 20484427 DOI: 10.2967/jnumed.109.073833]
89 **Preumont N**, Berkenboom G, Vachiery J, Jansens J, Antoine M, Wikler D, Damhaut P, Degré S, Lenaers A, Goldman S. Early alterations of myocardial blood flow reserve in heart transplant recipients with angiographically normal coronary arteries. *J Heart Lung Transplant* 2000; **19**: 538-545 [PMID: 10867333]
90 **Mollet NR**, Cademartiri F, van Mieghem CA, Runza G, McFadden EP, Baks T, Serruys PW, Krestin GP, de Feyter PJ. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation* 2005; **112**: 2318-2323 [PMID: 16203914 DOI: 10.1161/CIRCULATIONAHA.105.533471]
91 **Leber AW**, Knez A, von Ziegler F, Becker A, Nikolaou K, Paul S, Wintersperger B, Reiser M, Becker CR, Steinbeck G, Boekstegers P. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol* 2005; **46**: 147-154 [PMID: 15992649 DOI: 10.1016/j.jacc.2005.03.071]
92 **Hoffmann U**, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, Cury RC, Abbara S, Joneidi-Jafari H, Achenbach S, Brady TJ. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol* 2006; **47**: 1655-1662 [PMID: 16631006 DOI: 10.1016/j.jacc.2006.01.041]
93 **Sigurdsson G**, Carrascosa P, Yamani MH, Greenberg NL, Perrone S, Lev G, Desai MY, Garcia MJ. Detection of transplant coronary artery disease using multidetector computed tomography with adaptative multisegment reconstruction. *J Am Coll Cardiol* 2006; **48**: 772-778 [PMID: 16904548 DOI: 10.1016/j.jacc.2006.04.082]
94 **Iyengar S**, Feldman DS, Cooke GE, Leier CV, Raman SV. Detection of coronary artery disease in orthotopic heart transplant recipients with 64-detector row computed tomography angiography. *J Heart Lung Transplant* 2006; **25**: 1363-1366 [PMID: 17097502 DOI: 10.1016/j.healun.2006.06.018]
95 **Romeo G**, Houyel L, Angel CY, Brenot P, Riou JY, Paul JF. Coronary stenosis detection by 16-slice computed tomography in heart transplant patients: comparison with conventional angiography and impact on clinical management. *J Am Coll Cardiol* 2005; **45**: 1826-1831 [PMID: 15936614 DOI: 10.1016/j.jacc.2005.02.069]
96 **Schepis T**, Achenbach S, Weyand M, Raum P, Marwan M, Pflederer T, Daniel WG, Tandler R, Kondruweit M, Ropers D. Comparison of dual source computed tomography versus intravascular ultrasound for evaluation of coronary arteries at least one year after cardiac transplantation. *Am J Cardiol* 2009; **104**: 1351-1356 [PMID: 19892049 DOI: 10.1016/j.amjcard.2009.06.060]
97 **Bogot NR**, Durst R, Shaham D, Admon D. Cardiac CT of the transplanted heart: indications, technique, appearance, and complications. *Radiographics* 2007; **27**: 1297-1309 [PMID: 17848692 DOI: 10.1148/rg.275065107]
98 **Nunoda S**, Machida H, Sekikawa A, Shitakura K, Okajima K, Kubo Y, Ueno E, Otsuka K. Evaluation of cardiac allograft vasculopathy by multidetector computed tomography and whole-heart magnetic resonance coronary angiography. *Circ J* 2010; **74**: 946-953 [PMID: 20215697]
99 **Bae KT**, Hong C, Takahashi N, Gutierrez F, Sharkey AM, Hirsch R, Canter CE. Multi-detector row computed tomographic angiography in pediatric heart transplant recipients: Initial observations. *Transplantation* 2004; **77**: 599-602 [PMID: 15084942]
100 **Pinto TL**, Waksman R. Clinical applications of optical coherence tomography. *J Interv Cardiol* 2006; **19**: 566-573 [PMID: 17107374 DOI: 10.1111/j.1540-8183.2006.00201.x]
101 **Suter MJ**, Nadkarni SK, Weisz G, Tanaka A, Jaffer FA, Bouma BE, Tearney GJ. Intravascular optical imaging technology for investigating the coronary artery. *JACC Cardiovasc Imaging* 2011; **4**: 1022-1039 [PMID: 21920342 DOI: 10.1016/j.jcmg.2011.03.020]
102 **Tearney GJ**, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, Costa MA, de Silva R, Dijkstra J, Di Mario C, Dudek D, Falk E, Feldman MD, Fitzgerald P, Garcia-Garcia HM, Gonzalo N, Granada JF, Guagliumi G, Holm NR, Honda Y, Ikeno F, Kawasaki M, Kochman J, Koltowski L, Kubo T, Kume T, Kyono H, Lam CC, Lamouche G, Lee DP, Leon MB, Maehara A, Manfrini O, Mintz GS, Mizuno K, Morel MA, Nadkarni S, Okura H, Otake H, Pietrasik A, Prati F, Räber L, Radu MD, Rieber J, Riga M, Rollins A, Rosenberg M, Sirbu V, Serruys PW, Shimada K, Shinke T, Shite J, Siegel E, Sonoda S, Suter M, Takarada S, Tanaka A, Terashima M, Thim T, Uemura S, Ughi GJ, van Beusekom HM, van der Steen AF, van Es GA, van Soest G, Virmani R, Waxman S, Weissman NJ, Weisz G. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012; **59**: 1058-1072 [PMID: 22421299]
103 **Khandhar SJ**, Yamamoto H, Teuteberg JJ, Shullo MA, Bezerra

HG, Costa MA, Selzer F, Lee JS, Marroquin OC, McNamara DM, Mulukutla SR, Toma C. Optical coherence tomography for characterization of cardiac allograft vasculopathy after heart transplantation (OCTCAV study). *J Heart Lung Transplant* 2013; **32**: 596-602 [PMID: 23499356 DOI: 10.1016/j.healun.2013.02.005]

104 **Garrido IP**, García-Lara J, Pinar E, Pastor-Pérez F, Sánchez-Mas J, Valdés-Chavarri M, Pascual-Figal DA. Optical coherence tomography and highly sensitivity troponin T for evaluating cardiac allograft vasculopathy. *Am J Cardiol* 2012; **110**: 655-661 [PMID: 22640973 DOI: 10.1016/j.amjcard.2012.04.047]

105 **Cassar A**, Matsuo Y, Herrmann J, Li J, Lennon RJ, Gulati R, Lerman LO, Kushwaha SS, Lerman A. Coronary atherosclerosis with vulnerable plaque and complicated lesions in transplant recipients: new insight into cardiac allograft vasculopathy by optical coherence tomography. *Eur Heart J* 2013; **34**: 2610-2617 [PMID: 23801824 DOI: 10.1093/eurheartj/eht236]

106 **Kim WY**, Danias PG, Stuber M, Flamm SD, Plein S, Nagel E, Langerak SE, Weber OM, Pedersen EM, Schmidt M, Botnar RM, Manning WJ. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med* 2001; **345**: 1863-1869 [PMID: 11756576 DOI: 10.1056/NEJMoa010866]

107 **Botnar RM**, Kim WY, Börnert P, Stuber M, Spuentrup E, Manning WJ. 3D coronary vessel wall imaging utilizing a local inversion technique with spiral image acquisition. *Magn Reson Med* 2001; **46**: 848-854 [PMID: 11675634]

108 **Botnar RM**, Stuber M, Kissinger KV, Kim WY, Spuentrup E, Manning WJ. Noninvasive coronary vessel wall and plaque imaging with magnetic resonance imaging. *Circulation* 2000; **102**: 2582-2587 [PMID: 11085960]

109 **Uribe S**, Hussain T, Valverde I, Tejos C, Irarrazaval P, Fava M, Beerbaum P, Botnar RM, Razavi R, Schaeffter T, Greil GF. Congenital heart disease in children: coronary MR angiography during systole and diastole with dual cardiac phase whole-heart imaging. *Radiology* 2011; **260**: 232-240 [PMID: 21493790 DOI: 10.1148/radiol.11101659]

110 **Tangcharoen T**, Bell A, Hegde S, Hussain T, Beerbaum P, Schaeffter T, Razavi R, Botnar RM, Greil GF. Detection of coronary artery anomalies in infants and young children with congenital heart disease by using MR imaging. *Radiology* 2011; **259**: 240-247 [PMID: 21325034 DOI: 10.1148/radiol.10100828]

111 **Greil GF**, Stuber M, Botnar RM, Kissinger KV, Geva T, Newburger JW, Manning WJ, Powell AJ. Coronary magnetic resonance angiography in adolescents and young adults with kawasaki disease. *Circulation* 2002; **105**: 908-911 [PMID: 11864916]

112 **Schwitter J**, Wacker CM, van Rossum AC, Lombardi M, Al-Saadi N, Ahlstrom H, Dill T, Larsson HB, Flamm SD, Marquardt M, Johansson L. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. *Eur Heart J* 2008; **29**: 480-489 [PMID: 18208849 DOI: 10.1093/eurheartj/ehm617]

113 **Jahnke C**, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 2007; **115**: 1769-1776 [PMID: 17353441 DOI: 10.1161/CIRCULATIONAHA.106.652016]

114 **Muehling OM**, Wilke NM, Panse P, Jerosch-Herold M, Wilson BV, Wilson RF, Miller LW. Reduced myocardial perfusion reserve and transmural perfusion gradient in heart transplant arteriopathy assessed by magnetic resonance imaging. *J Am Coll Cardiol* 2003; **42**: 1054-1060 [PMID: 13678930]

115 **Steen H**, Merten C, Refle S, Klingenberg R, Dengler T, Giannitsis E, Katus HA. Prevalence of different gadolinium enhancement patterns in patients after heart transplantation. *J Am Coll Cardiol* 2008; **52**: 1160-1167 [PMID: 18804744 DOI: 10.1016/j.jacc.2008.05.059]

116 **Braggion-Santos MF**, Andre F, Lossnitzer D, Hofmann E, Simpfendörfer J, Dösch A, Katus HA, Steen H. Prevalence of different forms of infarct-atypical late gadolinium enhancement in patients early and late after heart transplantation. *Clin Res Cardiol* 2014; **103**: 57-63 [PMID: 24122145 DOI: 10.1007/s00392-013-0623-9]

117 **Hussain T**, Burch M, Fenton MJ, Whitmore PM, Rees P, Elliott M, Aurora P. Positive pretransplantation cytomegalovirus serology is a risk factor for cardiac allograft vasculopathy in children. *Circulation* 2007; **115**: 1798-1805 [PMID: 17353448 DOI: 10.1161/CIRCULATIONAHA.106.627570]

118 **Miller CA**, Sarma J, Naish JH, Yonan N, Williams SG, Shaw SM, Clark D, Pearce K, Stout M, Potluri R, Borg A, Coutts G, Chowdhary S, McCann GP, Parker GJ, Ray SG, Schmitt M. Multiparametric cardiovascular magnetic resonance assessment of cardiac allograft vasculopathy. *J Am Coll Cardiol* 2014; **63**: 799-808 [PMID: 24355800 DOI: 10.1016/j.jacc.2013.07.119]

119 **Blum A**, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. *Atherosclerosis* 2009; **203**: 325-330 [PMID: 18834985 DOI: 10.1016/j.atherosclerosis.2008.08.022]

120 **Anderson TJ**, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, Lieberman EH, Ganz P, Creager MA, Yeung AC. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol* 1995; **26**: 1235-1241 [PMID: 7594037]

121 **Treasure CB**, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Boccuzzi SJ, Cedarholm JC, Alexander RW. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995; **332**: 481-487 [PMID: 7830728 DOI: 10.1056/NEJM199502233320801]

122 **Wenke K**, Meiser B, Thiery J, Nagel D, von Scheidt W, Krobot K, Steinbeck G, Seidel D, Reichart B. Simvastatin initiated early after heart transplantation: 8-year prospective experience. *Circulation* 2003; **107**: 93-97 [PMID: 12515749]

123 **Mehra MR**, Uber PA, Vivekananthan K, Solis S, Scott RL, Park MH, Milani RV, Lavie CJ. Comparative beneficial effects of simvastatin and pravastatin on cardiac allograft rejection and survival. *J Am Coll Cardiol* 2002; **40**: 1609-1614 [PMID: 12427413]

124 **Mehra MR**, Raval NY. Metaanalysis of statins and survival in de novo cardiac transplantation. *Transplant Proc* 2004; **36**: 1539-1541 [PMID: 15251380 DOI: 10.1016/j.transproceed.2004.05.036]

125 **Costanzo MR**, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Uber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; **29**: 914-956 [PMID: 20643330 DOI: 10.1016/j.healun.2010.05.034]

126 **Valentine VG**, Weill D, Gupta MR, Raper B, Laplace SG, Lombard GA, Bonvillain RW, Taylor DE, Dhillon GS. Ganciclovir for cytomegalovirus: a call for indefinite prophylaxis in lung transplantation. *J Heart Lung Transplant* 2008; **27**: 875-881 [PMID: 18656801 DOI: 10.1016/j.healun.2008.05.009]

127 **Fearon WF**, Potena L, Hirohata A, Sakurai R, Yamasaki M, Luikart H, Lee J, Vana ML, Cooke JP, Mocarski ES, Yeung AC, Valantine HA. Changes in coronary arterial dimensions early

after cardiac transplantation. *Transplantation* 2007; **83**: 700-705 [PMID: 17414701 DOI: 10.1097/01.tp.0000256335.84363.9b]

128 **Mehra MR**, Ventura HO, Smart FW, Collins TJ, Ramee SR, Stapleton DD. An intravascular ultrasound study of the influence of angiotensin-converting enzyme inhibitors and calcium entry blockers on the development of cardiac allograft vasculopathy. *Am J Cardiol* 1995; **75**: 853-854 [PMID: 7717300]

129 **Schroeder JS**, Gao SZ, Alderman EL, Hunt SA, Johnstone I, Boothroyd DB, Wiederhold V, Stinson EB. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. *N Engl J Med* 1993; **328**: 164-170 [PMID: 8417382 DOI: 10.1056/NEJM199301213280303]

130 **Erinc K**, Yamani MH, Starling RC, Crowe T, Hobbs R, Bott-Silverman C, Rincon G, Young JB, Feng J, Cook DJ, Smedira N, Tuzcu EM. The effect of combined Angiotensin-converting enzyme inhibition and calcium antagonism on allograft coronary vasculopathy validated by intravascular ultrasound. *J Heart Lung Transplant* 2005; **24**: 1033-1038 [PMID: 16102438 DOI: 10.1016/j.healun.2004.06.005]

131 **Meiser BM**, Groetzner J, Kaczmarek I, Landwehr P, Müller M, Jung S, Uberfuhr P, Fraunberger P, Stempfle HU, Weis M, Reichart B. Tacrolimus or cyclosporine: which is the better partner for mycophenolate mofetil in heart transplant recipients? *Transplantation* 2004; **78**: 591-598 [PMID: 15446320]

132 **Grimm M**, Rinaldi M, Yonan NA, Arpesella G, Arizón Del Prado JM, Pulpón LA, Villemot JP, Frigerio M, Rodriguez Lambert JL, Crespo-Leiro MG, Almenar L, Duveau D, Ordonez-Fernandez A, Gandjbakhch J, Maccherini M, Laufer G. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients--a large European trial. *Am J Transplant* 2006; **6**: 1387-1397 [PMID: 16686762 DOI: 10.1111/j.1600-6143.2006.01300.x]

133 **Kobashigawa JA**, Miller LW, Russell SD, Ewald GA, Zucker MJ, Goldberg LR, Eisen HJ, Salm K, Tolzman D, Gao J, Fitzsimmons W, First R. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. *Am J Transplant* 2006; **6**: 1377-1386 [PMID: 16686761 DOI: 10.1111/j.1600-6143.2006.01290.x]

134 **Segovia J**, Gómez-Bueno M, Alonso-Pulpón L. Treatment of allograft vasculopathy in heart transplantation. *Expert Opin Pharmacother* 2006; **7**: 2369-2383 [PMID: 17109612 DOI: 10.1517/14656566.7.17.2369]

135 **Petrakopoulou P**, Anthopoulou L, Muscholl M, Klauss V, von Scheidt W, Uberfuhr P, Meiser BM, Reichart B, Weis M. Coronary endothelial vasomotor function and vascular remodeling in heart transplant recipients randomized for tacrolimus or cyclosporine immunosuppression. *J Am Coll Cardiol* 2006; **47**: 1622-1629 [PMID: 16631000 DOI: 10.1016/j.jacc.2005.10.073]

136 **Eisen HJ**, Kobashigawa J, Keogh A, Bourge R, Renlund D, Mentzer R, Alderman E, Valantine H, Dureau G, Mancini D, Mamelok R, Gordon R, Wang W, Mehra M, Constanzo MR, Hummel M, Johnson J. Three-year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. *J Heart Lung Transplant* 2005; **24**: 517-525 [PMID: 15896747 DOI: 10.1016/j.healun.2005.02.002]

137 **Kobashigawa JA**, Tobis JM, Mentzer RM, Valantine HA, Bourge RC, Mehra MR, Smart FW, Miller LW, Tanaka K, Li H, Gjertson DW, Gordon RD. Mycophenolate mofetil reduces intimal thickness by intravascular ultrasound after heart transplant: reanalysis of the multicenter trial. *Am J Transplant* 2006; **6**: 993-997 [PMID: 16611335 DOI: 10.1111/j.1600-6143.2006.01297.x]

138 **Kaczmarek I**, Ertl B, Schmauss D, Sadoni S, Knez A, Daebritz S, Meiser B, Reichart B. Preventing cardiac allograft vasculopathy: long-term beneficial effects of mycophenolate mofetil. *J Heart Lung Transplant* 2006; **25**: 550-556 [PMID: 16678034 DOI: 10.1016/j.healun.2006.01.003]

139 **Sehgal SN**. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc* 2003; **35**: 7S-14S [PMID: 12742462]

140 **Raichlin E**, Kushwaha SS. Proliferation signal inhibitors and cardiac allograft vasculopathy. *Curr Opin Organ Transplant* 2008; **13**: 543-550 [PMID: 19060540 DOI: 10.1097/MOT.0b013e32830fdf70]

141 **Eisen HJ**, Tuzcu EM, Dorent R, Kobashigawa J, Mancini D, Valantine-von Kaeppler HA, Starling RC, Sørensen K, Hummel M, Lind JM, Abeywickrama KH, Bernhardt P. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; **349**: 847-858 [PMID: 12944570 DOI: 10.1056/NEJMoa022171]

142 **Viganò M**, Tuzcu M, Benza R, Boissonnat P, Haverich A, Hill J, Laufer G, Love R, Parameshwar J, Pulpón LA, Renlund D, Abeywickrama K, Cretin N, Starling RC, Eisen HJ. Prevention of acute rejection and allograft vasculopathy by everolimus in cardiac transplants recipients: a 24-month analysis. *J Heart Lung Transplant* 2007; **26**: 584-592 [PMID: 17543781 DOI: 10.1016/j.healun.2007.03.005]

143 **Eisen H**. Long-term cardiovascular risk in transplantation--insights from the use of everolimus in heart transplantation. *Nephrol Dial Transplant* 2006; **21** Suppl 3: iii9-ii13 [PMID: 16815858 DOI: 10.1093/ndt/gfl295]

144 **Andreassen AK,** Andersson B, Gustafsson F, Eiskjaer H, Rådegran G, Gude E, Jansson K, Solbu D, Sigurdardottir V, Arora S, Dellgren G, Gullestad L. Everolimus Initiation and Early Calcineurin Inhibitor Withdrawal in Heart Transplant Recipients: A Randomized Trial. *Am J Transplant* 2014; **14**: 1828-1838 [PMID: 25041227 DOI: 10.1111/ajt.12809]

145 **Mancini D**, Pinney S, Burkhoff D, LaManca J, Itescu S, Burke E, Edwards N, Oz M, Marks AR. Use of rapamycin slows progression of cardiac transplantation vasculopathy. *Circulation* 2003; **108**: 48-53 [PMID: 12742978 DOI: 10.1161/01.CIR.0000070421.38604.2B]

146 **Keogh A**, Richardson M, Ruygrok P, Spratt P, Galbraith A, O'Driscoll G, Macdonald P, Esmore D, Muller D, Faddy S. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation* 2004; **110**: 2694-2700 [PMID: 15262845 DOI: 10.1161/01.CIR.0000136812.90177.94]

147 **Lyster H**, Panicker G, Leaver N, Banner NR. Initial experience with sirolimus and mycophenolate mofetil for renal rescue from cyclosporine nephrotoxicity after heart transplantation. *Transplant Proc* 2004; **36**: 3167-3170 [PMID: 15686720 DOI: 10.1016/j.transproceed.2004.10.062]

148 **Rothenburger M**, Teerling E, Bruch C, Lehmkuhl H, Suwelack B, Bara C, Wichter T, Hinder F, Schmid C, Stypmann J. Calcineurin inhibitor-free immunosuppression using everolimus (Certican) in maintenance heart transplant recipients: 6 months' follow-up. *J Heart Lung Transplant* 2007; **26**: 250-257 [PMID: 17346627 DOI: 10.1016/j.healun.2007.01.017]

149 **Groetzner J**, Kaczmarek I, Meiser B, Müller M, Daebritz S, Reichart B. Sirolimus and mycophenolate mofetil as calcineurin inhibitor-free immunosuppression in a cardiac transplant patient with chronic renal failure. *J Heart Lung Transplant* 2004; **23**: 770-773 [PMID: 15366440]

150 **Groetzner J**, Kaczmarek I, Landwehr P, Mueller M, Daebritz S, Lamm P, Meiser B, Reichart B. Renal recovery after conversion to a calcineurin inhibitor-free immunosuppression in late cardiac transplant recipients. *Eur J Cardiothorac Surg* 2004; **25**: 333-341 [PMID: 15019657 DOI: 10.1016/j.ejcts.2003.11.030]

151 **Hunt J**, Lerman M, Magee MJ, Dewey TM, Herbert M, Mack MJ. Improvement of renal dysfunction by conversion from calcineurin inhibitors to sirolimus after heart transplantation. *J Heart Lung Transplant* 2005; **24**: 1863-1867 [PMID: 16297793 DOI: 10.1016/j.healun.2005.02.018]

152 **Raichlin E**, Bae JH, Khalpey Z, Edwards BS, Kremers WK, Clavell AL, Rodeheffer RJ, Frantz RP, Rihal C, Lerman A, Kushwaha SS. Conversion to sirolimus as primary immunosuppression

attenuates the progression of allograft vasculopathy after cardiac transplantation. *Circulation* 2007; **116**: 2726-2733 [PMID: 18025531 DOI: 10.1161/CIRCULATIONAHA.107.692996]

153 **Topilsky Y**, Hasin T, Raichlin E, Boilson BA, Schirger JA, Pereira NL, Edwards BS, Clavell AL, Rodeheffer RJ, Frantz RP, Maltais S, Park SJ, Daly RC, Lerman A, Kushwaha SS. Sirolimus as primary immunosuppression attenuates allograft vasculopathy with improved late survival and decreased cardiac events after cardiac transplantation. *Circulation* 2012; **125**: 708-720 [PMID: 22207715 DOI: 10.1161/CIRCULATIONAHA.111.040360]

154 **Arora S**, Erikstad I, Ueland T, Sigurdardottir V, Ekmehag B, Jansson K, Eiskjaer H, Bøtker HE, Mortensen SA, Saunamaki K, Gude E, Ragnarsson A, Solbu D, Aukrust P, Gullestad L. Virtual histology assessment of cardiac allograft vasculopathy following introduction of everolimus--results of a multicenter trial. *Am J Transplant* 2012; **12**: 2700-2709 [PMID: 22958738 DOI: 10.1111/j.1600-6143.2012.04234.x]

155 **Zuckermann A**, Manito N, Epailly E, Fiane A, Bara C, Delgado JF, Lehmkuhl H, Ross H, Eisen H, Chapman J, Valantine H. Multidisciplinary insights on clinical guidance for the use of proliferation signal inhibitors in heart transplantation. *J Heart Lung Transplant* 2008; **27**: 141-149 [PMID: 18267219 DOI: 10.1016/j.healun.2007.08.014]

156 **Demopoulos L**, Polinsky M, Steele G, Mines D, Blum M, Caulfield M, Adamkovic A, Liu Q, Harler MB, Hahn C, Singh A. Reduced risk of cytomegalovirus infection in solid organ transplant recipients treated with sirolimus: a pooled analysis of clinical trials. *Transplant Proc* 2008; **40**: 1407-1410 [PMID: 18589118 DOI: 10.1016/j.transproceed.2008.03.084]

157 **Hill JA**, Hummel M, Starling RC, Kobashigawa JA, Perrone SV, Arizón JM, Simonsen S, Abeywickrama KH, Bara C. A lower incidence of cytomegalovirus infection in de novo heart transplant recipients randomized to everolimus. *Transplantation* 2007; **84**: 1436-1442 [PMID: 18091519 DOI: 10.1097/01.tp.0000290686.68910.bd]

158 **Nepomuceno RR**, Balatoni CE, Natkunam Y, Snow AL, Krams SM, Martinez OM. Rapamycin inhibits the interleukin 10 signal transduction pathway and the growth of Epstein Barr virus B-cell lymphomas. *Cancer Res* 2003; **63**: 4472-4480 [PMID: 12907620]

159 **Benza RL**, Zoghbi GJ, Tallaj J, Brown R, Kirklin JK, Hubbard M, Rayburn B, Foley B, McGiffin DC, Pinderski LJ, Misra V, Bourge RC. Palliation of allograft vasculopathy with transluminal angioplasty: a decade of experience. *J Am Coll Cardiol* 2004; **43**: 1973-1981 [PMID: 15172400 DOI: 10.1016/j.jacc.2004.02.045]

160 **Simpson L**, Lee EK, Hott BJ, Vega DJ, Book WM. Long-term results of angioplasty vs stenting in cardiac transplant recipients with allograft vasculopathy. *J Heart Lung Transplant* 2005; **24**: 1211-1217 [PMID: 16143235 DOI: 10.1016/j.healun.2004.10.005]

161 **Jonas M**, Fang JC, Wang JC, Giri S, Elian D, Har-Zahav Y, Ly H, Seifert PA, Popma JJ, Rogers C. In-stent restenosis and remote coronary lesion progression are coupled in cardiac transplant vasculopathy but not in native coronary artery disease. *J Am Coll Cardiol* 2006; **48**: 453-461 [PMID: 16875968 DOI: 10.1016/j.jacc.2006.01.081]

162 **Halle AA**, DiSciascio G, Massin EK, Wilson RF, Johnson MR, Sullivan HJ, Bourge RC, Kleiman NS, Miller LW, Aversano TR. Coronary angioplasty, atherectomy and bypass surgery in cardiac transplant recipients. *J Am Coll Cardiol* 1995; **26**: 120-128 [PMID: 7797740]

163 **Schnetzler B**, Drobinski G, Dorent R, Camproux AC, Ghossoub J, Thomas D, Gandjbakhch I. The role of percutaneous transluminal coronary angioplasty in heart transplant recipients. *J Heart Lung Transplant* 2000; **19**: 557-565 [PMID: 10867336]

164 **Doshi AA**, Rogers J, Kern MJ, Hauptman PJ. Effectiveness of percutaneous coronary intervention in cardiac allograft vasculopathy. *Am J Cardiol* 2004; **93**: 90-92 [PMID: 14697475]

165 **Fernández-Yáñez J**, Palomo J, Elízaga J, Moreno J, Sánchez A, Almendral J. Results of percutaneous revascularization in cardiac allograft vascular disease. *Transplant Proc* 2003; **35**: 1996-1998 [PMID: 12962874]

166 **Bader FM**, Kfoury AG, Gilbert EM, Barry WH, Humayun N, Hagan ME, Thomas H, Renlund D. Percutaneous coronary interventions with stents in cardiac transplant recipients. *J Heart Lung Transplant* 2006; **25**: 298-301 [PMID: 16507423 DOI: 10.1016/j.healun.2005.09.016]

167 **Musci M**, Loebe M, Wellnhofer E, Meyer R, Pasic M, Hummel M, Bocksch W, Grauhan O, Weng Y, Hetzer R. Coronary angioplasty, bypass surgery, and retransplantation in cardiac transplant patients with graft coronary disease. *Thorac Cardiovasc Surg* 1998; **46**: 268-274 [PMID: 9885117 DOI: 10.1055/s-2007-1010237]

168 **Patel VS**, Radovancevic B, Springer W, Frazier OH, Massin E, Benrey J, Kadipasaoglu K, Cooley DA. Revascularization procedures in patients with transplant coronary artery disease. *Eur J Cardiothorac Surg* 1997; **11**: 895-901 [PMID: 9196306]

169 **Topkara VK**, Dang NC, John R, Cheema FH, Barbato R, Cavallo M, Liu JF, Liang LM, Liberman EA, Argenziano M, Oz MC, Naka Y. A decade experience of cardiac retransplantation in adult recipients. *J Heart Lung Transplant* 2005; **24**: 1745-1750 [PMID: 16297775 DOI: 10.1016/j.healun.2005.02.015]

170 **Srivastava R**, Keck BM, Bennett LE, Hosenpud JD. The results of cardiac retransplantation: an analysis of the Joint International Society for Heart and Lung Transplantation/ United Network for Organ Sharing Thoracic Registry. *Transplantation* 2000; **70**: 606-612 [PMID: 10972218]

P- Reviewer: Izawa KP, Petix NR, Said SAM **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.294

World J Transplant 2014 December 24; 4(4): 294-298
ISSN 2220-3230 (online)

MINIREVIEWS

Role of liver transplantation in the management of hepatoblastoma in the pediatric population

Saira Khaderi, Jacfranz Guiteau, Ronald T Cotton, Christine O'Mahony, Abbas Rana, John A Goss

Saira Khaderi, Jacfranz Guiteau, Ronald T Cotton, Christine O'Mahony, Abbas Rana, John A Goss, Division of Abdominal Transplantation, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX 77030, United States

Author contributions: Khaderi S and Guiteau J wrote the manuscript; Cotton RT and Rana A performed the statistical analysis and assisting in writing the manuscript; O'Mahony C and Goss JA provided expertise regarding pediatric transplantation and assisted in writing the manuscript.

Correspondence to: Saira Khaderi, MD, MPH, Assistant Professor of Surgery, Division of Abdominal Transplantation, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, 6620 Main Street, Suite 1425, Houston, TX 77030, United States. khaderi@bcm.edu

Telephone: +1-832-3551400 Fax: +1-713-6102479
Received: August 12, 2014 Revised: October 21, 2014
Accepted: October 28, 2014
Published online: December 24, 2014

Abstract

Hepatoblastoma (HB) is the most common primary liver tumor in children and accounts for two-thirds of all malignant liver neoplasms in the pediatric population. For patients with advanced HB (unresectable or unresponsive to chemotherapy), combined treatment with chemotherapy and liver transplantation is an excellent option. The etiology of HB is mostly obscure because of its extreme rarity although some inherited syndromes and very low birth weight have been associated with it. The prognosis for children with HB has significantly improved in the past three decades thanks to advancements in chemotherapy, surgical resection and postoperative care. In 2002 a surgical staging system called pretreatment extent of disease (PRETEXT) was designed to allow a universal, multidisciplinary approach to patients with HB. Between one-third to two-thirds of patients initially present with unresectable tumors or distant metastases, but up to 85% of these tumors become operable after neoadjuvant chemotherapy. Patients with PRETEXT categories 1, 2, and some 3 are referred for neoadjuvant chemotherapy followed by surgical resection with the goal of complete tumor removal. Classic treatments regimens include a combination of cisplatin, fluorouracil, and vincristine or cisplatin and doxorubicin. Liver transplantation is the only treatment option for unresectable HB. In 2010 the pediatric end-stage liver disease, a pediatric-specific scoring system that determines a patient's ranking on the liver transplant list, began to award additional "exception" points for patients with HB. We analyzed the Standard Transplant Analysis and Research dataset to assess the impact of changes in exception point criteria for HB on outcomes after liver transplantation at Texas Children's Hospital in Houston, Texas. We found that patients who were listed for transplantation with current HB exception criteria experienced a shorter waitlist time but survival was similar between the two eras.

Key words: Liver transplant; Hepatoblastoma; Pediatric; Chemotherapy; Cancer

Core tip: Hepatoblastoma (HB) is the most common primary liver tumor in children. Between one-third to two-thirds of patients present with unresectable tumors or distant metastases, but up to 85% of these tumors become operable after neoadjuvant chemotherapy. Liver transplantation is the only treatment option for unresectable HB. In 2010 the pediatric end-stage liver disease scoring system began to award additional "exception" points for patients with HB. We analyzed the Standard Transplant Analysis and Research dataset and found that patients who were listed for transplantation with current HB exception criteria experienced a shorter waitlist time but survival was similar between the two eras.

Khaderi S, Guiteau J, Cotton RT, O'Mahony C, Rana A, Goss JA. Role of liver transplantation in the management of hepatoblastoma in the pediatric population. *World J Transplant* 2014; 4(4): 294-298 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/

i4/294.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.294

INTRODUCTION

Hepatoblastoma (HB) is the most common primary liver tumor in children and accounts for two-thirds of all malignant liver neoplasms in the pediatric population[1]. Standard treatment of HB includes neoadjuvant chemotherapy and surgical resection followed by adjuvant chemotherapy. For patients with advanced HB (unresectable or unresponsive to chemotherapy), combined treatment with chemotherapy and liver transplantation is an excellent option[2]. This article briefly reviews the epidemiology and treatment of HB in the pediatric population with an emphasis on the role of orthotopic liver transplantation (OLT).

EPIDEMIOLOGY

The etiology of HB is mostly obscure because of its extreme rarity. The rate of HB in the United States Surveillance, Epidemiology, and End Results (SEER) from 2002-2008 was 10.5 cases per million in children less than one year of age and 5.2 cases per million in children 1 through 4 years of age[3]. It is assumed the tumor originates *in utero* for two reasons. Histologically HB cells resemble embryonal liver cells and the incidence is highest at birth suggesting the process is initiated during gestation[4].

Some inherited syndromes have been associated with HB. Incidence of HB among children with Familial Adenomatous Polyposis was found to be 847 times the incidence in the SEER population[5]. Those with the Beckwith-Wiedemann overgrowth syndrome had an incidence 2280 times that of the United States population of the same age[6]. Although these inherited conditions raise the risk of HB, they account for only a few cases overall.

Very low birth weight (< 1500 g) increases the risk of HB in children 20-fold and moderate low birth weight (1500-2500 g) doubles the risk[7]. The association of low birth weight and HB has two explanations. HB may be initiated or promoted by iatrogenic hazards in the neonatal intensive care units[8] in combination with decreased antioxidant defense mechanisms of pre-term infants[9]. Alternatively, HB and very low birth weight may share a common mechanism and the increase in survival of these patients has made the association more apparent.

TREATMENT

The prognosis for children with HB has significantly improved in the past three decades thanks to advancements in chemotherapy, surgical resection and postoperative care[10]. Prior to the discovery of effective chemotherapy, cure was limited to completely resectable tumors and overall survival was dismal[10].

Early experiences with successful cure were sporadic at best and were limited to lesions that could be completely resected. In 2002 a staging system called the PRETreatment EXTent of disease (PRETEXT) was designed to allow a universal, multidisciplinary approach to patients with HB (Figure 1). The main aim of PRETEXT grouping was to identify patients in whom complete tumor resection was possible with a partial hepatectomy. Physicians placed patients in one of four PRETEXT categories based on the extent of their tumor on imaging. The liver is divided into four sectors in the PRETEXT system - anterior and posterior on the right and a medial and lateral sector on the left. Four groups were identified based on tumor extension: PRETEXT Ⅰ, tumor only in one sector; PRETEXT Ⅱ, tumor involves two sectors; PRETEXT Ⅲ, tumor involves three sectors or two non-adjoining sectors; and PRETEXT 4, tumor involves all four sectors[11]. These categories are further characterized by describing extrahepatic spread: V for involvement of the hepatic veins and/or inferior vena cava, P for involvement of the portal vein, E for extrahepatic tumor extension, and M for distant metastases[11].

Between one-third to two-thirds of patients initially present with unresectable tumors or distant metastases, but up to 85% of these tumors become operable after neoadjuvant chemotherapy[12]. Preoperative chemotherapy has many advantages. It is responsible for making tumors smaller and more demarcated from the surrounding liver. Most surgeons agree that operating on tumors that shrink with chemotherapy is easier because the tumor is more defined and less prone to bleeding. It also exposes metastases (both visible and micrometastases) to chemotherapy earlier. In one trial, up to 52% of patients with initial lung metastases achieved complete remission with chemotherapy alone[13]. Classic treatment regimens include a combination of cisplatin, fluorouracil, and vincristine or cisplatin and doxorubicin. Although an effective agent, patients treated with doxorubicin can have a higher incidence of treatment complications and toxic death-especially from heart failure[14]. More recent studies have shown the effectiveness of single-agent cisplatin treatment in both standard and high-risk patients with HB[15,16] decreasing the likelihood of chemotherapy-induced toxicity.

Patients with PRETEXT categories 1, 2, and some 3 are referred for neoadjuvant chemotherapy followed by surgical resection with the goal of complete tumor removal. Current chemotherapy at our institution consists of cisplatin, 5-fluorouracil, and vincristine or vincristine and doxorubicin. Patients will undergo four rounds of chemotherapy prior to resection and two rounds after resection. Disease-free survival following partial liver resection under these circumstances has been reported to be greater than 70%[2]. It has been argued that tumors with favorable prognostic factors, such as pure fetal histology and low mitotic rate, may not require toxic chemotherapy and should be treated with surgical resection only[17]. However, the treatment regimen at our institution closely follows the precedent set forth in European studies which emphasize the use of neoadjuvant chemotherapy in all HB patients because of the high frequency of HB chemosensitivity[11,18].

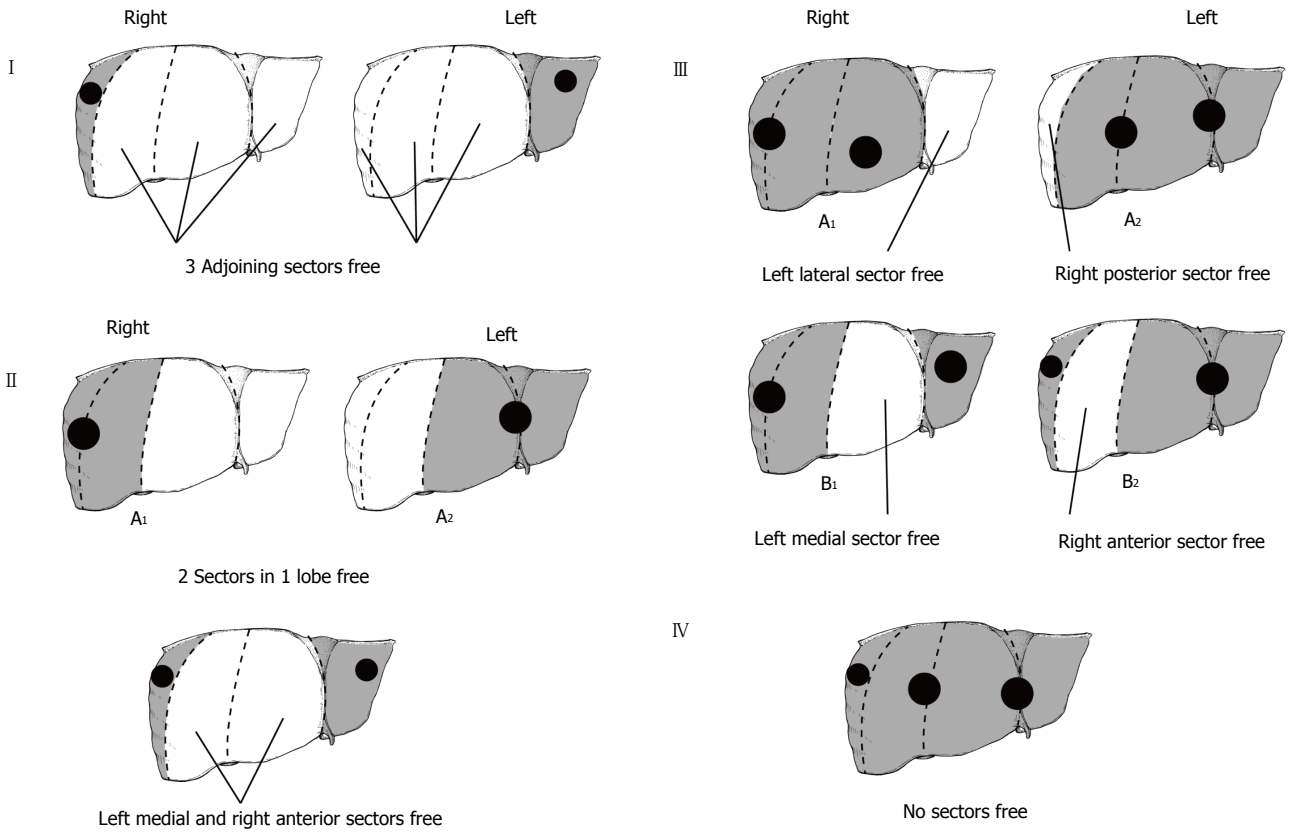

Figure 1 Pretreatment (pretreatment extent of disease) grouping system. Printed with permission from Baylor College of Medicine.

Liver transplant

Liver transplantation is the only treatment option for unresectable HB. Transplant should be considered in the following cases: multifocal disease (PRETEXT Ⅳ), PRETEXT Ⅲ with the tumor in close proximity to major vessels, and tumor extension into major vessels. Patients that fall into these categories at our institution are listed for OLT immediately after the diagnosis of HB is confirmed and undergo chemotherapy while they await transplantation. Overall patient survival at 6 years has been reported to be over 80% making OLT the preferred treatment modality in this group[19]. Patients with intrahepatic recurrence or residual tumor after resection are rarely candidates for transplant because of poor outcomes[19].

There are few contraindications to OLT for unresectable HB. Patients with persistent pulmonary metastases despite neoadjuvant therapy and those with viable extrahepatic tumor not amenable to resection are not candidates for OLT. Patients that present with lung metastases are candidates for OLT if their lung metastases resolve with chemotherapy or with resection. Those with extrahepatic disease that remains viable after full chemotherapy and not amenable to surgical resection represent the only absolute contraindication to OLT in patients with HB[19].

Organ allocation rules for children with HB have changed over the past decade. The pediatric end-stage liver disease (PELD) is a pediatric-specific scoring system that was adopted in 2002 to help determine a patient's ranking on the liver transplant list. The effect of the system has been to decrease the rate of death and removal from the transplant list and increase the percentage of children who receive a deceased donor organ. The score is based on total bilirubin, coagulopathy, serum albumin, age < 1 year and growth failure, but additional "exception" points may be awarded for risk factors not represented by the PELD equation. For example, patients with unresectable HB are listed with a PELD score of 30 for 30 d and are increased to status 1B if they have not been transplanted.

We analyzed the Standard Transplant Analysis and Research dataset to assess the impact of changes in exception point criteria for HB on outcomes after liver transplantation at Texas Children's Hospital in Houston, Texas. Patients who underwent orthotopic liver transplant in our center from 1987-2014 with recipient diagnosis of either HB, cirrhosis post-resection of HB, or for whom a MELD exception was granted for non-metastatic HB were selected for analysis. Patients were grouped based on date of initial listing for transplantation. The 1987-2009 era preceded the current policy for HB exception while the 2010-2014 era followed its implementation. Differences in age at listing, recipient gender, waitlist time, and post-transplant patient survival between the two groups were calculated. To examine the difference between the number of patients listed in each era, a one-sample binomial test was used. Independent samples Mann-Whitney U testing was performed to compute differences in means between the two groups, while Pearson's Chi-Squared was employed for

Table 1 Pediatric patients transplanted for hepatoblastoma at our center before (Era 1) and after (Era 2) implementation of pediatric end-stage liver disease exception points for hepatoblastoma

	Era 1 (1987-2009)	Era 2 (2010-2014)	Significance (*P*-value)
Total patients listed for transplantation	7	14	0.189
Gender			0.557
Male	57.10%	35.70%	
Female	42.90%	64.30%	
Age at listing (yr)	5.4	2	0.094
Age at transplant (yr)	5.6	2.1	0.110
Waitlist time (d)	45.6	25.4	0.025

differences in frequencies. Actuarial survival was assessed *via* the Kaplan-Meier Method. All statistical computations were performed with SPSS version 22 (IBM Armonk, New York).

Descriptive statistics for patients transplanted in each era are displayed in Table 1. A statistically similar number of patients were transplanted in each group (7 *vs* 14, $P = 0.189$). Similarly, there was no significant difference in gender, age at listing, and age at transplantation between the two eras. Patients listed for transplantation with the current HB exception criteria experienced a shorter waitlist time (45.5 d *vs* 25.4 d, $P = 0.025$).

Figure 2 demonstrates patient survival in our center before and after implementation of the revised HB exception policy. From 1987-2009, 30-d, one-year, and five-year survival following liver transplant in our center was 98.6%, 87.0%, and 77.4%, respectively. In comparison, 30-d, one-year survival following transplantation from 2010-2014 was 97.1% and 90.5%. Statistically, patient survival is similar between the two eras ($P = 0.7$).

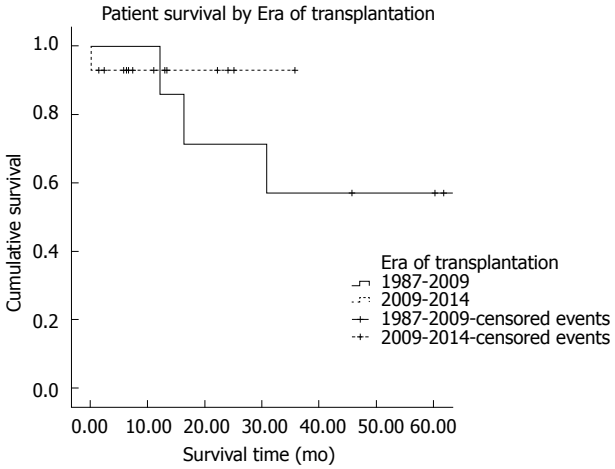

Figure 2 Patient survival by Era of transplantation.

CONCLUSION

In conclusion, standard treatment with neoadjuvant chemotherapy, surgical resection followed by adjuvant chemotherapy is a good option for most pediatric and adolescent patients with HB. For those with tumors that are unresectable or unresponsive to chemotherapy, combined treatment with chemotherapy and liver transplantation is an excellent option. PELD exception points for HB have decreased the wait time for most patients listed for transplant but it is too soon to determine if this translates into increased survival for the group.

ACKNOWLEDGMENTS

We would like to thank Scott Holmes, board certified medical illustrator with Baylor College of Medicine, for his help with the illustration.

REFERENCES

1 **Ries LAG**, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. National Cancer Institute, SEER Program. Bethesda, MD, NIH. Pub. 1999: 99-4649 Available from: URL: http://seer.cancer.gov/archive/publications/childhood/

2 **Ismail H**, Broniszczak D, Kaliciński P, Dembowska-Bagińska B, Perek D, Teisseyre J, Kluge P, Kościesza A, Lembas A, Markiewicz M. Changing treatment and outcome of children with hepatoblastoma: analysis of a single center experience over the last 20 years. *J Pediatr Surg* 2012; **47**: 1331-1339 [PMID: 22813792 DOI: 10.1016/j.jpedsurg.2011.11.073]

3 **Howlader N,** Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). National Cancer Institute. Based on November 2011 SEER data submission, posted to the SEER web site, April 2012 [Updated August 20, 2012]. Available from: URL: http://seer.cancer.gov/archive/csr/1975_2009_pops09/

4 **Litten JB**, Tomlinson GE. Liver tumors in children. *Oncologist* 2008; **13**: 812-820 [PMID: 18644850 DOI: 10.1634/theoncologist.2008-0011]

5 **Giardiello FM**, Offerhaus GJ, Krush AJ, Booker SV, Tersmette AC, Mulder JW, Kelley CN, Hamilton SR. Risk of hepatoblastoma in familial adenomatous polyposis. *J Pediatr* 1991; **119**: 766-768 [PMID: 1658283]

6 **DeBaun MR**, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *J Pediatr* 1998; **132**: 398-400 [PMID: 9544889 DOI: 10.1016/S0022-3476(98)70008-3]

7 **Spector LG**, Birch J. The epidemiology of hepatoblastoma. *Pediatr Blood Cancer* 2012; **59**: 776-779 [PMID: 22692949 DOI: 10.1002/pbc.24215]

8 **Lai TT**, Bearer CF. Iatrogenic environmental hazards in the neonatal intensive care unit. *Clin Perinatol* 2008; **35**: 163-181, ix [PMID: 18280881 DOI: 10.1016/j.clp.2007.11.003]

9 **Weinberger B**, Laskin DL, Heck DE, Laskin JD. Oxygen toxicity in premature infants. *Toxicol Appl Pharmacol* 2002; **181**: 60-67 [PMID: 12030843 DOI: 10.1006/taap.2002.9387]

10 **Davies JQ**, de la Hall PM, Kaschula RO, Sinclair-Smith CC, Hartley P, Rode H, Millar AJ. Hepatoblastoma--evolution of management and outcome and significance of histology of the resected tumor. A 31-year experience with 40 cases. *J Pediatr Surg* 2004; **39**: 1321-1327 [PMID: 15359384 DOI: 10.1016/j.jpedsurg.2004.05.020]

11 **Brown J**, Perilongo G, Shafford E, Keeling J, Pritchard J, Brock P, Dicks-Mireaux C, Phillips A, Vos A, Plaschkes J. Pretreatment prognostic factors for children with hepatoblastoma-- results

from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. *Eur J Cancer* 2000; **36**: 1418-1425 [PMID: 10899656 DOI: 10.1016/S0959-8049(00)00074-5]

12 **Pham TH**, Iqbal CW, Grams JM, Zarroug AE, Wall JC, Ishitani MB, Nagorney DM, Moir C. Outcomes of primary liver cancer in children: an appraisal of experience. *J Pediatr Surg* 2007; **42**: 834-839 [PMID: 17502194 DOI: 10.1016/j.jpedsurg.2006.12.065]

13 **Zsíros J**, Maibach R, Shafford E, Brugieres L, Brock P, Czauderna P, Roebuck D, Childs M, Zimmermann A, Laithier V, Otte JB, de Camargo B, MacKinlay G, Scopinaro M, Aronson D, Plaschkes J, Perilongo G. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. *J Clin Oncol* 2010; **28**: 2584-2590 [PMID: 20406943 DOI: 10.1200/JCO.2009.22.4857]

14 **Ortega JA**, Douglass EC, Feusner JH, Reynolds M, Quinn JJ, Finegold MJ, Haas JE, King DR, Liu-Mares W, Sensel MG, Krailo MD. Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *J Clin Oncol* 2000; **18**: 2665-2675 [PMID: 10894865]

15 **Perilongo G**, Maibach R, Shafford E, Brugieres L, Brock P, Morland B, de Camargo B, Zsiros J, Roebuck D, Zimmermann A, Aronson D, Childs M, Widing E, Laithier V, Plaschkes J, Pritchard J, Scopinaro M, MacKinlay G, Czauderna P. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. *N Engl J Med* 2009; **361**: 1662-1670 [PMID: 19846851 DOI: 10.1056/NEJMoa0810613]

16 **Zhang YT**, Feng LH, Zhong XD, Wang LZ, Chang J. Single-agent cisplatin treatment of children with high-risk hepatoblastoma. *J Pediatr Hematol Oncol* 2014; **36**: 271-275 [PMID: 24309602 DOI: 10.1097/MPH.0000000000000072]

17 **Finegold MJ**. Chemotherapy for suspected hepatoblastoma without efforts at surgical resection is a bad practice. *Med Pediatr Oncol* 2002; **39**: 484-486 [PMID: 12228904]

18 **Carceller A**, Blanchard H, Champagne J, St-Vil D, Bensoussan AL. Surgical resection and chemotherapy improve survival rate for patients with hepatoblastoma. *J Pediatr Surg* 2001; **36**: 755-759 [PMID: 11329582 DOI: 10.1053/jpsu.2001.22953]

19 **Otte JB**, Pritchard J, Aronson DC, Brown J, Czauderna P, Maibach R, Perilongo G, Shafford E, Plaschkes J. Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. *Pediatr Blood Cancer* 2004; **42**: 74-83 [PMID: 14752798 DOI: 10.1002/pbc.10376]

P- Reviewer: Hori T, Qin JM **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v4.i4.299

World J Transplant 2014 December 24; 4(4): 299-305
ISSN 2220-3230 (online)

RESEARCH REPORT

1400W reduces ischemia reperfusion injury in an *ex-vivo* porcine model of the donation after circulatory death kidney donor

Sarah A Hosgood, Phillip J Yates, Michael L Nicholson

Sarah A Hosgood, Phillip J Yates, Michael L Nicholson, Department of Infection, Immunity and Inflammation, Transplant Group, University of Leicester, LE5 4PW Leicester, United Kingdom
Sarah A Hosgood, Michael L Nicholson, Leicester General Hospital, University Hospitals of Leicester, LE5 4PW Leicester, United Kingdom
Author contributions: Hosgood SA, Yates PJ and Nicholson ML designed the study; Hosgood SA and Yates PJ carried out the experiments; Hosgood SA and Yates PJ analysed the data; Hosgood SA and Yates PJ wrote the manuscript; Nicholson ML revised the manuscript and approved the final version.
Correspondence to: Dr. Sarah A Hosgood, Department of Infection, Immunity and Inflammation, Transplant Group. University of Leicester, Gwendolen Road, LE5 4PW Leicester, United Kingdom. sarahhosgood@hotmail.com
Telephone: +44-116-2584658 Fax: +44-116-2490064
Received: May 28, 2014 Revised: July 8, 2014
Accepted: October 31, 2014
Published online: December 24, 2014

Abstract

AIM: To investigate the effects of 1400W-a selective inducible nitric oxide synthase (iNOS) inhibitor in a model of donation after circulatory death (DCD) kidneys.

METHODS: Porcine kidneys were retrieved after 25 min warm ischemia. They were then stored on ice for 18 h before being reperfused *ex vivo* with oxygenated autologous blood on an isolated organ perfusion system. The selective iNOS inhibitor 1400W (10 mg/kg) was administered before reperfusion (n = 6) vs control group (n = 7). Creatinine (1000 μmol/L) was added to the system, renal and tubular cell function and the level of ischemia reperfusion injury were assessed over 3 h of reperfusion using plasma, urine and tissue samples.

RESULTS: Kidneys treated with 1400W had a higher level of creatinine clearance (CrCl) [area under the curve (AUC) CrCl: 2.37 ± 0.97 mL/min per 100 g *vs* 0.96 ± 0.32 mL/min per 100 g, P = 0.004] and urine output [Total: 320 ± 96 mL *vs* 156 ± 82 mL, P = 0.008]. There was no significant difference in levels of fractional excretion of sodium (AUC, Fr ex Na+: Control, 186.3% ± 81.7%.h *vs* 1400W, 153.4% ± 12.1%.h, P = 0.429). Levels of total protein creatinine ratio were significantly lower in the 1400W group after 1 h of reperfusion (1h Pr/Cr: 1400W 9068 ± 6910 mg/L/mmol/L *vs* Control 21586 ± 5464 mg/L/mmol/L, P = 0.026). Levels of 8-isoprostane were significantly lower in the 1400W group [8-iso/creatinine ratio: Control 239 ± 136 pg/L/mmol/L *vs* 1400W 139 ± 47 pg/L/mmol/L, P = 0.041].

CONCLUSION: This study demonstrated that 1400W reduced ischaemia reperfusion injury in this porcine kidney model of DCD donor. Kidneys had improved renal function and reduced oxidative stress.

Key words: Kidney; Transplantation; Ischemia; Donation after circulatory death; Inducible nitric oxide

Core tip: It is important to examine the effects of therapies that can reduce ischemia reperfusion injury particularly in donation after circulatory death donor kidneys. The biological role of inducible nitric oxide synthase (iNOS) is somewhat controversial. This study uses a large animal *ex vivo* model to assess the effects of 1400W, an iNOS inhibitor. The model provides a functional assessment of each kidney, providing a close simulation to clinical transplantation. The study found that 1400W improved early renal function and reduced oxidative stress.

Hosgood SA, Yates PJ, Nicholson ML. 1400W reduces ischemia reperfusion injury in an *ex-vivo* porcine model of the donation af-

ter circulatory death kidney donor. *World J Transplant* 2014; 4(4): 299-305 Available from: URL: http://www.wjgnet.com/2220-3230/full/v4/i4/299.htm DOI: http://dx.doi.org/10.5500/wjt.v4.i4.299

INTRODUCTION

The pathophysiology of ischemia reperfusion (I/R) injury is a complex action involving many intercellular and molecular processes. It is characterised by the up-regulation of inflammatory processes, activation of endothelial cells, generation and release of reactive oxygen species (ROS), migration of inflammatory leucocytes, cellular oedema, cell membrane damage, apoptosis and necrosis[1-3]. Severe I/R injury causes significant disruption to the microcirculation and is associated with high rates of delayed graft function, primary non function and acute rejection after kidney transplantation[4,5]. This is of particular significance in kidneys from marginal or donation after circulatory death (DCD) donors that sustain both a period of warm and cold ischemic injury prior to transplantation. It is therefore important to investigate therapies to alleviate injury to improve the outcome of DCD transplantation.

Nitric oxide (NO) is an important mediator of normal biological processes. It is a free radical produced by all mammalian cells from the synthesis of L-arginine and oxygen, by the enzyme NO synthase (NOS)[6]. It is capable of regulating local blood flow, scavenging free radicals and inhibiting platelet and leukocyte activation[6,7]. There are three different isoforms of NO; neuronal, endothelial (eNOS) and inducible (iNOS)[8].

The biological role of iNOS is somewhat controversial[9]. iNOS is known to be up-regulated by certain disease states such as inflammation, ischemia and during reperfusion after transplantation[10]. Although NO is generally regarded as cytoprotective, excess NO derived from iNOS during these states can contribute to the injury process[11,12]. NO can augment I/R injury by reacting with superoxide generated by excess ROS to form peroxynitrite, causing severe oxidative damage ands cellular injury[10]. It also has a role in the mediation of neutrophil activation, although the processes are not fully understood[9].

Evidence suggests that the effects and role of iNOS are influenced by the microenvironment and bioavailability of the other forms of NO[9] and iNOS inhibitors have been shown to reduce I/R injury[11-13]. However, these have principally been studied in small animal models after a sole period of warm ischemic injury and reperfusion. The aim of this study was to assess the effects of 1400W a selective iNOS inhibitor on I/R injury in a model of the DCD donor using porcine kidneys.

MATERIALS AND METHODS

Under Home Office regulations (Scientific Act 1986, Schedule 1 procedure) female large white pigs (60-70 kg) were killed by electrocution followed by exsanguination. Approximately 2 L of blood was collected into a sterile receptacle containing 25000 units of heparin (Multiparin®; CP Pharmaceuticals, Wrexham, United Kingdom). The blood was then transferred into CPDA-1 blood bags (Baxter Healthcare, Thetford, United Kingdom) for storage at 4 ℃.

The kidneys were retrieved after 25 min of *in situ* warm ischemia and flushed with 500 mL of hyperosmolar citrate (Soltran; Baxter Healthcare) at 4 ℃ infused at a hydrostatic pressure of 100 cm H_2O. Kidneys were then placed in ice for a period of 18 h.

Reperfusion

After the preservation period kidneys were prepared for *ex vivo* reperfusion. The renal artery, vein and ureter were cannulated and kidneys flushed with Ringer's at 4 ℃ (Baxter Healthcare, United Kingdom) to remove the preservation solution before being placed immediately on the isolated organ preservation system. They were then reperfused with oxygenated autologous blood for 3 h at a temperature of 38 ℃ and set mean arterial pressure of 85 mmHg. The system has been previously described[14]. Creatinine (Sigma-Aldrich, Steinheim, Germany) was added to the perfusate to achieve an initial circulating concentration of 1000 μmol/L.

1400W (Sigma-Aldrich) -a highly selective iNOS inhibitor was prepared before use and stored at -20 ℃ until required.

Experimental design

Kidneys were divided into two groups; Control (n = 7) and 1400W at a dose of 10 mg/kg per kidney weight (n = 6). 1400W was added as a bolus to the arterial arm of the circuit 15 min before reperfusion of the kidney.

Parameters

Renal blood flow (RBF) and mean arterial pressure (MAP) were recorded continuously and intrarenal resistance (IRR) calculated (MAP/RBF). Urine output was also measured during reperfusion.

Biochemical analysis of serum and urine samples was carried out at hourly intervals. The following parameters were calculated:

Creatinine clearance (urinary creatinine × urinary volume/plasma creatinine), fractional excretion of sodium [(urinary sodium × urine volume) / (glomerular filtration rate × plasma sodium) × 100)] and the urinary total protein (mg/L) to creatinine (mmol/L) ratio.

Blood gas analysis was used to record P_aO_2, P_vO_2 and acid-base homeostasis. Oxygen consumption [(P_aO_2-venous P_vO_2) × flow rate/weight] was calculated

8-Isoprostane

Urine samples were taken at 1 and 3 h of reperfusion and stored at -80 ℃ until analyses. Levels of urine 8-isoprostane were determined by ELISA (Cayman Chemical Co, MI, United States). Urine samples were centrifuged at 10000 *g* for 2 min and the supernatant taken for analysis. Samples were diluted 10 fold prior to analysis. The sample and

standards were added in duplicate to the ELISA plate together with an 8-isoprostane-acetylcholinesterase (AChE) conjugate and incubated for 18 h at 4 ℃. During incubation 8-isoprostane present in the sample competed with the 8-isoprostane AChE conjugate for the 8-isoprostane rabbit antiserum binding sites on the pre-coated plate. The plate was then washed and developed by the addition of the substrate to AChE. The plate was read at 405 nm after colour development for 90 min.

Total nitric oxide

Plasma samples were taken pre and 3 h after reperfusion and urine samples taken at 1 and 3 h of reperfusion and stored at -80 ℃ until analyses. Urine levels of NO were quantified using the total NO test kit (Assay Designs, MI, United States) according to the manufacturers' instructions. This assay is based on the conversion of NO to nitrate and the subsequent conversion of nitrate to nitrite by the enzyme nitrate reductase. Nitrite is then detected colorimetrically at 540 nm as an azodye product of the Griess reaction. Briefly, plasma and urine sample were centrifuged at 10000 *g* and the supernatant withdrawn. Fifty μL of each sample were added in duplicate to a micro titre test plate. Twenty-five μL NADH and 25 μL nitrate reductase were added to each well and incubated at 37 ℃ for 30 min. One hundred μL Griess reagents (sulphanilamide and N-(l-Naphthyl) ethylenediamine in 2M HCl) were then added and incubated at room temperature for 10 min. Optical density was then read at 540 nm using a spectrophotometer and the concentration calculated using standards.

Histology

Wedge biopsies were taken after 25 min warm ischemia and after 3 h of reperfusion, fixed in 10% formal saline, dehydrated and embedded in paraffin wax. Sections of 4 μm were cut and stained with haematoxylin and eosin for evaluation using light microscopy. Sections were scored over five fields, assessing changes in four morphological variables; Tubular dilation, Tubular debris, vaculolation and interstitial oedema. Samples were scored from 0 to 3 according to the level of damage; 0 representing normal, 1 representing mild, 2 representing moderate and 3 representing severe morphological changes.

Myeloperoxidase activity

Immunohistochemical staining of MPO, a marker mainly for neutrophil granulocytes, was undertaken on post reperfusion paraffin sections using a DAKO ChemMate EnVision™ Detection Kit (DAKO, Glostrup, Denmark). The sections were digested by 40 μg/mL proteinase K for 15 min at 37 ℃ then blocked by peroxidase-blocking reagent. The sections were labelled by an anti-MPO antibody (1:600, DAKO) at 4 ℃ overnight. The antibody binding was revealed by 3'-amino-9-ethylcarbazole. MPO+ cells in the tubular, interstitial and glomeruli were semi-quantitatively scored by counting the number of positive cells in 20 fields at 400 × magnification.

Statistical analysis

Values are presented as mean ± SD. Levels of continuous variables such as RBF were plotted against time and the area under the curve (AUC) for individual perfusion experiments was calculated using Excel® software (Microsoft, Reading, United Kingdom) and Graphpad Prism (GraphPad Software, San Diego California, United States).

Mean AUC values were compared using Mann Whitney *U*-Test (GraphPad InStat version 3.00 for Windows 95, GraphPad Software, San Diego California, United States). Correlations between parameters were made with Spearman's non parametric rank correlation. $P < 0.050$ was taken as statistically significant.

RESULTS

Renal function

There was a significant fall in the level of RBF and an increase in intra-renal resistance in the 1400W group after 10 and 15 min of reperfusion compared to the control kidneys (RBF, $P = 0.002$ and 0.005, respectively; IRR, $P = 0.005$ and 0.014, respectively; Figure 1A and B). RBF then recovered and IRR fell with no significant difference between the groups throughout the rest of the reperfusion period (AUC, RBF: Control 270 ± 86 mL/min/100 g.h *vs* 1400W 274 ± 143 mL/min/100 g.h, $P = 0.999$; IRR: Control 13.4 ± 7.3 mmHg/min.h *vs* 1400W 17.8 ± 8.5 mmHg/min.h, $P = 0.234$). The level of oxygen consumption after reperfusion was higher in the 1400W group after 3 h of reperfusion but this did not reach statistical significance (3 h: Control 28.0 ± 13.9 mL/min/g *vs* 1400W 36.7 ± 22.8 mL/min/g, $P = 0.731$).

Levels of creatinine clearance were significantly higher after 1 and 2 h of reperfusion in the 1400W group compared to the control ($P = 0.026$ and 0.009 respectively; Figure 2A) and the AUC creatinine clearance was significantly higher (AUC, CrCl: 1400W 2.37 ± 0.97 mL/min/100 g.h *vs* Control 0.96 ± 0.32 mL/min/100 g.h, $P = 0.004$). Levels of serum creatinine fell more quickly in the 1400W group but the difference with controls was only marginally significant at the end of reperfusion ($P = 0.073$; Figure 2B).

Tubular function

There was no significant difference in levels of fractional excretion of sodium (AUC, Fr ex Na+: Control 186.3% ± 81.7%.h *vs* 1400W 153.4% ± 12.1%.h, $P = 0.429$), although total urine output was significantly higher in the 1400W group (Total urine output: 1400W 320 ± 96 *vs* Control, 156 ± 83 mL, $P = 0.008$).

Levels of total protein creatinine ratio were significantly lower in the 1400W group after 1 h of reperfusion (1h Pr/Cr: 1400W 9068 ± 6910 mg/L/mmol/L *vs* Control 21586 ± 5464 mg/L/mmol/L, $P = 0.026$). There was no further difference in the levels between the groups after 2 and 3 h of reperfusion ($P = 0.662$ and 0.628, respectively).

Acid base balance

Levels of pH fell significantly in both groups with no

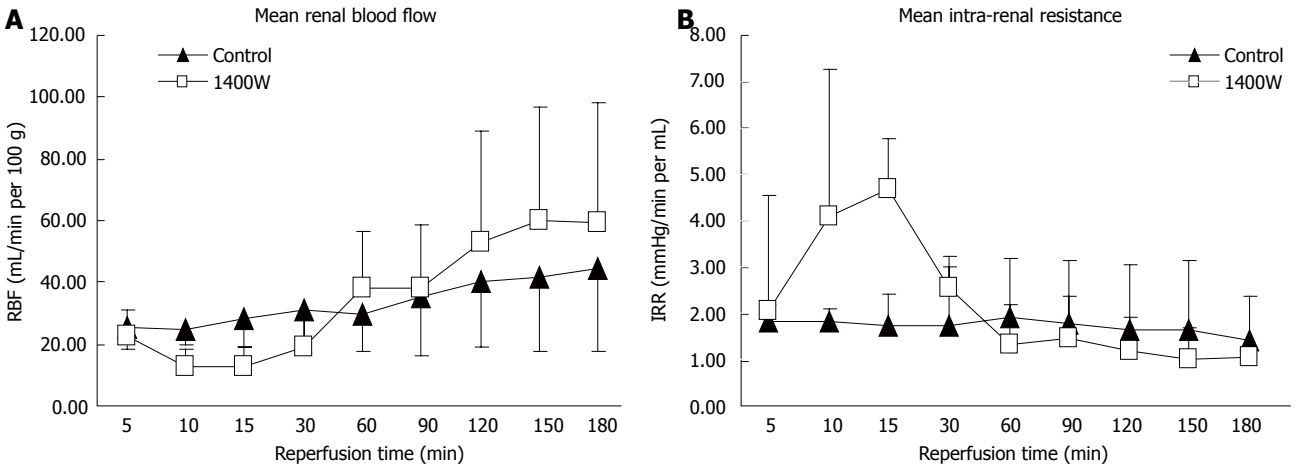

Figure 1 Mean renal blood flow over 3 h of reperfusion in the Control and 1400W groups. Area under the curve (AUC), *P* = 0.999 (A); Mean intrarenal resistance over 3 h of reperfusion in the Control and 1400W groups, AUC, *P* = 0.234 (B). Mann Whitney *U*-test. RBF: Mean renal blood flow.

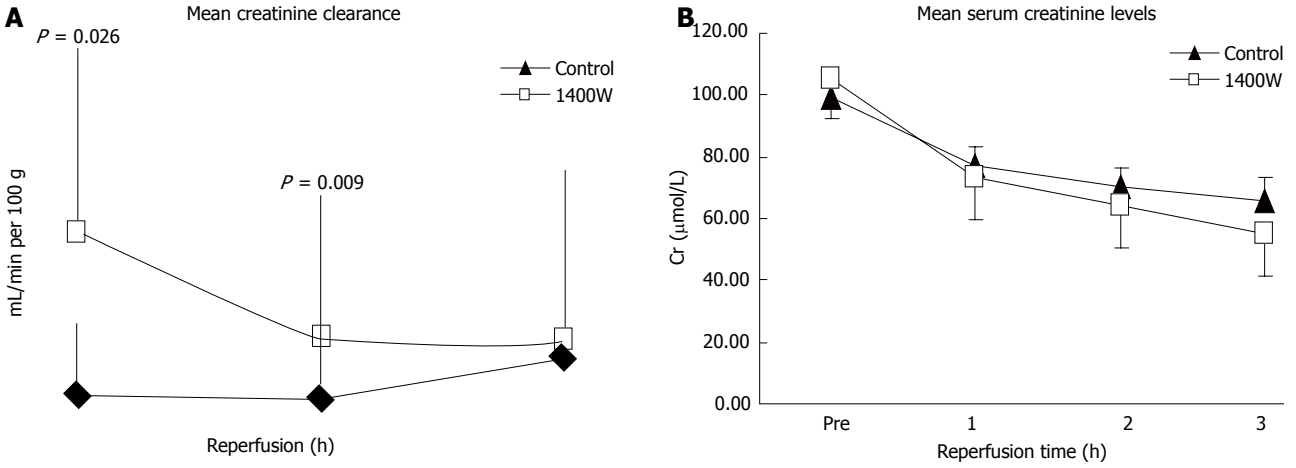

Figure 2 Mean creatinine clearance over 3 h of reperfusion in the Control and 1400W groups. (*P* = 0.026 and 0.009 after 1 and 2 h, respectively) (A); Mean serum creatinine levels over 3 h of reperfusion in the Control and 1400W groups, *P* > 0.050 between groups (B). Mann Whitney *U*-test.

Table 1 Acid base balance, levels of pH, bicarbonate and potassium pre and 3 h after reperfusion

	Control		1400W	
	Pre	3 h	Pre	3 h
pH	7.43 ± 0.03	7.30 ± 0.08	7.47 ± 0.04	7.24 ± 0.04
Bicarbonate (mmol/L)	21.2 ± 1.4	17.3 ± 3.0	23.4 ± 1.6	17.6 ± 2.1
Potassium (mmol/L)	5.5 ± 0.3[a]	10.7 ± 1.3	5.9 ± 0.2	11.9 ± 0.3

[a]*P* < 0.05 between groups. Mann Whitney *U*-test.

significant difference between groups at 3 h (*P* = 0.100; Table 1). There was also no significant difference in levels of bicarbonate or potassium after 3 h (*P* = 0.628 and 0.295, respectively; Table 1). Pre levels of potassium were significantly lower but within normal range in the control group compared to 1400W (*P* = 0.002; Table 1).

Oxidative damage/inflammation

Urinary levels of 8-isoprostane were significantly lower in the 1400W group after 3 h of reperfusion compared to the control group (*P* = 0.041; Figure 3A).

There was no significant difference in the pre or 3 h reperfusion plasma concentrations of total NO (Pre: Control 73.6 ± 43.1 pg/mL, 1400W 79.9 ± 14.5 pg/mL; 3h: Control 48.7 ± 21.7 pg/mL, 1400W 63.9 ± 20.2 pg/mL). Urinary levels of total nitric oxide were significantly higher in the 1400W group after 1 and 3 h of reperfusion (*P* = 0.002 and 0.002, respectively; Figure 3B).

There was a significantly higher amount of MPO positive cells in the control group compared to the 1400W (*P* = 0.002; Figure 3C). Positive cells were largely localised in the interstitium.

Histology

Baseline biopsies showed an increased level of tubular dilatation in the 1400W group compared to the control (*P* = 0.001; Table 2) and a higher level of interstitial oedema in the control group compared to the 1400W (*P* = 0.032; Table 2). After 3 h of reperfusion there was a significant increase in tubular dilatation and vacuolation in the control group (*P* = 0.0003 and 0.033, respectively; Table 2) and

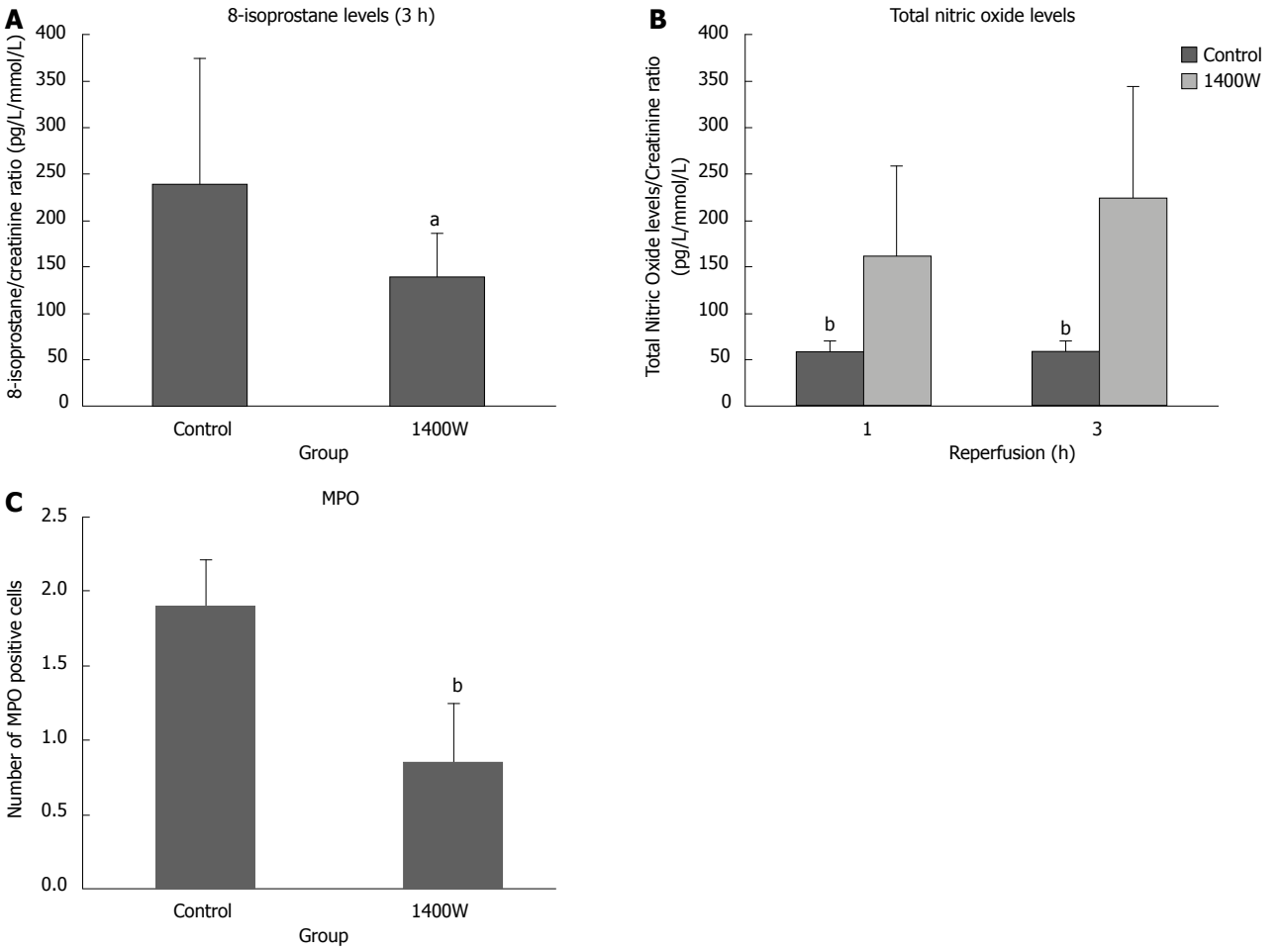

Figure 3 Urinary levels of 8-isoprostane after 3 h of reperfusion in the Control and 1400W groups (^{a}P = 0.041 between groups) (A); Levels of total nitric oxide in the urine after 1 and 3 h of reperfusion Control and 1400W groups (^{b}P = 0.002 and 0.002, respectively) between groups (B); Myeloperoxidase score after 3 h of reperfusion in the Control and 1400W (^{b}P = 0.002) between groups (C). Mann Whitney *U*-test, scored by counting the number of positive cells in 20 fields (× 400). MPO: Myeloperoxidase.

Table 2 Histology score

	Control		1400W	
	Pre	Post	Pre	Post
Tubular dilatation	0.91 ± 0.68	1.60 ± 0.60[a]	2.03 ± 0.80[b]	1.63 ± 0.81
Tubular debris	1.44 ± 0.50	1.14 ± 0.73	1.47 ± 0.50	2.07 ± 0.74[a,b]
Vacuolation	0.52 ± 0.76	1.09 ± 1.091	0.50 ± 0.60	1.00 ± 0.91[a]
Interstitial oedema	1.33 ± 0.48[b]	1.29 ± 0.52	0.93 ± 0.70	1.47 ± 0.82[a]

Pre and post reperfusion biopsies in the control and 1400W groups. Biopsies were scored over 5 fields assessing tubular dilatation, tubular debris, vacuolation and interstitial oedema. $^{a}P \leq 0.05$ between time points, $^{b}P \leq 0.05$ between groups. Mann Whitney *U*-test.

tubular debris, vacuolation and interstitial oedema in the 1400W group (P = 0.003, 0.040 and 0.011, respectively; Table 2). The 1400W group had a significantly higher level of tubular debris after reperfusion compared to the control (P = 0.0001; Table 2).

DISCUSSION

This study demonstrated that the administration of 1400W, a selective iNOS inhibitor, reduced the level I/R injury in porcine kidneys that were subjected to warm and cold ischemic injury. Kidneys had a higher level of creatinine clearance, reduced oxidative stress and neutrophil infiltration during reperfusion compared to untreated kidneys.

NO is generally regarded as cytoprotective: scavenging free radicals, relaxing the endothelium, inhibiting platelet aggregation and reducing neutrophil adherence[6,15].

However, the biological effects of NO derived from iNOS can be either deleterious or beneficial, depending on the disease state[9]. iNOS is known to be upregulated during ischemia and reperfusion and is widely expressed throughout the vasculature, tubule cells and glomeruli in the kidney. It is also expressed on monocytes, macrophages and neutrophils[16].

Warm and cold ischemic injury sustained before transplantation exacerbates the level of I/R injury[4,14]. The anoxic conditions, depletion of adenosine triphosphate (ATP) and accumulation of toxic substances results in severe cellular disruption[5]. The level of warm and cold ischemic injury in this porcine kidney model of the DCD donor was sufficient to cause severe renal dysfunction, alteration of acid base homeostasis and histological change during reperfusion. Kidneys treated with 1400W showed some ameliorate of injury with higher levels of creatinine clearance, urine output and reduced levels of protein excretion and oxidative stress compared to untreated kidneys. However, iNOS inhibition did not improve tubular cell function, acid base balance or reduce the level of histological injury.

1400W is a selective inhibitor of iNOS. It is relatively long acting and has been used successfully in several rat I/R injury models to reduce injury[13,17]. Mark *et al*[17] found that 1400W administered 20 min before ischemia, improved renal function and reduced the level of tubular dysfunction. Another study compared the effects of 1400W and melatonin: an antioxidant, iNOS inhibitor and scavenger of peroxynitrite[13]. They found that both agents reduced the level of oxidative damage, albeit melatonin to a greater extent due to its scavenging properties. Other selective iNOS inhibitors such as, L-N6-(L-iminoethyl) lysine (L-NIL)[16] and the novel iNOS inhibitor GW274150 have also been used to improved glomerular and tubular function and reduce levels of NO in rat models of I/R injury[12] and FR260330 in Vervet monkeys[18].

A key role of NO is the modulation of blood flow and NO derived from eNOS is thought to be particularly important during early reperfusion[6-8]. In this present study there was a marked reduction in renal blood flow and increase in intra-renal resistance during the first 15 min of reperfusion with iNOS inhibition. This warrants further investigation but was possibly due to low levels of NO derived from eNOS during the early reperfusion phase as a result of the level of ischemic injury and inhibition of iNOS. This suggests an important role for iNOS in the control of homeostasis during this acute phase.

The activation of neutrophils during reperfusion is a principle mediator of I/R injury causing microcirculatory disruption and release of superoxide[19]. NO can inhibit the expression of P-selectin on endothelial cells, preventing rolling, and expression of intercellular and vascular cell adhesion molecules-1 (ICAM-1, VCAM-1) reducing neutrophil adhesion and infiltration[11,17]. NO derived from iNOS is thought to enhance endothelial-leukocyte activation and inhibitors have demonstrated a reduction in neutrophil activation[12]. Contrary to this, in a model of endotoxic shock, NO released by cNOS and iNOS reduced neutrophil migration due to decreased rolling and adhesion[19]. Levels of neutrophil infiltration were reduced by almost half after iNOS inhibition in this present study. Hickey *et al*[9] suggested that the role of iNOS varies according to the cell type and location in which it is expressed, and that leukocyte recruitment could alter according to the type of inflammatory response. Evidence from this study supports the findings of others that iNOS inhibition prevents neutrophil infiltration during I/R injury, although the exact mechanisms are still to be elucidated. Nonetheless, the activation of neutrophils has also an important role in regeneration and repair and it is likely that a balance is needed to ensure optimal graft function[20].

Plasma concentrations of total NO were not affected by iNOS inhibition in this study and perhaps real time analysis of NO or the measurement of eNOS and iNOS expression may have provided more information on the significance and bioavailability of NO in this model. Urinary levels of total NO were however, significantly increased during reperfusion after iNOS inhibition possibly indicating a higher level of proximal tubular cell injury. Nonetheless, high levels were not associated with tubular cell dysfunction. Urinary levels of 8-isoprostane, a marker of lipid peroxidation, generated by free radical catalyzed attack on arachidonic acid, were significantly lower after the administration of 1400W[21]. Lower levels of lipid peroxidation suggest less oxidative damage and formation of peroxynitrite during reperfusion possibly due to less neutrophil infiltration.

In conclusion, the administration of 1400W a selective inhibitor of iNOS improved renal function, reduced oxidative stress and neutrophil infiltration in this porcine kidney model of the DCD. This study supports the evidence of the deleterious effects of iNOS during I/R injury.

COMMENTS

Background

The shortage of organ donors has led to increasing use of marginal donors. Although a valuable source of kidneys for transplantation these kidneys have more injury and a high percentage do not function immediately after transplantation. This injury is in part, mediated by an inflammatory action immediately after transplantation: ischaemia reperfusion injury. Targeting this inflammatory process by using therapies may improve early graft function. Despite an abundance of research into such therapeutic agents, none are used clinically as part of standard practice.

Research Frontiers

Inducible nitric oxide synthase (iNOS) is produced naturally by the body and thought to play a role in the injury process after transplantation. 1400W is an iNOS inhibitor that has been shown to reduce injury and improve graft function. However, the research hotspot is that it has not been trialed in a clinically relevant model such as the porcine kidney with similar ischaemic insults that human kidneys are subject to.

Innovations and breakthroughs

iNOS inhibitors such as 1400W have previously been used to reduce injury and improve renal function. However, some studies have found no benefit in inhibiting iNOS. Furthermore, most of these studies have used small animal models which do not necessarily represent the effect in humans. In this present study the authors used a porcine model with similar periods of ischaemic injury to

assess the effects of 1400W. Porcine kidneys have similar anatomy to human kidneys and their physiological response to ischaemic injury is also comparable. The authors found that 1400W significantly reduced the injury processes and improved renal function. This suggests that iNOS plays an important role in the injury process after transplantation.

Applications

This study suggests that iNOS inhibitors are a potential therapy for reducing renal ischaemia reperfusion injury after transplantation.

Terminology

Ischaemia reperfusion injury is a natural inflammatory like reaction that a transplanted organ suffers. It involves a cascade of events that can cause irreversible cellular damage. This can reduce renal function and also limit graft survival. Nitric oxide synthase (NOS) is a gaseous molecule that is produced naturally in the body. There are three different forms of NOS. Generally it has a protective role however iNOS is associated with inflammatory disease states.

Peer review

Ischaemia reperfusion injury is a critical problem in the transplant field. This study reported that 1400W reduced ischaemia reperfusion injury in a porcine model of the donation after circulatory death donor. This paper is well written and the results of renal function, oxidative stress and histology in 1400W reveal the protection from I/R injury.

REFERENCES

1 **Ponticelli C**. Ischaemia-reperfusion injury: a major protagonist in kidney transplantation. *Nephrol Dial Transplant* 2014; **29**: 1134-1140 [PMID: 24335382 DOI: 10.1093/ndt/gft488]

2 **de Vries DK**, Lindeman JH, Tsikas D, de Heer E, Roos A, de Fijter JW, Baranski AG, van Pelt J, Schaapherder AF. Early renal ischemia-reperfusion injury in humans is dominated by IL-6 release from the allograft. *Am J Transplant* 2009; **9**: 1574-1584 [PMID: 19459788 DOI: 10.1111/j.1600-6143.2009.02675.x]

3 **Frangogiannis NG**. Chemokines in ischemia and reperfusion. *Thromb Haemost* 2007; **97**: 738-747 [PMID: 17479184]

4 **Gok MA**, Shenton BK, Pelsers M, Whitwood A, Mantle D, Cornell C, Peaston R, Rix D, Jaques BC, Soomro NA, Manas DM, Talbot D. Ischemia-reperfusion injury in cadaveric nonheart beating, cadaveric heart beating and live donor renal transplants. *J Urol* 2006; **175**: 641-647 [PMID: 16407015 DOI: 10.1016/S0022-5347(05)00170-9]

5 **Perico N**, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. *Lancet* 2004; **364**: 1814-1827 [PMID: 15541456 DOI: 10.1016/S0140-6736(04)17406-0]

6 **Vos IH**, Joles JA, Rabelink TJ. The role of nitric oxide in renal transplantation. *Semin Nephrol* 2004; **24**: 379-388 [PMID: 15252777 DOI: 10.1016/j.semnephrol.2004.04.009]

7 **Yates PJ**, Hosgood SA, Nicholson ML. A biphasic response to nitric oxide donation in an ex vivo model of donation after cardiac death renal transplantation. *J Surg Res* 2012; **175**: 316-321 [PMID: 21592523 DOI: 10.1016/j.jss.2011.03.073]

8 **Joubert J**, Malan SF. Novel nitric oxide synthase inhibitors: a patent review. *Expert Opin Ther Pat* 2011; **21**: 537-560 [PMID: 21338328 DOI: 10.1517/13543776.2011.556619]

9 **Hickey MJ**, Granger DN, Kubes P. Inducible nitric oxide synthase (iNOS) and regulation of leucocyte/endothelial cell interactions: studies in iNOS-deficient mice. *Acta Physiol Scand* 2001; **173**: 119-126 [PMID: 11678734 DOI: 10.1046/j.1365-201X.2001.00892.x]

10 **Joles JA**, Vos IH, Gröne HJ, Rabelink TJ. Inducible nitric oxide synthase in renal transplantation. *Kidney Int* 2002; **61**: 872-875 [PMID: 11849440 DOI: 10.1046/j.1523-1755.2002.00235.x]

11 **Korkmaz A**, Kolankaya D. Inhibiting inducible nitric oxide synthase with rutin reduces renal ischemia/reperfusion injury. *Can J Surg* 2013; **56**: 6-14 [PMID: 23187035 DOI: 10.1503/cjs.004811]

12 **Chatterjee PK**, Patel NS, Sivarajah A, Kvale EO, Dugo L, Cuzzocrea S, Brown PA, Stewart KN, Mota-Filipe H, Britti D, Yaqoob MM, Thiemermann C. GW274150, a potent and highly selective inhibitor of iNOS, reduces experimental renal ischemia/reperfusion injury. *Kidney Int* 2003; **63**: 853-865 [PMID: 12631066 DOI: 10.1046/j.1523-1755.2003.00802.x]

13 **Ersoz N**, Guven A, Cayci T, Uysal B, Turk E, Oztas E, Akgul EO, Korkmaz A, Cetiner S. Comparison of the efficacy of melatonin and 1400W on renal ischemia/reperfusion injury: a role for inhibiting iNOS. *Ren Fail* 2009; **31**: 704-710 [PMID: 19814638 DOI: 10.3109/08860220903085989]

14 **Hosgood SA**, Bagul A, Yang B, Nicholson ML. The relative effects of warm and cold ischemic injury in an experimental model of nonheartbeating donor kidneys. *Transplantation* 2008; **85**: 88-92 [PMID: 18192917 DOI: 10.1097/01.tp.0000296055.76452.1b]

15 **Lo Faro ML**, Fox B, Whatmore JL, Winyard PG, Whiteman M. Hydrogen sulfide and nitric oxide interactions in inflammation. *Nitric Oxide* 2014; **41**: 38-47 [PMID: 24929214 DOI: 10.1016/j.niox.2014.05.014]

16 **Legrand M**, Almac E, Mik EG, Johannes T, Kandil A, Bezemer R, Payen D, Ince C. L-NIL prevents renal microvascular hypoxia and increase of renal oxygen consumption after ischemia-reperfusion in rats. *Am J Physiol Renal Physiol* 2009; **296**: F1109-F1117 [PMID: 19225052 DOI: 10.1152/ajprenal.90371.2008]

17 **Mark LA**, Robinson AV, Schulak JA. Inhibition of nitric oxide synthase reduces renal ischemia/reperfusion injury. *J Surg Res* 2005; **129**: 236-241 [PMID: 16140334 DOI: 10.1016/j.jss.2005.06.019]

18 **Qi S**, Xu D, Ma A, Zhang X, Chida N, Sudo Y, Tamura K, Daloze P, Chen H. Effect of a novel inducible nitric oxide synthase inhibitor, FR260330, in prevention of renal ischemia/reperfusion injury in vervet monkeys. *Transplantation* 2006; **81**: 627-631 [PMID: 16495814 DOI: 10.1097/01.tp.0000199282.05021.0c]

19 **Dal Secco D**, Paron JA, de Oliveira SH, Ferreira SH, Silva JS, Cunha Fde Q. Neutrophil migration in inflammation: nitric oxide inhibits rolling, adhesion and induces apoptosis. *Nitric Oxide* 2003; **9**: 153-164 [PMID: 14732339 DOI: 10.1016/j.niox.2003.11.001]

20 **Ysebaert DK**, De Greef KE, Vercauteren SR, Ghielli M, Verpooten GA, Eyskens EJ, De Broe ME. Identification and kinetics of leukocytes after severe ischaemia/reperfusion renal injury. *Nephrol Dial Transplant* 2000; **15**: 1562-1574 [PMID: 11007823 DOI: 10.1093/ndt/15.10.1562]

21 **Waller HL**, Harper SJ, Hosgood SA, Bagul A, Yang B, Kay MD, Kaushik M, Nicholson ML. Biomarkers of oxidative damage to predict ischaemia-reperfusion injury in an isolated organ perfusion model of the transplanted kidney. *Free Radic Res* 2006; **40**: 1218-1225 [PMID: 17050175 DOI: 10.1080/10715760600907368]

P- Reviewer: Tomohide H **S- Editor**: Yu J **L- Editor**: A
E- Editor: Lu YJ

World Journal of Transplantation

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
www.wjgnet.com

World J Transplant 2014 December 24; 4(4): I-V
ISSN 2220-3230 (online)

INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Transplantation (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

WJT covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation, and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, and xenotransplantation. The current columns of *WJT* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography.

We encourage authors to submit their manuscripts to *WJT*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

WJT is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 43 OA clinical medical journals, including 42 in English, has a total of 15471 editorial board members or peer reviewers, and is a world first-class publisher.

Columns

The columns in the issues of *WJT* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers; (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, *etc.*; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-quality clinical case conference; (11) Original Articles: To report innovative and original findings in transplantation; (12) Research Report: To briefly report the novel and innovative findings in transplantation; (13) Meta-Analysis: Covers the systematic review, mixedtreatment comparison, meta-regression, and overview of reviews, in order to summarize a given quantitative effect, *e.g.*, the clinical effectiveness and safety of clinical treatments by combining data from two or more randomized controlled trials, thereby providing more precise and externally valid estimates than those which would stem from each individual dataset if analyzed separately from the others; (14) Case Report: To report a rare or typical case; (15) Letters to the Editor: To discuss and make reply to the contributions published in *WJT*, or to introduce and comment on a controversial issue of general interest; (16) Book Reviews: To introduce and comment on quality monographs of transplantation; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

Name of journal

World Journal of Transplantation

ISSN

ISSN 2220-3230 (online)

Launch date

December 24, 2011

Frequency

Quarterly

Instructions to authors
Full instructions are available online at http://www.wjgnet.com/2220-3230/g_info_20100722180909.htm.

Indexed and Abstracted in
PubMed Central, PubMed, and Digital Object Identifier.

SPECIAL STATEMENT

All articles published in journals owned by the BPG represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

Biostatistical editing
Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJT* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions
Manuscripts should be submitted through the Online Submission

System at: http://www.wjgnet.com/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2220-3230/g_info_20100722180909.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to bpgoffice@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, *e.g.*, Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, *e.g.*, Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision on acceptance is made only when at least two experts recommend publication of an article. All peer-reviewers are acknowledged on Express Submission and Peer-review System website.

Abstract

There are unstructured abstracts (no less than 200 words) and structured abstracts. The specific requirements for structured abstracts are as follows:

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, *e.g.*, 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine con-

tributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, *e.g.*, PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood

CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2220-3230/g_info_20100725073806.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

All types of articles' writing style and requirement will be found in the link: http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15

RESUBMISSION OF THE REVISED MANUSCRIPTS

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade A certificate (for non-native speakers of English), should be submitted to the online system *via* the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2220-3230/g_info_20100725073726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2220-3230/g_info_20100725073445.htm.

Proof of financial support

For papers supported by a foundation, authors should provide a copy of the approval document and serial number of the foundation.

Statement about anonymous publication of the peer reviewers' comments

In order to increase the quality of peer review, push authors to carefully revise their manuscripts based on the peer reviewers' comments, and promote academic interactions among peer reviewers, authors and readers, we decide to anonymously publish the reviewers' comments and author's responses at the same time the manuscript is published online.

PUBLICATION FEE

WJT is an international, peer-reviewed, OA online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium and format, provided the original work is properly cited. The use is non-commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 698 USD per article. All invited articles are published free of charge.

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com