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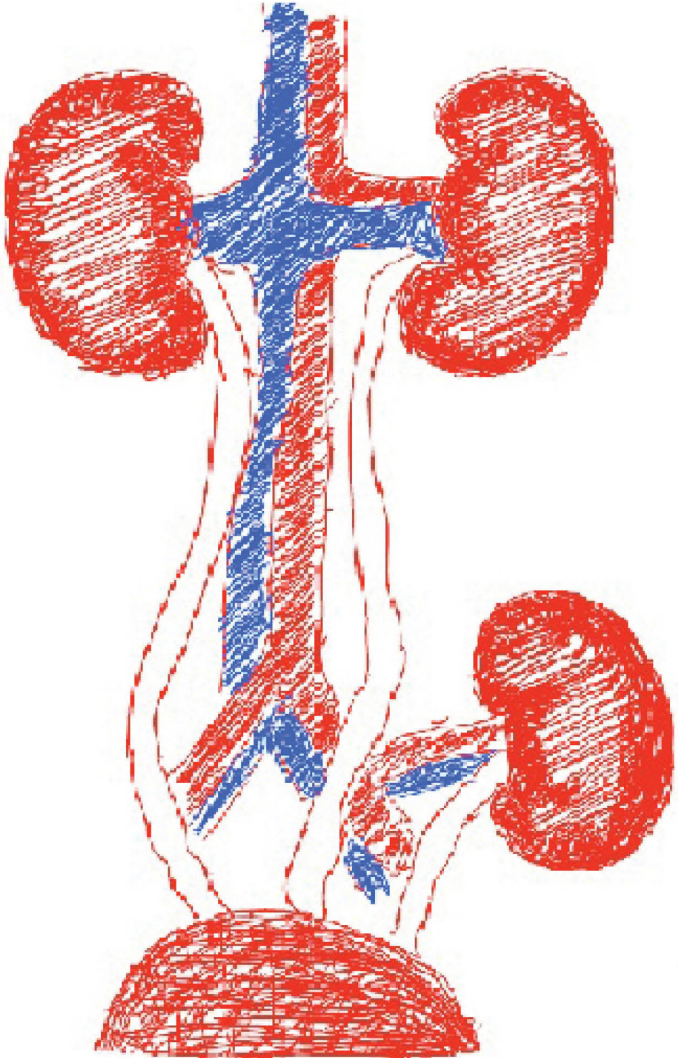
Transplantation
Current Barriers and Prospectives



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Transplantation: Current Barriers and Prospective

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About Editor

I was graduated from my home city Mansoura University, Faculty of Medicine 1993 with grade of honor. I was lucky to start my residency at Nephrology at Urology & Nephrology center, Mansoura, Egypt. After achieving Master degree in general medicine and nephrology I was granted a nephrology fellowship in transplantation in the same center. Then I received a fellowship grant from the international society of nephrology (ISN) to have training in transplantation immunology with Professor Kathryn wood, one of the greatest mentors in transplantation science research, at Transplantation Research Immunology Group, Nuffield Department of Surgery, Oxford University, United Kingdom. My focus was on the investigation of the cellular mechanisms of graft tolerance. During my training, I received Distinguished Fellow's Award recognition for my work from the ISN, plus many accepted publication and Chapter in one of the prestigious Textbooks in Inflammation. Once I finished my doctoral degree in Egypt, I continued my transplantation clinical practice, during that period I have focused my research in artificial intelligence and multivariate models to predict long-term graft survival. After two years of clinical practice I moved to France to start post-doctoral fellowship in Transplantation science for two years with Prof. Jean-Paul Soulillou and Dr. Sophie Brouard, Nantes University, France and the division of Nephrology, Northwestern University, USA. My knowledge and orientation was shifted from T cells mechanisms of rejection and tolerance to B cells mediated rejections. Beside that I have participated in many clinically applicable biostatistical models and several clinical publications in Transplantation and Cancer. Transplantation science is my passionate, surfing between the barriers & risks and searching for solutions with new modifications of our approaches to deliver the best aid to those humans unluckily been found to have one of their organs stopped.

Ahmed AKL

Acknowledgement

Transplantation is considered the optimal choice for end stage organ diseases. However, numerous challenges and barriers affect graft outcome. The scoop of this ebook is an attempt to outline where we stand today and what we expect in the future to improve the quality of transplantation.

Special thanks to Prof. Mohamed Ghoneim the pioneer of transplantation in Egypt and Middle East and founder of the urology and Nephrology center, Mansoura, Egypt for his endless support and kind help in preparing of this ebook.

Furthermore, special thanks to Sir Roy Calne the pioneer of liver transplantation and leader of transplantation research for his kind agreement to write the chapter of history of transplantation and kind support. Prof. Diego Cantrovitch the leader of pancreatic transplantation in France and EU for his kind support and wonderful chapter.

I would like to express my thanks and gratitude to all authors and co-authors for their highly appreciated contribution in this book. I appreciate all the efforts and support from my colleagues in Mansoura, Egypt and worldwide.

Ahmed AKL, M.D.,PhD

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INTRODUCTION

Transplantation is considered the optimal choice for end stage organ diseases. However, numerous challenges and barriers affect graft outcome. The scoop of this ebook is an attempt to outline where we stand today and what we expect in the future to improve the quality of transplantation.

Prof. Mohamed Ghoneim the pioneer of transplantation in Egypt and Middle East and the founder of the urology and Nephrology center, Mansoura, Egypt draw his vision of the future of assessing transplantation outcome, starting with various statistics tools, artificial intelligence and to predict the outcome of transplantation. Ending with future tailoring and individualization of management using sophisticated robotics. I would like to acknowledge his contribution not only in this book but in my whole scientific life.

Sir Roy Calne for his contribution in the book. Sir Roy Calne is the pioneer of liver transplantation and his talent modification of immunosuppression in transplantation starting with azathioprine & reaching Alemtuzomab led to evolution of outstanding progress in transplantation outcome in addition to advancement of research not only in Cambridge University, UK but all over the world. I am deeply grateful for his contribution; He illustrated the transplantation history and achievements in past and what is expected in future.

Painting of Prof. Mohamed A. Ghoneim by Sir Roy Calne.

Prof. Diego Cantrovitch, is a nephrology consultant and the leader of pancreatic transplantation in Nantes University, France and European community, his vision & experience in identifying the medical dilemma associated with diabetes specially when reaching renal failure. The success the fate of pancreatic and kidney transplantation in a wonderful chapter.

Different medical and transplantation barriers were covered by several chapters written by outstanding expertise in nephrology including professors & young generations from the unique WHO certified Urology & Nephrology center, Mansoura University, Egypt. I would like to express my thanks and gratitude to all authors and co-authors for their highly appreciated contribution in this book. I hope our aim in highlighting the most important barriers facing transplantation and our trial for outlining the solutions finds its way to your hearts and minds.

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Organ Transplantation – Historical Background

Sir Roy Calne*

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Keywords: History of transplantation, Organ transplantation; Transplantation

In the past 50 years organ transplantation has been established as an extremely important branch of therapeutic medicine, starting from nothing in the 1950s to the achievement of treating more than a million patients worldwide today.

This new discipline advanced medicine and surgery but also it introduced new ethical features which previously did not exist and these are causing more concern each year as the results of transplantation improve. The idea of transplantation was embedded in mythology since medieval times with the legend of the miracle performed by Saints Cosmos and Damien who transplanted a leg from a dead donor to a man with a cancer. There was no way in which this could be realised (by surgeons) in medieval times, it required modern medicine to provide scientific concepts with repeatable experiments in the 16th Century led by William Harvey's demonstration of the circulation of the blood, verified by simple experiment. The most outstanding feat of Harvey's science was to postulate that circulation proceeded from the arteries to the veins via minute vessels that could not at that time be seen. He thus laid the ground for an understanding of physiology with a beginning of identifying some of the vital stepping stones.

At the beginning of the 20th century Alexis Carrel [1] described a repeatable method of joining blood vessels together surgically using fine needles and silk sutures. This technique was utilised in a practical manner by Carrel in experimental transplantation [2]. He showed that a kidney could be removed and transplanted and would function after restoration of arterial inflow and venous outflow, provided the surgery was performed rapidly and did not allow damage to occur to the organ by ischaemia. Carrel and Guthrie showed that "autologous grafts", namely removing a kidney from its normal position and transplanted elsewhere in the same animal, could function for long periods after the opposite kidney was removed. However within the same species transplantation from one individual to another, called "allografts", after initial function of some days was usually irreversibly destroyed by what came to be recognised as an immunological reaction.

In the 1940s and 50s Simonsen in Denmark [3] and Dempster [4] in London performed numerous experiments with kidney grafts and studied the histology of the grafted organs. The peritubular capillaries became surrounded with mononuclear cells which were thought to have originated in the donor organ but in fact were shown later to have come from the recipient and were part of the cellular immune response against the grafted kidney [5]. The scientific basis of graft rejection was determined by Peter Medawar and his colleagues, who

showed that a specific sensitisation resulted from the first graft so that a second graft from the same donor to the same recipient was destroyed almost immediately, these were the features of an immune reaction [6].

The early development of the immune system became a focus of study worldwide, following the unexpected observation by Medawar's group that skin grafts between non-identical cattle twins were accepted in a similar manner to skin grafts between identical twins [7]. An explanation of this phenomenon rested on the supposition that during intra-uterine development the immune system is in a pliable state and will accept antigenic material from any source, but after birth this state rapidly changes and the immune reaction occurs instead. The lack of immunity in cattle twins is attributed to the fact that cattle have a unique circulation in the pregnant uterus when non-identical twins present. The blood from one twin circulates through the recipient and visa versa. This was consistent with the previous observations of Ray Owen that non-identical cattle twins frequently had blood groups of more than one type circulating without harm in healthy animals [8]. Medawar's group performed experiments with inbred mouse strains, in which the individuals following intensive inbreeding became similar to identical twins from an immunological point of view. Cells from one strain injected in the foetus of another strain would render the injected animals unable to react against the donor strain, they became "tolerant" and this was a strain specific phenomenon [9]. If the injected cells contained lymphocytes they could cause a fatal illness in the injected animal which would later be called graft-versus-host disease [10]. Some of the most important mechanisms of rejection in the immune system have now been uncovered although the application of experimental immunological tolerance can still not be applied directly in the clinic. It was shown that in the foetus two types of lymphocyte develop, T cells from the thymus and B cells from the bone marrow. They have different roles, T cells being responsible primarily for cellular immune reactions and B cells for antibody production.

In the 1950s David Hume performed a series of kidney grafts in patients joining the renal to the femoral vessels and bringing the ureter out through the skin [11]. Some of the grafts functioned longer than might have been expected. The histology of these grafts showed severe arterial narrowing, a feature of chronic rejection. It was postulated that the sick patients suffering from prolonged uraemia had impaired the immune systems allowing the grafts to function longer than was observed in experimental animals. The kidneys grafted into the thigh were unsatisfactory and a much improved technique of renal transplantation into the pelvis was described by Rene Kuss in 1953 [12]. This technique has been used ever since. A year after Kuss's technique was published the first successful kidney transplant between human twins was performed at the Peter Bent Brigham by Dr Murray and his colleagues [13]. This was a landmark achievement fulfilling the expectations from animal experiments. An excellent long term outcome could be expected, but the question remained "was there any way in which patients requiring a life-saving organ graft could be helped if there was no identical twin available to be a donor?".

Meanwhile in the laboratory the concept of destroying the immune system with X-irradiation and restoring the damage with a bone marrow transplant was found to be successful, albeit with the danger of a graft-versus-host disease developing. Total body irradiation in varying doses was utilised in the clinic to condition the recipients for kidney grafts who had no identical twin donor. There were many attempts but irradiation either killed most of the recipients or failed to prevent rejection. Only two patients did well and both received kidneys from non-identical twins. In order to mitigate the toxic effects of total body irradiation Slavin and Strober in Stanford developed techniques of lymphoid irradiation in which most of the bone marrow was protected [14]. This had some good results with this conditioning especially in grafts between close relatives and is still being investigated and perfected 50 years later.

It was clear that something new had to be found and the possibility of using drugs to control the immune system was investigated following the demonstration that the anti-leukaemia compound, 6-mercaptopurine would prevent rabbits challenged with foreign protein antigens from producing antibody [15]. I investigated 6-mercaptopurine in experimental renal allografts in London and found that there was some prolongation and sometimes remarkable longevity of kidneys in animals treated with this drug [16]. Working with Hitchings and Elion who had synthesized 6-mercaptopurine, we found azathioprine, a derivative of 6-mercaptopurine, was slightly superior and this became the chief immunosuppressive drug used in clinical transplantation following its efficacy demonstration in animals [17]. The early results in the clinic were disappointing until the steroids were added so that the patients received a cocktail of two agents [18]. Previously steroids had been investigated experimentally and it was shown that they could reverse rejection reactions in patients. In a few centres 50% of kidneys were surviving and functioning at a year and surgeons started experimenting with techniques for transplanting the liver and the heart. In the meantime the definition of tissue groups led to tissue typing using human leucocyte antigens and the results of matching had a definite correlation with kidney graft outcomes. The compatible typing of red blood cell groups was also needed.

Transplantation of the heart and liver was slowly accepted and the appalling early results were gradually improved due to the focus of intense care of the patients under anaesthesia and post-operatively in the ICU and identification of the many technical pitfalls that had to be avoided.

New immunosuppressive agents were investigated and antibodies produced against lymphocytes injected into animals, could delay rejection. However these polyclonal antibodies tended to vary from batch to batch.

The modern era of new immunosuppression followed the discovery of the effect of a fungal cyclic peptide cyclosporine by Borel working in the Sandoz laboratories [19]. Borel showed that cyclosporine was a powerful immunosuppressive agent both *in vitro* and *in vivo* with skin grafts and we studied this compound in rat heterotopic cardiac allografts, canine renal allografts and orthotopic cardiac allografts in pigs [20]. In these species cyclosporine was shown to be effective with few side effects. But when first used in the clinic it was shown to be remarkably nephrotoxic, a property that had not been suspected from the experiments. Cyclosporine proved to be a watershed in the management of organ grafts with a one year graft survival increased from 50 to 80% [21]. Organ grafting was now perceived by the medical profession as a potentially important new treatment following the initial scepticism. Instead of a few centres doing transplants worldwide, three to four years after cyclosporine was introduced there were more than a thousand and this highlighted the shortage of potential donors. New immunosuppressant acting on the same pathway as cyclosporine, but with greater efficacy and a different pattern of toxicity was described from the Fujisawa Company in Japan by Ochiai and colleagues [22]. Their substance, tacrolimus, was fully investigated by Starzl's group in Pittsburg [23].

The production of monoclonal antibodies by Kohler and Milstein in 1975 had considerable theoretical and practical advantages over polyclonal anti-lymphocyte preparations, since monoclonal antibodies, by definition, had a singular molecular target [24]. A number of monoclonal antibodies were tried in the clinic and one of the most effective was the humanised monoclonal antibody Campath 1H which was extremely powerful in eliminating lymphocytes from the circulation. It was developed for the treatment of chronic lymphatic leukaemia and found to be a valuable induction agent in clinical kidney transplants. The concept of a powerful induction treatment followed by a low maintenance immunosuppression was well tolerated by patients and lowered the cost of treatment. We call this protocol almost or "*prope tolerance*" [25].

Liver transplantation provided important new observations in the immune system. In pigs and rodents we found that liver transplants would sometimes survive for prolonged periods without the recipients receiving any immunosuppression. There was a tendency for acute rejection to subside spontaneously which was a new and very interesting phenomenon [26]. In the clinic some patients from Denver and Pittsburg deliberately stopped taking their maintenance immunosuppression without telling their doctors, some of them had acute rejection, others have accepted their grafts for several decades but even an extremely low dose of immunosuppressant may be all that is necessary in many recipients of organ grafts but particularly liver graft patients.

The engagement of foreign tissue with the recipients immune system involves not only recognition and reaction but also a second signal binding cells presenting the antigen to the immune reactive cells. There has been much study of the second signal and methods of blocking it. Early results in the clinic have become encouraging [27].

The ethics of organ grafting

In the past half century organ grafting has evolved from a fanciful theoretical concept to established therapy. In most patients now allograft rejection can be controlled but the recurrence of the patient's original disease and the development of malignancy secondary to the immunosuppressive agents are recurring complications that can lead to disaster. The success of organ grafting and the ever increasing demand for donor organs has led to many worrying ethical dilemmas like a "can of worms". The number of potential recipients increases from year to year but the number of donors does not. The need to optimise the donors that could be used requires active participation by government and the provision of financial assistance for the necessary infrastructure and education to exhort public opinion to be favourable to organ donation after death. Spain has led the field in this venture and has been extremely successful obtaining more than 30 donors per million population per year.

Since the beginning of clinical transplantation living donors have been used, usually between family members and especially from parents to children. There have however been many worries of ethical matters. In China many thousands of people had their organs removed for transplantation after execution. Recently a child in China sold his kidney without his parent's permission to obtain cash to buy an iPad [28]. The transplant community is acutely aware of these ethical concerns, including the use of organs to generate income from rich foreign "organ tourists". More subtly the relations of patients may have pressure put upon them to be an organ donor or feel guilty if they refuse. In New York a surgeon who gave a kidney to his wife later was involved in a divorce and was awarded considerable damages in lieu of his "altruistic" gift [29]. Liver donation from an adult to a child has a defined but low risk, however the danger, is very much increased in adult to adult liver donation. Five liver donors were reported to have developed liver failure themselves, four died and one was rescued with a transplant. Organs may be bought illegally, usually the recipient being rich. Seldom do the rich donors give to poor recipients. Alternative sources of organ transplantation have been sought over many years, particularly transplanting organs from animals to man and more recently the actual construction of organs by seeding themselves to an inert scaffold. To date however these have not survived in the clinic, apart from a flurry of kidney xenografts from primate species to man, one of which from a chimpanzee did function for nine months before it was rejected.

This brief historical sketch has traced organ grafting from nothing to a huge worldwide therapeutic endeavour. Many problems remain to be solved and it is incumbent on our profession to scrutinise all organ transplant practices and ensure that to the best of our ability ethical transgressions do not occur.

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Computer Based Decision Supporting Tools in Transplantation

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Keywords: Computer supportive tools; Medical bioinformatics; Neural Networks; Nomogram; prediction models; Transplantation

Introduction

Clinical Informatics

Transplantation informatics is a complex information based field that uses multichannel health information technology in order to improve patient health care. The data channels include medical and surgical clinical patient data, biomedical information science, computer & social science, behavioral & management science, and others. Medical informatics tools include clinical guidelines, formal medical terminologies, and information communication systems [1]. It is applied to all clinical aspects including nursing, clinical care, pharmacy, physical therapy and biomedical research [2]. Clinical informaticians transform health care by analyzing, designing, implementing, and evaluating information and communication systems that enhance individual and population health outcomes, improve patient care, and strengthen the clinician-patient relationship. Collaboration between clinicians and information technology professionals leads to the development of health informatics tools which promote patient care that is safe, efficient, effective, timely and patient-centered. Development of the field of clinical informatics leads to creation of large data sets with electronic health record data. Large data warehouses are often described as clinical data repositories [3, 4].

History

Worldwide use of computer technology in medicine began in the early 1950s with the rise of the computers [5]. The first informatics professional organization was established by Gustav Wagner In 1949 in Germany [6,7]. In the 1960s, specialized university departments and Informatics training programs began in Europe [France, Germany, Belgium and The Netherlands]. During 1970s, Medical informatics research units began to appear in Poland and in United States [6]. Since then the development of high-quality health informatics research, education and infrastructure has been a goal of United States and European

Union [6]. Early names for health informatics included medical & biomedical computing, medical software & computer technology. Since the 1970s the most prominent international coordinating body has been the International Medical Informatics Association (IMIA) [8].

Human bioinformatics

Translational bioinformatics

With the completion of the human genome and the recent advent of high throughput sequencing and genome-wide association studies of single nucleotide polymorphisms, molecular bioinformatics, biostatistics and clinical informatics are converging into the emerging field of translational bioinformatics [9-11]. The relationship between bioinformatics and health informatics is still not very clear while conceptually related under the umbrella of biomedical informatics [12].

Clinical Research Informatics

Clinical research informatics takes the principles, and a technology related to health informatics and applies these to clinical research contexts [13]. Interest and activities in clinical research informatics have increased greatly in recent years given the overwhelming problems associated with the explosive growth of clinical research data and information [14].

Statistical based models

Prediction of graft outcome after transplantation occupies great importance. Prediction would give a choice of the best possible conditions to achieve graft outcome success including donor parameters and immunosuppression medications. Construction of such prognostic models is based on multivariate analysis of all valid variables with clinical impact on the graft. Prognostic model has been used to predict the outcome of renal transplantation from deceased donor in an attempt to optimize the allocation of the recovery of organs [15]. Another model was used to predict creatinine levels in recipients of kidneys from living donors [16]. The probability of deceased donor-graft survival was studied using a tree regression model [17]. To generate an accurate prediction model, a number of conditions should be fulfilled: use of a robust dataset that represents a large patient population, and the incorporation of prognostically significant variables into the model [18]. In addition, the generated model should be validated using an independent testing group [19].

Nomogram

Nomograms are graphic representation of statistical model, which incorporate multiple continuous variables to predict a patient's risk of developing a specific endpoint (recurrence, survival, complications) [18]. Each variable is assigned a scale of points according to its prognostic significance. The total score for all the variables is converted to an estimated probability of reaching the endpoint [20] [Figure 1]. Statistical approaches require guesses as to how outputs functionally depend on inputs.

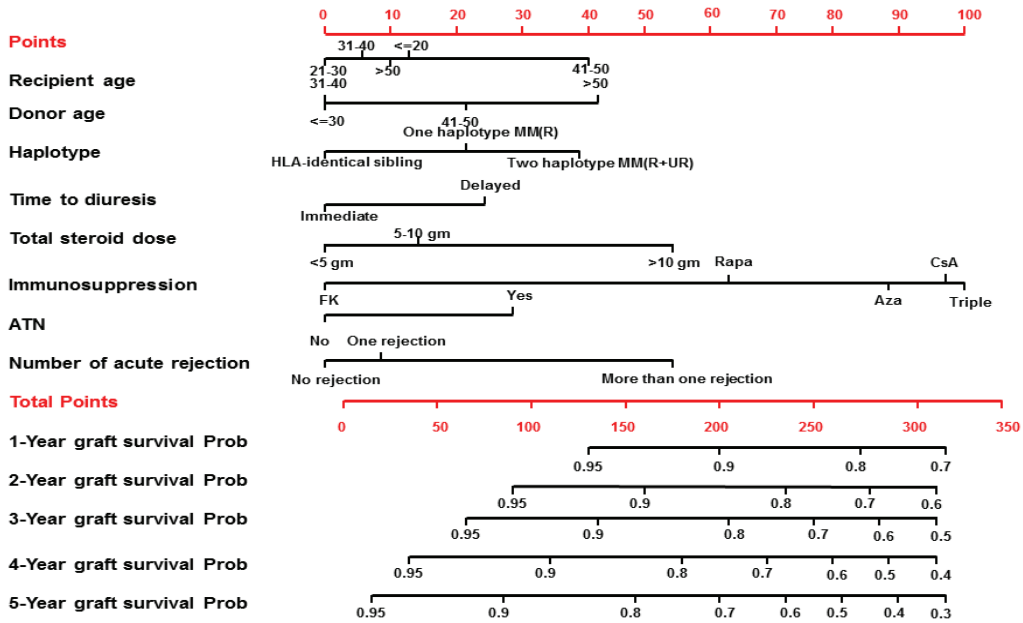

Figure 1: Five-year nomogram inputs are assigned points according to the degree of their impact on graft survival. The 5-year graft survival probabilities (prob) are estimated according to the total risk points earned for each patient [20].

Artificial intelligence "Neural networks"

Artificial Neural Networks (ANNs) does not have the articulation of mathematical model, they have been used for evaluation of clinical data to provide results similar to conventional modeling methods [21]. ANNs are complex computational systems able to analyze nonlinear data. The ANNs extract features from input patterns; assign them weights, summing weights with activation functions, and propagating decisions to output nodes once activation thresholds are exceeded through a complex mapping between input and output nodes. Typical networks are organized into three layers of computational units (nodes) in which input/output layers are linked by hidden layers of nodes. Subject factors determine the number of input units, and the classification complexity determines the number of output units. The number of hidden units is determined by trial and error (training). Common routines start with one hidden unit and assign small arbitrary weights to all nodal connections. The network is fed sample data with known outcomes, and an error term is calculated by means of differences between known and predicted outputs. Learning consists of adjusting weights by backward pass of errors through the connections to network nodes in response to input data. Hidden units are added to achieve minimum error criteria, while constraining the number to promote generalization of input patterns and prevent over fitting (memorization). Interconnection density determines the network's ability to correctly discriminate the outcomes. ANNs models are a form of nonlinear discriminant analysis with input units, weights, and activation functions resembling covariates, coefficients, and generalized additive models.

For the development of our ANNs, we have opted to use a feed-forward with back-propagation model since it is known for its stability and tendency not to over fit [22]. The algorithm is often described as a decision making process functioning like the human brain [23]. It is not surprising that ANN applications are undermined by similar limitations and misuses afflicting conventional discriminant analysis. Schwarzer identified four frequent mistakes when applying ANNs [24]

- Over fitting models by training large, multilayer networks with small data sets.
- Neglecting traditional statistical methods due to inadequate bench marks or lack of significance testing.
- Applying naïve approaches to survival data, sometimes ignoring censorship.
- Claiming overly optimistic generalization properties.

In our study only significant univariate variables were incorporated as input units, but in multivariate cases, insignificant univariate variables sometimes become relevant confounders or effect modifiers. Since ANNs are touted as having the ability to select those items most important in performing classifications, this prior variable selection seems unnecessary. Our study was designed to predict 5-year survival using cases with complete data (81 with missing data were dropped) divided into training (n=1500) and test (n=319) sets for building and validating models, respectively. We followed steps to guard against these problems. To avoid over-fitting, the ANN was restricted to one hidden layer, and the number of hidden nodes was controlled by reasonable stopping criteria. Also, the ratio of number of observations in the training set (1500) to number of parameters in the model (361) was greater than 2, a recommended guideline [24] [Figure 2]. Preprocessing or normalizing data entering the ANN was done. This is an important step that usually requires a floating-point value between 0 and 1 to be assigned for each input node, with special consideration for missing values.

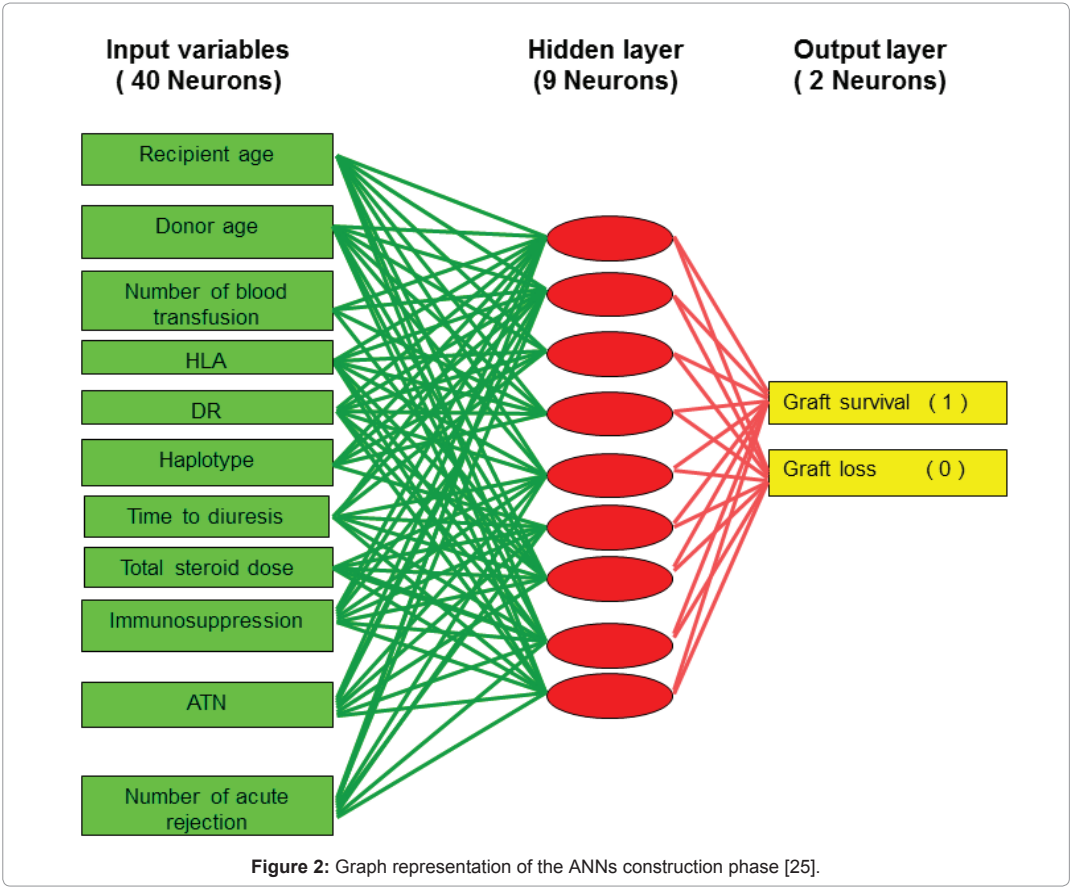

Figure 2: Graph representation of the ANNs construction phase [25].

The constructed ANNs model could predict graft outcome accurately when confronted with a new subset of patients not included in the training phase. Even ANNs was superior to the multivariate statistical model. ANNs carries many advantages; they do not require statistical training, they can deal with complex nonlinear relationships and detect possible interactions among predictor variables.

Watson Computer

In a more advanced and complex step in computer evolution, IBM started a project named Watson. Watson was named after IBM's first CEO and industrialist Thomas J. Watson. Watson is a Question Answering (QA) artificial intelligence computing system that IBM built to apply advanced natural language processing, information retrieval, knowledge representation, automated reasoning, and machine learning technologies to the field of open domain question answering [26]. The key difference between QA technology and document search is that document search takes a keyword query and returns a list of documents, ranked in order of relevance to the query (often based on popularity and page ranking), while QA technology takes a question expressed in natural language, seeks to understand it in much greater detail, and returns a precise answer to the question [26]. According to IBM, "more than 100 different techniques are used to analyze natural language, identify sources, find and generate hypotheses, find and score evidence [26].

Watson's main innovation was not in the creation of a new algorithm for this operation but rather its ability to quickly execute hundreds of proven language analysis algorithms simultaneously to find the correct answer. The more algorithms that find the same answer independently the more likely Watson is to be correct [27]. Once Watson has a small number of potential solutions, it is able to check against its database to ascertain whether the solution makes sense [27].

Description of Watson algorithm

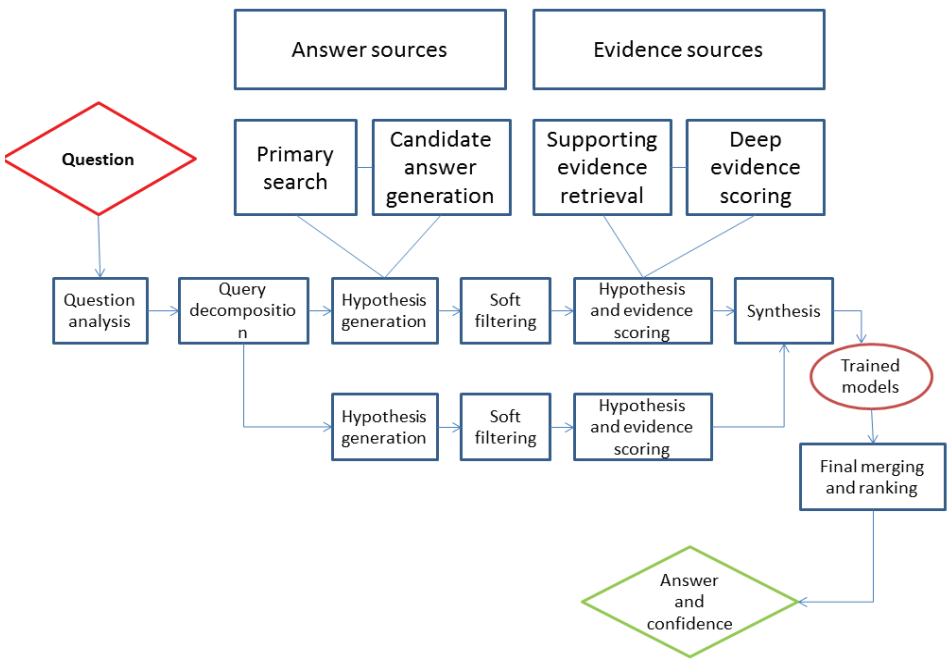

Figure 3: The high-level architecture of IBM's DeepQA used in Watson.

Current and future applications

IBM announced that Watson software system's first application for utilization management decisions in lung cancer treatment at Memorial Sloan Kettering Cancer Center in conjunction with health insurance company WellPoint [27]. Watson is expected to enter the field of transplantation in the coming years.

Conclusion

Decision making in transplantation is a complex and dynamic task that affects patient condition outcome. Advances in computer based decision supporting tools are inevitable. Emerging intelligent software's is expected to integrate with newly advanced tools in the field of medicine starting with google lens and ending with robotic surgeries ending with more precise, timely and safe medical decision in transplantation.

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Induction Therapy

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Introduction

Induction immunosuppression is not a compulsory stage of immunosuppressive treatment in renal transplant recipients; however, it is often considered essential to improve outcomes, particularly in high-risk patients, such as highly sensitized patients, recipients with a previous history of transplantation, and those receiving a calcineurin inhibitor or corticosteroid minimization or withdrawal protocols [1].

The aim of induction therapy is to prevent acute rejection during the early post-transplantation period by providing a high degree of immunosuppression at the time of transplant surgery. This type of therapy is started perioperatively and is concluded within the first week or two weeks after transplantation [2].

These agents are classified into depleting agents and nondepleting agents, depending on their ability to deplete T cells.

Depleting agents

Antithymocyte globulins

Antithymocyte Globulin [ATG] is a polyclonal antibody prepared by immunization of either horses or rabbits with human lymphocytes and then harvesting and stabilizing the resultant immune serums. The use of antithymocyte globulins leads to peripheral-blood lymphocytes depletion resulting in disturbance of both cell-mediated and antibody mediated immunity [2].

The dose of equine antithymocyte globulin ranges from 10 to 30 mg/kg for 4 to 14 days, administered intravenous and is infused over four to six hours [3,4]. Short courses of therapy are currently preferred in view of high financial costs and technical obstacles to be administered in outpatient basis as the need of high-flow or central veins and prolonged infusion. To overcome these obstacles, many centers started to use a 15mg/kg/day dosing strategy, with stoppage once optimizing the maintenance immunosuppressive treatment regimen [5].

Despite being unlabeled for induction therapy, antithymocyte globulin (rabbit) is used as an induction agent more than being used for other labeled indications as acute renal allograft rejection [6]. The administered doses range from 1 to 4 mg/kg/day for 3–10 days after transplantation. The most common regimen is 1.5 mg/kg/day for 3–5 days [7]. The initial dose of antithymocyte globulin (rabbit) is better to be administered intraoperatively

before allograft perfusion to prevent ischemic reperfusion injury and delayed graft function [8]. Dosing adjustment may be required in patients with hematologic complications. Short-term adverse effects of the ATG include bone marrow suppression, specifically leucopenia and thrombocytopenia, and cytokine release syndrome (fever, chills, rigors, hypotension, nausea, diarrhea, malaise, dizziness) [9]. To decrease the severity of these reactions and avoid allergic reactions, premedication with methylprednisolone, antihistaminic drug and acetaminophen should be administered [2].

Alemtuzumab

Alemtuzumab is a humanized, anti-CD52 monoclonal antibody which is labeled only for use in the treatment of B-cell chronic lymphocytic leukemia and relapsing multiple sclerosis [10,11]. However, it is commonly used in induction therapy in kidney transplantation.

Induction with alemtuzumab in kidney transplant could allow use of a steroid-calcineurin inhibitor-free regimen [12].

There are various regimens regarding alemtuzumab dosage in induction therapy. Initial regimens used doses of 30 mg at the time of transplantation and repeated on postoperative day 1 [13]. The use of a single intraoperative dose of 30 mg with early steroid withdrawal was reported to be more superior to ATG (rabbit) in preventing BPAR in the first year after transplantation [14].

Adverse effects associated with alemtuzumab use include myelosuppression (neutropenia, thrombocytopenia, and anemia), autoimmune hemolytic anemia, gastrointestinal manifestations [nausea, vomiting and diarrhea], headache and dizziness [11]. Premedication with steroids, antihistaminic drug and acetaminophen may decrease these adverse events [2].

Muromonab-CD3

Muromonab-CD3 [OKT3] is a murine monoclonal antibody that depletes T cells by binding to the T-cell-receptor–61associated CD3 glycoprotein. Muromonab-CD3 has been used without being FDA approved as an induction agent. Muromonab-CD3 has many adverse events including first-dose effect, pulmonary edema, nephropathy, infection, and malignancy. Preparations of ATG are better than muromonab-CD3 regarding its safety profile and decreasing the incidence of acute rejection. Therefore, use of muromonab-CD3 was decreased and production was stopped in 2009 [15].

Nondepleting agents

Basiliximab

Basiliximab, a chimeric monoclonal antibody, is an antagonist to the alpha subunit of the IL-2 receptor [CD25] inhibiting activation and proliferation of T-cell [2,15]. It is labeled as an induction agent in renal transplant recipients.

Basiliximab, 20 mg i.v, is administered two hours prior to the operation followed by a second dose four days postoperative. The dosage in children or adults weighting then less than 35 kg is 10 mg with same regimen. The most evident advantage of basiliximab is its safety profile as there is no increased risk of infection or malignancy. [2,15]. Hypersensitivity reactions are considered the most serious adverse effects associated with the use of basiliximab but occur very rare (<1%) [2,15].

Daclizumab

Daclizumab is a humanized monoclonal antibody, similar to basiliximab that acts as an antagonist to alpha subunit of the IL-2 receptor and was approved for induction therapy in renal transplant recipients [16]. The efficacy and safety profile of daclizumab is comparable to that of basiliximab. The remarkable difference is that daclizumab has a more sophisticated structure and is much more expensive [16]. Daclizumab was withdrawn from the market by the manufacturing company in October 2008 for commercial reasons [2].

Investigational drugs

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20, an antigen that is expressed on most B cells. Rituximab was approved in 1997 for treatment of refractory B-cell lymphoma, and it has been used to treat autoimmune diseases. In kidney transplant, rituximab has been used for treatment of antibody-mediated rejection and desensitization in transplants incompatible in ABO antigens and/or HLA profile [17]. Thus an interest has developed in induction therapies that deplete B-lymphocytes to prevent both alloantibody production and antigen presentation, which may in turn reduce rates of both humoral and cellular rejection. Clatworthy and his colleagues commenced a RCT comparing induction therapy with rituximab and methylprednisolone to daclizumab. Despite planning to recruit 120 patients, the study was halted after the first 13 patients due to a high incidence of Acute Cellular Rejection (ACR) in the rituximab group. 5/6 patients treated with rituximab [83.3%] developed an episode of acute rejection within the first 3 months compared to 1/7 in the daclizumab group (14.3%) [18]. The lack of evidence suggests adequately powered studies are required before we can make more evident conclusions regarding the efficacy and safety of rituximab [2].

Efalizumab

Efalizumab functions as an immunosuppressant by binding to the CD11a subunit of lymphocyte function-associated antigen 1 and inhibiting white blood cell migration. Efalizumab was indicated for the treatment of chronic moderate-to-severe plaque psoriasis [19]. Clinical trials in kidney transplant recipients failed. The frequency of patient survival, graft survival, and acute rejection was similar between combination therapy with efalizumab (0.5 or 2 mg/kg, subcutaneous, once weekly for 12 weeks), cyclosporine, mycophenolate mofetil, and steroids compared with half-dose cyclosporine, sirolimus, and prednisone. However, 3 of 38 patients (8%) who were treated with higher doses of efalizumab after transplant developed lymphoproliferative disease; thus, efalizumab was withdrawn from clinical use in April 2009 [20].

Alefacept

Alefacept is an inhibitor of the costimulation of T cells by CD2 and lymphocyte function-associated antigen 3. It was approved by the FDA for treatment of moderate-to-severe chronic plaque psoriasis in adults (15 mg/week, intramuscular, for 12 weeks). The most common adverse event is lymphopenia, and dosage adjustments are made by monitoring CD^{4+} lymphocyte counts. No cumulative adverse events were observed in a study of multiple courses of alefacept; however, infections and malignancy may occur in patients treated with alefacept, and liver function tests should be monitored.

Alefacept was developed for use in conjunction with tacrolimus, mycophenolate mofetil and steroids after kidney transplant [21]. A multicenter, randomized, double-blinded, placebo-controlled, parallel-arm study in adult kidney transplant patients compared alefacept (n=105) to placebo(n=107).Study patients received alefacept (7.5 mg ,intravenous, on days 0 and 3; 15 mg, subcutaneous, on day 7 and weekly; total, 12 weeks). Follow-up at 6 months showed that the incidence of delayed graft function, renal function, biopsy-proven acute cellular rejection, patient survival, and graft survival were similar between patients who received alefacept or placebo. The overall incidence of infection was similar between patient groups, but alefacept was associated with a higher frequency of cytomegalovirus and a lower incidence of BK virus infection [22]. Alefacept was withdrawn from clinical trials in transplantation due to the high incidence of humoral rejection, malignancy and lower levels of CD^{4+} and CD^{8+} memory T cells early post-transplantation.

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Pediatric Kidney Transplantation Barriers Challenges and Outcome

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Abstract

Renal transplantation is the best treatment for ESKD in pediatric as better patient survival, better quality of life (Dialysis is more disruptive to family lifestyle, schooling, and social interactions) and better growth, so when estimated GFR ≤ 30 ml. minute the child should be prepared for transplantation for pre-emptive transplantation or to shorten time of dialysis to prevent vascular calcification and decrease risk cardiovascular events.

The outcome of kidney transplantation is better in last years and there are many factors that contributed to that especially advances in immunosuppressive drugs that decreased incidence of rejection and allowed to us low steroids dose and free steroid immunosuppression protocols. And this decreased incidence of diabetes mellitus, hypertension and high lipid profile level.

Introduction

Pediatric kidney transplantation is the preferred treatment for children with end-stage renal disease the first successful pediatric kidney transplantation was reported in 1966 [1]. Since then, the outcomes have steadily improved and kidney transplantation.

is now the preferred treatment modality for children with End-Stage Kidney Disease (ESKD) Pediatric kidney transplantation is generally performed in specialized centers due to complex technical, metabolic, immunologic, and physiologic factors. Pediatric kidney transplantation involves a multiple teams as transplant surgeons, nephrologists, and urologists who are supported by psychologists, nurses, and social workers.

End stage kidney disease in children

The estimated incidence of End Stage Kidney Disease (ESKD) defined as a GFR <15 mL/min per 1.73 m2 in children varies throughout the world. It has been reported to be as high as 14.8 cases per million children in the United States and as low as four cases per million children below the age of 19 in Japan [2]. A number of factors influence incidence and prevalence rate variability of childhood ESKD. Factors such as racial and

ethnic distribution, type of prevalent renal disease, and quality of medical care available for pre-terminal Chronic Kidney Disease (CKD) patients have a significant impact on patient outcome [2].

Causes of End- Stage of Kidney Diseases (ESKD) in children according to the North American Pediatric Renal Trials and Collaborative Studies [3]

Etiology	PRECENT %
Aplasia/hypoplasia/dysplasia	15.8%
Obstructive uropathy	15.3%
Focal segmental glomerulosclerosis	11.7%
Reflux nephropathy	5.2%
Polycystic disease	3%
Chronic glomerulonephritis	3.2%
Medullary cystic disease	2.7%
Hemolytic uremic syndrome	2.6%
Prune belly	2.5%
Congenital nephrotic syndrome	2.6%
Familial nephritis	2.3%
Cystinosis	2.1%
Pyelo/interstitial nephritis	2.7%

Renal Replacement Therapy (RRT)

RRT choices in children with CKD include renal transplantation, hemodialysis, and peritoneal dialysis. The choice of RRT varies as illustrated by the following findings from the North American Pediatric Renal Trials and Collaborative Studies [4]

- 25% underwent preemptive renal transplantation.
- 50% were started on Peritoneal Dialysis (PD).
- 25%were started on HemoDialysis (HD).

General principles of kidney transplantation in children

Once the estimated Glomerular Filtration Rate (GFR) declines to less than 30 mL/min per 1.73 m2 and the child is in stage 4 chronic kidney disease, it is time to start preparing the child and the family for renal replacement therapy**.**

Combined liver-kidney transplantation

The most common indications were type 1 primary hyperoxaluria, autosomal recessive polycystic kidney disease, and primary liver disease with irreversible kidney injury. Other indications included congenital congestive heart failure due to Caroli disease, metabolic diseases of the kidney for which liver transplantation addressed the enzyme deficiency (methylmalonic acidemia, atypical hemolytic uremic syndrome), and metabolic diseases affecting both organs (alpha-1 antitrypsin deficiency, tyrosinemia) [5].

Donor source

a) Living donors

Pre-emptive kidney transplantation from living donors has the best outcomes in children. About one third of pediatric living donor transplants are performed pre-emptively in the USA. Parents are the living donors for approximately three quarters of the children, and nearly two thirds of the children who receive living donor kidneys are Caucasian males. A majority of transplant recipients (39%) are in the age group of 13–17 years followed by 6-12 years (33%) [6].

b) Deceased donors

Kidneys from pediatric deceased donors, particularly those younger than five years, have traditionally not been used for pediatric recipients due to higher rates of graft thrombosis and technical failures [7].The results of kidney transplantation with a living donor are superior to those with a deceased donor. The NAPRTCS data reveal that five year allograft survival is greater in living donor compared with deceased donor allografts (80 versus 66 percent) [9].

Evaluation of the potential renal transplant recipient

a) History and physical examination

Preliminary information about the recipient should include a thorough medical, surgical and psychosocial history, and a detailed physical examination, special attention is directed at the patient's dentition and the presence or absence of peripheral arterial pulses, a careful examination of the abdomen for previous abdominal operations is also important [10].

Children with vascular access issues, previous intra-abdominal procedures like bilateral nephrectomy, or hypercoagulable states like nephrotic syndrome, or thrombosis of the major intra-abdominal vessels like the inferior vena cava must be carefully evaluated. Such patients may benefit from preoperative magnetic resonance angiography to demonstrate collateral venous channels draining the lower extremities and pelvis. This assists in selection of an appropriately sized donor kidney that may be accommodated to the smaller collateral vessels in the abdomen [11].

Urinary tract abnormalities

Pediatric urologic evaluation is valuable in patients with a history of Lower Urinary Tract Dysfunction (LUTD) such as posterior urethral valves, reflux, or other congenital problems.

The mainstay of most protocols is a thorough pretransplant assessment of bladder urodynamics to quantify hostile bladders based on estimates of bladder capacity, compliance, and voiding pressures, when the native bladder is deemed unsuitable, there are three categories of possible intervention including drainage procedures, augmentation, and urinary diversion [12].

Native nephrectomy

The indications for native nephrectomy prior to transplantation include intractable urinary tract infection, a history of severe hypertension (particularly those with severe renin dependent hypertension) and vesicoureteric reflux [13].

Surgical procedure

The surgical techniques for kidney transplantation in teenagers and in children weighing more than 30 kg are generally similar to those in adults, with retroperitoneal exposure and anastomosis to the external iliac artery and vein. In children weighing 20 kg or less, the renal vessels are anastomosed to the aorta and vena cava. In children weighing 20–30 kg, the common iliac artery and vena cava are frequently used for vascular anastomoses via a retroperitoneal or an intraperitoneal approach [14].

Immunosuppression in pediatric renal transplant patients

Improved therapeutic strategies have been associated with better patient and graft survival rates. however, the adverse effects associated with these agents and the risks of long-term immunosuppression present a number of challenges for the clinician. With all the successes of immunosuppressive therapies come the obligations to tailor treatments to meet the individual patient's characteristics and to balance the risks and benefits of these medications.

Induction therapy

About 45% of all pediatric kidney transplant recipients received some form of induction immunosuppression therapy. Lymphocyte-depleting agents such as antithymocyte globulin were used in up to 22% of recipients for a median duration of five days. (3) There has been a gradual increase in the use of monoclonal IL-2 receptor antagonists, mirroring a decrease in the use of OKT3 due to its more severe systemic effects and higher risk of post-transplant lymphoproliferative disease (PTLD) [15].

Maintenance Immunosuppression

Tacrolimus was the dominant calcineurin inhibitor and used in 74% of pediatric kidney transplants in the United States, whereas cyclosporine was used in less than 2% of recipients [3] Tacrolimus has been shown to be superior to cyclosporine in preventing rejection in adults and children in randomized trials [16]. In addition to calcineurin inhibitors, maintenance regimens in children also commonly include an antimetabolite. Azathioprine was used in 49% of transplants in 1996, but its use had decreased to 2.5% in 2009 in favor of the less toxic agent, mycophenolate mofetil. Currently, a maintenance regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone is used in 55%–63% of all pediatric kidney transplants in the United States [3].

Harmon et al., undertook a trial of calcineurin inhibitor avoidance after living donor pediatric kidney transplantation. Their regimen included induction with monoclonal IL2-inhibitor antibody, prednisone, mycophenolate mofetil, and sirolimus. Their series was associated with six-month and 12-month rejection rates of 21.8% and 31.5%, respectively,[17] so complete calcineurin inhibitor avoidance is now rarely pursued.

Steroid-free immunosuppressive protocols

Multiple centers have found that steroid avoidance or withdrawal is associated with increased catchup growth, fewer adverse cardiovascular effects, and a lower incidence of post-transplant diabetes mellitus, without any increase in rates of graft failure or acute rejection [18] Benfield et al., prospectively evaluated a regimen of steroid withdrawal at 6 months post-transplant after induction therapy with anti-CD25 monoclonal antibody and maintenance with sirolimus and calcineurin inhibitors. Compared with regimens using continued low-dose steroids, steroid withdrawal was associated with increases in standard height velocity and no difference in the rate of acute rejection [19].

In most studies, there is a reported failure rate of steroid-sparing therapy of about 10%, and the most frequent reasons for requiring conversion back to steroids is refractory acute rejection and recurrence of glomerulonephritis [20]. steroid-sparing regimens with induction antibody therapy and calcineurin inhibitor maintenance regimens appear to be safe in immunologically low-risk pediatric recipients [14].

Complications of renal transplantation in children

Delayed Graft Function (DGF)

Delayed graft function is defined as the need for dialysis in the first week after transplantation. In pediatric recipients, a delayed graft function rate of 5% and 15% has been observed after living and deceased donor transplantation, respectively [3]. The risk factors for delayed graft function include prolonged cold ischemia time (.24 hours), prolonged warm ischemia time, and perioperative hypotension. Extreme donor ages, ie, younger than 2 years and older than 50 years, are also associated with a higher risk of delayed graft function [14].

Acute rejection

With increased laboratory surveillance, asymptomatic increases in creatinine are currently the primary modality for screening rejection. Definitive diagnosis through biopsy

and surveillance biopsy is gaining favor due to improved detection of acute and chronic rejection in pediatric transplantation [21].

Antibody-mediated rejection is characterized histologically by a peritubular and glomerular neutrophilic and monocytic infiltrate, and deposition of complement C4d in peritubular capillaries. Antibody-mediated rejection is more common among highly sensitized patients, retransplants, and high-mismatch or ABO-incompatible donors [22].

Vascular thrombosis

The rate of vascular thrombosis in pediatric kidney transplant recipients ranges from 2% to 12% internationally and is about 7% in the United States [23]. Thrombosis-induced graft failure is seen in 1.9% of living donors and 3% of deceased donors [3].

Urologic complications

Urologic complications include urinary obstruction, urinary leak, vesicoureteral reflux, and urolithiasis. The incidence varies between 3% and 15%, and correlates with the presence of pretransplant obstructing uropathy or bladder dysfunction [24].

Infections

Cytomegalovirus viremia is associated with inferior graft function, an increase in acute rejections, hypertension, and graft loss [25]. BK virus infection occurs in 4.6% of pediatric renal transplants in the USA, and BK virus nephropathy may lead to graft loss in up to 11% of patients [26]. No correlation between a history of urinary tract infection (either before or after transplant) and decreased allograft survival [27].

Malignancy

In the NAPRTCS database, 2.4% of pediatric renal recipients experienced a malignancy. Over 50% of all malignancies in pediatric renal transplant recipients are PTLD [3].

Outcomes of renal transplantation in children

The outcome of renal transplantation in children has improved over the last several decades primarily due to the introduction and widespread use of calcineurin inhibitors and other immunosuppressive agents [28].

In the United States, one-year and 5-year graft survival for living donors has increased from 80.4% and 74.6%, respectively, in 1987–1990 to 96.5% and 84.3% in 2003–2010 [3].

Over the same time period, deceased donor one-year and 5-year graft survival has improved from 75.1% and 54.8% to 95.1% and 78.0%, respectively. Factors that appear to be associated with inferior graft survival include black race, male gender, a previous transplant history, a history of more than five blood transfusions, HLA-mismatches, and lack of induction therapy [3].

Factors that affect allograft survival in children [29].

1. Immunosuppressive drugs.
2. Source of donor kidney.
3. HLA compatibility.
4. Age of the donor and recipient.
5. Presence of preformed anti-HLA antibodies (sensitization).
6. Prolonged cold ischemia time.
7. Ethnicity of the recipient.

8. Delayed allograft function.
9. Acute rejection episodes.
10. Infections.
11. Non adherence.
12. Underlying primary disease.

Nonadherence

Nonadherence to immunosuppressive treatment contributes to both acute and chronic rejection. An analysis of the United States Renal Data System (USRDS) showed that among

pediatric renal transplant recipients, greater adherence was significantly associated with improved long term allograft survival [30].

In 16 studies included in a systematic review of the literature, the rate of nonadherence ranged from 5 to 70 percent. Amongst these studies, there was variability on how adherence was assessed ranging from drug level assays, pill counting to patient self-reporting. Factors associated with nonadherence included: [31].

- Poor socioeconomic status.
- Family stress and conflicts.
- Lack of parental supervision.
- Patient depression.
- Cosmetic side effects of medications.
- Large number of medications.
- Size of tablets and difficulty swallowing tablets.
- Taste of medication.
- Poor patient knowledge.

Growth after renal transplantation

Growth and development are unique considerations in pediatric transplantation.

Growth assessment and management should be performed in any pediatric transplant recipient [32]. Anthropometric parameters, including height, body weight, body mass index (plus head circumference in children less than 3 years of age), should be monitored every 3 months in children less than 3 years of age, then every 6 months until final height is reached [33].

As dialysis is associated with decreased growth velocity, preemptive renal transplantation may optimize final height. Some authors reported better height scores in the first years post-transplantation in those children who received a pre-emptive renal transplant compared to those with dialysis prior to transplantation [34].

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Pancreas Transplantation

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Introduction

The goal of pancreas transplantation is to induce long-lasting complete insulin independence and normal glucose metabolism in type 1 diabetic patients. In 1966, the first human pancreas transplantation was performed in Minnesota. Today, after several years of experimentation, this surgical approach is accepted as a therapeutic modality to treat diabetes and is covered by most all insurances all over the world.

In more than 95% of cases, the pancreas is harvested from a deceased donor aged less than 50 years. In rare cases, living related donor pancreas transplantation can be performed. Almost all cases of living related pancreas transplantation were done in Minneapolis by David Sutherland and colleagues. Around 2,000 pancreas transplantations are performed every year, mostly in US and Europe.

In the big majority of cases, pancreas transplantation is performed simultaneously with a kidney (SPK) in type1 diabetic patients with End-Stage Renal Failure (ESRF). This could be done before dialysis (pre-emptive transplantation) or after initiation of chronic dialysis. In our center in Nantes, 40% of SPK are done pre-emptively. By univariate comparison, better results are obtained in this group of patients than in those on dialysis. In 10-15% of cases, the pancreas is transplanted in diabetic kidney transplant recipients already under immunosuppression (PAK). This group of patients exhibited same short and long-term results than SPK. Finally, in selected diabetic patients without advanced renal dysfunction and with brittle diabetes, Pancreas Transplantation Alone is realized (PTA). This group of patient is the most challenging group of diabetics and unfortunately the less investigated. Efforts should be done to perform studies of pancreas or islet transplantation in these diabetic patients with uncontrolled diabetes despite optimized medical treatments.

Islet transplantation is also a procedure which may cure diabetes Indications are in theory the same as for pancreas transplantation. However, islet transplantation is mainly performed in a selected patient population with brittle diabetes or in diabetic patients already transplanted with a kidney. Commonly, candidates for islet transplantation are those not accepted for pancreas transplantation. Results of islet transplantation are now achieving those of pancreas transplantation. Nevertheless, it should be noted that the transplanted patient population is not the same than pancreas transplantation one and comparisons of results are so far biased by patient selection.

Background

So me attempts to transplant a pancreas began before the discovery of insulin. The first pancreatic transplantation in man was performed in 1893 in London (it was a xenotransplantation). In 1966, Kelly et al., performed the first human, whole organ pancreatic transplant at the University of Minnesota. Thereafter, very few transplants were done. In 1976, Dubernard and Traeger in Lyon introduced a new surgical technique characterized by a segmental pancreas transplant (body and tail) injected with neoprene. Since this date, number of pancreas transplantations significantly increased all over the world.

Type 1 diabetes is an auto-immune disease where the insulin producing beta cells of the pancreas are selectively destroyed. This process starts early in young patients and can be treated with immuno-suppressants at a very early stage. However, despite enormous efforts done in the management and treatment of diabetes, the only therapeutic tool to overcome hyperglycemia is still the exogenous insulin.

Pancreas and islet transplantation are the sole procedures to achieve normal or near normal glycemic control and to stop the progression of long-term diabetic complications. A successfully pancreas transplantation induces a long-term normoglycemic and insulin-independent state. This state could last for more than 30 years. Several studies clearly showed that successful pancreas transplantion (i.e. insulin-independence) can ameliorate degenerative diabetic complications including nephropathy, retinopathy, vascular and nerve ones.

In order to achieve long-term success, immunosuppression should be administered throughout life. This includes today the association of Calcineurin Inhibitors (CNI) and Mycophenolate Mofetil (MMF). Irreversible rejection is a rare complication and accounts for less than 5% of failures. The main cause of failure is graft thrombosis and/or technical complication of the surgical procedure. This accounts for 10-15%.

Numbers

Approximately 1,500 pancreas transplantations are performed each year in the US, 800 in Europe and 300 elsewhere. An International Pancreas Transplant Registry located in Minneapolis registered all procedures performed in the world. However, numbers are underestimated since it is not mandatory to send the center's data to this registry. Candidate for the procedure is commonly a type 1 diabetic patient, generally aged less than 55 years. It should be notified that some patients with type 2 diabetes can be accepted for pancreas transplantation if they are under exogenous insulin and their BMI is less than 35. In our center in Nantes, positive C peptide before transplantation is not a contra-indication for pancreas transplantation.

Therefore, a complete and detail pre-transplantation check-up must be done to detect any possible contra-indication to undergo general anesthesia, major surgery and to receive chronic immunosuppression. This check-up must be evaluated annually whilst awaiting transplantation.

Mortality/Morbidity

Not many years ago, a patient diagnosed with type 1 diabetes had an average life expectancy of only 2 years. The development of insulin as a therapeutic agent revolutionized the treatment of diabetes by changing it from a rapidly fatal disease to a chronic illness. Unfortunately, this increased longevity allowed the development of secondary complications, including nephropathy, neuropathy, retinopathy, and macrovascular and microvascular complications, occurring 10-20 years after disease onset in almost half of patients.

As said before, pancreas transplantation results from the US and some European countries are reported to the International Pancreas Transplant Registry (IPTR). Based on this information, the national 1-year patient, kidney, and pancreas survival rates for

recipients of an SPK are 95%, 91%, and 86%, respectively. Compared to patients with diabetes who receive a kidney alone, the addition of a pancreas improves long-term patient and kidney graft survival rates, although no randomized trial is available comparing SPK to kidney alone. Recipients of a pancreas after kidney (PAK) or a Pancreas Transplant Alone (PTA) have an average 1-year pancreas graft survival rate of 70-80%.

Pancreas after living donor kidney transplantation resulted in significantly higher patient survival and kidney graft survival compared with living donor kidney transplant alone. In addition, pancreas transplant during the first year after kidney transplant has shown improved long-term patient survival compared to living donor kidney transplant alone.

Pre-Transplantation Evaluation

A complete pre-transplantation recipient medical evaluation is mandatory before indicating the procedure and is outlined below. The emphasis of the evaluation should be to identify and treat all co-existing medical problems that may increase the rate of morbidity and mortality of the surgical procedure and adversely impact the post-transplantation course. In addition to this medical evaluation, social issues of the patient should be evaluated to determine conditions that may jeopardize the outcome of transplantation, such as financial and travel limitations or a pattern of non-compliance. Blood chemistries, liver function tests, CBC count, coagulation profile, hepatitis B and C (as well as D and E) serologies, Cytomegalovirus (CMV) serologies, Epstein-Barr virus serologies, varicella-zoster serologies, syphilis and toxoplasma, HIV serology, chest radiography, exercise/dipyridamole thallium scintigraphy, coronary arteriography (if indicated), stress cardiac ultrasonography (if indicated), C-peptide level confirms that transplantation candidate has type 1 diabetes are requested. However, positive C-peptide is not a contra-indication to undergo transplantation. In these cases, stimulation of the insulin secretion (i.e. C-peptide) is recommended. In case of non-response, the procedure can be accepted. In case of normal response, the pancreas procedure could be contra-indicated.

Evaluation of candidates for pancreas transplantation involves the following:

- Renal disease: a complete evaluation of renal function is done. A kidney biopsy is only recommended in case of PTA.
- Diabetic retinopathy: all lesions should be treated before transplantation. A non-cured lesion related to proliferative retinopathy could be aggravated and even cause blindness after transplantation following the rapid normoglycemia state created by the pancreatic transplant. Transplantation should not be performed if retinopathy is not stabilized.
- Gastroparesia: patients with severe gastroparesis may have difficulty tolerating oral immunosuppressive medications. They may also experience severe pain after transplantation because of the normal glucose control. These complications are very difficult to be solved after transplantation and require psychological help.

Cardiovascular: this is the most important comorbidity in patients with type 1 diabetes. Clinical symptoms are often not evident and even silent. So far, a detail evaluation is required before transplantation. All types of explorations are recommended as previously detailed, including routine coronary arteriography in patients on dialysis. Lower extremity peripheral vascular disease is significant in patients with diabetes. Patients with ESRD are at risk for amputation of a lower extremity. These problems typically begin with a foot ulcer associated with advanced somatosensory neuropathy. Ultrasound doppler should be done frequently while awaiting transplantation. Smoking should be avoided.

- Autonomic neuropathy: Autonomic neuropathy is prevalent and may manifest as gastroperis, cystopathy, and orthostatic hypotension. The extent of diabetic autonomic

neuropathy commonly is underestimated. Neurogenic bladder dysfunction is an important consideration in patients undergoing bladder drained procedure. Sensory and motor neuropathies are also common in patients with longstanding diabetes. This may have implications for rehabilitation after transplantation. It also is an indicator for potential risk of injury to the feet and subsequent diabetic foot ulcers.

Mental or emotional: mental illnesses, including neuroses and depression are very common. Diagnosis and appropriate treatment of these illnesses is important before transplantation for ensuring a good medical compliance. Mental and emotional illnesses are of extreme importance in recipients of Pancreas Transplant Alone without uremia (PTA).

Pancreas Transplantation Surgery

The Cold Ischemia Time (CIT) of the pancreas should be minimized to less than 10 hours to obtain the best results. More than 10 hours of CIT, the incidence of graft thrombosis increases each hour. However, good results can be observed even with CIT greater than 15 hours in case of young donor without any comorbidity. Reducing CIT by avoiding cross-matches can be easily done today in patients evaluated for anti-HLA immunisation by Luminex techniques.

The surgical technique for pancreas transplantation is mostly a whole pancreas with enteric diversion or a whole pancreas with bladder diversion. Venous anastomosis can be done into the systemic circulation or into the portal one. Pancreas graft arterial revascularization typically is accomplished using the recipient right common or external iliac artery. The Y-graft of the pancreas is anastomosed end-to-side. Positioning of the head of the pancreas graft cephalad or caudad is not relevant with respect to successful arterial revascularization. When the pancreas transplantation is performed simultaneously with kidney transplantation, the kidney transplantation is performed into the left iliac fossa after pancreas transplantation is finalized in the left iliac fossa. Some centers transplant first the kidney and then the pancreas. Both organs may be transplanted through a midline incision and placed intra-peritoneally or retro-peritoneally.

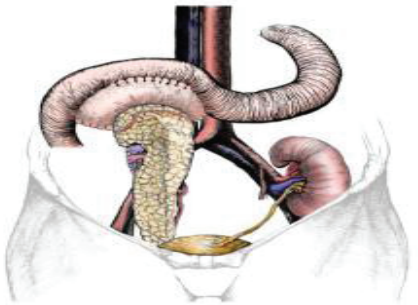
Enteric drainage of the pancreas transplantation is the most popular technique today. Markers for rejection include clinical signs and symptoms of pancreas graft pancreatitis and measurement of serum amylase or lipase levels coupled with biopsy. Biopsy of the pancreas is routinely performed by ultrasound guidance and most easily and securely performed when the organ is placed retro-pritoneally. If the pancreas is drained into the bladder, measurement of urinary amylase and lipase levels is and easy and not costly method for detecting rejection. Biopsy of the pancreas can be done via cystoscopy in this last case.

As previously mentioned, venous revascularization could be systemic or portal. No real clinically relevant difference in glycemic control has been documented, although it seems more physiological to do it into the portal system. Systemic venous drainage commonly involves the right common iliac vein or the right external iliac vein. Hyperinsulinemia may result of this non physiological anastomosis. In case of portal venous drainage the Superior Mesenteric Vein (SMV) is used. The pancreas portal vein is anastomosed end-to-side to a branch of the SMV. This may influence the methodology of arterial revascularization using a long Y-graft placed through a window in the mesentery to reach the right common iliac artery. Portal venous drainage is more physiologic with respect to immediate delivery of insulin to the recipient liver. This results in normal insulin levels and may impact long-term graft survival as well as degenerative complications.

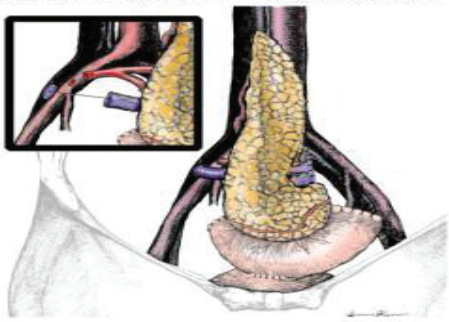
Several methods exist to drain the exocrine liquid of the graft. Duct injection is no more used since 20 years. Pancreatic exocrine drainage is handled by means of anastomosis of the duodenal segment to the bladder or anastomosis to the small intestine. Currently, approximately 80% of pancreas transplantations are performed with enteric drainage; the remaining 20% are performed with bladder drainage.

Each transplant center must perform the surgical procedure elected by the transplant team in accordance to personal experience and volume of transplants performed.

PANCREAS TRANSPLANT WITH ENTERIC DRAINAGE IN SITU



PANCREAS TRANSPLANT WITH BLADDER DRAINAGE



The bladder-drained pancreas transplantation was a very important modification introduced in about 1985 in Madison. This technique significantly improved the safety of the procedure by minimizing occurrence of intra-abdominal abscess from leakage of enteric drained pancreas grafts.

With the successful application of new immunosuppressant agents (CNI/MMF) and the reduction of the incidences of rejection, enteric drainage of the pancreas transplantations has enjoyed a successful rebirth. Enteric drainage of pancreas grafts is physiologic with respect to the delivery of pancreatic enzymes and bicarbonate into the intestines for reabsorption. Enterically drained pancreases can be constructed with or without a Roux-en-Y. The enteric anastomosis can be made side-to-side or end-to-side with the duodenal segment of the pancreas. The risk of intra-abdominal abscesses is extremely low, and avoidance of the bladder-drained pancreas has significant implications with respect to the potential complications that include the following: bladder infection, cystitis, urethritis, urethral injury, balanitis, hematuria, metabolic acidosis, and the frequent requirement for enteric conversion.

Diet

Following successful pancreas transplantation, no dietary restrictions are required. In fact, the diet can be liberalized to include virtually anything because blood sugar control is restored to normal. Nevertheless, BMI should remain within normal ranges since significantly lower graft survival was observed when recipient's BMI is above 25.

Medication Summary

All pancreas transplant recipients require life-long immunosuppression to prevent rejection. Two classifications of immunosuppressive agents exist, induction and maintenance immunotherapy agents. No consensus exists as to the single best immunosuppressive protocol and each transplant program utilizes various combinations of agents slightly differently. The goals are to prevent acute or chronic rejection, minimize drug toxicity, minimize rates of infection and malignancy, and achieve the highest possible rates of patient and graft survival rates.

Induction immunotherapy

consists of a short course of intensive treatment with intravenous agents. Antilymphocyte antibody induction therapeutic agents are varied and include polyclonal antisera, mouse monoclonals, and so-called humanized monoclonals. Antithymocyte globulin (ATG) is the most common agent used for 5-7 days; it is purified immunoglobulin solution produced by the immunization of rabbits with human thymocytes. Basiliximab (Simulect), a chimeric monoclonal antibody that specifically binds to and blocks the IL-2 receptor on the surface of activated T cells, is also used in low-risk candidates. Alemtuzumab (Campath), a humanized monoclonal antibody against the CD52 antigen induces lympholysis from complement-mediated lysis or other effector mechanisms.This agent is used in a short course of one or two perfusions.

Maintenance immunotherapy

Several immunosuppressive agents currently are in use. The current standard maintenance immunosuppression includes CNI/MMF/Steroids. Prednisone decreases inflammation by reversing increased capillary permeability and suppressing PMN activity. Mycophenolate mofetil (MMF, CellCept, EC-MPA, Myfortic),both inhibitors of enzyme inosine monophosphate dehydrogenase (IMPDH), which results in inhibition of lymphocyte proliferation, are used in place of azathioprine. Cyclosporine (CsA, Sandimmune, Neoral) was the first calcineurin inhibitor (CNI) used that diminish IL-2 production in activated T cells. This agent bind to the intracellular immunophilin cyclophilin, interfering with the action of calcineurin, which inhibits nuclear translocation of the nuclear factor of activated T cells (NFAT).Tacrolimus (Prograf, Advagraf), the second CNI used, binds to intracellular immunophilin, FKBP, interfering with the action of calcineurin, which inhibits nuclear translocation of the NFAT. Tacrolimus is the most popular CNI currently used in pancreas transplantation. More recently, m-TOR inhibitors (Sirolimus, Everolimus) were included in the immunosuppressive menu after pancreas transplantation. These drugs inhibit lymphocyte proliferation by interfering with signal transduction pathways. They bind to immunophilin FKBP to block action of mTOR. Although less nephrotoxic and less diabetogenic than tacrolimus, it used is hampered by numerous side-effects and adverse events. In our center in Nantes, The use of Rapamune following pancreas transplantation, as part of a randomized trial in comparison with Tacrolimus, was followed by an increased incidence of acute rejection, and 50% of patients were switch to Tacrolimus because of side-effects or adverse events. Our current protocol includes ATG for 5 days, prednisolone for 5 days, and Tac/MMF indefinitively. From 1987, we introduced a steroid-free regimen, first stopping steroids between 2 to 3 months after transplantation and since 2,000 avoiding them completely since the day of surgery or 5 days after.

Transplantation patient follow-up care

Typical visit schedule (if non complicated Tx) following discharge from the hospital is as follows, 2 visits in week 1, 1 visit in week 2 and 3, monthly thereafter, until 6 months post-transplantation, every 3 months through the first year, every 6 months through the second year, and annually thereafter. This schedule can of course be modified according to the evolution of the graft function. In my own experience, it is important to follow this

patient population very closely since the percentage on non-compliance is higher than in a non-diabetic population.

Surgical and non-immunological complications of pancreas transplantation

Surgical complications are more common after pancreas transplantation as compared to kidney transplantation. Non-immunological complications of pancreas transplantation account for graft losses in 5-10% of cases.

Thrombosis

Vascular thrombosis is a very early complication, typically occurring within 48 hours and usually within 24 hours of the transplantation. I can also occur later after the first or the second week. This generally is due to venous thrombosis of the pancreas portal vein. The etiology is not defined entirely but is believed to be associated with reperfusion pancreatitis and the relatively low flow state of the pancreas graft. Prudent selection of donor pancreas grafts, short CIT and meticulous surgical technique are all necessary to minimize graft thrombosis.

Transplantation pancreatitis

Pancreatitis of the allograft occurs to some degree in all patients postoperatively. Temporary elevation in serum amylase levels after transplantation is common. These episodes are transient and mild, without significant clinical consequence. Pancreatitis is secondary to CIT and reperfusion injury. In severe case of pancreatitis, a pancreas thrombosis may occur and graft removal is mandatory.

Complications of bladder drained pancreas transplantation

The pancreas transplantation eliminates approximately 500 mL of richly bicarbonate fluid with pancreatic enzymes into the bladder each day. Change in PH level of the bladder accounts, in part, for a greater increase in urinary tract infections. In some cases, a foreign body, such as an exposed suture from the duodeno-cystostomy, acts as a nidus for urinary tract infections or stone formation.

Acute postoperative hematuria of the bladder-drained pancreas usually is due to ischemia/reperfusion injury to the duodenal mucosa or to a bleeding vessel on the suture line that is aggravated by the antiplatelet or anticoagulation protocols to minimize vascular thrombosis. These cases are self-limited but may require change in bladder irrigations and, if severe, cystoscopy to evacuate the clots. Occasionally, performing a formal open cystotomy and suture ligation of the bleeding vessel is necessary intra-operatively. If relatively late chronic hematuria occurs, transcystoscopic or formal operative techniques may be necessary treatments.

Sterile cystitis, urethritis, and balanitis may occur after bladder-drained pancreas transplantation. This is due to the effect of the pancreatic enzymes on the urinary tract mucosa and is experienced more commonly in male recipients. Urethritis can progress to urethral perforation and perineal pain. Conservative treatment with Foley catheterization and operative enteric conversion represent the extremes of the continuum of treatment.

Metabolic acidosis routinely develops as a consequence of bladder excretion of large quantities of alkaline pancreatic secretions. Patients must receive oral bicarbonate supplements to minimize the degree of acidosis. Because of the relatively large volume losses, patients also are at risk of episodes of dehydration exacerbated by significant orthostatic hypotension.

Reflux pancreatitis can result in acute inflammation of the pancreas graft, mimicking acute rejection. It is associated with pain and hyperamylasemia and is believed to be

secondary to reflux of urine through the ampulla and into the pancreatic ducts. Often, the urine is found to be infected with bacteria. This frequently occurs in a patient with neurogenic bladder dysfunction. This complication is managed by Foley catheterization. Reflux pancreatitis will resolve quickly. The patient may require a complete workup of the cause of bladder dysfunction, including a pressure-flow study and voiding cystourethrogram. Interestingly, in older male patients, even mild hypertrophy of the prostate has been described as a cause of reflux pancreatitis. If recurrent graft pancreatitis occurs, enteric conversion may be indicated.

Urine leak from breakdown of the duodenal segment can occur and is usually encountered within the first 2-3 months following transplantation but can occur years following transplantation. This is the most serious postoperative complication of the bladder-drained pancreas. The onset of abdominal pain with elevated serum amylase, which can mimic reflux pancreatitis or acute rejection, is a typical presentation. A high index of suspicion for urinary leak is necessary to make the diagnosis accurately and swiftly. Supporting imaging studies using a cystogram or CT scan are necessary to confirm the diagnosis. Operative repair is usually required with exploration. The degree of leakage can be determined best intra-operatively, and proper judgment can be made whether direct repair is possible or more aggressive surgery involving enteric diversion or even graft pancreatectomy is indicated.

Complications of enteric drained pancreas transplantation

The most serious complication of the enteric drained pancreas transplantation is leak and intra-abdominal abscess. This serious problem usually occurs 1-6 months after transplantation but could occur much later. Patients present with fever, abdominal discomfort, and leukocytosis. A high index of suspicion is required to make a swift and accurate diagnosis. Imaging studies involving CT scan are very helpful.

Percutaneous access of intra-abdominal fluid collection for Gram stain and culture is essential. The flora typically is mixed with bacteria and often fungus, particularly *Candida.* Broad-spectrum antibiosis is essential. Surgical exploration and repair of the enteric leak is necessary. A decision must be made on whether the infection can be eradicated without removing the pancreas allograft. Incomplete eradication of the infection will result in progression to sepsis and multiple organ system failure. Peri-pancreatic infections can result in development of a mycotic aneurysm at the arterial anastomosis that could cause arterial rupture. Transplantation pancreatectomy is indicated if mycotic aneurysm is diagnosed.

Occurrence of intra-abdominal abscess has been reduced greatly with greater recognition of the criteria for suitable cadaveric pancreas grafts for transplantation. Improved perioperative antibiosis, including antifungal agents, has contributed to the decreased incidence of intra-abdominal infection, as well. No convincing evidence exists that a Roux-en-Y intestinal reconstruction decreases its incidence. Perhaps the most significant contribution to reducing the incidence of intra-abdominal abscess is the efficacy of the immunosuppressive agents in reducing the incidence of acute rejection and thereby minimizing the need for intensive antirejection immunotherapy.

GI bleeding occurs in the enteric-drained pancreas from a combination of perioperative anticoagulation and bleeding from the suture line of the duodeno-enteric anastomosis. Conservative management will suffice; the necessity for re-operative exploration is extremely unusual.

Prognosis

Today, survival rates are as follows: one-year survival rates were 95-100% for patients, 90% for kidney grafts, and 86% for pancreas grafts. Statistically and clinically, the outcome of kidney transplantation is significantly superior in patients receiving SPK transplantation versus patients with type I diabetes receiving kidney transplantation alone (in non-randomized analysis).

For pancreas-after-kidney transplantation, patient survival rates have steadily improved with a current 1-year patient survival rate similar to that of SPK. Similarly, pancreas graft functional survival rates have greatly improved from a nadir of 65% to a high of 86% at 1 year after transplantation. The immunologic risk for graft loss for the technically successful cases has been reduced from a high of 28% to only 9% at 1 year. The relative risks for pancreas graft loss in the pancreas after kidney recipient include increasing donor and recipient age, increasing HLA mismatches, and re-transplantation. Positive effects are shown with the use of the CNI Tacrolimus maintenance immunosuppression (although non-randomized compared to CsA).

For patients receiving pancreas transplantation alone, patient survival rates have been increasing with a current rate of 97.6% at 1 year post-transplantation. Pancreas graft functional survival rates have improved significantly to the current rate of 81% at 1 year post-transplantation. The immunological risk for graft loss for the technically successful cases is approximately 10% at 1 year. The relative risks for pancreas graft loss for pancreas transplantation alone recipients are increasing donor age and HLA mismatches, and a positive affect can be observed with the use of anti–T-cell induction immunotherapy and use of Tacrolimus maintenance immunotherapy.

Effect of pancreas transplantation on secondary complications of diabetes

Recipients of successful pancreas transplantation maintain normal plasma glucose levels without the need of exogenous insulin therapy. This results in normalization of glycosylated hemoglobin levels and a beneficial effect on many secondary complications of diabetes. The durability of the transplanted endocrine pancreas has been established with the demonstration that normalization of glycosylated hemoglobin is maintained as long as the allograft functions. The potential lifespan of the transplanted pancreas is not known precisely because, at present, survivors with functioning pancreas transplantations still are doing well more than 25 years after transplantation. The implications of prolonged normalization of glycemia and glycosylated hemoglobin levels are significant with respect to patients' quality of life, kidney structure, and motor-sensory and nerve function.

The quality of life of pancreas transplantation recipients has been well studied. Patients with a functioning pancreas graft describe their quality of life and rate their health significantly more favorably than those with nonfunctioning pancreas grafts. Satisfaction encompasses not only the physical capacities but also relates to psychosocial and vocational aspects. The functioning pancreas graft leads to even better quality of life when compared to recipients of kidney transplantation alone. Virtually all patients with successful pancreas transplantation report that managing their life, including immunosuppression, is much easier since the transplantation. Successful pancreas transplantation will not elevate all patients with diabetes to the level of health and functioning of the general population, but transplant recipients consistently report a significantly better quality of life than do patients who remain diabetic.

The development of diabetic nephropathy in transplanted kidneys residing in patients with type I diabetes has been well established. Marked variability is observed in the rate of renal pathology, including mesangial expansion and a widening of the glomerular basement membrane, in patients with type I diabetes and kidney transplantation alone. The onset of pathological lesions can be detected within a few years of kidney transplantation. Clinical deterioration of renal allograft function can lead to loss 10-15 years after transplantation.

A successfully pancreas transplantation prevents glomerular structure changes of kidney allografts in patients with type I diabetes. This has been observed in transplanted kidneys of patients undergoing SPK transplantation, as well as in kidneys of recipients undergoing

pancreas after kidney transplantation. These studies provide evidence of the efficacy of normalizing blood glucose and glycosylated hemoglobin levels to prevent the progression of diabetic glomerulopathy in renal allografts.

Furthermore, successful pancreas transplantation will halt or reverse the pathology in the native kidneys of patients with type I diabetes. Pancreas transplantation recipients all had persistently normal glycosylated hemoglobin values after transplantation for 5-10 years. The thickness of the glomerular and tubular basement membranes and mesangial volume steadily decrease over a 10-year interval and this despite the use of high-dose CsA. These early studies have important implications for the role of pancreas transplantation alone in patients with type I diabetes and very early changes in native renal function.

Successful pancreas transplantation has been shown to halt, and in many cases, reverse motor-sensory and autonomic neuropathy 12-24 months after transplantation. This has been studied most extensively in recipients of SPK transplantations. This raises the possibility that improvement of diabetic neuropathy occurs, in part, because of improvement of uremic neuropathy. However, pancreas transplantation alone in pre-uremic patients also has been shown to result in improvement in diabetic neuropathy. Many patients express subjective improvements of peripheral sensation 6-12 months after pancreas transplantation. Very interestingly, the effect of reversal of autonomic neuropathy in patients with type I diabetes with pancreas transplantation has been associated with better patient survival rates than patients with failed or no transplantation.

Pancreas transplantation does not have an immediate dramatic beneficial effect on pre-established diabetic retinopathy. Retinopathy appears to progress for at least 2 years following transplantation of the pancreas, but it begins to stabilize in 3-4 years compared to diabetic recipients of kidney transplantation only. Longer-term studies of 5-10 years, similar to those described above, have not been reported.

During hospitalization, transplant recipients are prepared for discharge with respect to expectations of medical compliance, education about the pharmacology of their new immunosuppression medications, and lifestyle issues. Patients usually are provided a booklet that delves into the above-mentioned topics.

Compliance with medical therapy may be one of the most important variables affecting transplant outcome. Transplant recipients must take immunosuppressive medications daily for the rest of their lives.

Nantes University Pancreas Transplant Program

Our clinical pancreas transplant program started in 1987. Today (June, 2015), 520 pancreas transplantations and 3 islet transplantations were performed. As previously described, our constant goal is to develop PTA in non-uremic patients with brittle diabetes, increase the number of pre-emptive SPK and increase the number of PAK. Main clinical research is focused on the prevention of cellular and humoral rejection, and graft thrombosis. Since the initiation of our program in 1987, steroid free immunosuppression was applied as part of an ATG induction and CNI maintenance regimen. Today, more than 25 years later, this regimen is the standard regimen in almost all centers in the world.

Acute rejection represents 5-10%. Mostly all cases were observed in case of low CNI concentrations and in patients with poor immunosuppression compliance. DSA is a direct consequence of acute rejection and represents 15-20%. Patients with *de novo* DSA experienced significantly lower graft survival as compared to patients without DSA or those with positive non-DSA.

Thrombosis represents 5-10% of immediate graft failures. Lowering CIT beyond 10 hours is the best way to prevent and avoid pancreas thrombosis. Machine perfusion of the pancreas could be another way of decreasing this severe complication.

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Antibody Mediated Rejection: HLA-Specific B-Cells Role in Kidney Transplantation

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Introduction

Naïve B cells have been associated with long-term allograft survival, while memory B cells have been linked to poor allograft survival. Role of HLA-specific B cells in chronic allograft rejection is still unknown. Quantifying HLA-specific B cells (donor specific or not) might be of importance to better understanding of the mechanisms of graft lesions, for an earlier diagnosis of chronic rejection, and eventually to guide specific B cell-targeted therapy. This review article provides overview of research surrounding the importance of HLA specific B cells in kidney transplantation.

HLA antibodies and graft rejection

Donor specific HLA antibodies have been associated with acute and chronic rejection of organ allograft [1-3]. However, this correlation is not absolute. When no antibodies against the donor are detected, it is not clear whether it is because the amounts of antibodies are too small, whether antibodies are removed from the serum due to sequestration in the transplanted organ [4], or whether none are produced because of unresponsiveness of the recipient against donor antigens [5,6]. Moreover, it is not unusual to see patients who developed antibodies post transplantation demonstrating a decrease in antibody titer to complete elimination of these antibodies. Such patient will develop antibodies rapidly after re-exposure to the sensitizing antigen. Similar observations were seen in multiparous women who developed antibodies at some stage of their lives but later on no antibodies were detectable in the circulation despite the clear presence of quiescence memory cells. Thus, detection of antibodies against HLA in the serum after transplantation depend on a balance between production of antibodies, sequestration of the antibodies by the transplanted organ and inhibition of antibody production by regulatory factors [7].

Detecting HLA specific B cells (HSB)

Memory B cells may be more cross-reactive than antibodies produced by Long Lived plasma cells [8]. Recent evidence show, during a secondary infection, serum could only protect when challenged with a homologous virus, whereas memory B cells could protect against both homologous and heterologous variant virus when challenged. In transplantation, such finding high lights an important implications. First, during stage of pre-transplant

preparation, it suggests that estimation of the reactivity against the Human Leukocyte Antigen (HLA) of sensitized patients using serum alone may be insufficient for optimal HLA matching. Second, it suggests that, after secondary transplantation in sensitized patients, denovo DSA associated with unpredicted or multiple HLA specificities may be arising from memory B-cell precursors.

The ability to detect and identify the specificity of circulating B cells with the potential to make HLA antibodies should provide tool to analyze antibody formation and shed light on the balance between production, inhibition and sequestration at any given time in the post-transplant period. Perry et al. recently reported on an assay to detect in vitro HLA specific antibody secreting cells from the bone marrow of sensitized kidney transplant recipients [9]. T and B-cell ELISPOT have also been used to measure HLA specific B cell frequency against a given antigen. ELISPOT assay does not measure the frequency of cells that actually bind the antigen and only measures biological events such as cytokine release [10] or production of immunoglobulin after differentiation in vitro [11,12].

Based on the structural similarity between B cell receptor and immunoglobulin binding sites, it is postulated that HLA-specific B cells should bind to HLA molecules with specificity comparable to that of the secreted immunoglobulin. Indeed, identification of HLA specific B cells by staining through binding of the B cell receptor using fluorescently labeled tetramers of identified HLA class I specificities has been described [13]. A different approach is to utilize commercially available single antigen coated, color-coded microspheres, multiplexed in an assay that is currently the mainstay of soluble antibody detection in the circulation [14-16]. However, this powerful assay has also highlighted the challenges of cross- and poly-reactivity of allo-antibodies [17]. Degauque et al. have recently described a method utilizing single HLA coated beads to enumerate HLA committed B cells [18]. Class I HSB identified in non-transplanted individuals were described by Newman et al. [19] who identified HLA specific B cells using tetramers and of Mulder et al. who isolated B cells from blood donors using HLA-A2 tetramers [20]. Up to our knowledge no studies reported identification of HSB class II in transplanted recipients. Frequency of HSB from transplanted recipients was higher than in non-transplanted individuals that has been observed with tetramers studies [21,22] especially frequency of HSB in the poor outcome group. CD27 and CD38 [23] phenotypes considered markers of memory and transitional immunoglobulin secreting cells among total B cells. An observation of memory B cells depletion following alemtuzumab induction therapy, majority of CD27 positive B cells and CD38hi/IgDhi, CD38+/IgD- were depleted in the 3 months samples compared to pre-transplant samples and re-populated at 12 months that was reported by Heidt et al. [24] and Marta et al. [25] with alemtuzumab induction therapy. Interestingly, majority of B cells remaining in the memory compartment were HLA specific B cells especially in the group of recipients with poor outcome and that may be because they could escape depletion by induction therapy. Zachary et al., [21,22] reported similar findings when they identified HLA class I specific B cells from end-stage renal patients and healthy volunteers using tetramers. While in Degauque et al., study majority of HSB identified by HLA-coated beads were within the mature naïve (CD27-IgD+) compartment from five immunized transplant recipients [18]. A phenomenon of anti-HLA antibodies generation has been described after some bacterial or autoantibodies directed against the heavy chain of soluble HLA-E could explain HLA class I reactivity [26,27] and even after vaccination [28]. Further, in the case of induction therapy at time of transplantation it has been shown that depletion of T and B cells below certain level can lead to homeostatic proliferation of memory B cells that escape the depletion producing de novo expansion of anti-HLA B cells and production of circulating HLA antibodies that may lead to humoral chronic rejection if the antibodies cross-react with shared epitopes presented by donor graft [29].

Targeting HLA specific B cells

Understanding the basic biology of HSB allow for use of specific therapeutics for instance, anti-CD20 (Rituximab) successfully control memory and active naive B cell responses,

targeting the B cell survival factor with anti-BAFF/BLyS (anti-BAFF; belimumab) reduces mature B cell pool as well germinal center B cell responses, additional inhibition of plasma cells can be achieved by combined inhibition of BAFF and APRIL with TACI-Ig; (atacicept) [30]. Depletion of short-lived antigen specific cells can be achieved with the small molecule inhibitor of proteasome, bortezomib (Velcade), which promotes plasma cell apoptosis and inhibits cell proliferation [31].

In conclusion comparable assays are being used to quantify plasma cells and memory B cells specific for HLA or pathogens in transplant patients. These assays will guide clinicians to quantify the efficacy of immunosuppression targeting each B cell or plasma cell subset.

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Functional Magnetic Resonance Imaging of Kidney Transplant: Current Status and Future Prospective

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Introduction

Kidney transplantation is one of therapeutic choice for patients with End-Stage Renal Disease (ESRD). It can be from live or cadaveric donors. Diagnosis of graft dysfunction and its cause represent a challenge and important clinical problem; in particular, distinguishing transplant rejection from other causes, including drug toxicity and acute tubular necrosis. Biopsy of the kidney and histopathology is the gold standard for diagnosis of kidney transplant dysfunction, the invasive biopsy beside its high cost it carry the risk of complications such as hemorrhage and vascular injury.

Many diagnostic attempts have been made to reduce the need for an invasive transplant biopsy, considered the "gold standard" for the diagnosis of parenchyma dysfunction. In a study done by Benozzi et al., they confirmed that contrast enhanced US (CEUS) using micro-bubbles is a noninvasive, easy technique, which provides information on renal tissue microcirculation and regional parenchyma flow. It identified the early graft dysfunction [1]. In another study done by Eisenberger et al., they found that diffusion weighted (DW)-MRI allows reliable determination of diffusion and microcirculation contributions in renal allograft shortly after transplantation; deviations in acute rejection indicate potential clinical utility of this method to non-invasively monitor derangements in renal allograft [2]. Some authors used the dynamic contrast enhanced MRI with MR renographic curves to evaluate the changes in the kidney [3,4].

Magnetic Resonance Imaging (MRI) is a non-invasive technique bringing essential information in the diagnostic of kidney transplant rejection since it can provide data on the anatomic and functional status of the transplanted kidney [5].

MRI is promising due to its multiplanar capabilities and lack of ionizing radiation, invasiveness, and contrast medium-induced nephrotoxicity.

Conventional MRI techniques including Gadolinium-enhanced Magnetic Resonance Angiography (MRA), Magnetic Resonance Urography (MRU), gadolinium and gadolinium-enhanced T1-weighted coronal parenchyma imaging (MR nephrography) offers what is called a onestop diagnostic technique in the evaluation of the entire renal transplant and peritransplant region. “Onestop shop” MR protocols have been used for comprehensive evaluation of the transplant kidney in the same session with the same injected dose of contrast to evaluate the kidney vasculature, parenchyma and pelicalyceal system as well as the ureter and bladder, it provides morphological details and improve the diagnostic accuracy of the routine conventional sequences including T1-weighted, T2-weighated images and the static MRU. The use of gadolinium enhanced conventional techniques provides some functional data about the excretory function of the kidney [6,7].

There are many trials to use the recent MRI techniques such as Dynamic Contrast Enhanced (DCE) MRI, Diffusion Weighted (DW) MRI, Arterial Spin Labeling (ASL) and Blood Level Oxygenation (BOLD) MRI and MR Spectroscopy (MRS) in the diagnosis of kidney dysfunction specially cases of acute kidney rejection.

In this review we will present the different MRI techniques used for evaluation of the transplanted kidney and the future prospects including biomedical technology and computer aided diagnosis.

Dynamic Contrast Enhanced MRI (DCE MRI)

In Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI), a contrast agent called Gd-DTPA is injected into the bloodstream, and as it perfuses into the organ, the kidneys are imaged rapidly and repeatedly. During the perfusion, Gd-DTPA causes a change in the relaxation times of the tissue and creates a contrast change in the images. As a result, the patterns of the contrast change give functional information, while MRI provides good anatomical information which helps in distinguishing the diseases that affect different parts of the kidneys (Figure 1). However, even with an imaging technique like DCE-MRI, there are several problems: (i) the spatial resolution of the dynamic MR images is low due to fast scanning, (ii) the images suffer from motion induced by the breathing patient, which necessitates advanced registration techniques, (iii) the intensity of the kidney changes non-uniformly as the contrast agent perfuse into the cortex, which complicates the segmentation procedures [8]. There are many studies done to use motion corrected MR renography to diagnose the cause of kidney transplant dysfunction such as study done by About El-Ghar et al., and they introduced a new computer aided approach to classify normal kidney function from kidney rejection using dynamic contrast enhanced magnetic resonance imaging. They realized that the medulla region has specific responses to DCE-MRI that were helpful identifying kidney rejection. The response of medulla regions to DCE-MRI in their study was helpful in distinguishing kidneys with impaired function from normal kidneys. The limitation of the study was the overlap between SI of the cases with acute tubular necrosis and acute rejection [3].

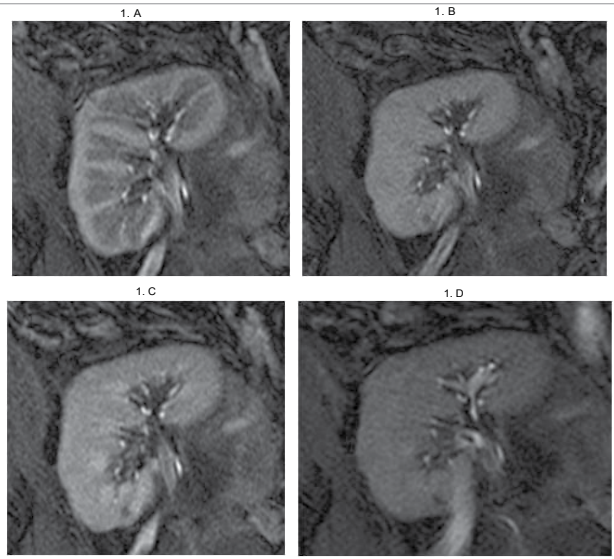

Figure 1: A case of dynamic contrast MRI in normal kidney transplant using coronal GRE T1-weighted sequence shows contrast transition from cortex to medulla with time; (a) early post- contrast scan shows enhancing cortex, (b) after one minute the contrast is equal in cortex and medulla, (c) later on the medulla is more hyper intense than cortex and at delayed image after 5 minutes the contrast excreted into calyces (d).

There is also another limitation for use of contrast media in patients with renal impairment and GFR < 30 ml/min due to the risk of nephrogenic systemic fibrosis.

Diffusion Weighted MRI (DWMRI)

Diffusion-Weighted Imaging (DWI) is a technique used to provide quantification of Brownian motion of water protons by calculating the Apparent Diffusion Coefficient (ADC), and can be used for in vivo quantification of the combined effects of capillary perfusion and diffusion [9].

The kidney function depends upon the transportation of water (glomerular filtration, active and passive tubular reabsorption, and secretion). So; diffusion characteristics may provide a useful insight into the functional consequences of different renal diseases [10].

There are some studies have involved measurement of water diffusion in the kidneys [11-15]. Some investigators have reported higher values in the medulla than in the cortex of the kidney [11,15] whereas others have reported the opposite [13,14].

Comparison of these results is difficult because of the different imaging strategies employed in these studies.

A study by Thoeny et al., [16] evaluated 15 patients with a renal allograft with stable function and compared them with healthy volunteers. They reported that the ADC values were virtually identical in the cortex and the medulla of transplanted kidneys. Yang et al., [17] used DW MRI to assess transplanted kidneys in rats; in addition, they observed a small difference in ADC between the cortex and medulla, in contrast with the findings of Thoeny et al., [16]. Allografts exhibited significant decreased ADC values and isografts exhibited similar ADC values compared with native kidneys. Reduction in renal blood flow with the

use of a renal vasoconstrictor, angiotensin II, also resulted in a concomitant decrease in ADC values [17]. Blondin et al., [18] assessed the clinical value of DWI in the functional evaluation of transplanted kidneys. They found that, the difference in ADC between patients with normal function and those with kidney dysfunction.

Eisenberger et al., [2] evaluated the DWI in 15 patients at the early transplant period, 5–19 days after transplantation, using a 3 T MRI machine. They found that DWI allows reliable determination of diffusion and microcirculation contributions in renal allografts shortly after transplantation; deviations in acute rejection might indicate the potential clinical use of this method to non-invasively monitor derangements in renal allografts.

In a recent study done by Abou El-Ghar et al., [10] done at 1.5T MRI and used high b value (800 mm^2/sec) they found that the ADC values in patients with stable kidney function were significantly higher than in patients with altered kidney function.

The lack of contrast media in DWI MRI is a great advantage with no limitations due to impaired renal function (Figure 2).

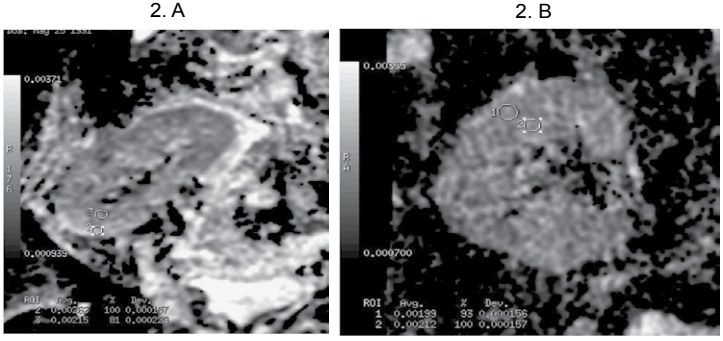

Figure 2: Diffusion weighted MRI of kidney transplant with Apparent Diffusion Coefficient (ADC) of the cortex is less than medulla in normal kidney transplant (a), while in kidney transplant dysfunction the ADC is still high in cortex than medulla but both are of low value than the normal kidney (ADC of cortex and medulla is 2.15x $10^{-3}/s^2$ and 2.5 x $10^{-3}/s^2$ in normal kidney, and 1.99 x $10^{-3}/s^2$ and 2.12 x $10^{-3}/s^2$ in kidney dysfunction).

Blood Oxygen Level-Dependent MRI (BOLD MRI)

Assessment of parenchymal oxygen bioavailability can be done by the Non-Invasive Blood Oxygen Level Dependent MRI (BOLD MRI) [19]. BOLD imaging determines the relative local tissue oxygen concentration, It can diagnose early renal transplant dysfunction as the blood oxygen level changes occur during the pathophysiological courses of early kidney allograft dysfunction [20].

BOLD technique is based on the paramagnetic properties of deoxyhaemoglobin, the unpaired electrons of deoxyhemoglobin generates magnetic moments in the magnetic field. Deoxyhaemoglobin concentration changes will result in increased magnetic spin dephasing of blood water protons and decreased signal intensity on T2*-weighted MR imaging sequences [21].

Djamali *et al.*, and Sadowski *et al.*, found that there is significant changes of medullary oxygen availability during BOLD MRI study of allografts with biopsy-proven ATN and acute rejection [22,23].

In a study done by Han et al., they found that in acute allografts rejection the tissue

oxygen bioavailability (oxyhaemoglobin concentrations) increased significantly, as R2* levels decreased (P <0.001) both in the cortex and medulla compared to normal functioning allografts, but oxygen bioavailability in the medulla seemed to change more remarkably. While in cases of acute allograft tubular necrosis there was decreased oxygen bioavailability both in the cortex and medulla compared to normal functioning allografts (P<0.05) [20].

Arterial Spin Labeling (ASL)

MRI with contrast has been used to evaluate the perfusion and hemodynamic changes of renal allografts [24]. Renal artery stenosis is the most frequent complication in the renal allograft after transplantation [25], Doppler sonography is generally used as a screening tool for renal artery stenosis, but findings depend on the operator's skills and experience. MR angiography with gadolinium is highly sensitive for diagnosis of renal artery stenosis, gadolinium is considered problematic in transplant recipients with impaired renal function due to the potential risks for the development of nephrogenic systemic fibrosis [26]. Non-enhanced MR imaging is gaining more importance in patients with an impaired function of the transplant kidney [16].

ASL technique has the ability to perform perfusion measurements without the use of gadolinium-based contrast material [16].

ASL imaging is a promising technique in grading of renal artery stenosis in native kidneys [27].

The basic principle of ASL techniques is the labeling of arterial blood at the tissue of interest by alteration of its longitudinal magnetization. With Flow-Sensitive Alternating Inversion Recovery (FAIR) ASL techniques, the difference between acquisitions with nonselective and slice-selective inversions is proportional to tissue perfusion [28,29].

Heusch et al., in their study found a good correlation between quantitative perfusion determined with ASL MRI and the eGFR as a marker of clinical function [30].

Moderate dysfunction in the kidney leads to a significant reduction of blood perfusion for both the medulla and the cortex of native kidneys [31]. Therefore, in kidney transplant patients with a decreasing allograft function, ASL-perfusion has the potential to become a useful diagnostic tool. The clinical potential of ASL MRI is highlighted by the observation, that ASL perfusion was significantly higher in patients with poor allograft function and recovery of renal function as compared to those who developed chronic allograft failure and required dialysis [30].

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Pathology of Renal Allograft Rejection: The Banff Classification System: Scoring and Pitfalls

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Abstract

The histopathologic scoring of renal allograft rejection for diagnosis and grading of transplant biopsy is widely based on the Banff classification. The Banff classification is refined through biannual open meeting to reach consensus on addition/changes based on published, confirmed evidence. The adequacy of specimen to apply Banff scoring system is 7 glomeruli and 2 arteries should be noted. The individual Banff scoring categories included interstitial inflammation; tubulitis; vascular inflammation; glomerulitis; interstitial fibrosis; tubular atrophy; arterial fibrointimal thickening; transplant glomerulopathy; mesangial matrix increase; arteriolar hyalinosis; peritubular capillary (ptc) inflammation, C4d score in Peritubular capillary and total inflammation. The Banff diagnostic categories included normal, antibody mediated rejection C4d positive either acute or chronic; Borderline or suspicious for acute cellular rejection; T-cell mediated rejection; interstitial fibrosis and tubular atrophy, no evidence of any specific etiology. Other pathology of non-immunologic reasons such as calcineurin inhibitor toxicity; polyomavirus infection and others. The Banff classification is currently based on light microscopy, immunofluorescence, immunohistochemistry, and in some instances on electron microscopy. The diagnosis categories are defined by semi-quantative scores with the opportunity to add other modalities such as Panel Reactive Antibody (PRA), Donor Specific Antibodies (DSA) and gene expression profile. However, many pitfalls of the classification were encountered such as the detailed criteria is established only for rejection categories the pathologic categories were not pathognomonic for the diagnostic categories.

Biopsy processing

Sample

The 16-gauge needle better than 18-gauge for sample adequacy. For 18 gauge single cores, it was found that 47% were inadequate, contained less than 7 glomeruli and one artery versus 24% inadequate for the 16-gauge biopsies. It was reported that the sensitivity for acute rejection was 90% in single core while raised to 99% if 2 cores were obtained.

Specimen adequacy

The Banff requirement for specimen adequacy was minimum 7 glomeruli and 2 arteries. However some lesions could be diagnosed in medularly tissue as antibody mediated rejection and polyoma virus infection.

Routine pathology techniques

Light microscopy Serial sections of 2-3 microns prepared, stained for H&E, PAS, trichrome, and other stains.

Immunohistochemistry for cell phenotype, viruses when required. Immunohistochemistry for C4d on paraffin if immunofluorecence was unavailable.

Immunoflurescence microscopy On frozen tissue for C_4d. Full panel for immunoglobulinsm IgG, IgA, IgM, C3, C1q, fibrinogen, kabba and lambda light chains if glomerular disease was susbected.

Electron microscopy If there is suspicion for glomerular disease.

Graft biopsy evaluation

Examination of serial sections is mandatory as most lesions were focal as endarteritis. Thorough examination of the four anatomical components, the glomeruli, tubules, interstitium and vessels. Reporting the extent of changes. The number of glomeruli and arteries per core/cores. Quantization of the percent of pathologic features e.g. the extent of inflammatory infiltrate or fibrosis of the renal cortex, the glomeruli were examined for sclerosis, glomerular basement membrane duplication. The tubules were scored for tubulitis, extent of tubular atrophy. The arteries were inspected for endarteritis, fibrinoid necrosis or intimal fibrosis. The findings at the current biopsy have to compared with previous biopsy if any. The diagnostic findings were reported according to the Banff scoring system for diagnosis and grading of allograft biopsy. Interpretation of findings needs to be made in conjunction with clinical information [1].

Clinical information needed

Clinical data needed included the donor information, time post transplant, whether kidney had good initial function, drug therapy, original disease, renal function and anti-donor HLA antibodies. Multiple disease may be present e.g. rejection, drug toxicity, viral infection, donor disease comparison with a previous biopsies for progression or resolution process, as late samples may be non-diagnostic of the cause [2].

Acute Rejection

Acute rejection, acute cellular rejection, acute T-cell mediated rejection.

Definition

Acute immunologic reaction to renal alloantigens mediated by T cells. It has 3 morphologic grades. Type I: tubulointerstitial; type II: endarteritis; type III: fibrinoid arterial necrosis or transmural inflammation [3].

Etiology/pathogenesis

Acute cellular rejection mediated by alloreactive T cells against donor antigen either Major HistoCompatibility MHC (HLA) or non-MHC. The target antigen varied and included capillary and arterial endothelium, tubules, and glomeruli [2].

Clinical features

Acute rejection represented 5-10% in the first year post-transplant. Type I: less than 65%, type II about 30% and type III less than 5%. Acute rejection patients presented by

acute renal failure, or decreased urine output, or graft tenderness in severe cases. Type I acute rejection patients and cases of borderline/suspicious for acute cellular rejection are usually responsive to pulse steroid therapy. Type II usually resistant to pulse steroid therapy; additional treatment may consisted of anti T-cell therapies. The one year graft survival for type I was 95%; type II: 75% and for type III less than 15% [1].

Microscopic pathology

Histologic features

Glomeruli

The glomeruli usually spared, occasionally may showed glomerular capillaries. The glomerulitis were more common in humoral rejection and the macrophages are predominate cell type. glomerulitis was not included as criterion for acute cellular rejection. Acute allograft glomerulopathy was observed in less than 5% of acute rejection, markedly swollen endothelial cells occluding the capillary lumen, mesangiolysis with PAS positive webs. It usually associated with type II ACR [4].

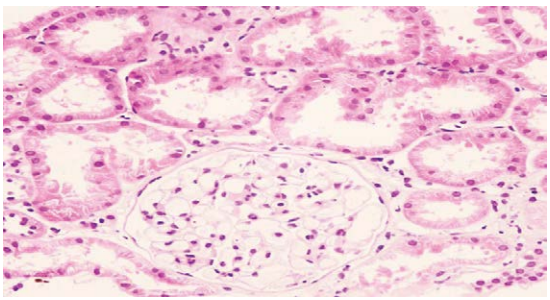

Figure 1: Normal graft cortex

Interstitium

The interstitium showing mononuclear cell inflammation in the interstituim [figure 2,3]

The Banff crieterion requires more than 25% of non scarred cortex to have mononuclear infiltrate for the diagnosis of ACR. Lesser degrees of inflammation considered suspicious or borderline for rejection. The cells mostly CD4 +ve and CD8 +ve T cells and CD68 +ve macrophages. B cell usually not prominent. Eosinophils, plasma cells, and a few neutrophils may also present in the infiltrate. Plasma cell-rich rejection has a a worse prognosis. Interstitial edema accompanied the inflammation; interstitial haemorrhage could be found in severe cases [4].

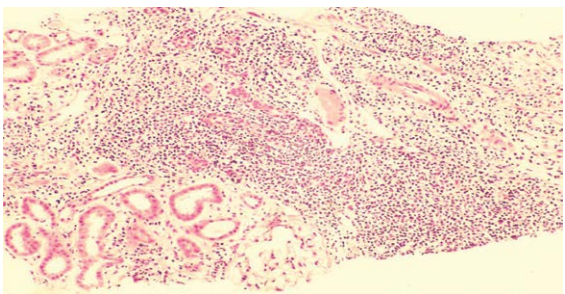

Figure 2: Interstitial inflammatory infiltrate of mononuclear cells is of the defining feature of type I acute cellular rejection, moderate amount score i-2.

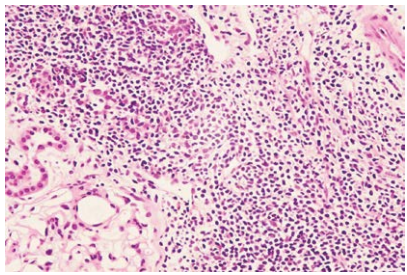

Figure 3: Interstitial inflammatory infiltrate of mononuclear cells is of the defining feature of type I acute cellular rejection, marked amount score i-3.

Tubules

The tubules were remarkable for tubulitis (Figure 4) which denotes for the presence of T-cell and macrophages within the tubule. The Banff criteria evaluation is for the non atrophic tubules only. Tubular cell injury with loss of brush border, apoptosis may be evident. Rupture of the tubular basement membrane could occur in case of sever tubulitis. The tubulitis scoring included t-1 for mild tubulitis with 1-4 mononuclear cells/tubular cross section, t-2 for moderate tubulitis with 5-9 mononuclear cells and t-3 severe tubulitis with >10 mononuclear cells [3].

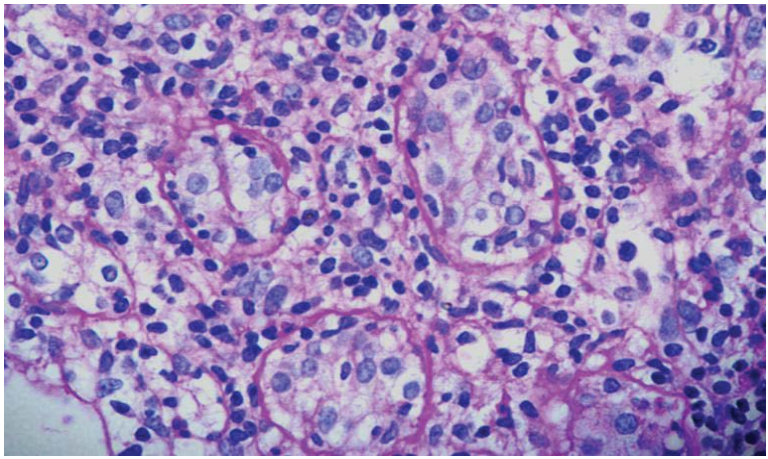

Figure 4: Tubulitis and interstitial mononuclear inflammation are the defining feature of type I acute cellular rejection.

Arteries

Mononuclear inflammatory cells beneath endothelium in arteries, endarteritis (Figure 5,6,7,8) or endothelialitis. The immunophenotype of the mononuclear cells revealed C3 +ve T-cells and CD68 +ve monocyte/ macrophages. If the endarteritis involved less than 25% of the luminal areas at cross section of the arteries or about 12% of the arterioles, so the lesion is focal. Endarteritis involved large arteries than arterioles. The endotheliatitis observed in arterioles sometimes seen in conjunction with endothelialitis in arteries has the same significance. Marginated mononuclear cells a long endothelial surface does not count for endarteritis, but associated it. Venulitis formed in some cases of ACR, but it did not prognostically significant. Activation of endothelium with basophilic cytoplasm and enlarged active nuclei could be seen. Severe endarteritis cases with transmural inflammation, fibrinoid necrosis occasionally seen in severe cases, however it is commonly observed with cases of antibody-mediated rejection [1].

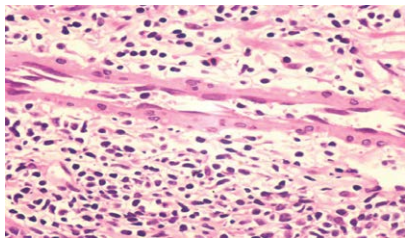

Figure 5: Endarteritis in a renal transplant biopsy a defining feature of acute cellular rejection with intimal infiltration by few inflammatory cells, score V-1. The endothelial cells appeared swollen and activated.

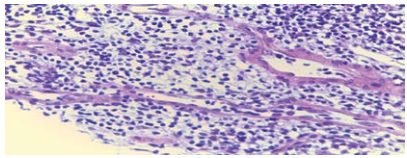

Figure 6: Endarteritis in a renal transplant biopsy a defining feature of acute cellular rejection with intimal infiltration by few inflammatory cells, score V-1. The endothelial cells.

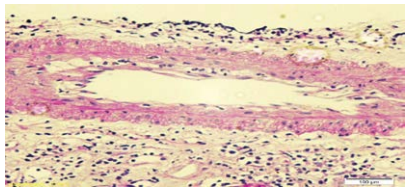

Figure 7: Endarteritis in a renal transplant biopsy, the defining feature of type II acute cellular rejection with intimal infiltration by many mononuclear inflammatory cells, score V-2.

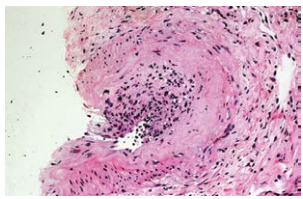

Figure 8: Severe endarteritis in a renal transplant biopsy with large number of inflammatory cells involved the intima with narrowed lumen.

Definition

Rejection immediately minutes to hours upon implantation and perfusion of the graft.

Etiology / pathogenesis

Antibody mediated

Pre-existing antibodies to donor endothelium at time of transplantation. It may be due to anti-donor ABO blood group or HLA antibody class I or class II. Non-HLA or non-blood group antibody-mediated hyper-acute rejectionwere rarely encountered. Anti-donor antibody titers high enough to cause immediate rejection. Lower levels of antibody titres cause acute humoral rejection with a delayed onset within days. The antibodies activate complement, endothelial cells and platelets. T-cell mediated with premed cytotoxic T-cells may have a role very rare [5,6].

Clinical features

Hyperacute rejection accounted for less than 0.5% of transplants. Improvement of pretransplant testing for antibody against donor resulted in decreased incidence. Patients with hyperacute rejection presented with either anuria, primaly nonfunction of the graft, fever and lack of graft perfusion by imaging studies. Currently there is no effective treatment. Preventive therapy in ABO-incompatible or positive cross match transplants by plasma pheresies to remove the donor – specific antibody, intravenous immunoglobulin, rituximab (anti-CD_{20}), splenectomy, experimental panticomplement drugs. The prognosis usually is rapid graft loss [1,7,8].

Macroscopic pathology

The graft looks cyanotic minutes to hours after perfusion, then it becomes swollen, hemorrhagic with focal necrosis over 12-24 hours [9].

Microscopic pathology

The hislologic features

- Early (1-12 hours)

There are platelet and neutrophil margination in glomeruli and peritubular capillaries with compacted red blood cells. Some glomeruli and arterioles may showed scattered thrombi [10].

- Later (12-24 hours)

The interstitium is remarkable for edema and haemonhage. There is widespread thrombi (Figure. 10) in glomeruli and arteries. Fibrinoid necrosis of arteries. Cortical and medullary necrosis. Histologic features resemble severe acute humoral rejection [10].

Immunohistochemistry

Staining for C4d and CD61 for paletelets in peritubular capillaries and glomeruli.

Immunofluorescence

- Most cases showed positive staining for C4d in peritubular capillaries. Cases with negative or granular staining for C4d did not excluded for hyperacute rejection diagnosis. Technical staining difficulties may resulted because of poor perfusion early and lack of tissue viability late; the possibility of C4d negative antibody mediated hyperacute rejection; the possibility of T-cell-mediated hyperacute rejection [11].
- Staining for IgG, IgM, and/or C3 may be present in capillaries; IgM is the most common in ABO-in-compatible grafts.
- Thrombi are stained for fibrin.

Electron microscopy

The glomeruli may be remarkable for swollen, enlarged endothelial cells; subendo thelial lucency; loss of endothelium leaving bare basement membrane in glomeruli. Detection of fibrin tactoids, platetet aggregates, neutrophils. Similar changes may be noted in the peritubular capillaries [12].

Differential diagnosis

- Major vascular thrombosis-renal artery or vein.
- It may resulted from technical problems of the vascular anastomosis or as a result of hypercoagulable state. There may be infarction (Figure 9,10) the thrombosis is usually limited to larger vessels. Staining for C4d is negative in viable tissue.

- Perfusion nephropathy there is extensive loss of endothelium, thrombi and congestion within capillaries, negative staining for C4d [1,13].

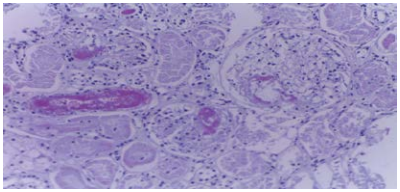

Figure 9: Graft cortical infarction.

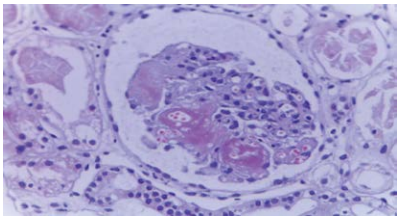

Figure 10: Acute humoral rejection severe example showing massive glomerular capillary thrombosis.

Acute Humoral Rejection

Etiology/pathogenesis

Donor-Specific Antibody (DSA), DSA usually directed against HLA class I or II on endothelium.ABO blood group antigen in ABO-incompatible grafts. Other, unknown, non-MHC antigens on the endothelium. DSA activates complement via classical pathway; the C4d is an inactive fragment of C4b of the classical complement pathway; C4d is covalently bound at the site of complement activation on the endothelium; complement fixing DSA associated with greater acute graft injuries [11].

Clinical features

Acute humoral rejection incidence is less than 25% of acute rejection episodes are due to antibody. Patients with acute humoral rejection are presented by acute renal failure and oliguria. Tests detected circulating donor-specific anti-HLA class I or II antibody in 88-95% of acute humoral rejection with C4d deposition [14].

Minority 5-10% have undetectable DSA, this may be due to non-HLA antibody, possibility of antibody absorption by the graft. Acute humoral rejection patients treated by plasmapheresis, increased immunosuppression, intravenous immunoglobulin, rituximab anti-CD20, B cell, anti-plasma cell therapy.

Experimental as bortezomib,proteosome inhibitor, complement inhibition-experimental as aculizumab, inhibitor of C5 and others. The prognosis of patients with acute humoral rejection is 30% graft loss within one year versus 4% graft loss for acute cellular rejection. There is increased risk for development of transplant glomerulopathy. The plasma cell-rich variant is resistant to treatment and has poor clinical outcome [15].

C4d- Negative ABMR.

C_4d- negative ABMR is defeined by Microvasculas Injury (MVI, glomerulitis, resitubulas capillaritis. Thrombotic microangiopathy) in the presence of DSA. Colvin R showing that even in for-cause biopsies with acute MVI and DSA analyzed by the most sensitive indirect IF method about 20% of such biopsies showed no detectable C_4d staining [16,17].

Microscopic pathology

Histologic features

The glomeruli displayed glomerulitis, neutrophils, monocytes, fibrin. Glomerular thrombosis or mesangiolysis could be evident specially in cases of ABO blood group-incompatible grafts. The peritubular capillaries are remarkable for dilatation, neutrophils and mononuclear cells. In a minority of cases fibrinoid necrosis of arteries could occur. Interstitial edema, sparse interstitial infiltrate and occasionally interstitial haemorhage are usually an accompanied findings. Cases with plasma cell rich infiltrate; termed plasma cell rich variant showed interstitial edema and high interferon gamma. The tubules showing acute tubular injury, little or no tubulitis, sometimes there are intraluminal neutrophils intraluminal [10].

The Banff classification of acute humoral rejection (Table 1) included; Type I: acute tubular injury, minimal inflammation, Type II: peritubular capillary and/or glomerular capillary inflammation and/or thrombosis, (Fig. 10, 11) Type III: Arterial fibrinoid necrosis or transmural inflammation-V-3 lesion. In addition to these histologic patterns, cases should be positively stained for C4d in peritubular capillaries and there is a serologic evidence of Donor Specific Antibodies (DSA). If there is only one of these two criteria is present beside the histologic changes, so the biopsy reported as suspicious for AHR [18].

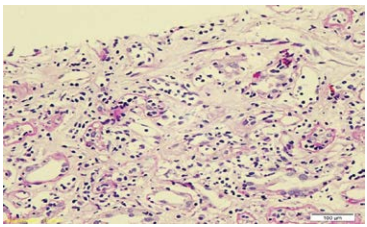

Figure 11: The peritubular capillaries were remarkable for being dilated, contained mononuclear inflammatory cells.

	Acute / active ABMR, all three features must be present for diagnosis.
1	Histologic evidence of acute tissue injury, including one or more of the following: microvascular inflammation (9>0 and / or ptc>0). Intimal or transmusal artesitis (v>0). Acute thrombotic microangiopathy, in the absence of any other cause. Acute tubular injury, in absence of any other apparent cause.
2	Evidence of current / recent antibody interaction with vascular endothelium, including at least one of the following: linear C4d staining in presitubular capillaries c4d 2 or c4d3 by if on frogen sections, or c4d>0 by IHC on paraffein sections. At least moderate microvascular inflammation gt ptc ≥ 2. Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury.
3	Serologic evidence of Donor- Specific Antibodies (DSAs) HLA or other antigens.

Table(1): The revised Banff 2013 classification of Antibody-Mediated Rejection (ABMR) in renal allografts [17].

ABMR, antibody mediated rejction; g, glomerulitis score;
ptc, peritubular capillary inflammation score;
V, Banff arteries score;
IF, immunofluorescence;
IHC immunohistochemistry;
DSAs, donor specific antibodies;

HLA, human leukocyte antigen.

Immunofluorescence

Staining for C4d by immunofluorescence showing diffuse, bright positive staining in the peritubular capillaries (Figure 12). However there is some cases of probable AHR that are negative for C4d. The score of focal C4d with (10-50%) of positive peritubular capillaries was less commonly showing detectable DSA. Positive staining for C4d remained for 5-7 days after removal of the antibodies from the circulation [18].

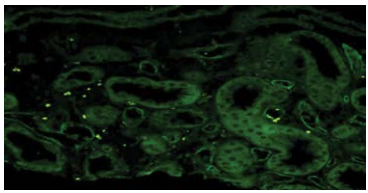

Figure 12: Diffuse bright staining of peritubular capillaries for C4d by immunofluorescence.

Immunohistochemistry

Immunostaining for C4d on paraffin section (Figure 13) is less sensitive than the immunoflurescence on the frozen section and required diffuse staining of the peritubular capillaries [6].

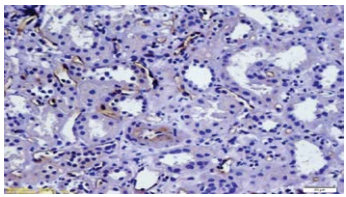

Figure 13: Immunohistochemical stain for C4d showing diffuse positivity in peritubular capillaries.

Electron microscopy

Examination of the peritubular capillaries and glomerular endothelium changes may revealed cell enlargement. Loss of endothelial fenestration, microvillous changes, detachment from the basement membrane, lysis or apoptosis [12].

Differential diagnosis

Chromic humoral rejection,

Chronic humoral rejection showing transplant glomerulopathy, thickened peritubular capillaries with evidence of multilayering on ultrastructure, presence of transplant arteriopathy. Graft function are usually stable or showing slowly decline clinical course. The associated inflammatory infiltrate is mononuclear rather than neutrophils [12].

Acute cellular rejection

About one third of cases of acute rejection are positively stained for C4d indicative of concurrent antibody-mediated rejection [6].

Accomodation

Cases that showed no histologic evidence of graft tissue injury and without graft dysfunction but showed positive staining for C4d are commonly seen in ABO blood group-incompatible grafts [1].

Acute pyelonephritis

The presence of neutrophils and neutrophilic tubulitis are a common features for AHR and acute pyelonephritis. The presence of neutrophilic casts on biopsy and positive urine calture for bacterial infection favor pyelonephritis. C4d staining is negative in pyelonephritis.

Acute tubular necrosis/ injury, showed Negative C4d staining [3,19].

Chronic humoral rejection

- Chronic Humoral Rejection (CHR) or chronic Antibody-Mediated Rejection (Chronic AMR)

- Etiology/pathogensis
- Donor-specific antibody

Episodes of antibody-mediated endothelial injury/activation/ repair. The antibodies activates the complement by the classical pathway that is expressed morphologically by C4d deposition (table 3). Endothelial damage by antibody without complement as evident by in vitro studies and animal models. The donor specific antibody (DSA) against HLA class II are the most common [20].

Transplant arteriopathy as manifestation of CHR

A mouse model RAG-1 Knockout mice with passive transfer of complement-fixing, anti-MHC antibody develop C4d deposition and Transplant Arteriopathy (TA).

The antibody is sufficient for the development of TA in the absence of functioning B and T cells. TA remains after the administration of alloantibody and after disappearance of C4d. The non-complement fixing, anti-MHC antibody can also produce TA and this can explain some cases of C4d negative CHR [6].

Clinical features

The presentations of CHR are chronic renal failure, proteinuria or hypertension. Serum tests for donor specific antibody direct against HLA class I or class II are usually detected but it might not be detected in serum at the time of biopsy. There is no effective treatment, rituximab (anti-CD20), intravenous immunologlobulin, bortezomib (proteosome inhibitor) to deplate plasma cells that produce alloantibody. The graft survival at five year is 50% after the diagnosis of transplant glomerulopathy. Cases positive for C4d have poorer prognosis. Subset of cases with molecular markers of endothelial activation have poorer survival even if they were negative for C4d [21].

Histologic features

Transplant glomerulopathy (Chronic allograft glomerulopathy) is the duplication of the Glomerular Basement Membrance (GBM), the quantitative crieteria for the chronic transplant glomerulopathy is illustrated in table (2). Absence of evidence of immune complex glomerulonephritis or chronic thromotic microangiopathy. Glomerulitis may be present, the majority of mononuclear cells stained for CD68 monocytes and a minority of cells stained for CD3 T cells. Transplant arteriopathy (Figure 14) (chronic allograft arteriopathy where the arteries showed fibrous initial thickening, the inflammatory cells present within the thickned the initima stained for CD3 T cells and/or CD68 the marker for monocytes/, acrophages. Peritubular capillaropathy which is best delineated by electron microscopy that showed duplication or multilayering. Eventually loss of peritubular capillaries over time and this loss of the peritubular capillaries is correlated with increasing serum creatinine [22].

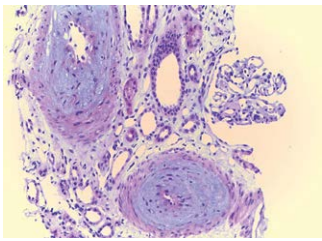

Figure 14: Chronic rejection with chronic transplant arteriopathy that cause subtotal arterial occlusion by intimal fibrosis appeared swollen and activated.

Peritubular capillaritis with the presence of mononuclear cells of moderate or severe, Banff ptc >1, is often seen in CHR and it may preceed the development of TG or other

CHR features in the presensitized patients with normal graft function. Some cases stained positive for C_4d. The interstitial fibrosis and tubular atrophy are a non specific features, may be seen in CHR and they were correlated with loss of PTCs [23].

Scoring for cg based on the fraction of involved Glomerular Basement Membrane (GBM) (Table 2) double contours in at least one capillary loop in a single glomerulus as opposed to the current threshold that based on involvement of ≥ 10% of capillary loops in the most severaly involved glomerulus which is better correlated with anti-class II DSA and ENDATs [24]. The aforementioned scoring of cg was based on light microscopy. Wavamunno MD et al. [25] demonstrated that endothelial and GBM lesions detected within the first 3 months posttransplantation by electrol microscopy are highly correlated with later development of overt transplant glomerulopathy. Endothelial swelling, subendothelial electron-lucent widening and early GBM duplication by EM was found to be highly correlated with DSA.

Cg-o-no	GBM double contours by light miscroscopy or EM.
Cgla-no	GBM double contours by light miscroscopy but GBM double contours (incomplete or circumferential) in at least three glomerular capillaries by EM with associated endothelial swelling and/or subendothelial electron lucent widening.
Cglb-	one or more glomerular capillaries with GBM double contours in ≥1 non-sclerotic glomerulus by light microscopy; EM confirmation is recommended.

Table (2): Quantitative criteria for chronic transplant glomerulopathy [3].

	Chronic, active ABMR, all three features must be present for diagnosis
1	Morphologic evidence of chronic tissue injury, including one or more of the following: Transplant glomerulopathy TG (cg >0), if no evidence of chronic thrombotic microangiopathy. Severe peritubular capillary basement membrane multilayering (requires EM). Arterial intimal fibrosis or new onset, excluding other causes.
2	Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following: - Linear C4d staining in peritubular capillaries C4d2 or C4d3 by IF on frozen section, or C4d >0 by IHC on paraffin sections. - At least moderate microvascular inflammation g + ptc ≥ 2 - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury.
3	Serologic evidence of DSAs (HLA or other antigens).

Table (3): Revised Bnaff 2013 classification of antibody-mediated rejection ABMR in renal allografts [17].

Immunohistochemistry

Immunostaining for C_4d in the PTCs may be a diagnostic clue for CHR. Glomerular capillary staining for C4d in paraffin sections is suggestive for CHR, but it seen in other causes as immune complex disease and thrombotic microangiopathy [17].

Immunofluorescence

Staining for C4d deposition in PTCs is either diffuse, focal or negative. More than 40% of cases with TG may not be C4d positive on biopsy, this may be because of the antibody levels vary with time that may be below threshold for C4d at the time of biopsy. The duplication of GBM represents previous active endothelial injury by antibody. C_4d negative cases may represent non-complement-fixing DSA [11].

Electron microscopy

Electron microscopy is more sensitive for TG than light microscopy. Early changes that detected by electron microscopy included hypertrophied endothelium and vacuolization, expenaded lamina rara interna subendothelial serration of GBM with early GBM duplicatoion. Peritubular capillaries basement membrane multilamellation PTCBMML is graded as mild when there is 2-4 layers; moderate 5-6 layers, severe when 7 or more layers [26,27].

Differential diagnosis

Transplant glomerulopathy is differentiated from chronic thrombotic microangiopathy that sometimes associated with calcineurin inhibitor toxicity. Immune complex

glomerulonephritis recurrent or de nova, acute or chronic. In case of membranoproliferative glomerulonephritis or other, the cause of GBM duplication is related to immune depositis, and not due to antibody mediated. The transplant arteriopathy is differentiated from arteriosclerosis that is related to hypertension or may be donor disease. Arteries in arteriosclerosis showing fibrous intimal thickening that could be highlighted by elastic stain and there is no inflammatory cells in the intima. Chronic T-cell mediated rejection, transplant arteriopathy may be resulted from humoral rejection, T-cell mediated rejection or both. C_4d staining and the presence of donor-specific antibodies help in differentiation [6].

Chronic Cellular Rejection

Chronic cellular rejection (chronic T-cell mediated rejection or chronic active T-cell mediated rejection)

Definition

Persistent or recurrent T-cell mediated rejection leading to chronic changes in allograft ex. Transplant arteriopathy, interstitial fibrosis, and tubular atrophy.

Etiology/pathogenesis

T- cell mediated injury to arteries, tubules, and vasculature due to alloresponse to HLA antigens, other antigens including autoantigens. Macrophages and mast cells are participitating.

Clinical features

Patients are presented by chronic renal failure, hypertension, proteinuria, may be asymptomatic (subclinical rejection). The presence of interstitial fibrosis with inflammation has lower graft survival. The presence of chronic transplant arteriopathy also shorten the graft survival [3].

Pathological findings

Light microscopy

The glomeruli showing global glommerulosclerosis or focal segmental glomerulosclerosis. There is mononuclear interstitial infiltrate with the criteria of acute cellular rejection, interstitioal fibrosis. The presence of inflammation in areas of fibrosis was not counted in standard Banffi score, plasma cells often prominent. The tubules showed tubulitis in the non atrophic tubules, and tubulitis also in the atrophic tubules but it did not counted in the Banff t score. The arteries may showing intimal fibrosis (Figure 14) that lacks duplication of elastic in intima, typical of hypertension. The intima showed mononuclear cellular infiltrate or foam cells [6].

Immunoflurescence

There is no significant findings at immunofluorescence examination. Negative stain for C4d in the peritubular capillaries [6].

Differential diagnosis

Chronic antibody medicated rejection is differentiated by positivity for C4d and the presence of circulating donor-specific antibody. Presence of transplant glomerulopathy and the multilammelation of the peritubular capillaries.

Chronic calcineurin inhibitor toxicity is differentiated by the presence of severe arteriolar hyalinosis with peripheral nodular hyalinosis [20].

Late stage of BK polyoma virus nephropathy is differential by prior biopsies showing polyoma virus inflection. Hypertensive arteriosclerosis, the intima showing abundant duplication of elastiac and minimal or no mononuclear infiltrate [17].

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Vaccinations of Kidney Transplants: Updates for Optimal Protection

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Keywords: Transplantation; Vaccination post transplantation; Viral infections post transplantation

Background

Vaccination of immuno-compromised patients is important because impaired host defenses predispose patients to an increased risk or severity of vaccine preventable diseases [1]. With respect to vaccine preventable diseases, this risk includes:

- A higher attack rates and risks for severe and complicated illness.
- Limited efficacy and duration of vaccine induced protection in patients with chronic renal failure and due to post-transplant immunosuppressive treatments.

These patients may also have greater exposure to pathogens due to frequent contact with medical environments [2] however, vaccination rates are frequently low [3]. Under vaccination of immuno-compromised patients may occur because clinicians have insufficient or inaccurate information concerning the safety, efficacy and contraindication to vaccination of such patients [1]. There is a potential for serious illness and death in both the under immunization and over immunization of solid organ transplant recipients. Every effort should be made to ensure that transplant candidates, their household members and healthcare workers have completed the full complement of recommended vaccination prior to transplantation. Since the response to many vaccines is diminished in organ failure, transplant candidates should be immunized early in the course of their disease [4].

While every effort should be made to vaccinate prior to transplantation, inactivated vaccines are generally safe after solid organ transplantation. For inactivated vaccines where data are lacking specifically for transplant candidates or recipients, recommendations made by Advisory Committee on Immunization Practices (ACIP) in the United States for the general population should be followed. There is no evidence to link clinical rejection episodes to vaccination [4], thus the potential benefits outweigh the harm of immunization with inactivated vaccines.

In general, live vaccines are not administrated after transplantation. Therefore, when possible it is recommended to administer live vaccines such as measles, mumps, rubella

(MMR), Varicella vaccine and Zoster vaccine prior to transplantation. For patients who are incompletely or unvaccinated prior to transplant, construction with an infectious diseases specialist is recommended [4].

Clinicians are often concerned about the efficacy of vaccination in kidney transplant recipients who are on chronic immunosuppression or on hemodialysis. In a study by [5], seroconversion rates were low and not statistically different in both renal transplant (42%) and hemodialysis (33%) patients, but were much higher in healthy control (82%). For the transplant subgroup, seroconversion was associated with a longer time after transplantation and proteinuria. Numerous other factors including type of immunosuppression did not influence response to vaccination. In hemodialysis group, only younger age was associated with response. Thus, these data are not broadly applicable to all transplant and hemodialysis patients, but only to those who had no prior seroconversion. To achieve the optimal response to vaccination, clinicians should consider timing after transplant, because the first few months after transplant are likely to result in a reduced response to vaccination. Additionally, they should consider giving more frequent booster doses of vaccines because immunity wanes more rapidly in immunocompromised hosts [6].

Recommendations

An international panel of experts prepared an evidenced based guideline for vaccination of immunocompromised adults and children [1]:

A. Recommendations for adult and child solid organ transplant candidates and living donors during pretransplant evaluation: (Table 1) and see recommendations # 88 – 97 of Rubin el al.

B. Recommendations for solid organ transplant recipients:

see recommendations # 98 – 104 of Rubin el al.

Vaccine	Pretransplant		Starting 2-6 mo posttransplant	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilic influenzae b conjugate	U	Strong, Moderate	U	Strong, moderate
Hepatitis A	U: age 12-23 mo	Strong, Moderate	R, if not completed pre transplant	Strong, moderate
	R: ≥2 y	Strong, Moderate		
Hepatitis B	U:age 1-18 y	Strong, Moderate	R, if not completed pre transplant[a]	Strong, moderate
	R: ≥ 18 y	Strong, Moderate		Strong, moderate
Diptheria toxoid, tetanus toxoid, Acellular pertussis; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, Moderate	U, if not completed pre transplant	Strong, moderate
Human papillomavirus	U:females 11-26 y	Strong, Moderate	U:females 11-26 y	Strong, Moderate
	U:males 11-26 y	Strong, low	U:males 11-26 y	Strong, low
Influenza- inactivated(inactivated influenza vaccine)	U	Strong, Moderate	U[b]	Strong, Moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, low	X	Weak, low
Measles,mumps, and rubella-live	R[c]: 6-11 mo	Weak, very low	X	Strong, low
	U[d]: age ≥ 12 mo	Strong, Moderate		
Measles,mumps, and rubella-varicella-live	U[d]	Strong, Moderate	X	Strong, low
Meningococcal conjugate	U	Strong, Moderate	U	Strong, Moderate
Pneumococcal conjugate (PCV13)	U:age ≤5 y	Strong, moderate	U:Age 2-5 y	Strong, Moderate
	R: age ≥ 6y[e]	Strong, very low	R; age ≥ 6 y if not administered pretransplant[e]	Strong, very low

Pnumococcal polysaccharide (PPSV23)	R: age ≥ 2y	Strong, moderate	R: age ≥2y, if not administered pretransplant	Strong, Moderate
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong,moderate	U	Strong, moderate
Rotavirus-live	U[e]	Strong,moderate	U	Strong,low
Varicella-live	R[f]:6-11mo	Weak, very low	X[g]	Strong,low
	U[d]	Strong, low		
Zoster-live	R[h]: age 50-59 y	Weak,low	X	Strong, low
	U[i]: age ≥ 60 y	Strong, moderate		

Table 1 Vaccinations Prior to or After Solid Organ Transplant [1]

Abbrevations: R, recommended-administer if not previously administered or nor current; such patients may be at increased risk for this vaccine-preventable infection; U, usual-administer if patient not current with annually updated Centers for Disease Control and Prevention recommendation for immunocompetent persons in risk and age categories; X, Contraindicated.

[a] Consider hepatitis B vaccine for hepatitis B- infected liver transplant patients(weak, low)

[b] Inactivated influenza vaccine may be administered to solid organ transplant receipients despite intensive immunosuppression (eg. During the immediate post transplant period), particularly in an outbreak situation (weak, low).

[c] Administer only if patient is not immunosuppressed and the timing is ≥ 4 weeks prior to transplant.

[d] Administer only if patient is nonimmune, not severly immuno suppressed, and the timing is ≥ 4 weeks prior to transplant.

[e] For patients aged ≥ 19 years who have received PPSV23, PCV13 should be administered after an interval of ≥1 yr after the last PPSV23 dose (week, low).

[f] Administer only if patient is not immunosuppressed and the timingis ≥ 4 weeks prior to transplant. This recommendation deviates from recommendations of the Advisory committee on Immunization Practices, Centers for Disease Control and Prevention.

[g] Selected seronagative patients with renal or liver transplant have been safely vaccinated. This recommendation deviates from recommendations of the Advisory committee on Immunization Practices, Centers for Disease Control and Prevention.

[h] Administer only if patient is not severly immunosuppressed, the timing is ≥ 4 weeks prior to transplant. And the patients is varicella immune as defined by documentation of age-appropriate varicella vaccination, serologic evidence of immunity, documentation of varicella or zoster infection, or birth in the United States before 1980 [45,375]. This recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

[i] Administer only if patient is not severly immunosuppressed and the timing is ≥4 weeks prior to transplant

Conclusion

In the last several years, we have witnessed significant changes in the licensed vaccines. The human papilloma virus vaccine, zoster vaccine, and tetanus-reduced diphtheria acellular pertussis (Tdap) vaccine have been introduced. Conjugated meningococcal and pneumococcal vaccines have been developed to enhance immunogenicity. Further evidence has been provided regarding the safety of influenza vaccination and lack of association with rejection. Finally, the adequate immunization of the transplant candidates, transplant recipient and transplant clinician should be a prominent goal of transplant centers in accordance with increasing emphasis on patient safety and adherence to existing guidelines [7]. So, we are in need of research studies to determine the optimal timing of immunization and durability of immunologic response in kidney transplant recipients vaccinated before and after transplantation.

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Viral Infections Post Transplantation

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Keywords: Hepatitis C; Kidney transplantation

Hepatitis C Infection

Hepatitis C Virus (HCV) is its most leading cause of hepatic disease post renal transplantation. In the long term, HCV can lead to advanced liver cirrhosis, hepatocellular carcinoma and death in some infected recipients [1]. Although Chronic HCV infection remains an important health problem which is associated with deleterious consequences post transplantation that includes hepatic and multiple extra-hepatic complications, it is not considered as a contraindication for renal transplantation because patient survival is better with transplantation than on dialysis [2].

Epidemiology & Transmission

HCV infection is prevalent much higher in developing than developed countries that is mostly attributed to poorer hygiene with lack of practicing of infection control protocols. Its prevalence is estimated to be approximately 2.4% worldwide with high geographic variability, ranging from <0.5% in Northern Europe up to 15% in Egypt [3]. Transmission is mainly parenteral. Thus it is common in hemodialysis units through nosocomial transmission by medical and para-medical staff, the use of multi-dose vials or blood transfusion which occurs currently at lower frequencies by the introduction of erythropoietin prescription. Donor organs itself may be accused in transmission of HCV to renal transplant recipients [4]. Sexual transmission of HCV might be possible, but is much at lower frequencies than that of other viruses, like hepatitis B or HIV. Thus, the adoption of special precautions for preventing the sexual transmission of hepatitis C is not recommended [5].

Diagnosis

Various tests are available for the diagnosis and follow up of HCV infection. Serological tests of the third generation are highly sensitive and specific, and are suitable for screening of dialysis patients. False-negative tests are nowadays rare, while false-positive tests may occur in dialysis patients with autoimmune disorders or other infections. Confirmation of HCV infection is obtained by qualitative or quantitative HCV RNA assay. ALT is a helpful although non-specific marker of the presence of HCV infection in the dialysis population. Serial determinations of ALT imprecisely reflect the severity of liver disease and do not correlate with the liver histology or viral load. Only liver biopsy provides information on the extent of HCV-associated liver disease. This invasive procedure is associated with an

increased risk of bleeding in dialysis patients. Trans jugular biopsy is associated with a lower risk, and nowadays liver biopsy seems mandatory to evaluate the severity of liver disease in order to choose the most suitable treatment option [6].

The presence of HCV RNA in serum or liver is the first evidence of HCV infection. HCV RNA is detectable in serum by PCR within days to eight weeks following exposure, depending in part upon the size of the inoculums [7]. But the minimal interval following suspected exposure after which a persistently negative HCV PCR test excludes infection has not been definitely established**.** Serum aminotransferases become elevated approximately 6 to 12 weeks after exposure (range 1 to 26 weeks). Serum ALT levels are variable. Anti-HCV ELISA tests become positive as early as eight weeks after exposure but the development of HCV antibodies may be delayed in patients who have subclinical infection or those who receive immunosuppression like kidney transplant recipients.

Consequences of HCV

HCV viral loads increase around 1.0 to 1.5 $\log_{10}$ IU/ml post-transplantation, and transaminitis rates also increase in transplant recipients with previously normal liver tests and rise even higher in those with preexisting ALT elevations [8]. Chronic active hepatitis and its sequelae are the principal forms of liver involvement. Fibrosing cholestatic hepatitis is a rare but fatal form of hepatic involvement post- transplantation [9].

To better assess the effects of hepatitis C virus on outcomes post-transplant, a 2005 meta-analysis was performed of eight clinical trials that included 6365 patients. The presence of anti-HCV antibodies increased the risk for death and allograft failure. Hepatic cancer and cirrhosis were significantly more frequent causes of death in those with anti-HCV antibodies [10]. As regard the HCV impact on the transplanted kidney, it increases post-transplantation morbidity by enhancing the risk for de novo or recurrent HCV-associated glomerulopathies like membrano-proliferative glomerulonephritis with/without cryoglobulinaemia and membranous nephropathy [11]. Also, Renal Thrombotic Microangiopathy (RTMA) may be observed in HCV-infected renal transplant recipients, especially in those with anticardiolipin antibodies [12]. A recent meta-analysis of 10 studies in 2502 renal transplant recipients showed a strong link between anti-HCV seropositivity and post-transplantation diabetes [**10**] especially in the tacrolimus-treated ones [13].

Immunosuppression & HCV

At the present time, there are relatively few studies that examine the impact of immunosuppression on HCV-related outcomes in kidney transplant patients, and it is not clear whether the impact of immunosuppression on outcomes in liver transplant patients with HCV infection can be extrapolated to HCV-infected kidney transplant recipients. Therefore, all currently available maintenance immunosuppressive therapies can be used in kidney transplant recipients with HCV infection [14].

Hepatitis C virus Therapy

IFN-α therapy is relatively contraindicated after kidney transplantation, because of increased risk of allograft rejection and failure [15]. So, trial for treatment with standard interferon montherapy, as ribavirin is contraindicated in dialysis patients, should be started in transplant candidates before transplantation. Ribavirin monotherapy may be used as a viristatic single agent post-transplantation. Approval of new direct anti-viral nucleotide analogs have promising data for most of HCV genotypes. However, no data are available regarding the added benefit concerning transplant candidates but many prospective and promising studies are currently ongoing [16].

Hepatitis B Infection

More than half a million people with Hepatitis B Virus (HBV) infection die annually

from complications of Chronic Hepatitis B (CHB), mainly the development of liver de-compensation and/or Hepatocellular Carcinoma (HCC) [17]. Untreated patients with HBV decompensated cirrhosis (HBV-DeCi) have a 5-year survival rate of only 14%-35% [18]. HBV is highest in sub-Saharan Africa and East Asia, where between 5–10% of the adult population is chronically infected. High rates of chronic infections are also found in the Amazon and the southern parts of eastern and central Europe. In the Middle East and the Indian subcontinent, an estimated 2–5% of the general population is chronically infected. Less than 1% of the population in Western Europe and North America is chronically infected [19].

There is scarce information regarding clinical evolution of HBV infection in renal transplant patients [20]. HBV infection continues to be an important cause of morbidity and mortality, although its incidence declined after the introduction of hepatitis B vaccine in 1982 and as a result of improved overall care during hemodialysis [21]. The prevalence of chronic hepatitis B after kidney transplantation ranges from 2 to 21% according to geographic regions [22]. Although data about the natural course of HBV infection in renal transplant recipients are scarce, evidence indicates that viral replication is accelerated by immunosuppression and that HBV-related liver disease is more aggressive in renal transplant recipients [23]. Reactivation of HBV infection in immunosuppressed patients can be separated into three phases: (1) increase in HBV replication; (2) appearance of hepatic injury (ALT flares)and (3) recovery [23].

Biochemical evidence of reactivation is characterized by ALT flares and sometimes associated loss of liver function from ranging 30–70% in different case series [24]. More recently, Murakami et al.,[25].

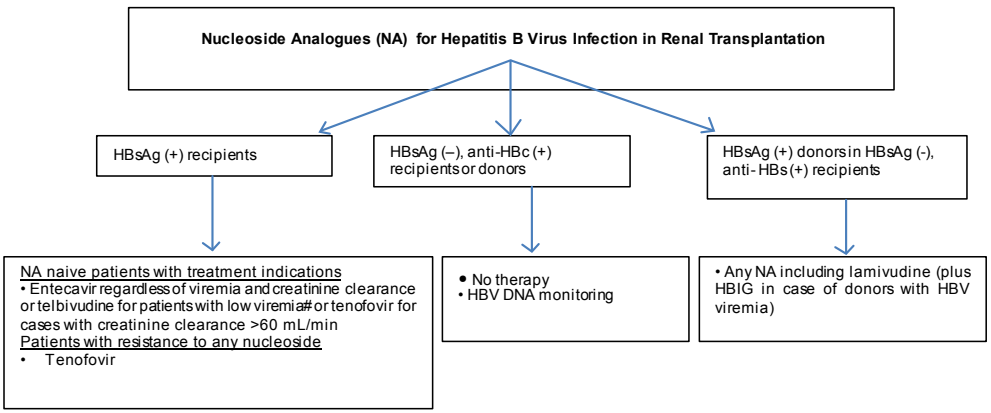

Figure 1: Proposed algorithm for the management of patients with chronic hepatitis B infection and kidney diseases.

Low viremia is considered as HBV DNA levels < 108 or < 106 IU/mL for HBeAg-positive and HBeAg negative patients, respectively [26].

Treatment with a NA is recommended for all HBsAg-positive RT recipients. NA therapy should ideally start at CHB diagnosis in RT candidates with HBV DNA >2000 IU/mL or 2 weeks before RT in candidates with HBV DNA ≤2000 IU/mL and should continue for life as long as the patients remain under any immunosuppressive agent (s) [27,28]. NAs should be continued after RT to retain viral load clearance and prevent liver de-compensation and fibrosis [19]. Oral antiviral treatment raised patient and graft survival significantly; whereas a decade ago, HBsAg positivity was a significant predisposing factor for high mortality and graft loss [29,30].

The choice of the NA for HBsAg-positive RT is decided on an individual basis, according

to the patient' s HBV-DNA levels before transplantation and the previous exposure to NA(s). Lamivudine has been used extensively in this setting, but its results have been similar to those in other CHB populations. Thus, Entecavir (ETV), regardless of viremia and creatinine clearance, or telbivudine for patients with low viremia (i.e., HBV DNA levels < 108 or < 106 IU/mL for HBeAg-positive and HBeAg-negative patients respectively) or TDF for cases with creatinine clearance > 60 mL/min (or history of resistance to lamivudine) could be proposed as the best choices (Figure 1). Although NAs should be continued lifelong after RT, there is a recent study showing safe antiviral withdrawal in four HBV positive RT patients who presented complete suppression of HBV infection having received antivirals for 14.3 mo. They remained negative for HBV DNA for a median 60.5 mo, but physicians should be aware of the necessary drug dose adjustments according to creatinine clearance as well as the potential nephrotoxicity and long-term drug efficacy [31, 32].

Cytomegalovirus

Cytomegalovirus (CMV) is the most common and single most important viral infection in solid organ transplant recipients. CMV infection usually develops during the first few months after transplantation and is associated with clinical infectious disease (eg, fever, pneumonia, GI ulcers, hepatitis) and acute and/or chronic graft injury and dysfunction [33,34] Exposure to the virus, as indicated by the presence of detectable immunoglobulin G (IgG) anti-CMV antibodies in the plasma, increases with age in the general population and is present in more than two-thirds of donors and recipients prior to transplantation [35]. CMV can be transmitted from the donor either by blood transfusion or by the transplanted kidney; the concurrent administration of immunosuppressive drugs to prevent rejection further increases the risk of clinically relevant CMV disease, with induction therapy principally being associated with an increased risk of disease [36, 37].

If a prophylactic strategy is used, we suggest oral valganciclovir for all patients except seronegative recipients of seronegative grafts. Doses should be adjusted based on estimated glomerular filtration rate. Most transplant centers administer such therapy for a total duration of 100 days, extending to 180 days in high-risk (CMV donor-positive/recipient-negative) recipients. When a lymphocyte-depleting therapy is administered in a quadruple immunosuppressive regimen, prophylaxis should be extended to six to nine months for seronegative recipients of a kidney from a seropositive donor [38].

Based on the currently available evidence, pre-emptive therapy and antiviral prophylaxis are equally successful in preventing major complications of CMV infection in kidney allograft recipients, including CMV disease, allograft loss and patient death. This is also confirmed by a recent meta-analysis looking at 40 trials including more than 5000 patients, demonstrating a lower incidence of early viraemia, but higher incidence of late onset CMV infection and neutropenia with prophylaxis, but no differences in mortality, graft loss and acute rejection rates between the two approaches [39].

Parvovirus B19

Parvovirus B19 (PVB19V) is a single-stranded DNA virus of the family Parvoviridae and genus Erythrovirus. The presence of immunoglobulin antibodies to this virus in the serum of half of the adult population was established by epidemiological surveys, suggesting acquisition of immunity during childhood [40]. Parvovirus B19 may cause erythema infectiosum (Fifth disease) in children, hydrops fetalis in pregnant women, and transient aplastic crisis in patients with chronic hemolytic anemia. Immunosuppressed patients can fail to mount an effective immune response to B19, resulting in prolonged or persistent viremia. Renal transplant recipients can develop symptomatic B19 infections as a result of primary infection acquired via the usual respiratory route or via the transplanted organ, or because of reactivation of latent or persistent viral infection. The most common manifestations of B19 infection in immunosuppressed patients are pure red cell aplasia and

other cytopenias. Thus, this diagnosis should be considered in transplant recipients with unexplained anemia and reticulocytopenia or pancytopenia. Collapsing glomerulopathy and thrombotic microangiopathy have been reported in association with B19 infection in renal transplant recipients, but a causal relationship has not been definitively established. Prompt diagnosis of B19 infection in the renal transplant recipient requires a high index of suspicion and careful selection of diagnostic tests, which include serologies and polymerase chain reaction. Most patients benefit from intravenous immunoglobulin therapy and/or alteration or reduction of immunosuppressive therapy. Conservative therapy might be sufficient in some cases [41].

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Impact of Recurrent Glomerular Kidney Disease Following Kidney Transplantation

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Recurrent glomerulonephritis following kidney transplantation affects between 10% and 20% of patients, and accounts for up to 8% of graft failures at 10 years Post transplant [1] it's the third most common risk factor for graft failure. Estimated risk for recurrence and graft loss reported in many studies are summarized in the Table 1.

	Recurrence rate	Graft loss risk
Primary diseases		
IgA Nephrpathy	30-60%	10-30%
Focal segmental glomerulosclerosis	30-60%	50%
Idiopathic Membranous Nephropathy	3-30%	30%
Membranoproliferative glomerulonephritis type 1 (MPGN-1)	25-65%	33%
Dense Deposit Disease (DDD)	90%	10-20%
Secondary diseases		
Lupus nephritis	2-9%	< 5%
Henoch- Schonlein nephritis	15-60%	10%
Light Chain Deposition Disease	50%	Unknown
Fibrillary glomerulonephritis	50%	50%
Mixes Cryoglobulinemia	50%	Unknown
ANCA vasculitis	20-25%	< 5%
Hemolytic Uremic Syndrome	25-50%	40-60%

Graft survival rates within 10 years of transplantation have improved since current immunosuppressive protocols were introduced. However, the impact of these agents on reduction of the recurrence of glomerulonephritis after kidney transplantation remains controversial [2].

Recurrent Glomerulonephritis post kidney transplantation can be caused by either recurrent or de novo disease. However, most of cases of transplant glomerulopathy are impossible to classify into recurrent or de novo type as histological confirmation of the native kidney disease is mandatory, However, it's lacking in many renal transplant recipients. In many countries, allograft biopsies are generally only performed when allograft

function deteriorates or if proteinuria develops. Asymptomatic histological recurrence in renal allografts may be missed if protocol biopsies are not available. So, protocol biopsy are important to accurately estimating the incidence of recurrence [3] Another important aspect that many transplant biopsies are not routinely processed using immunofluorescence and electron microscopy. The most relevant Limitations in the diagnosis of recurrent glomerulonephritis are summarized in the following points

1. Unknown original kidney disease in many patients.
2. Transmitted hidden glomerular diseases from donor side..
3. Lack of protocol biopsy in many centers.
4. Lack of immunofluorescence and electron microscopy examinations.

Post-Transplant Recurrence of Primary Glomerulonephritis

IgA Nephropathy (IgAN)

IgAN is a primary GN characterized by diffuse mesangial deposition of IgA1. The disease usually runs an indolent course but may lead to ESRD in 30% to 50% of patients within 25 years or more of follow-up. IgAN is one of the most common recurrent GN after transplantation, approximately 33% risk for recurrence post transplantation [4,5]. some apparently normal donors (living or deceased) may have "hidden" IgA deposits in the kidney [6] may have important relevance for pathogenesis of the recurrent disease.

Recurrences of IgAN can be discovered accidentally on a protocol renal biopsy in an asymptomatic patient or presented clinically by abnormalities in the urine and/or renal function leading to a renal biopsy. Clinical recurrence of IgAN may occur usually, 3 years after transplantation [6] and usually presented by hematuria and low-grade proteinuria however, it may occur immediately after transplantation. The results of renal transplantation in patients with IgAN have been differently estimated. Some authors reported better outcome of the renal allograft in patients with IgAN than in other transplant recipients, but others found that graft survival in an IgAN group was similar to other transplant recipients [7,8]. Risky factors for Recurrence include younger patients and those with a rapid progression of the original disease [9]. It is unclear if there's association between recurrence and using related donors [10-11].

No specific treatment for recurrent IgAN is currently available. the use of cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, sirolimus, and prednisone may decrease the risk of graft failure due to recurrent IgAN [12]. Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) may be beneficial as their use could reduce proteinuria and blood pressure in transplant recipients with IgAN [13]. However, using these drugs may result in significant reduction in GFR and hematocrit [14]. Tonsillectomy has been suggested to be of benefit among Japanese patients [15].

Focal Segmental Glomerulosclerosis (FSGS)

Idiopathic FSGS characterized by Nephrotic Syndrome (NS) that may affect children and adults. If treatments failed to induced remission, FSGS commonly progresses to ESRD. More than 30% of patients develop recurrence of FSGS in the first kidney allograft [16]. Risky factors for recurrence include younger patients, interval to end-stage renal disease, history of graft loss due to recurrent FSGS, circulating permeability factors, circulating urokinase receptors and mesangial proliferation. The risk of recurrence with a second graft in patients who lost a first graft because of recurrence may approach 100% [17]. The histologic variant type of FSGS observed in the native kidneys does not seem to reliably predict either recurrence or type of FSGS seen on the allograft [18]. Recurrence of FSGS may be early (the most frequent) characterized by a massive proteinuria within hours to days

after implantation or late recurrence that develops insidiously several months or years after transplantation.

A review of the U.S. Renal Data System data reported that living donor transplantation for FSGS patients was associated with superior overall graft survival [19]. Regarding patients affected by familial FSGS, the current opinion was that patients with familial FSGS caused by mutations of NPHS2 (the gene encoding podocin) did not run any risk of recurrence after transplantation. However, there is now evidence that the risk of recurrence in patients with the NPHS2 mutation is approximately 8% (but not zero) [20]. Therefore, caution should be observed while transplanting patients with NPHS2 mutations using the kidney of their parents who are obligate carriers of the NPHS2 mutation [21].

The management of patients with recurrent FSGS is difficult and controversial. Reduction of proteinuria has been reported in children treated with intravenous cyclosporine at high doses [22]. The most commonly used therapeutic approach is the use of Plasma Exchange (PE) or immuno-adsorption with protein A [22]. A review of the literature reported that 70% of children and 63% of adults with recurrent FSGS who received PE entered complete or partial remission of proteinuria. However, all studies were retrospective, uncontrolled, and most of them had only short term follow-ups. A protective role of prophylactic PE before transplantation has also been reported [23]. Several reports pointed out the benefit of Rituximab when given alone or in combination with PE [24], but failures were also reported [25]. Currently, PE combined with high-dose calcineurin inhibitors with or without Rituximab seems to be the most promising approach, but further studies are needed to define the best regimens to treat recurrent FSGS [26].

Despite the risk of recurrence, patients with FSGS should not be excluded from transplantation. Regarding living donation, the possibility of recurrence should be clearly explained to the donor and the recipient and pre-transplant PE should be done. An early and aggressive treatment should be provided if proteinuria develops [27].

Idiopathic Membranous Nephropathy (IMN)

IMN is characterized histologically by uniform thickening of the glomerular capillary due to immune-complex deposits in the outer or subepithelial aspect of the glomerular basement membrane. IMN is a frequent cause of NS in adults and may lead in 40% to 50% of patients to ESRD in the long term [28].

A recurrence of IMN after renal transplantation is probably more frequent than generally estimated. However, the true proportion of recurrence is difficult to assess because the indications for graft biopsy are extremely variable among transplant centers. Moreover a de novo form of secondary MN may develop in transplanted kidneys showing a histologic pattern indistinguishable from recurrent IMN. Recurrence of IMN is usually diagnosed between the 2nd and 3rd year after transplantation, but earlier and later cases have been described. So far, no clinical or histologic factor seems to reliably predict the risk of recurrence. The initial clinical manifestations of recurrent IMN may be mild or absent, and in several patients recurrence could be detected only by protocol renal biopsies [29]. However, many patients show a progressive increase in proteinuria over time and can eventually develop a full-blown NS. The mechanisms leading to IMN recurrence are still far from being elucidated. There is now evidence that MN is triggered by autoantibodies directed against podocyte proteins. Recently, circulating autoantibodies directed against other podocyte enzymes, such as M-type phospholipase-2 receptors [30] and aldose reductase and manganese superoxide dismutase [31], have been detected in adults with IMN and are uniformly absent in secondary forms of MN.

Symptomatic treatment with diuretics, ACEIs, ARBs, hypolipemic drugs, and anticoagulants may help in reducing the signs and symptoms related to the NS in recurrent IMN. No convincing evidence exists that corticosteroids, cytotoxic drugs, or

other immunosuppressive agents are of benefit in recurrent IMN. Rituximab has shown very promising effects in patients with IMN in native kidneys [32] and has also been used successfully in anecdotal cases of posttransplant IMN recurrence [33].

Membranoproliferative Glomerulonephritis (MPGN Types I)

MPGN is "pattern of injury" rather than a disease [34]. It is now known to have a very diverse array of underlying causes, and the group designated as 'idiopathic" MPGN has correspondingly declined in size [34]. Nevertheless. MPGN is common cause of recurrent GN in allografts. The reported rate of recurrence of MPGN has been quite variable (27% to 65%) [35]. In previous series, types I and II MPGN (DDD) were considered together, whereas the current trend is to separate DDD as a unique clinicopathologic entity having a higher risk of recurrence than typical type I MPGN [36]. Differences in recurrence rates between type I MPGN and DDD may relate more to the superimposition of crescents than to the underlying ultrastructural features [37]. Risk of recurrence may be marginally higher in living related donors. Recurrent MPGN type I can have significant deleterious effects on graft survival, especially when superimposed extensive crescentic disease is present [37], and thus should be prevented in so far as is possible by careful pre-transplant evaluation.

Intensification of immunosuppressive therapy in recurrent MPGN can be hazardous because it may lead to over immunosuppression and has little documented effect on the outcome of the recurrence, except perhaps when extensive crescentic disease is present. Occasional anecdotes and small series have suggested that improvement may be seen in recurrent MPGN type I with cyclophosphamide [38] or high-dose mycophenolate mofetil [39], but no controlled trial has yet confirmed the efficacy or safety of these approaches. Treatment of truly "idiopathic" recurrent MPGN is generally very disappointing and graft loss due to recurrence is common [35].

Dense Deposit Disease (DDD)

This disease has a very high risk of recurrence (approaching 100%). Most patients have low serum C3 levels, and 70% to 80% also have a circulating autoantibody to C3Bb known as C3 nephritic factor (C3Nef). Some patients with DDD may also have an abnormality in complement cascade regulation such as deficiencies of factor H) [40]. Thus, hypocomplementemia and/or isolated C3 deposits suggesting DDD in a native kidney biopsy showing a pattern of MPGN is a feature highly associated with risk for recurrence [35].

The successful treatment of an established recurrence of DDD is problematical, so prevention and anticipatory management based on precise assessment of the underlying mechanism responsible for the MPGN is very important. Patients with complement dysregulation (e.g., factor H deficiency) should receive replacement infusions (fresh frozen plasma) before and after grafting [41], although no controlled trials of the efficacy of this approach have yet been conducted [42]. PE (with fresh frozen plasma replacement) and/or rituximab might also be helpful in patients with a neutralizing autoantibody to factor H. Eculizumab (a monoclonal antibody to C5a) may also be beneficial [41]. Patients with genetic causes for factor H or I deficiency may require combined liver and kidney transplantation to avoid recurrences [43].

Recurrence of Secondary Glomerulonephritis

Lupus Nephritis

The reported risk of recurrence of lupus nephritis (LN) after renal transplantation has been quite variable. Some investigators found that the recurrence rate was quite low, < 5% [44], whereas others reported that about 10% of patients with LN experienced recurrence [45]. An additional group of investigators pointed out that the risk of recurrence was even higher, when diligently searched for, ranging between 30 and 54% [46]. A number of reasons may account for these discrepancies:

(1) The indication for renal allograft biopsy varies among transplant units.

(2) some studies reported the results seen in single centers whereas others collected data through national or multinational registries.

(3) the follow-up was short in many studies—an important point because recurrences may occur more than a decade after transplantation [45].

(4) the risk of recurrence may vary in different ancestral groups [47].

(5) a diagnosis of recurrence of LN requires a graft biopsy examined by light microscopy, immunofluorescence, and electron microscopy, which were not always routinely performed [48].

Factors that tend to be associated with recurrent LN are black non-Hispanic ancestry, female gender, and young age [45]. Patients with Antiphospholipid (aPL) autoantibodies [49] and those receiving the kidney from living donors [46] also have a higher risk of recurrence.

Clinically, recurrence of GN in the renal allograft may be heralded by mild proteinuria and microscopic hematuria, and is seldom accompanied by arthralgias or cutaneous rash. The histologic lesions of recurrent LN are usually mild, mostly consisting of mesangial lesions or atypical pauci-immune proliferative GN in those studies which adopted a policy of elective surveillance biopsy [46]. However, patients of diffuse proliferative nephritis have been reported when the decision to undertake a renal biopsy was made on clinical grounds [47]. The effect of recurrent LN on graft survival is usually of minor significance. A review of the United Network for Organ Sharing (UNOS) data reported that graft failure in patients with recurrent LN was attributable to recurrence in only 7% of patients, rejection being the main cause of graft failure [45]. Several retrospective analyses of UNOS and United States Renal Data System (USRDS) reported no difference in patient and graft survival rates between adults with LN and other transplant recipients of living or deceased donor kidneys, after adjusting for confounding factors [50]. Also a retrospective analysis of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database found that the results of renal transplantation in young patients with LN were comparable to those seen in an age-, ancestry-, andngendermatched control group, in spite of an unexplained increase in recurrent rejections in the living donor LN patients [51].

The basic posttransplant immunosuppression for LN patients does not differ from that normally used in management. In patients with LN recurrence, an intensification of immunosuppression should be reserved for the exceptional cases showing a severe (life threatening) lupus flare-up because of the potential risks of serious or lethal infection.

In summary, LN may recur after renal transplantation but in most patients recurrence neither causes severe histologic lesions nor has a relevant clinical effect on the long-term outcome [52]. The results of renal transplantation are at least as good in LN patients as in patients with other renal diseases. Pretransplantation screening for aPL antibodies in renal transplant candidates with LN is recommended as it may indicate which patients will benefit from anticoagulant therapy [53].

Henoch-Schonlein Nephritis

A review of the literature reported that histologic recurrence of IgA mesangial deposits occurred in 52 out of 67 (78%) renal allografts in patients with Henoch-Scho¨nlein nephritis (HSN), whereas a clinical recurrence occurred in only 15 out of 67 (22%) patients at 5 years posttransplantation [54]. However, after longer follow-up clinical recurrence may be evident in 29 to 42% of patients [55], more frequently in children [56]. Henoch-Schonlein nephritis patients with circulating IgA-ANCA (ANCA, antineutrophil cytoplasm antibody) are particularly prone to recurrence after transplantation [57]. Hematuria, sometimes macroscopic, moderate proteinuria, and hypertension are common in patients with clinical evidence of recurrence. Histologically, focal and segmental necrotizing GN with mesangial IgA deposits is observed.

Recurrence of HSN can lead to graft failure in about 10% of patients, the prognosis being more guarded in adults than in children [54]. In a European survey, graft survival in patients with HSN recurrence was 57% at 2 years [58]. Alternatively, in a small single-center study [59], the 5-year graft survival was 78%. Therefore, recurrent HSN should not be regarded as a benign condition.

Recurrence is more frequent and severe in patients who had a rapidly progressive course and necrotizing/crescentic GN in the native kidneys [59]. Living related donor transplantation also shows a trend of higher recurrence compared with those receiving unrelated grafts. However, the graft survival rate in related-donor recipients was not less than that found in unrelated-donor recipients [55].

Patients with recurrent HSN and extensive crescents in the transplant biopsy have a decidedly poor prognosis. Methyl Prednisolone Pulses (MPP), antiplatelet agents, or cytotoxic drugs have been used without any notable benefits [54]. In a single patient proteinuria resolved and renal biopsy demonstrated marked reduction in mesangial IgA deposition after 4 cycles of plasmapheresis [60].

In summary, HSN recurs more frequently in children but the outcome after recurrence is more severe in adults and in patients with extensive crescentic GN. In spite of recurrence, the cumulative long-term graft survival in patients with HSN is similar to that seen in patients with other renal diseases.

Amyloidosis

Previous studies have shown that Amyloid Light-Chain (AL) amyloidosis and hereditary amyloidosis regularly recur after kidney transplantation, but only a few have been reported in the literature [61]. However, a successful renal transplant without recurrence of amyloidosis after 9 years was described in a patient with familial apolipoprotein II amyloidosis [62] and a series of 22 renal transplant recipients with AL amyloidosis reported that no renal graft failed because of recurrent amyloidosis after a mean follow-up of 48 months. The patient survival was 95% at 1 year and 67% at 5 years [63]. The Collaborative Transplant Study (CTS) reported that the patient and renal graft survival at 5 years were inferior in patients with secondary amyloidosis than in patients with GN or polycystic kidney disease, but adequate enough to justify kidney transplantation [64]. Two main issues with renal transplantation in amyloidosis are life-threatening infections and cardiovascular complications [65], particularly when cardiac involvement is present.

The risk of recurrence for secondary AA amyloidosis depends on the type and the activity of original disease. Up to 26% of patients with amyloidosis secondary to chronic inflammation (such as rheumatoid arthritis) may develop a renal recurrence [66] whereas no case of recurrent renal amyloidosis has yet been reported in patients with amyloidosis secondary to Behcet's disease [67]. Amyloidosis may also recur after transplantation in patients with familial Mediterranean fever, but the early administration of colchicine, 1 to 2 mg/d indefinitely, can prevent the deposition of amyloid in the transplanted kidney [68].

In summary, patients with renal amyloidosis without other organ involvement (especially cardiac) may undergo kidney transplantation. However, in view of the increased risk of postoperative complications, a preoperative cardiovascular evaluation is mandatory even in asymptomatic patients. Specific treatment should be considered for particular forms of amyloidosis, that is, chemotherapy and autologous stem cell transplantation followed by kidney transplantation in progressive primary AL amyloidosis [69], a dual liver and kidney transplantation in hereditary amyloidosis and multivisceral involvement [70], a dual heart and kidney transplantation in severe and irreversible cardiac and renal involvement [71]. Patients with familial Mediterranean fever should be treated regularly with colchicine [72].

Light-Chain Deposition Disease

Patients with Light-Chain Deposition Disease (LCDD) have a very high risk of recurrence of the monoclonal Kappa or Lambda chain deposition in the graft [73]. Recurrence of LCDD developed in 5 out of 7 renal transplant patients after a mean period of 33 months [74]. In spite of a high risk of recurrence and death, renal transplantation may be offered to patients with LCDD who respond satisfactorily to chemotherapy, as demonstrated by serial serum-free light-chain assays. Preliminary results have shown the possibility of preventing an early recurrence of LCDD with the proteasome inhibitor bortezomib [75] or with rituximab [76]. The best current therapeutic approach is chemotherapy and autologous stem cell transplantation followed by kidney transplantation in case of good hematologic response [77].

Fibrillary/Immunotactoid Glomerulonephritis

The high risk of early graft failure due to recurrent fibrillary/immunotactoid glomerulonephritis (F/ITGN) [78] was considered as a contraindication to renal transplant in the past. However, Samaniego et al., [79] reported 14 cases of F/ITGN in which, in spite of histologic recurrence in 6 cases, the allografts functioned in four patients for 4, 5, 11, and 13 years whereas a fifth patient died with stable graft function 7 years posttransplantation. In another series, five patients with F/ITGN were followed in mean for 52 months posttransplantation [80]. Only one patient lost the graft (because of thrombo-embolism). Thus, in spite of an increased risk of recurrence, renal transplantation may be considered as a viable option for patients with F/ITGN.

Mixed Cryoglobulinemic Nephritis

Up to 40% of patients, particularly those who are HCVpositive, may develop mixed IgG/IgM cryoglobulinemia and eventually a membranous omembranoproliferative GN after renal transplantation [81]. Histology of recurrence usually showed a membranoproliferativetype GN with extensive monocyte and polymorphonuclear leukocyte accumulation in capillary loops and small cellular crescents. Immunofluorescence showed C3, IgG, and IgM deposition in a mesangial and capillary wall [82].

It is unclear whether the recurrence of MCN will interfere with the long-term survival of the transplanted kidney; as in reported cases graft failure was usually caused by rejection whereas some patients showed good graft function for 4 to 10 years in spite of histologic recurrence [82]. Rituximab has proven to be an effective treatment for de novo MCN in transplant patients [83] but in some transplant patients rituximab may cause life-threatening infections [84].

Diabetic Nephropathy

It is difficult to estimate the actual rate of recurrence of Diabetic Nephropathy (DN) in renal allografts because about 20% of transplant patients may develop de novo onset of diabetes post-transplantation (PTDM), which can also eventually lead to de novo DN [85]. Recurrence of DN accounted for only 1.8% of graft losses in one of the largest series of renal transplants in diabetic recipients [86]. This low risk may depend on the short duration of follow-up because the mean interval between the onset of insulin dependent diabetes and the development of overt nephropathy in renal transplant recipients requires several years [87].

The progression of histologic, diabetes-related lesions in the transplanted kidney is slow, but more rapid than in the original disease, perhaps because of the lower nephron mass, the use of nephrotoxic calcineurin inhibitors, and glucocorticoid therapy, and the frequency of concomitant hypertension. Thus, recurrent DN has little effect on graft function in the short term but can eventually contribute to graft loss in the long term.

Present day, DN is not considered a contraindication to renal transplantation. However, measures are recommended to prevent the development of DN and other diabetes-related complications, including strict glycemic control [88], early use of ACE inhibitors and/or angiotensin receptor antagonists [89], a preemptive kidney transplantation in patients with type 2 diabetes [90], and a double pancreas and kidney transplantation in selected patients with type 1 diabetes [91].

Small Vessel Vasculitis

The risk of Small Vessel Vasculitis (SVV) recurrence on renal graft is approximately 6% [92]. Recurrence may develop within a few weeks after renal transplantation or many years later, with an average time from transplantation to recurrence of 31 months [93]. Around 60% of recurrences involved the graft alone or in association with other organs, whereas the other 40% were primarily extrarenal [93]. Microscopic hematuria and proteinuria are the heralding signs for renal recurrences of SVV. These are generally associated with or followed by the deterioration of graft function. The histologic picture is characterized by focal or diffuse pauci-immune extracapillary necrotizing glomerulonephritis.

The ANCA pattern or titers at time of transplantation, the duration of the original disease, the duration of dialysis, treatment with cyclosporine, and the source of donors do not influence the risk of recurrence (102), nor are clinical parameters very useful in predicting the risk of recurrence of SVV [94]. No differences in the rate of recurrence after transplantation was observed between Wegener granulomatosis, microscopic polyarteritis, or renal limited vasculitis [93].

Patient and graft survival are quite similar in SVV and in the general transplant population. The UNOS registry reported a 3-year graft survival rate of 78% for deceased donor transplants, and 84% for living donor transplants in 114 recipients with Wegener granulomatosis [95]. The ERA-EDTA registry reported a 70% graft survival at 3 years in 115 patients with SVV [58].

The optimal timing for renal transplant in patients with SVV remains an unresolved question. Because clinical remission of SVV for 1 year is associated with a high mortality rate [92], SVV candidates for renal transplantation should be in stable clinical remission at the time of transplantation. Prolonged immunosuppression may also expose patients to the risk of life-threatening infections after transplantation [96] thus, it's believed that transplantation should be delayed for several months after starting dialysis in patients who have received a prolonged or intense period of immunosuppression for treatment of their underlying disease [97].

Despite the unpredictable potential for recurrence, transplantation is an acceptable option for patients with SVV. Persistent positivity of ANCA tests should not preclude transplantation [92]. A careful monitoring of the urinary sediment during the first few years after transplantation may help in making a prompt diagnosis and treatment of a recurrence or relapse of SVV. Treatment of relapses is mainly based on MPP, cyclophosphamide, and plasmapheresis or possibly rituximab [97].

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Post Renal Transplant Malignancy

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Introduction

Kidney transplantation is generally accepted as the best treatment for patients with End Stage Renal Disease (ESRD) requiring renal replacement therapy which improves both the quality of life and life span of patients [1]. Although the new and potent immunosuppressive agents have successfully reduced the risk of rejection after kidney transplantation; however, cardiovascular disease, infectious and neoplastic complications are increasing .Cancer is the second cause of death in renal transplant recipients and it is expected that the mortality due to cancer will be moved to become the first cause of death within the next two decades [2].

Types of Malignancy

We can categorize post-transplantation malignancy into four major groups according to their types [3].

Group 1: Skin cancers divided into Kaposi sarcoma and Non-Kaposi tumors which include Squamous cell carcinoma, Basal carcinoma, and melanoma and Merkel cancer)

Group 2: Post-Transplant Lymphoproliferative Disorder (PTLD).

Group 3: Solid tumors are malignancies rather than skin, urinary and post-transplant lymphoproliferative disorder.

Group 4: urinary tumors. Including cancer bladder and renal cell carcinoma.

Skin Cancers (Group 1)

The most common cancers following transplantation are those involving the skin [4] (including the lips).

Kaposi's sarcoma (KS)

Is an angioproliferative disorder that requires infection with human herpes virus 8 (HHV-8), also known as Kaposi sarcoma-associated Herpes virus (KSHV), for its development. The disease is named for Moritz Kaposi, a Hungarian dermatologist on the faculty of the University of Vienna, who first described the entity in 1872 as "idiopathic multiple pigmented sarcoma of the skin [5].

Types of Kaposi's sarcoma

Classic Kaposi's sarcoma: is characterized by the appearance of purplish, reddish blue, macules, plaques, and nodules on the skin [6].

Endemic Kaposi's sarcoma: The endemic form of KS is found in all parts of equatorial Africa, and may be accompanied by dissemination to lymph nodes, bone, and skin [7].

C-Organ transplant-associated Kaposi's sarcoma: may occur after solid organ transplantation. Transplant-associated KS is similar to AIDS KS in its clinical manifestations and usually regresses with reduction in immunosuppression [8].

AIDS-related Kaposi's sarcoma: is the most common tumor arising in HIV-infected persons, KS is over 20,000 times more common in persons with AIDS than in the general population [9]. Clinical aspect: Kaposi sarcoma usually appears early (a mean interval of 13 months from transplantation) [10]. KS has cutaneous lesions, mucosal lesions, or both. For unclear reasons, visceral involvement is less common in recipients of kidney allograft as compared to liver or heart allograft (25% to 30% versus 50%) [11]. Treatment of post-transplantation Kaposi sarcoma: The mainstay of treatment of post-transplant KS is reduction of immunosuppression for a minimum of 1 month before other forms of therapy were introduced [12].Withdrawal of the most potent immunosuppressive agent, namely CNI, because they may have direct oncogenic potential.

A wide variety of therapies have been used for Kaposi's sarcoma:

1. The mammalian target of rapamycin inhibitors (mTORis) mTOR is exerting their immunosuppressive activity by impeding the response to interleukin-2 (IL-2) and thereby blocking the activation of T- and B-cells [13]. Rapamycin further inhibits signal transducer and transcription activator 3 (STAT3) signaling, STAT3 mediates the expression of a variety of genes in response to cell stimuli and is involved in many cellular processes such as cell growth [14].
2. Radiation therapy all forms of KS are very sensitive to radiotherapy (RT), there is marked variation in total RT doses (6 to 60 Gy) [15].
3. Intralesional therapy; Intralesional injection of chemotherapy (most often vinblastine) leads to local regression of cutaneous KS lesions [16].
4. Antiviral to HHV-8; virus is resistant to acyclovir, sensitive to ganciclovir [15].
5. Chemotherapy bulky, or rapidly progressive KS, indicated for systemic chemotherapy, these include pegylated liposomal doxorubicin, vinblastine [17].

Squamous Cell Carcinoma (SCC)

SCC can develop on any cutaneous surface, including the head, neck, trunk, extremities, oral mucosa, and anogenital areas (English DR et al., 2008). The risk of SCC increases with both the length and the level of Immunosuppression, there is a steady rise of SCC cumulative incidence with time after transplantation [18]. The lesions usually appear as a nodule or an elevated, infiltrated, and erythematous plaque with hyperkeratotic crusti. Management of Squamous Cell Carcinoma: Mohs Micrographic Surgery (MMS) is recommended as the optimum surgical approach. Revision of immunosuppression conversion from calcineurin inhibitor to a regimen based on mTOR inhibitors (sirolimus or everolimus) should be recommended [19].

Basal Cell Carcinoma (BCC)

Arises from the basal layer of the epidermis, The incidence of BCC is increased by a factor 10 to 16 in renal transplant recipients, compared to the general population [20]. BCC can be divided in three groups: nodular BCC (a pink or flesh-colored papule),

superficial BCC (scaly, light red plaque) and morphea form BCC (smooth, flesh-colored, plaques) [21]. Modulation of immunosuppression; Reduction of immunosuppression is considered in patients who develop numerous lesions, recurrent disease, or metastatic disease [22].

Melanoma

The risk of developing melanoma is 3.6 times greater in renal transplant recipients than in the general population [23]. Malignant melanomas can be classified into lentigo malignant melanomas, superficial spreading malignant melanomas, nodular malignant melanomas, and malignant melanomas on mucous membranes [24]. Once the diagnosis of melanoma is confirmed, patients undergo wide local excision, in renal transplant recipients, sentinel lymph node biopsy may be required. More aggressive alteration of immunosuppression, or possibly discontinuation, may be warranted for high-risk melanoma [25].

Post-Transplant Lympho proliferative Disorders (Ptld) (Group 2)

Are lymphoid and/or plasmacytic proliferations occur in solid organ transplantation as a result of immunosuppression, PTLD account for approximately 20 percent of all cancers post solid organ transplantation [26]. The pathogenesis of PTLD related to B cell proliferation induced by infection with Epstein-Barr virus (EBV) in the setting of chronic immunosuppression and decreased T cell immune surveillance [27]. There are three main categories of PTLD: Plasmacytic hyperplasia and infectious mononucleosis-like PTLD, Polymorphic PTLD, Monomorphic PTLD [28]. The diagnosis of PTLD should be suspected in a patient presented by adenopathy, symptoms (fever, weight loss, night sweats), unexplained hematologic or biochemical abnormalities, and/or signs or symptoms attributable to the infiltration of extralymphatic tissue [29]. The main options for initial treatment are reduction of immunosuppression, Immunosuppression should be reduced to the lowest tolerated level, and reduction up to 25 to 50 percent of baseline can be used [30]. Immunotherapy with the CD20 monoclonal antibody rituximab, rituximab will result in complete remissions in approximately 20 percent of patients with PTLD [31]. Chemotherapy; Chemotherapy is usually administered in conjunction with rituximab, chemotherapy such as cyclophosphamide plus prednisone.

Solid Tumors (Group 3)

Colorectal Cancer (CRC)

CRC is the fourth most common malignancy. It is the second most common cause of cancer-related death, with an estimated 60,000 deaths per year, however there is no consensus on screening surveillance for transplant patients [32]. The majority of patients presenting with symptomatic CRC have melena, abdominal pain, otherwise unexplained iron deficiency anemia and/or a change in bowel habits [33]. Colonoscopy is the single best diagnostic test in symptomatic individuals, it can localize and biopsy lesions throughout the large bowel, detect synchronous neoplasm, and remove polyps [34]. Surgical resection is the curative modality for colon cancer. Postoperative (adjuvant) chemotherapy eradicates micrometastases, reduces the likelihood disease recurrence, and increases cure rates [35].

Hepatocellular Carcinoma (HCC)

Liver cancer is the fifth most frequently diagnosed cancer worldwide, and is the third leading cause of cancer-related death in the world, but in RTRS incidence only 2.5% of malignancy post transplantation [36]. Mild upper abdominal pain, weight loss, early satiety, or a palpable mass, Suspicion for HCC should be heightened in patients with previously compensated cirrhosis who develop decompensation such as ascites, encephalopathy, jaundice, or variceal bleeding [37]. The preferred therapy for HCC is surgical resection. Patients who are not surgically resectable, liver transplantation is only curative option [38].

Urinary tumors (group 4)

Cancer Bladder The incidence of neoplasia of the Genitourinary System After (RTRs) varies from 0.64% to 1.67%, Patients with bladder cancer classically present with painless hematuria, although irritative voiding symptoms (frequency, urgency, dysuria) can be the initial manifestation [39]. A full urologic evaluation of the entire urinary tract is indicated [40]. This evaluation should consist of cystourethroscopy, urinary cytology, and an evaluation of the upper tracts, also [41]. Radiographic imaging a helical Computed Tomography (CT) scan of the abdomen/pelvis and renal ultrasound (US) to evaluate both the collecting systems and the renal cortex [42]. Noninvasive tumours were treated by TURBT (Transuretheral Resection of Bladder Tumor) [43]. Surgical removal of the bladder is recommended as well as standard pelvic Lymphadenectomy in invasive tumor [44]. This poor outcome might be attributed to the aggressive nature of the disease; the limited lymph node dissection on the graft side might be an additional factor [44].

Renal Cell Carcinoma (RCC)

Renal transplant recipients are at increased risk of developing carcinoma of the native kidneys, particularly if they have undergone prolonged periods of dialysis, the incidence is approximately 100 times greater than expected (Denton et al., 2006).Urinalysis every three months for microscopic or gross hematuria [45]. If this is positive, we obtain a urine culture, urine cytology, (US) of the native, transplant kidney, and bladder, and urine (PCR) for BK (45). RCC were successfully managed with radical nephrectomy, radiofrequency ablation and without a change in immunosuppression (45).

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Hematological Abnormalities Post Renal Transplantation

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Introduction

Renal transplantation is considered the surgical procedure used in renal replacement therapy. It has better patient survival. Although it may has some hematological disorders which may be categorized into two groups.

A-Common Disorders

1-Post renal transplant anemia.

2-Post renal transplant lymphoproliferative disorder.

3-Post renal transplant erythrocytosis.

4-Post renal transplant cytopenias (PTC, leukopenia / neutropenia, thrombocytop- enia, and pancytopenia).

B-Less Common Disorders

1-Hemophagocytic syndrome.

2-Thrombotic microangiopathy.

3-Therapy related myelodysplasia.

4-Therapy related acute myeloid leukemia.

Post renal transplant anemia

It is a well-known complication after renal transplantation; it raises attention more in urological community [1]. It could be classified in to acute (within 6 months post-renal transplant) and chronic (more than 6 months post-renal transplant). Anemia after renal transplantation may persist or reoccur transplantation. It had occurred at least once in 38.3%, and reoccurred in 42% of renal transplant recipients within 5 years [2]. Post renal transplant anemia may occurs due to several factors in renal transplant recipients, including renal allograft dysfunction, drugs [immunosuppressive agents, angiotensin II receptor antagonists, Angiotensin-Converting Enzyme (ACE) inhibitors, and antiviral and

antimicrobial medications], acute rejection, nutritional deficiency, viral infections and blood group ABO incompatibility [3]. Treatment of Post-Transplant Anemia (PTA) is to restore EPO production, to maintain hemoglobin at an adequate level, to enhance kidney graft survival, and to treat underlying cardiovascular disorders [4]. The use of ESAs (even with high doses) in treatment of PTA has been found to slow the progression of post-transplant CKD and improve the quality of life in renal transplant recipients [5].

Post Renal Transplant Lymphoproliferative Disorder

Epstein-Barr virus (EBV) infection after renal transplantation is considered the main cause of Post-Transplant Lymphoproliferative Disorder (PTLD) [6]. PTLD occurs in 1 - 5% of renal transplant recipients [7].

Potential Treatments

(I) Immunomodulator agent (rituximab).

(II) Antiviral therapy against cytomegalovirus (CMV): acyclovir, valacyclovir, ganciclovir, or foscarnet.

(III) Passive immunization with anti-EBV monoclonal antibodies (anti-B-cell monoclonal antibody, anti-CD21 antibody, or anti-CD24 antibody).

(IV) Interferon Alfa-2b (Intron A) therapy.

(V) T-cell–based therapy (specific cytotoxic T lymphocytes).

(VI) Intravenous gamma globulin (IVIG) therapy (gamimune, gammagard S/D, sandoglobulin).

(VII) Combination chemotherapy: rituximab followed by cyclophosphamide, adriamycin, oncovin, and prednisone.

(VIII) Antineoplastic agents (prednisone, cyclophosphamide, doxorubicin, vincristine, etc.).

(IX) Surgical excision.

(X) Localized radiation therapy [8].

Post Renal Transplant Erythrocytosis (PRTE)

It is defined as elevated hemoglobin (Hb) (>17 g/dL) and hematocrit (>51%) that persists for more than 6 months [9]. In renal transplant recipients the incidence rate of Post-Transplant Erythrocytosis (PRTE) varies between 10-20% of renal transplant recipients and usually develops within 2 years after transplantation. Clinically the patient may complains of malaise, headache, dizziness, lethargy, plethora, and thromboembolism. Complications of PRTE may end by death in 1-2% of patients [10]. PRTE usually undergoes spontaneous remission but may occasionally persist for years. Its etiology is not clearly known, multiple mechanisms have been proposed to explain its occurrence, including:

- Erythropoietin overproduction [11].
- Rennin–angiotensin system activation [10, 11].
- Increase in endogenous androgens production post transplantation [10, 11].
- Insulin-like Growth Factor1 (IGF-1) has been recognize d to be involved [11, 12].

Many underlying conditions had been linked to PRTE including; male, gender, smoking, duration of dialysis, presence of native kidneys, transplant artery stenosis, type and dose of immunosuppressive therapy, the extent of allograft function, acute and chronic graft rejection [10, 13].

A number of therapies are available for the management of PRTE. These include Serial phlebotomy [14, 15], native kidney nephrectomy [16], theophylline [14] and Angiotensin Converting Enzyme Inhibitors (ACEI) [14, 17]. The prevalence of PRTE, however, has seen a steady decline over the years, probably due to the increased prescription of ACEI/ARBs and/or the more intensive use of antiprolifirative immunosuppressant [4].

Post renal Transplant Cytopenias (PTC)

Cytopenia is defined as marked reduction or cessation in the production of one or more blood cell types. It is caused by immunosuppressive therapy, chemotherapy, and viral infections after transplantation. Cytopenia may occur in the form of anemia (RBCs deficiency), leukopenia or neutropenia (WBCs or leukocytes deficiency), thrombocytopenia (platelets deficiency), and pancytopenia (a deficiency of all three blood cell types—RBC, WBC, and platelet [18].

Leukopenia or Neutropenia

Leukopenia commonly occur following organ transplantation. It is defined as total WBC count less than 3000–4000 cells/μL [19]. Neutropenia (abnormally low count of neutrophils) is the most common form of leukopenia, which is defined as neutrophilic count of 1500 or fewer cells/μL [20]. Leukopenia/neutropenia may occur in about 20–63% of kidney recipients. It usually occurs around day 100 after transplantation and may last for 1 to 4 weeks [21]. Many factors are involved in occurrence of leukopenia/neutropenia

- AZA is a known immunosuppressive agent that causes leukopenia/neutropenia in 50% of renal transplant recipients. However, this could be reversed with decrease or discontinuation of the drug [22].
- T-cell depleting agents: Thymoglobulin, Atgam, Alemtuzumab, and Basiliximab all may induce some degree of leukopenia/neutropenia by eliminating targeted lymphocytes [23].
- Mycophenolate Mofetil (MMF) induced leukopenia/neutropenia occur in about 13–35% of renal transplant recipients. This is related to active metabolite, Mycophenolic Acid (MPA).
- The anti-CMV medications: Valganciclovir & Ganciclovir were found to cause leukopenia/neutropenia in 50% of transplant patients in a dose-dependent manner [24].
- Antibiotics such as: Trimethoprim-sulfamethoxazole, Beta-lactam antibiotics, and Piperacillin may also cause leukopenia/neutropenia [25].
- Deficiencies of some essential nutrients, such as folic acid, vitamin B12, zinc, and copper, may also lead to leukopenia/neutropenia [26].
- Viral infections have marked myelosuppression effects in renal transplant recipients that may result in leukopenia/neutropenia as a manifestation, including PVB19, herpes virus-6 (HHV-6), CMV, and influenza [27].

As regard treatment of leukopenia/neutropenia after renal transplantation, the most effective way to improve leukopenia/neutropenia is to discontinue the accused medications such as MMF, valganciclovir, cyclosporin, and Tacrolimus (FK-506) or decrease their doses. Recombinant granulocyte-colony stimulating factors (G-CSF), such as: filgrastim (Neupogen), may be used in treating leukopenia/neutropenia. In addition, stem cell transplants may be useful in treating some types of severe leukopenia/neutropenia, including those caused by the myelosuppressive agents [28].

Thrombocytopenia

Thrombocytopenia is defined as that a total platelet count is less than 50,000/μL. It is common during the first year after transplantation especially the firquite prevalent in the

first year after renal transplantation. The first three months the clinical manifestations of thrombocytopenia include bruising, mild to serious bleeding, petechial, fatigue, malaise, and general weakness [29]. It occurs due to bone marrow suppression by immunosuppressant agents, infection, chemotherapy, antiplatelet antibody therapy, acute rejection episodes, microangiopathy, or deficiencies of folate and Vitamin B12 [30]. Causes of thrombocytopenia are similar to those of anemia and leukopenia in renal transplant recipients. The use of sirolimus and/or calcineurin inhibitors may lead to microangiopathy as a cause of thrombocytopenia in renal transplant recipients [31]. Many drugs can cause thrombocytopenia including rabbit antithymocyte globulin, valganciclovir, ganciclovir, linezolid, and heparin [32]. Viral infections, particularly CMV or EBV infection, can cause thrombocytopenia and Hemophagocytic Syndrome (HPS) [33].

The goals of therapy in thrombocytopenia are to stimulate the bone marrow production of platelets, to maintain adequate platelet level, and to treat microangiopathy, this could be achieved by stoppage of the offending drugs [34]. Corticosteroids may be used to increase platelet production. Lithium carbonate or folate may also be used to stimulate the bone marrow production of platelets. Rituximab, daclizumab, and other new antibody preparations may be effective for patients with transplant associated TMA. Thrombopoietin growth factors: Romiplostim and Eltrombopag have been used as second line therapy of immune thrombocytopenia for hematopoietic stem cell transplant patients [35], and may be effective in treating post-transplant thrombocytopenia.

Pancytopenia, the deficiency of all three blood cell types (RBCs, WBCs, and platelets), is characteristic of aplastic anemia, a potentially life-threatening disorder that requires a stem cell transplant. Pancytopenia has widespread effects on the entire body by leading to oxygen shortage as well as problems with immune function [36]. Pathologies involving the WBC and platelet population often exist in the context of pancytopenia, which can probably be a manifestation of systemic infection [37]. In renal transplant recipients, PVB19 infection is a common cause of pancytopenia and leads to various forms of glomerulopathy and allograft dysfunction [38]. In addition, visceral leishmaniasis, a disease caused by protozoan parasites of the genus Leishmania and spread by the bite of certain types of sandflies, can also cause pancytopenia in some immunocompromised renal transplant recipients [39]. Other potential factors involved in the development of pancytopenia include immunosuppressive drugs (azathioprine, MPA, anti-thymocyte globulins, and alemtuzumab), chemotherapy drugs that cause bone marrow suppression, antibiotics (linezolid and chloramphenicol), and radiation therapy [37]. Symptoms of pancytopenia can include bleeding, bruising, fatigue, shortness of breath, and weakness. Treatments for pancytopenia include drugs that suppress the immune system, bone marrow stimulant drugs, blood transfusion, bone marrow transplant, and stem cell replacement therapy [38].

Other Hematological Complications of Renal Transplantation

There are less common hematologic complications post renal transplantation include HPS, Thombotic Microangiopathy (TMA), and therapy-related Myelodysplasia (t-MDS) and therapy-related acute Myeloid Leukemia (t-AML) [37]. Death may occur in more than 50% of patients with these hematologic complications [40].

Hemo Phagocytic Syndrome (HPS)

HPS, also known as Macrophage Activation Syndrome (MAS) or Hemophagocytic Lymphohistiocytosis (HLH), is characterized by uncontrolled proliferation of hematophagic monocytes/macrophages/ histiocytes that are actively ingesting other blood cells. In most cases, HPS is associated with opportunistic infection following intensive immunosuppression. HPS is seen in association with viral infections [such as CMV, adenovirus, EBV, human herpes virus-8 (HHV-8), , human herpes virus-6 (HHV-6), Parvo virus-19 (PVB19), and polyoma virus, bacterial infections such as tuberculosis, Bartonella henselae, and Escherichia

coli and protozoal infections such as toxoplamosis, leishmaniasis, pneumocystis carini pneumonia, and babebiosis [41, 42].

Pathogenesis of post-transplant HPS is multifactorial including:

(a) The activation of T helper-1 (Th-1) cells and the increased the production of cytokines, tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) caused by severe infection.

(b) Abnormalities of CD8 + T lymphocyte and natural killer-cell (NK-cell) cytotoxicity caused by immunosuppression.

These cellular and biochemical alterations may lead to excessive Th-1 lymphocyte and macrophage activation and uncontrolled proliferation under lack of NK cell and T lymphocyte cytotoxicity, thus causing hemophagocytosis [42].

HPS usually occur within two month after renal transplantation, but it may occur years after transplantation in recipients with parasitic infection or neoplasia. Generally, post-transplant HPS is associated with a higher rate (53%) of renal transplant recipients may die due to HPS [43]. Patients with HPS may present with fever, cytopenia of two lines, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia (>500 μg/L), hemophagocytosis, elevated soluble interleukin-2 receptor (CD25), decreased NK-cell activity, and hepato-splenomegaly [42].

Treatment of HPS aims to recognize and treat the etiological microorganism. Reduction or withdrawal of the accused drugs is usually recommended in order to control infection. Intravenous methylprednisolone may reduce the activation of macrophages and cytokines, although it may worsen the underlying infection [41]. CMV infection could be treated with intravenous ganciclovir. Reduction of immunosuppression and the administration of foscarnet might be used in HH-8 infection. Treatment of BK virus infection includes withdrawal of immunosuppressive therapy, infusion of intravenous IVIg and increasing prednisone [42]. The use of IVIg may also be useful for treating bacterial and protozoan infections. In patients with resistant HPS graft nephrectomy may be a possible therapeutic option for renal transplant recipients [43].

Thrombotic Microangiopathy (TMA)

TMA is a group of disorders characterized by thrombocytopenia, MAHA (intravascular hemolysis and presence of peripheral blood schistocytes), purpura, microvascular occlusion (thrombi and coagulation) neurological symptoms, fever, and renal dysfunction. TMA has two major causes HUS and Thrombotic Thrombocytopenic Purpura (TTP) [44]. TMA can also occur in both renal transplantation and HSCT that are closely associated with calcineurin inhibitors and often cause graft failure [45]. The calcineurin inhibitors (CsA and FK-506) are toxic to microvascular endothelial cells and can induce microvascular constriction and platelet aggregation that may result in TMA in renal transplant recipients. Intravascular thrombi of aggregated platelets lead to thrombocytopenia and various degrees of organ ischemia and anemia. Furthermore, viral infections (CMV, HIV, and PVB19), antibody-mediated acute humoral rejection and severe renal ischemia may also be implicated in TMA [45].

In renal transplant recipients, the majority of TMA cases occur de novo (triggered by immunosuppressive drugs and acute antibody-mediated rejection), sometimes it recur in patients with previous history of HUS [46]. Clinical presentations of de novo TMA include anemia (hemoglobin <10 g/dL), thrombocytopenia, increased lactate dehydrogenase decreased haptoglobin and schistocytes [47]. The first step in the management of post-transplantation TMA is to stop or decrease the dose of Calcineurin inhibitor, then to start plasma therapy (fresh frozen plasma infusion or plasmapheresis) [46]. Some of these patients may also need dialysis therapy [47]. The targeted complement C5 inhibitor therapy (eculizumab for atypical HUS and rituximab for TTP) could be effective in treating TMA [44]. Rituximab (with or without cyclophosphamide) may be efficacious as treatment for TTP [45].

Therapy-Related Myelodysplastic Syndromes (T-MDS) and Acute Myeloid Leukemia (T-AML)

t-MDS (also called myelodysplasia) means ineffective production of all blood cells. It is characterized by blood cytopenias, ineffective hematopoiesis,dyserythropoiesis, dysgranulopoiesis, dysmegakaropoiesis, and increased myeloblast. t-MDS develops 3-5 years after tranplantation [48]. Patients with t-MDS usually have severe anemia, cytopenias and refractory AML.

t-AML, also known as acute myelogenous leukemia or Acute Non-Lymphocytic Leukemia (ANLL), is a disorder of the myeloid line of blood cells, in which rapid growth of abnormal white blood cells occur and accumulate in the bone marrow and thus interfere with the production of normal blood cells. Timing of t-AML is usually 5 years after transplantation. Clinically the patient of t-AML may have fatigue, shortness of breath, petechiae, bone and joint pain, easy bruising and bleeding, and persistent or frequent infections. Untreated t-AML progresses rapidly and the patients may die within weeks or months [49]. Both t-MDS and t-AML are two therapy-related complications that occur in organ transplant recipients maintained on immunosuppressive agents. The two conditions are often associated with heavy post-transplant immunosuppression by azathioprine (a thiopurine prodrug) [50] or by ATG [51].

Genetic variation (deletions or translocations of different chromosomal bands caused by different drugs) may play a role in the development of t-MDS/t-AML [48]. Furthermore, epigenetic changes in DNA structure have been considered as a mechanism of t-MDS/t-AML [52-54]. Other predisposing factors may include (polymorphisms in detoxification and DNA repair enzymes), granulocyte-colony-stimulating factor, topoisomerase II inhibitors, and radiotherapy, may cause chromosome abnormalities (of bone marrow cells. These factors may induce t-MDS/t-AML [55, 56].

Stoppage or replacing azathioprine with a nonthiopurine alternative (such as mycophenolate, sirolimus, or everolimus), was proved to reduce the incidence of post-transplantation t-MDS/t-AML [57], Three DNA methyltransferase inhibitors (5-azacytidine, decitabine, and lenalidomide) can restore normal blood counts and retard the progression of MDS to acute leukemia and thus it was approved for treatment of t-MDS [58]. Supportive care with blood product support (RBC transfusion), iron chelators (deferoxamine and deferasirox), and hematopoeitic growth factors (erythropoietin), is the mainstay of therapy for t-MDS/t-AML [59]. Chemotherapy with the hypomethylating agents (5-azacytidine and decitabine) might slow the progression of MDS to AML [60].

Treatment for AML is usually divided into two phases:

- Induction and consolidation therapy, with cytarabine (Ara-C) and anthracylines reduce the number of leukemic cells to an undetectable level and this achieve a complete remission.
- Consolidation therapy, it is the intensive chemotherapy to eliminate any residual disease [61].

After the completion of consolidation therapy, relapse of AML could be prevented by a combination Immunotherapy with Histamine Dihydrochloride (INN) and interleukin 2 [62]. For patients with relapsed t-AML or t-MDS, HSCT can be considered as a potentially curative therapeutic option [63].

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