Kidney Transplantation

Chapter 2

Kidney Transplantation in China

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Abstract

Kidney transplantation work in China started about 10 years later than abroad. However, the source of donors has gradually transitioned to donation after citizen's death (DCD) since 2012, and kidney transplantation in China has made steady progress step by step. This chapter is aimed to elaborate the kidney transplant work in China from the history and immunological assessment, donor maintenance and donor quality assessment, operation methods, postoperative major complications, and application of immunosuppressive agents to the postoperative follow-up. Kidney transplantation is a meaningful and challenging work in current China, all the Chinese transplant surgery and scholar are devoting themselves to this work in order to give more effective help to the patients.

Keywords: Kidney transplantation; China; DCD; immunological assessment; donor quality assessment; kidney transplant complications; immunosuppressant; follow-up

1. The Developing History of Kidney Transplantation in China

As far as clinical organ transplantation is concerned, our organ transplant work started about 10 years later than abroad. As in foreign countries, organ transplantation in China also begins with kidney transplantation. Since 1956, animal experiments on kidney transplantation have been carried out. In 1958, kidney transplant animal experiments were carried out in various places [1]. China's clinical kidney transplantation began in the 1960s and gradually developed in the late 1970s. It formed a certain scale in the 1980s and reached a large scale in the 1990s. In 1960, Wu Jieping performed the first cadaveric kidney transplantation in the

First Affiliated Hospital of Beijing Medical College. The patient had early renal urination after surgery, but he did not know enough about immunosuppressive agents. The patient lost kidney function after 3-4 weeks after surgery. The transplanted kidney was removed. In 1972, the First Affiliated Hospital of Guangzhou Zhongshan Medical College and Beijing Friendship Hospital successfully carried out the first kidney transplant in China. The patient died of severe hepatitis after one year of survival. In 1970, Xiong Yucheng of Zhongshan hospital of Shanghai First Medical College began to implement cadaveric kidney transplantation, followed by Beijing Friendship Hospital, Shanghai First People's Hospital, and Wuhan Tongji Hospital, which successively carried out clinical kidney transplantation one after another and promoted the development of kidney transplantation in these areas. It also inspired other areas such as Guangzhou, Hangzhou, Xi'an, Changchun and Nanjing to carry out clinical work on kidney transplantation [1-3].

In 1980, the Shanghai Second Military Medical University Changzheng Hospital and the Shanghai Central Blood Station jointly developed the compound citrate-adenine hyperosmotic solution (HCA), which filled the gap in China and promoted the development of organ transplantation in China. The improvement of organ preservation solution not only saves more preparation and transportation time for clinical transplantation, but also reduces the incidence of graft non-function and functional recovery delay, and reduces the organ rejection rate [4,5].

By the middle and late 1970s, the same kind kidney transplantation was successfully carried out in various parts of China. By 1989, kidney transplants had more than 1000 cases per year, and kidney transplants accumulated more than 4,500 cases. By the end of 1999, there were more than 29,000 kidney transplants. In the 21st century, kidney transplantation has been further developed. In 2004, it reached 10,000 cases of kidney transplantation. Subsequently, the Chinese Ministry of Health (now the National Health Committee) approved the organ transplant units in China for further standardization management. By the end of 2014, according to the statistics of Organ Transplantation Branch of Chinese Medical Association, more than 120,000 cases of various large organ transplants have been implemented in China, of which kidney transplants accounted for more than 83%, with a cumulative total of more than 100,000 cases, among them, there are more than 10,000 cases of living kidney transplantation. The recipient has the longest functional survival of more than 37 years [6].

In March 2006, the Ministry of Health issued the Interim Provisions on the Clinical Application Management of Human Organ Transplantation Technology [7]. In April of the same year, the Ministry of Health established the Clinical Application Committee for Human Organ Transplantation Technology. Two months later, the management specifications for transplantation techniques for liver, kidney, heart, lung and other organs were issued. Since the source of donors in China had relied mainly on organ donation of condemned prisoners for a period of

time, this has caused the organ transplanting industry in China to be criticized by the international community for a long time. In response to this situation, in recent years, China has intensified its efforts to regulate the management of organ donation and organ transplantation. The State Council passed the Regulations on Human Organ Transplantation on March 21, 2007 [8]. In August 2009, the Chinese Red Cross and the Ministry of Health jointly held a national human organ donation work conference in Shanghai, jointly announced the establishment of a human organ donation system. In 2009, the Ministry of Health revised the "Brain Death Judgment Criteria (Adult)" (revised version) [9]. On March 1, 2010, the Chinese Red Cross and the Ministry of Health announced in Tianjin, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Jiangxi, Shandong, Hubei, Guangdong and Hunan provinces. A total of 11 provinces first carried out pilot work on human organ donation [10]. In December 2010, the Ministry of Health promulgated the "Fundamentals of Human Organ Distribution and Sharing in China and Core Policies of Liver and Kidney Transplantation "[11]. In addition to the Brain Death Law, the related system construction has been basically completed. At the end of 2011, domestic scholars revised and released the "China organ donation after cardiac death work guidance (the Second Version)" [12]. From the pilot project of human organ donation in March 2010 to the end of December 2014, 38 pilot units completed 1699 human donations. 4638 organs were donated, of which Guangdong Province has the largest number.

In 2011, China Human Organ Transplantation Technology Clinical Application Committee passed and announced the Chinese human organ donation classification standers, that is, the following three categories [12]:

1) China Category I (C-I): Internationally-standardized donation after brain death (DBD), that is, brain death cases. After rigorous medical examination, the indicators meet the current international brain death standers and newest Chinese brain death standards [13], by the Ministry of Health commissioned by the agency certified brain death experts clearly identified as brain death by experts who trained and certified by agency that authorized by the Ministry of Health. Family members fully understand the situation and choose to stop the treatment and donate organs, at the same time, having obtained the approval and support from the hospital and relevant leading departments.

2) China Category II (C-II): Internationally standardized cardiac death organ donation (DCD) includes the I-III case of the Maastricht standard classification.

3) China Category III (C-III): donation after brain death awaiting cardiac death (DBCD). Similar to Maastricht's standard class IV, it is a controlled type and meets the diagnostic criteria for brain death. Since the brain death law has not yet been established, and family members cannot accept donations of organs under cardiac beating, donor donations should be made according to the DCD procedure, i.e., life support should be removed, and donations should be

made after cardiac arrest. The C-III is in line with China national conditions.

In the past 50 years, the same kind kidney transplantation in the world has made great progress. Due to the continuous improvement of tissue matching and kidney preservation methods, the emergence of powerful immunosuppressant's, advances in transplant immunology and the accumulation of clinical experience, the recent effect of kidney transplantation is significantly improved, hyper acute rejection is very rare, and acute rejection is greatly reduced. However, it still faces problems such as how to greatly improve long-term survival rate. In addition, the serious shortage of transplant organ donors also affects the development of kidney transplantation, so it is necessary to adopt an expanded standard donor kidney, and cannot completely avoid living kidney transplantation (In China, living donor transplantation only between parents and children, brothers and sisters, and between husband and wife).

Kidney transplantation still plays a critical role in the field of organ transplantation. The basic and clinical research of kidney transplantation is very important in promoting the development of various other organ transplants. Chinese transplant experts and related staff are also working hard for this career and successfully treated a large number of patients with end-stage renal disease. After half a century of development, despite various difficulties and facing various problems, with the support of the Chinese government and the help of the international transplant community, Chinese kidney transplantation has been moving towards a more standardized and healthier direction with a solid and powerful pace.

2. Immunological Assessment for Kidney Transplantation

To achieve successful kidney transplantation, the potential candidate must receive detailed assessments. These include the matches of ABO blood group and the major histocompatibility complex (MHC, or human leukocyte antigen, HLA), as well as the presence of preexisting anti-HLA antibodies that might cause the failure of the graft. With the rapid development of the detecting technology, novel techniques have been applied in clinic and help transplant practitioners make careful evaluation.

The ABO blood group is the initial and the most important barrier to kidney transplantation. Incompatibility of ABO blood group with a large amount of antibodies against the donor's blood group antigen would lead to rejection immediately at the time of transplantation. Thus, compatibility of ABO blood group is the primary requirement of kidney transplantation. However, due to the shortage of donation, several groups developed protocols to succeed in ABO-incompatibility kidney transplantation (ABOi-KT) [14-19]. Plasmapheresis, intravenous immunoglobulin (IVIG), splenectomy and rituximab are employed to reduce the titer of anti-A or anti-B antibodies. In China, the guideline for the ABOi-KT was published in 2017, but only available for the living donor kidney transplantation (LDKT) [20].

The HLA poses another important barrier. The human MHC, located on the chromosome 6p21.31, comprises only about 3.6 Mb DNA but is the most gene-dense region of the human genome. It can be divided into three regions: class I, class II and class III. The classic class I genes (HLA-A, -B and -C) and the classic class II genes (HLA-DR, -DQ and -DP) encode HLA antigens closely related to kidney transplantation. They are highly polymorphic, co-dominantly expressed and inherited in a haplotype, thus leading to the diversity and linkage disequilibrium of HLA in human population. Except for the identical twins, it is almost impossible to achieve identity of HLA between the donor and the recipient. The mismatched donor HLA would be recognized by the alloreactive T cells of the recipient through direct, indirect or semi-direct pathway, and initiate alloimmune response that causes rejection. Besides, B cells can also be activated and produce alloreactive antibodies. Blood product transfusions, pregnancy or transplantation can lead to the development of anti-HLA antibodies, thus making the candidate sensitized before kidney transplantation. Therefore, the match of HLA typing between the donor and recipient and the preexisting HLA antibodies consist of the major content for pretransplant immunological assessment.

2.1. HLA-typing methods

Previously, HLA was classified by serological typing, which was complicated and inaccurate. The development of polymerase chain reaction (PCR) technique brings HLA typing into the DNA-based era. Based on the HLA DNA sequence data, three basic methods are widely used in conjunction with PCR, namely sequence-specific oligonucleotide probes (SSOP or SSO), sequence-specific primers (SSP) and sequencing-based typing (SBT). In SSO, locus- or group-specific primers are used to amplify the HLA DNA, and then hybridized with specific oligonucleotide probes. It includes forward SSO and reserve SSO techniques. In forward SSO, the PCR products are attached to the membrane and hybridized with probes tagged with enzymatic or fluorescent markers for detection. The reserve SSO is just opposite, in which the specific probes are attached to the membrane and the PCR products are tagged. Currently, the commercial PCR-SSO kits are based on the reserve SSO, and make use of the Luminex technique to identify the specific probes attached to the beads with different colors. The tagged PCR products are hybridized with probes and then detected in the Luminex machine. This technique is fast, convenient and accurate, so that it is widely used in clinic. SSP uses special designed primers to amplify HLA DNA, and then detects the products in gel electrophoresis. The result is interpreted by the size of the products. SBT offers the most accurate result at high-resolution, which directly sequences the polymorphic region of the HLA genes. With the rapid development of the next-generation gene sequencing, this technique will be easier, faster and less expensive. However, the intermediate level of HLA typing provided by SSO may be sufficient for most cases.

2.2. Antibody detection

The assessment of anti-HLA antibodies consists of determining the breadth and strength of the antibodies prior to kidney transplantation. The classic method is detecting the panel reactive antibody (PRA), which is expressed as a percent and only describes the breadth. A panel of cells from donors who together possess as many HLA antigens as possible, are incubated with the serum from the candidate and complement, and then detect the cytotoxicity. The PRA percent is simply calculated by dividing the number of positive wells by the total number of wells. Currently, the PRA assay has evolved from cell-based technique to bead-based technique. Multiple HLA antigens, which are from digested cells or recombinant technique, are coated on the beads and react with the candidate's serum. Fluorescent anti-human immunoglobulins are added as secondary antibodies, and then the beads are detected in the Luminex machine or flow cytometer. Similarly, the PRA percent is calculated by dividing the number of positive beads by the total number of the beads. The mean fluorescence intensity (MFI) value can be regarded as the strength of the antibodies. Although the coated antigens may be more diverse, it still can't represent the accurate frequency of HLA in the donor pool.

The PRA assay can serve as the screening test. When PRA is positive, it is important to identify the specific locus to which the antibody react. The high-throughput characteristic of Luminex technique makes it possible to detect the reactivity to the single HLA antigen. The test process is similar to the PRA assay, but each bead has a specific color which can be recognized by the Luminex system, and is coated with the corresponding single HLA antigen. According to the result of each bead, the reactivity to each single HLA antigen is revealed. In the commercial kits of Luminex single antigen bead (LSAB) assay, nearly 100 representative antigens are selected for class I and class II respectively, covering the common HLA antigen repertoire in the population. All the beads can be detected at the same time, and the result is informative of antibody specificity and strength. This technique completely changes the way how antibody is evaluated, and is widely used for kidney transplantation all over the world.

2.3. Cross match

It is essential to perform the crossmatch before kidney transplantation to ensure that the recipient should not possess any antibody that could lead to hyperacute rejection or early graft failure. Depending on whether cells from the donor and serum from the recipient are used to react directly, the crossmatch can be classified in to the physical crossmatch and the virtual crossmatch.

2.3.1. The physical cross match

In 1964, Terasaki firstly reported the importance of crossmatch by the complement-depending cytotoxicity (CDC) assay [21]. Briefly, donor lymphocytes are collected and in-

cubated with recipient serum at room temperature for 30 minutes. Then rabbit complement is added to the mixture, and incubate at room temperature for 60 minutes. After the second incubation, vital dye is used to dye the dead cells and the mixture is observed under the microscope. If the percentage of dead cells is over 20%, the result is positive (0 – 10%, negative; 11 – 20%, doubtful negative). In the report, 24 of 30 cases (80.0%) with positive CDC result suffered from immediate graft failure, while it was only 8 of 195 cases (4.1%) in the negative CDC group [21]. Since then, the CDC assay has been the standard protocol before kidney transplantation worldwide, and a positive CDC result is regarded as the contraindication to kidney transplantation.

Although the CDC assay has a high specificity, the sensitivity is relatively low. Great efforts have been made to improve the sensitivity, including adding washes, increasing incubation time and separation of T and B cells, but the most effective method is adding anti-human globulin [22-24]. The process of anti-human globulin enhanced CDC (AHG-CDC) is similar to standard CDC. Anti-human globulin is added before the addition of complement, which helps cross-linking of the antibody and activation of the complement. Thus, even though the preexisting antibodies are non-complement binding (IgG4) or at a low level, they can be detected with AHG-CDC.

The flow cytometric crossmatch (FCXM) provides a more sensitive method. Donor lymphocytes are incubated with recipient serum, and fluorochrome-tagged anti-human globulins are added after several washes. At the same time, T cells and B cells can be labeled by fluorochrome-tagged anti-CD3 antibodies and anti-CD19 antibodies respectively so that class I and class II antibodies can be distinguished. Then cells are run through the flow cytometer, and the intensity of fluorescence in different channels is recorded. The result is based on the data of a large amount of cells so that it is more objective than the CDC assay, which is observed by the technician under the microscope. The high sensitivity of flow cytometry also makes it available to detect a low level of donor specific antibody (DSA). If needed, IgG and IgM antibodies can be distinguished by different secondary antibodies. Because FcγR is expressed on B cells, which may cause non-specific binding to the Fc region of IgG antibodies and lead to a high background, pronase is recommended to pretreat the donor cells to cleave the FcγR, and use the fluorochrome-tagged anti-human IgG F(ab)'2 for detection [25,26]. Meanwhile, the IgM, immune complexes and activated complement components in the serum may cause the prozone effect, which leads to the false negative result. High speed or ultracentrifugation, pretreatment with dithiothreitol (DTT)/C1q inhibitor/EDTA, or setting titration series of the serum can help reduce the impact [26, 27].

A crucial disadvantage of FCXM is that it is difficult to standardize. Even though a standard operating procedure is recommended by the American Society for Histocompatibility & Immunogenetics (ASHI), the reagents used, the setting of flow cytometer and the cut-off

value chosen will all have an impact on the results. Evolving from cells to beads may be one of the choices, and the commercial kits are available. Lyse the donor cells first, capture the donor HLA antigens with anti-HLA antibody-coated beads, and then incubate the beads with recipient serum. Finally, use the fluorochrome-tagged anti-human IgG to detect the DSA in the Luminex system. Unlike antibody screening or LSAB assay talked above, the beads are only coated with the whole repertoire of HLA from the donor, thus only the preexisting DSA can be detected.

2.3.2. The virtual crossmatch

In comparison to the physical crossmatch, donor cells and recipient serum do not react directly in the virtual crossmatch. Benefiting from the high sensitivity and high resolution of detecting techniques nowadays, DSA can be easily identified based on the donor's HLA typing and the recipient's antibody from LSAB assay. Therefore, the unacceptable HLA antigen can be determined. When entering the unacceptable HLA antigen, the UNOS would calculate the PRA (cPRA) for each candidate in the waiting list. The donor pool is based on the HLA typing data of more than 12000 donors in US, so that it precisely represents the actual HLA frequency in the population [28]. cPRA is an important reference for organ allocation, and this strategy reduces the organ refusals due to positive physical crossmatch [29,30]. Similar system has been set up in China, but it needs to be further improved.

Although HLA tying and LSAB assay provide an intermediate result (4-digit level like HLA-A*02:01), the virtual crossmatch is performed at a low resolution level of serology for most cases. In fact, what the antibodies actually bind is the epitope, which consists of about 15 to 25 amino acid residues, and each antigen is composed of a string of epitopes [31-33]. HLA antigens in the same serological group share the majority of epitopes ("public" epitopes), but allele-specific epitopes ("private" epitopes) exist and can lead to the difference of reactivity. On one hand, antibodies against the "private" epitope may only react with the corresponding allele-encoded antigen, and on the other hand, the minor difference of the sequence between alleles can lead to the distinct reactivity to the same alloantibody which is against the "public" epitope [33]. To solve this problem, virtual crossmatch based on epitopic analysis has been advocated in recent years. One of the tools for epitopic analysis is the HLAMatchmaker, which is an algorithm developed to theoretically predict the epitopic DSA. When entering the 4-digit HLA tying of the donor and the recipient, HLAMatchmaker automatically identifies the mismatched epitopes, and then determines the reactive ones by removing the negative ones according to the LASB assay and the cut-off value [34]. This strategy makes full use of the information derived from HLA typing and LSAB assay, and provides a more precise crossmatch result. It should be noted that the result is theoretically predicted, and the reactivity of the epitopic antibody needs to be verified [33].

2.4. Immunological assessment in clinic

Detailed immunological assessment with all the methods above guarantees the success of kidney transplantation. In China, most of the transplant centers have introduced the Luminex techniques for HLA typing and antibody detection, and have applied physical and virtual crossmatches for making final clinical decision. For patients with a negative result of CDC/AHG-CDC assay and no DSA detected by virtual crossmatch, transplant can be safely operated. Oppositely, if the CDC/AHG-CDC assay is positive, or the patient has a strong level of DSA, transplant is strictly prohibited. The confusion and controversy lie in the situation where the patient has a low or intermediate level of DSA identified by the virtual crossmatch, but the physical crossmatch is negative. It is well-recognized that the LSAB assay is more sensitive than the physical crossmatch, but whether the low or intermediate level of preexisting DSA in the setting of negative physical crossmatch has an impact on the prognosis is controversial [35-37].

The root of the problem is how to evaluate the antibody strength. Currently, the MFI of the antibody derived from the LSAB assay is widely used to evaluate the antibody strength, and the cut-off value for risk stratification is MFI-based. Various criteria to determine the unacceptable cut-off value are used in different centers. Based on the data from the Proficiency Testing Program organized by ASHI, the correlation between the MFI and the physical crossmatch was reviewed [38]. It was recommended that when the cumulative MFI of the DSA was < 3000, the likelihood of a positive physical crossmatch was very low and it could proceed to transplant without physical crossmatch; when the MFI was 3000 – 8000, further physical crossmatch was needed; when the MFI was > 8000, the likelihood of a positive physical crossmatch was very high and the transplant should be canceled [38]. It provided a good reference based on the experimental data, but some scholars challenged the concept of MFI and even the LSAB assay [39-41]. MFI is only a relative value to reflect the antibody strength, not an absolute number to quantify it. Many factors can influence the MFI tested by LSAB assay, like the source, the conformation (intact or denatured) and the density of HLA antigens coated on the beads. The prozone effect caused by the interfering factors also exists in LSAB assay [39-41]. More importantly, the complement-binding and -activating ability of the antibody, which was reported to have a better clinical relevance, cannot be reflected by the MFI directly [42,43]. The MFI is not perfect, but there is no better choice available for us at present.

In conclusion, when a patient needs kidney transplantation, immunological assessments including ABO blood group, HLA typing and antibody detection are necessary. Before transplantation, both physical and virtual crossmatches are recommended. MFI from LSAB assay is a good reference to identify the risk, but better indicator is still needed for clinical practice.

3. Donor Kidney

3.1. Donor kidney quality evaluation

The quality of donor kidneys is one of the important factors affecting the survival rates of both patients and grafts after kidney transplantation (KT). With the growing demand for KT, transplant professionals first tried to use nontraditional donor kidneys (typically referred as "external criteria donor kidney") in the 1990s. Although the donor pool is expanded, external criteria donor (ECD) kidneys have demonstrated relationships with a high incident of delayed graft function (DGF) and poor outcomes of both patients and grafts when compared with standard criteria donor (SCD) kidneys [44].

The criterions to assess the kidney graft quality are different in live and brain/circulatory death donors. To ensure the safety of the live donor, nearly all transplantation centers have established a set of strict guidelines to screen the suitable donors in accordance with the recommendations of UNOS and OPTN. Age, kidney-concerned disease history (such as obesity, hypertension, malignancy, diabetes, autoimmune disease and so on) and glomerular filtration rate (GFR) assessment are the most critical factors influencing the quality of the kidney graft. Besides, abnormal anatomy (especially multiple vessels) may increase the difficulty of the donor nephrectomy, which may bring accidental injuries and make the quality of the kidney graft decline.

For brain/circulatory death donors, the concept of ECD is proposed to distinguish some "non-ideal" but still applicable donors from those "ideal" donors. Although the criteria of ECD are dissimilar in transplantation centers, the fundamental elements are age, terminal creatinine level and the cause of death (**Table 1**). Another widely used criterion is the Kidney Donor Risk Index (KDRI), which is a score that estimates the risk of graft failure and takes into account donor age, race/ethnicity, height and weight, history of hypertension and diabetes, serum creatinine, cerebrovascular cause of death, DCD, and hepatitis C status (**Table 2**). KDRI values can help allocate kidneys and determine whether to transplant a single kidney or 2 kidneys.

Table 1: Definition of extended criteria kidney donor.

	A	B
Age	Age 60 or older	50–59 and two of the following characteristics
Terminal creatinine level		>1.5 mg/dL (132.6ummol/L)
Hypertension		Hypertension History
Cause of donor death		Cerebrovascular death

*ECD donors are considered present if the donor has characteristics from either column A or B
*The risk of graft failure is 70 % higher than a standard criteria donor.

Table 2: Calculation of kidney donor risk index.

Donor factor
Age
Race
Hypertensive
Diabetes
Serum creatinine (mg/dl)
Cause of death
Height (cm)
Weight (kg)
Donation after cardiac death
Hepatitis C
Number of HLA-B mismatch
Number of HLA-DR mismatch
Cold time (hr)
Enbloc kidney transplant
Double kidney transplant

*KDRI = Exp(-0.0194×I[age<18 yr] ×[age-18 yr]+ 0.0128×[age-40 yr]+ 0.0107×I[age>50 yr] ×[age-50 yr]+ 0.179×I[race=African American]+ 0.126×I[hypertensive]+ 0.130×I[diabetes] +0.220×I[serum creatinine-1 mg/dL]-0.209×I[serum creatinine>1.5mg/dL] ×I[serum creatinine-1.5mg/dL]+ 0.0881×I[cause of death=cerebrovascular accident]- 0.0464×[{height-170cm }/10]-0.0199×I[weight<80kg] ×[{weight-80kg}/5]+ 0.133×I[donation after cardiac death]+ 0.240×I[hepatitis C positive]-0.0766×I[HLA-B mismatch=0]-0.0610×I[HLA-B mismatch=1]-0.130×I[HLA-DR mismatch=0]+0.0765×I[HLA-DR mismatch=2]+ 0.00548×[cold ischemia time-20 hr]-0.364×I[en bloc transplant]-0.148×I[double kidney transplant]), where I (A) is set to 1 if condition A is applies to the donor kidney of interest (i.e., if the donor kidney of interest possesses condition A), and otherwise it is set to 0.

*KDRI, kidney donor risk index.

With the rapid development of organ preservation and pathological examination, more parameters are inducted to evaluate kidney grafts before transplantation. Lifeport kidney transporter, a device which can provide pulsatile hypothermic machine perfusion (HMP), is now widely used in transplantation centers. The perfusion pressure (usually no more than 45mmHg), flow rate and the renal resistance (RR) are dynamic parameters which reflect the initial and evolving status of renal microcirculation. If the RR and flow rate cannot be significantly improved after a certain period of perfusion, it suggests that the kidney is seriously damaged and should be considered for abandonment. Based on the experiences of different centers, it is generally accepted that kidney grafts with a RR <0.4 mmHg/ml/min and a flow rate >80 ml/min can be used for transplantation; grafts with a RR >0.8 mmHg/ml/min and a flow rate <50 ml/min should be abandoned, while grafts with a RR of 0.4–0.8 mmHg/ml/min or a flow rate 50-80 ml/min should be comprehensively assessed using clinical and biopsy data. The histological parameters to be evaluated include glomerular, vascular, tubular and interstitial injury. Histological evaluation of the donor biopsy can be performed at harvesting, preimplantation or just post-reperfusion periods (the “zero hour biopsy”). The specimens can

be obtained through a wedge resection, needle core biopsy or punch biopsy. At present, there is still no single, fixed pathological indicator which can directly predict the function of kidney grafts. Therefore it is not recommended that the donor kidney should be judged only on the basis of pathological evaluation, and any single lesion in pathological observation cannot be used as the basis of kidney grafts selection. Instead, the comprehensive histopathological scoring system, including glomerulus, renal vessels, renal tubules and renal interstitial lesions, should be adopted. There are about 15 sets of such scoring systems reported successively, and almost all of them are based on the chronic lesion scoring system of the Banff diagnostic criteria.

It should be stressed that the surgical appraisal of kidney grafts by the transplant team is often fundamental to the decision to accept or reject a donor kidney. It is important to identify renal tumors, vascular and anatomical variations or damage, thrombosis, atherosclerosis, infarction, fibrosis and scarring, and to evaluate the quality of perfusion of the graft after procurement. Surgeons also need to consider donor and recipient factors, preservation and biopsy parameters in their global assessment of the suitability of a kidney for transplant.

3.2. Donor kidney procurement

At the present stage in China the sources of kidney are DCD and living-related donation. For living-related donors, the kidney graft procurement procedure is similar with uninephrectomy, which can be performed by open surgery technique or minimal invasive technique (including laparoscopy and robot assistance methods). However, in order to be convenient for anastomosis, the renal artery and vein need to be skeletonized to their origins from the aorta and the inferior vena cava (IVC). The ureter is usually transected and ligated distally on the pelvis inlet plane. For DCD donors, the kidney graft retrieval is often included in the multiple organs procurement procedure which will be detailed below.

The multiple organ procurement, based on the Starzl's report in 1984 [45], may be differences in specific process depending on the grafts. Since the liver and kidneys are the most commonly harvested organs, it is recommended in most centers the "rapid cold perfusion and en-bloc liver-kidney procurement" technique. Following administration of 30,000 IU or 300IU/Kg of heparin, expeditious access to the abdominal cavity is obtained through a midline incision from the xiphoid to the pubic symphysis. The abdominal aorta and IVC are dissected and cannulated and the cold flush (0°C-4°Cnormal saline) is initiated immediately. Superior mesenteric vein is isolated and cannulated at the root of small bowel mesentery followed with perfusion. Ice and slush are packed around the liver and kidneys and subsequent dissection is carried out after completion of cold perfusion. The liver is mobilized by dividing the round ligament, falciform, left triangular, and gastrohepatic ligaments. The hepatoduodenal ligament, posterior peritoneum nearby and the adhesions between the head of pancreas and duodenum are dissected with modified Kocher maneuver; the common bile duct is exposed and transected

at the inferior margin of pancreas. The whole colon, stomach and duodenum are isolated successively; then the bilateral peritoneum are cut open and the peritoneal attachments in the retroperitoneal space are divided until the spine. The ureters are isolated and transected at the common iliac artery level. After the procedure, only the liver, spleen, kidneys and most part of pancreas are still left in the abdominal cavity. The pericardium and diaphragm are incised bilaterally: on the left, extending to the esophagus, and on the right, extending posterior the right lobe of the liver, adrenal gland, and IVC. The thoracic aorta and IVC are transected and the adhesions with the spine are divided until the common iliac artery level. The en-bloc liver-kidney-spleen organs cluster can be harvested with the aorta and IVC transection just below the cannulas.

Once the multiple-organs cluster is taken out, it must be put into the sterile basin filled with 0℃-4℃ organ preservation solution (usually UW solution) immediately. Additional perfusion usually is needed in order to eliminate the residual blood and sustain the low core temperature of the organs. The posterior wall of the aorta is longitudinal cut out and the origins of celiac truck, superior mesenteric artery (SMA) and bilateral kidney arteries are exposed. The adhesions between the right kidney, adrenal gland and the hepatic right lobe are divided until the inferior IVC exposed. IVC is transected just above the kidney veins level and aorta is transected below the origin of SMA level; the liver and kidneys are separated and packaged respectively.

In some cases, surgeons only need to harvest the kidneys. The SMA cannulating, portal vein infusion and the liver mobilizing steps can be omitted in above procedure. The kidneys are mobilized by dividing the adhesions with the posterior abdominal wall and the adjacent organs. The aorta and IVC are transected at the SMA origin level after the hepatoduodenal ligament being dissected. The en-bloc double kidneys and part of the aorta and IVC can be separated from the spine by sharp dissection. The additional bench cold perfusion should be performed after the aorta is longitudinal cut off and the openings of bilateral renal arteries are identified.

3.3. Donor kidney preservation

After the bench perfusion, the kidneys can then be preserved either in standard cold storage or in continuous machine perfusion and ready for transportation. Continuous machine perfusion offers persistent and homogenous core cooling that mimics the physiological pulsate blood flow and seems to offer better results compared to static hypothermic preservation.

Nowadays, the most prevalence kidney preservation method is still static cold storage. Numerous preservation solutions have been evaluated to minimize the ischemic injury when the kidneys are isolated from the body. To date, UW solution is considered the gold standard preservation solution for the kidney. The shortages of UW solution are high prices and high

viscosity, which may lead to slower washout of blood and initially patchy reperfusion of grafts. Other solutions, such as histidine–tryptophan–ketoglutarate solution (HTK) and Celsior solution, can also safely preserve kidney grafts within 24 hours. However, kidneys preserved over 24 hours by HTK or Celsior solution may have a higher risk of DGF compared with UW solution [46].

With the increasing use of more marginal kidneys from DCD donors, HMP preservation is now gaining more and more attention. Many retrospective studies and a few random controlled trials showed that HMP had a beneficial effect on reducing the incidence of DGF and increasing the graft survival rate, especially in high-risk groups. HMP machines can offer infusion parameters to help surgeons to evaluate the qualities of kidneys or predict outcome, and the perfusate biomarkers, such as glutathione-S-transferase (GST) and n-acetyl-β-d-glucosaminidase (NAD), have been shown to reliably reflect renal tubular injury and correlate with DGF [47].

3.4. Bench work of donor kidney

The aim of bench surgery is to remove the unnecessary tissues attached to the kidneys and trim the main vessels and ureters for a convenient anastomosis. The bench should be set up with a suitable sized bowl in which the graft is kept in sterile slush ice and organ preservation solutions at 0℃- 4℃ for the duration of the procedure to avoid rewarming.

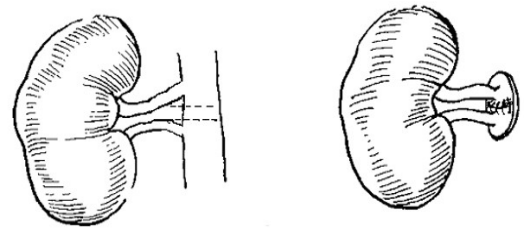
Usually when the kidneys are transported to the operation room, they are still connected as a cluster with the aorta and IVC. The first step is to separate the bilateral kidneys from each other. The kidneys should be placed in the anatomical position and the ureters are first identified and labeled to avoid being damaged. IVC is lifted and the connective tissues attached are removed until the bilateral renal veins are exposed. The left renal vein is cut off at its junction with the IVC and IVC remains with the right kidney. From the posterior aspect, the openings of the bilateral renal arteries at the anterior aorta wall are identified and the aorta is split along the longitudinal midline. In this procedure, every artery branch from the aorta must be carefully dissected to ensure not the accessory renal artery which enters the upper or lower pole of the kidney. After the separation of the renal artery and vein, the connective tissues between the bilateral kidneys can be cut apart and the kidneys are completely separated.

Bench preparation begins from the dissection of the renal vein and artery. The extra tissue attached on the renal vein and the IVC are trimmed, and the gonadal, adrenal, and any other veins coming from extra renal tissue are divided and ligated. A similar procedure is performed with the renal artery. However, it should be taken into account that even small branches coming from the main artery are likely to supply the kidney. Any branches from the artery should be followed very carefully and only tied off if it is proven beyond doubt that they do not go into the renal parenchyma. Do not get too deep into the renal hilum with the risk of damaging

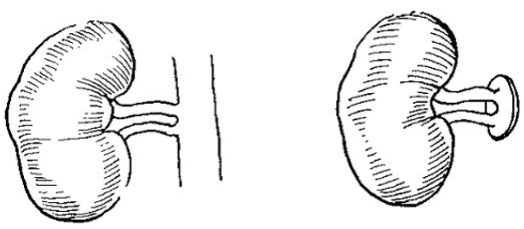
the vascular structures, which is very difficult to repair and may lead to kidney discarded.

Once the renal main vessels are dissected and trimmed, the renal fascia and the fatty capsule are cut open on the dorsal side of the kidney until the renal fibrosa exposed. The perinephric fat is carefully removed by stripping the fatty capsule from the fibrosa. However, enough fat around the renal hilum should be preserved in order not to damage vital structures such as main vessels and ureter. Ligation should be performed at the cut edge of the fatty to avoid bleeding and lymphorrhagia after graft reperfusion. The adrenal gland is separated from the kidney and removed with the perinephric fat. In some donors especially who are smokers or have a perinephritis history, the fat can be tightly adherent to the renal fibrosa. There is no need to peel off too much fat to avoid hurting the renal fibrosa or parenchyma. The periureteral tissues should be removed appropriately to maintain ureter intact and sufficient blood supply. The periureteral fat bordered by the ureter and the lower pole of the kidney (the so called "golden triangle zone") should be preserved to prevent the likelihood of ureteral ischemia.

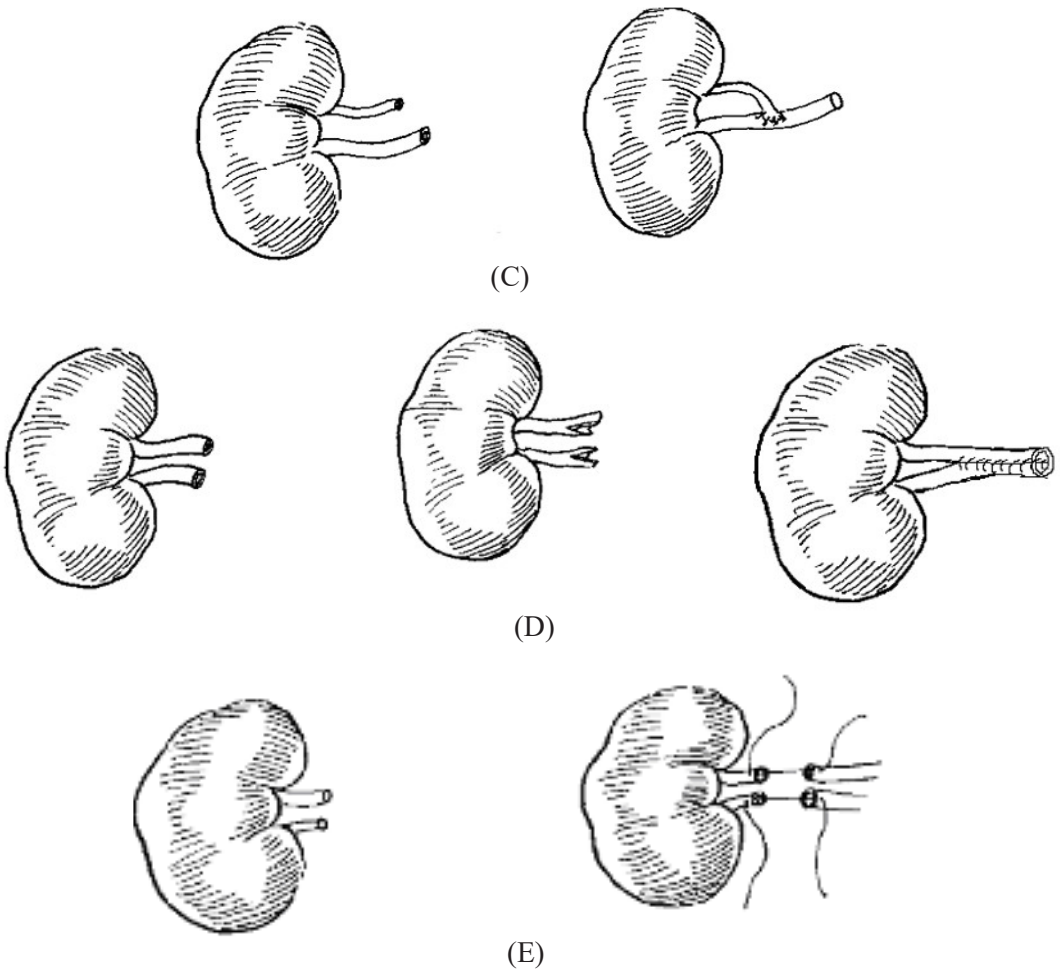
It is a troublesome problem to handle the anatomical variation about multiple renal vessels, especially the renal artery. Trivial accessory arteries (especially to the upper pole) may be sacrificed without apparent negative outcomes; however, significant accessory vessels, especially those to the lower pole likely nourishing ureter, should be reserved. Multiple arteries may be reconstructed to form a common Carrel aortic patch to allow an easy arterial anastomosis in the recipient, or be kept separately and anastomosed to the recipient arteries independently. Also the accessory artery may be sewn to the main artery in end-to-side fashion (**Figure. 1**). Compared with artery, small accessory veins can be ligated, for renal veins having extensive rami communicans in parenchyma. However, if there exists two main renal veins with nearly the same caliber, it is recommended to preserve both to reduce the risk of insufficient draining of the kidney. Usually the trunk of right renal vein is short and delicate; it needs to be extended by using the IVC connected (**Figure 2**).



(A)



(B)



(C)

(D)

(E)

Figure 1: Different ways to handle multiple arteries in donor kidney.

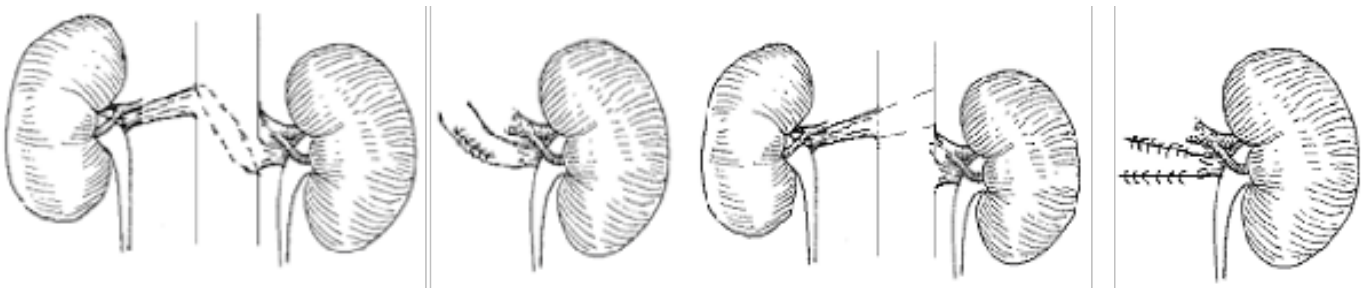


Figure 2: Different ways to extend the right renal veins by using the IVC connected.

After the vessels and ureter being prepared and perinephric fat being removed, all vessels should be flushed manually with cold heparinized saline or organ preservation solutions to ensure no leaks requiring ligation or suture. Put the kidney graft to a special double-layer ice-filled gauze bag in which the kidney and ice are not direct contacted.

4. Kidney Transplantation Operation

Nowadays over 90% kidney transplantations (KTx) are still performed in an open surgery style. Although minimally invasive operations, including laparoscopic and robot-assisted techniques, have been reported since 2002, most centers are not preferred to adopt them. The KTx operational procedure has got into form on the whole after decades' development. Kidney is lying in the right iliac fossa in the retroperitoneal space, due to the relative superficial location of the right external iliac vessels and overall facility for right-handed surgeons. Patch of

aorta containing renal artery is anastomosed end to side of external iliac artery or end to end of internal iliac artery. Venous anastomosis is end renal to side external iliac. Donor ureter is anastomosed with recipient's bladder by ureteroneocystostomy.

4.1 Exposure

Following induction of anesthesia, the patient is catheterized and the operative site prepared and draped. An oblique or J-shaped right lower quadrant incision, extending from the midline supra pubic area to the level of the anterior superior iliac crest, is made. The oblique muscles are divided, however in most cases it is necessary to leave the rectus abdominis intact. The inferior epigastric vessels can be divided or retracted aside. The peritoneum is mobilized and pushed cephalad to expose iliac fossa. During this procedure, the round ligament is usually transected in females and the spermatic cord is retracted downwards in males. Usually an automatic retractor here is utilized to improve exposure of iliac vessels. The iliac artery and vein are dissected free from the surrounding connective tissues with suture ligation and division of the overlying lymphatics. Either the external or internal iliac artery can be used for anastomosis, however if there is a risk of anastomotic rupture caused by infection, the internal iliac artery should be the first choice.

4.2 Venous anastomosis

In the vast majority of cases, the external iliac vein is used for venous anastomosis because it is relatively superficial and has fewer branches. A vascular clamp (usually Satinsky or "C" shape clamp) is carefully applied to obtain proximal and distal occlusion of the iliac veins. The allograft renal vein is typically sewn in end-to-side fashion to the recipient external iliac vein using a fine (generally 5-0) running polypropylene suture.

In cases of external iliac vein thrombosis, the common iliac vein can be useful to perform the anastomosis, and only in rare cases is the inferior vena cava of the recipients anastomosed with the graft renal vein with an intraperitoneal approach.

Once the venous anastomosis is completed, a bulldog vessel clamp is put near the renal hilum to block the renal vein and the vascular clamp occluding the iliac vein is released to detect anastomotic leakage. Some surgeons prefer to examine leakage after all vascular anastomoses completed.

4.3 Arterial anastomosis

The donor renal artery is usually sewn to the external iliac artery in an end-to-side fashion using a 6-0 polypropylene suture. In a deceased donor kidney, the donor renal artery or arteries are usually kept in continuity with a Carrel aorta patch, which makes the anastomosis much easier. However in a living related donor kidney, the donor renal artery without a Carrel

patch can be sewn to the internal iliac artery in an end-to-end fashion. In cases involving multiple donor renal arteries, both external and internal iliac arteries may be utilized for anastomosis. It is very important to prevent the intima exfoliated or introrsus when suturing the arteries. When the anastomosis is completed, similar leakage examine steps need to be performed, and the bleeding points should be eliminated with interrupted stitches.

4.4 Reperfusion

After the vascular anastomoses and leakage examination, the vascular clamps are released to restore flow from and to the lower extremi¬ties as well as to the newly implanted kidney. The kidney should be soon recovered with the appearance of healthy pink color, good tension, and production of urine. Flushing the kidney with warm saline may help to relieve the arterial spasm caused by clamping and traction when suturing. Initial poor graft perfusion often indicates technical problems such as vascular twisting, thrombosis, pseudoaneurysm or vascular stenosis. Once the abnormal situations are confirmed, kidney should be taken out from the operative field immediately and re-flush with the cold organ storage solution on the back table to prevent the prolonged warm ischemia. Reestablish the anastomosis at new place of the vessels, cutting off the vascular parts through which the old stitches pass.

4.5 Ureteroneocystostomy

After completion of the vascular anastomoses the ureterocystostomy is performed. It is important in males that the ureter should be slipped under the spermatic cord structures. The ureter is cut to an appropriate length with the end splitted and trimmed to be an inverted triangle shape. The most common approach is the anterior ureteroneocystostomy in which the ureter is directly sutured to the bladder mucosa, followed by approximation of the muscular is to create a tunnel over the distal 2 cm of the ureter. The mucosa-to-mucosa ureter to bladder anastomosis is usually sewn with a fine absorbable monofilament suture (typically 5-0 PDS) in running fashion. A double-J ureteral stent is either routinely or selectively used based on surgeon’s preference. The bladder muscular tunnel is to provide a potential antireflux mechanism and prevent excess tension on the anastomosis when the bladder is distended. Care is taken to avoid creating an excessively tight tunnel potentially leading to obstruction.

4.6 Closure

Before incision closure, it should be identified that the kidney has been placed properly without twisting, kinking, or obstruction of vessels or ureter. Examine the anastomotic stomata and the renal hilum to make sure there is no active bleeding. Drains are routinely placed in most centers to detect the hemorrhage and urine leak in early postoperative period.

4.7 Kidney retransplantation and multiple transplantations

Since the shortage of donor kidneys and putative poor outcomes, kidney retransplantation and multiple transplantations (three times and more) are rare in most centers. However, it is likely that the majority of pediatric renal allograft recipients will require one or more retransplants during their lifetime. Kidney retransplantation and multiple transplantations also present a surgical challenge due to possible adhesions, difficulties reaching the iliac vasculature or earlier manipulation of the bladder to establish the ureterovescial anastomosis. In most centers, if a retransplantation has to be performed, the use of the contralateral iliac fossa is advocated. However, in case of a third or even fourth retransplant, it is unavoidable to explore an iliac fossa that has already been dissected for the previous implantation and for removal of the non-functioning graft. Before operation, a careful angiography about the bilateral iliac vessels should be performed to examine which vessel can be used for anastomoses. In multiple transplantations patients, the venous anastomosis can also be connected to the common iliac vein or the inferior vena cava if the external iliac vein is unusable and the arterial anastomosis can be connected to the common iliac artery if both the external and internal iliac arteries are not suitable for a recurrent vascular anastomosis. Patients performed kidney retransplantation or multiple transplantations have a significantly higher risk for thrombotic events of the renal vessels. Preventing thrombotic events of the renal vessels in patients who receive a kidney retransplant in the ipsilateral fossa, should be one of the main priorities in the postoperative care.

Although retransplantation is accompanied by more frequent complications and shorter graft survival, the results are superior to life time dialysis. The quality of life and patient survival are higher by avoiding lifelong dialysis.

4.8. Combined transplantation of kidney and other organs

4.8.1. Liver-kidney combined transplantation

Simultaneous liver and kidney transplantation (SLKT) has become a well-established therapeutic option for end-stage renal and liver disease since the first SLKT performed by Margreiter in 1984 [48]. SLKT recipients can be well-compensated cirrhosis with end-stage renal disease (ESRD) or severely decompensated chronic liver patients with acute kidney injury (AKI) requiring continuous hemodialysis or hemofiltration. Compared with kidney after liver transplantation (KALT) and liver after kidney transplantation (LAKT), SLKT increases the mortality and morbidity in recent postoperative period but has enhanced long-term outcomes.

There are 2 kinds of operational techniques for the SLKT. One is to perform the liver transplantation and kidney transplantation sequentially. The other is to transplant liver-kidney

cluster continuity with the same aorta patch including the celiac trunk and the renal artery. However, the latter technique is often applied in pediatric recipients.

4.8.2. Pancreas-kidney combined transplantation

Simultaneous pancreas-kidney (SPK) transplantation is currently considered the preferred therapeutic option in beta-cell-penic diabetic patients with ESRD. The procedure renders patients free of renal failure and provides a physiological means of achieving normoglycaemia, which associates with beneficial impact on vascular complications caused by diabetes. The first kidney and pancreas transplant was performed in 1966 by William Kelly and Richard Lillehei at the University of Minnesota, USA [49]. Although there is controversy about the benefits of the pancreas transplantation for diabetes patients, SPK has definitely beneficial effects on life expectancy and quality of life in type 1 diabetic patients with ESRD (on dialysis or in the pre-emptive stage). Selected type 2 diabetic patients (not obese, with progressive vascular diabetic complications) with ESRD can also be considered as candidates for SPK transplantation. Since the pancreas is intolerant to ischemic and mechanical injury, the accept criteria of donor pancreas is very critical. The ideal pancreas donor is a brain-dead donor, aged between 10 and 45 years, with a BMI ≤30 kg/m 2, who died for causes other than cerebrovascular diseases. Additional factors which should be considered are duration time of stay in the intensive care unit, use of high-dose vasopressors, history of cardiac arrest, and hypernatremia.

The SPK transplantation technique can also be divided into 2 modes according to the different implantation methods of donor pancreas. Typically, the pancreas is transplanted on the right side, because of the more convenient venous anatomy, and the kidney on the left iliac fossa. Ipsilateral SPK transplantation can also be accomplished to spare one iliac axis because of specific recipient needs. Some centers prefer to put the pancreas into the abdominal cavity and the exocrine secretions be drained in the gut. Enteric drainage occurs in the small bowel either directly or through a Roux-en-Y loop. Kidney transplantation usually employs the standard technique, but if performed through a trans peritoneal approach, the graft should be well settled to avoid the renal pedicle twisting.

5. Complications after Kidney Transplantation

Despite there have been tremendous progress in conservative renal replacement treatment, renal transplantation remains the most effective therapy for patients with end-stage renal failure. Advances in surgical techniques and improvements in immunosuppression enable kidney recipients to achieve prolonged renal graft survival and a longer life longevity. Particularly, advanced immunosuppressant targeting the active immune cells enables excellent success in short-term transplant, as well as a good long-term outcome. However, renal transplant recipients are exposed to the risk of multiple potential complications post renal transplantation that may threaten their outcomes. In this part, we provide an overview of the complications af-

ter renal transplantation, as well as a concise update on the most relevant post renal transplant complications.

5.1 Primary non-function and delayed graft function

Primary non-function of renal allograft, presenting as permanent loss of renal allograft function immediately following kidney transplantation, accounts for 0.6% to 8% of all renal graft loss and is obviously associated with poor recipient survival[50]. The major risk factors include older donors, donors with hypertension or increased serum creatinine, as well as prolonged cessation of perfusion. However, abnormal graft function mediated by rejection or surgical complications can't be defined as primary non-function.

Delayed graft function (DGF) is generally defined as suboptimal renal function following transplantation and the need for dialysis within 7 days of renal transplantation. DGF generally can be caused by accelerated rejection or acute rejection, nephrotoxic drugs, surgical complications post renal transplantation, and recurrence of primary disease [51]. Although part of patients with DGF have no definite nosogenesis, the major cause of DGF is acute tubular necrosis (ATN). ATN post renal transplantation is mainly caused by ischemia-reperfusion injury (IRI). Meanwhile, nephrotoxicity and immunological factor will contribute to this process [52]. Increased use of marginal donor and DCD results in higher rate of DGF. DGF occurs more frequently after deceased donor renal transplantation compared to living donor renal transplantation [53]. Diagnosis of DGF depends on clinical manifestation, laboratory examinations, and imaging tests, while biopsy of transplanted kidney is the gold standard for diagnosis of DGF. Of note, prevention DGF is always more important than cure.

5.2. Surgical complications post renal transplantation

As advances in surgical technology, the incidence of surgical complications post renal transplantation has been reduced year by year. These complications are threats to graft survival, and can be life-threatening in certain situations. Therefore, surgical complications are gaining more attentions lately.

5.2.1. Vascular complications

Hemorrhage post renal transplantation is an early serious complication, and is regarded as a prognostic factor for transplant success. Statistically, hemorrhage post renal transplantation occurs in 1.9-8.3% of recipients. Coagulopathy is one of the most important risk factors for postoperative early hemorrhage. Moreover, early hemorrhage may also occur as a result of blood vessel damage caused by anastomotic leakage, rupture of an aneurysm or infection. Thus, keeping normal coagulation function perioperatively, reducing bleeding and achieving effective haemostasis during operation, accurate anastomosis of blood vessels with vascular

patency, as well as preventing and controlling infection, can contribute to prevention of this complication. Therapeutically, correcting the clotting problem via giving blood products and coagulants is usually effective. However, patients with persistent hemodynamic instability, which indicates active hemorrhage, usually require emergency exploratory laparotomy for hemostasis.

Renal allograft vascular thrombosis is a graft threatening complication, as it interrupts blood supply of the allograft and induces early graft loss. The incidence of renal arterial or vein thrombosis is around 0.2%-7.5% and the incidence of renal venous thrombosis is about0.1%-8.2% in adult, while a higher incidence is observed in pediatric recipients [54]. Risk factors for the development of renal vascular thrombosis include technical imperfection with the anastomosis, renal arterial intimal injury, aberrant arterial anatomy, as well as high-resistance microvascular arterial outflow mediated by severe ischemic-reperfusion injury. Sudden oliguria or anuresis with rapid deterioration in renal function is the main feature of renal arterial thrombosis, while renal allograft venous thrombosis is characterized by sudden oliguria or anuresis, acute renal graft pain, hematuresis and renal graft tenderness pain. Color Doppler ultrasonography examination is of great significance in diagnosis, indicating increased renal vascular resistance index, reversal of diastolic flow and reduced blood perfusion. Once renal graft arterial thrombosis is detected, emergency exploratory laparotomy is needed. Early diagnosis and early intervention is the only possible chance for saving renal graft, therefore more attention should be paid in anuresis or hematuresis of unknown reason.

Renal artery stenosis is the most common vascular complication following renal transplantation, which occurs to about 1%-23% patients [54]. This stenosis can lead to renal hypertension post renal transplantation and even graft loss or death. Renal arterial stenosis most commonly occurs in anastomosis site, and is most commonly observed in 3 months-2 years post transplantation. Risk factors associated with renal artery stenosis include renal arterial intimal injury, distortion of renal artery, atherosclerotic plaque within renal artery or iliac vessels, hematoma compression. Clinical presentation includes malignant or refractory hypertension and decreasing renal function. Color Doppler ultrasonography, renal arteriography and magnetic resonance angiography are effective in diagnosis of renal graft arterial stenosis. Therapeutically, conservative treatment with ACEI or ARB is effective when patients with stable renal function and renal arterial stenosis less than 60%, while percutaneous transluminal renal angioplasty (PTRA) is current major treatment for those with renal arterial stenosis more than 70% and worsening renal function. However, prevention remains the best treatment for renal graft arterial stenosis.

5.2.2. Urologic complications

Although urologic complications after renal transplant are not common, they are as-

sociated with risk of graft loss and impact patients' life quality. These complications occur in about 4%-20% patients, including urine leak, ureteral stenosis, and ureteral necrosis due to compromised vascularization. Moreover, the presence of a ureteral stent is associated with lower incidence of urologic complications post renal transplantation.

Urine leak is most commonly observed within 1-week post transplantation. High tension in suture between ureter and bladder and imperfect suture are the major causes of urine leak post renal transplantation [55]. Clinical manifestation is featured by increased drainage liquid, reduced uresis, and fever. Fluid collection can be detected by ultrasound test. Besides, biochemical analysis of the drained liquid is essential for diagnosis, and drained liquid creatinine should be compared with that in a concomitant serum sample. Furthermore, when suspected urine leak is significant, surgical exploration is indicated.

Ureteral stenosis occurs in about 2.6%-6.5% patients for various reasons [54]. Early ureteral stenosis is closely associated with anastomosis technique related factors, while stenosis occurred 3-month post transplantation is mainly caused by ureter avascular necrosis and fibrosis due to poor blood supply at lower ureter [54]. And, BK virus infection can also lead to ureter scar stricture. Patients with ureteral stenosis show oliguria or anuresis and increasing serum creatinine. Diagnosis of ureteral stenosis depends on ultrasound test and intravenous urography. Therapeutically, surgery is indicated if early acute ureteral stenosis is caused by surgical techniques, while endoscopic treatment is suggested for late ureteral stenosis due to ischemia.

5.3. Rejection

When end stage renal failure patients received renal graft from donors with different genetic background, the renal graft will be recognized and attacked by immune cells and antibodies, which is call graft rejection. Without immune suppression, slight genetic difference between the recipient and the donor is sufficient to reject the renal graft, which indicates necessity of the administration of continuous immune suppressants to those who received renal transplantation. According to the time of occurrence of allograft rejection, rejection response can be categorized into hyperacute rejection (HAR), accelerated rejection (ACR), acute rejection (AR) and chronic rejection (CR) [56]. These kinds of rejection have different clinical manifestations, therapies, as well as prognosis. With advances in immunosuppression, the incidence of rejection after renal transplantation has been decreased annually, and the current incidence of AR within 1 year after transplantation is now less than 15% [56]. But rejection remains a major complication post renal transplantation, and acts as a major cause of graft dysfunction. Although the mechanism of rejection is not fully defined, it is accepted that T cells play a dominant role in rejection responses. Moreover, the last decade has seen increased significance of antibody mediated rejection.

HAR is a unique kind of acute antibody mediated rejection, which occurs almost immediately after renal transplantation, or within 24 hours to 48 hours post transplantation. Hyperacute rejection make the renal allograft appear flaccid and mottled. Repeated transplants, multiple pregnancies, or multiple blood transfusion lead to generation of substantial cytotoxic antibodies against human leukocyte antigens (HLA). These preformed antibodies rapidly attack renal graft endothelial cells which contains HLA antigens. And it will also activate the classic complement system within renal graft, and lead to endothelial necrosis, platelet deposition, as well as local coagulation [56]. Currently there is no effective treatment for HAR. Once HAR occurs, the renal allograft has to be removed. However, with improvements in sensitive cross-matching techniques and the application of the single-antigen Luminex assays, hyperacute rejection has largely been eliminated [56].

ACR occurs within 24 hours to a few days after renal transplantation. Compared with HAR, ACR has a similar mechanism and pathological manifestations. This anti-graft response involves both cellular and antibody-mediated immune mechanism, including memory T cells and B cells/plasma cells. Risk factors for ACR include multiple blood transfusions, multiple pregnancies, as well as previous transplants. Clinical manifestations of HAR are featured by sudden decreased urine output, worsening allograft function, swelling renal allograft, tenderness pain, fever and hypertension. The current therapeutic strategies for ACR are limited, including using ATG, ALG or anti-CD3 monoclonal antibody as early as possible, high-dose intravenous immunoglobulin, and removing antibodies by plasma exchange or immunoadsorption. However, most HAR can't be controlled and renal graft has to be removed. Fortunately, similar to HAR, advances in technologies has virtually eliminated ACR [56].

AR is the most common rejection responses. AR typically happens between the first week and the first few months after renal transplantation. AR is a major cause of the immunological graft loss. Typical AR presents with the "classic" triad of fever, oliguria and a tender, swollen graft. However, the diagnosis depends on renal biopsy. High dose pulse steroids is a first-line and most commonly used treatment for acute rejections and antibody treatment with OKT3, ALG or ATG may be required for steroid resistant AR. For acute antibody-mediated rejection, current treatments include intravenous immunoglobulin, Rituximab, plasma exchange and immunoadsorption [57,58]. Totally, the key to management of AR is positive prevention, early diagnosis and treatment.

CR accounts for many of long-term graft loss. The pathogenesis remains poorly defined, but it is recognized that CR involves both cellular and humoral immune response. The major risk factors of CR include histocompatibility mismatch, suboptimal immunosuppression, renal allograft ischemia-reperfusion injury, acute rejection episodes and infections [59]. The manifestations of CR are characterized by a progressive decline in renal function, anemia, proteinuria and hypertension. The diagnosis of CR depends on biopsy. There is no effect treatment

for CR, and reversal or arrest in the progressive deterioration in renal graft function is seldom possible. Thus, positive prevention and protecting renal graft function is recommended.

6. Characteristics of Infection after Kidney Transplantation

Infection is one of the most important complications after kidney transplantation [60]. In the first year after transplantation, 75% of cases have different types of infections, and in the early stage after kidney transplantation, the mortality rate of infected patients is as high as 40% to 78% [61]. Thus, patients after kidney transplantation have a higher risk of infection and a poorer prognosis. The use of immunosuppressive after transplantation results in low immunity should be responsible for it. In addition, patients after kidney transplantation often require hospitalization, which also increases the risk of hospital-acquired infections.

In addition to the high risk, infections after kidney transplantation are also characterized by a broad spectrum of pathogens. Pathogens that are weak or non-pathogenic in generally considered can cause infection in kidney transplant recipients, this is related to the recipient being in an immunosuppressed state. Bacteria, viruses, fungi, mycoplasma, chlamydial rickettsia and even protozoa can cause postoperative infection in kidney transplant recipients, but in general, common pathogens are still dominated by bacteria, viruses and fungi.

In terms of the infected site, lung is the most common site in the kidney transplant recipient. Pulmonary infection is also the leading cause of death in patients after transplantation. About 70% of deaths are caused by lung infections. In addition, gastrointestinal infections, central nervous system infections, skin infections, and urinary tract infections are also common in kidney transplant recipients.

6.1. Bacterial infections

64% of infections in kidney transplant patients are caused by bacteria. Common pathogens include Klebsiella, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus, and often have mixed infections. Bacterial infections mostly occur in the early one month after renal transplantation, in which respiratory infections account for 54.6% and urinary tracts account for 40.7% [61]. The case fatality rate was 21.9% [61]. Therefore, the diagnosis of bacterial infection and anti-infective treatment after transplantation is particularly important.

It should be noted that bacterial infection in kidney transplant patients is sometimes difficult to diagnose. The use of immunosuppressant alters the patient's immune status, giving the infected person an atypical clinical appearance. Despite this, its diagnosis still relies on local and systemic inflammatory response symptoms, as well as the detection of pathogens. The detection of pathogens is particularly important because of the atypical symptoms.

In terms of treatment, in principle, whether it is prophylactic antibiotic or antibacterial

treatment, narrow-spectrum application is required, and antibiotics are adjusted according to the results of bacterial culture and drug sensitivity test to prevent the occurrence of multi-drug resistant bacteria [62]. The choice of antibiotics after infection with pathogens are presented on **Table 3**.

Table 3: The choice of antibiotics after infection with bacterial infection.

Bacterial	Drug of choice	Alternative medicine
Pneumococcal	Penicillins	Erythromycin, Cefotaxime,Cefazolin
MRSA	Vancomycin	Muramycin, Lalocephalosporin, Amikacin, Streptomycin, Oxazolanone
Escherichia coli	Ceftriaxone	Cefotaxime, Cefepime
Klebsiella pneumoniae	Semi-synthetic broad spectrum penicillin	Cefoperazone/Sulbactam, Ceftazidime, Imipenem/Cilastatin, Cefepime
Pseudomonas aeruginosa	Ceftazidime	Cefoperazone/Sulbactam, Ceftazidime or Imipenem/Cilastatin, Ciprofloxacin or Meropenem
Acinetobacter baumannii	Amikacin + ceftazidime	Ampicillin/Sulbactam, Cefoperazone/Sulbactam, Cefepime, Imipenem/Cilastatin
Legionella pneumophila	Eryphilin	Doxycycline, Azithromycin,Rifampicin

6.2. Viral infection

Viral infection accounted for 31% in the infected kidney transplant patients [61]. Common pathogens include human papillomavirus (HPV), herpesviruses such as CMV, EB, and herpes simplex virus (HSV). For the normal population, these viruses are often in a latent state or cause self-limiting diseases, but due to the use of immunosuppressant, recipients are in an immunosuppressed state, resulting in the virus being activated leading to serious infection. It should be noted that in addition to these opportunistic pathogenic viruses, renal transplant recipients are much more likely to be infected with hepadnaviruses such as HBV and HCV than the normal population. This is because during the dialysis process, patients need to receive blood transfusion due to anemia, which increases the risk of virus transmission through the blood. Besides, the use of immunosuppressive cause the latent virus are activated lead to the hepatitis.

The viral infections post-transplantation occurred mostly six months after operation. The different virus and infection sites lead to complex clinical manifestations, which makes the diagnosis difficult. A preliminary diagnosis is currently made with the help of clinical manifestations and is diagnosed based on its antibody or antigen or viral nucleic acid detection. The treatment of viral infections is mainly based on the application of antiviral drugs against different pathogens. The immunosuppressive regimen should be adjusted according to the condition, as well as immunomodulatory therapy should be performed [62].

6.3. Fungal infection

Fungal infections accounted for 5% of all infections after renal transplantation [61], mostly occur six months after kidney transplantation, and can also be seen for many years after surgery. Common pathogens are Candida albicans, Cryptococcus neoformans, Aspergillus, Mucor, Coccidioides and Coccidioides. Note that deep fungal infections are very dangerous and have a higher mortality rate than bacterial infections.

There are two sources of fungal infections:

1) Disseminated primary or recurrent infections, regional prevalence, often leading to serious deep infections.

2) The normal flora in the body, such as Candida albicans, can cause disease in the immune suppression state of the body.

The diagnosis of fungal infections relies on correct pathogenic diagnosis. Repeat fungal smears and examinations, and if necessary, organize a case to confirm the cause.

The treatment is based on antifungal drugs [62]. The choice of antifungal drugs after infection with fungi are presented on **Table 4**.

Table 4: The choice of antifungal drugs after infection with fungi.

Fungus	Drug of choice	Alternative medicine
Candida	Fluconazole	Itraconazole, Voliconazole, Varbophenazole
Cryptococcus meningitis	Amphotericin B (AmB) and 5 -fluorouracil	Liposome AmB and fluconazole, or itraconazole
Aspergillus	Voriconazole	AmB, Liposome AmB, Micafungin, White saponin,
Mucor	Amphotericin B	Liposomal AmB, Fluconazole, Itraconazole
Pneumocystis	SMZ/TMP	Pentane, Atovaquone, Artemether

6.4. Other: tuberculosis infection

The pathogen of tuberculosis infection is mainly M. tuberculosis [63]. In kidney transplantation recipients the incidence of active tuberculosis is 20-74 times than normal population. And the incidence of tuberculosis has significant regional differences: in most developed countries, the reported infection rate is 1.2%-6.4%. In Highly endemic area this number is up to 12%.

In kidney transplant recipients, most of the tuberculosis occurs in the first year after transplantation. The clinical manifestations of TB after transplantation are often different from those of ordinary TB infected individuals. In recipients, 1/3 to 1/2 of the TB is diffuse or occurs outside the lung, while in the general population, the site of tuberculosis infection often occurs

in the lungs. And the clinical symptoms of TB infected patients after transplantation are often atypical, which increases the difficulty of diagnosis.

In terms of diagnosis, the detection rate of anti-tuberculosis antibodies, tuberculin test in tuberculosis patients, and acid-fast bacilli in sputum after renal transplantation is low. It is generally required to be sent repeatedly, and if necessary, it can be sent by fiber optic bronchoscopy. However, the culture of Mycobacterium tuberculosis takes a long time and often delays treatment. Therefore, clinically, renal transplant patients with high suspicion of tuberculosis infection are often treated with diagnostic anti-tuberculosis (isoniazid, rifampicin, pyrazinamide or ethambutol). It should be noted that infection occurs after kidney transplantation, indicating excessive immunosuppression, and it is necessary to reduce the dose of immunosuppressant to assist anti-binding therapy.

7. Pathology of Kidney Transplantation

Pathological diagnosis has always been regarded as the "golden standard" for disease diagnosis. With the development of pathological observation in organ transplantation, pathological diagnosis of transplant organ biopsy has become a basic examination in transplantation, which has gone through the whole process of donor organ selection, post-operative complications diagnosis and post-operative follow-up. And, it is also indispensable in the basic research of transplantation. The pathology of kidney transplantation in China started in 1970s. In the 21st century, the pathology of kidney transplantation has developed rapidly in China.

7.1. Donor pre-existing disease

Donor pre-existing disease refers to the existing lesions of the donor organ itself before transplantation. It mainly includes inflammation and cancer, of which inflammatory diseases account for the majority [64]. Pathological changes mainly include systemic diseases involving the donor kidney or in situ lesions of the donor kidney, which contains vascular sclerosis, glomerulosclerosis and abandonment of donor arterioles caused by hypertension [65], diabetic nephropathy [66], and glomerulonephritis [67], etc. Its definite diagnosis mainly depends on procurement biopsy [68] and time-zero biopsy [69]. For marginal donor kidneys, special attention should be paid to the factors of pre-existing disease. Serious pre-existing disease may affect the long-term survival of transplanted kidneys.

7.2. Delayed graft function and primary non-function

In kidney transplantation, the effect of ischemia reperfusion injury (IRI) could lead to allograft dysfunction, including delayed graft function (DGF) and primary non-function (PNF). The pathological manifestations were allograft tubular necrosis [70, 71]. DGF often causes degeneration or even necrosis of a large number of renal tubular epithelial cells in transplanted

kidneys Severe and difficult-to-recover DGF is called PNF. Its definite diagnosis depends on biopsy and pathological diagnosis. Histopathologic ally, the renal tubular epithelial cells show varying degrees of water-like degeneration and even severe necrosis. Acute tubular necrosis (ATN) caused by IRI is the most common cause of DGF [72]. It is generally thought that DGF is a clinical diagnosis, ATN is a pathological diagnosis, and IRI is a pathophysiological process caused by a number of etiological and risk factors.

7.3. T cell-mediated rejection

T cell-mediated rejection (TCMR) means that antigen-presenting cells initiate rejection by presenting transplanted antigens [73]. CD4 + T cells promote rejection by triggering delayed hypersensitivity inflammation, while CD8 + T cells induce rejection damage by killing target cells directly [48]. The main pathological features of TCMR are the infiltration of mononuclear cells, including T lymphocyte, B lymphocyte, macrophage and NK cell in the interstitium of transplanted kidney. Inflammatory cells infiltrated into the renal tubules could form allograft tubulitis. In severe cases, it could be also formed arterial vasculitis of arteries branches in the transplant kidney. In some cases, interstitial edema of the allograft kidney could be seen [74].

7.4. Antibody-mediated rejection

Antibody-mediated rejection (ABMR) is also called humoral rejection. In recent years, more and more attention has been paid to its role in immune injury of transplanted kidney. It is mainly caused by antibodies, complements and other humoral immune components [75]. The diagnosis of ABMR should follow the comprehensive diagnostic principle of combining clinical renal transplantation function monitoring, pathological observation and DSA monitoring of recipient serum. Pathologically, IgG, IgM and complement C3, C1q, C5b-9 were usually stained by immunofluorescence [76], but these indices are lack of specificity. At present, immunofluorescence or immunoenzymatic histochemical staining of complement fragment C4d is mainly used for definite diagnosis. However, in recent years, according to the Banff standard of 2013, the revised content of ABMR diagnosis has been introduced (**Figure. 3**) C4d is no longer a diagnostic marker of ABMR [77], because some cases show obvious renal allograft dysfunction and DSA positive, but the immunohistochemical staining of C4d was always negative, suggesting that some ABMR cases were C4d (-) [78], which should be paid attention in clinical and pathological diagnosis. The most severe ABMR in clinic is hyperacute rejection (HAR) of transplanted kidney, which usually occurs within 24 hours after vascular anastomosis in kidney transplantation. The naked eye can see that the transplanted kidney rapidly swells or even ruptures after the blood supply is restored after the vascular anastomosis is opened, and the color of the transplanted kidney turns dark red or even purple black. Microscopically, arterial vessel closure, cellulose-like necrosis, extensive micro thrombosis in capillaries, infil-

tration of a large number of neutrophils in tissues, obvious hemorrhage, edema and massive hemorrhagic necrosis in parenchymal tissues were observed. Grafts had to be removed because of rapid functional failure [79].

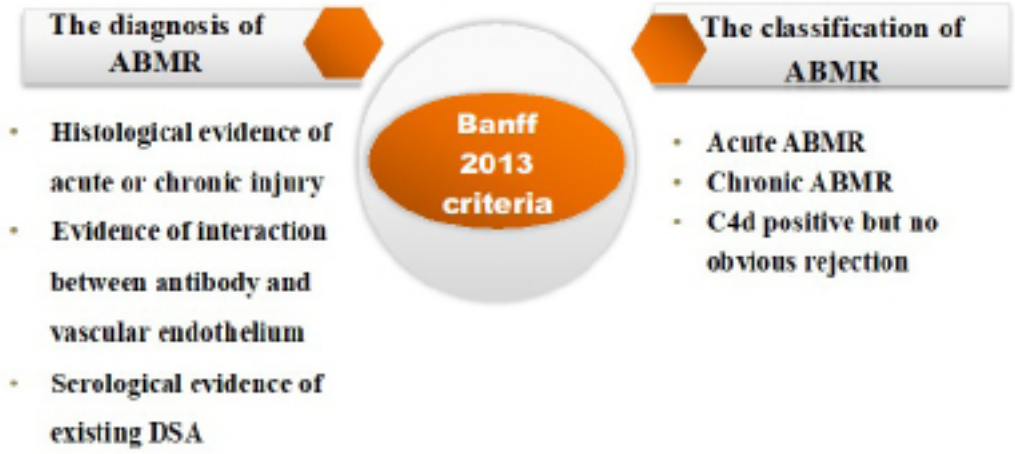


Figure 3: Revised version of ABMR diagnosis of Banff 2013 criteria.

7.5. Toxic injury of immunosuppressants in transplant kidney

Cyclosporine A (CSA) and FK506 are the main causes of toxic injury of immunosuppressive agents. Typical acute toxic lesions caused by CSA result in a large number of small and large vacuoles and giant mitochondria in the cytoplasm of renal tubular epithelial cells [80]. Chronic toxic injury induced by CSA results in interstitial fibrosis and hyaline degeneration in the wall of glomerular entry arterioles [81]. Because of the lack of specificity of pathological changes, the diagnosis of immunosuppressive toxic injury must be combined with drug concentration in peripheral blood besides pathological observation.

7.6. Infection after kidney transplantation

Infection after kidney transplantation refers to all kinds of infections caused by opportunistic pathogenic microorganisms, including bacteria, viruses, fungi and other infections. In a few cases, Pneumocystis carinii, Toxoplasma gondii and other parasitic infections also occur. Escherichia coli, Pseudomonas aeruginosa and Enterococcus are the main pathogenic bacterials of infection after kidney transplantation. Pathologically, acute interstitial nephritis of transplanted kidney was formed. Inflammatory infiltration of neutrophils was observed in the interstitium of transplanted kidney biopsy tissue [82]. Viral infection after kidney transplantation mainly includes cytomegalovirus (CMV) and BK virus infection. Detection of cytomegalovirus inclusion bodies or positive CMV immunohistochemical or in situ hybridization staining in renal tubular epithelial cells is necessary for the diagnosis of CMV infection in renal transplant pathological biopsy tissues [83]. BK virus nephropathy (BKVN) of transplanted kidney caused by polyomavirus BK virus mostly occurs about one year after operation. Under light microscopy, the number of abnormal renal tubular epithelial cells containing viral inclusions was varied, necrosis and exfoliation of tubular epithelial cells were common in the lumen, and there were mixed inflammatory cells infiltration including neutrophils and lympho-

cytes around seriously infected renal tubules, and even micropus formed around infected renal tubules. Viral inclusions can be also seen under electron microscopy [84].

7.7. Post transplantation lymphoproliferative disorder

Post transplantation lymphoproliferative disorder (PTLD) is a group of syndromes with multiple disease forms, ranging from benign hyperplasia such as monocytosis to dysplasia such as malignant lymphoma, usually associated with EB virus infection [85]. Histologically, PTLD manifests in a variety of diffuse B-cell proliferation, from intermediate polymorphic diffuse B-cell lymphoma to true monocyte large cell immunoblastic lymphoma [86]. At present, the basic way of diagnosis is biopsy and pathological diagnosis of tumors. In this process, we should make full use of a variety of auxiliary diagnostic methods, such as immunohistochemistry of cell phenotype, EBV test, gene rearrangement detection, etc.

8. Immunosuppressants for Kidney Transplantation

In past decades, kidney transplantation has saved numberless patients with end-stage kidney disease. This depends not only on the maturity of surgical techniques, but also on the continuous development of immunosuppressive agents.

Immunosuppressants can inhibit the immune response of the body by influencing humoral and cellular immunity, so as to achieve the clinical effect of preventing rejection after kidney transplantation.

In 1963 Joseph Murray et al. succeeded in preventing rejection with azathioprine (Aza) and prednisolone (Pre) for the first time. This combination (Aza + Pre) is the first breakthrough in immunosuppressive agents and has continued to play an important role in the next 20 years. With the advent of cyclosporine (CsA) in 1972, a new generation of immunosuppressants, represented by mycophenolate mofetil (MMF) and mizoribin, came onto the stage of history in the same period. From then on, immunosuppressants entered the second era. Thereafter came the era of tacrolimus (Tac). Tac has been widely recognized for its excellent anti-rejection effect. So far, Tac-based triple immunosuppressive therapy (Tac+MMF+Pre) is still the mainstream immunosuppressive maintenance choice.

Nowadays, the emergence of various new immunosuppressive agents, such as sirolimus (SRL), everolimus (EVE) and belatacept, has given clinicians more choices. Each drug has its advantages and disadvantages, accurate individualized treatment has gradually become the mainstream of research. This paragraph will mainly introduce commonly used drugs in induction therapy, maintenance therapy and their common combination.

8.1. Induction therapy

Immunosuppressive induction therapy refers to short-term immunosuppressive therapy using monoclonal or polyclonal antibodies during perioperative period. In order to reduce the rejection after surgery, or reduce the severity of rejection. At the same time, it can also reduce the need for maintenance therapy drugs as much as possible and reduce the side effects of long-term drug use. And of course, the best scenario is to induce immune tolerance.

At present, agents used for induction therapy can be roughly divided into two categories: immune cell scavenging and non-scavenging. And the most commonly used induction therapy drugs might be rabbit anti-human thymocyte globulin (rATG) and anti-IL-2 receptor monoclonal antibodies (such as basiliximab). Here we would briefly introduce these two agents.

8.1.1. rATG

rATG is a polyclonal antibody produced by rabbits receiving immune stimulation from children's thymus tissue. It is a very potent immunoinducer. After being used in human body, rATG can quickly induce the clearance of CD2+, CD3+, CD4+, CD8+, CD16+, CD25+ and CD45+ lymphocytes, and even kill some plasma cells. In clinic, rATG is the preferred choice for many doctors in kidney transplantation with high risk of delayed recovery of transplanted kidney function [87].

At present, there is no global consensus on the optimal dosage and method of rATG. It can be used in large doses single time or in small doses multiple times. Compared with the United States, the dosage of rATG used in kidney transplantation in China is generally lower. Common programs may as follow.

- rATG 50mg/d, for 3 days. (day 0-2, day 0 refers to the day of kidney transplantation)
- rATG 50mg on day 0, then 25mg/d for the following 4 days
- rATG 25mg/d for 3 days. (day 0-2)

Generally speaking, patients with different risk levels need to choose high or low dose regimens accordingly.

8.1.2. Basiliximab (IL2RA)

Basiliximab is a human-mouse chimeric IgG1 monoclonal antibody against CD25. The use of Basiliximab does not lead to lymphocyte killing, but can change the function of T cells, thereby significantly reducing the rejection rate after kidney transplantation. Generally speaking, the side effects of Basiliximab are small, and the incidence of serious infection or tumor

after operation is also low [88]. Basiliximab is currently widely used in low-risk kidney transplant recipients. The regular scheme is:

- 20mg on both day 0 and day 4, and the time of intravenous administration should be no less than 20min.

8.2. Maintenance therapy

Maintenance therapy for kidney transplantation is a long-term immunosuppressive regimen after kidney transplantation. It is usually a combination of different oral immunosuppressive agents. The aim is to minimize the toxic and side effects of drugs used alone while exerting the anti-rejection effect.

At present, oral immunosuppressants commonly used in clinic can be divided into calcineurin inhibitors (CNIs, mainly Tac and CsA), anti-cell proliferation inhibitors (mainly MMF and myfortie), mTOR inhibitors (mTORi, mainly SRL and EVE) and corticosteroids (mainly Pre). The classic triple immunosuppressive therapy is “CNIs+MMF+Pre”, which has been approved by the vast majority of transplant centers. Besides, there are also combinations such as “CNIs+MMF”, “CNIs+mTORi+Pre”, and “mTORi+MMF+Pre” etc. We will give a brief introduction below.

8.2.1. CNIs

CsA was first extracted from Trichoderma polyspora from soil in southern Norway by Thiele and Kis in 1970. Since then, it has gradually been recognized by the transplantation community and has an important position in the history of organ transplantation. CsA mainly produces immunosuppressive effect by selectively inhibiting T lymphocyte activation, especially in the early stage of T cell activation [89].

Oral administration is better than intravenous injection for CsA. The initial dosage of oral medication is usually 6-8 mg/(kg*d), which is taken twice. The dosage should be adjusted according to the different dosage forms or the different combination regimens. Because the therapeutic window of CsA is narrow, its blood concentration is closely related to the efficacy and toxicity, so the monitoring of drug concentration is very important. The incidence of infection in patients with CsA is low, and most of the serious adverse reactions are related to excessive dosage and high blood drug concentration. When combined with MMF, the whole blood trough concentration of CsA is generally maintained at 100-200 ng/ml, which can meet the needs of treatment and is relatively safe. CsA should be used cautiously in cases of hepatic insufficiency, hyperkalemia, infection, intestinal malabsorption and kidney insufficiency. If serious adverse reactions have been caused, the dosage should be reduced or even discontinued as appropriate, or other immunosuppressive agents should be used instead. By the way,

the clearance rate of CsA in children was higher, and the dosage could be increased appropriately.

Since CsA is nephrotoxic, kidney function should be closely monitored when combined with other nephrotoxic drugs such as aminoglycosides and amphotericin B.

Tac is a potent macrolide immunosuppressant extracted from broth medium of soil fungi by Kino et al. in 1984. It was first used in clinical organ transplantation in 1989 and achieved remarkable results. Subsequently, it was approved by FDA for clinical kidney transplantation in 1997 [90].

Tac has been widely used in various kinds of solid organ transplantation. Compared with CsA, Tac has a stronger immunosuppressive effect. Nowadays, most kidney transplant recipients in China choose Tac as their first choice. The toxicity and side effects of Tac are similar to CsA, but adverse reactions such as hypertrichosis and gingival hyperplasia are rare. It is more likely to lead to post transplantation diabetes mellitus than CsA. The toxicity and side effects of Tac are closely related to blood concentration. Most of the adverse reactions can disappear after withdrawal or reduction. Therefore, the monitoring of blood concentration is particularly critical.

Compared with the orally initial dosage of 0.1-0.3 mg/(kg*d) in foreign countries, the dosage of Tac in China is generally 0.08-0.15 mg/(kg*d). Take it twice a day, 12 hours apart. It is recommended to take it on an empty stomach or at least one hour before meals or two hours after meals. The initial dose for children should be 1.5-2 times the recommended dose for adults, and the use of Tac for the elderly can reduce the dose appropriately. In addition, for patients with liver function damage the dosage should also be reduced. Avoid mixing with potassium-sparing diuretics or potassium supplements as far as possible, nor with nephrotoxic drugs. At present, Tac sustained-release capsules (taken only once a day) have been gradually used in clinical practice, which can improve patients' compliance with medication.

8.2.2. mTORi

SRL, also known as rapamycin, was isolated by Sehgal in 1975 from Streptomyces hygroscopicus collected from soil on Easter Island. SRL was first developed as an antifungal drug, and then found its immunosuppressive effect. In 1989, Morris et al. first used SRL as an anti-graft rejection drug.

SRL selectively inhibits T cell rejection by blocking the proliferation of T cells initiated by IL-2. Compared with CNIs, SRL has the advantages of low nephrotoxicity, less side effects and no neurotoxicity [91]. In addition, SRL has outstanding advantages in anti-tumor effect. At present, SRL is mainly used in organ transplantation in two ways, one is to use it immediately

after transplantation, called initial treatment, the other is to replace other immunosuppressive agents in stable period, called conversion therapy.

• Initial therapies are mainly “SRL+CNI+Pre” or “SRL+MMF+Pre” or “SRL+Pre”. The aim of such therapies is to minimize the nephrotoxicity caused by CNIs. However, the clinical efficacy of this scheme has been controversial. SRL may increase the nephrotoxicity of CNI in CNI-containing regimens, while those without CNI have a higher risk of acute rejection. In addition, SRL has obvious antiproliferative effect, which may lead to surgical complications such as wound healing disorder and lymphocyst.

• Conversion therapy can be used in early stage (2-6 months after transplantation) and late stage (6 months after transplantation). Generally speaking, the purpose of SRL replacement is to fight tumors, viral infections, graft dysfunction, cardiovascular adverse events and so on. The main form of conversion is CNIs reduction or removal, replaced by SRL. The target concentration of SRL for conversion therapy is generally recommended to be 4-10 ng/L.

EVE, a derivative of SRL, is currently mainly used to prevent rejection after kidney and heart transplantation. Relevant research and data are relatively few, so we will not introduce them in detail here.

8.2.3. Antiproliferative drugs

Azathioprine (Aza) was synthesized by Nobel laureates Eliton and Hitchings in the 1940s and used clinically in the treatment of leukemia. In 1963, Aza was combined with corticosteroids by Starzl et al. and became a classic immunosuppressive regimen after kidney transplantation until the advent of CsA. Aza has a strong inhibitory effect on the first immune response, but has little effect on the second reaction. Therefore, it is only suitable for preventive treatment of rejection after organ transplantation, but has no therapeutic value for rejection that has occurred [92]. Nowadays, Aza has been gradually replaced by other Antiproliferative drugs in clinical use.

Mycophenolate mofetil (MMF) is a precursor of mycophenolic acid (MPA). Its main active ingredient is MPA. MPA was found in Penicillium culture medium by Gosio in 1896. It is a highly effective, selective and non-competitive reversible inhibitor of hypoxanthine mononucleotide dehydrogenase (MPDH). Compared with Aza, MMF can significantly improve the long-term survival rate of recipients and kidneys after transplantation and reduce the incidence of acute rejection [93].

The recommended dose for clinical kidney transplantation is 0.75-1.0g, taken twice, immediately after kidney transplantation or within 72 hours. High dose of MMF (2g/d) can be used as a salvage treatment for persistent or refractory acute rejection. Its reversal effect is bet-

ter than that of high dose corticosteroids. It can reduce the loss of transplanted kidney, improve kidney function and reduce the incidence of death or other treatment failure. Of course, with the increase of dosage, the incidence of drug toxicity will increase correspondingly, which needs to be handled as appropriate. MMF is characterized by no hepatotoxicity, nephrotoxicity and neurotoxicity. The common side effects were opportunistic infection, bone marrow suppression and digestive tract symptoms.

Mycophenolate sodium enteric-coated tablets are MPA sodium salts of enteric-coated tablets. One of the main purposes of developing this drug is to improve the gastrointestinal side effects of MPA. Its mechanism of action and side effects are consistent with those of MMF. Especially when combined with proton pump inhibitors (PPI), it has more advantages than MMF [94]. It should be noted that the whole tablet should be swallowed to maintain the integrity of the tablet enteric-coated.

Mizoribin (MZR) is an imidazole nucleocapsid, which was isolated by Mizuno in 1971. MZR was also developed as an antifungal drug in its early stage, and its immunosuppressive effect was found later. In 1984, MZR was approved by the Ministry of Health and Welfare to prevent rejection after kidney transplantation. In Japan, MZR has replaced Aza and is widely used in clinical transplantation [95]. The commonly used oral regimen is to take medicine on the day of transplantation or the next day. The initial dose is 2-3 mg/(kg*d), taken after morning, and then gradually reduced to the maintenance dose of 1-2 mg/(kg*d). MZR does not require drug concentration monitoring, but mainly adjusts dosage according to tolerance. The most common adverse reaction of MZR is hyperuricemia. Long-term hyperuricemia will lead to kidney insufficiency. If necessary, it should be replaced with other antimetabolic drugs.

Leflunomide (LFT) is a new immunosuppressive agent mainly for the treatment of rheumatoid arthritis. In recent years, some scholars have tried to use it in clinical kidney transplantation to prevent rejection. Studies have confirmed that LFT can indeed prolong graft survival and replace MMF or Aza. However, it is not the first choice in clinical application, mainly because of its many side effects and poor long-term tolerance. One of the advantages of LFT is that it can significantly inhibit polyoma cell viruses (such as BK virus) [96, 97]. It is recommended to monitor blood drug concentration during medication.

8.2.4. Corticosteroid

Corticosteroids used in organ transplantation mainly refer to glucocorticoids. Methylprednisolone and prednisolone (Pre) are commonly used in clinic. Today, corticosteroids still play an important role in immunosuppressive therapy of organ transplantation. Glucocorticoids can reduce rejection after organ transplantation by inhibiting cellular and humoral immune reactions. At low doses, glucocorticoids mainly inhibit cellular immune reactions. At high doses, glucocorticoids can inhibit the production of antibodies by plasma cells, which has

the function of inhibiting humoral immunity.

There is no uniform standard for the use of corticosteroids. Generally speaking, the induction therapy is to use methylprednisolone 500-1000 mg (10-15 mg/kg) intravenously during transplantation, 250-500 mg intravenously every day for the first three days after operation, and the dose of methylprednisolone is smaller when other induction drugs are used at the same time. The initial dose of prednisone was 30 mg once a day from the 4th day after operation, and gradually decreased to 10-15 mg at the 30th day after operation, once a day, and entered the maintenance treatment stage. At present, most transplantation centers use low-dose maintenance therapy, usually 10 mg per day at 2-3 months, 5-10 mg per day at half a year and 5-7.5 mg per day after half a year.

When shock therapy is needed for acute rejection, methylprednisolone 250-500 mg (5-10 mg/kg) is usually given intravenously for 3-5 days, and then oral prednisone 30 mg/d, gradually decreasing to the dosage before shock therapy.

Glucocorticoids have a strong anti-inflammatory effect, but also have many side effects. Short-term use may lead to cardiovascular disease, glycometabolism disorders, poor wound healing, etc. Long-term use can lead to cataract, diabetes, hypertension, obesity, osteoporosis, gastrointestinal ulcer and so on [98]. Close observation is needed in clinical use.

After so many years of continuous efforts, the variety of immunosuppressive agents is rich. While providing clinicians with more choices, how to rationally match various immunosuppressive agents to meet the needs of individualized treatment has become a new topic. The mechanism of action of many drugs has not been fully understood up to now. This paragraph only introduces some of the most common immunosuppressants and their clinical applications. It is hoped that through more in-depth research, more perfect drug regimens will be put forward in the future, so as to benefit thousands of patients who need organ transplantation treatment.

9. Postoperative Follow-up of Kidney Transplantation

Nowadays, with the improvement of the surgical techniques and the update of immunosuppressive agents, the short-term survival rate of kidney transplantation was significantly enhanced [99]. Unfortunately, there was no significant change in the annual organ loss rate after transplantation for more than 1 year, and the long-term survival rate was not satisfactory [100,101]. Kidney transplant recipients need to take immunosuppressive drugs for life, which require the therapeutic drug monitoring and dose adjustment for their narrow therapeutic window [102]. Therefore, it is of great significance to attach importance to postoperative follow-up of kidney transplantation for improving the long-term survival and quality of life of kidney transplant recipients.

The follow-up of kidney transplantation is a long and complex work, which is mainly characterized by large data volume, individual differences, and long follow-up period (generally, lifelong follow-up). An efficient and reasonable follow-up system can not only improves the efficiency of the transplant center, but also increases the rate of survival of patients [101]. With the gradual standardization of kidney transplantation, an ideal postoperative follow-up system has become an important indicator of a mature kidney transplantation center.

9.1. Meaning of regular follow-up

Through regular follow-up, the clinicians can dynamically observe the rehabilitation, mental state and medication situation of kidney transplant recipients, and give necessary guidance and health education. In the follow-up, the clinicians can detect and deal with the complications after kidney transplantation in time, improve the quality of life, prolong the survival period after the operation [103]. Moreover, follow-up is the need of medical model transformation, which makes up for the shortage of medical resources, is a tracking service and also an active service. In today's China acute contradiction between doctors and patients, follow-up is a very good way of communication, which can make the relationship between doctors and patients more harmonious and understand each other more. Meanwhile, collection of information of the regular follow-up can accumulate valuable experience for clinical and scientific research.

9.2. Development and method of follow-up in China

Kidney transplantation centers in China are in different stages of development, and each center should choose a suitable follow-up method according to its outpatient follow-up volume and staffing. With the increase of kidney transplantation cases, our center has established the database for recipients' management and follow-up since 2002, which is constantly updated and improved. In the early stage of kidney transplantation, many centers in China lack a sound follow-up system, which is passive and sporadic. On March 1, 2009, Chinese Scientific Registry of Kidney Transplantation (CSRKT) came into use, the first kidney transplantation scientific registration system in China, which is an intelligent data collection and management system in line with the characteristics of organ transplantation in China [100]. It sets up a good platform for clinical evidence-based medicine and the scientific research and provides patients with high quality medical service at the same time. In our center, we set specialized transplant clinic and establish a complete follow-up procedure. The patients should follow the standard follow-up program in the absence of complications, including outpatient frequency and inspection items of follow-up (**Table 5**). Because exceed or insufficient immunosuppressive agent has a negative effect on graft function, its concentration must be monitored regularly. In addition, there is a big problem in China now that all the candidates and recipients are lack of health education related with organ transplantation, which lead to many problems of long

survival and better quality of life. Our center is aware of it and gives the patients regular health education during follow-up through PPT, video and handbook, etc.

Table 5: Frequency and inspection items of follow-up.

Inspection items	1m~3m post-KT	3m~6m post-KT	6m~12m post-KT	>12m post-KT
Blood routine	Once a week	Once two weeks	Once a month	Once half year
Liver function	Once a week	Once two weeks	Once a month	Once half year
Renal function	Once a week	Once two weeks	Once a month	Once half year
Blood glucose and lipids	Once a week	Once two weeks	Once a month	Once half year
Immunosuppressive agent concentration	Once a week	Once two weeks	Once a month	Once half year
TBNK	Once a month	Once a month	Once half year	Once a year
HLA antibody	Once a month	Once a month	Once half year	Once a year
Color ultrasound of transplanted kidney	Once a month	Once a month	Once half year	Once a year
Tumor markers	None	None	None	Once a year
CT of abdomen and lungs	None	None	None	Once a year

9.3. Follow-up of living related donor

The shortage of donor organs is a serious problem for transplant physicians; the living related kidney donors are still an important way to expand the source of donors in China. Although a large number of studies have shown that living transplantation does not pose a significant threat to the health of donor, the quality of life and mental state of donor still require long-term attention because of its own sensitive and cumbersome ethical issues [104].

Regular follow-up helps to detect early risk factors that may affect the retained renal function. It has been reported that the mortality of living kidney donor is 0.03%, and the incidence of complications is about 10%, including hypertension, proteinuria, incisional hernia, intestinal obstruction and so on [105]. It is of great significance to ensure regular postoperative follow-up of donors and improve their quality of life and health to improve the current shortage of organ sources in China. Living kidney transplantation can continue to exist and develop healthily only if the rights and security of donors are more fully guaranteed.

As is well-known, the success of kidney transplant surgery only means the beginning of a new life for patients. The long-term survival of kidney transplant recipients depends not only on the surgical skills of surgeons, but also on the high quality and efficient follow-up after kidney transplantation [106]. With the increase in the number of kidney transplantation and the application of CSRKT, the experts and scholars in China will have more experience to help the patients benefit from kidney transplantation.

10. Prospect of Kidney Transplantation in China

At present, the ratio of supply and demand for organ transplantation in China is about 1:30, which is the main reason that restricts the number of organ transplants in China. In recent years, China has intensified efforts to regulate the management of organ donation and organ transplantation. Since the Ministry of Health (now the National Health Committee) and the Chinese Red Cross Society launched the voluntary DCD work in March 2010, At the beginning of the DCD work, hospitals were waiting to see and test. Up to now, almost all hospitals with kidney transplant admission are actively carrying out transplant work (**Figure. 4**). However, most of the donation cases are concentrated in Guangdong, Guangxi, Zhejiang, Shanxi, Hunan, Hubei and other places, and the development of DCD work in China is still uneven. The donation rate is also far from the European and American countries, and the donation rate per million populations is only 2.98 [107]. Although the organ donation rate in China is extremely low so far, there is still great potential for developing DCD in China. There are more than 9 million normal deaths each year in China, including 20.3% of cardiovascular diseases, 21.0% of cerebrovascular diseases, injuries or accidents (including Poisoning) 7.0% and the diseases above are the main sources of organ transplant donors. China has the potential for DCD development. With the support of the Chinese government and relevant regulatory authorities, China will become a major organ donation and transplanting country. But still have to face many problems:

1) The laws related to organ donation and transplantation must be constantly improved and complete

2) The management system related to organ transplantation needs to be continuously improved and complete

3) Clinical and basic research related to transplantation needs to be further developed

4) Rational application and individualized application of immunosuppressant need to be further strengthened

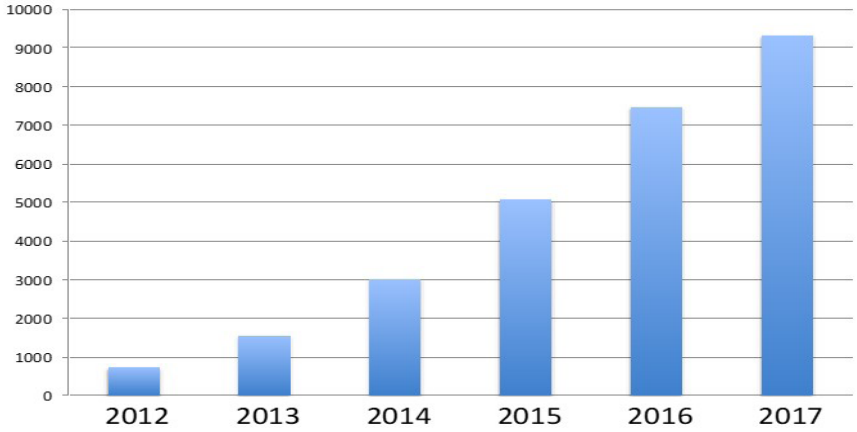


Figure 4: The DCD numbers of China from 2012 to 2017. (Data from CSRKT)

It is believed that with the correct leadership of the Chinese government and the strong support of the management department, China's transplantation will certainly progress healthily and rapidly, and make contributions to the development of the international transplantation career.

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