07 - 325 Kidney Transplantation

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Kidney Transplantation Kidney transplantation is the treatment of choice for patients with end-stage kidney disease (ESKD). Worldwide, tens of thousands of kidney transplants have been performed, and >220,000 patients are living with a functioning kidney transplant in the United States today. The first successful kidney transplant was performed in Boston in 1954 between identical twins. The introduction of immunosuppressive therapies such as azathioprine and prednisone in the 1960s established kidney transplantation across nonidentical individuals (allografts). During the 1970s and 1980s, the success rate at the 1-year mark for deceased-donor allografts markedly improved after the introduction of calcineurin inhibitors. Currently, 1-year survival rates for living-donor and deceased-donor allografts are 98 and 93%, respectively, in the United States. However, long-term survival has not improved as much over time, and the average allograft survival time is 19 and 12 years for living-donor and deceased-donor grafts, respectively. Age-related mortality rates after transplantation are highest in the first year due to the surgical risks: 2% for ages 18–34 years, 3% for ages 35–49 years, and 6.8% for ages ≥50–60 years. Despite this, the actual survival benefit of transplantation compared to chronic dialysis becomes apparent within days to months following transplantation, even after risk adjustments for age, diabetes, and cardiovascular status. While the loss of kidney transplant due to acute rejection is now a rare event, most allografts eventually succumb at varying rates to a chronic process consisting of interstitial fibrosis, tubular atrophy, vasculopathy, and glomerulopathy, the pathogenesis of which in varying degrees is likely a combination of an alloimmune response, drug toxicity, and the result of a variety of other insults. Overall, transplantation results in an improved life expectancy with a higher quality of life compared to patients who remain on dialysis. RECENT ACTIVITY AND RESULTS In 2022, >19,000 deceased-donor kidney transplants and approxi mately 6000 living-donor transplants were performed in the United States, with the ratio of deceased-donor to living-donor transplants remaining stable over the past few years. As the number of patients with ESKD increases, the number of patients on the transplant waitlist also increases. The donor shortage remains a critical challenge; as of 2022, there were nearly 139,000 adult kidney transplant candidates on the waiting list, with 25,000 patients being transplanted yearly. This imbalance is set to worsen over the coming years with the predicted increased rates of kidney failure associated

with obesity and diabetes worldwide. In an attempt to increase utilization of marginal kidneys and allocate organs equitably, a new allocation system within the United States was implemented in 2014. The guiding principles of the changes were to offer an opportunity for transplantation to patients who were highly sensitized and, thus, less likely to find a suitable donor, while at the same time allowing patients expected to survive the longest to receive the best-quality deceased donor organs. The Kidney Donor Profile Index (KDPI) score, which ranges from 0 to 100%, was introduced to estimate the potential risk of graft failure after kidney transplant based on 10 donor factors. The lower KDPI values are associated with higher expected posttransplant survival. Hence, the kidneys with a KDPI <20% are allocated to the 20% of the potential recipients with the highest expected posttransplant survival. Kidneys with a KDPI >85% (previously called expanded criteria donor [ECD] kidneys) are directed toward patients who are expected to fare less well on dialysis and would benefit from being transplanted earlier even if it means accepting a lower-quality organ. In 2021, a new distance-based kidney allocation policy was intro duced. Under this policy, deceased-donor kidneys are to be offered first to candidates listed at transplant hospitals within 250 nautical miles of

the donor hospitals. While intended to reduce geographic disparities in access to kidney transplantation, this program has resulted in more complex organ sharing, unintended higher kidney discard rates, and increased cold ischemia time. A variety of other means to increase the donor pool and equity have also become more popular. Kidneys from donors after cardiac death (DCD) are now commonly used to overcome the demand for organs, consisting of 30% of total deceased kidney transplants (Table 325-1). Furthermore, with the advance ment of the direct-acting antiviral therapies for hepatitis C virus (HCV), transplantation from HCV-positive donors to HCV-positive or -negative recipients has been performed since 2017 in order to increase the donor pool. Now this practice is becoming more common, consisting of 9% of deceased kidney transplants. Recently, the HOPE (Human Immunodeficiency Virus [HIV] Organ Policy Equity) Act authorized organ donation from HIV-positive candidates, and >100 transplants have been performed. As patients with blood group B wait longer for deceased donor offers, eligible B blood type candidates who have low anti-A titer are eligible for an allograft from A blood type donors. This helps improve access and reduce disparities in wait time for minorities, especially for the African-American ESKD population, in whom blood type B is more common than in other ethnicities. Finally, with recent advances in gene editing technology, xenotrans plantation is becoming a more realistic endeavor. Using kidneys from genetically engineered pigs, three experimental kidney transplanta tions into brain-dead recipients were performed in 2022. There are still multiple issues to overcome, including xenoimmunity, transmission of zoonosis, and ethical challenges, but xenotransplantation has the potential to provide an unlimited source of organs.

CHAPTER 325 Kidney Transplantation The overall results of transplantation are presented in Table 325-2. At the 1-year mark, allograft survival is higher for living-donor recipi ents. This is most likely related to less ischemic injury of the transplant organ. The introduction of more effective immunosuppression and more accurate matching between recipients and donors has almost equalized the risk of graft rejection in the majority of patients within the first year. At 5- and 10-year follow-up, however, there remains a steeper decline in survival of those with deceased-donor kidneys. RECIPIENT EVALUATION Virtually all patients with ESKD benefit from transplantation with a longer life expectancy and a better quality of life. While the mortality rate after transplantation is highest in the first year due to perioperative complications, recipient evaluation is critical in

identifying patients at risk. It involves a multidisciplinary approach that requires thorough medical, surgical, social, and psychosocial evaluations to identify the risk factors that prohibit transplantation or mandate treatment before proceeding, as well as ensuring the appropriate use of limited organs. There are a few absolute contraindications to kidney transplanta tion: chronic illness that limits predicted survival for <2 years, active malignancy, active infection, psychosocial issues affecting adherence to the medical care, and active substance abuse. Cardiovascular risk assessment is crucial during both the perioperative and postoperative periods. Patients with ESKD are at higher cardiovascular mortality risk, TABLE 325-1 Definition of a Non-Heart-Beating Donor (Donation After Cardiac Deatha [DCD]) I: Brought in dead II: Unsuccessful resuscitation III: Awaiting cardiac arrest IV: Cardiac arrest after brainstem death V: Cardiac arrest in a hospital patient aKidneys can be used for transplantation from categories II–V but are commonly only used from categories III and IV. The survival of these kidneys has not been shown to be inferior to that of deceased-donor kidneys. Note: Kidneys can both have a Kidney Donor Profile Index (KDPI) score >85% and be DCD. High KDPI kidneys have been shown to have a poorer survival, and there is a separate shorter waiting list for those kidneys. They are generally utilized for patients for whom the benefits of being transplanted earlier outweigh the associated risks of using a lower-quality kidney.

TABLE 325-2 Mean Rates of Graft and Patient Survival for Kidneys Transplanted in the United States from 1999 to 2018a 1-YEAR FOLLOW-UP 5-YEAR FOLLOW-UP 10-YEAR FOLLOW-UP GRAFTS, % PATIENTS, % GRAFTS, % PATIENTS, % GRAFTS, % PATIENTS, % Deceased donor

Living donor

aAll patients transplanted are included, and the follow-up unadjusted survival data from the 1-, 5-, and 10-year periods are presented to show the attrition rates over time within the two types of organ donors. Source: Data from Summary Tables, 2021 Annual Reports, Scientific Registry of Transplant Recipients. and thorough cardiovascular evaluation for coronary artery diseases, valvular diseases, and heart failure is critical. At most centers, there is no official age limit for transplantation, with >20% of waitlisted candidates currently being older than 65. However, overall physical and cognitive function of the candidates needs to be fully assessed. While history of malignancy itself is not a contraindication for kidney transplantation, potential recipients should be treated to ensure cancer-free wait time of 2–5 years depending on the type and stages of malignancy to decrease the risk of cancer recur rence. Latent or indolent infection (HIV, hepatitis B or C, tuberculosis) should be a routine part of the candidate workup. While historically transplant centers considered overt AIDS and active hepatitis absolute contraindications to transplantation because of the high risk of oppor tunistic infection, with the introduction of potent antiviral regimens, many centers are now transplanting individuals with hepatitis and HIV infection under strict protocols. PART 9 Disorders of the Kidney and Urinary Tract One of the few “immunologic” contraindications to transplantation is the presence of preformed antibodies against the donor kidney at the time of the anticipated transplant that can cause hyperacute rejection. Those harmful antibodies include natural antibodies against the ABO blood group antigens and antibodies against human leukocyte antigen (HLA) class I (A, B, C) or class II (DR, DQ, DP) antigens. These antibodies are routinely excluded by proper screening of the candidate’s ABO compatibility and direct cytotoxic cross-matching of candidate serum with lymphocytes of the donor. Removal of these antibodies directed at donor tissue through a variety of strategies (desensitization) is now routinely performed with varying levels of success. TISSUE TYPING AND CLINICAL IMMUNOGENETICS

Matching of HLA major histocompatibility complex antigens (Chap. 361) is an important criterion for the selection of donors. Each mammalian species has a single chromosomal region that encodes the major histocompatibility antigens, and this region on the human chromosome 6 codes the HLA genes. HLA is highly polymorphic; therefore, it can be an immunologic target of organ rejection when mismatched between the donor and the recipient. Historically, HLA antigens have been defined by serologic techniques by adding sera of a recipient (potentially containing anti-HLA anti bodies) with a “library” of leukocytes with known serotypes. How ever, currently, molecular typing of HLA by genomic sequencing is almost universally used. Other “minor,” non-HLA antigens may also elicit an alloimmune response in addition to the ABH(O) antigens and endothelial antigens that are not expressed on lymphocytes. The number of HLA antigen mismatches in A, B, and DR loci correlates with allograft survival; the more mismatches, the higher is the risk of allograft rejection. Nevertheless, some HLA-identical renal allografts are rejected, often within the first few weeks after transplantation. These observations may represent prior sensitization to non-HLA antigens. Non-HLA minor antigens are relatively weak when initially encountered and are, therefore, suppressible by conventional immu nosuppressive therapy. If prior exposure to the antigen and priming of the recipient immune system have occurred, secondary exposure at the time of transplantation may lead to an immune response refrac tory to treatment. More recently, a genetics study of donor-recipient pairs revealed that non-HLA antigen polymorphisms in the LIMS-1 locus can contribute to the risk of acute rejection; more of these nonHLA antigens are likely to be discovered.

DONOR EVALUATION ■ ■LIVING-DONOR EVALUATION Living kidney donors experience the immediate risk of surgery and the long-term potential risk of developing kidney dysfunction pre maturely; thus, the basic principle of “first, do no harm” (Chap. 12) is important. Therefore, donor evaluation must take every effort to exclude any medical conditions that may cause morbidity and mor tality after kidney donation, such as hypertension, diabetes, and/or proteinuria. Although studies have shown that the risk of ESKD after kidney donation is not greater than that of the general population, donation is associated with a small but significant potential lifetime risk of ESKD (0.3–0.4%; absolute risk increased by 0.2–0.3% compared to that of healthy nondonors). The mechanism of premature renal failure is thought to be due to increased blood flow and hyperfiltration injury in the remaining kidney. There are a few reports of the develop ment of hypertension, proteinuria, and even lesions of focal segmental sclerosis in donors over long-term follow-up. In family members of type 1 diabetics, anti-insulin and anti-islet cell antibodies should be measured, and a glucose tolerance test should be performed. AfricanAmerican donors have a higher risk of ESKD after donation (in line with their higher risk of kidney failure in general), and the genetic screening for APOL1 risk alleles may be appropriate (Chap. 326). Additionally, as more robust genetic testing becomes available, predo nation genetic testing per protocol is being introduced to stratify the risks of kidney donors. From the surgical perspective, selective renal arteriography is essential to reveal any anatomic anomaly and to assess the size imbalance and laterality of donor kidneys. In most cases, donor nephrectomy is performed laparoscopically to minimize the surgical scar and to enhance a faster postsurgical recovery. Lastly, although financial and nonfinancial conflicts of interest between kidney donors and recipients are strictly prohibited, removing financial disincentives is increasingly accepted to reduce barriers toward living donation, and legislative efforts to protect kidney donors are ongoing (Chap. 12). ■ ■DECEASED-DONOR EVALUATION Deceased donors should be free of malignant neoplastic disease, hepa titis, and HIV owing to possible transmission to the recipient, although under certain circumstances, HCV- and

HIV-positive organs may be used. Increased risk of graft failure exists when the donor is elderly or has acute kidney injury or when the kidney experiences a prolonged period of ischemia. In the United States, there is a national system of regulations, alloca tion support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. Studies have shown that deceased-donor kidneys can be maintained for up to 48 h on cold pulsatile perfusion or on ice before being used for transplantation. Normothermic perfusion of donated organs has been studied, but it has not been part of clinical care as of yet. Generally, an ischemic time of <24 h is preferred; this approach permits adequate time for typing, cross-matching, transportation, and selection issues to be resolved. ■ ■PRESENSITIZATION The presence of antibodies against donor antigens, either HLA or nonHLA, can be a potential cause of allograft injury after transplantation, and, hence, it is important to perform crossmatching prior to trans plantation. For the purposes of crossmatching, donor T lymphocytes, which express class I but not class II HLA, are used as a surrogate target for detection of circulating anti–class I (HLA-A and -B) antibodies

in the recipient. Note that T cells are used as surrogate cells to detect class I HLA as a matter of convenience and this is unrelated to the risk of "T cell–mediated" rejection. A positive cytotoxic crossmatch of recipient serum with donor T lymphocytes indicates the presence of preformed donor-specific anti-HLA class I antibodies and is usually predictive of an acute vasculitic event termed hyperacute rejection. This finding represents the only widely accepted absolute immunologic contrain dication for kidney transplantation. Recently, an increasing number of tissue-typing laboratories have shifted to a more sensitive flow cyto metric crossmatch assay, which detects the presence of anti-HLA IgG antibodies that are not necessarily detected on a cytotoxic crossmatch assay and may not be an absolute contraindication to transplantation. The known sources of sensitization are blood transfusion, a prior transplant, pregnancy, and less commonly, vaccination or infection. Preformed anti–class II (HLA-DR and -DQ) antibodies against the donor also carry a higher risk of graft loss, particularly in recipients who have suffered early loss of a prior kidney transplant. B lympho cytes (again, used for convenience), which express both class I and class II HLA, are used as a surrogate target in these assays. Some nonHLA antigens restricted in expression to endothelium and monocytes have been described, but their clinical relevance is not well established. A series of minor histocompatibility antigens do not elicit antibodies, and sensitization to these antigens is detectable only by cytotoxic T cells, an assay too cumbersome for routine use. Recent studies revealed the importance of "eplet" matching in antigen recognition. Eplets are short sequences of polymorphic amino acids on the surface of HLA antigens, recognized by HLA antibodies, and can be shared among different HLA antigens. Especially in class II HLA DQ loci, eplet mismatches are shown to be important risk factors for acute rejection. Desensitization prior to transplantation by reducing the level of anti donor antibodies utilizing plasmapheresis and/or the administration of pooled immunoglobulin (IV immunoglobulin [IVIG]) has been useful in reducing the risk of hyperacute rejection following transplantation. In addition, kidney paired donation programs where living donor kidneys are swapped so each recipient receives a compatible transplant organ are increasingly popular to transplant presensitized candidates safely. IMMUNOLOGY OF REJECTION Both T cell–mediated and antibody-mediated effector mechanisms can play roles in kidney transplant rejection. T cell–mediated rejection is caused by recipient T lymphocytes that respond to donor HLA antigens expressed within the transplanted TCR Indirect Pathway Direct Pathway MHC II Tfh CD4 T Cell Allogeneic peptide Th1 Plasma Cell Self APC Th2 CD4 T Cell Th17 CD4 MHC I CD8 T Cell Allogeneic APC CD8 FIGURE 325-1 Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T

lymphocytes (TH) having antigen receptors that bind to specific complexes of peptides and MHC class II molecules on antigen-presenting cells (APC). In transplantation, in contrast to other immunologic responses, there are two sets of T-cell clones involved in rejection. In the direct pathway, the class II MHC of donor allogeneic APCs is recognized by CD4 TH cells that bind to the intact MHC molecule, and class I MHC allogeneic cells are recognized by CD8 T cells. The latter generally proliferate into cytotoxic cells (TC). In the indirect pathway, the incompatible MHC molecules are processed into peptides that are presented by the self-APCs of the recipient. The indirect, but not the direct, pathway is the normal physiologic process in T-cell recognition of foreign antigens. Once TH cells are activated, they proliferate and, by secretion of cytokines and direct contact, exert strong helper effects on macrophages, TC, and B cells. (Courtesy of Andrew Badoui and Nadim Al Rahy.)

organ. CD4+ lymphocytes respond to class II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of the immune system. CD8+ cytotoxic lym phocytes respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells that cause organ damage through direct con tact and lysis of donor target cells. Full T-cell activation requires not only T-cell receptor binding to the alloantigens presented by self or donor HLA molecules (known as indirect and direct presentation, respectively) but also engagement of costimulatory molecules such as CD28 on T cells and CD80 and CD86 ligands on antigen-presenting cells (Fig. 325-1). Signaling through both of these pathways induces activation of the kinase activity of calcineurin, which, in turn, activates transcription factors leading to upregulation of multiple genes, includ ing interleukin (IL) 2 and interferon γ. IL-2 signals through the target of rapamycin (TOR) to induce cell proliferation in an autocrine fashion.

Antibody-mediated rejection is caused by circulating antibodies against donor antigens. After transplantation, donor-derived antigens are delivered to the recipient’s draining lymph nodes and activate an alloimmune response. A subset of CD4+ T cells called follicular helper T cells (Tfh) are activated and promote differentiation of B cells into antibody-secreting plasma cells. Plasma cells produce donor-targeting antibodies against HLA and non-HLA antigens, which can deposit in allograft kidney and cause injury via complement-dependent and independent mechanisms. C4d deposition in peritubular capillaries and glomerular basement membrane is a footprint of complement acti vation and is one of the diagnostic criteria of antibody-mediated rejec tion, together with the presence of circulating donor-specific antibody. CHAPTER 325 Kidney Transplantation IMMUNOSUPPRESSIVE TREATMENT Kidney transplant recipients need to take immunosuppressive drugs for life, except identical twins or simultaneous bone marrow–kidney transplant recipients. Currently clinically available immunosuppres sive therapies suppress all immune responses nonspecifically, includ ing those to exogenous pathogens (bacteria, viruses, and fungi) and even malignant tumors, and tend to spare memory immune responses. Immunosuppressive agents are divided into induction and mainte nance agents. Those currently in clinical use are listed in Table 325-3. ■ ■INDUCTION THERAPY Induction therapy is given to most kidney transplant recipients in the United States at the time of transplant to reduce the risk of early acute rejection and to minimize or eliminate the use of either steroids or B Cell Activation Naïve B Cell Cytokine Production Antibody Mediated Rejection GzmB Cellular Rejection and Organ Damage CD8 Activation Cytotoxic CD8 T Cell Perforin Attack on Target Cells

TABLE 325-3 Maintenance Immunosuppressive Drugs AGENT PHARMACOLOGY MECHANISMS SIDE EFFECTS Glucocorticoids Increased bioavailability with hypoalbuminemia and liver disease; prednisone/prednisolone generally used Binds cytosolic receptors and heat shock proteins. Blocks transcription of IL-1, -2, -3, -6, TNF-α, and IFN-γ Cyclosporine (CsA) Lipid-soluble polypeptide, variable absorption, microemulsion more predictable Trimolecular complex with cyclophilin and

calcineurin → block in cytokine (e.g., IL-2) production; however, stimulates TGF-β production Tacrolimus Macrolide, well absorbed Trimolecular complex with FKBP-12 and

calcineurin → block in cytokine (e.g., IL-2) production; may stimulate TGF-β production Azathioprine Mercaptopurine prodrug Hepatic metabolites inhibit purine synthesis Marrow suppression (WBC > RBC > platelets) Mycophenolate mofetil/sodium Metabolized to mycophenolic acid Inhibits purine synthesis via inosine monophosphate dehydrogenase Sirolimus/everolimus Macrolide, poor oral bioavailability Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation Belatacept Fusion protein, intravenous injections Binds CD80 and CD86, prevents CD28 binding and T-cell activation Abbreviations: FKBP-12, FK506 binding protein 12; IFN, interferon; IL, interleukin; RBC, red blood cells; TGF, transforming growth factor; TNF, tumor necrosis factor; WBC, white blood cells. PART 9 Disorders of the Kidney and Urinary Tract calcineurin inhibitors and their associated toxicities. Induction therapy consists of antibodies that could be depleting or nondepleting. Depleting Agents Antithymocyte globulin (ATG) is a lympho cyte-depleting agent. Peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas are injected into horses or rabbits to produce antilymphocyte serum, from which the immunoglobulin fraction is then separated. Those polyclonal antibod ies induce lymphocyte depletion, and the immune system may take several months, if not years, to fully recover. Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. Alemtuzumab is directed against CD52, widely expressed on immune cells such as B and T cells, natural killer cells, macrophages, and some granulocytes. Nondepleting Agents Another more selective approach is to target the 55-kDa alpha chain of the IL-2 receptor, which is expressed only on activated T cells. This approach is used as prophylaxis for (but not treat ment of) acute rejection in the immediate posttransplant period and is effective at decreasing the early acute rejection rate with few adverse side effects. ■ ■MAINTENANCE THERAPY The most frequently used combination is a calcineurin inhibitor (CNI), usually tacrolimus, and an antimetabolite, usually mycophenolic acid, with or without early steroid withdrawal. Belatacept is a co-stimulatory bocking antibody, used as an alternative to long-term toxic CNI therapy. The mammalian TOR (mTOR) inhibitors sirolimus and everolimus are infrequently used as first-line maintenance immunosuppression. Antimetabolites Azathioprine is a prodrug that must first be acti vated to form thioguanine nucleotides. Thiopurine S-methyltransferase (TPMT) inactivates azathioprine. Patients with two nonfunctional TPMT alleles experience life-threatening myelosuppression when treated with azathioprine, and those who carry one nonfunctional TPMT allele may also have significant side effects; therefore, the U.S. Food and Drug Administration (FDA) recommends TPMT genotyping or phenotyping before starting treatment with azathioprine. Azathioprine, which inhibits synthesis of DNA and RNA and thereby inhibits T-cell proliferation, was the keystone of immunosuppressive therapy in kidney transplant recipients until the 1990s but has been replaced by more effective agents. Concomitant use of allopurinol is best avoided and, if used, very care fully monitored, owing to inhibition of xanthine oxidase. Mycophenolate mofetil and mycophenolate sodium, both of which are metabolized to mycophenolic acid, are now used in

place of azathioprine based on superior efficacy. Mycophenolic acid has a similar mode of action as azathioprine and is associated with a mild degree of gastrointestinal toxicity but less bone marrow suppression.

Hypertension, glucose intolerance, dyslipidemia, osteoporosis Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums Similar to CsA, but hirsutism/hyperplasia of gums unusual, and diabetes more likely Diarrhea/cramps; dose-related liver and marrow suppression is uncommon Hyperlipidemia, thrombocytopenia Posttransplant lymphoproliferative disease (PTLD) Steroids Glucocorticoids are important adjuncts to immunosup pressive therapy and used as both induction and maintenance ther apy. In general, methylprednisolone 250–500 mg is given immediately before or at the time of transplantation, and the dose is tapered to 20 mg

within a week. The side effects of the glucocorticoids, particularly impairment of wound healing and predisposition to infection, make it desirable to taper the dose as rapidly as possible in the immediate postoperative period. Early discontinuation or avoidance of steroids is common to avoid long-term adverse effects on bone, skin, and glu cose metabolism. Most patients whose renal function is stable after 6 months or a year do not require large doses of prednisone; mainte nance doses of 5–10 mg per day are the rule. A major effect of steroids is preventing the release of IL-6 and IL-1 by monocytes-macrophages. Calcineurin Inhibitors Cyclosporine is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to inhibit transcription of IL-2 and other proinflammatory cytokines, thereby inhib iting T-cell proliferation. It works synergistically with glucocorticoids and mycophenolate. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, and diabetes), nephrotoxicity presents a serious management problem and is further discussed below. Tacrolimus (FK506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side effect profile; it does not, however, produce hirsutism or gingival hyperplasia; in contrast, it can be associated with hair loss. Posttransplant diabetes mellitus more com monly occurs with tacrolimus. An extended-release formulation of tacro limus is now available and is given once daily. Owing to its nephrotoxicity and narrow therapeutic window, the drug level of CNIs should be moni tored, and drug–drug interactions should be carefully examined. Antibi otics and antifungals (e.g., erythromycin, ketoconazole, fluconazole) and nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) inhibit the activity of cytochrome P450 C3A enzyme and cause elevated levels of CNIs. On the other hand, antiepileptics, such as phenytoin and carbamazepine, increase metabolism, resulting in lower levels. mTOR Inhibitors Sirolimus (previously called rapamycin) is another fungal macrolide but has a different mode of action from tacrolimus; i.e., it inhibits T-cell growth factor signaling pathways, pre venting the response to IL-2 and other cytokines. Sirolimus can be used in conjunction with cyclosporine or tacrolimus, or with mycophenolic acid, to avoid the use of CNIs. Everolimus is another mTOR inhibitor with similar mechanism of action as sirolimus but with better bioavailability. mTOR inhibitors are modestly tolerated and are associated with gastrointestinal disturbance, stomatitis, mucositis, and pneumonitis. Poor wound healing associ ated with mTOR inhibitors makes them less preferable agents during the perisurgical period. While the PI3K-mTOR is the most commonly

mutated cellular pathway in malignant cells, mTOR inhibitors have been used more frequently in transplant patients who develop cancers, in particular recurrent skin cancers. Belatacept

Belatacept is a fusion protein composed of the Fc frag ment of human IgG1 immunoglobulin and the extracellular domain of cytotoxic T-lymphocyte associated protein 4 (CTLA-4). It binds to its costimulatory ligands (CD80 and CD86) on antigen-presenting cells, interrupting their binding to CD28 on T cells. This inhibition leads to T-cell anergy and apoptosis. Belatacept is FDA approved for kidney transplant recipients and is given monthly as an intravenous infusion. The 7-year follow-up of the Belatacept Evaluation of Nephroprotec tion and Efficacy as First-Line Immunosuppression Trial (BENEFIT) showed improved patient and graft survival for the belatacept-treated group compared to patients treated with cyclosporine, despite shortterm risks of higher rates of acute rejection. CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT Adequate hemodialysis should be performed within 48 h prior to the surgery as needed to control serum potassium to prevent cardiac arrhythmias. During the transplantation surgery, the kidney allograft is usually placed in the recipient's iliac fossa using a retroperitoneal approach. An anastomosis is made between donor renal artery and recipient external iliac artery and donor renal vein to recipient external Recipient high %PRA (sensitized) Recipient with prior transplant Recipient with autoimmune GN Donor cold ischemia time >24 h or Donor age >60 years or Donor with high KDPI High risk Low risk Antithymocyte globulin induction Steroids, mycophenolic acid Calcineurin inhibitor (a few days after) Persistent allograft dysfunction Delayed graft function/HD support Good urine output Improvement in Cr Allograft biopsy Acute rejection No rejection Adjust CNI dose. Supportive care (BP control, fluid) Outpatient follow-up FIGURE 325-2 A typical algorithm for early posttransplant care of a kidney recipient. If any of the recipient or donor "high-risk" factors exist, more aggressive management is called for. Low-risk patients can be treated with a standard immunosuppressive regimen with no or less-potent induction therapy (e.g., basiliximab). Patients at higher risk of rejection or early ischemic transplant dysfunction are often induced with an antithymocyte globulin to provide more potent early immunosuppression or to spare calcineurin use in the immediate posttransplant period. When there is early transplant dysfunction, prerenal, obstructive, and vascular causes must be ruled out by ultrasonographic examination. The panel reactive antibody (PRA) is a quantitation of how much antibody is present in a candidate against a panel of cells representing the distribution of antigens in the donor pool. BP, blood pressure; CNI, calcineurin inhibitor; Cr, creatinine; DM2, type 2 diabetes; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; KDPI, Kidney Donor Profile Index.

iliac vein. The donor ureter is anastomosed to the recipient bladder mucosa. Native kidney nephrectomy is rarely performed except in the case of an extremely enlarged polycystic kidney or chronic pyelone phritis. In many cases, especially after living kidney transplantation, the allograft starts to produce urine immediately after anastomosis. The allograft often has some degree of acute tubular injury due to ischemia, which accounts for postoperative diuresis. Large amounts of sodium, potassium, and water may be lost postoperatively, which requires close monitoring and replacement. The recipient's serum creatinine should start to fall as the allograft starts to function, and recovery usually occurs within 2 weeks, although periods as long as 6 weeks have been reported. Slow recovery or oliguria should prompt an allograft biopsy because superimposition of rejection on acute tubular injury is common and difficult to distinguish without an allograft biopsy. Induction immunosuppression therapy and maintenance steroids and antimetabolites start on the day of surgery, and it is usually safe to delay introduction of a CNI for a few days if a lymphocyte-depleting induc tion agent is used. Figure 325-2 illustrates a typical algorithm followed by transplant centers for early posttransplant management of recipients at high or low risk of early renal dysfunction.

■ ■MANAGEMENT OF REJECTION Early diagnosis of rejection allows prompt institution of therapy to preserve allograft function and prevent irreversible damage. Clinical CHAPTER 325 Recipient PRA <10% (unsensitized) Recipient first transplant, or >65 years old Original disease non-immune related (DM2, HTN) Kidney Transplantation Living donor Donor cold ischemia time <12 h or Donor age 15–35 years old Basiliximab induction Steroids, mycophenolic acid Calcineurin inhibitor (day 1–2) Good urine output Improvement in Cr --> Outpatient follow-up Adjust CNI dose. If kidney function remains inadequate or low. IV steroid (methylprednisolone, 0.5–1 g/d × 3 days), or antithymocyte globulin

evidence of rejection is rarely characterized by fever, swelling, and tenderness over the allograft. Rejection may present only with a rise in serum creatinine, with or without a reduction in urine volume. The focus should be on ruling out other causes of functional deterioration, such as acute tubular injury, calcineurin toxicity, BK nephropathy, and recurrent glomerular diseases.

Doppler ultrasonography is useful in ascertaining changes in the allograft vasculature and in blood flow. Thrombosis of the renal vein occurs rarely; it may be reversible if it is caused by technical factors and intervention is prompt. Diagnostic ultrasound is also helpful in identifying urinary obstruction or the presence of perirenal collections of urine (urinoma), blood (hematoma), or lymph (lymphocele). Allograft biopsy is the gold standard for diagnosis of acute T cell– mediated and antibody-mediated rejection. Acute T cell–mediated rejection is diagnosed by the presence of immune cell infiltration in the interstitial, tubular, or vascular compartments, according to the Banff classification. Treatment of T cell–mediated rejection involves a high-dose steroid, e.g., IV administration of methylprednisolone, 500–1000 mg daily for 3 days. Failure to respond is an indication for antibody therapy, usually with ATG. Evidence of antibody-mediated rejection is present when endothe lial injury and deposition of complement component C4d is detected in peritubular capillaries. This is usually accompanied by detection of the circulating donor-specific antibody in the recipient’s blood. Treatment of antibody-mediated rejection remains a challenge, and aggressive use of plasmapheresis, IVIG, anti-CD20 monoclonal antibody (rituximab) to target B lymphocytes, and bortezomib to target antibody-producing plasma cells is indicated. Recently, noninvasive biomarkers such as cir culating donor-derived cell-free DNA, urine chemokine markers (e.g., CXCL9), and characterization of the urine exosome have been used as adjunct diagnostic markers for rejection. Future studies to identify prognostic, noninvasive biomarkers that predict response to therapy, that risk stratify, and that provide personalized immunosuppression strategies will be needed. PART 9 Disorders of the Kidney and Urinary Tract ■ ■MANAGEMENT OF CHRONIC COMPLICATIONS Cardiovascular events (29%), infection (18%), and malignancy (17%) are the major causes of death in kidney transplant recipients. Typi cal time courses of opportunistic infections after transplantation are shown in Table 325-4. The signs and symptoms of infection may be atypical due to immu nosuppression, which makes diagnosis challenging. In addition to commensal infections, opportunistic infections should be considered based on the clinical presentation. Diagnostic measures such as culture (blood, urine, drain fluids), viral load in plasma, and imaging (allograft ultrasound and computed tomography [CT]) should be obtained. Overall therapy involves adequate source control, anti-microorganism therapy, and reduction of immunosuppression. Pneumocystis jirovecii is a rare but critical opportunistic infec tion (Chap. 227). Aggressive diagnostic procedures, includ ing transbronchial and open-lung biopsy, are frequently indicated. TABLE 325-4 The Most Common Opportunistic Infections in Renal Transplant Recipients Peritransplant (<1 month) Late (>6 months) Wound infections Aspergillus Herpesvirus

Nocardia Oral candidiasis BK virus (polyoma) Urinary tract infection Herpes zoster Early (1–6 months) Hepatitis B Pneumocystis carinii Hepatitis C Cytomegalovirus Legionella Listeria Hepatitis B Hepatitis C

Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice; amphotericin B has been used effectively in systemic fungal infections. Prophylaxis against P. jirovecii with daily low-dose TMPSMX for 6 months is effective. Involvement of the oropharynx with Candida (Chap. 222) may be treated with local nystatin. Tissueinvasive fungal infections require treatment with systemic agents such as fluconazole or one of the newer antifungal agents. Aspergillus (Chap. 223), Nocardia (Chap. 179), and especially cytomegalovirus (CMV) (Chap. 200) infections also occur. CMV infection is a serious complication after kidney transplanta tion associated with increased morbidity and mortality. While the seronegative recipients of seropositive donors are at the highest risk, presentation varies from asymptomatic CMV viremia to a systemic syndrome (fever, leukopenia) and tissue-specific manifestation (hepa titis, gastroenteritis, and retinopathy). Plasma viral load and a rise in IgM antibodies to CMV are diagnostic. Valganciclovir has proved effective in both prophylaxis and treatment of CMV disease. Acyclovir is an effective therapy for herpes simplex virus infections. BK virus is a latent polyomavirus that lies dormant in the kidney and urothelial tract and can be activated in the setting of immunosup pression. Reactivation of BK, if left untreated, will lead to progressive fibrosis and loss of the graft within 1 year in most cases. However, as risk of reactivation of BK infection is associated with the overall degree of immunosuppression, in most cases, BK infection can be managed by regular testing of BK viral load and judicious reduction of mainte nance immunosuppression. Renal biopsy can be useful in examining for the presence of interstitial nephritis, tubular cytopathic changes of BK nephropathy, and viral antigens in the allograft. In difficult to treat cases beyond reduction in immunosuppression, a variety of therapies including leflunomide, cidofovir, and quinolone antibiotics (which are effective against polyoma helicase) and IVIG have been tried but with inconsistent results. ■ ■CHRONIC LESIONS OF THE TRANSPLANTED KIDNEY Although current 1-year transplant survival is excellent, most recipi ents experience a progressive decline in kidney function over time thereafter. Chronic renal transplant dysfunction can be caused by chronic active antibody-mediated rejection, recurrent glomerular disease, hypertension, CNI nephrotoxicity, secondary focal glomeru losclerosis, or a combination of these pathophysiologies. Chronic vascular changes with intimal proliferation and medial hypertrophy are commonly found. Control of systemic and intrarenal hypertension with calcium channel blockers is thought to have a beneficial influence on the rate of progression of chronic allograft dysfunction. Kidney allograft biopsy can distinguish subacute cellular rejection from recur rent disease or secondary focal sclerosis. MALIGNANCY The incidence of tumors in patients on immunosuppressive therapy is 5–6%, or ~100 times greater than that in the general population in the same age range. The most common lesions are cancer of the skin and lips. Hence, surveillance for skin cancers and protection from ultra violet radiation are necessary. Solid organ transplant recipients are at higher risk to develop posttransplant lymphoproliferative disease, most frequently seen early (<1 year) or late (7–10 years) after transplanta tion. Most cases are associated with Epstein-Barr virus infection, and the prognosis is poor. The overall malignancy risks are increased in proportion to the total immunosuppressive load administered and the time elapsed since transplantation. Treatment of cancer after transplant involves the reduction of immunosuppression, surgery, conventional cytotoxic chemotherapy, and radiotherapy. Cancer immunotherapy is associated with a high risk of allograft rejection (30–40%), and the multidisciplinary risk-benefit discussion should be made before the initiation of therapy. ■ ■OTHER COMPLICATIONS Both chronic dialysis and renal

transplant patients have a higher incidence of death from myocardial infarction and stroke than the

Revision #1
Created 2026-01-06 16:34:22 UTC by Omar Ayman
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