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TRANSPLANTATION IN THE TREATMENT OF RENAL FAILURE: INTRODUCTION

Transplantation of the human kidney is the treatment of choice for advanced chronic renal failure. Worldwide, tens of thousands of such procedures have been performed. When azathioprine and prednisone were initially used as immunosuppressive drugs in the 1960s, the results with properly matched familial donors were superior to those with organs from deceased donors—namely, 75–90% compared with 50–60% graft survival rates at 1 year. During the 1970s and 1980s, the success rate at the 1-year mark for deceased-donor transplants rose progressively. By the time cyclosporine was introduced in the early 1980s, deceased-donor grafts had a 70% 1-year survival and reached the 82% level in the mid-1990s. After the first year, graft survival curves show an exponential decline in numbers of functioning grafts from which a half-life ($t_{1/2}$) in years is calculated; this has increased by only 2 years since the 1980s.

Mortality rates after transplantation are highest in the first year and are age-related: 2% for ages 18–34 years, 3% for ages 35–49 years, and 6.8% for ages ≥ 50 –60 years. These rates compare favorably with those in the chronic dialysis population, even after risk adjustments for age, diabetes, and cardiovascular status. Occasionally, acute irreversible rejection may occur after many months of good function, especially if the patient neglects to take the prescribed immunosuppressive drugs. Most grafts, however, succumb at varying rates to a chronic vascular obliterative process termed *chronic allograftnephropathy*, the pathogenesis of which is incompletely understood. Overall, transplantation returns most patients to an improved lifestyle and an improved life expectancy compared with patients on dialysis. There are at least 100,000 patients with functioning kidney transplants in the United States, and when one adds in the numbers of kidney transplants in centers around the world, the total activity is doubled.

RECENT ACTIVITY AND RESULTS

In 1994 there were more than 7000 deceased donor kidney transplants and 3000 living donor transplants in the United States. Table 276-1 shows an increase in numbers of transplants for deceased and living donors over the decade ending in 2003. Whereas deceased donor availability rose by 11%, the living donor rate more than doubled. The backlog of patients with end-stage renal disease (ESRD) has been increasing every year, and it always lags behind the number of available donors. In this decade, the size of the waiting list more than doubled, and the percentage of those on the waiting list receiving deceased donor transplants dropped from 28 to 14%. The increase in the living donor rate is in response to the demand; it continues to rise to exceed the number of deceased donor grafts. As there were 16,534 new registrants added to the waiting list in 1994 and 24,493 in 2003, demand will continue to exceed supply. Waiting lists continue to grow, and the average wait time for a cadaver kidney is now >4 years in many locations.

Table 276-1 Growth in Kidney Transplantation from 1994 to 2003 in the United States

	1994			2003		
	Number of Transplants	Size of Wait List	Patients Receiving Grafts, %	Number of Transplants	Size of Wait List	Patients Receiving Grafts, %
Deceased donor	7533	27,196	28	8389	57,211	14
Living donor	3007			6464		
Total	10,540			14,853		

Source: Data from Summary Tables, 2004 and 2005 Annual Reports, Scientific Registry of Transplant Recipients.

The overall results of transplantation are presented in Table 276-2 as the survival of grafts and of patients. At the 1-year mark, graft survival is higher for living donor recipients, most likely because those grafts are not subject to as much ischemic injury. The more powerful drugs now in use for immunosuppression have almost equalized the risk of graft rejection in all patients for the first year. At 5 and 10 years, however, there has been a steeper decline in survival of those with deceased-donor kidneys.

Table 276-2 Mean Rates of Graft and Patient Survivals for Kidneys Transplanted in the United States from 1992 to 2002^a

	1-Year Follow-Up		5-Year Follow-Up		10-Year Follow-Up	
	Grafts, %	Patients, %	Grafts, %	Patients, %	Grafts, %	Patients, %
Deceased donor	89	95	67	81	41	61
Living donor	95	98	80	90	56	76

^a All 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, 2004 and 2005 Annual Reports, Scientific Registry of Transplant Recipients.

RECIPIENT SELECTION

There are few absolute contraindications to renal transplantation. The transplant procedure is relatively noninvasive, as the organ is placed in the inguinal fossa without entering the peritoneal cavity. Recipients without perioperative complications can often be discharged from the hospital in excellent condition within 5 days of the operation.

Virtually all patients with ESRD who receive a transplant have a higher life expectancy than risk-matched patients who remain on dialysis. Even though diabetics and older candidates have a higher mortality rate than other transplant recipients, their survival is improved with transplantation compared

with remaining on dialysis. This global benefit of transplantation as a treatment modality poses substantial ethical issues for policy makers, as the number of deceased kidneys available is far from sufficient to meet the current needs of the candidates. The current standard of care is that the candidate should have a life expectancy of >5 years to be put on a deceased organ wait list. Even for living donation, the candidate should have >5 years of life expectancy. This standard has been established because the benefits of kidney transplantation over dialysis are realized only after a perioperative period in which the mortality is higher in transplanted patients than in dialysis patients with comparable risk profiles.

All candidates must have a thorough risk-versus-benefit evaluation prior to being approved for transplantation. In particular, an aggressive approach to diagnosis of correctable coronary artery disease, presence of latent or indolent infection (HIV, hepatitis B or C, tuberculosis), and neoplasm should be a routine part of the candidate workup. Most transplant centers consider overt AIDS and active hepatitis to be absolute contraindications to transplantation because of the high risk of opportunistic infection. Some centers are now transplanting individuals with hepatitis and even HIV infection under strict protocols to determine whether the risks and benefits favor transplantation over dialysis.

Among the few absolute "immunologic" contraindications to transplantation is the presence of a potentially harmful antibody against the donor kidney at the time of the anticipated transplant. Harmful antibodies that can cause very early graft loss 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) antigens. These antibodies are routinely excluded by proper screening of the candidate's ABO compatibility, HLA typing of donor and recipient, and direct cross-matching of candidate serum with lymphocytes of the donor.

DONOR SELECTION

Donors can be deceased or volunteer living donors. The latter are usually family members selected to have at least partial compatibility for HLA antigens. Living volunteer donors should be normal on physical examination and of the same major ABO blood group, because crossing major blood group barriers prejudices survival of the allograft. It is possible, however, to transplant a kidney of a type O donor into an A, B, or AB recipient. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries because the surgical procedure is difficult and the ischemic time of the transplanted kidney long when vascular abnormalities exist. Transplant surgeons are now using a laparoscopic method to isolate and remove the living donor kidney. This operation has the advantage of less evident surgical scars, and, because there is less tissue trauma, the laparoscopic donors have a substantially shorter hospital stay and less discomfort than those who have the traditional surgery. Deceased donors should be free of malignant neoplastic disease, hepatitis, and HIV because of possible transmission to the recipient. Increased risk of graft failure exists when the donor is elderly or has renal failure and when the kidney has a prolonged period of ischemia and storage.

In the United States, there is a coordinated national system of regulations, allocation support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. It is now possible to remove deceased donor kidneys and to maintain them for up to 48 h on cold pulsatile perfusion or simple flushing and cooling. This approach permits adequate time for typing, cross-

matching, transportation, and selection problems to be solved.

TISSUE TYPING AND CLINICAL IMMUNOGENETICS

Matching for antigens of the HLA major histocompatibility gene complex (Chap. 309) is an important criterion for selection of donors for renal allografts. Each mammalian species has a single chromosomal region that encodes the strong, or major, transplantation antigens, and this region on the human sixth chromosome is called *HLA*. HLA antigens have been classically defined by serologic techniques, but methods to define specific nucleotide sequences in genomic DNA are increasingly being used. Other "minor" antigens may play crucial roles, in addition to the ABH(O) blood groups and endothelial antigens that are not shared with lymphocytes. The Rh system is not expressed on graft tissue. Evidence for designation of HLA as the genetic region encoding major transplantation antigens comes from the success rate in living related donor renal and bone marrow transplantation, with superior results in HLA-identical sibling pairs. Nevertheless, 5% of HLA-identical renal allografts are rejected, often within the first weeks after transplantation. These failures represent states of prior sensitization to non-HLA antigens. Non-HLA minor antigens are relatively weak when initially encountered and are, therefore, suppressible by conventional immunosuppressive therapy. Once priming has occurred, however, secondary responses are much more refractory to treatment.

Living Donors

When first-degree relatives are donors, graft survival rates at 1 year are 5–7% greater than those for deceased-donor grafts. The 5-year survival rates still favor the partially matched (3/6 HLA mismatched) family donor over a randomly selected cadaver donor (Table 276-3). In addition, living donors provide the advantage of immediate availability. For both living and deceased donors, the 5-year outcomes are poor if there is a complete (6/6) HLA mismatch.

Table 276-3 Effect of HLA-A, -B, -DR Mismatching on Kidney Graft Survival

Degree of Donor Mismatch	1-Year Survival, %	5-Year Survival, %
Cadaver donor (all)	89.2	61.3
0/6-HLA mismatch	91.3	68.2
3/6-HLA mismatch	90.1	60.8
6/6-HLA mismatch	85.2	55.3
Living related donor (all)	94.7	76.0
0/6-HLA mismatch	96.7	87.0
3/6-HLA mismatch	94.3	73.2
6/6-HLA mismatch	92.7	57.7
Living unrelated donor	95.3	77.4

Note: 0-mismatched related donor transplants are virtually all from HLA-identical siblings, while 3/6-mismatched transplants can be one haplotype mismatched (1-A, 1-B, and 1-DR antigen) from parent, child or sibling; 6/6-HLA-mismatched living related kidneys are derived from siblings or relatives outside of the nuclear family.

The survival rate of living unrelated renal allografts is as high as that of perfectly HLA-matched cadaver

renal transplants and comparable to that of kidneys from living relatives. This outcome is likely a consequence of both short cold ischemia time and the extra care taken to document that the condition and renal function of the donor are optimal before proceeding with a living unrelated donation. It is illegal in the United States to purchase organs for transplantation.

Concern has been expressed regarding the potential risk to a volunteer kidney donor of premature renal failure after several years of increased blood flow and hyperfiltration per nephron in the remaining kidney. There are a few reports of the development of hypertension, proteinuria, and even lesions of focal segmental sclerosis in donors over long-term follow-up. Difficulties in donors followed for ≥ 20 years are unusual, however, and it may be that having a single kidney becomes significant only when another condition, such as hypertension, is superimposed. It is also desirable to consider the risk of development of type 1 diabetes mellitus in a family member who is a potential donor to a diabetic renal failure patient. Anti-insulin and anti-islet cell antibodies should be measured, and glucose tolerance tests should be performed in such donors to exclude a prediabetic state.

Presensitization

A positive cross-match of recipient serum with donor T lymphocytes representing anti-HLA class I is usually predictive of an acute vasculitic event termed *hyperacute rejection*. Patients with anti-HLA antibodies can be safely transplanted if careful cross-matching of donor blood lymphocytes with recipient serum is performed. The known sources of such sensitization are blood transfusion, prior transplant, and pregnancy. Patients sustained by dialysis often show fluctuating antibody titers and specificity patterns. At the time of assignment of a cadaveric kidney, cross-matches are performed with at least a current serum. Previously analyzed antibody specificities and additional cross-matches are performed accordingly. Techniques for cross-matching are not universally standardized; however, at least two techniques are employed in most laboratories. The minimal purpose for the cross-match is avoidance of hyperacute rejection mediated by recipient antibodies to donor HLA class I antigens. Sensitive tests, such as the use of flow cytometry, can be useful for avoidance of accelerated, and often untreatable, early graft rejection in patients receiving second or third transplants. Donor T lymphocytes, which express only class I antigens, are used as targets for detection of anti-class I (HLA-A and -B) antibodies. Preformed anti-class II (HLA-DR) antibodies against the donor carry a higher risk of graft loss as well, particularly in recipients who have suffered early loss of a prior kidney transplant. B lymphocytes expressing both class I and class II antigens are used in these assays. Non-HLA antigens restricted in expression to endothelium and sometimes monocytes have been described, but clinical relevance is not well established. A series of minor histocompatibility antigens do not elicit antibodies, and sensitization to these is detectable only by cytotoxic T cells, an assay too cumbersome for routine use. Desensitization prior to transplantation by reducing the level of antidonor antibodies via plasmapheresis of blood, administration of large doses of immunoglobulin, or both has been useful in reducing the hazard of hyperacute rejection.

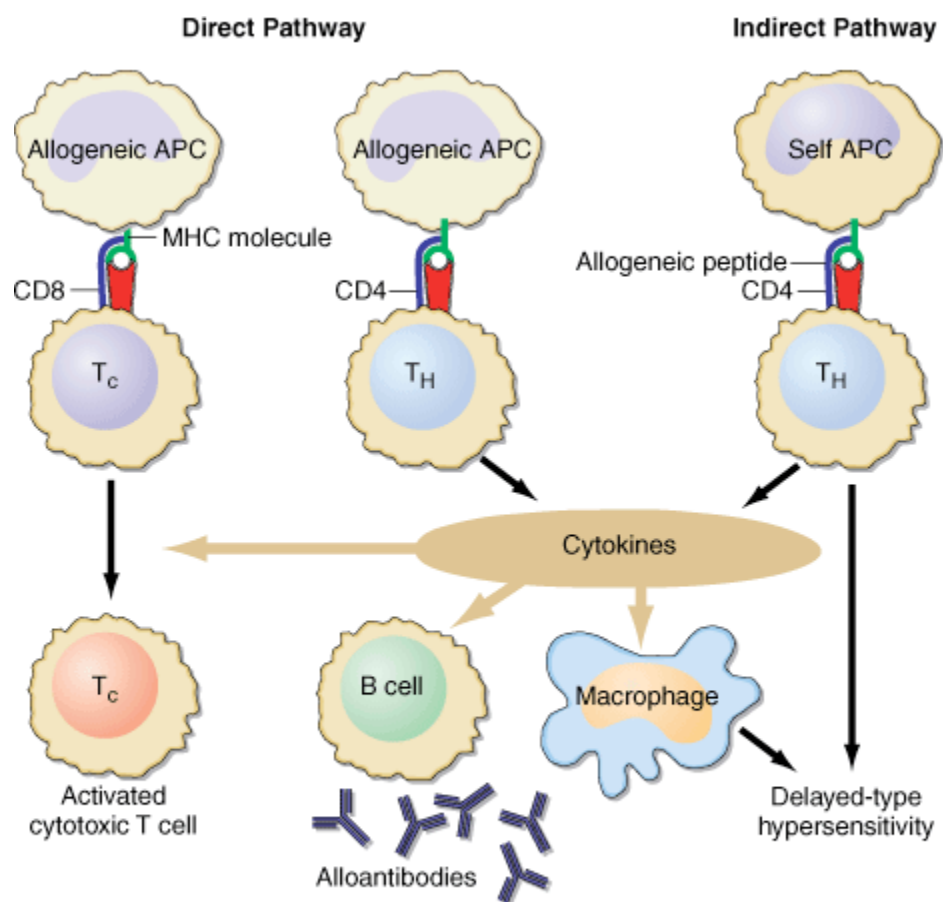
IMMUNOLOGY OF REJECTION

Both cellular and humoral (antibody-mediated) effector mechanisms can play roles in kidney transplant rejection. Antibodies can also initiate a form of antibody-dependent but cell-mediated cytotoxicity by recipient cells that bear receptors for the Fc portion of immunoglobulin.

Cellular rejection is mediated by lymphocytes that respond to HLA antigens expressed within the organ. The CD4⁺ lymphocyte responds to class II (HLA-DR) incompatibility by proliferating and releasing

proinflammatory cytokines that augment the proliferative response of both CD4+ and CD8+ cells. CD8+ cytotoxic lymphocyte precursors respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells. The cytotoxic effector ("killer") T cells cause organ damage through direct contact and lysis of donor target cells. The natural role of HLA antigen molecules is to present processed peptide fragments of antigen to T lymphocytes, the fragments residing in a "groove" of the HLA molecule distal to the cell surface. T cells can be directly stimulated by intact non-self HLA molecules expressed on donor parenchymal cells and residual donor leukocytes residing in the kidney interstitium. In addition, donor HLA molecules can be processed by a variety of donor or recipient cells capable of antigen presentation of peptides and then presented to T cells in the same manner as most other antigens. The former mode of stimulation is sometimes called *direct presentation* and the latter mode called *indirect presentation* (Fig. 276-1). There is evidence that non-HLA antigens can also play a role in renal transplant rejection episodes. Recipients who receive a kidney from an HLA-identical sibling can have rejection episodes and require maintenance immunosuppression, while identical twin transplants require no immunosuppression. There are documented non-HLA antigens, such as an endothelial-specific antigen system with limited polymorphism and a tubular antigen, that can be targets of humoral or cellular rejection responses, respectively.

Figure 276-1



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>

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Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T lymphocytes (T_H) 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 T_H 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 (T_C). 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 T_H cells are activated, they proliferate, and by secretion of cytokines and direct contact exert strong helper effects on macrophages, T_C , and B cells. (From Sayegh and Turka, Copyright 1998, Massachusetts Medical Society. All rights reserved.)

IMMUNOSUPPRESSIVE TREATMENT

Immunosuppressive therapy, as presently available, generally suppresses all immune responses, including those to bacteria, fungi, and even malignant tumors. In the 1950s when clinical renal transplantation began, sublethal total-body irradiation was employed. We have now reached the point where sophisticated pharmacologic immunosuppression is available, but it still has the hazard of promoting infection and malignancy. In general, all clinically useful drugs are more selective to primary than to memory immune responses. Agents to suppress the immune response are discussed in the following paragraphs, and those currently in clinical use are listed in Table 276-4.

Table 276-4 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	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Cyclosporine (CsA)	Lipid-soluble polypeptide, variable absorption, microemulsion more predictable	Trimolecular complex with cyclophilin and calcineurin \rightarrow block in cytokine (e.g., IL-2) production; however, stimulates TGF- β production	Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums
Tacrolimus (FK506)	Macrolide, well absorbed	Trimolecular complex with FKBP-12 and calcineurin \rightarrow block in cytokine (e.g., IL-2) production; may stimulate TGF- β production	Similar to CsA, but hirsutism/hyperplasia of gums unusual, and diabetes more likely
Azathioprine	Mercaptopurine analogue	Hepatic metabolites inhibit purine synthesis	Marrow suppression (WBC > RBC > platelets)

Agent	Pharmacology	Mechanisms	Side Effects
Mycophenolate mofetil (MMF)	Metabolized to mycophenolic acid	Inhibits purine synthesis via inosine monophosphate dehydrogenase	Diarrhea/cramps; dose-related liver and marrow suppression is uncommon
Sirolimus	Macrolide, poor oral bioavailability	Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation	Hyperlipidemia, thrombocytopenia

Note : IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; TGF, transforming growth factor; FKBP-12, FK506 binding protein 12; WBC, white blood cells; RBC, red blood cells.

Drugs

Azathioprine, an analogue of mercaptopurine, was for two decades the keystone to immunosuppressive therapy in humans but has now given way to more effective agents. This agent can inhibit synthesis of DNA, RNA, or both. Because cell division and proliferation are a necessary part of the immune response to antigenic stimulation, suppression by this agent may be mediated by the inhibition of mitosis of immunologically competent lymphoid cells, interfering with synthesis of DNA. Alternatively, immunosuppression may be brought about by blocking the synthesis of RNA (possibly messenger RNA), inhibiting processing of antigens prior to lymphocyte stimulation. Therapy with azathioprine in doses of 1.5–2.0 mg/kg per d is generally added to cyclosporine as a means of decreasing the requirements for the latter. Because azathioprine is rapidly metabolized by the liver, its dosage need not be varied directly in relation to renal function, even though renal failure results in retention of the metabolites of azathioprine. Reduction in dosage is required because of leukopenia and occasionally thrombocytopenia. Excessive amounts of azathioprine may also cause jaundice, anemia, and alopecia. If it is essential to administer allopurinol concurrently, the azathioprine dose must be reduced. As inhibition of xanthine oxidase delays degradation, this combination is best avoided.

Mycophenolate mofetil (MMF) is now used in place of azathioprine in most centers. It has a similar mode of action and a mild degree of gastrointestinal toxicity but produces minimal bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection. Patients with hyperuricemia can be given allopurinol without adjustment of the MMF dose. The usual dose is 2–3 g/d in divided doses.

Glucocorticoids are important adjuncts to immunosuppressive therapy. Of all the agents employed, prednisone has effects that are easiest to assess, and in large doses it is usually effective for the reversal of rejection. In general, 200–300 mg prednisone is given immediately prior to or at the time of transplantation, and the dosage is reduced to 30 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. Many centers have protocols for early discontinuance or avoidance of steroids because of long-term adverse effects on bone, skin, and glucose metabolism. For treatment of acute rejection, methylprednisolone, 0.5–1.0 g IV, is administered immediately upon diagnosis of beginning rejection and continued once daily for 3 days. When the drug is effective, the results are usually apparent within 96 h. Such "pulse" doses are not effective in chronic rejection. Most patients whose renal function is stable after 6 months or a year

do not require large doses of prednisone; maintenance doses of 10–15 mg/d are the rule. Many patients tolerate an alternate-day course of steroids without an increased risk of rejection. A major effect of steroids is on the monocyte-macrophage system, preventing the release of interleukin (IL) 6 and IL-1.

Cyclosporine is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for IL-2 and other proinflammatory cytokines, thereby inhibiting T cell proliferation. Although it works alone, cyclosporine is more effective in conjunction with glucocorticoids and MMF. Clinical results with tens of thousands of renal transplants have been impressive. Of its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, diabetes), only nephrotoxicity presents a serious management problem and is further discussed below.

Tacrolimus (previously called 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. De novo diabetes mellitus is more common with tacrolimus. The drug was first used in liver transplantation and may substitute for cyclosporine entirely or be tried as an alternative in renal patients whose rejections are poorly controlled by cyclosporine.

Sirolimus (previously called rapamycin) is another fungal macrolide but has a different mode of action, i.e., it inhibits T cell growth factor signaling pathways, preventing the response to IL-2 and other cytokines. Sirolimus can be used in conjunction with cyclosporine or tacrolimus, or with MMF, to avoid calcineurin inhibitors. Its use with tacrolimus alone shows promise as a steroid-sparing regimen, especially in patients who would benefit from pancreatic islet cell transplantation, where steroids have an adverse effect on islet survival.

Antibodies to Lymphocytes

When serum from animals made immune to host lymphocytes is injected into the recipient, a marked suppression of cellular immunity to the tissue graft results. The action on cell-mediated immunity is greater than on humoral immunity. A globulin fraction of serum [antilymphocyte globulin (ALG)] is the agent generally employed. For use in humans, peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas have been injected into horses, rabbits, or goats to produce antilymphocyte serum, from which the globulin fraction is then separated. A rabbit antithymocyte globulin (Thymoglobulin) is the most common agent currently in use. Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. OKT3 is directed to the CD3 molecules that form a portion of the T cell antigen-receptor complex and is thus expressed on all mature T cells.

Another approach to more selective therapy is to target the 55-kDa alpha chain of the IL-2 receptor, expressed only on T cells that have been recently activated. Two such antibodies to the IL-2 receptor, in which either a chimeric protein has been made between mouse Fab with human Fc (basiliximab) or the antibody has been "humanized" by splicing the combining sites of the mouse into a molecule that is 90% human IgG (daclizumab), are in use for prophylaxis of acute rejection in the immediate posttransplant period. They are effective at decreasing the acute rejection rate and have few adverse side effects.

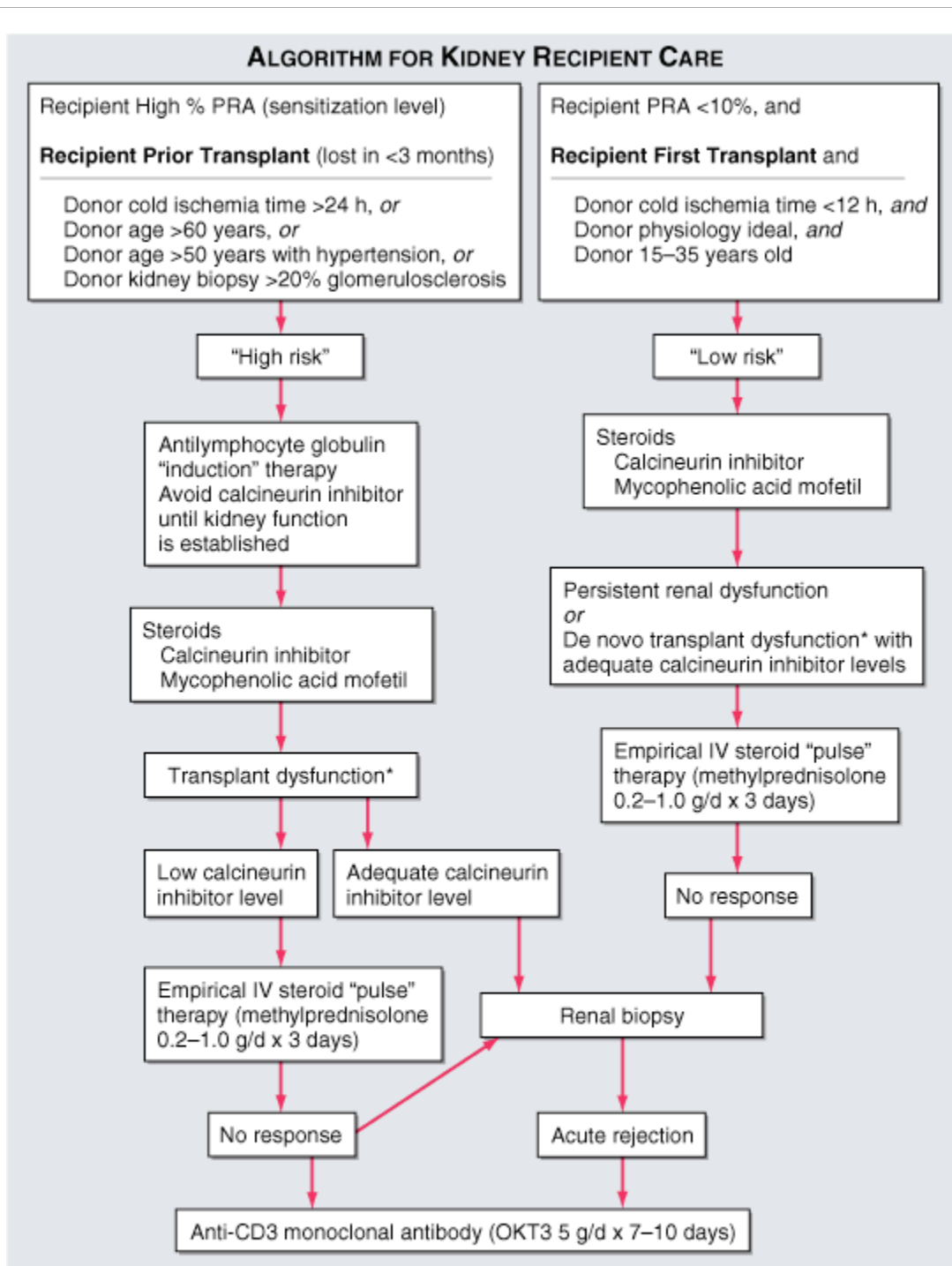
More recently, two new strategies have involved administration of engineered biologic agents: a depleting T cell antibody (alemtuzumab) as induction therapy to minimize maintenance immunosuppression, and a fusion protein (LEA29Y) to block B7 T cell co-stimulatory signals. The latter has shown promise in phase 2 trials and is currently being tested in phase 3 trials in kidney

transplantation.

CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT

Adequate hemodialysis should be performed within 48 h of surgery, and care should be taken that the serum potassium level is not markedly elevated so that intraoperative cardiac arrhythmias can be averted. The diuresis that commonly occurs postoperatively must be carefully monitored; in some instances, it may be massive, reflecting the inability of ischemic tubules to regulate sodium and water excretion; with large diureses, massive potassium losses may occur. Most chronically uremic patients have some excess of extracellular fluid, and it is useful to maintain an expanded fluid volume in the immediate postoperative period. Acute tubular necrosis (ATN) may cause immediate oliguria or may follow an initial short period of graft function. ATN is most likely when cadaveric donors have been underperfused or if the interval between cessation of blood flow and organ harvest (warm ischemic time) is more than a few minutes. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Superimposition of rejection on ATN is common, and the differential diagnosis may be difficult without a graft biopsy. Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is drastically reduced. Many centers avoid starting cyclosporine for the first several days, using ALG or a monoclonal antibody along with MMF and prednisone until renal function is established. Figure 276-2 illustrates an algorithm followed by many transplant centers for early posttransplant management of recipients at high or low risk of early renal dysfunction.

Figure 276-2



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>

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A typical algorithm for early posttransplant care of the 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. Patients at higher risk of rejection or early ischemic and nephrotoxic transplant dysfunction are often induced with an antilymphocyte globulin to provide more potent early immunosuppression or to spare calcineurin nephrotoxicity. *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.

The Rejection Episode

Early diagnosis of rejection allows prompt institution of therapy to preserve renal function and to prevent irreversible damage. Clinical 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.

Doppler ultrasonography or magnetic resonance angiography may be useful in ascertaining changes in the renal vasculature and in renal blood flow, even in the absence of changes in urinary flow.

Thrombosis of the renal vein occurs rarely; it may be reversible if caused by technical factors and intervention is prompt. Diagnostic ultrasound is the procedure of choice to rule out urinary obstruction or to confirm the presence of perirenal collections of urine, blood, or lymph. When renal function has been good initially, a rise in the serum creatinine level is the most sensitive and reliable indicator of possible rejection and may be the only sign.

Calcineurin inhibitors (cyclosporine or tacrolimus) may cause deterioration in renal function in a manner similar to a rejection episode. In fact, rejection processes tend to be more indolent with these inhibitors, and the only way to make a diagnosis may be by renal biopsy. Calcineurin inhibitors have an afferent arteriolar constrictor effect on the kidney and may produce permanent vascular and interstitial injury after sustained high-dose therapy. Addition of angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs are likely to raise serum creatinine levels. The former are generally safe to use after the early months, while the latter are best avoided in all renal transplant patients. There is no universally accepted lesion that makes a diagnosis of calcineurin inhibitor toxicity, although interstitial fibrosis, isometric tubular vacuolization, and thickening of arteriolar walls have been noted by some. Basically, if the biopsy does not reveal moderate and active cellular rejection activity, the serum creatinine will most likely respond to a reduction in dose. Blood levels of drug can be useful if they are very high or very low but do not correlate precisely with renal function, although serial changes in a patient can be useful. If rejection activity is present in the biopsy, appropriate therapy is indicated. The first rejection episode is usually treated with IV administration of methylprednisolone, 500–1000 mg daily for 3 days. Failure to respond is an indication for antibody therapy, usually with OKT3 or antithymocyte globulin.

Biopsy may be necessary to confirm the presence of rejection; when evidence of antibody-mediated injury is present with endothelial injury and deposition of complement component C4d is detected by fluorescence labeling, one can usually detect the antibody in recipient blood. The prognosis is poor, and aggressive use of plasmapheresis, immunoglobulin infusions, or anti-CD20 monoclonal antibody (rituximab) that targets B lymphocytes is indicated.

Management Problems

The usual clinical manifestations of infection in the posttransplant period are blunted by immunosuppressive therapy. The major toxic effect of azathioprine is bone marrow suppression, which is less likely with MMF, while calcineurin inhibitors have no marrow effects. All drugs predispose to unusual opportunistic infections, however. The typical times after transplantation when the most

common opportunistic infections occur are tabulated in Table 276-5. The signs and symptoms of infection may be masked or distorted. Fever without obvious cause is common, and only after days or weeks may it become apparent that it has a viral or fungal origin. Bacterial infections are most common during the first month after transplantation. The importance of blood cultures in such patients cannot be overemphasized because systemic infection without obvious foci is frequent, although wound infections with or without urinary fistulas are most common. Particularly ominous are rapidly occurring pulmonary lesions, which may result in death within 5 days of onset. When these become apparent, immunosuppressive agents should be discontinued, except for maintenance doses of prednisone.

Table 276-5 The Most Common Opportunistic Infections in the Renal Transplant Recipient

Peritransplant (<1 month)	Late (>6 months)
Wound infections	<i>Aspergillus</i>
Herpesvirus	<i>Nocardia</i>
Oral candidiasis	BK virus (polyoma)
Urinary tract infection	Herpes zoster
Early (1–6 months)	Hepatitis B
<i>Pneumocystis carinii</i>	Hepatitis C
Cytomegalovirus	
<i>Legionella</i>	
<i>Listeria</i>	
Hepatitis B	
Hepatitis C	

Aggressive diagnostic procedures, including transbronchial and open lung biopsy, are frequently indicated. In the case of *Pneumocystis carinii* (Chap. 200) infection, trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice; amphotericin B has been used effectively in systemic fungal infections. Prophylaxis against *P. carinii* with daily or alternate-day low-dose TMP-SMX is very effective. Involvement of the oropharynx with *Candida* (Chap. 196) may be treated with local nystatin. Tissue-invasive fungal infections require treatment with systemic agents such as fluconazole. Small doses (a total of 300 mg) of amphotericin given over a period of 2 weeks may be effective in fungal infections refractory to fluconazole. Macrolide antibiotics, especially ketoconazole and erythromycin, and some calcium channel blockers (diltiazem, verapamil) compete with calcineurin inhibitors for P450 catabolism and cause elevated levels of these immunosuppressive drugs. Analeptics, such as phenytoin and carbamazepine, will increase catabolism to result in low levels. *Aspergillus* (Chap. 197), *Nocardia* (Chap. 155), and especially cytomegalovirus (CMV) (Chap. 175) infections also occur.

CMV is a common and dangerous DNA virus in transplant recipients. It does not generally appear until the end of the first posttransplant month. Active CMV infection is sometimes associated, or occasionally confused, with rejection episodes. Patients at highest risk for severe CMV disease are those without anti-CMV antibodies who receive a graft from a CMV antibody-positive donor (15% mortality).

Valganciclovir is a cost-effective and bioavailable oral form of ganciclovir that has been proven effective in both prophylaxis and treatment of CMV disease. Early diagnosis in a febrile patient with clinical suspicion of CMV disease can be made by determining CMV viral load in the blood. A rise in IgM antibodies to CMV is also diagnostic. Culture of CMV from blood may be less sensitive. Tissue invasion of CMV is common in the gastrointestinal tract and lungs. CMV retinopathy occurs late in the course, if untreated. Treatment of active CMV disease with valganciclovir is always indicated. In many patients immune to CMV, viral activation can occur with major immunosuppressive regimens.

The polyoma group (BK, JC, SV40) is another class of DNA viruses that can become dormant in kidneys and can be activated by immunosuppression. When reactivation occurs with BK there is a 50% chance of progressive fibrosis and loss of the graft within 1 year by the activated virus. The use of tacrolimus has been associated with the highest risk.

Renal biopsy is necessary for the diagnosis. There are promising results with leflunomide and cidofovir, but it is most important to reduce the immunosuppressive load.

The complications of glucocorticoid therapy are well known and include gastrointestinal bleeding, impairment of wound healing, osteoporosis, diabetes mellitus, cataract formation, and hemorrhagic pancreatitis. The treatment of unexplained jaundice in transplant patients should include cessation or reduction of immunosuppressive drugs if hepatitis or drug toxicity is suspected. Therapy in such circumstances often does not result in rejection of a graft, at least for several weeks. Acyclovir is effective in therapy of herpes simplex virus infections.

Chronic Lesions of the Transplanted Kidney

While 1-year transplant survival is excellent, most recipients experience progressive decline in kidney function over time thereafter. Chronic renal transplant dysfunction can be caused by recurrent disease, hypertension, cyclosporine or tacrolimus nephrotoxicity, chronic immunologic rejection, secondary focal glomerulosclerosis, 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 ACE inhibitors is thought to have a beneficial influence on the rate of progression of chronic renal transplant dysfunction. Renal biopsy can distinguish subacute cellular rejection from recurrent disease or secondary focal sclerosis.

MALIGNANCY

The incidence of tumors in patients on immunosuppressive therapy is 5–6%, or approximately 100 times greater than that in the general population of the same age range. The most common lesions are cancer of the skin and lips and carcinoma in situ of the cervix, as well as lymphomas such as non-Hodgkin's lymphoma. The risks are increased in proportion to the total immunosuppressive load administered and time elapsed since transplantation. Surveillance for skin and cervical cancers is necessary.

Other Complications

Hypercalcemia after transplantation may indicate failure of hyperplastic parathyroid glands to regress. Aseptic necrosis of the head of the femur is probably due to preexisting hyperparathyroidism, with aggravation by glucocorticoid treatment. With improved management of calcium and phosphorus metabolism during chronic dialysis, the incidence of parathyroid-related complications has fallen dramatically. Persistent hyperparathyroid activity may require subtotal parathyroidectomy.

Hypertension may be caused by (1) native kidney disease; (2) rejection activity in the transplant; (3) renal artery stenosis, if an end-to-end anastomosis was constructed with an iliac artery branch; and (4) renal calcineurin inhibitor toxicity. This toxicity may improve with reduction in dose. Whereas ACE inhibitors may be useful, calcium channel blockers are more frequently used initially. Amelioration of hypertension to the range of 120–130/70–80 mmHg should be the goal in all patients.

While most transplant patients have a robust production of erythropoietin and normalization of hemoglobin, *anemia* is commonly seen in the posttransplant period. Often the anemia is attributable to bone marrow-suppressant immunosuppressive medications such as azathioprine, MMF, or sirolimus. Gastrointestinal bleeding is a common side effect of high-dose and long-term steroid administration. Many transplant patients have creatinine clearances of 30–50 mL/min and can be considered in the same way as other patients with chronic renal insufficiency for anemia management, including supplemental erythropoietin.

Chronic hepatitis, particularly when due to hepatitis B virus, can be a progressive, fatal disease over a decade or so. Patients who are persistently hepatitis B surface antigen-positive are at higher risk, according to some studies, but the presence of hepatitis C virus is also a concern when one embarks on a course of immunosuppression in a transplant recipient.

Both chronic dialysis and renal transplant patients have a higher incidence of death from myocardial infarction and stroke than does the population at large, and this is particularly true in diabetic patients. Contributing factors are the use of glucocorticoids and sirolimus, as well as hypertension. Recipients of renal transplants have a high prevalence of coronary artery and peripheral vascular diseases. The percentage of deaths from these causes has been slowly rising as the numbers of transplanted diabetic patients and the average age of all recipients increase. More than 50% of renal recipient mortality is attributable to cardiovascular disease. In addition to strict control of blood pressure and blood lipid levels, close monitoring of patients for indications of further medical or surgical intervention is an important part of management.

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