hyperkalemia, seizures, exacerbation of gout, dyslipidemia, and gingival hypertrophy. The most significant of these effects is nephrotoxicity, and this is often related to decreased glomerular blood flow. *Tacrolimus* has a mechanism of action and side-effect profile similar to those of cyclosporine but with the additional problems of hyperglycemia and an increased tendency toward neurotoxicity. Both cyclosporine and tacrolimus can cause calcineurin inhibitor nephrotoxicity, which may contribute to chronic allograft nephropathy and, ultimately, graft loss.

Mycophenolate mofetil (also called *mycophenolic acid*) specifically inhibits proliferation of T and B lymphocytes by interfering with purine synthesis and thus DNA synthesis. Side effects include anemia and leucopenia as well as gastrointestinal symptoms.

Rapamycin is a macrolide antibiotic produced by the fungus *Streptomyces hygroscopicus.* Rapamycin binds to the mTOR (mammalian target of rapamycin) receptor, thus blocking the phosphorylation of p70 S6 kinase (RBS6KB1) and the eukaryotic initiation factor 4E–binding protein 1 (EIF4EBP1, also known as phosphorylated heat- and acid-stable protein regulated by insulin 1 [PHAS-1]). This action leads to the dampening of cytokine and growth factor activity on T, B, and nonimmune cells. The major side effects are thrombocytopenia and dyslipidemia.

Because of the persistence of episodes of rejection and graft loss over time, novel immunosuppressive agents continue to be developed. Most recently, *belatacept*, a fusion protein that inhibits T-cell activation by blocking the CD80 and CD86 sites on antigen-presenting cells. Clinical trials have established its efficacy and demonstrated a side effect profile similar to those of existing immunosuppression options, leading to its approval for use in the United States and other regions.

Acute Rejection

T lymphocytes recognize foreign antigens, especially when they are presented in association with class II major histocompatibility complex (MHC) antigens. This prompts lymphocyte activation. Activated cytotoxic lymphocytes invade the tubular interstitial region of the transplanted kidney, with resulting tubulitis. Clinically, acute rejection is detected by graft tenderness, a rise in serum creatinine levels, oliguria, and, in some instances, fever. Acute humoral rejection involves the intrarenal arteries and leads to vasculitis, carrying a poor prognosis. This type of rejection is often resistant to steroids, necessitating antilymphocyte and possibly plasmapheresis therapy.

Post-transplantation Infection

Infection is second only to cardiovascular disease as the leading cause of mortality in kidney transplant recipients. Prophylaxis therapies are often used immediately after kidney transplantation to prevent infectious diseases that are of particularly high risk, including *Pneumocystis jirovecii* pneumonia, urinary tract infections, and cytomegalovirus infection. In addition to common community-acquired bacterial and viral infections, kidney transplant recipients are susceptible to numerous viral, fungal, and other opportunistic infections that usually do not cause severe illness in an immunocompetent host.

Post-transplantation Malignant Disease

Immunosuppression increases the risk of developing malignant disease; this is thought to be, in part, the result of impaired immune surveillance. Skin cancer (mostly squamous cell) has the highest incidence of any type of malignancy among transplant recipients. With continuous surveillance and aggressive management, metastasis from skin cancers is rare. Transplant recipients are also at high risk for development of non-Hodgkin's lymphoma and Kaposi's sarcoma. In addition to age-appropriate screening, cancer surveillance should be an essential part of post-transplantation care.

PROGNOSIS

The prognosis of CKD varies depending on the underlying cause, severity at presentation, and response to therapy. Moreover, CKD in general is a significant risk factor for cardiovascular disease and death. Mortality from cardiovascular disease in CKD patients, especially those with stage 3 to stage 5 disease, is 3.5 times that of an age-matched population (E-Fig. 32-8), accounting for more than 50% of the deaths in ESRD patients. Research to understand the underlying mechanisms and final pathway, as well as those effects specific to patients with unique characteristics, are necessary to advance efforts to reduce related risks and cure kidney disease.

For a deeper discussion on this topic, please see Chapter 130, "Chronic Kidney Disease," in Goldman-Cecil Medicine, *25th Edition.*

SUGGESTED READINGS

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