New techniques

**FIGURE 9-8**
Fine-needle aspiration cytology technique for the transplanted kidney. A 23- or 25-gauge spinal needle is used under aseptic conditions. A 20-mL syringe containing 5 mL of RPMI-1640 tissue culture medium is connected to the needle. Ultrasound guidance may be used on the rare occasions when the graft is not easily palpable [8].

Monitoring of other products of inflammation such as neopterin and lymphokines continues to be explored. It has been shown that acute rejection is associated with elevated plasma interleukin (IL)-1 in azathioprine-treated patients and IL-2 in cyclosporine-treated patients. IL-6 is also increased in the serum and urine immediately after transplantation and during acute rejection episodes. The major problem, however, is that infection, particularly viral, can also elevate cytokine levels. Recently, polymerase chain reaction (PCR) has also been used to detect mRNA for IL-2 in fine-needle aspirate of human transplant kidney [7,8]. Using the PCR approach, IL-2 could be detected 2 days before rejection was apparent by histologic or clinical criteria. Reverse transcriptase–PCR has also been used to identify intrarenal expression of cytotoxic molecules (granzyme B and perforin) and immunoregulatory cytokines (IL-2, -4, -10, interferon gamma, and transforming growth factor-β1) in human renal allograft biopsy specimens [9]. Molecular analyses revealed that intragraft display of mRNA encoding granzyme B, IL-10, or IL-2 correlates with acute rejection, and intrarenal expression of transforming growth factor (TGF)-β1 mRNA is associated with chronic rejection. These data suggest that therapeutic strategies directed at the molecular correlates of rejection might refine existing antirejection regimens.

Treatment

**FIGURE 9-9**
Immunosuppressive therapy protocols. Standard immunosuppressive therapy in renal transplant recipient consists of 1) baseline therapy to prevent rejection, and 2) short courses of antirejection therapy using high-dose methylprednisolone, monoclonal antibodies or polyclonal antisera such as antilymphocyte globulin (ALG) and antithymocyte globulin (ATG). 

Antilymphocyte globulin is prepared by immunizing rabbits or horses with human lymphoid cells derived from the thymus or cultured B-cell lines. Disadvantages of using polyclonal ALS include lot-to-lot variability, cumbersome production and purification, nonselective targeting of all lymphocytes, and the need to administer the medication via central venous access. Despite these limitations, ALG has been used both for prophylaxis against and for the primary treatment of acute rejection. A typical recommended dose for acute rejection is 10 to 15 mg/kg daily for 7 to 10 days. The reversal rate has been between 75% and 100% in different series. In contrast to murine monoclonal antibodies (eg, OKT3), ALS does not generally induce a host antibody response to the rabbit or horse serum. As a result, there is a greater opportunity for successful readministration.
**A. INDUCTION PROTOCOLS**

- Standard induction
- Corticosteroids
- Azathioprine or mycophenolate
- Cyclosporine or FK506
- Antibody induction
  - OKT3 or antithymocyte gamma globulin

**B. MAINTENANCE IMMUNOSUPPRESSION**

- Cyclosporine or FK506
- Mycophenolate
- Prednisolone

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**FIGURE 9-10**

Induction (panel A) and maintenance (panel B) immunosuppression protocols. These immunosuppressive protocols differ from center to center. There are numerous variations, but the essential features are 1) the prednisone dosage is high initially and then reduced to a maintenance dose of 10 to 15 mg/d over 6 to 9 months, and 2) the cyclosporine dosage is 8 to 12 mg/kg/d given as a single or twice daily dose, and dosage is adjusted according to trough plasma and serum blood levels. To maintain immunosuppression provided by cyclosporine and to reduce the incidence of cyclosporine side effects, azathioprine or mycophenolate has also been used with lower dosages of cyclosporine. The results of this triple therapy are excellent, with first-year graft survival greater than 85% reported in most instances and with a substantial number of patients having no rejection at all. Although this type of regimen was the most common, there have been a number of exceptions [2,10]. Recently, mycophenolate mofetil has been approved by the US Food and Drug Administration for prophylaxis of renal transplant rejection [11]. This agent was developed as a replacement to azathioprine for maintenance immunosuppression. FK506 is a new immunosuppressive agent that has been approved by the FDA. FK506 is similar to cyclosporine in its mode of action, efficacy, and toxicity profile. The drug has been used in kidney transplantation. FK506 may be beneficial in renal transplantation as rescue therapy in patients taking cyclosporine who have recurrent or resistant rejection episodes [12–14].

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**FIGURE 9-11**

Mechanism of action of immunosuppressive drugs. A, The sites of action of the commonly used immunosuppressive drugs. Immunosuppressive drugs interfere with allograft rejection at various sites in the rejection pathways. Glucocorticoids block the release of interleukin (IL)-1 by macrophages, cyclosporine (CsA) and FK506 interfere with IL-2 production from activated helper T cells, and azathioprine (AZA) and mycophenolate mofetil (MPA) prevent proliferation of cytotoxic and helper T cells.

(Continued on next page)
Transplant Rejection and its Treatment

A. ANTIREJECTION THERAPY REGIMENS

Intravenous methylprednisolone, 0.5 or 1 g x 3 d
OKT3
Antithymocyte gamma globulin
Rabbit antithymocyte globulin
Humanized anti-CD25 (IL-2 receptor) intravenously every 2 wk
Anti-ICAM-1 and anti-LFA-1 antibodies

B. ACUTE REJECTION TREATMENT ALGORITHM

Treatment algorithm for acute rejection

Acute rejection
Mild
Steroid bolus
Resolves
Severe
Rising creatinine
OKT3 or polyclonal antibodies x 10 d
Resolves
Persistent acute rejection on repeat biopsy
Evaluate OKT3 antibody titer
Low
ATG or OKT3
High
ATG

FIGURE 9-11 (Continued)

B, Mechanism of action of CsA, FK506, and rapamycin (RPM). CsA and FK506 block the transduction of the signal from the T-cell receptor (TCR) after it has recognized antigen, which leads to the production of lymphokines such as IL-2, whereas RPM blocks the lymphokine receptor signal, e.g., IL-2 plus IL-2 receptor (IL-2R), which leads to cell proliferation.

The addition of a prophylactic course of antithymocyte globulin (ATG) or OKT3 with delay of the administration of CsA or FK506 during the initial postoperative periods has been advocated by some groups. OKT3 prophylaxis was associated with a lower rate of early acute rejection and fewer rejection episodes per patient. Prophylactic use of these agents appears to be most effective in high-risk cadaver transplant recipients, including those who are sensitized or who have two HLA-DR mismatches or a prolonged cold ischemia time [2,10]. IFN-γ—interferon gamma; TNF-α—tumor necrosis factor-α.