Liver Transplantation
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David H. Van Thiel
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During the past decade, liver transplantation advanced rapidly to the forefront of therapies available for patients with end-stage liver disease and has had a dramatic impact on the practice of hepatology. Advances in immunosuppression, refinement of surgical technique, new methods of organ procurement and preservation, improved perioperative patient care, new agents for prophylaxis and treatment of opportunistic infection, and wider public and professional acceptance of voluntary cadaveric organ donation have all contributed significantly to the progress in this field.

Figure 43-1 demonstrates the linear increase in case experience in Europe and the United States during the last 5 years of the 1980s. Since October 1, 1987, a national liver transplant registry has been maintained by the United Network for Organ Sharing, which operates under federal contract as the national organ sharing and procurement network. Through December 1989, 66 transplant centers had reported 4193 liver transplantations in 3610 patients (Fig. 43-2). During the same period, 2706 patients in 26 liver transplantations in 2706 patients (Fig. 43-3).

Indications for Liver Transplantation

Liver transplantation is performed for many diseases that lead to irreversible acute and chronic liver failure, for which no reasonable medical or surgical alternative therapy exists. In both Europe and the United States, the leading indications for liver replacement are cirrhosis, cholestatic liver disease (primary biliary cirrhosis [PBC], sclerosing cholangitis, biliary atresia), inborn errors of metabolism, fulminant hepatic failure, and neoplasms (Fig. 43-4). Among the patients with cirrhosis, posthepatitic and alcoholic cirrhosis are the most common types for which liver transplantation is performed (Fig. 43-5). Patient survival rates after liver transplantation in the United States and Europe for common indications are summarized in Table 43-1.

PARENCHYMAL LIVER DISEASE

Postnecrotic Cirrhosis

Patient survival rates after liver transplantation for postnecrotic cirrhosis, excluding hepatitis B surface antigen (HBsAg)-positive patients, are 73% to 75% at 1 year and 67% to 73% at 2 years (see Table 43-1). The hepatitis C virus (HCV), a ribonucleic acid virus recently cloned by Choo and associates, is believed to be the agent responsible for most cases of transfusion-related non-A, non-B hepatitis. The precise incidence of posttransplantation HCV-related hepatitis is not known, but preliminary studies from the Mayo Clinic suggest that HCV is an important cause of posttransplantation chronic hepatitis and that a significant proportion of cases represent recurrent HCV-related disease.

Reinfection after liver transplantation in HBsAg-positive patients is common, and overall patient and graft survival rates have not been as high as for other forms of cirrhosis. Although many patients enjoy a prolonged period of rehabilitation after liver transplantation for hepatitis B virus (HBV)-related cirrhosis, most retain the carrier state, and there is a high reinfection rate. At the University of Pittsburgh, 1- and 2-year patient survival rates for postnecrotic cirrhosis in HBsAg-negative patients are 76% and 73%, respectively, but the same rates for HBsAg-positive patients are 58.6% and 48.6%, respectively. Registry survival rates in Europe (68% at 2 years) have been better than survival rates reported in the United States (43% at 2 years) in HBsAg-positive patients for reasons that are not known but that may relate to differences in strategies used to alter the incidence and course of HBV infection.

Several approaches have been reported to alter the course of HBV reinfection of a liver allograft, including active immunization with hepatitis vaccine, passive immunization with hyperimmune globulin, and immunomodulation with α-interferon. In some of these reports, there was evidence that perioperative and postoperative therapy with hyperimmune globulin may delay the reappearance and, in some cases, provide long-term clearance of HBsAg. Further trials of long-term passive immunophrophylaxis appear warranted. On the other hand, treatment with α-interferon, which has shown some promise in altering the course of HBV infection in the nontransplantation situation, has yet to show any significant promise in transplant recipients.

Alcoholic Cirrhosis

Alcoholic cirrhosis is the most common cause of chronic liver disease in Western society. Because of the hazards associated with surgery in such patients and a high risk of recidivism, Laennec's cirrhosis had been considered a contraindication to liver transplantation. In fact, recent experience has shown that patient survival rates after liver transplan-
Indications for Liver Transplantation

2,500
2,000
1,500
1,000
500
0

EUROPE
USA

284 602 924 821 1,199 1,689 1,551 2,160

FIGURE 43.1 Liver transplantations performed per year in the United States and Europe, 1985 to 1989.

Recidivism for alcoholic cirrhosis are comparable with patient survival rates after liver transplantation for postnecrotic cirrhosis and cholestatic liver disease. Actual rates of recidivism are difficult to determine, since patient denial is common but not always truthful and objective pathology is not always available. Recidivism rates are probably higher than those published so far, but it is clear that the patients at greatest risk are those who are actively drinking just before transplantation. It is difficult to justify demanding a prolonged period of abstinence before transplantation, since many patients are too ill to wait. The excellent patient survival rates that have been achieved must now be matched by similar improvements in methods of rehabilitation and behavior modification.

CHOLESTATIC LIVER DISEASE

Sclerosing Cholangitis

Cholestatic liver diseases, including sclerosing cholangitis, PBC, and biliary atresia, are among the best established indications for liver transplantation, but issues remain concerning patient selection, alternative surgical procedures, and timing of transplantation.

Primary sclerosing cholangitis (PSC) is a progressive disease with a substantial morbidity and mortality, even when it is detected in asymptomatic patients. Although only a small percentage of patients with inflammatory bowel disease eventually develop PSC, as many as 70% of cases of sclerosing cholangitis have been associated with inflammatory bowel disease.
bowel disease. The disease is associated with an increased risk of cholangiocarcinoma. In patients with ulcerative colitis, there is also an increased risk of adenocarcinoma of the colon. Thus, the evaluation of patients with PSC should include a complete evaluation of the biliary tree and gastrointestinal tract. Multiple percutaneous or endoscopic brushings of the biliary tree are recommended. A negative brushing on one examination is insufficient, in our experience, to exclude the presence of biliary tract tumor.

Conventional biliary tract reconstructive surgery is advocated for cases that have not progressed to persistent jaundice, refractory cholangitis, secondary biliary cirrhosis, and portal hypertension, especially for patients in whom obstructive disease is limited to the hepatic duct bifurcation or extrahepatic biliary tree. Only a minority of patients may qualify for such surgery, given the usual distribution of the disease and its progressive nature. In a series of 178 cases recently reviewed by the Lahey Clinic, 71\% of patients had intrahepatic or diffuse disease. Although they reported some benefit of biliary surgery in 75\% of cases, subsequent operations were associated with a higher morbidity and mortality. Involvement of the extrahepatic bile ducts alone may be more common in patients without associated inflammatory bowel disease.

Survival after liver transplantation for PSC in patients free of cancer is comparable with survival after liver transplantation for other cholestatic liver diseases and for postnecrotic cirrhosis (see Table 43-1). Given the excellent results that are attainable with this form of surgery, we recommend conservative use of conventional biliary tract reconstructions, except in those patients without cirrhosis and portal hypertension and with distribution of disease that is easily approached. Reoperation should be avoided. Many patients who require biliary tract decompression but who probably will require
Indications for Liver Transplantation

1213

Posthepatitic

<table>
<thead>
<tr>
<th></th>
<th>EUROPE</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>991 patients</td>
<td>1,617 patients</td>
</tr>
</tbody>
</table>

Alcoholic

|   | 631 |

Autoimmune

|   | 175 |

Cryptogenic

|   | 528 |

Other

|   | 220 |

FIGURE 43.5 Causes of postnecrotic cirrhosis in patients receiving liver transplants in the United States and in Europe.

TABLE 43.1 Patient Survival Rates After Liver Transplantation in Europe and the United States

<table>
<thead>
<tr>
<th>Indication</th>
<th>Registry*</th>
<th>Patients</th>
<th>6 mo</th>
<th>12 mo</th>
<th>18 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
<td>ELTR</td>
<td>235</td>
<td>70</td>
<td>68</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>413</td>
<td>81</td>
<td>78</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>ELTR</td>
<td>102</td>
<td>79</td>
<td>76</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>319</td>
<td>85</td>
<td>81</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>ELTR</td>
<td>347</td>
<td>78</td>
<td>75</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>398</td>
<td>84</td>
<td>81</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>ELTR</td>
<td>353</td>
<td>61</td>
<td>59</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>385</td>
<td>65</td>
<td>61</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Postnecrotic cirrhosis'</td>
<td>ELTR</td>
<td>347</td>
<td>78</td>
<td>75</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>1536</td>
<td>76</td>
<td>73</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>HBsAg-positive</td>
<td>ELTR</td>
<td>164</td>
<td>89</td>
<td>75</td>
<td>72</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>204</td>
<td>72</td>
<td>64</td>
<td>55</td>
<td>43</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>ELTR</td>
<td>199</td>
<td>73</td>
<td>69</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>432</td>
<td>78</td>
<td>76</td>
<td>76</td>
<td>71</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>ELTR</td>
<td>38</td>
<td>85</td>
<td>61</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>40</td>
<td>87</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatoma</td>
<td>ELTR</td>
<td>279</td>
<td>67</td>
<td>58</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>UNOS</td>
<td>81</td>
<td>77</td>
<td>67</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

ELTR, European Liver Transplant Registry; UNOS, United Network for Organ Sharing; HBsAg, hepatitis B surface antigen.

*Based on actuarial patient survival data from the ELTR and the UNOS for the period October 1987 to December 1989. ELTR data provided courtesy of Professor Henri Bismuth.

*Except patients positive for HBsAg.
transplantation can be managed by percutaneous stenting until livers can be found.

The incidence of cholangiocarcinoma in patients with PSC has been similar, in our experience, in patients with and without associated inflammatory bowel disease. Results after liver transplantation for sclerosing cholangitis in patients with coexisting cholangiocarcinoma have been disappointing. In a series of 10 patients, 6 died of recurrent cancer, usually within 1 year of transplantation. Only three patients were alive at 4 months to more than 2 years at the time of the report. The role of aggressive adjunctive radiotherapy remains to be established.

Prior colectomy and ileostomy for ulcerative colitis were once considered contraindications to liver transplantation, but this is no longer true. In recent experience, these patients have fared well and most have not proved to be difficult technical cases. Patients in whom prior colectomy has not been performed may have persistent disease after transplantation, despite immunosuppression with regimens that usually include steroids. Careful surveillance for the development of adenocarcinoma is important and may necessitate subsequent colectomy. In a series of 36 patients given liver transplants for sclerosing cholangitis associated with ulcerative colitis, 2 patients died of recurrent cholangiocarcinoma that was not appreciated before transplantation and 2 patients were found to have adenocarcinoma of the colon 11 and 21 months after transplantation.

**Primary Biliary Cirrhosis**

Primary biliary cirrhosis has been one of the most common and most successful indications for liver transplantation. Although the disease has a higher prevalence in older patients, especially women, a number of compensating factors may contribute to the good outcome after liver transplantation. Most patients have had little, if any, upper abdominal surgery (prior cholecystectomy is the most common), and the large liver usually found in patients with PBC is easy to remove compared with the contracted, fibrotic organs encountered in many patients with postnecrotic cirrhosis. The recipient hepatic artery is often friable in patients with PBC and is easily damaged during dissection. Construction of a new inflow vessel using a donor arterial homograft has proved to be a safe and durable method of arterial reconstruction in patients with an unsuitable native vessel.

Several drugs, including colchicine, methotrexate, and cyclosporine, have been evaluated for their effects on the progression of bile duct damage and hepatic fibrosis in PBC. All have shown some efficacy, but their use has been limited by toxicity. Most recently, ursodeoxycholic acid (ursodiol) has shown promise in a multicenter controlled trial. Progression of disease is associated with jaundice, pruritus, fatigue, hepatic osteodystrophy, and, eventually, diminished hepatic synthetic function with hypoalbuminemia, peripheral edema, and prolonged prothrombin time. An increase in the progression of jaundice, total serum bilirubin level greater than 10 mg/dL, intractable pruritus, diminished hepatic synthetic function, advancing bone disease, and variceal hemorrhage have been good indicators of the need for transplantation. Several statistical models have favorably compared liver transplantation with other management strategies, and such models may be useful in management planning.

Development of esophageal varices is common and often the major life-threatening complication of PBC. In the Mayo Clinic experience, 31% of patients who initially presented without esophageal varices subsequently developed them. Of these, 48% had one or more episodes of hemorrhage. Of those who bled, 33% did so within 1 year of diagnosis and 41%, within 3 years. We consider a history of variceal bleeding to be a firm indication to evaluate the patient for liver transplantation.

Rehabilitation after liver transplantation typically is good to excellent. Encephalopathy, pruritus, and jaundice usually clear rapidly after successful liver transplantation. Skin xanthomas commonly regress within weeks. The deep skin pigmentation characteristic of patients with PBC may require several months to improve. Resolution of ascites depends on its severity before transplantation and on renal function. Variceal bleeding is rare after successful liver transplantation, since the new liver provides the ideal relief of portal hypertension. Particular attention must be paid to physical rehabilitation after liver transplantation to facilitate restoration of muscle mass and assist in recovery from bone disease. Hepatic osteodystrophy may be the most serious disabling complication of PBC and can be slow to improve after transplantation. Calcium and vitamin D supplements are routinely given, and braces to support patients with vertebral compression fractures frequently are used. Despite these measures, some patients experience a long-term disability from severe osteodystrophy. Patients should be cautioned about the risk of fractures.

Recurrence of PBC after liver transplantation was reported in three cases by the Cambridge group but has never been substantiated in our own experience. Antimitochondrial antibodies usually remain positive after transplantation, even without evidence of disease in the graft. The Cambridge group subsequently reported finding pathology resembling that seen in PBC in liver grafts of recipients who did not have PBC as their original disease. In a more recent study, the same group has reported liver biopsies taken beyond 1 year after transplantation for PBC showing features of the disease in 9 of 10 patients. In 50 biopsy specimens from patients without PBC, 12 showed similar features of bile duct damage but with other distinguishing findings not suggestive of PBC. Further study is needed to resolve this question, since it may be difficult to discriminate between findings suggestive of recurrent disease, possibly altered by immunosuppression, and bile duct damage from chronic rejection.

**Biliary Atresia**

About 60% of liver transplants performed in infants and children are for biliary atresia. Patient survival rates in the United States and Europe are 68% to 78% at 1 year and 68% to 75% at 5 years. Mortality is highest among small infants. Associated congenital anomalies are present in many of these children, including polysplenia, mid-gut malrotations, preduodenal portal vein, absent prerenal inferior vena cava with atypical continuation, situs inversus, symmetric liver, hepatic arterial anomalies, and pulmonary anomalies. These rarely preclude liver transplantation.

The role of biliary drainage procedures for biliary atresia, especially the Kasai portoenterostomy, is being reassessed now that liver transplantation is a realistic alternative. Success rates after hepaticoportoenterostomy vary from 30% to 60%, depending on the authors' definition of success and the length of follow-up. In essence, less than one third of patients experience a long-term benefit of operation. After 111 successful operations, Lilly and coworkers reported that 68 pa-
nally eventually died, including 55 from complications of liver failure. Only 35 surviving patients had normal to near-normal liver function. Grosfeld and colleagues\textsuperscript{31} reported successful results (clearing of jaundice) in 25\% of patients. In Gilles\textsuperscript{32} recent report on patients surviving at least 10 years after surgery for biliary atresia, it was stated that 80\% of children who underwent a Kasai procedure would eventually need liver transplantation.

Despite the limited prospects for avoiding liver transplantation, in properly selected patients, the Kasai procedure still deserves consideration. In patients in whom jaundice is cleared, normal growth and development can be expected.\textsuperscript{75} Even if liver transplantation is eventually needed, valuable time can be bought. Mortality after liver transplantation in small infants has been higher than for older children, mostly because of a higher incidence of technical complications, especially hepatic arterial thrombosis. Improved methods of arterial reconstruction and better preservation of the hepatic microcirculation are reducing this risk. Donor organs are also more difficult to find for young children. Piggyback placement of donor organs on the recipient vena cava (see later discussion) and reduced-size liver grafts are approaches to increase the number of organs suitable for use in young children.\textsuperscript{34,108,147}

The Kasai procedure is unlikely to succeed if performed beyond 120 days after birth, and the best chance of obtaining successful bile drainage is seen when operation is performed within 90 days of birth. Reoperation usually is fruitless if bile drainage is not achieved at a first operation. Cholangitis is the most troublesome complication seen in patients with successful drainage and has a significant mortality.\textsuperscript{146} Surgical modifications used to control this include creation of stomal vents and conduit intussusception valves. Valves. These procedures should be used with great discretion. A single Kasai procedure does not add significantly to the technical difficulty of liver transplantation, but additional procedures often do.

Despite a technically successful operation, persistent jaundice, especially a serum bilirubin greater than 10 mg/dL, and moderate jaundice with evidence of persistent portal hypertension (esophageal varices) are indications for liver transplantation.\textsuperscript{147}

Infants and children with biliary atresia usually present with severe nutritional deficiencies and growth retardation. Fat-soluble vitamin and zinc deficiencies are common in patients with cholestasis. Attention to nutritional requirements in these patients is important.\textsuperscript{24}

\section*{INBORN ERRORS OF METABOLISM}

After transplantation, a liver graft retains the synthetic functions of the donor. In fact, a defect in donor hepatic synthesis of a coagulation factor has been incidentally conferred on a recipient.\textsuperscript{33} Liver transplantation has been performed in both adults and children for various diseases based on inborn errors of hepatic metabolism.\textsuperscript{135,136} About 7\% of adults and 30\% of children have received transplants for these disorders, and patient survival has been high both in Europe and in the United States (see Table 43-1). In many of these conditions, such as Wilson's disease, \textalpha\textsubscript{1}-antitrypsin deficiency, tyrosinemia, and glycogen storage disease, the liver as well as other organs and tissues are affected by the disease. Correction of the metabolic defect is coincidental with treatment of the liver failure.

In other conditions, such as oxalosis (type I hyperoxal-uria),\textsuperscript{\textasteriskcentered,163} familial hypercholesterolemia,\textsuperscript{9} and protein C deficiency,\textsuperscript{18} the liver itself is essentially normal but fails to produce a critical metabolite, resulting in severe systemic disease that affects other organs and tissues. Both type A and type B hemophilia have also been corrected by liver transplantation, although many of the liver replacements in such patients were required because of viral hepatitis acquired as a result of exposure to contaminated blood products.\textsuperscript{27,41,84,96}

Experience with liver transplantation for inborn errors of metabolism has recently been reviewed by Starzl and co-workers\textsuperscript{138} and is reproduced in Table 43-2.

\section*{VASCULAR DISORDERS}

Acute Budd-Chiari syndrome with evidence of hepatocyte necrosis on liver biopsy may require portocaval or mesoaarial decompressive shunting.\textsuperscript{67} Chronic Budd-Chiari syndrome with hepatic fibrosis is an indication for liver replacement. Excellent patient survival rates and a low incidence of recurrent disease can be obtained if patients are maintained on permanent anticoagulation therapy after transplantation.\textsuperscript{17,54}

\section*{CANCER}

It was once hoped that liver transplantation would offer improved prospects for cure of patients with malignant hepatic or biliary tract neoplasms that could not be satisfactorily managed by subtotal resection of the liver. Indeed, patient survival early after liver transplantation for cancer of the liver or biliary tree is high. Unfortunately, recurrent cancer within 6 to 18 months of transplantation is common, even in patients in whom gross tumor appears to be confined to within the liver capsule and has not invaded the regional lymph nodes or the portal vein.\textsuperscript{68,76,105,111} Tumor histology, concurrent cirrhosis, lymph node involvement, and vascular invasion influence the frequency and rapidity of recurrence. The liver graft frequently is an early site of recurrence, suggesting that microscopic nests of metastatic cells serve as a source of malignant cells able to home back to and thrive in the favorable environment of the new liver in an immunosuppressed host.\textsuperscript{68}

Chronic viral hepatitis B, alcoholic cirrhosis, and hemochromatosis are associated with an increased incidence of hepatoma. Small, incidental tumors (less than 2.5 cm in diameter) may only be recognized at pathologic examination of the hepatectomy specimen, but such small lesions seldom are invasive and have a low incidence of recurrence.

Fibrolamellar hepatoma is a better differentiated histologic variant of hepatocellular carcinoma that is not associated with cirrhosis, alcohol abuse, chronic B virus hepatitis, or use of oral contraceptives and tends to occur in younger patients. These tumors usually recur more slowly after liver transplantation than do conventional hepatomas, and the chance of cure may be somewhat higher.\textsuperscript{97} Significant disease-free intervals have also been seen after liver transplantation for epithelioid hemangioendothelioma, but results after liver transplantation for most other sarcomatous neoplasms have been poor.

In children with tyrosinemia, progression to macronodular cirrhosis is associated with hepatoma formation. Therefore, transplantation of children with tyrosinemia before age 2 has been recommended.\textsuperscript{26}

Results in children with liver transplantation for hepatoblastoma have been encouraging, with 50\% survival reported.
**TABLE 43-2 Inborn Errors of Metabolism**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cause/Description</th>
<th>Correction of Metabolic Defect</th>
<th>Longest Survival</th>
<th>Associated Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>Structural abnormality of protease inhibitor synthesized in the liver</td>
<td>Yes</td>
<td>13 y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Abnormal biliary copper excretions, decreased copper binding to ceruloplasmin, copper accumulation in tissues. Autosomal recessive, gene mapped to chromosome 13</td>
<td>Yes</td>
<td>16½ y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>Fumaroylacetacetate hydrolase deficiency</td>
<td>Nearly complete</td>
<td>7½ y</td>
<td>Cirrhosis, hepatoma, Hepatomegaly, fibrosis, liver tumors</td>
</tr>
<tr>
<td>Type I glycogen storage disease</td>
<td>Glucose-6-phosphatase deficiency</td>
<td>Yes</td>
<td>7 y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Type IV glycogen storage disease</td>
<td>Amlyo-1,4-transglucosidase defect (branching enzyme)</td>
<td>Incomplete</td>
<td>4½ y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Genetic defect recently identified. Pancellular disease often affecting the liver</td>
<td>Not known</td>
<td>4½ y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Niemann-Pick disease</td>
<td>Sphingosineinase deficiency, sphingomyelin storage</td>
<td>Not known</td>
<td>2 y (died)</td>
<td>None</td>
</tr>
<tr>
<td>Sea-blue histiocytic syndrome</td>
<td>Unknown, neurovisceral lipochrome storage</td>
<td>No</td>
<td>7 y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Erythropoietic protoporphyria</td>
<td>Hepatic ferrochelatase deficiency, possible overproduction of protoporphyrin by erythropoietic tissues</td>
<td>Incomplete</td>
<td>1½ y</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome</td>
<td>Glucuronosyltransferase deficiency</td>
<td>Yes</td>
<td>4 y</td>
<td>None</td>
</tr>
<tr>
<td>Type I hyperoxaluria</td>
<td>Peroisominal alanine-glyoxalate aminotransferase deficiency</td>
<td>Yes</td>
<td>8 mo</td>
<td>None</td>
</tr>
<tr>
<td>Urea cycle enzyme deficiency</td>
<td>Ornithine carbamoyltransferase deficiency</td>
<td>Yes</td>
<td>8 mo</td>
<td>None</td>
</tr>
<tr>
<td>C protein deficiency</td>
<td>Defective C protein synthesis</td>
<td>Yes</td>
<td>2½ y</td>
<td>None</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>Low-density lipoprotein receptor deficiency, overproduction of low-density lipoprotein</td>
<td>Incomplete</td>
<td>6 y</td>
<td>None</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>Factor VIII deficiency</td>
<td>Yes</td>
<td>4 y</td>
<td>Cirrhosis as a complication of blood component therapy</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>Factor IX deficiency</td>
<td>Yes</td>
<td>6 mo</td>
<td>Cirrhosis as a complication of blood component therapy</td>
</tr>
</tbody>
</table>


at 24 to 70 months of follow-up in the US experience. 77 Unifocal and intrahepatic tumors, tumors without microscopic vascular invasion, and tumors with predominantly fetal rather than embryonal or anaplastic epithelium have the best prognosis. The tumor may respond to chemotherapy, but a larger experience with combined chemotherapy and transplantation is needed to determine efficacy. Resection of solitary metastases may also be beneficial. One child with a solitary pulmonary metastasis resected at 7 months after liver transplantation has remained tumor-free at 70 months of follow-up.

Dismal results have also been seen after liver transplantation for most lesions metastatic to the liver. Neuroendocrine tumors, however, may be more amenable to treatment, especially with techniques of extended total hepatectomy, which may also remove the insidious primary lesions. 79,158 New approaches are needed to improve the prospects for treatment of liver and biliary tract cancers with transplantation. In carefully selected cases, liver transplantation combined with aggressive application of chemotherapy or radiotherapy may yet offer some hope to those afflicted with these formidable lesions.
FULMINANT HEPATIC FAILURE

The management of fulminant hepatic failure (FHF) requires a high level of expertise. Early transfer to a liver unit where facilities for specialized monitoring, medical management, and transplantation services are available should be considered. Special precautions are necessary during patient transfer. Patients with encephalopathy above stage II level should be intubated to protect against aspiration. Survival depends on cause, expert care, and, in cases complicated by advanced stages of coma, cerebral edema, renal failure, or metabolic acidosis, prompt replacement of the liver.

The King's College Hospital Liver Unit found a strong correlation between survival (without transplantation) and the cause of FHF. Survival by etiologic group was fulminant hepatitis A, 66.7%; acetaminophen toxicity, 52.9%; fulminant hepatitis B, 38.9%; non-A, non-B hepatitis, 20.0%; and halothane or idiosyncratic hepatitis, 12.5%. Outcome was also correlated with complications, especially cerebral edema, oliguric renal failure, and uncompensated metabolic acidosis. Uncompensated metabolic acidosis was associated with less than 10% survival. Only 37% of patients in stage 4 coma and 50% of patients in stage 3 coma survived.

Of 42 patients who received liver transplants over a 7-year period for FHF in our Pittsburgh series, survival after transplantation for HBV-related disease was 87.5%; for non-A, non-B hepatitis, 63%; and for toxic hepatitis, 33.3%. Only 5 of 10 patients with stage IV encephalopathy who survived more than 1 week after transplantation had complete neurologic recovery. Vickers and colleagues also found a strong correlation between stage of encephalopathy and survival. Eighteen of 19 patients (95%) with stage I or II encephalopathy survived compared with only 13 of 38 patients (34%) with stage III or IV encephalopathy.

With prompt recognition of poor prospects for medical recovery and transfer to a liver transplant center, more than 50% of patients with FHF can be saved. Although this is not as good as can be achieved for patients with chronic liver failure, the results are a significant achievement, given the circumstances.

PATIENT SELECTION AND PREOPERATIVE MANAGEMENT

Evaluation of the candidate for liver transplantation includes establishment of the primary diagnosis, stage of disease, and prognosis; assessment of liver size and portal vein patency; and, in the case of patients with (or suspected of having) hepatic tumors, determination of the extent of disease. Most patients are referred to the transplant center with an established diagnosis and a poor prognosis without transplantation. A major gastrointestinal bleed, a history of repeated bouts of encephalopathy, progressive neuropathy, refractory ascites, a recent precipitous deterioration in liver function (eg, a recent increase in the rate of rise of serum bilirubin level), rapid progression of bone disease, spontaneous bacterial peritonitis, poor hepatic synthetic function, loss of liver volume, and progressive muscle wasting are indications for early transplantation.

Portal vein patency usually can be determined by ultrasonography or magnetic resonance imaging (MRI), but occasionally arteriography is necessary. MRI is probably the most reliable of the noninvasive screening studies for determining portal vein patency, but it is not always readily available. Portal vein thrombosis is not an absolute contraindication to liver transplantation, and venous phase arteriography may be necessary for adequate study of the mesenteric venous circulation. Computed tomography (CT) scans are useful to detect the presence of tumors, with or without extraportal extension, and can be used to determine liver volume. Upper gastrointestinal endoscopy to check for varices is indicated in patients who have not had such an examination within the past 3 months. We do not recommend prophylactic sclerotherapy if esophageal varices are present but the patient has no history of bleeding.

Patients with sclerosing cholangitis should have multiple endoscopic or percutaneous brushings of the biliary tree to evaluate for the presence of cholangiocarcinoma. Patients with liver masses detected by ultrasonography or CT scan should have an appropriate diagnostic evaluation for extrahepatic spread of disease. This includes CT examinations of the abdomen and chest and a bone scan. Blood tumor markers, including carcinoembryonic antigen, vitamin B12 binding protein, ferritin, α-fetoprotein, and PIKA-2, are also screened in our protocols for the management of suspected tumor. If a neuroendocrine lesion is suspected, appropriate tests for these neoplasms should be performed. Baseline studies in preparation for chemotherapy include electrocardiography, a multiple-gated acquisition heart scan, 24-hour creatinine clearance, and biopsy proof of tumor.

A complete serologic screen for hepatitis A, B, and C should be performed. All patients without demonstrable immunity to hepatitis B should receive a complete course of recombinant vaccine for HBV, before transplantation if feasible. As discussed previously, HBV carriers (HBsAg-positive) may benefit from administration of hyperimmune globulin beginning during surgery and continuing indefinitely.

Cyto megalovirus (CMV), varicella-zoster virus (VZV), and Toxoplasma immunoglobulin titers should be obtained as part of the pretransplantation evaluation. CMV infections, both primary infections and reactivation infections, are among the most common and most serious encountered after transplantation. Purified protein derivative (PPD) status must be known before transplantation. It is also important to know if the patient is anergic to other antigens, such as Trichophyton, Candida, or mumps. Antiviral and antitubercular prophylaxis are discussed in a later section.

Attention to the nutritional requirements of patients with liver failure is also important. Many such patients have severe deficiencies of fat-soluble vitamins and trace elements.

MANAGEMENT OF PORTAL HYPERTENSION

Asites

Refractory ascites can be a challenging management problem and can lead to serious complications, including spontaneous bacterial peritonitis and ulcerating umbilical hernia. Judicious use of diuretics and colloid is required, and large-
does not make liver transplantation prohibitive. Survival rates after liver transplantation in patients with or without a history of variceal hemorrhage and in those with or without a history of a shunt procedure are not significantly different.1,56

Finally, acutely bleeding patients can be managed by immediate liver transplantation. The transplant corrects the underlying liver disease and provides immediate portal decompression. Most patients stop bleeding once the graft is in place. Unfortunately, a suitable liver graft seldom is available on such an urgent basis.

CONTRAIINDICATIONS TO LIVER TRANSPLANTATION

There are few absolute contraindications to liver transplantation. Severe systemic conditions, not also amenable to medical or surgical correction, may contraindicate liver transplantation if the ability of the patient to withstand the stress of operation is in serious doubt, the life expectancy of the patient would not be significantly prolonged, or a poor quality of life would not be improved. Uncontrolled sepsis outside the liver or biliary tree, acute hemodynamic instability with compromise of other vital organs, active substance abuse, extraneoplastic or metastatic cancer (with some exceptions as noted previously), irreversible brain damage or neurologic dysfunction, and a history of behavioral or psychiatric disorders that would interfere with the patient's ability to comply with the necessary medical regimen are contraindications to liver transplantation. Spontaneous bacterial peritonitis that would interfere with the patient's ability to comply with the necessary medical regimen are contraindications to liver transplantation. Spontaneous bacterial peritonitis should be treated for at least 48 hours and preferably for 7 days before liver transplantation is attempted.

Advanced age was once considered to be a contraindication, but excellent results have recently been reported for patients over age 60.1,11 The oldest patient to receive a liver graft in Pittsburgh was 76 years old at the time of operation, and as of this writing, she is alive and well at age 81.

Most problematic is whether or not patients with positive serology for the human immunodeficiency virus (HIV) should be candidates for liver transplantation.17 A retrospective survey of stored sera from patients given liver transplants between 1981 and 1986 revealed a 2.6% incidence of HIV.5,12 HIV antibodies predated the transplantation in one third of these recipients, and the rest seroconverted afterward. Among the 10 children in the HIV-positive group, only 1 died of a complication related to HIV. Among the 16 adults in this series, the acquired immunodeficiency syndrome (AIDS)-related mortality was 37%.

It is clear that HIV positivity carries an increased risk of AIDS-related morbidity and mortality in the transplant population. Many patients who, despite evidence of past exposure to HIV, are still free of clinical manifestations of AIDS can receive substantial, prolonged benefit from liver transplantation. For these patients, the immediate threat is end-stage liver disease, not AIDS, and these patients can do well despite the risks of immunosuppression required for transplantation.

Intrapulmonary shunting with hypoxemia is a complication of advanced liver disease and sometimes has been considered a contraindication to liver transplantation. After transplantation, the shunts eventually close and the extrapulmonary manifestations reverse.13 In severe cases, this can take several months, and an extended period of ventilatory support may be required. Patients with significant pulmonary artery hypertension, however, usually cannot tolerate operation. Therefore right-sided heart catheterization should be performed before surgery to measure pulmonary artery pressure.

Patients with the most advanced degrees of muscle wasting and nutritional deprivation may be unable to survive liver
transplantation. If operation is attempted in severely debiliated patients, tracheostomy should be considered at the same time as transplantation, since these patients inevitably also require prolonged ventilatory as well as intensive nutritional support after surgery.

Organ Preservation

The University of Wisconsin (UW) preservation solution introduced in 1987 by Belzer and Southard represents the first major advance in liver preservation since the original descriptions of slush preservation more than a decade earlier. Using this solution, it has been possible to extend liver preservation from a mean preservation time of about 5 hours to 12 hours and to extend the limits of preservation out to at least 18 hours with comparable quality of graft function and a low incidence of primary graft failure. Although we have seen perfect liver function even with organs kept in cold storage in UW solution for 20 to 34 hours, the rate of retransplantation and the incidence of primary graft failure increase significantly with longer preservation times (Fig. 43-6). It is, therefore, recommended that organs be used within 20 hours of storage.

The practical benefits of longer preservation time are significant, and this has changed liver transplantation from an urgent operation to a semielective procedure in many cases. Patients have more time to be called in to the transplant center for surgery, and thus, more patients can wait at home. Grafts can be sent to transplant centers from distant sources. Surgeons can explore patients and have time to arrange for a backup patient if the intended recipient proves to be inoperable. The incidence of primary graft failure after liver transplantation is 5% to 10% in most reported series. There is no accepted and reliable test to predict which grafts will function and which will fail before implantation. Pretransplantation biopsies can be useful if certain findings are present. Significant fatty infiltration (macrovesicular steatosis), extensive ballooning of hepatocytes (hydropic degeneration), and pericentral and panlobular individual hepatocyte necrosis are associated with a higher risk of primary graft failure. In postperfusion biopsies, the presence of zonal or severe focal necrosis and a severe neutrophilic exudate (findings that may suggest hyperacute rejection) have been associated with a difficult postoperative course but not with inevitable graft failure. A normal pretransplantation biopsy is not a guarantee of graft viability, since irreversible subcellular ischemic damage may not be detectable with conventional histology.

Availability of a simple, rapid test for graft viability would significantly reduce the incidence of primary graft function. MEGX, a metabolite of lidocaine, has been compared favorably with other methods of assessment, such as indocyanine green clearance, and is easily and rapidly measured. It has shown some promise as a test of pretransplantation graft viability, but prognostic sensitivity and specificity are only about 75%. It may prove useful when used in combination with other parameters of graft quality.

Surgical Procedure

Details of the operative techniques of liver transplantation are beyond the intended scope of this chapter and have been addressed elsewhere. In brief, the operation is performed in four stages. The first stage, recipient hepatectomy, can be formidable if the patient has had extensive previous surgery in the upper abdomen, has a severe, uncorrectable coagulopathy, or has a small contracted liver. The second, an hepatic phase, during which the recipient vessels are anastomosed to the vessels of the graft, has been greatly facilitated in larger children and adults by routine use of a partial veno-venous bypass. The bypass effectively decompresses the systemic and mesenteric venous drainage and maintains delivery of an adequate blood volume to the right side of the heart during the period of interruption of the suprarenal inferior vena cava and portal vein. This reduces mesenteric venous congestion, renal vein hypertension, and bleeding from the usually rich and fragile venous collateral bed in patients with long-standing portal hypertension. The third phase begins on revascularization of the new liver, when both surgical and medical bleeding commonly is encountered, and requires considerable skill on the part of both the surgical and the anesthesia teams to control. Once hemostasis has been achieved, the final stage of the procedure, a biliary reconstruction, is performed.

INFERIOR VENA CAVA

In the conventional reconstruction, the suprahepatic vena cava of the graft is anastomosed end to end to a cuff of infra-diaphragmatic recipient inferior vena cava followed by anastomosis of the infrahepatic graft vena cava end to end to a cuff of suprarenal recipient inferior vena cava. The infrahepatic portion of the recipient vena cava is removed with the native liver. The right adrenal vein must be ligated, and this can lead to venous infarction of the gland with hemorrhage. An alternative to the standard technique is to piggyback the suprahepatic portion of the graft vena cava to the confluence of the recipient hepatic veins and oversew the infrahepatic end of the graft vena cava. The native liver is first
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carefully dissected off the recipient vena cava, which is left in place (Fig. 43-7). The right adrenal vein is, therefore, left intact. The end of the infrahepatic graft vena cava is simply oversewn.

The piggyback approach can be advantageous in selected cases in which the graft size is mismatched with the recipient or there is a large discrepancy in the diameter of the recipient and graft veins. It provides an alternative to the use of the veno-venous bypass, since the recipient vena cava is left in continuity, and is, therefore, a method of choice in patients in whom venous bypass cannot be used, such as patients with thrombosis of the subclavian veins after failed peritoneal-venous shunts. Care must be taken to avoid excessive traction on the vena cava during dissection, which might obstruct blood flow. The longer period of portal vein obstruction endured with this approach may predispose to translocation of infectious organisms from the gut during a period of splanchnic congestion and increase the risk of postoperative sepsis. The cuff of vena cava constructed from the recipient hepatic veins must be generous enough to provide for unobstructed outflow, and the liver must not be free to twist in the abdomen on the axis of the vena cava anastomosis.

Advanced cirrhosis may result in retrograde portal vein flow, which may progress to portal vein thrombosis. Thrombosis may involve only the main portal vein or may also involve the mesenteric or splenic veins (Fig. 43-8). This is also a potential complication of central or selective portosystemic shunting procedures. Cavernous transformation of the portal vein with generous venous collaterals in the hilum may develop, and ultrasonographers may mistake this high venous flow for a patent portal vein. Even if thrombosis of the portal vein does not occur, the vein wall may become diseased, rendering the vessel unsuitable for anastomosis.

FIGURE 43.7 The piggyback technique for implantation of a liver allograft with preservation of the recipient inferior vena cava. (A) After completion of the hilar dissection, the left lobe is rotated, individual hepatic veins are ligated, and the main hepatic veins are exposed. (B) If difficulty is encountered in exposing the hepatic veins, the parenchyma can be split and the veins controlled from inside the liver. (C) The hepatic vein cuffs are prepared for anastomosis. The middle and left hepatic veins usually are used for anastomosis and the right hepatic vein is oversewn, as shown here. (D) The completed implant lying on the intact recipient vena cava. The infrahepatic portion of the graft vena cava has been oversewn. (Tzakis A, et al. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg 210:649, 1989)
If the confluence of the mesenteric and splenic veins is suitable, a graft of iliac vein from the liver donor can be used to extend the recipient portal vein (Fig. 43-9). In rare cases, a large collateral vein, such as a coronary vein or a choledochal vein, has been used for anastomosis to the portal vein. In most patients, however, it is possible and preferable to construct a venous jump graft of donor iliac vein from either the superior mesenteric vein or one of its large branches, such as the right colic vein, to the graft portal vein (Fig. 43-10). This graft can be tunneled through the transverse mesocolon, over the pancreas, and beneath the pylorus to emerge in an ideal location for anastomosis, a route also used for arterial grafts. If venous phase arteriography fails to visualize a suitable mesenteric vein in a patient with portal vein thrombosis, it may be necessary to explore the patient to determine if such revascularization is feasible and to have a backup patient available if it is not.

HEPATIC ARTERY

Hepatic artery thrombosis is one of the most common and dreaded technical complications after liver transplantation. It is best prevented by meticulous surgical technique and liberal use of alternative reconstruction techniques if there is any doubt about the integrity of a conventional anastomosis. In most adult patients, the celiac artery of the graft is sewn end to end to the common hepatic artery of the recipient. In young children, the anastomosis may be placed closer to the recipient aorta at the level of the celiac axis. In about 12% of adults and 50% of children, the native recipient artery is unsuitable for anastomosis and a new hepatic artery must be reconstructed. This usually is performed by anastomosis of the donor hepatic or celiac artery to an iliac artery graft taken from the liver donor and placed on the anterior surface of the proximal infrarenal recipient aorta. The graft is tunneled
through the transverse mesocolon, over the pancreas, and behind the pylorus (Fig. 43-11) or posterior to the superior mesenteric artery, duodenum, and pancreas to emerge between the inferior vena cava posteriorly and the portal vein anteriorly.

**BILIARY RECONSTRUCTION**

When possible, direct end-to-end anastomosis of the recipient bile duct to the donor bile duct over a T-tube stent externalized through a stab wound in the distal recipient duct is the preferred method of biliary tract reconstruction (Fig. 43-12, inset). The ampulla of Vater is preserved and the T-tube permits monitoring of the quantity and quality of bile output and radiographic examination of the biliary tract. Progressive dilatation of the bile duct, presumably from spastic dysfunction of a denervated ampulla of Vater, is a common complication that can necessitate conversion to a Roux-en-Y choledochojejunostomy.Leaks and strictures are also important complications (discussed further under technical complications).

End-to-side anastomosis of the donor bile duct to a Roux-en-Y limb of proximal jejunum is the preferred alternative to duct-to-duct reconstruction and is the method of choice in patients with disease of the extrahepatic bile ducts (see Fig. 43-12). Although more complex, it has proved to be a durable and reliable method of reconstruction. Ascending cholangitis is uncommon after this reconstruction when properly performed. Bile leak after this reconstruction can be more serious than after duct-to-duct reconstruction because of open bowel contamination of the abdominal cavity. Contrast examination of the biliary tree requires percutaneous cholangiography.

Another technique of biliary reconstruction that uses the donor gallbladder as a conduit between the donor and the recipient bile ducts has a few advocates (Fig. 43-13). We have limited use of this reconstruction to highly selected cases when previous surgery has caused extensive scarring or previous extensive intestinal resection prohibits reconstruction of an appropriate Roux limb for choledochojejunostomy. In our experience, half of these reconstructions were complicated by biliary stones or sludge formation. The King's College Hospital group reported abnormal cholangiograms in 80% of patients with this type of reconstruction who were observed for 3 years. Findings included biliary strictures, inspissated bile, bile leak, and malpositioned T-tubes. This method has been used by Wall and associates in London, Ontario, without a T-tube or internal stent with a reported complication rate of 13.6%.

**Postoperative Care**

Postoperative care of the liver transplant recipient is demanding and requires a lifelong commitment to the patient. Mistakes in management after surgery are just as dangerous as...
technical misadventures in the operating room. Coordination of effort and continuous liaison between the transplant center staff and primary care providers are essential to the patient's welfare.

**EARLY POSTOPERATIVE RECOVERY**

In typical cases, if the graft functions well immediately after implantation and the recipient has no extraordinary risk factors, a prompt recovery with a 24- to 48-hour stay in the intensive care unit and a 14- to 21-day stay on the regular hospital floor can be anticipated. In many respects, the care of the postoperative liver transplant recipient resembles the care of other general surgical patients, but there are some important differences.

On leaving the operating room, the patients are always in a state of volume excess with considerable third spacing of fluid, but many patients are oliguric for 24 to 48 hours. Diuretics and colloid often are required, but crystalloid should be limited to modest maintenance requirements to avoid pulmonary edema. Potassium should be given as an intermittent infusion when needed rather than added to maintenance fluids. Graft necrosis (primary nonfunction, hepatic artery thrombosis, hyperacute rejection) can result in sudden increases in serum potassium levels. Hypertension is common and must be treated aggressively. The moderate prolongation of prothrombin time and the thrombocytopenia commonly seen early after liver transplantation when combined with hypertension leave the patient at significant risk of intracerebral bleeding.

Except in patients with active bleeding, a prothrombin time elevated within 15 to 20 seconds of control and platelet counts as low as 30,000/μL are not corrected. Inappropriate correction of moderate coagulation abnormalities may contribute to hepatic artery thrombosis, especially in children. Patients at high risk of vascular thrombosis, such as young children, are anticoagulated with low-molecular-weight dextran (Dextran 40), 5 mL/h intravenously for 5 days, and given aspirin and dipyridamole (Persantine). Once the prothrombin time is less than 18 seconds, heparin, 50 IU/kg subcutaneously, is given every 12 hours. This regimen seldom is needed in adult patients.

Intraabdominal bleeding and primary graft failure are the two most common major problems seen in the immediate postoperative period. Reexploration is advised for the patient who bleeds significantly after surgery, even if the patient stabilizes. If the abdomen is distended with blood or noninvasive imaging studies show a significant volume of clot in the abdomen, it is best to evacuate the abdomen and check the integrity of all vascular anastomoses, lest one be faced with an infected hematoma or a false or mycotic aneurysm later. Patients who require blood should not be permitted to become hypotensive or anuric before reexploration is considered.

Primary graft failure may not be evident immediately because some grafts have partial function for a few days before it becomes evident that the liver cannot sustain the patient. Causes of immediate graft failure include ischemic preservation injury, vascular thrombosis, and hyperacute rejection. Persistent abnormal liver function tests, uncorrectable prolongation of the prothrombin time, elevated lactate levels, oliguria, and central nervous system (CNS) changes (lethargy, seizures) are the common early findings. Narcotics and sleep medications should be avoided early after liver transplantation, since they impair assessment of CNS status. Bedside Doppler ultrasound studies are useful in assessing the patency of the portal vein and hepatic artery. Coma, alkalemia, hyperkalemia, and hypoglycemia characterize the ad-

**FIGURE 43-10** Portal vein reconstruction using a jump graft of donor iliac vein from the superior mesenteric vein to the donor portal vein. The graft is passed through a tunnel in the base of the transverse mesocolon, superior to the pancreas and inferior to the distal stomach, to reach the hepatic hilum. This is the preferred method of reconstruction when the recipient portal vein and the confluence of the mesenteric and splenic veins are thrombosed but the main superior mesenteric vein is patent. (Tzakis AG, et al. Venous jump grafts for liver transplantation in patients with portal vein thrombosis. Transplantation 48:530, 1989)
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FIGURE 43.11 Route of a freestanding donor iliac arterial graft from the infrarenal abdominal aorta to the hepatic hilum. The graft passes through a rent in the transverse mesocolon (not shown) to pass anterior to the pancreas and behind the pylorus. Note the anomalous donor arterial supply to the liver graft with separate origins of hepatic arterial branches. Complex donor arterial anomalies are best handled by this method of reconstruction. (Tzakis AG, et al. The anterior route for arterial graft conduits in liver transplantation. Transplant Int 2:121, 1989)

Advanced stage of primary graft failure. Potassium infusions must be avoided, and dextrose 10% in water may need to be given to support blood glucose levels. Ultimately, only urgent retransplantation before pneumonia or irreversible coma sets in can save the patient with primary graft failure.

COMPLICATIONS

Technical complications are common after liver transplantation and associated with an increase in postoperative mortality. Postoperative bleeding and biliary leak or obstruction are the most common complications that require reoperation.\(^3\)

Intraabdominal bleeding early after surgery has already been discussed and usually is the result of technical problems. Another rare but important cause of hemorrhage is rupture of a preexisting splenic artery aneurysm.\(^3,13\) These lesions may be identified on preoperative studies such as CT scans and ultrasonography. At the time of transplantation, the course of the splenic artery along the upper margin of the pancreas should be palpated. If a splenic artery aneurysm is present, the artery should be ligated.

Biliary Complications

Biliary leak or obstruction are among the most frequent complications after liver transplantation.\(^2,6,146\) The most common site of biliary leakage after liver transplantation is from the exit site of the T-tube from the common bile duct in patients with a duct-to-duct reconstruction. The diagnosis is confirmed by cholangiography. If the leak is discovered incidentally on a routine cholangiogram and the patient is asymptomatic, no treatment may be necessary. Even most symptomatic leaks are minor and can be managed by retrograde endoscopic placement of a nasobiliary stent or simple suture repair.\(^17\) Leaks from the duct-to-duct anastomosis are more serious, and most require reconstruction by conversion to a Roux-en-Y choledochojunostomy. Simple suture repair usually fails. If the leak is the result of necrosis of the duct from hepatic artery thrombosis, external drainage of the biliary tree may be required until retransplantation can be performed.

Most T-tube stents are removed about 3 months after transplantation. This may be accompanied by bile leakage.

FIGURE 43.12 Methods of biliary reconstruction. Roux-en-Y choledochojunostomy over an internal stent and choledochocholedochostomy over a T-tube stent (inset).
Patients complain of abdominal or shoulder pain, usually within 1 hour of T-tube removal. Symptomatic patients should be observed in the hospital and kept lying on the right side. If symptoms persist and signs of peritonitis progress, the patient should be explored and the T-tube exit site sutured to stop the leak.

Leaks from the choledochojejunostomy after a Roux-en-Y limb reconstruction are less common but more serious because of the violation of the intestinal tract. A fresh anastomosis to a less inflamed site on the Roux-en-Y limb should be performed when feasible. If severe infection is present, external drainage and deferred reconstruction may be required. Necrosis of the bile duct from hepatic artery thrombosis should be suspected.

Biliary strictures typically occur later in the postoperative course and may present insidiously with alterations in liver function similar to those seen with rejection, hepatitis, or drug toxicity. Liver biopsy, hepatitis serology, ultrasonography, and cholangiography are used to make the differential diagnosis. Patterns of biliary obstruction include anastomotic stricture, donor distal duct narrowing, multiple intrahepatic strictures, dilatation of the donor and recipient ducts without a demonstrable point of obstruction, iatrogenic obstruction by T-tubes or internal stents, and unusual causes, such as a mucocele of the cystic duct stump, or recurrent biliary tract disease, such as sclerosing cholangitis or cancer.

An indwelling catheter, which usually can be placed percutaneously by the interventional radiologist, should be left in patients with a demonstrable obstruction at cholangiography. If the obstruction is localized, balloon cholangioplasty may be tried. Obstructions with biliary stones or biliary dilatation without an obvious site of obstruction (as commonly is seen in patients with ampullary dysfunction after a duct-to-duct reconstruction) require surgical correction (usually conversion to a Roux-en-Y choledochojunostomy) or endoscopic sphincterotomy. An obstructing mucocele is resected.

Multiple intrahepatic strictures present a more difficult problem. Hepatic artery thrombosis or stricture may be the cause. Biliary stenting and, occasionally, balloon dilation may be useful in achieving some decompression of the biliary tree, but surgical correction by retransplantation usually is necessary. In those cases in which the strictures are confined to an appropriate anatomic distribution in the liver, subtotal hepatic resection can be done.

Vascular Complications

Hepatic artery thrombosis is one of the most serious complications after liver transplantation. It usually is the result of a technical error, but it can also result from preservation injury of the graft with ischemic injury to the hepatic microcirculation, inappropriate correction of coagulation parameters after operation, high hematocrit, a posttransplantation hypercoagulable state, and uncontrolled allograft rejection with increased intrahepatic vascular resistance and in association with pancreatitis.

Arterial thrombosis should be suspected in any liver transplant recipient with a sudden high temperature and an elevation in liver function studies. Blood cultures that grow enteric organisms (Klebsiella sp, Escherichia coli, enterococci) are almost pathognomonic. Doppler ultrasonography is an effective noninvasive screening device, but arteriography is necessary even if ultrasonography is negative when there is a high index of clinical suspicion.

Hepatic arterial thrombosis has three general presentations: (1) acute hepatic gangrene with fulminant liver failure, (2) delayed biliary leak with or without bile abscess, and (3) relapsing bacteremia with minimal, if any, liver dysfunction. Treatment depends on cause and presentation. If a technical flaw is quickly identified, immediate surgical correction sometimes is possible and can save the graft. In a few cases, hepatic arterial thrombosis has been successfully treated with intravascular fibrinolytic therapy. Acute hepatic gangrene requires urgent retransplantation. Bile duct necrosis also requires retransplantation but can be controlled with antibiotics and appropriate surgical drainage until a new graft can be found. Relapsing bacteremia is treated with intravenous antibiotics followed by a course of oral suppressive therapy. If
the patient remains afebrile with satisfactory liver function, retransplantation may be avoided or only become necessary when chronic ischemic biliary strictures develop. Most patients with persistent bacteremia and most of those who develop intrahepatic abscesses require retransplantation. Percutaneous drainage of an intrahepatic biloma or abscess usually is only a temporizing maneuver.

Portal vein thrombosis is much less common than hepatic artery thrombosis. It may result in fulminant graft failure, especially when it occurs soon after transplantation, but it should also be suspected in patients with severe ascites or a variceal hemorrhage after transplantation. In patients with a viable graft but complications of portal hypertension, a distal splenorenal shunt has been used successfully. 

Complications of the vena cava anastomoses are rare. Stenosis of the suprahepatic inferior vena cava anastomosis may impair venous drainage enough to cause a Budd-Chiari syndrome and should be considered in any patient with persistent, massive ascites after an otherwise successful liver transplantation. Percutaneous transluminal balloon dilatation has been successfully used in some cases as an alternative to surgical repair or retransplantation.

Intestinal Complications

Bowel obstruction is uncommon after liver transplantation. Most admissions are confined to the suprapubic portion of the abdomen. If the base of the mesentery of a Roux-en-Y limb is not tacked down, the small bowel may herniate through and obstruct. Overuse of aluminum-containing antacids may result in inspissation and obstruction of the intestine. Pseudo-obstruction of the colon is much less common than after renal transplantation but must be treated aggressively to avoid disastrous colon perforation.

The gastrointestinal tract is one of the common sites for lymphoproliferative lesions in immunosuppressed patients, and these may obstruct or perforate the bowel. Segmental resection of involved bowel is recommended for localized lesions.

Most intestinal perforations that occur early after transplantation are anastomotic leaks, perforation in an area of denuded serosa, or perforation of bowel injured by electrocautery. Anastomotic leaks are more common in children and should be suspected whenever there is evidence of intraabdominal polymicrobial or candidal infection. Hematogenous or abdominal wound candidiasis is also suggestive of a violation of the gut. Prompt surgical exploration is indicated. Most late perforations are caused by diverticulitis, appendicitis, CMV enteritis, or lymphoproliferative lesions.

Gastrointestinal Bleeding

Bleeding may occur anywhere in the gastrointestinal tract after liver transplantation. Endoscopy, radionuclide scanning, and angiography are indicated to localize the bleeding site. A common site of bleeding after liver transplantation in patients with a Roux-en-Y biliary reconstruction is from the suture line of the jejunojejunostomy. The bleed typically is from a single arteriole and usually can be managed by opening the anterior portion of the anastomosis to find and repair the site. Less commonly, the bleeding is from the closed end of the Roux loop. Variceal hemorrhage after liver transplantation suggests either portal vein thrombosis or esophageal stenosis.

Mucous ulceration of the esophagus, stomach, small bowel, or colon may result from opportunistic infection, such as in CMV gastroenteritis or colitis and Clostridium difficile pseudomembranous colitis, and present with bleeding. Management is red blood cell replacement, reduction of immunosuppression, and appropriate antibiotic therapy (eg, ganciclovir, metronidazole [Flagyl]). Total colectomy or subtotal gastrectomy is only necessary in unusually severe or persistent cases.

A rare but particularly dangerous cause of gastrointestinal bleeding after liver transplantation is a fistula between the gastrointestinal tract and a vascular anastomosis, either the hepatic arterial anastomosis or anastomosis of an iliac artery conduit to the aorta. Ligation of the involved vessel usually is required, since most of these fistulas are the result of an infected false aneurysm, often with Candida, and cannot be repaired primarily without a high risk of breakdown and hemorrhage. In some cases, the liver has tolerated arterial ligation and retransplantation has not been necessary.

Ascites

Ascites may persist for several weeks or months after liver transplantation. Technical faults, such as portal vein or suprahepatic inferior vena cava obstruction or thrombosis, should be ruled out. Ascites usually can be managed with salt restriction and diuretics and gradually diminishes with time. In some cases, placement of a peritoneal-venous shunt may be required. Late recurrence of ascites suggests cirrhosis and should be investigated to determine its cause (rejection, hepatitis, recurrence of original disease).

Pancreatitis

Many patients have a mild, asymptomatic pancreatitis with a mild ileus and modest hyperamylasemia (500 IU/dL) early after liver transplantation. This usually resolves without sequelae. Edema and enlargement of the pancreas on a CT scan or ultrasound are more ominous and may lead to abscess, pseudocyst, and, occasionally, frank hemorrhagic pancreatitis.

The cause of pancreatitis after liver transplantation is uncertain but may be multifactorial. Manipulation of the pancreas during dissection of the hepatic artery or creation of tunnels for vascular grafts, ischemic insult from ligation of the gastroduodenal artery, venous congestion of the pancreas during the anhepatic phase of the liver transplantation procedure, and use of high-dose steroids for induction of immunosuppression may contribute. Significant clinical pancreatitis is also more common in patients with active viral liver disease, particularly in patients with acute hepatitis B in the allograft.

Aplastic Anemia

Patients undergoing liver transplantation for non-A, non-B hepatitis are at special risk of developing aplastic anemia. In a series of 32 patients with acute non-A, non-B hepatitis, 9 patients developed aplastic anemia 1 to 7 weeks after transplantation. Four of these died of infectious complications. Two patients followed for at least 1 year developed recovery of marrow function.

Liver Biopsy Complications

Liver biopsy is the most common procedure performed on patients after liver transplantation. Complications include pneumothorax, hemothorax, intraperitoneal hemorrhage.
intrahepatic or subcapsular hematoma, bacteremia, and pseudoaneurysm of an intrahepatic artery or arteriobiliary fistula with hemobilia.

Infection

Infections are the cause of most of the morbidity and mortality after organ transplantation. Organisms that normally colonize the gastrointestinal tract and skin can become dangerous pathogens in the immunosuppressed transplant recipient. Modern immunosuppressive regimens are more selective in their effects and have permitted less reliance on azathioprine and steroids. This has reduced the risk of bacterial infections and made them easier to manage, but 50% to 70% of organ recipients experience at least one bacterial infection. Latent viral infections often are present in otherwise sterile tissues, and immnosuppression may permit viral replication with clinical infection. About 30% to 60% of patients experience a symptomatic viral infection. Herpes simplex virus (HSV), CMV, Epstein-Barr virus (EBV), and VZV infections are the most frequently encountered. Invasive fungal infections are also more common.

EVALUATION OF FEVER

Fever is always an important clinical finding in a transplant recipient. All fevers over 38.5°C must be thoroughly investigated. The basic evaluation includes liver function tests, a chest film, urinalysis, Gram stain of sputum, and cultures of blood, sputum, urine, and all drains, indwelling tubes, and lines. Viral cultures should be taken of Buffy coat blood, throat washes, and urine. An abdominal CT scan usually is indicated. Additional studies to be considered include acute-phase serum samples (including EBV, HSV, and CMV titers), arterial blood cultures for candidiasis, stool for ova and parasites, pelvic examination, head CT scan, skin tests for tuberculosis and mycoses, Legionella titers, spinal fluid examination, cholangiography, and hepatitis serology screens. Bronchosalveolar lavage and liver biopsy specimens should be stained and cultured for viruses and fungi when pneumonitis or hepatitis is suspected.

VIRAL INFECTIONS

Cytomegalovirus infections are the most common viral infections encountered in patients after liver transplantation. In a review of 121 liver transplantations at the University of Pittsburgh, the overall incidence of CMV infection was 59%, compared with 35% for HSV, 25% for EBV, and 7% for VZV. Symptomatic and disseminated CMV infections are more common in primary CMV infection than with reactivation CMV infection. Infection may involve the urinary tract, gastrointestinal tract (esophagus, stomach, duodenum and small bowel, or colon), lungs, liver, and CNS. Transmission from the organ donor is the most important source of primary CMV infection. Disseminated primary CMV infection has been associated with prior treatment with monoclonal antibody but reactivation infection has not.

There is evidence that prophylactic high-dose acyclovir and intravenous immune globulin may be of value for CMV disease in transplant recipients. High-dose acyclovir, 800 mg orally four times a day, is begun as soon as the patient has resumed oral intake. Patients are maintained on acyclovir for at least 6 months. Dosage should be adjusted for patients with impaired renal function, but doses of less than 800 mg/d are probably ineffective in preventing CMV infection. Patients who tend to have recurrent oral or genital herpes infections may be continued on acyclovir at a reduced dose (200 mg twice a day) beyond 6 months. High-risk patients, such as seronegative recipients who receive an organ from a seropositive donor, should also receive a course of CMV immune globulin.

HSV infections are typically limited to oral and genital herpetic but HSV may also produce pneumonitis or hepatitis. HSV hepatitis commonly occurs earlier (median, 18 days) than CMV hepatitis, which usually occurs 30 to 40 days after transplantation, and may be focal or diffuse in the liver. Symptomatic reactivation of HSV in seropositive patients is more common in those who have received therapy for rejection with monoclonal antibody. Disseminated HSV infection has a poor prognosis, and early therapy with high-dose acyclovir is essential. Prophylactic acyclovir may be effective in preventing disseminated HSV disease.

Exposure to VZV infection can have serious consequences. Seronegative patients should receive VZV immune globulin (VZIG) within 72 hours of exposure to an infected person. In cases of strong exposure, such as to a family member with chickenpox, it is advisable to give VZIG even to seropositive patients and to administer acyclovir to seronegative patients, since clinical disease has occurred in susceptible people even after administration of VZIG. Disseminated VZV requires high-dose acyclovir therapy.

PNEUMOCYSTIS PNEUMONIA

Pneumocystis pneumonia has long been one of the dreaded complications of immunosuppression in organ transplantation patients. Oral prophylaxis with sulfamethoxazole-trimethoprim (one single-strength tablet per day) is highly effective in preventing this infection. Patients who are unable to be treated with sulfamethoxazole-trimethoprim can be treated with dapsone, 100 mg/d, or aerosolized pentamidine, 300 mg once a month. Prophylaxis should be continued for life, but the frequency of sulfamethoxazole-trimethoprim can be reduced to three times per week. We have seen Pneumocystis carinii pneumonia develop shortly after withdrawal of suppressive therapy in patients 3 or more years after transplantation. Furthermore, suppressive prophylaxis may also afford protection from Legionella, Nocardia, and toxoplasmosis.

FUNGAL INFECTIONS

Candidal infections are common in immunosuppressed patients. Noninvasive overgrowth of oropharyngeal, esophageal, and vaginal cavities is most common and can be managed with topical therapy. Mycostatin suspension, 500,000 IU (5 mL) every 6 hours, is given orally or through a nasogastric tube beginning after surgery and continued for several months until the dosage of immunosuppression is reduced. It should be re instituted whenever immunosuppression is increased, such as for treatment of rejection. Clofotimazole (Mycalex troche), which dissolves slowly in the mouth, can be used instead of mycostatin. Candidal infections are more common and often more troublesome in patients with dia-
betes. It is advisable to continue Candida prophylaxis longer and perhaps indefinitely in these patients.

Invasive candidal infection requires treatment with systemic therapy, such as amphotericin B or fluconazole. High-risk patients should be considered for pretransplantation prophylaxis to reduce Candida colonization of the gut. This may also be accomplished as part of a program of selective decolonization of the gut, which may reduce the incidence of gram-negative and candidal infections after transplantation. We have used a combination of colistin, gentamicin, and nystatin or paste in Orabase (polymyxin B, gentamicin 2%, and nystatin 2%) for patients waiting for transplantation in a critical care setting.

Aspergillus infections may involve the lungs, upper respiratory tract, skin, soft tissues, or CNS. The disease commonly presents as a diffuse pneumonia with patchy infiltrates rather than as a fungus ball in the lungs. Blood vessel invasion with metastatic spread of infection occurs early. Development of brain abscess is insidious and cure is difficult. Definitive diagnosis requires intracranial biopsy. A long course of systemic therapy with amphotericin B is indicated in patients with aspergillus infections. Fluconosine may benefit patients with ophthalmic or CNS involvement. Itraconazole, a new agent, has shown promise for the treatment of aspergillosis in our limited experience with it.

Cryptococcal infections (lung, CNS, disseminated cutaneous infection) are another hazard in immunosuppressed patients. A spinal fluid examination with India ink stains and analysis for cryptococcal antigen should be considered in patients with persistent headache or signs of meningism and in all patients with pulmonary cryptococcal infection.

Infections with Mucor or Rhizopus species are rare but may produce severe CNS or soft tissue infections that are difficult to eradicate. Treatment requires reduction of immunosuppression, local excision, and a long course of systemic antifungal therapy.

**ANTITUBERCULAR PROPHYLAXIS**

Patients who are PPD-positive, especially those from areas with a high endemic rate of tuberculosis or those who travel to such areas, should receive antitubercular prophylaxis. Patients with a history of potential exposure and anergic skin reactivity should also be considered for prophylaxis with isoniazid (INH). INH prophylaxis usually is begun in the third week after liver transplantation and continued for at least 6 months.

**EPSTEIN-BARR VIRUS AND LYMPHOPROLIFERATIVE DISORDERS**

A ubiquitous DNA virus, EBV can produce a spectrum of syndromes in immunocompromised patients ranging from a typical mononucleosis syndrome to frank lymphoma. In addition to a classic mononucleosis presentation, the viral syndrome may be characterized by atypical findings such as jaw pain, arthralgias, joint space effusions, diarrhea, encephalitis, pneumonitis, mediastinal lymphadenopathy, ascites, and hepatitis. Changes in the liver allograft in EBV infection range from findings typical of infectious mononucleosis to a distinctive histopathology characterized by a mixed mononuclear and sinusoidal infiltrate, lobular hepatitis, and mild duct damage not in proportion to the severity of the inflammatory infiltrate.

Lymphoproliferative disease is seen in patients with congenital and acquired immunodeficiency states, including transplantation patients receiving immunosuppressive medications. Most are associated with EBV infection. In some patients, EBV DNA cannot be found in tumor specimens. Also, EBV is trophic for B cells and about 15% of lymphomas are of T-cell origin. In our experience, lymphomas after transplantation have occurred in 4.6% of combined heart and lung recipients, 2.2% of liver recipients, 1.8% of heart recipients, and 1% of kidney recipients. The higher incidence in extrarenal transplant recipients may be related to the higher levels of immunosuppression used in patients for whom there is no alternative artificial organ support if therapy for graft rescue fails.

Posttransplantation lymphomas are believed to be a consequence of overall levels of immunosuppression rather than treatment with any particular agent. The disease may present as a diffuse involvement of multiple organ systems with massive infiltration of many tissues with immunoblasts or mature plasma cells or as solid tumors that involve the tonsils, lungs, and spleen with spread to the liver, kidneys, lymph nodes, and brain. Most patients who survive this complication have evidence of primary or reactivated EBV infection, polyclonal lesions, solid tumors rather than diffuse disease, and B-cell hyperplasia rather than lymphoma. In liver recipients, the hepatic allograft is involved in one third of cases, and tonsils, kidneys, and small bowel often are involved.

Early recognition, reduction, or withdrawal of immunosuppression and systemic antiviral therapy with acyclovir or ganciclovir are important for successful management of these lesions. Localized solid lesions in the gastrointestinal tract may obstruct or perforate and should be resected. α-Interferon has been used in an effort to prevent early lymphoma transformation. Anti-CD21-specific and anti-CD24-specific (anti-B-cell) monoclonal antibodies have recently been shown to be effective in controlling diffuse, severe oligoclonal B-cell lymphoproliferative disease in patients without CNS involvement. Sometimes more aggressive monoclonal lymphomas require conventional anticancer therapy.

**Immunosuppression**

Recent improvements in immunosuppression have been responsible for much of the success now being experienced in solid organ transplantation. We can expect further significant advances in the near future as another generation of agents is introduced into clinical practice. This section briefly reviews the immunosuppressive agents currently in use and the management strategies for induction immunosuppression and treatment of rejection.

**CYCLOSPORINE**

Cyclosporine was isolated from a fungus found growing in a soil sample taken from the largest highland plateau in Europe, the Hardanger Valda in southern Norway. Borel first described the immunosuppressive properties of cyclosporine in 1976, and clinical trials were begun by Calne in 1978. The systematic use of cyclosporine in combination with low-dose prednisone was begun by Starzl in 1980. The improved survival achieved by Starzl in his first trials with the drug in liver transplant recipients demonstrated that liver transplantation was a practical therapy for patients with end-stage liver
disease. A National Institutes of Health Consensus Development conference held in 1983 supported this conclusion. The Health Care Financing Administration now provides Medicare reimbursement for some of the most common indications for pediatric and adult liver transplantation.

Cyclosporine is a highly lipid-soluble drug, and its absorption depends on the enterohepatic circulation. It is metabolized in the liver, and the major route of excretion is in bile. Toxicity is most commonly manifested by hypertension, tremulousness, gingival hyperplasia, and nephrotoxicity. Acute nephrotoxicity is characterized by hyperkalemic renal tubular acidosis and chronic cyclosporine nephrotoxicity, by a progressive interstitial fibrosis of the kidneys. A low serum magnesium level potentiates neurotoxicity, and this may result in seizures, especially when cyclosporine is administered intravenously. Cyclosporine can produce changes in personality, including paranoid delusions and hallucinations. Liver function may also be impaired by cyclosporine, but this is much less common than nephrotoxicity and other causes of liver dysfunction (rejection, hepatitis, technical complications) must be ruled out.

Cyclosporine is initially administered intravenously as a continuous infusion, usually at a dose of 3 to 5 mg/kg/d. As soon as patients are able to tolerate oral intake, oral cyclosporine, 12 to 15 mg/kg/d in two divided doses, is begun. Daily trough levels of serum or whole blood are monitored and levels adjusted to maintain an appropriate therapeutic range. Once oral dosage is well established and blood levels are stable, patients are weaned off the intravenous form.

Because of concern about the nephrotoxicity of cyclosporine, various cyclosporine-sparing protocols have been adopted by transplant centers during the induction phase of immunosuppression. In this approach, no cyclosporine is given during the first 2 to 7 days after transplantation until good urine output and creatinine clearance are demonstrated. During the period of cyclosporine sparing, patients may be treated with various combinations of azathioprine, prednisone, and either polyclonal or monoclonal antibody. Once good renal function is established, oral cyclosporine is started.

Drugs that affect hepatic enzyme systems, especially the cytochrome P-450 system, can alter the metabolism of cyclosporine. Two of the more common drugs that do this are phenytoin (Dilantin), which causes a fall in cyclosporine serum concentration, and erythromycin, which causes significant increases and may precipitate acute toxicity. These drugs must be used with caution and with careful attention to the monitoring of blood levels.

CORTICOSTEROIDS

Although cyclosporine has permitted a significant reduction in the amounts of steroid required to maintain a liver allograft, corticosteroids still have an important role in the induction and maintenance of immunosuppression in liver transplant recipients. At most centers, patients receive a 1-g bolus of methylprednisolone during surgery followed by a high-dose taper of steroids until a daily maintenance dose of 20 mg is reached (less in young children). In patients with diabetes, advanced osteoporosis, or refractory hypertension, an attempt usually is made to lower the dose of steroids further early in the course, but this is not always possible. Steroids are also important in the management of acute rejection. The lower maintenance doses of steroids able to be used in combination with cyclosporine allows pediatric patients to resume normal growth and development after liver transplantation.19

AZATHIOPRINE

Azathioprine is widely used in transplantation to spare cyclosporine during the early recovery phase when renal function may be compromised, to provide an adjunctive agent in patients unable to tolerate usual doses of cyclosporine, or to augment immunosuppression in patients with persistent or recurrent rejection despite appropriate therapy with cyclosporine and steroids. Therapy usually is started at 1 mg/kg and may be gradually increased to 1.5 to 2 mg/kg as needed. If the peripheral leukocyte count falls below 5000/μL, the dose is reduced. If the count falls below 3000/μL, the drug is discontinued.

ANTIBODY THERAPY

Muromonab-CD3 (Orthoclone OKT3) is a mouse antihuman monoclonal antibody with activity against the CD3 determinant on human T cells. A highly effective immunosuppressive agent, it is used for induction immunosuppression as part of cyclosporine-sparing protocols; for induction immunomunophylaxis, especially in high-risk patients (patients with high titers of cytotoxic antibody or patients with a history of graft rejection); and for the treatment of steroid-resistant allograft rejection.23,48,98 A recent report could find no long-term benefit to the routine use of prophylactic OKT3 and recommended that OKT3 be reserved for the treatment of steroid-resistant rejection and for cyclosporine intolerance.93 OKT3 is usually administered as a 5-mL intravenous bolus over 5 minutes repeated daily for 10 to 14 days. Fluid overload should be corrected before OKT3 is given. Patients should be premedicated with steroids, antihistamine, and acetaminophen for the first few doses. Adverse effects such as headache, joint pains, fever, chills, tachycardia, nausea, and abdominal discomfort are common and probably a result of the sudden lysis of lymphocytes and release of cytokines with the first few administrations. Seizures may occur after administration and are potentiated by hypocalcemia or hypotension. Aseptic meningitis has been reported in less than 5% of patients. It causes fever and headache, and some patients experience nuchal rigidity and altered mentation. Polymorphonuclear leukocytes and lymphocytes may be present in spinal fluid, but spinal fluid cultures are negative. The syndrome is self-limited and does not require the drug to be stopped.

Other monoclonal agents directed against T-cell determinants and interleukin receptors are under investigation, but OKT3 is the only Food and Drug Administration–approved monoclonal antibody in use. Because OKT3 is a mouse protein, patients may develop antimurine antibodies that inactivate the drug. Most patients develop only low titers of antimurine antibody with a first course of treatment, and this titer decreases with time. Thus, many patients can be retreated with a second course of OKT3 if rejection recurs. It often is helpful to monitor CD3 cell counts and OKT3 levels in patients being retreated with OKT3, especially if there is a poor clinical response. The drug is ineffective if CD3 cell counts do not drop or effective serum levels cannot be achieved.22,38,130

Now that monoclonal therapy is available, there is much less use of polyclonal agents. These preparations are still used
by some centers for cyclosporine-sparing during induction and as an alternative therapy to the monoclonal agents in patients with recurrent rejection or a poor response to OKT3.

**FK 506 AND OTHER NEW AGENTS**

FK 506 represents the first of a new generation of immunosuppressive agents. It is a macrolide antibiotic belonging to the same family of compounds as erythromycin and a potent immunosuppressive agent. Its actions on T cells are similar to those of cyclosporine, including suppression of interleukin-2 production, but it is many times more potent and acts on a different cell receptor. In extensive clinical trials at the University of Pittsburgh, FK 506 has been found to be remarkably effective in preventing and controlling liver allograft rejection, and many patients can be weaned off steroids early in their course after transplantation. Most patients who develop steroid-resistant rejection during therapy with FK 506 can be treated with a short, 3- to 5-day course of OKT3. FK 506 has also proved to be a highly effective rescue drug for patients who cannot be maintained on cyclosporine and those with failing grafts despite aggressive cyclosporine therapy.

The toxicity profile of FK 506 differs from that of cyclosporine. It is less nephrotoxic, and troublesome hypertension is less common. Gastrointestinal adverse effects, especially nausea and diarrhea, are common early complaints and may be related to an antibiotic action of the drug in the gut. Headache and insomnia are common complaints and are dose-related. Tremors are much less common than with cyclosporine, and the drug may cause mild hair loss rather than the hirsutism commonly experienced by patients on cyclosporine. The severest neurologic complications seen with FK 506 are seizures and central pontine myelinolysis with severe speech and motor disturbances. As with cyclosporine, these complications are most common early after transplantation, when the drug is being given intravenously. Metabolic disturbances, especially significant fluctuations in serum sodium levels, have also been associated with such neurologic disorders in transplant recipients.

When FK 506 is given, much of it is cleared on the first pass through the liver. Therefore, graft function has a significant effect on drug activity and blood levels. Early in the period after transplantation, FK 506 levels may rise rapidly to toxic levels if graft function is poor. Appropriate monitoring of blood levels and adjustments in dosage must be made during periods of graft dysfunction.

In addition to its impressive immunosuppressive effects, FK 506 has a remarkable hepatotrophic effect that is stronger than that seen with cyclosporine. In an experimental animal model in which portal blood supply is diverted by an Eck fistula to the vena cava and FK 506 is selectively infused into one lobe of the liver, the size, anatomic quality, and replication of hepatocytes is enhanced in the FK 506–infused portion of the liver. This effect of FK 506 on hepatic regeneration and repair may make it particularly advantageous for use in liver transplantation.

Several other interesting agents are under investigation and may become important for clinical practice in the near future. Among these are rapamycin, an antibiotic with some similarities to FK 506, and RS-61143, a guanine monophosphate inhibitor.

**Allograft Rejection**

Antibody-mediated hyperacute rejection of the liver has been demonstrated in animal models but is rare in the clinical setting. In kidney transplantation, hyperacute rejection usually occurs on the operating table because antibody deposition and accumulation of formed blood elements rapidly destroy the microcirculation of the kidney. In the case of a liver graft, the process may evolve over 24 to 48 hours after surgery and after a brief initial period of good graft function. It is most likely to occur in patients in whom an ABO incompatibility between donor and recipient has been crossed and occasionally occurs in a patient with a strongly positive antibody crossmatch. Hyperacute rejection usually is characterized by a severe hemorrhagic necrosis of the liver within hours or days of implantation. Submassive necrosis with a sparse polymorphonuclear infiltrate in the portal tracts and hepatic lobules has also been described in a patient with a high titer of lymphocytotoxic antibody. Patchy deposits of immunoglobulin, C3 complement component, factor P, and fibrinogen are characteristic. Accelerated acute cellular rejection can also occur in the first few days after transplantation. Liver biopsy is necessary to distinguish between early forms of rejection and ischemic graft injury.

Acute cellular rejection may occur at any time after liver transplantation and may be characterized by any or all of the following: malaise, fever, graft tenderness or enlargement, and diminished graft function with elevated levels of bilirubin and aminotransferase or canalicular enzymes. The presence of preformed antidonor lymphocytotoxic antibody is not predictive of hyperacute rejection but may be an important warning that the recipient is more likely to experience acute cellular rejection and that rejection may be more difficult to treat.

Acute cellular rejection is characterized by a portal infiltrate with damage to small bile ducts in the portal tracts. Inflammatory cells may also accumulate beneath the portal and terminal hepatic veins (central venulitis). An inflammatory arteritis may also be present, but the vessels involved typically are in the hilum and not accessible by liver biopsy. The hepatic lobule usually is spared, but in severe rejection, the inflammatory infiltrate may spill over into the hepatic lobule and be associated with hepatic necrosis. The histologic picture is different from the piecemeal necrosis seen with hepatitis.

Chronic rejection is an oblitrative arteriopathy that results in an insidious and relentless loss of small bile ducts. It typically presents with elevated levels of canalicular enzymes and progressive jaundice. Hepatic synthetic function usually is well preserved, and most patients feel well until late in the course. In some cases, chronic rejection may progress rapidly, a syndrome that has been called the acute vanishing bile duct syndrome. Vanishing bile duct syndrome may be more commonly seen in patients with a positive lymphocytotoxic antibody crossmatch. The syndrome has also been reported to be less frequent in patients treated with combination immunosuppressive regimens, such as triple therapy with cyclosporine, prednisone, and azathioprine or quadruple regimens including these agents and prophylactic antibody ther-
Hepatic lobular changes of chronic rejection also reflect progressive ischemic damage and include centrilobular cholestasis, patchy acidophilic necrosis, centrilobular ballooning or atrophy of hepatocytes, perivenular sclerosis, and intrasinusoidal foam cells.

The differential diagnosis of allograft rejection commonly includes preservation injury, vascular compromise, biliary tract obstruction, viral or toxic hepatitis, systemic infection, and recurrent disease. Liver biopsy usually is required for definitive diagnosis, but Doppler ultrasonography, cholangiography, angiography, and CT scanning may be needed as well, depending on the clinical setting. Serologic screens for hepatitis and other infectious disease evaluations may also be required.

**MANAGEMENT OF REJECTION**

No effective therapy exists for hyperacute rejection of the liver other than urgent retransplantation of the liver. Acute cellular rejection usually is treated with steroids and, if there is an inadequate response, a course of antibody therapy. In cases of chronic rejection in which bile ducts are still present in some portal tracts on liver biopsy, conversion from cyclosporine to FK 506 may rescue the graft or significantly slow the progression of the rejection process. Otherwise, chronic rejection is refractory to further therapy. The inevitability of retransplantation should be accepted, and overtreatment of the patient should be avoided.

**Timing of Transplantation**

Outcome is related to patient condition at the time of transplantation. Liver grafts are allocated in the United States according to a point system that is based mainly on medical urgency, as defined by the required level of medical care, and waiting time. Patients with the highest urgency and longest waiting times receive the highest priority. Experience shows, however, that these patients also have the highest mortality after liver transplantation. Patients in the lowest urgency classes have 6-month survival rates approaching 90%, whereas those who go to the operating room from an intensive care unit to receive a liver transplant have only a 65% chance of survival.

Liver transplantation is not experimental, and it is now widely available in North America, Europe, and Australia. It is not an option to be considered only for a patient with end-stage liver disease who has reached a desperate or debilitated state. Excellent results can be achieved if patients are referred before their condition deteriorates to the point at which survival is jeopardized. The severely ill deserve to be treated and can be served, but early referral is essential to further reduce morbidity, mortality, and cost.

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