

Medical Aspects of Liver Transplantation

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The methods used to screen prospective candidates for orthotopic liver transplantation are described. Both the indication and the contraindications for the procedure are discussed. The timing of the procedure during the course of an individual candidate's liver disease is also discussed. Additionally, the institutional requirements of a liver transplant center are identified. Finally, the problems experienced by a liver transplant patient and his physician during the postoperative period are identified and discussed.

Orthotopic liver transplantation is becoming an increasingly frequent, albeit still somewhat heroic, operative therapy for advanced irreversible chronic liver disease. During the decade from January, 1971 through December, 1980, a total of 192 such procedures were performed by Dr. Thomas E. Starzl at the University of Colorado (1). This figure averages out to approximately 16 procedures being performed per year. During 1981, with Dr. Starzl in Pittsburgh, this figure doubled with a total of 34 operations being performed. In 1982, the number of such procedures performed increased further to an annual rate of 80. Moreover, during the first 4 months of 1983, this accelerated rate of performance has continued with 27 procedures having been performed. Not only are those who have developed the procedure continuing to refine it and make it an acceptable therapeutic option for patients with advanced, otherwise hopeless liver disease, but also other surgeons at distant institutions have either begun to develop their own experience or are in the process of planning to actively enter the field within the next year or two.

The recent success achieved in improving the surgical mortality and the coincidental success of cyclosporin A as an immunosuppressant in improving the long-term prognosis for transplant patients has raised new challenges for the internist who also cares for these patients (2). Thus, the physician seeing patients with advanced liver disease is now faced with the following questions: (i) who should be transplanted? and (ii) conversely, who should not be transplanted? What are the options available for rejected patients? (iii) When should transplantation be offered to a patient? (iv) What is the prognosis

for a given patient with a given disease process, such that an adequate decision concerning liver transplantation can be made? (v) What is the quality of one's life following successful transplantation? (vi) Are there any unique medical problems that develop or to which the patient is susceptible as a consequence of a successful liver transplant?

The answers to these questions are the object of the following presentation.

SELECTION OF THE TRANSPLANT CANDIDATE

Several factors are mandatory accompaniments of candidacy for orthotopic liver transplantation (Table 1). These are first, that the individual under consideration indeed have an irreversible, chronic progressive liver disease. This necessitates that the specific disease process dictating the procedure be identified, that its prognosis be understood, and that either death or inevitable vegetative existence be the only alternatives to transplantation. Second, and as a corollary to the first condition, the patient's liver disease should have progressed to a stage such that all other forms of therapy have already been exhausted (e.g., the disease condition must have reached the state of intractability). The third mandatory requirement for candidacy is that the patient have no contraindications for orthotopic liver transplantation.

Contraindications to orthotopic liver transplantation can be divided readily into those that are absolute and those that are relative (Table 2). Assuming that the requirements for candidacy have been fulfilled, the absolute contraindications for orthotopic liver transplantation include portal vein thrombosis, such that the transplanted liver cannot be provided with the necessary portal venous vascular input with all of its contained nutrients, hormones, and hepatotrophic factors. A second contraindication is severe hypoxemia due to right to left intrapulmonary shunts with an arterial $pO_2 < 50$ mm

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TABLE 1. REQUIREMENTS FOR CANDIDACY

Presence of a chronic irreversible and progressive liver disease
Medical-surgical intractability
No contraindications
Ability to accept the procedure, understand its nature and/or costs

TABLE 2. ABSOLUTE AND RELATIVE CONTRAINDICATIONS

Absolute contraindications
Portal vein thrombosis
Severe hypoxemia due to right to left shunts
Sepsis outside the hepatobiliary system
Primary malignant disease outside the hepatobiliary system
Metastatic hepatobiliary malignancy
Active alcoholism
Advanced cardiopulmonary or renal disease
HBsAg- and HBeAg-positive state
Age >55 years
Inability to accept the procedure or understand its nature and/or costs
Relative contraindications
Intrahepatic or biliary sepsis
Advanced alcoholic liver disease in the abstinent alcoholic
Age >50 years
HBsAg-positive state
Prior abdominal surgery particularly in the right upper quadrant

Hg. Such shunts occur in some patients with advanced liver disease and are thought to be a result of the liver disease rather than a primary cardiovascular or pulmonary disorder. Despite such reasoning, we have found empirically that such shunts do not close postoperatively for periods of up to several weeks and that the resultant hypoxemia experienced postoperatively is yet another adverse factor that frequently turns a hopeful situation into a hopeless effort. Obviously, sepsis outside the hepatobiliary system is an absolute contraindication to transplantation as it consistently determines failure in the immediate perioperative period due to the requirement of intense immunosuppression during this same time period. Obviously, primary malignant disease outside the hepatobiliary system or metastatic hepatobiliary malignant disease is an absolute contraindication for surgery. In all such cases transplanted to date (inadvertently because of failure to recognize such disease), the malignancy has had a markedly accelerated course post-transplantation presumably as a result of the immunosuppression. Although active alcoholism is an absolute contraindication to hepatic transplantation, we have not categorically ruled out transplantation for this particular indication. Should the alcoholic have a verifiable or documented period of sobriety of 6 months or greater in duration, and successfully complete a preoperative evaluation, we would consider the alcoholic for transplantation. Even with such prerequisites, however, alcohol abusers are not particularly good candidates. Not only are they always at risk to return to their prior alcoholism, but also their alcohol abuse frequently has injured not only the liver but also their lungs and other vital organ systems such that their ability to undergo liver transplantation is effected adversely.

In a similar vein, nonalcoholics with advanced cardiopulmonary or renal disease are also poor if not horrible candidates because their nonhepatic disease frequently is the factor that will determine their survival, not their liver disease. Individuals with viral-induced liver disease who are both HBsAg and HBeAg positive are at extremely high, if not prohibitive risk because of the universal risk of infection of the transplanted liver. Moreover, the immunosuppression required postoperatively appears to be a factor that accelerates the course of the viral infection in the transplanted liver, presumably by limiting the protective immune response of the recipient.

Finally, the inability of the patient to either accept the procedure or to understand its nature and/or costs in terms of the need for life-long medical follow-up should be an absolute contraindication to its performance. Similarly, patient age greater than 55 years (pragmatic upper limit) prohibits successful liver transplantation.

Transplantation of patients with the former contraindications will only lead to problems of recurrent or chronic rejection, inadequate or excessive immunosuppression, and probably recurrent sepsis in the postoperative period. Thus, patients with the latter contraindications usually are unable to withstand the rigors of the operation and postoperative period and frequently are likely to die as a result of some nonhepatic problem rather than their primary hepatobiliary disease.

The relative contraindications to hepatic transplantation include intrahepatic or biliary sepsis that cannot be resolved prior to transplantation. Although such problems may be the same factors that are necessitating the procedure, they act also to increase the risk of death following transplantation and therefore, such patients have to be carefully evaluated and screened prior to such surgery. As discussed above, the many nonhepatic problems associated with alcohol abuse and present in the abstinent alcoholic make such patients poor risks for the procedure.

Hepatitis B antigenemia in the absence of HBeAg positivity is a relative rather than an absolute contraindication for hepatic transplantation. Such individuals may not always infect the donor liver and therefore can be considered high risk, albeit not unreasonable, candidates for the procedure.

Finally, advanced renal disease may be a relative contraindication as both cyclosporin A therapy, and the surgical procedure itself is capable of worsening renal function, at least temporarily. This latter contraindication may be less of a problem with a larger experience, and of course, may be remedied with either dialysis or renal transplantation.

TIMING OF THE PROCEDURE

The second major question the internist has to ask concerning liver transplantation is when should the procedure be performed, once an acceptable candidate has been identified. This, like the former question, is difficult to answer specifically, but some common sense guidelines can be identified (Table 3). Obviously, the procedure should be performed prior to the development or acquisition of any of the absolute contraindications identified

TABLE 3. WHEN SHOULD LIVER TRANSPLANTATION BE OFFERED?

General guidelines applicable to all disease states

1. prior to the development of any of the absolute contraindications for hepatic transplantation
2. prior to irreversible extrahepatic deterioration occurring as a consequence of the primary liver disease.

Disease specific indications

1. Chronic liver disease
 - (a) prior to preterminal variceal bleeding
 - (b) prior to the irreversible hepatorenal syndrome
 - (c) prior to the development of catabolic state inconsistent with surgical survival
 - (d) prior to irreversible brain injury occurring as a consequence of or as a part of hepatic encephalopathy
 - (e) bilirubin levels >20 mg/dl
 - (f) albumin level <1.8 gm/dl
 - (g) prior to the development of an uncorrectable coagulopathy
 - (h) prior to the onset of vascular instability associated with anasarca, ascites, and pleural effusions
 - (i) prior to irreversible metabolic bone injury associated with the primary liver disease
2. Subacute liver disease
 - (a) bilirubin >25 mg/dl
 - (b) factors a, b, c, g, h listed above for chronic liver disease
3. Acute or fulminant liver disease
 - (a) only if patient at site capable of transplantation at recognition
 - (b) fulminant form of Wilson's disease

in Table 1. Moreover, the relative contraindications should also be kept at an absolute minimum or not be present as problems. In addition, the procedure cannot be offered to someone who has progressed to a stage in the course of their liver disease at which an irreversible extrahepatic complication such as brain injury, spontaneous consumption coagulopathy, or vasomotor instability is present.

In general, when one or another of the following parameters is present, liver transplantation is indicated: bilirubin exceeding 20 mg per dl; albumin below 1.8 gm per dl; encephalopathy unresponsive to the combination of a low protein diet (<40 gm per day), lactulose and neomycin. In addition, should a physician be contemplating portal caval shunting, or any of a variety of other portal decompressive procedures, liver transplantation should become an alternative option. With the former procedures, the patient's encephalopathy may worsen with either unaltered or worsened hepatic disease, while with the latter procedure (transplantation) both the portal hypertension and the primary liver disease are resolved.

With fulminant hepatic failure, be it due either to drugs, toxins, or viral injury, transplantation remains a therapeutic option; however, because of the precarious condition of these patients, it can only be offered to those who progress to Stage 3 or Stage 4 coma at the institution where liver transplantation is being performed. In our experience, patients with a fulminant hepatic failure in Stage 3 or Stage 4 encephalopathy cannot be safely transferred to a transplantation center with any degree of certainty. The majority that we have accepted for transplantation with this indication have experienced

brain stem herniation or intracerebral hemorrhage en route to our institution or soon after their arrival, making the procedure untenable and consuming valuable resources and manpower that otherwise would have been used for transplantation.

WHERE SHOULD PROCEDURE BE PERFORMED?

Numerous institutions are beginning to embark in the broad area of organ transplantation. Many of these institutions are planning to include liver transplantation as a component of their overall transplantation experience. Such a plan is both wise and cost-effective as many of the skills and facilities of a transplantation program are directly applicable to liver as well as other organ transplantation programs. The minimal obligatory requirements of a liver transplantation centers are identified in Table 4. In addition, useful, but not absolutely necessary other services that should be included in the development of a transplantation program are identified also in the table.

Any institution that has made a commitment to fulfill these requirements can legitimately enter the field. Moreover, each such institution should be encouraged to do so, as the number of acceptable candidates for transplantation and the number of available donor organs far exceed the capabilities of the few centers presently performing the procedure. When more centers begin to offer the procedure, regional resources and facilities could be used to better advantage and at lower costs, in terms of patients lost while waiting for the procedure, wastage of valuable donor organs, and dollars and time spent in caring for such patients.

With more centers performing the procedure, fewer patients should die as a result of progressive deterioration while waiting for surgery. In support of this latter statement, at our institution during the last 2 years, twice as many patients have died waiting for liver transplantation once they have been accepted as transplant candidates

TABLE 4. INSTITUTIONAL REQUIREMENTS OF A SUCCESSFUL LIVER TRANSPLANT PROGRAM

- I. Obligatory requirements
 - (a) surgeons capable of and willing to perform the procedure
 - (b) hepatologists capable of caring for and identifying candidates who have a working relationship with the operating surgeons
 - (c) an active renal dialysis program capable of providing the renal support required by such patients and the program
 - (d) adequate intensive care and operating room facilities and staff capable of accommodating the surgery when donor organs become available
 - (e) an active infectious disease program capable of recognizing and identifying unusual viral, fungal, and protozoal infections
 - (f) a blood bank capable of providing the necessary blood and blood products on demand often with little or no advanced warning of need
- II. Useful programs
 - (a) psychiatric service for patients and families
 - (b) an active immunology transplantation program
 - (c) broad-based community support for the program to include housing for patients and their families

than those who have died having once been operated upon.

Similarly, as can be seen in Table 5, many donor organs have not been used because of surgical team fatigue, unavailability of surgeons, anesthesiologists, intensive care unit space or operative room facilities, or lack of an appropriate recipient for the donor organ presently available.

Equally important to actually having both the medical and surgical expertise to perform the surgery and to care for the patient pre- and postoperatively at a given institution, is the successful interaction between these services. This requirement is often overlooked and neglected but is of paramount importance if a program is to be successful. Moreover, a common goal and commitment by both services involved is readily recognized by patients and their families and greatly facilitates the care and education of such patients both before and after the surgery.

AFTER THE OPERATION

The medical physician's responsibilities do not dissipate with the performance of the procedure. Instead, they shift their emphasis (Table 6). Their intensity, however, remains unchanged. Prerenal azotemia and acute tubular necrosis complicated further by antibiotic-induced renal disease and the administration of cyclosporin A are almost universal concomitants of the postoperative period. Similarly, careful attention to pulmonary and cardiovascular problems occurring as a consequence of massive shifts in body fluids occurring during and following the operation is a mandatory obligation during the perioperative period. Such acute postoperative responsibilities are quickly replaced by concerns about rejection, (its recognition and management), infection, (its recognition and control), the possibility of recurrent or new (transplant-associated) forms of liver disease, and the psychosocial adjustments that occur with successful rehabilitation.

Differentiation of a rejection episode from new or recurrent hepatic injury is difficult if not impossible. All manners of presentation have been seen with rejection

TABLE 5. LIVER DONOR REFERRALS AND DISPOSITION OTHER THAN FOR TRANSPLANTATION

Liver donor referrals	523
Disposition of donor referrals	
Declined: concurrent donor	74
Declined: surgical team busy in OR	12
Declined: surgical team unavailable	39
Declined: surgical team exhausted/understaffed	51
Declined: OR/anesthesia is unavailable	4
Declined: no ICU beds	43
Declined: donor clinically unsuitable	49
Declined: unacceptable donor age	34
Declined: no compatible recipient	85
Declined: donor center too distant	3
Donor family refused	35
Local M.D. or medical examiner refused	3
Donor experienced cardiopulmonary arrest prior to organ recovery	6
Recipient expired prior to transplantation	5
Livers recovered and transplanted	80

TABLE 6. POSTOPERATIVE PROBLEMS IN LIVER TRANSPLANTATION PATIENTS

I. Renal dysfunction
(a) Cyclosporin injury
(b) Tubular necrosis due to hypoperfusion
(c) Antibiotic injury
II. Rejection crisis
III. Biliary tree infection/obstruction
(a) Stenosis
(b) Leaks
(c) Infection
IV. Graft vascular injury
(a) Hepatic vein obstruction
(b) Hepatic artery thrombosis/stenosis
(c) Portal vein thrombosis/stenosis
V. Infections (bacterial and viral, fungal)
(a) Abdominal—perihepatic abscess
(b) Biliary tree
(c) Pulmonary
(d) Reactivated virus
(e) Gastrointestinal tract
(f) Catheter associated (intravenous, urinary tract, and endotracheal)

including evidence for hepatocellular, cholestatic, or mixed hepatocellular-cholestatic syndromes. The parameters which have proved to be the most useful in the recognition of a rejection episode and in clinical management of patients during this period include the serum bilirubin level, the alkaline phosphatase level, efforts at visualization of the biliary tree, and identification of fluid collections (abscesses) in and about the operative field. Injury to the hepatic artery, portal vein or vena cava, or biliary tree occurring at time of surgery may go unrecognized at operation or be occult until several days or weeks have elapsed since the operation. Changes in the size and/or consistency of the transplanted liver, as determined by repeated careful physical examinations, are excellent indicators of such untoward events. Any increase in liver size or consistency must alert the physician to the possibility of either a rejection crisis or the development of a vascular injury and should suggest other studies. An increase in either the serum bilirubin level or in alkaline phosphatase activity should suggest the possibility of a biliary tract problem (leak or stenosis) or rejection. The latter condition may be resolved with the techniques of ultrasonography, T-tube, or percutaneous transhepatic cholangiography. Vascular problems are best evaluated with angiographic studies and liver spleen scanning techniques. Unfortunately, organ rejection must remain a diagnosis of exclusion.

Liver biopsy, particularly when it suggests another mechanism for the observed postoperative hepatic injury, helps on occasion in resolving this difficult differential problem. Unfortunately, it has not proven to be of consistent help in establishing the specific diagnosis of rejection. Fine intralobular hepatocellular regeneration, centrilobular bland hepatocellular necrosis, and a paucity of bile ducts are occasionally seen and should suggest rejection, although they are not entirely specific. Even when sophisticated techniques of lymphocyte subtyping and enumeration have been utilized, the diagnosis of rejection has not been an easy one to establish with liver

biopsy. Both T and B lymphocytes can be seen in rejecting livers but no specific pattern of such cellular infiltrates has been recognized (3). Moreover it appears, based upon limited and to date rather anecdotal experience, that liver biopsy is more dangerous in patients posttransplantation than it is in other clinical situations. This increased risk appears to be the result of a greater incidence of postbiopsy bleeding, presumably due to the hypervascularity of the transplanted liver.

Finally, infections in and about the operative site involving the liver, biliary tree, and lung are common and must be carefully watched for, recognized, and treated when found. With long hospitalization in the surgical intensive care unit, nosocomial pulmonary infections and fungal infections of the upper gastrointestinal tract are common and may prove to be difficult additional problems with which the physician has to reckon. Thus, 44% of our patients have had fungal infections of which 16% have had fungemia (4). *Candida* infections have been the most frequent, but in addition aspergillosis, mucor, and cryptococcal infections have occurred. Viral infections of the herpes group (cytomegalovirus, herpes simplex virus, herpes zoster virus, and Epstein-Barr virus) are particularly common after liver transplantation. Cytomegalovirus reactivation or new infection has been almost universal and is followed in order by herpes simplex virus and Epstein-Barr virus infections.

Despite the numerous difficulties with patient selection, preparation, and postoperative care experienced in clinical liver transplantation and enumerated above, the overall success and improvement in patient status following successful procedures is of such magnitude that it is indeed a reasonable and worthwhile endeavor. Specifically in terms of psychiatric status, social and behavioral functioning and intelligence, patients surviving liver transplantation do not differ from levels defining the normal population (5). Thus, compared to their pretransplant state, they are remarkably improved and effectively have been transferred from a population of chronically ill hospital-bound patients to that of normal working individuals who are capable of enjoying and contributing to their own life and to society at large.

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